Ageing Research Reviews 104 (2025) 102599

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

An overview of the genes and biomarkers in Alzheimer's disease

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ARTICLE INFO

Keywords:
Alzheimer's disease
Neurofibrillary tangles
Amyloid plaque
Biomarker
Preclinical
Preventive measures

ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia and neurodegenerative disease characterized by neurofibrillary tangles (NFTs) and amyloid plaque. Familial AD is caused by mutations in the *APP, PSEN1*, and *PSEN2* genes and these mutations result in the early onset of the disease. Sporadic AD usually affects older adults over the age of 65 years and is, therefore classified as late-onset AD (LOAD). Several risk factors associated with LOAD including the *APOE* gene have been identified. Moreover, GWAS studies have identified a wide array of genes and polymorphisms that are associated with LOAD risk. Currently, the diagnosis of AD involves the evaluation of memory and personality changes, cognitive impairment, and medical and family history to rule out other diseases. Laboratory tests to assess the biomarkers in the body fluids as well as MRI, CT, and PET scans to analyze the presence of plaques and NFTs are also included in the diagnosis of AD. It is important to diagnose AD before the onset of clinical symptoms, i.e. during the preclinical stage, to delay the progression and for better management of the disease. Research has been conducted to identify biomarkers of AD in the CSF, serum, saliva, and urine during the preclinical stage. Current research has identified several biomarkers and potential biomarkers in the body fluids that enhance diagnostic accuracy. Aside from genetics, other factors such as diet, physical activity, and lifestyle factors may influence the risk of developing AD. Clinical trials are underway to find potential biomarkers, diagnostic measures, and treatments for AD mainly in the preclinical stage. This review provides an overview of the genes and biomarkers of AD.

1. Introduction

Alzheimer's disease (AD), the most common type of dementia, is characterized by progressive neurodegeneration involving neuritic plaques and neurofibrillary tangles (NFT) due to the accumulation of amyloid beta (Aβ) and hyperphosphorylated tau, respectively, in the medial temporal lobe and neocortical structure (De-Paula, et al., 2012). Emil Kraepelin coined the term Alzheimer's disease after the German psychiatrist, Alois Alzheimer, who observed the amyloid plaques and massive neuronal loss while examining the brain of a patient with memory loss and personality changes (Blass, 1985; Cipriani, et al., 2011). AD progresses slowly and symptoms are observed decades after Aβ plaque and NFT accumulation. The Mini-Mental State Examination (MMSE) monitors the subtle cognitive decline in AD patients and studies have reported that patients tend to lose 3–4 MMSE every year. Recent memory loss is the most common symptom that is usually reported in the initial stages of the disease, however, personality changes and irritability are also observed during the early stages in a few individuals. Aphasia, apraxia, agnosia, and motor and gait disturbances are reported during the later stages of AD and patients are usually bedridden by this stage (Small, et al., 1997).

AD can be divided into preclinical, mild/early AD, moderate AD, and severe AD/dementia. Patients are usually asymptomatic in the preclinical stage and studies have identified early biomarkers that can be detected during this stage. Plaque and NFT accumulation in the hippocampus and cortex begin at this stage and the preclinical stage lasts several years with no impairment to day-to-day activities (De-Paula, et al., 2012; Dubois, et al., 2016). Impairment of memory, executive functions, and language are observed during mild/early AD. Mood swings, loss of concentration, disorientation, and depression are also common during this stage (Wattmo, et al., 2016). Moderate AD is distinguished by accelerating memory loss, trouble recognizing friends

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https://doi.org/10.1016/j.arr.2024.102599
Received 3 September 2024; Received in revised form 25 November 2024; Accepted 25 November 2024
Available online 28 November 2024

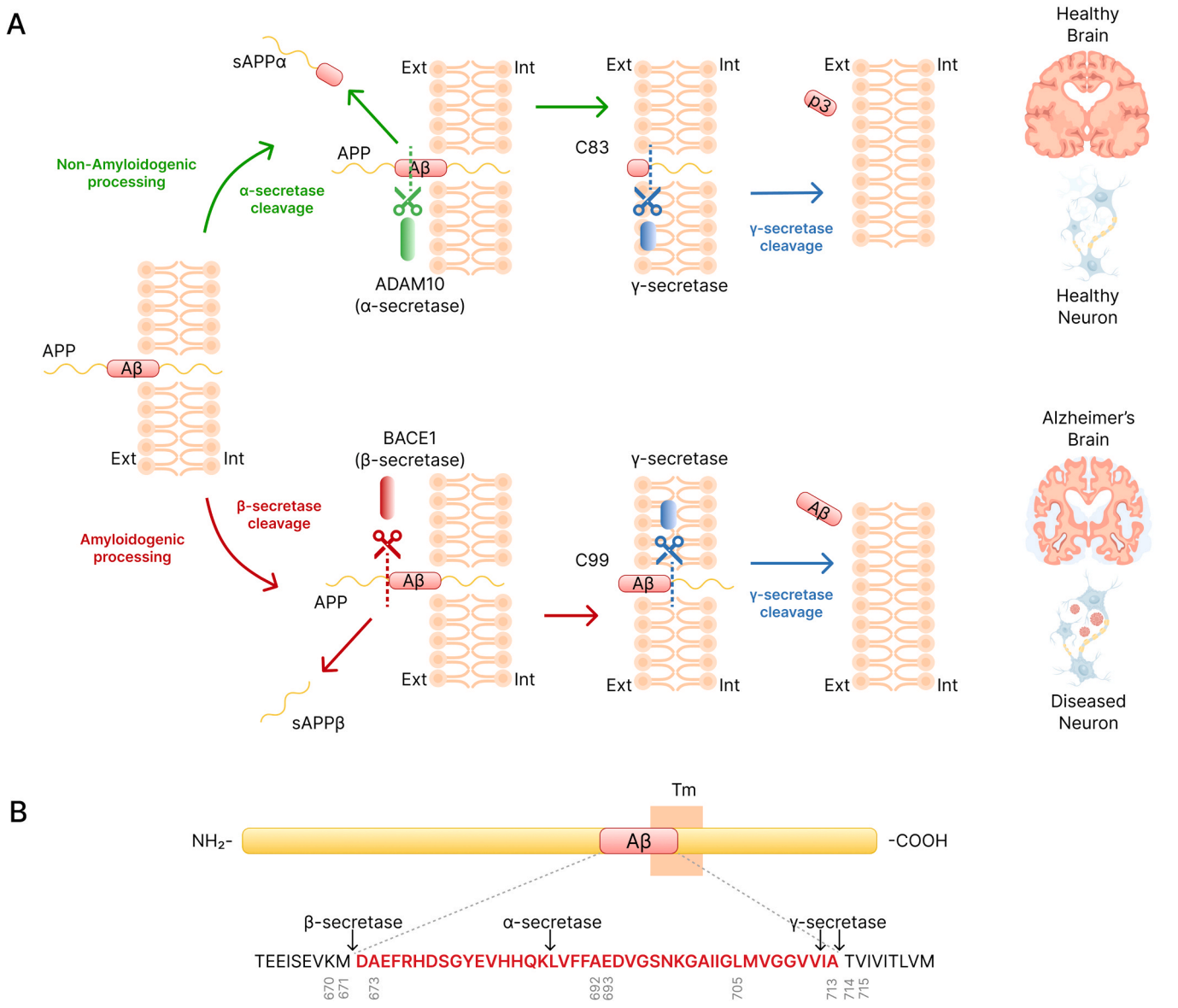

Fig. 1. The overview of APP processing and Aβ peptide formation.

and family members, increased difficulty in reading, speaking, and writing, and loss of impulse control. In the final stage, severe accumulation of plaques and NFTs are observed throughout the cortex which results in progressive loss of cognitive and functional abilities. Patients are unable to recognize family and friends and are bedridden with no control over swallowing and urination (De-Paula, et al., 2012; Apostolova, 2016). Around 20–40% of AD patients suffer from delusions. Visual, auditory, and olfactory hallucinations are also reported. Sleep is fragmented due to disruption of the circadian rhythm. Disruptive behaviors are common in ≈50% of AD patients (Breijyeh and Karaman, 2020).

Accurate diagnosis of AD is difficult, especially during the preclinical stage when the patients are asymptomatic (Holsinger, et al., 2007; Galvin, et al., 2005). Currently, physicians evaluate memory and personality changes, cognitive impairment, medical and family history to rule out other diseases. Laboratory tests to assess the biomarkers in the body fluids as well as MRI, CT, and PET scans to analyze the presence of plaques and NFTs are also conducted to diagnose AD. The current available diagnostic tools can diagnose AD with an accuracy of 77% (Sabbagh et al., 2017). Several studies have suggested beginning AD treatment/intervention during the preclinical stage. Early biomarkers of AD are present in the cerebrospinal fluid (CSF), blood, urine, and saliva of patients. However, measuring biomarker levels from CSF and blood is not practical due to their invasive nature, cost, and the unavailability of appropriate equipment needed to collect the sample in rural areas, underdeveloped countries, and underserved communities (Biagioni and Galvin, 2011).

Identifying the genetic markers can help with the early diagnosis and better management of AD. Certain genes associated with AD can be inherited and identification of the causative gene in the affected individual makes it possible for the family members to get tested. However, AD is caused by more than one gene and it is difficult to predict the symptoms and age of onset during presymptomatic testing (Quaid, 2011). Identification of the causative genes also helps researchers to correlate the gene with pathology, biomarkers, imaging, and clinical features of the disease. These correlations help to create diagnostic criteria that are specific, sensitive, and more accurate. A well-characterized patient sample including genetic information can help to understand the pathogenesis and progression of the disease as well as provide necessary information to start clinical trials for potential

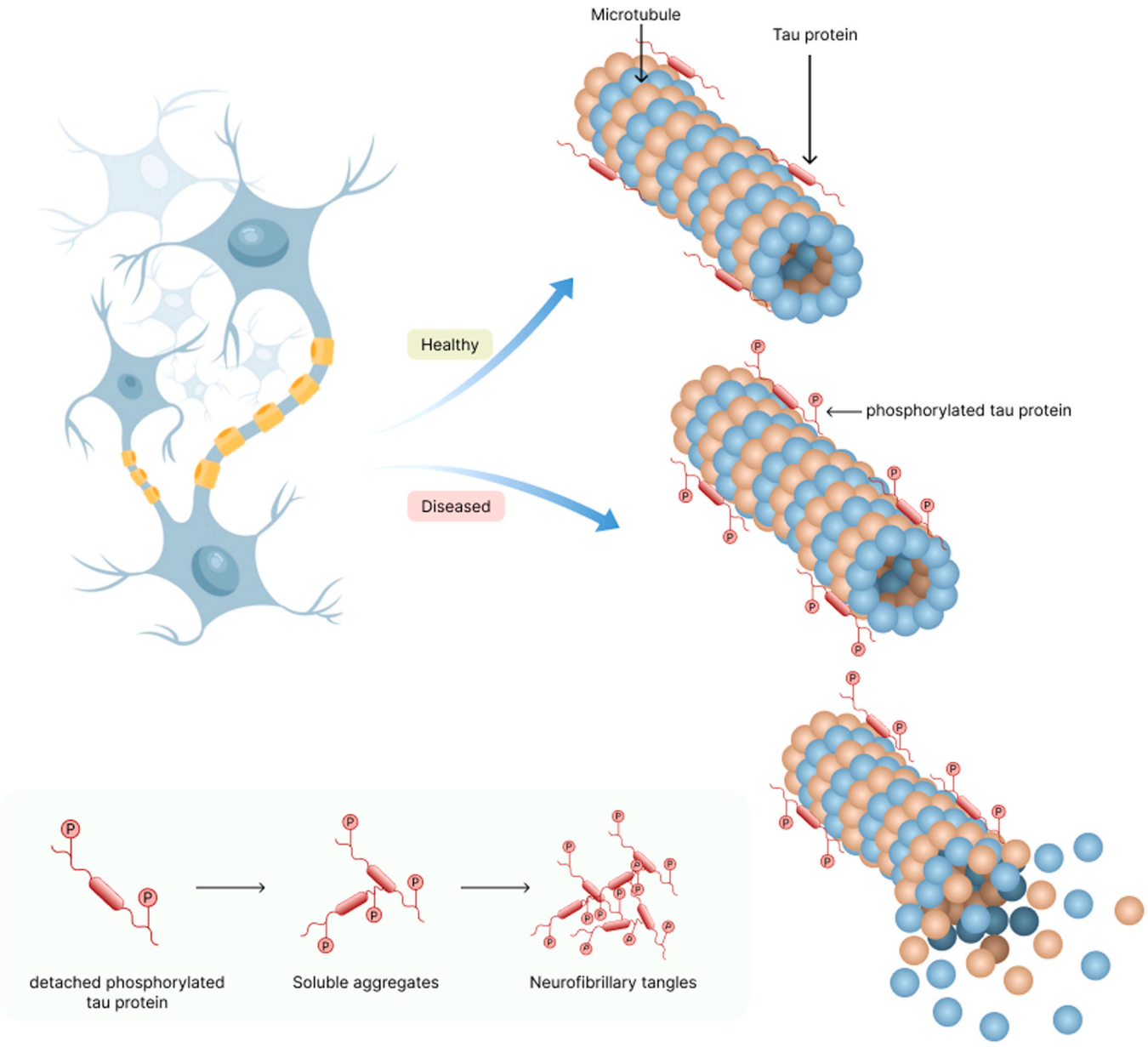

Fig. 2. Hyperphosphorylation of Tau.

treatments (Bateman, et al., 2012). Predicting at-risk individuals with genetics may enable researchers to design clinical trials for preventing or delaying the onset of AD (Van Deerlin, 2012). This review provides a detailed account of the genetics and biomarkers of Alzheimer's disease along with diet and exercises to prevent/manage AD.

2. Amyloid beta formation

The amyloid precursor protein or APP is the precursor to amyloid beta (Aβ). APP is processed via the amyloidogenic and the non-amyloidogenic pathways. APP is cleaved by β-secretase and γ-secretase resulting in the formation of Aβ peptides in the amyloidogenic pathway whereas the APP is cleaved by α-secretase and γ-secretase without the formation of Aβ peptides in the non-amyloidogenic pathway. Under normal, healthy conditions, APP is processed by the non-amyloidogenic pathway and an equilibrium of Aβ production and their clearance is maintained in the human brain (Vetrivel and Thinakaran, 2006). In this pathway, α-secretase cleaves APP within the Aβ domain resulting in the formation of sAPPα and C-terminal fragment C83. Neuronal activity and activation of muscarinic acetylcholine receptors increase sAPPα production, thus favoring the non-amyloidogenic pathway (Haass, et al., 1995). The C83 fragment is further cleaved by γ-secretase to produce P3 peptide (Kahle and De Strooper, 2003). However, under pathological conditions, the equilibrium is disturbed as APP is cleaved by the amyloidogenic pathway leading to the accumulation of Aβ in the brain (Kunjathoor, et al., 2004). In the amyloidogenic pathway, APP is cleaved by β-secretase to produce the C-terminal fragment C99 and the soluble sAPPβ fragment. The sAPPβ fragment is released into the extracellular matrix whereas the C99 fragment is further cleaved by γ-secretase at multiple sites resulting in the production of Aβ peptides with 43, 45, 46, 48, 49, and 51 amino acids. These peptides are further cleaved to form the main Aβ peptides (40 and 42) found in the human brain (Olsson, et al., 2014; Takami, et al., 2009). Along with the Aβ peptides, the APP intracellular domain or AICD is also formed when C99 is cleaved by γ-secretase. AICD is translocated to the nucleus and has a role in regulating gene expression such as the apoptotic genes (Chen et al., 2017). Several factors like mutations in the *APP* and *PSEN* genes, overexpression of the APP

Table 1
Overview of mutations associated with AD genes.

Gene	Mutation (Bagaria, et al., 2022; Cai, et al., 2015; Bi, et al., 2019)
PSEN1	Asp40del, Ala79Val, Leu85Pro, Pro88Arg, Met84Val, Cys92Ser, Ile83Thr, Val96Phe, Ile83_Met84del, Val89Leu, Glu120Lys, Glu120Asp, Glu120Gly, Met139Val, Met139Thr, Met139Leu, Met146Leu, Met146Ile, Met146Val, Thr147Ile, Ala136Gly, Leu153Val, Ile143Val, Trp165Cys, Leu173Phe, Leu166Pro, Leu166Val, Leu166Arg, Ser170Phe, Ser169Leu, Leu174Arg, His163Arg, His163Pro, Phe176Leu, Phe177Val, Ile168Thr, Ala164Val, Phe175Ser, Ser163Pro, Gly206Asp, Gly206Val, Gly206Ala, Gly209Val, Gly209Glu, Gly209Arg, Met210, Ile213Ph, His214Arg, His214Asp, His214Tyr, Leu219Pro, Leu219Arg, Leu202Phe, Gly217Arg, Gly217Asp, Ser212Tyr, Leu113Gln, Pro117Leu, Pro117Ser, Thr119Ile, Glu123Lys, Thr116_117delSer, Leu113indel, Tyr115His, Thr116indel, Pro117Ala, Met233Val, Leu235Val, Leu235Pro, Ser237Cys, Met233Ile, Leu226Phe, Met233Leu, Gln223Arg, Ser230Asn, Leu235Arg, Ala246Glu, Pro267Ser, Arg278Ile, Ile249Leu, Ala275Ser, Leu272Asp, Leu262Val, Pro264Leu, Tyr256Asn, Arg269Gly, Cys263Trp, Leu272Ala, Gly266Ser, Val261Leu, Ile250Val, Ile250Ser, Leu271Val, Leu282Val, Leu286Val, Glu280Gly, Pro284Leu, Leu286Pro, Trp294Ter, Asp333Gly, Ser357Ter, Arg377Trp, Pro293Leu, Arg352dup, Pro355Ser, Lys311Arg, Glu218Gly, Ser365Tyr, Gly384Ala, Leu381Val, Val391Gly, Gly378Glu, Tyr389His, Ser390Asn, Leu392Val, Ala396Thr, Gly378Arg, Pro388Leu, Thr389Ser, Asn405Ser, Arg377Trp, Ser357Trp, Gly378Val, Ala431Val, Ala431Glu, Met457Val, Leu418Trp, Leu420Arg, Cys410Tyr, Gly417Ala, Leu418Phe, Leu424His, Leu424Arg, Gly417Ser, Ile408Thr, Ala31Glu, Leu424Val, Leu424Arg, Pro433Ser, Ala434Cys, Pro436Gln, Ala434Thr, Thr440del, Ile413Thr, and Ile439Val.
PSEN2	Arg29His, Gly34Ser, Arg62Cys, Arg62His, Pro69Ala, Arg71Trp, Thr122Arg, Thr122Pro, Glu126fs, Glu126Lys, Ser130Leu, Val139Met, Asn141Ile, Asn141Tyr, Leu143His, Val148Ile, Lys161Arg, Met174Val, Ser175Cys, Val214Leu, Gln228Leu, Ile235Phe, Ala237Val, Met239Ile, Met239Val, Ala252Thr, Thr301Met, Lys306fs, Pro334Ala, Pro334Arg, Ala337Val, Val393Met, Thr430Met, and Asp439Ala.
APP	A201V, A235V, D243N, E246K, T276S, V287G, E296K, P299L, R328W, V340M, R468H, A479S, K496Q, A500T, K510N, Y538H, V562I, E599K, T600M, S614G, P620A, P620L, N660Y, T663M, E665D, H677R, G708G, G709S, V710G, A713V, I718L, T719N, L720S, M722K, H733P, A741S, KM670/671NL, A673V, D678H, D678N, E682K, K687N, A692G, E693del, E693G, E693K, E693Q, D694N, T714I, V715A, V715M, I716F, I716T, I716T, V717F, V717G, V717I, V717L, L723P, K724N, K724M, E693N, L705V, A713T, T714A, I716M, T719P, L723R, and A673T.

protein, overexpression of β-secretases, inflammation, oxidative stress, environmental factors, interactions between tau and APP, and impaired Aβ clearance mechanisms can favor the amyloidogenic pathway (De Paula, et al., 2009). Fig. 1 depicts the processing of the APP protein.

3. Tau hyperphosphorylation

Tau protein is the one of the main microtubules associated protein or MAP found in neurons (Weingarten, et al., 1975). The main function of tau is to maintain the structure and assemble microtubules (Köpke, et al., 1993). Microtubules are part of the cytoskeleton and is essential to maintain the structure and shape of cells and are involved in intracellular transportation, cellular division, and cell movement. Six isoforms of tau (0N3R, 0N4R, 1N3R, 1N4R, 2N3R, 2N4R) have been identified. A normal tau protein consists of 2–3 moles of phosphate per mole of the protein and this phosphorylation is required for its interaction with tubulin and promoting and maintaining microtubule assembly (Jicha, et al., 1997). However, in AD, tau protein is hyperphosphorylated and forms NFTs. Abnormally phosphorylated tau is a characteristic of AD and related neurodegenerative diseases called tauopathies like Pick disease, dementia pugilistica, fronto-temporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) caused by tau mutations, corticobasal degeneration, and progressive supranuclear palsy. Deposition of hyperphosphorylated tau in the neocortex is associated with dementia in all the above-mentioned diseases. All six isoforms of tau are hyperphosphorylated in AD.

Conformational changes and truncation of tau after hyperphosphorylation have been reported in AD (Novak, et al., 1991; Alonso et al., 1994). However, abnormal hyperphosphorylation is the most common cause of tau protein dysfunction (Iqbal, et al., 1986; Khatoon, et al., 1992). Tau protein is soluble in the brains of cognitively normal individuals. In AD patients, tau protein exists three different states, ie, oligomeric, fibrillated, and soluble states (Jicha, et al., 1997; Khatoon, et al., 1992). Even though the amount of normal tau protein is the same in the AD brain and normal brain, the AD brain tends to have four to eight-fold higher levels of hyperphosphorylated tau than the normal brain (Alonso et al., 2006). Tau that forms NFTs are dysfunctional and have no role in maintaining the structure and assembly of microtubules (Li, et al., 2007). 40% of hyperphosphorylated tau in AD do not form NFTs and are present in the cytosol (Jicha, et al., 1997; Khatoon, et al., 1992). The hyperphosphorylated tau protein that does not form NFTs disrupts the structure and assembly of microtubules (Iqbal, et al., 1986; Alonso et al., 1997). Hyperphosphorylated tau sequesters normal tau and other neuronal microtubule-associated proteins like MAP1 A/B and MAP2 (Brickell, et al., 2006). This toxic behavior is due to abnormal hyperphosphorylation as studies have shown that dephosphorylation of tau converts it into the normal state (Iqbal, et al., 1986; Alonso et al., 1997). Fig. 2 shows the hyperphosphorylated tau protein.

4. Genetics of Alzheimer's Disease

AD can be classified into early-onset Alzheimer's disease or EOAD and late-onset Alzheimer's disease (LOAD). 90% of AD cases are sporadic with an age of onset at 60–65 years (LOAD). The age of onset of EOAD ranges from 30 years to 60–65 years and 13% of familial EOAD is inherited in an autosomal dominant manner (Campion et al., 1999; Roses, et al., 1995). The genes *APP, PSEN1,* and *PSEN2* are associated with EOAD whereas the only gene associated with LOAD is *APOE* (Selkoe, 2001; Kang, et al., 1987). However, many individuals with the *APOE* ε4 allele do not develop AD and live into their 90 s suggesting the possibility of other environmental and genetic risk factors of LOAD. Several susceptibility genes associated with LOAD have been identified over the years. Table 1 provides an overview of AD genes and the mutations associated with them.

4.1. Amyloid Precursor Protein (APP)

The amyloid precursor protein, APP is the precursor to Aβ found in the plaques of AD patients. *APP* was identified by Kang and colleagues and was mapped to the 21st chromosome (Giaccone, et al., 1989). Individuals with Down syndrome (trisomy of chromosome 21) developed amyloid plaques in their 40 s which can account for the position of the *APP* gene (Turner, et al., 2003). *APP* gene encodes the amyloid precursor protein, an integral membrane protein (Giaccone, et al., 1989). This protein is highly concentrated in the synapses and is thought to have a role in maintaining neural plasticity and regulating synapses (Priller, et al., 2006; Walter, et al., 2001). APP protein is broken down into amyloid α peptide by α-secretase and into amyloid β peptide by β-secretase. APP proteolysis by β and α secretases results in the formation of C terminal fragments which may be broken down by γ-secretase to release Aβ peptide to the extracellular matrix (Bird, 2008).

69 different missense mutations of *APP* have been identified so far. The mutations within the *APP* gene leads to 10–15% early-onset familial AD (EOFAD) (Scheuner, et al., 1996). Most of the EOFAD mutations in the *APP* gene is closer to the Aβ sequence. These mutations usually alter APP processing thereby increasing Aβ42 levels (Walker, et al., 2005; Esler and Wolfe, 2001). Individuals with these mutations usually start showing symptoms of AD by the age of 40 years (Hardy, 2001; Goate, et al., 1991). Missense *APP* mutations like the Swedish mutations (*APP*SW, M67IL, *APP*K670N), and the London mutations (*APP*V717I, *APP*LON) increase Aβ production and lead to AD (Mullan, 1992; Kwok, et al., 2000). The London mutation, V717I was the first *APP* mutation to be identified. This mutation is within the transmembrane domain near to the γ-secretase cleavage site (Mullan, 1992). Other studies have

Table 2
Novel polymorphisms associated with AD risk.

Gene	Polymorphism	Description (Giri, et al., 2016; Misra, et al., 2018)
INPP5D	rs35349669	*INPP5D* gene encodes a protein that has a role in cytokine signaling. The SNP in this gene, rs35349669, is associated with increased risk of LOAD.
CASS4	rs7274581 rs6024870 rs16979934	The *CASS4* gene is widely expressed in the lung and spleen and has a role in cellular migration, motility, and adhesion. It also has a role in calcium signaling and microtubule stabilization. The SNP, rs7274581, is associated with reduced risk of LOAD whereas the SNPs, rs6024870 and rs16979934 are associated with an increased risk of LOAD.
NME8	rs2718058	*NME8* encodes a protein that has a role in neuronal proliferation and differentiation. The SNP, rs2718058, is associated with reduced risk of LOAD.
MEF2C	rs190982	*MEF2C* gene encodes a transcription factor, MEF2C, that has a role in myogenesis and neurogenesis. The SNP, rs190982, is associated with an increased risk of LOAD.
PTK2B	rs28834970	The *PTK2B* gene a cytoplasmic protein tyrosine kinase that has a role in the activation of MAP kinase pathway and calcium-induced regulation of ion channels. The SNP in this gene, rs28834970, is associated with increased LOAD risk.
FERMT2	rs17125944	*FERMT2* gene encodes a protein called kindlin-2 that has a role in myogenesis and angiogenesis. The SNP rs17125944 is associated with an increased risk of LOAD.
ZCWPW1	rs1476679	*ZCWPW1* gene encodes a protein that may have a role in epigenetic regulation by histone modification. The SNP in this gene rs1476679 is associated with LOAD.
DSG2	rs8093731	The *DSG2* gene encodes the calcium binding transmembrane glycoprotein desmoglein. The SNP rs809731 is associated with LOAD.
UNC5C	rs137875858	*UNC5C* gene is expressed in the hippocampal and cerebellar neurons. The SNP rs137875858 increases the risk of LOAD.
ADAM10	rs2305421	*ADAM10* is expressed in various cells and the SNP in this gene, rs2305421, is associated with AD.
SLC24A4/ RIN3	rs10498633	The *SLC24A4* gene encodes a member of the potassium-dependent sodium/calcium exchanger. The SNP, rs10498633, is associated with AD risk. The *RIN3* gene is located near to this SNP.
HLA-DRB5/ HLA-DRB1	rs9271192	The HLA-DRB5/HLA-DRB1 is a member of the major histocompatibility complex class II and is found on chromosome 6p21.3. HLA-DRB5/ HLA-DRB1 is involved in immune responses and is expressed on the microglia. The SNP, rs9271192, is associated with LOAD risk as well as multiple sclerosis.
CELF1	rs10838725	The *CELF1* gene is situated on chromosome 11 and has a role in mRNA editing, mRNA translation, and pre-mRNA alternate splicing. The SNP, rs10838725, is associated with LOAD risk and increased tau toxicity in *Drosophila* models.
PLD3	rs145999145	The *PLD3* gene is situated on chromosome 19 and encodes a protein that is associated with the endoplasmic reticulum. This protein is expressed in hippocampus and the frontal, occipital, and temporal cortices. This protein may be involved in cell differentiation, signal transduction, and neurotransmission. The SNP, rs145999145, is associated with the risk of LOAD. Studies have also reported that low expression of PLD3 is associated with elevated levels of extracellular Aβ42 and Aβ40.
AKAP9	rs144662445 rs149979685	The *AKAP9* gene is located on chromosome 7 and encodes a protein that is expressed in cortex, cerebellum, and hippocampus. The SNPs, rs144662445 and rs149979685, are associated with AD risk.

reported various other substitutions at this site and these mutations have been identified in families with no relation to the initial London family. Several *APP* mutations have been identified near the γ-secretase cleavage site and most of these mutations are associated with altering the Aβ levels. For instance, the L723P mutation, identified in an Australian family, increases Aβ42 levels in the Chinese hamster ovary cell line or CHO cell lines (Sherrington, et al., 1995).

4.2. Presenilin 1 (PSEN1)

The *PSEN1* gene is located on chromosome 14 and it encodes a polytopic membrane protein (Takasugi, et al., 2003). The protein encoded by this gene is part of the catalytic core of the γ-secretase complex. PSEN1 protein along with other proteins is needed for maintaining the stability and activity of γ-secretase complex (Theuns, et al., 2000). γ-secretase is needed for cleaving type-I transmembrane proteins like APP and NOTCH. *PSEN1* missense mutations are responsible for 18%-50% of autosomal dominant cases of EOFAD (Citron, et al., 1997). Research shows that these mutations increase the Aβ42 to Aβ40 ratio (Lippa, et al., 1998). Deposition of Aβ42 could be an early preclinical event in individuals with this mutation (Yu et al., 2001). Mouse models are used for a better understanding of the function of this gene. MCI in long-term spatial reference memory and retention was found in conditional *PSEN1* knockout mouse models (Holcomb, et al., 1998). These studies show that the *PSEN1* gene has a role in cognitive memory. Similar studies using animal models have shown an association between increased Aβ production and mutations in *APP* and *PSEN1* genes (Mineur, et al., 2005; Wolfe, 2007).

Mutations in this gene are known to cause severe forms of AD with age of onset at around 30 years and complete penetrance. AD due to mutations in the *PSEN1* gene is inherited in an autosomal dominant manner. The characteristics of this type are impaired notch signaling, dementia, parkinsonism, and Aβ intracellular domain generation (Rudzinski, et al., 2008). Atypical AD symptoms like spatial paraparesis are also observed in some patients. A Greek family with N135S mutation showed memory loss, variable limb spasticity, and seizures (Heckmann, et al., 2004). Another *PSEN1* mutation was identified in an African family. The age of disease onset was 50 years and the duration of the illness was short. Autopsy results revealed AD characteristics like neuronal loss, Aβ plaques, neurofibrillary tangles, and brainstem degeneration (Scheuner, et al., 1996). 300 different mutations of this gene have been identified so far. Most of these are missense mutations and result in amino acid substitutions throughout the PSEN1 protein. These substitutions increase Aβ42 production and decrease Aβ40 production resulting in an increase of the Aβ42 to Aβ40 ratio in the brain leading to increased Aβ42 deposition (Moehlmann, et al., 2002). For instance, individuals with *PSEN1*-L166P mutation have high levels of Aβ42, age of onset at adolescence, and impaired notch signaling (De Strooper, et al., 1998).

4.3. Presenilin 2 (PSEN2)

The *PSEN2* gene is found on chromosome 1 and encodes the protein PSEN2. This protein is a component of γ-secretase (Wolfe, et al., 1999; Bentahir, et al., 2006). The gene is expressed primarily in the neurons and like *PSEN1*, mutations in *PSEN2* also increase Aβ42 to Aβ40 ratio

Table 3
Overview of CSF biomarkers.

Biomarker	Directionality for increased risk	Description
Aβ42	↓	The levels of Aβ42 drop in the CSF in AD as it is deposited and accumulated into plaques in the brain.
Aβ40	No change	Aβ40 is a peptide cleaved from APP and is non-toxic compared to the toxic Aβ42 peptide. Studies have observed no significant change in the Aβ40 levels in the CSF of AD patients.
Aβ42/ Aβ40	↓	The Aβ42/ Aβ40 ratio in the CSF is low for AD patients compared to normal individuals as the Aβ42 levels are low in the CSF of AD patients.
t-tau	↑	Total (t)-tau is a marker of neuronal injury and its levels are high in the CSF of AD patients.
p-tau 181	↑	Tau phosphorylated at threonine 181 or p-tau 181 is a marker of AD and its levels in the CSF increases before the onset of cognitive impairment.
p-tau 217	↑	Tau phosphorylated at threonine 217 or p-tau 217 is a marker of AD and its levels in the CSF increases during the preclinical stage of AD.
p-tau 231	↑	Tau phosphorylated at threonine 231 or p-tau 231 is a marker of AD and its levels in the CSF are high in AD patients compared to normal individuals.
BACE1	↑	BACE1 is the β-secretase that cleaves the APP protein to generate Aβ peptides. BACE1 levels are elevated in the CSF of AD patients and this increase is associated with low hippocampal volume.
NF-L	↑	NF-L or neurofilament light is involved in axonal support. This filament is released into the CSF during neuronal damage or neurodegeneration and its levels are high in the CSF of AD patients.
VILIP-1	↑	VILIP-1 or visinin-like protein 1 is a neuronal calcium sensor protein and is a marker for neuronal injury. The level of this protein is elevated in the CSF of AD patients.
Neurogranin	↑	Neurogranin is expressed in the dendritic spines and is involved in the post-synaptic signaling pathways. High levels of neurogranin were observed in the CSF of patients with MCI and AD.
SNAP-25	↑	SNAP-25 has a role in the synaptic vesicle exocytosis and its levels in the CSF are elevated in AD patients when compared to patients with MCI and normal individuals.
Synaptotagmin	↑	Synaptotagmin is a pre-synaptic protein and its levels are high in patients with AD and MCI that progresses to AD.

(Lippa, et al., 1998). 33 different *PSEN2* mutations associated with AD have been identified. These mutations affect the APP processing at the γ-secretase cleavage site. For instance, the L166P mutations reduces Aβ production while the G384A mutation increases Aβ42 production (Sherrington, et al., 1996). However, *PSEN2* mutations produce low levels of Aβ42 when compared with *PSEN1* mutations (Sherrington, et al., 1996). Missense mutations in the *PSEN2* gene rarely lead to EOFAD compared to *PSEN1* mutations. Moreover, the age of onset of EOFAD varies among the affected members of the same family (Levy-Lahad, et al., 1995). It is also suggested that these mutations may be modified by environmental factors and other genes. N141I is the first *PSEN2* mutation to be identified and described (Lindquist, et al., 2008). The V393M mutation in the seventh transmembrane domain of the gene was recently identified (Krishnamurthy et al., 2023).

4.4. APOE

The *APOE* gene is located on chromosome 19 and encodes the protein apolipoprotein E. This gene is found in a cluster with genes *APOC1*, *APOC2*, and *APOC4*. ApoE protein is the major apolipoprotein of chylomicron in the brain. ApoE is synthesized in the astrocytes, microglia, and neurons (Corder, et al., 1993). Cholesterol and lipids are transferred onto nascent ApoE proteins which form lipoprotein particles. ApoE then redistributes cholesterol and lipids to neurons. The ε4 loci of the *APOE* gene is located on exon 4 and has three alleles: ε2, ε3, and ε4. These alleles are defined by polymorphisms rs7412 and rs429358. ApoE3 is the most common isoform of ApoE. Even though the complete mechanism through which ApoE becomes toxic to the brain is unknown, studies have shown that the *APOE* ε4 allele is associated with a high risk of AD and results in tau hyperphosphorylation and amyloid aggregation (Huang, 2006; Tang, et al., 1996). This allele is also associated with earlier onset of AD (Liu, et al., 2002) and worse outcomes after stroke (Nicoll, et al., 1995) and head trauma (Mahley and Rall, 1999). The *APOE* polymorphisms are found only in humans and are thought to have evolved due to changes in diet (Finch and Stanford, 2004; Murphy, et al., 2013).

Imaging studies show that the *APOE* ε4 allele is associated with Aβ deposition in patients with mild cognitive impairment (MCI) and AD (Fleisher, et al., 2013; Mishra, et al., 2018). Longitudinal studies showed that in individuals with the *APOE* ε4 allele, the effect of this allele on Aβ accumulation was high during the initial phase of Aβ aggregation (Morris, et al., 2010) (Jansen, et al., 2015). The *APOE* ε2 allele is associated with reduced Aβ deposition in patients with MCI (Lim, et al., 2017). The *APOE* ε2 allele protects against longitudinal Aβ deposition (Shinohara, et al., 2016). However, the presence of an ε4 allele outweighs the protective effect of ε2. For instance, individuals with ε4/ε2 and ε4/ε3 genotypes had Aβ accumulation (Lim, et al., 2017). Hence, it can be concluded that the *APOE* ε4 allele results in Aβ deposition irrespective of the presence of the other two alleles. Studies have also reported that the *APOE* ε2 allele reduced cognitive decline during aging (Neumann, et al., 2006). The *APOE* ε4 allele increased the risk of TDP43 (Dickson, et al., 2018), α-synuclein (Ossenkoppele, et al., 2016), and tau pathologies (Arendt, et al., 1997) in the brains of AD patients. However, the correlation between these and AD risk is still unknown. Moreover, studies performed on animal models and cell lines show the effect of the *APOE* ε4 allele on neuroinflammation, synaptic function degeneration (Ji, et al., 2003), reduction in dendritic density and plasticity (Sweet, et al., 2016), reduction in the number of glutamate receptors (Koffie, et al., 2012), and accumulation of Aβ oligomers at synapses (Yu and Tan, 2012).

5. Susceptibility genes

Genome-wide association studies (GWAS) have found several genes that can increase the susceptibility of an individual to develop AD. However, these genes are relatively novel and their complete function in AD pathogenesis remains unknown. 11 susceptibility genes including *CLU, CD33, BIN1, PICALM, ABCA7, SORL1, CR1, EPHA1, CD2AP, MS4A,* and *TREM2* have been described so far. Recently, SNPs associated with 15 more genes have been identified. However, there is limited information regarding their function and contribution to AD pathogenesis. A detailed description of these polymorphisms is provided in the Table 2.

CLU gene or the clusterin gene encodes a chaperone protein CLU or apolipoprotein J (Trougakos, 2013). This protein is expressed in the peripheral and central nervous system and studies have reported its involvement in neurodegeneration and hypoxic-ischemic neuronal death (Lidström, et al., 1998). High levels of CLU are observed in the frontal cortex and hippocampus of AD patients (Karch, et al., 2012). Elevated levels of this protein are found in the CSF and serum of AD patients and has the potential of being a prognostic/diagnostic marker of AD. Plasma levels of CLU can also indicate brain atrophy due to

Table 4
Overview of Serum/plasma biomarkers.

Biomarker	Directionality for increased risk	Description
Aβ42	↓	The levels of Aβ42 drop in the serum of AD patients as it is deposited and accumulated into plaques in the brain.
Aβ40	↑	Studies have reported that high plasma levels of Aβ40 is associated with an increased risk of dementia.
Aβ42/ Aβ40	↓	The Aβ42/ Aβ40 ratio in the serum is low for AD patients compared to normal individuals as the Aβ42 levels are low in the serum of AD patients.
Aβ43	↑	Aβ43 is a longer amyloid beta peptide that is prone to aggregate and form plaques in the brain. Like the Aβ42 peptide, this peptide is also toxic to the brain. A study reported that its levels are high in the serum of AD patients.
Aβ42/ Aβ43	↓	The Aβ42/ Aβ43 ratio is low in AD patients as Aβ42 levels are low and Aβ43 levels are high.
t-tau	↑	Total (t)-tau is a marker of neuronal injury and its levels are high in the plasma of AD patients compared to MCI patients and healthy individuals.
p-tau 181	↑	Tau phosphorylated at threonine 181 or p-tau 181 is a marker of AD and its levels in the serum are high in AD patients and patients with MCI that progressed into AD. Serum p-181 levels can also differentiate AD dementia from other types.
p-tau 217	↑	Tau phosphorylated at threonine 217 or p-tau 217 is a marker of AD and its levels in the plasma increases during the preclinical stage of AD.
p-tau 231	↑	Tau phosphorylated at threonine 231 or p-tau 231 is a marker of AD and its levels in the plasma is elevated in AD patients.
NF-L	↑	NF-L or neurofilament light is involved in axonal support. This filament is released during neuronal damage or neurodegeneration and its levels are high in the serum of AD patients.
BDNF	↓	Brain derived neurotrophic factor or BDNF is a growth factor that is involved in the growth, maturation, and survival of neurons. BDNF levels in the serum are high during the initial stages of AD and its levels drop with disease progression. The low levels of BDNF are the serum are associated with neuronal apoptosis, Aβ aggregation, tau hyperphosphorylation, and inflammation in the brain.

Table 5
Overview of urinary biomarkers.

Biomarker	Directionality for increased risk	Description
Formaldehyde	↑	Formaldehyde has a role in spatial memory formation and according to a few studies it is involved in crosslinking Aβ monomers to form toxic Aβ oligomers. High levels of formaldehyde are found in the urine of AD patients compared to normal controls.
Formic acid	↑	Formic acid is a metabolic product of formaldehyde metabolism and its levels are elevated in the urine of AD patients during the preclinical, MCI, and dementia stages.
AD7c-NTP	↑	Alzheimer-associated neuronal thread protein (AD7c-NTP) is a c-DNA that encodes a phosphoprotein. This protein is overexpressed in the brains of AD patients and its levels in the urine is positively correlated with AD severity.
Lipid peroxidation compounds	↑	Lipid peroxidation has an important role in AD pathology and high levels of lipid peroxidation compounds are found in the urine of AD patients.

neurodegeneration and Alzheimer's disease severity (Deming, et al., 2016). CLU has an important role in AD pathology as evidences suggests that this protein is found in Aβ plaques and binds to amyloid peptides. CLU also interacts with Aβ40. Deming et al. reported that CLU levels influenced CSF tau/ Aβ ratio as well as AD status (Harold, et al., 2009). Studies also reported that CLU decreases Aβ deposition, oxidative stress, apoptosis, and inflammation in AD. The SNP associated with gene, rs11136000, was found to be negatively associated with the risk of developing AD (Kim et al., 2006).

The *ABCA7* gene belongs to the family of ATP-binding cassette transporter genes and is expressed in the hippocampal neurons and microglia in the brain (Lambert, et al., 2013). The protein encoded by this gene is involved in the transport of lipids from cells to lipoproteins and high-density lipoprotein cholesterol. It also has a role in immune responses and cholesterol homeostasis. GWAS has identified two SNPs associated with this gene, rs764650 and rs3752246 (Holton, et al., 2013; Kim et al., 2013). ABCA7 protein is involved in the phagocytosis of Aβ by macrophages as well as regulates APP processing (Chan, et al., 2008; Andersen, et al., 2005). Studies conducted in mice show that this protein is expressed in macrophages (approx. tenfold higher than neurons) and *ABCA7* knockout mice showed higher Aβ accumulation (Chan, et al., 2008).

SORL1 gene belongs to Vsp10p receptor family and encodes a receptor that is involved in the intracellular transport and processing of APP (Gustafsen, et al., 2013). The presence of the functional protein reduces Aβ production. The risk loci for AD within the *SORL1* gene is unknown, however studies have reported the involvement of this gene in AD pathogenesis (Capsoni, et al., 2013). Under-expression of this gene increases the risk of AD as it leads to the accumulation of Aβ (De Strooper and Annaert, 2000; Wang, et al., 2016). Studies showed that the SNP associated with this gene, rs12285364, increases the risk of AD (Wilson, et al., 1987).

The gene *CR1* encodes a protein (CR1 or CD35) that is a part of the complement system expressed by RBCs, WBCs, and splenic dendritic cells (Khera and Das, 2009). CR1 is involved in the classical and alternate pathways and forms a complex with C3b/C4b to induce phagocytosis (Bonifati and Kishore, 2007; Nayak, et al., 2010). CR1 has a protective role in AD as it regulates Aβ clearance. Classical pathway is involved in accelerated clearance of Aβ. The process is set in motion when Aβ interacts with C1q component of the pathway (Bradt, et al., 1998)). This activates the C3b/C4b complex and in turn activates a cascade of events that result in the clearance of Aβ (Brouwers, et al., 2012). Studies have also shown that CR1 is associated with elevated levels of CSF Aβ42 (Lambert, et al., 2009). GWAS has reported two SNPs, rs3818361 and rs6656401, associated with *CR1* that increases the risk of AD (Cirrito, et al., 2008).

The phosphatidylinositol binding clathrin assembly protein gene or *PICALM* gene PICALM protein that has a role in intracellular trafficking and clathrin-mediated endocytosis. Experiments conducted in cell cultures showed that clathrin-mediated endocytosis internalized full-length APP from the cell surface which resulted in its cleavage by β-secretase leading to high levels of Aβ peptides (Thinakaran and Koo, 2008; Xiao, et al., 2012). Studies conducted in PICALM knockdown mice showed that even though APP was internalized, Aβ production and release was reduced (Zhao, et al., 2015). PICALM also has a role in transfer of Aβ across BBB, tau clearance, and autophagy (Moreau, et al., 2014; Baig, et al., 2010). Hence, PICALM can be considered as an important mediator of APP internalization, amyloid load, and Aβ production in AD. Elevated PICALM expression is observed in the frontal cortex of AD patients (Melville, et al., 2012). Two SNPs, rs3851179 and rs541458,

Table 6
Sensitivities and specificities of biomarkers.

Test/biomarker (Creavin, et al., 2016; Salis, et al., 2023; Dautzenberg, et al., 2020; Marcus, et al., 2014; McGrowder, et al., 2021; Dorey, et al., 2015; Baiardi, et al., 2019; Spiegel, et al., 2016; Janelidze, et al., 2020; Kivisäkk, et al., 2024; Dhiman, et al., 2020; Halbgebauer, et al., 2022; Lewis, et al., 2021; Chen, et al., 2021; Keshavan, et al., 2021; Souchet, et al., 2023; Pais, et al., 2023; Li, et al., 2023; Chen, et al., 2022; Wang, et al., 2022; Ma, et al., 2016)	Comments	Sensitivity	Specificity
MMSE	Cut off at 24 (MMSE cutoff is usually between 24 and 26 for clinical studies)	85%	90%
MMSE	Cutoff at 25	87%	82%
MMSE	Cutoff at 26	77.2%	61.75%
MoCA	Dementia; cutoff at 26	97.5%	72.6%
Fluorodeoxyglucose PET		91%	86%
CSF Aβ42		80%	82%
CSF Aβ40		94.7%	91%
CSF Aβ40/ Aβ42		51%	82%
CSF Aβ42/ Aβ40		87%	88.2%
CSF t-tau		82%	90%
CSF p-tau 181		75–94%	62–88%
CSF p-tau 217		80–95%	87–94%
CSF p-tau 231		85%	94%
CSF NF-L		63–81%	79.7–90%
CSF VILIP-1		78%	63%
CSF SNAP-25	Mainly used to differentiate early and late MCI	75%	96%
Plasma Aβ42		88%	81%
Plasma Aβ42/ Aβ40	Measured during the preclinical stage of AD	45.1%	78%
Plasma t-tau		90%	87%
Plasma p-tau 181	Measured during the preclinical stage of AD	70.7%	68.3%
Plasma p-tau 217	Used for differentiating amyloid-positive patients clinically diagnosed with AD dementia from amyloid-negative, clinically diagnosed patients with a dementia other than AD	93%	89%
Plasma p-tau 231		81.2%	93.3%
NF-L	Measured in individuals with and without Aβ pathology	67%	38%
Serum VILIP-1		58%	67%
BDNF		58%	62%
Formaldehyde		83.3%	83.3%
Formic acid		66.7%	78.9%
AD7c-NTP		89.3%	84.7%

associated with the *PICALM* gene has been identified. Studies have observed the association of rs3851179 with hippocampal degeneration (Schjeide, et al., 2011). Moreover, the risk allele of rs541458 is associated with low levels of Aβ42 in the CSF (Sakamuro, et al., 1996).

BIN1 gene encodes a nucleo-cytoplasmic tumor suppressor adapter protein called Myc box-dependent-interacting protein 1 (Tan, et al., 2013). This protein is involved in intracellular APP trafficking, apoptosis, clathrin-mediated endocytosis, immune responses, and synaptic vesicle endocytosis (Chapuis, et al., 2013). The exact role of this gene in neurodegeneration is unknown, however recent data suggest its involvement in tau pathology. Studies conducted in *BIN1* knockdown models showed that underexpression of this gene reduced tau-mediated neurotoxicity (Griciuc, et al., 2013). Two SNPs associated with this gene are rs744373 and rs7561528.

CD33 gene encodes a type I transmembrane protein (CD33) that is expressed on microglia and myeloid cells (Jandus, et al., 2011). This protein regulates cell growth and survival by inducing apoptosis, inhibits immune cell functions, mediates cell-cell interaction, and regulates clathrin-independent endocytosis (Hollingworth, et al., 2011). Studies have shown that CD33 inhibits Aβ clearance and a positive correlation exists between CD33 expression on microglia and plague burden and cognitive decline in AD (Bradshaw, et al., 2013). Two SNPs of CD33, rs3865444 and rs3826656, are associated with LOAD (Bradshaw, et al., 2013). The minor allele of rs3865444 is protective against AD as it reduces CD33 and amyloid plaque levels in AD (Jandus, et al., 2011). Studies also showed that the risk allele of rs3865444 elevated the expression of CD33 on microglia and amyloid plaque levels in the brain (Lai, et al., 2009). Reduced Aβ42 levels and increased Aβ clearance were observed in *CD33* knockout models.

The *EPHA1* gene encodes a receptor protein that has a role in nervous system development and synapse formation (Wang, et al., 2015). This protein also has a role in synaptic plasticity, immune responses, chronic inflammation, and cell membrane processes. Two *EPHA1* SNPs has been identified; rs11771145 and rs11767557. These SNPs are associated with reduced risk of developing LOAD (Holton, et al., 2013; Bradshaw, et al., 2013). A study showed that rs11771145 functionally modified the hippocampus, inferior temporal and later occipitotemporal gyri to reduce the risk of LOAD (Tang and Brieher, 2013).

The *CD2AP* gene encodes a scaffolding protein called CD2-associated protein that has a role in the regulation of actin cytoskeleton (Monzo, et al., 2005). It also has functions like intracellular trafficking, cytokinesis, apoptosis, cell adhesion, and receptor-mediated endocytosis (Liao, et al., 2015). CD2AP favors Aβ generation by aiding APP metabolism. A study conducted on *CD2AP* knockdown mice showed Aβ levels were altered and Aβ42/ Aβ40 ratio was low (Shulman, et al., 2013). Two SNPs, rs9296559 and rs9349407, have been identified. The SNP rs9349407 increases the neuritic plaque pathology (Zuccolo, et al., 2013).

MS4A gene encodes a transmembrane protein that is expressed on hematopoietic cells and has a role in immunity and regulating calcium influx (Mattson, 2007). Dysregulation of calcium influx is associated with the pathogenesis of AD (Antúnez, et al., 2011). Three SNPs, rs610932, rs670139, and rs4938933, has been identified (Jonsson, et al., 2013).

The *TREM2* gene encodes a single pass type I membrane receptor protein expressed on microglia that mediates phagocytosis and down-regulates inflammation (Seshadri, et al., 2010). This protein is found throughout the CNS with its highest concentration in the white matter (D'Andrea, et al., 2004). TREM2 increases the phagocytic ability of microglia resulting in accelerated Aβ clearance (Takahashi, et al., 2005). Reduced phagocytic activity of microglia was observed in *TREM2* knockdown mice (Guerreiro, et al., 2013). A SNP, rs75932628, associated with *TREM2* increases the risk of developing AD (Seshadri, et al., 2010). This SNP was found to increase the risk of other neurodegenerative disorders like ALS, Parkinson's disease, and frontotemporal dementia (Rayaprolu, et al., 2013; Bagaria, et al., 2022).

6. Biomarkers of AD

Biomarkers of AD found in the CSF have been studied for around two decades. These markers can be used for prognosis, diagnosis, and even to predict the onset of AD. However, the collection of CSF is an invasive process and it is impractical to use CSF to screen for AD in large populations of asymptomatic people. Blood biomarkers are an alternative to CSF markers mainly due to the less invasive, safe, and accessible means

Table 7
An overview of diet in Alzheimer's disease.

Diet	Description (Khalsa and Perry, 2017; Stefaniak, et al., 2022)
Mediterranean Diet	The Mediterranean diet includes large quantities of vegetables, fruits, nuts, seeds, legumes, and low quantities of meat and dairy. This diet consists of high quantities of omega fatty acids, polyphenols, and antioxidants which have neuroprotective effects. Research shows that this diet lowered the levels of Aβ plaques and neurofibrillary tangles, maintained cognitive function and improved the thickness of areas in the brain that deal with memory, executive functions, and language, and is associated with 20% lower risk of dementia.
Dietary Approaches to Stop Hypertension (DASH) diet	The DASH diet includes whole grains, fish, nuts, legumes, and lean meat. This diet is low in fats, both saturated fats and cholesterol. This diet is high in calcium, magnesium, fiber, potassium, and low in sodium. This diet is associated with better cognitive function, higher MMSE scores, reduced cognitive decline, and reduced risk of AD.
Mediterranean-DASH diet Intervention for Neurodegenerative Delay or MIND diet	The MIND diet, a combination of the Mediterranean and DASH diets, was created to reduce the risk of developing cognitive disorders like AD. This diet is plant-based and consists of food items that have neuroprotective effects. This diet recommends ten food groups that are brain-friendly. Groups like green leafy vegetables, vegetables, nuts, berries, legumes, whole grains, fish, poultry, olive oil, and red wine. This diet is associated with reduced cognitive decline, improved semantic and episodic memory, and reduced risk of AD. T the MIND diet is most suitable for individuals susceptible to developing AD, individuals showing symptoms of AD, or general cognitive decline.

of acquiring the sample (blood). In the last few years, blood biomarkers for AD have been extensively studied, and a few markers have been selected. For instance, high levels of p-tau 181 and low levels of Aβ42 in the blood can be an indication of neurofibrillary tangles and Aβ accumulation even during the early stages of the disease. With better research blood-borne biomarkers may be available for making a clear diagnosis of AD in the coming years (Zhao et al., 2015).

7. CSF Markers

7.1. *Aβ markers*

CSF is an ideal source for AD markers as it is in direct contact with the extracellular matrix of the brain and changes in the brain are reflected in the CSF (Blennow and Hampel, 2003). Aβ levels can be measured in the CSF. Identification of AD patients using CSF Aβ42 levels has sensitivity and specificity above 80% (Skoog, et al., 2003). A study by Skoog et al. found that CSF Aβ42 levels were low before sporadic dementia onset (Gustafson, et al., 2007). Studies reported the ability of low CSF Aβ42 levels to predict cognitive decline in older women (Shoji, et al., 1998). It was also reported that the levels of other Aβ species like Aβ40, did not change significantly in AD patients when compared to normal healthy adults. Nutu et al. reported that Aβ40 levels in AD patients were higher than in patients with Parkinson's disease dementia and Lewy body dementia. This study shows that Aβ40 levels can be used to differentiate

Table 8
Pathophysiological Pathways affected by physical activity in Alzheimer's disease.

Pathways	Description (Khalsa and Perry, 2017; López-Ortiz, et al., 2021)
Immune system and inflammation	Moderate physical activity can boost the immune system and reduce inflammation by inducing anti-inflammatory responses. Several studies on animal models have shown that regular, moderate physical activity reduced microglial activation, improved cognition, reduced the release of pro-inflammatory cytokines, and increases the release of anti-inflammatory cytokines and neurotrophic factors.
Cerebrovascular insufficiency and endothelial function	Regular physical activity can improve endothelial function without affecting the blood pressure, body-mass index, lipid levels, or glucose tolerance. Several studies showed that aerobic exercise improved cerebral blood flow in older individuals and patients with preclinical AD and MCI. Aerobic exercise also improved logical memory in MCI patients.
Apoptosis	Regular physical activity helps to delay apoptosis or cell death by regulating concentration of hormones, cytokines, growth factors, and oxidative state. Regular physical activity also increases the levels of neurotrophic factors like BDNF which helps to improve cell survival and neuroprotection. Aerobic exercises increase the levels of telomere-stabilizing proteins which helps to reduce apoptotic regulators and offers protection against cellular senescence.
Intercellular communication	Physical activity stimulates neurogenesis by increasing the synthesis of neurotrophic factors. The increase in the levels of neurotrophic factors may improve cognitive function. Regular physical activity also increases the levels of neurotransmitters like acetylcholine, serotonin, and noradrenaline as well as neurotrophins like nerve growth factor. This promotes long-lasting neural connections.
DNA damage and repair	Mild-moderate physical activity is positively associated with DNA repair. However, high levels of physical activity and repeated physical activity without rest or recovery can increase ROS, inflammation and reduce the efficiency of antioxidant system and DNA repair mechanisms thereby exacerbating DNA damage.
Cytoskeleton and membrane proteins	Regular physical activity increases the levels of cytoskeletal proteins like β-tubulin and specific neuronal protein, Shank. Shank regulates actin cytoskeleton in dendritic spines and their regression. Physical activity also increases the levels of microtubule associated protein 2 in the hippocampus which improves axonal regeneration. In animal models, mild to moderate physical activity changed the expression of cytoskeletal neurofilaments and synaptic proteins.
Synaptic Plasticity	Physical activity modulates several signaling pathways involved in synaptic plasticity. Animal studies have shown that aerobic exercises improved long-term potentiation. Physical activity also improved structural plasticity, plasticity in the dentate gyrus and dendrite ramification in animal models. Physical activity also increased the expression of the protein FNDC5 or irisin which is associated with long-term potentiation and memory.
Oxidative stress and neurotoxicity	Regular physical activity is associated with reduced oxidative stress and improved activity of Aβ clearing enzymes. Regular physical activity also improves lipid profile and reduces lipid peroxidation. Strength training increases antioxidant enzymes whereas aerobic exercises

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Table 8 (*continued*)

Pathways	Description (Khalsa and Perry, 2017; López-Ortiz, et al., 2021)
	improve insulin sensitivity. However, high levels of physical activity without rest or recovery can increase oxidative stress.

AD from other dementias (Nutu, et al., 2013). This finding was further supported by other studies which showed that Aβ42/Aβ40 ratio and Aβ42/Aβ38 ratio in the CSF can differentiate AD from other dementias better than just the CSF Aβ42 levels (Janelidze, et al., 2016; Selkoe and Hardy, 2016). Recent studies have shown that CSF Aβ42 levels can predict preclinical AD in individuals with AD genes. The CSF Aβ42 levels will first increase and then start to decrease 25 years before the onset of AD symptoms but the amyloid deposition can only be detected 15 years before the symptoms (Bateman, et al., 2012). This suggests that CSF Aβ42 can be used as an early biomarker for AD but obtaining CSF is an invasive process and it is impractical to screen healthy individuals.

Aβ42 can form oligomers and accumulate as plaques and this process is considered to be the main pathogenic event of AD (Walsh and Selkoe, 2007; Fukumoto, et al., 2010). Fumumoto et al. designed an ELISA method using which they detected Aβ oligomers in the CSF. They reported that high levels of Aβ oligomers were present in the CSF of AD and MCI patients when compared to age-matched normal controls (Skillbäck, et al., 2014). However, more studies are required in this field.

7.2. Tau markers

CSF total tau or t-tau levels serve as neuronal injury markers and high levels of t-tau are found in diseases like Creutzfeldt-Jakob disease, AD, Lewy body dementia, and frontotemporal dementia (Thijssen, et al., 2021). p-tau 181, p-tau 217, and p-tau 231 are the three main diagnostic biomarkers of AD found in the CSF and plasma during the preclinical stage (Moloney, et al., 2022). These three biomarkers are present in the NFTs and were observed in the post-mortem brains of AD patients (Barthélemy, et al., 2020). Studies have reported that the levels of p-tau 181 and p-tau 217 in the CSF increase two decades before tau PET positivity in patients with dominantly inherited AD (Mattsson-Carlgren, et al., 2020). Moreover, p-tau 181 and p-tau 217 levels in the CSF increases before Aβ-PET positivity in individuals with no cognitive impairment (Suárez-Calvet, et al., 2020). Studies have also suggested that p-tau 217 can detect AD better than p-tau 181 during the preclinical stage whereas the CSF levels of p-tau 181 gradually increases in MCI and dementia stage (Blennow, et al., 1995). A study by Blennow et al. showed that t-tau and PHF-tau are found in the CSF of AD patients. However, they are also found in the CSF of patients with other dementias like vascular dementia and frontotemporal dementia. Vanmechelen et al. used sandwich ELISA to detect CSF p-tau 181 and found that p-tau 181 levels were high in AD patients when compared with age-matched healthy controls. They also reported that p-tau 181 levels were low in patients with frontotemporal dementia. This suggests that p-tau 181 levels in the CSF may be specific to AD patients (Vanmechelen, et al., 2000). A similar study using sandwich ELISA to detect p-tau 231 levels in the CSF showed that the method had 85% sensitivity and 97% specificity to differentiate AD patients from non-AD controls (Kohnken, et al., 2000). These findings have already been confirmed by several studies (Holsinger, et al., 2004).

7.2.1. β-site APP cleaving enzyme 1 or (BACE1)

BACE1 is the β-secretase that cleaves APP to generate Aβ. A study by Holsinger et al. showed that high BACE1 activity was observed in the CSF of AD patients (Zhong, et al., 2007). A similar study by Zhong et al. showed that high BACE1 levels in the CSF can predict AD risk in patients with MCI (Ewers, et al., 2011). Ewers et al. showed that high BACE1 levels in the CSF were associated with the *APOE4* genotype in AD and

Table 9
A detailed overview of the role of supplements and lifestyle factors in determining the risk of AD.

Intervention	Description (Shah, et al., 2023; Pan, et al., 2016; Morris, 2004; Jannusch, et al., 2017; Chen, et al., 2021; Jia, et al., 2019; Presse, et al., 2013; Hans, et al., 2022; Ma, et al., 2022; Yuan, et al., 2022; Velazquez, et al., 2019; Blusztajn, et al., 2017; Lemke, et al., 1995; Shen, et al., 2019; Stefaniak, et al., 2022; Crous-Bou, et al., 2017; Barnard, et al., 2014; Kushwah, et al., 2023; Bukhari, 2022; Shi, et al., 2010; Jayaprakasam, et al., 2010; Kosuge, 2019; Cuya, et al., 2018; Momtaz, et al., 2018)
Supplements	
Vitamin A	Vitamin A improves cognition and destabilizes and prevents the formation of Aβ fibrils. Moreover, in vitro studies showed that vitamin A modifies the toxic Aβ42 peptide to a non-toxic aggregate via hydrogen bonding and hydrophobic interactions. Studies in mice models showed that vitamin A deficiency may result in the downregulation of insulin-degrading enzyme, ADAM10, and BDNF that are needed for Aβ clearance.
Vitamin B1	Vitamin B1 or thiamine deficiency is associated with altered Aβ metabolism resulting in increased plaque formation in mice models. Moreover, thiamine deficiency in mice also increased oxidative stress by increasing the levels of BACE1 and β-CTF99. Only a few human studies have been conducted to understand the effect of thiamine on AD risk. These studies reported that thiamine is neuroprotective and its deficiency increases AD risk and progression. Thiamine supplementation was found to reverse the neurological damage in mice models.
Vitamin B3	Dietary intake of vitamin B3 or niacin is associated with reduced risk of cognitive decline. Nicotinamide supplementation in animal models reduced the phosphorylation of p-tau231 and improved cognition. An FDA-approved formulation of niacin, Niaspan, activated HCAR2 receptor resulting in the reduction of neuronal loss, amyloid plaque, and neuronal dystrophy and improved working memory in mice models. Activation of microglia needed for Aβ phagocytosis is mediated via the HCAR2 receptors.
Vitamin B6	A study reported that vitamin B6 is positively correlated with local cortical folding throughout the brain in older adults. Since aging is associated with brain atrophy and diminution of folds in the cortical areas, vitamin B6 may have a role on the brain structure during aging. Vitamin B6 has a role in the metabolism of homocysteine and several studies have reported that vitamin B6 supplementation reduces the plasma levels of homocysteine resulting in a reduced risk of MCI, cognitive decline, and dementia. Animal studies showed that vitamin B6 supplementation reduces Aβ and p-tau levels and increases cognition.
Vitamin B12	Several observational studies have found a link between vitamin B12 deficiency and AD risk. Deficiency of vitamin B12 in AD increases the level of proinflammatory cytokines like TNFα and IL-6 which in turn increases the production of Aβ and tau hyperphosphorylation. Vitamin B12 has a role in the metabolism of homocysteine and a deficiency in vitamin B12 increases the homocysteine levels resulting in an increased risk of AD. However, a study showed that homocysteine levels were high in AD irrespective of vitamin B12 levels in the plasma or its intake indicating the possibility of an impaired vitamin B12 metabolic function in AD.
Vitamin D	Recently, several studies have found an association between low vitamin D levels in the serum and higher incidence of cognitive decline, dementia, or AD. In animal models, vitamin D deficiency is associated with increased Aβ aggregation, neuronal loss, synaptic dystrophy, and tau hyperphosphorylation. Daily supplementation of vitamin D reduced Aβ42 levels in plasma and improved MMSE scores in older adults with AD. Similarly, daily supplementation of vitamin D reversed neuronal loss by inhibiting proapoptotic proteins and activating anti-apoptotic proteins in animal models of AD.
Vitamin K	Vitamin K has a role in the regulation of sphingolipid metabolism which in turn is associated with

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Table 9 (*continued*)

	neuroinflammation and neurodegeneration. High levels of vitamin K are associated with improved episodic memory during aging. Elevated levels of vitamin K in the diet are associated with high MMSE scores in older adults. A couple of invitro studies showed that supplementation with vitamin K resulted in tau dephosphorylation, ROS formation by Aβ peptides, and cell death. It has been suggested vitamin K regulates the PI3K signalling pathway and inhibits the caspase-3-mediated apoptosis resulting in the protective effects.
Phosphatidylserine	Phosphatidylserine or PS increases spine density of hippocampal pyramidal neurons. Increased cognitive impairment in AD is associated with reduced dendritic spines which is improved by PS. PS reduces the depletion of phosphatidylcholine by regulating the activity of phosphatidylserine synthases which increases the release of acetylcholine. Elevated acetylcholine release improves the activity of cholinergic neurons and cognitive function in AD. Moreover, studies conducted in cell lines showed that PS reduced Aβ production and toxicity. PS can be used with other drugs as a drug carrier to improve symptoms associated with AD. Dietary supplementation of PS improved memory and cognition in humans and animal models.
Phosphatidylcholine	Dietary intake of phosphatidylcholine is associated with improved cognitive function and a lower risk of dementia. Metabolomic profiling of AD patients with *APOE* ε4 allele showed significant changes in the phosphatidylcholine.
Choline	Perinatal supplementation of choline reduced Aβ plaques and the number of Aβ plaques remained stable with increased age suggesting a reduction in the synthesis of Aβ or its increased clearance in animal models. Moreover, the levels of the cholinergic marker, CHAT, were high in mice supplemented with choline. Lifelong supplementation of choline in animal models reduced the levels of C99 peptides thereby reducing Aβ synthesis, improved spatial reference memory, and reduced microglial activation resulting in a decrease in the neuroinflammation. Low intake of dietary choline is associated with an increased risk of AD and dementia in humans.
Magnesium	Magnesium is associated with multiple neurological disorders including neurodegeneration. Low magnesium may alter glutaminergic system which is a characteristic of several disorders like AD, PD, and epilepsy. Low magnesium levels are observed in the blood of AD and MCI patients when compared to healthy controls. Moreover, low magnesium levels are observed in the entorhinal cortex, globus pallidus, and Ammon's horn in the brain of AD patients. Synaptic function, working memory, learning, tau hyperphosphorylation, Aβ accumulation, neuroinflammation, and Aβ clearance improved in animal models after magnesium supplementation suggesting its role in neuroprotection.
Zinc	Disruption of zinc homeostasis is observed in AD and ALS. Serum levels of zinc are associated with cognitive decline. Low zinc levels in the serum are also associated with increased Aβ accumulation. Moreover, high levels of copper/zinc ratio and low levels of selenium and zinc in the serum of AD patients are associated with low MMSE scores. However, a few animal studies showed that zinc ions bind to a domain on the tau protein resulting in a complex that increases the levels of ROS. Zinc also binds to Aβ peptides to form a more toxic version of Aβ oligomers.
Iron	Iron (ferritin) has a role in several CNS functions and accumulation of iron in the brain increases after the age of 60 years. However, human studies have reported mixed association between circulating iron levels and AD risk. Animal studies showed that supplementation with iron reduced Aβ accumulation and tau hyperphosphorylation in the hippocampus. Iron chelators prevent the accumulation of iron, aggregation of Aβ, neuroinflammation, and oxidative stress in animals.
Selenium	Low levels of selenium were observed in the serum of AD patients when compared to healthy controls. A study showed that high selenium levels in the serum is associated with low levels of Aβ42 and Aβ40 in the serum. Moreover, selenium supplementation also improves cognitive function and MMSE score. Several animal studies have shown that selenium supplementation reduced Aβ and p-tau levels in the serum while improving cognition.
Polyunsaturated fatty acids	PUFAs like omega-3 fatty acids have a beneficial role in reducing inflammation. EPA and DHA have several neuroprotective effects including promoting synaptogenesis, alleviating inflammation, improving neuroplasticity, and modulating signal transduction pathways. A combination of omega-3 and α-lipoic acid supplements for 12 months delayed cognitive and functional decline in patients with mild-moderate AD. Similarly, a combination of omega-3 fatty acids, omega-6 fatty acids, and vitamins A and E delayed cognitive and functional deterioration in older patients with MCI.
Curcumin	Curcumin alters Aβ synthesis and increases its clearance resulting in reduced deposition of Aβ. It alters the APP metabolism which reduces the synthesis of Aβ. Due to its antioxidant properties, it can reduce oxidative stress in AD. Animal studies also showed a decrease in the Aβ plaque formation and oligomerization of Aβ fibrils after administering curcumin.
EGCG	EGCG reduces the aggregation of Aβ fibrils by forming adducts with them via hydrogen bonds. The presence of these adducts reduces the ability of Aβ to aggregate. It also regulates β secretase activity thereby reducing the formation of Aβ.
Tannic acid	Tannic acid is a polyphenol that regulates the processing of APP by inhibiting BACE1 enzyme thereby reducing the formation of Aβ peptides. Moreover, this polyphenol also has anti-inflammatory and anti-oxidative properties that increases its neuroprotective effects.
Quercetin	Quercetin is an antioxidant that reduces oxidative stress in neurological disorders. It inhibits the activity of the BACE1 enzyme in the APP metabolism thereby reducing the production of Aβ peptides. It further modulates APP processing by NFκβ inhibition. Moreover, quercetin also inhibits AChE and BuChE thereby increasing acetylcholine levels which is usually reduced in AD patients.
Ginkgo biloba	The Ginkgo biloba extract EGb 761 prevents Aβ aggregation and apoptosis. It has several other neuroprotective effects including modulation of tau phosphorylation, ion homeostasis, and stimulation of growth factor production. Several studies reported improved cognition after using Gingko biloba supplements in humans and animal models.
Ashwagandha	Ashwagandha roots scavenge free radicals as well as neutralize the toxicity induced by Aβ peptides in the CNS. Stimulation studies showed that the components of ashwagandha root, withanamides A and C, bind to Aβ active motif and prevent the formation of fibrils. Continuous use of this extract resulted in the regeneration of axons and dendrites. In animal models, use of ashwagandha extract improved peptide-induced memory loss and cellular regeneration.
Gotu Kola	Gotu Kola has antioxidant properties and it reduces DNA damage and lipid peroxidation. Moreover, its extract modulates the antioxidant system, promotes Aβ cell death, and protects against Aβ-induced neurotoxicity.
Garlic	Aged garlic extract or AGE was recently studied for its neuroprotective effects. A component of AGE was found to protect against ER-stress induced neuronal cell death in AD. AGE also reduced the accumulation of Aβ in the hippocampus thereby improving cognitive abilities. Garlic extract may also have the ability to defibrillate Aβ fibrils. Animal studies showed that the use of AGE improved working memory and reference memory.
Ginger	Ginger and ginger extracts are good anti-inflammatory agents and recent studies have shown that ginger extracts reduced the activity of inflammatory markers in cell lines. A few components of ginger inhibit the activity of acetylcholinesterase as effective as donepezil which is the current recommended treatment for AD.

(*continued on next page*)

Table 9 (*continued*)

Cinnamon	Cinnamon consists of phenolic compounds like EGCG and catechin that can cross the BBB and inhibit Aβ accumulation and aggregation and tau hyperphosphorylation as well as degrade the Aβ plaques. In cell lines, cinnamon reduces the formation and accumulation of Aβ. Animal studies also showed similar results. Moreover, it reduces acetylcholinesterase activity, proinflammatory cytokines, and oxidative stress.
Shankhpushpi	Shankhpushpi ethanolic extract has antioxidant properties and reduces oxidative stress. Animal studies showed that this extract reduced Aβ accumulation and improved learning and memory. It also reduced tau-induced oxidative stress and improved memory by promoting the functional growth of neurons in rats.
Diabetes Mellitus	Several studies have suggested that hyperinsulinemia can disrupt Aβ clearance as it competes with the insulin-degrading enzyme that has a role in clearing Aβ. Hence, individuals with diabetes mellitus may have an increased the risk of Aβ accumulation thereby increasing the risk of AD. However, according to a few other studies, diabetes may be associated with an increased risk of cerebrovascular pathology and not AD pathology.
Hypertension	Mild-life hypertension may result in a 50% increased risk of AD and dementia. Vascular integrity of the BBB reduces with high blood pressure and this decrease in integrity leads to protein extravasation into the brain tissue thereby resulting in apoptosis, cell damage, and Aβ accumulation. However, a few studies reported that hypertension could be a protective response to cerebral hypoperfusion which is usually observed ten years before the onset of AD.
Obesity	Weight and cognition have a U-shaped relationship, wherein low and high body weight is associated with a high risk of cognitive impairment and AD. Studies also reported that cognitive impairment observed in the pre-dementia phase of AD may lead to weight loss. Age may also have a role in the relationship between weight and AD. Mid-life obesity may increase the risk of AD by 60%. Studies are still underway to determine the exact mechanism of how weight may affect AD onset and the preliminary studies suggest that diabetes and insulin resistance may have a role in this.
Smoking	The relationship between smoking and AD is controversial and unclear. Observational studies reported that an increased risk of AD, cognitive decline, and dementia is related to current smoking habits. However, the of AD and cognitive decline due to smoking is 14% and is less compared to other factors. Studies suggest that smoking increases oxidative stress and inflammation which can ultimately increase the risk of AD

MCI patients. This study also showed that CSF BACE1 levels were associated with low hippocampal volume in AD (Ewers, et al., 2008; Yuan, et al., 2012). However, this marker needs to be studied further to be considered as a potential diagnostic marker.

7.3. Other markers in CSF

Biomarkers that indicate activation of glial cells, synapse loss, and axonal neurodegeneration can also be detected in the CSF. Neurofilaments provide structural support to axons, especially myelinated axons. They consist of four subunits such as neurofilament light (NF-L), neurofilament heavy, neurofilament middle, and α-internexin. Neurofilaments are (Zetterberg, et al., 2016) released into the CSF and systemic circulation during neuronal injury and neurodegeneration (Sjögren, et al., 2000). A study by Sjogren et al. found that NF-L levels in the CSF were high in patients with LOAD and frontotemporal dementia when compared to healthy controls. They also reported that NF-L levels were higher in frontotemporal dementia patients when compared to LOAD patients (Sjögren, et al., 2001). High CSF NF-L levels are also observed in conditions like vascular dementia (Lycke, et al., 1998), multiple sclerosis (Forgrave, et al., 2019), amyotrophic lateral sclerosis (Agren-Wilsson, et al., 2007), and normal pressure hydrocephalus (Laterza, et al., 2006) indicating that NF-L levels could be a marker of neurodegeneration and may not be specific to AD. However, Zetterberg et al. reported that NF-L levels in the CSF are associated with brain atrophy and cognitive decline over time in patients with AD and MCI. This finding suggests that NF-L levels have the potential to be a marker of AD progression (Zetterberg, et al., 2016).

A neuronal calcium sensor protein called visinin-like protein 1 or VILIP-1 can be used as a marker of brain injury (Lee, et al., 2008). VILIP-1 levels in the CSF were found to be higher in AD patients when compared to normal controls (Tarawneh, et al., 2011). A study by Tarawneh et al. found that CSF VILIP -1 levels and CSF VILIP-1/Aβ42 ratio were higher in early AD suggesting that it can be used as a prognostic marker for AD (Tarawneh, et al., 2015). They also reported that the VILIP-1 levels in the CSF were able to predict whole brain and regional atrophy. Several other studies confirmed that the levels of CSF VILIP-1 in AD patients were higher than normal controls (Mroczko, et al., 2015; Luo, et al., 2013). However, more research is required before VILIP-1 levels can be used as a specific marker for AD.

Proteins like neurogranin, synaptotagmin, and synaptosome-associated protein 25 (SNAP-25) can be detected in CSF of AD patients. The postsynaptic protein neurogranin is mainly expressed in dendritic spines. It has a role in postsynaptic signaling pathways. Thorsell et al. reported that high levels of neurogranin were found in the CSF of AD patients when compared with normal controls (Thorsell, et al., 2010). This finding was confirmed by several other studies (Kvartsberg, et al., 2015; Lista, et al., 2017). A study by Kester et al. reported that high levels of neurogranin were found in the CSF of patients with MCI that progressed to AD when compared to patients with stable MCI (Kester, et al., 2015). This study suggests that neurogranin can be used as a marker that predicts the progression of MCI to AD. Lista et al. reported that CSF neurogranin levels were higher in AD when compared to frontotemporal dementia (Lista, et al., 2017). However, further research is required to understand neurogranin levels in other conditions. Brinkmalm et al. used a novel affinity mass spectrometry to study CSF SNAP-25 levels and reported that high levels of CSF SNAP-25 fragments were found in patients with AD when compared to healthy control (Brinkmalm, et al., 2014). Sutphen et al. conducted a longitudinal study and found that SNAP-25 levels were higher in the CSF of AD patients when compared to MCI patients but SNAP-25 levels in AD patients reduced with time (Sutphen, et al., 2018). So far, SNAP-25 fragments in the CSF are an excellent synaptic biomarker that can differentiate AD patients from non-AD patients (Tible, et al., 2020). High levels of the presynaptic protein, synaptotagmin were found in the CSF of AD patients and patients with MCI that progressed to AD (Öhrfelt, et al., 2016). A study by Tible et al. reported that all three synaptic biomarkers were elevated in the CSF of AD patients and patients with MCI that developed into AD (Tible, et al., 2020). However, synaptic markers indicate synaptic dysfunction and hence cannot be used as specific AD markers.

7.4. Blood Biomarkers

7.4.1. Aβ markers

During the early 2000s, studies conducted to analyze Aβ42 and Aβ40 levels in the plasma of AD patients were inconsistent. In a study by Mayeux et al. Aβ42 levels in the plasma were high in both AD patients at baseline and patients who developed AD within 3 years in a follow-up study. They also reported that AD risk was increased by more than 2-fold in individuals with high plasma Aβ42 levels (Mayeux, et al., 2003). A study conducted by Oijen et al. showed that high plasma Aβ40 levels were associated with an increased risk of dementia (van Oijen, et al., 2006). These studies were unable to differentiate the different types of dementia from AD leading to mixed results. The use of MRI to analyze hippocampal volumetry and amyloid PET technology can help to differentiate AD patients and MCI patients who developed AD from patients with other types of dementia that do not develop into AD. A

study by Zou et al. showed that high levels of Aβ43 and low levels of Aβ42 were observed in the serum of AD patients when compared to age-matched normal controls. Like Aβ42, Aβ43 is a longer amyloid beta protein and is prone to aggregate and form oligomers and plaques that are toxic. This study also shows that Aβ42 to Aβ43 ratio can be used as a blood diagnostic marker for AD (Zou, et al., 2013). More studies are needed to better understand the function of this peptide in AD.

Other studies have also reported low levels of Aβ42 in the serum of amyloid-positive AD patients and MCI patients when compared to normal individuals. Moreover, these studies also reported that Aβ42 to Aβ40 ratio and Aβ42 to APP669–711 ratio were the stable markers in predicting amyloid levels in the brain at an individual level (Nakamura, et al., 2018; Pérez-Grijalba, et al., 2019). Similarly, Perez-Grijalba et al. reported that low levels of the Aβ42 to Aβ40 ratio can accurately detect the early stages of AD (Pérez-Grijalba, et al., 2019). Kim et al. used a multiplex sensor array to show that low Aβ42 to Aβ40 ratio and high plasma t-tau to Aβ42 ratio and p-tau 181 to Aβ42 ratios differentiated AD patients from healthy controls (Kim, et al., 2020). A study by Nabers et al. reported the changes in the secondary structure of Aβ in human plasma and this can be used as a marker to detect prodromal AD. The changes to the β sheet of Aβ are correlated with amyloid PET imaging and CSF markers (Nabers, et al., 2018). However, the main drawback of analyzing the structure of Aβ as a marker is the unstable nature of Aβ and more studies are required to perfect this method. Hence Aβ42/Aβ40, Aβ42/APP669–711, Aβ42/Aβ43, Aβ42/p-tau 181, and Aβ42/t-tau ratios may predict or diagnose AD.

7.4.2. Tau markers

Lately, plasma tau has been studied as a potential marker for diagnosing and predicting AD due to the cost and invasiveness of CSF tau. Zetterberg et al. developed an ultra-sensitive assay to detect t-tau in plasma since their levels were low. They reported high levels of plasma t-tau in AD patients compared to MCI patients and healthy controls (Zetterberg, et al., 2013). However, a study by Mattsson et al. reported an overlap in the plasma t-tau levels between AD patients and age-matched healthy controls, suggesting that t-tau may not be an ideal AD diagnostic marker (Mattsson, et al., 2016). A novel ultrasensitive immunoassay was recently developed by Tatebe et al. to quantify plasma p-tau 181. They reported high levels of p-tau 181 in AD patients and individuals with Down's syndrome compared to healthy controls (Tatebe, et al., 2017). A study by Karikari et al. also showed that plasma p-tau 181 levels were high in AD patients and patients with MCI who later developed AD. They also reported that p-tau 18 levels were able to differentiate normal young and older adults, frontotemporal dementia, corticobasal syndrome, Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, and vascular dementia from AD dementia (Karikari, et al., 2020). The plasma levels of p-tau 181, p-tau 231, and p-tau 217 increase with increase in tau and Aβ pathologies (Gonzalez-Ortiz, et al., 2023). Plasma p-tau 181 and p-tau 217 levels were high in individuals with *APP* and *PSEN1* mutations compared to normal controls (Gonzalez-Ortiz, et al., 2023). Studies also showed that plasma p-tau 217 levels were high two decades before the onset of MCI in AD patients (Palmqvist, et al., 2020). A recent study showed that plasma p-tau 217 levels can differentiate between patients in the MCI stage and those progressed to the dementia stage with high accuracy compared to p-tau 181 and p-tau 231 (Janelidze, et al., 2023).

7.5. Other blood biomarkers

Studies were conducted to measure the levels of neuronal injury markers and synaptic markers in blood. Benussi et al. found that serum NF-L levels were high in patients with AD and frontotemporal dementia (Benussi, et al., 2020). Plasma NF-L levels were high in both AD and progressive supranuclear palsy (Rojas, et al., 2016). Studies on SNAp-25, VILIP-1, and synaptotagmin are inconsistent and limited (Molinuevo, et al., 2018). Lipids, proteins, and metabolites in the plasma of AD patients have been studied. Studies have found an association between plasma proteins and AD progression. However, these results have not yet been replicated. Mass spectrometry and quantitative and targeted metabolomics are used to study lipid metabolism in the blood of AD patients. A study by Mapstone et al., 10 phospholipids from the blood of healthy elderly individuals and was able to predict conversion to either MCI or AD within the next 2–3 years. The accuracy of prediction was 90% suggesting that these phospholipids can be used to detect early neurodegeneration in AD (Mapstone, et al., 2014). In a recent study by Varma et al., four sphingolipids levels were found to be higher in cognitively healthy individuals who later developed AD (Varma, et al., 2018). The sphingolipid and phospholipid changes in the blood could be an indication of lipid metabolism impairment or neuronal degeneration before the onset of cognitive symptoms. Further studies are required to understand whether they are specific to AD. A main component of exosomes, flotillin was identified by Abdullah et al. They reported low levels of flotillin in the serum and CSF of AD patients and amyloid-positive MCI patients when compared to patients with vascular dementia and MCI patients without amyloid (Abdullah, et al., 2019). The low levels of flotillin could be due to low exosome secretion mediated by Aβ oligomers (Abdullah, et al., 2016). Hence, it has the potential to be a novel AD marker.

7.5.1. BDNF

The brain derived neurotropic factor or BDNF is a member of neurotrophin family of growth factors and is involved in differentiation, maturation, and survival of neurons. Several studies have reported low levels of serum BDNF in AD patients (Gezen-Ak, et al., 2013; Plášteník, et al., 2014). However, several other studies observed an elevation in BDNF levels in the serum of AD patients (Faria, et al., 2014). This elevation could be due to the activation of immune cells or a compensatory mechanism to fight off neurodegeneration (Faria, et al., 2014). These high levels dropped with the progression of the disease. Hence, serum BDNF levels can be used as an early marker for AD (Mori, et al., 2021). The low levels of BDNF are associated with tau phosphorylation, Aβ accumulation, neuronal apoptosis, and neuroinflammation (Wang, et al., 2019). Inflammatory cytokine levels are increased as BDNF levels are reduced. High levels of inflammatory cytokines initiate the JAK2/-STAT3 pathway which leads to the overexpression of the transcription factor C/EBPβ. This leads to overexpression of δ-secretase, Aβ formation, and death of neurons (Wang, et al., 2019). PKCε expression was reduced due to high oxidative stress and Aβ accumulation. A decrease in PKCε reduces BDNF levels in the hippocampus resulting in loss of synaptic plasticity and high oxidative stress (Sen et al., 2018). Studies showed that overexpression of BDNF and BDNF gene delivery reversed the behavioral deficits, synaptic degradation, and neuronal abnormality in AD patients. It also reduced further neuronal loss but did not have any effect against tau hyperphosphorylation (Jiao, et al., 2016). In mouse models, BDNF from astrocytes improved synaptic properties, spine density, and memory deficits (de Pins, et al., 2019).

Mutations in the *BDNF* gene can affect learning and memory (Rantamäki, et al., 2013). BDNF genetic variations are associated with the risk of Alzheimer's Disease-related depression (Borroni, et al., 2009). Prefrontal cortex *BDNF* gene expression is associated with aging, Alzheimer's disease neuropathology, and rs6265 carrier status (Aarons, et al., 2019). The precursor form of BDNF or pro-BDNF is also associated with AD and tau. A toxic interaction between pro-BDNF and Aβ peptides is reported (Lim, et al., 2015). Pro-BDNF levels are associated with p-tau and amyloid load in the hippocampus of AD patients (Bharani, et al., 2020). It was observed that the ratio of pro-BDNF to mature BDNF in the brain of AD patients increased by more than thirty-fold (An and Gao, 2015). This ratio could be a biomarker for AD. In conclusion, low levels of BDNF in the blood and brain of AD patients have the potential to be early diagnostic markers of AD. Since BDNF overexpression alleviates neuronal loss, synaptic degeneration, neuronal abnormality, and behavioral deficits, it has the potential to be used as a therapeutic agent

for AD. However, more research is required in this field.

7.6. Urine biomarkers

7.6.1. Formic acid and formaldehyde

Research has shown that urine metabolites can serve as biomarkers for oxidative stress, injury, and even neurodegenerative diseases (Yu, et al., 2014). Recent studies have reported that abnormal formaldehyde metabolism seen in AD can be associated with cognitive impairment (Yu, et al., 2003). Formaldehyde is present in the brain, blood, and urine (Morellato, et al., 2021). Formaldehyde has a role in cellular metabolism and modifying DNA, RNA, and amino acids (Li, et al., 2021; Tulpule and Dringen, 2013). In the brain, formaldehyde promotes spatial memory formation and high concentrations of formaldehyde can impair memory (He, et al., 2010). Formaldehyde concentrations were found to be higher in the brains of AD patients (Fe et al., 2021). Studies also reported that formaldehyde had a role in crosslinking non-toxic Aβ monomers to form toxic oligomers or dimers (Zhao, et al., 2021; Tong, et al., 2017). Urine formaldehyde is easier to analyze as the process is non-invasive and there is a smaller number of interfering proteins. The formaldehyde levels increase in aging and AD (Lu, et al., 2013). The 'formaldehyde stress' hypothesis states that the abnormal accumulation of endogenous formaldehyde may influence the abnormal change in proteins resulting in tau hyperphosphorylation (Tong, et al., 2013), DNA damage (Tong, et al., 2013), reduced long-term potentiation (Szende and Tyihák, 2010), and cell death (Tong, et al., 2011) which can lead to neurodegenerative diseases.

Several studies have reported that urine formaldehyde levels were higher in AD patients than in healthy controls (Tong, et al., 2013; Lu, et al., 2013). An autopsy study by Tong et al., also revealed that formaldehyde concentration in the hippocampus of AD patients was higher compared to age-matched healthy controls (Tong, et al., 2013). In a study conducted by (Wang et al., 2022) urine formaldehyde was found to be higher in preclinical AD patients. They also reported that urine formaldehyde was high in patients with AD compared to MCI patients and healthy controls (Wang, et al., 2022). Formic acid is a metabolic product of formaldehyde and formic acid in the urine reflects the formaldehyde metabolism. Another study showed that urinary formic acid was high in the preclinical, prodromal, and dementia stages of AD when compared to normal healthy controls (Wang, et al., 2022). They also reported that urinary formic acid was negatively correlated with MMSE scores and that it could differentiate between AD and healthy controls (Wang, et al., 2022). This study also showed that urine formaldehyde levels were higher in individuals with the *APOE* ε4 allele when compared to individuals without the allele (Wang, et al., 2022). Hence, urinary formic acid and formaldehyde have the potential to become diagnostic markers of AD.

7.6.2. Alzheimer-associated neuronal thread protein (AD7c-NTP)

AD7c-NTP was identified in 1996. It is a cDNA that encodes a phosphoprotein (De La Monte, et al., 1996a; De La Monte, et al., 1996b). This protein is expressed in the brain and its levels are high during the proliferation, differentiation, brain development, and neurodegeneration caused by AD (De La Monte and Wands, 2001a; De La Monte and Wands, 2001b). It is overexpressed in the brains of AD patients. Studies have reported that abnormal AD7c-NTP activity is observed before the formation of neurofibrillary tangles (De La Monte, et al., 1996a; De La Monte, et al., 1996b; De La Monte and Wands, 2001a; De La Monte and Wands, 2001b). Studies have also confirmed the presence of AD7c-NTP in early AD in cortical neurons, CSF, urine, and brain tissue extracts. The sensitivity and specificity of AD7c-NTP in urine are similar to that of CSF (Ghanbari, et al., 1998; Ma, et al., 2016). AD7c-NTP levels in urine are high during the early stages of AD and MCI and are considered to be an early marker of AD (Li, et al., 2019). Studies conducted on AD7c-NTP urine levels for the past twenty years consistently reported that urine AD7c-NTP levels positively correlate with AD severity. As cognitive decline worsens, AD7c-NTP levels in the urine increase (Li, et al., 2019). It is easy to measure the levels of this protein in urine as it is a non-invasive, non-radiative method, and easily reproducible (Youn, et al., 2011). However, studies are required to analyze the factors (like physiological) that can affect other metabolites present in the urine. Studies reported that AD7c-NTP levels increase with age and are higher in females than males (Jin, et al., 2018; Ma, et al., 2014). However, the protein levels are unaffected by demographic factors or the presence of chronic diseases like hypertension, stroke, depression, and others (Li, et al., 2019; Zhang, et al., 2018).

7.6.3. Lipid peroxidation compounds

Lipid peroxidation has an important role in the pathogenesis of AD (Sultana, et al., 2013). A study by Benseny-Cases et al. found that oxidized lipids co-localized with senile plaques. They also observed high levels of oxidized lipids in the plasma of AD patients when compared to healthy individuals (Benseny-Cases, et al., 2014). Similar studies were conducted using urine as a sample and found high levels of F2 isoprostanes in the urine of AD patients when compared to healthy controls (Tuppo, et al., 2001; Kim, et al., 2004). A study by Peña-Bautista et al. identified high levels of lipid peroxidation compounds including F2 isoprostanes in the urine of AD patients (Peña-Bautista, et al., 2018). However, more follow-up studies with larger population sizes are required in this field.

7.7. Saliva Biomarkers

Saliva has a connection to the nervous system; the glossopharyngeal nerve innervates the parotid gland and the facial nerve innervates the submandibular and sublingual glands. Hence, saliva could be a source of biomarkers for nervous system disorders (Farah, et al., 2018). Saliva can be easily collected in a non-invasive manner (Jasim, et al., 2018). AD biomarkers like Aβ peptides, p-tau, t-tau, lactoferrin, acetylcholine, and trehalose can be measured in saliva (Tvarijonaviciute, et al., 2020). Even though the number of studies on salivary biomarkers is less, the existing studies show that Aβ42 is high in AD patients while there is no change in Aβ40 levels (Sabbagh, et al., 2018; Lee, et al., 2016; Gleerup, et al., 2019). As of now, there are no studies discussing the Aβ42/Aβ40 ratio in saliva. A few studies have shown that p-tau, t-tau, and p-tau/t-tau ratio were high in AD patients (Pekeles, et al., 2018; Ashton, et al., 2018). However, the results are not consistent as tau proteins are secreted and released by acinar cells which are subunits of salivary glands (Ashton, et al., 2018). Recent studies have shown that acetylcholinesterase has a role in Aβ fibril formation. Acetylcholinesterase diffuses into saliva. The limited studies conducted on acetylcholinesterase levels in saliva reported that low levels of the enzyme in found in the saliva of AD patients and during aging (Liang and Lu, 2019). Antimicrobial peptides are considered biomarkers for brain disorders. Lactoferrin is a non-hemic iron-binding glycoprotein and is synthesized in the neutrophils and glandular epithelial cells (Mudgil and Barak, 2019). Due to its iron-binding activity, it has antiviral, antibacterial, antioxidant, antifungal, immunomodulatory, anti-cancer, anti-allergenic, and anti-inflammatory properties (Mohamed, et al., 2019). Evidence shows that lactoferrin is present in the human brain and its levels are increased in AD, possibly due to Aβ-binding ability (Carro, et al., 2017). It has been detected in amyloid plaques, microglia, and neurofibrillary tangles of AD patients. Limited studies show that lactoferrin levels in the saliva of AD patients are low when compared with healthy controls (González-Sánchez, et al., 2020). It has the potential to be an early AD detection biomarker as its accuracy of AD diagnosis was better than Aβ42 and t-tau in CSF (Farah, et al., 2018).

Table 7 & 8 provides a detailed overview of different diets and physical activity that may help delay the progression of the disease or manage cognitive decline. Table 9 provides a detailed overview of the effect of external factors like supplements, smoking, obesity, diabetes mellitus, and hypertension in the development of AD.

8. Conclusion

Alzheimer's disease is considered to be a health concern worldwide and it is estimated that 6.7 million Americans are affected by this disease. Several studies have already identified novel and potential biomarkers of AD and genes associated with the risk of AD. Moreover, ongoing clinical trials will determine whether the treatment options administered during the preclinical or asymptomatic phase help in delaying or preventing the progression of the disease. Diet and physical activity have an important role in reducing the effects of aging which may help delay or reduce the risk of AD. Lifestyle factors like obesity, hypertension, diabetes, smoking, and mental and social activity should also be addressed to reduce the risk of AD. Hence, with better research effective diagnostic techniques and treatments for AD can be determined.

Authors' contributions

Conception: HKK, JJR, and VJ. Manuscript preparation: CC, HKK, VJ, KK, TW, KB and JJR.

Funding

Vibrant America provided funding for this study in the form of salaries for authors [HKK, CC, VJ, KK, TW, KB and JJR]. The specific roles of these authors are articulated in the 'author contributions' section. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Competing Interest

The authors have read the journal's policy and the authors of this manuscript have the following competing interests: CC is a paid employee of Vibrant America LLC. HKK, VJ, KK, TW, KB, and JJR are paid employees of Vibrant Sciences LLC. There are no patents, products in development, or marketed products to declare. This does not alter our adherence to *Ageing Research Reviews* policies on sharing data and materials.

Acknowledgements

We acknowledge Vibrant America LLC for supporting this research.

Consent for publication

NA

Data Availability

No data was used for the research described in the article.

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