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Role of Vascular Risk Factors and Vascular Dysfunction in Alzheimer's Disease

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Abstract

Recent findings indicate that vascular risk factors and neurovascular dysfunction play integral roles in the pathogenesis of Alzheimer's disease. In addition to aging, the most common risk factors for Alzheimer's disease are apolipoprotein e4 allele, hypertension, hypotension, diabetes, and hypercholesterolemia. All of these can be characterized by vascular pathology attributed to conditions such as cerebral amyloid angiopathy and subsequent blood-brain barrier dysfunction. Many epidemiological, clinical, and pharmacotherapeutic studies have assessed the associations between such risk factors and Alzheimer's disease and have found positive associations between hypertension, hypotension, and diabetes mellitus. However, there are still many conflicting results from these population-based studies, and they should be interpreted carefully. Recognition of these factors and the mechanisms by which they contribute to Alzheimer's disease will be beneficial in the current treatment regimens for Alzheimer's disease and in the development of future therapies. Here we discuss vascular factors with respect to Alzheimer's disease and dementia and review the factors that give rise to vascular dysfunction and contribute to Alzheimer's disease.

Keywords

Alzheimer's disease; apolipoprotein; blood-brain barrier; cholesterol; diabetes; hypertension; risk factors

The prevalence of dementia, particularly Alzheimer's disease (AD), is increasing and it is one of the most important neurodegenerative disorders in the elderly. It is estimated that 5% to 10% of the elderly in the age range of 65 to 74 years are affected and that 25% to 50% of the elderly over the age of 85 years are affected. Of these cases, AD accounts for 50% to 60%, and the risk for AD doubles every 5 years after the age of 65 years.¹ It is projected that by 2040, 81.1 million people will be affected worldwide with dementia,² with frequencies for AD and vascular dementia (VaD) of 70% and 15%, respectively.³ The neuropathological

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hallmarks of AD are intraneuronal protein aggregates of hyperphosphorylated tau protein [neurofibrillary tangles (NFTs)], aggregation of neurotoxic amyloid beta ($A\beta$) protein in the brain parenchyma and in blood vessel walls,⁴ and neuronal degeneration and loss. Currently, one of the prevailing theories of AD pathophysiology is the amyloid cascade hypothesis, which implicates $A\beta$ as the key player in the formation of senile plaques and neuronal death.⁴ However, recent evidence from epidemiological, clinical, pathological, and neuroimaging studies implicates neurovascular dysfunction as an integral part of AD and has given rise to the vascular hypothesis of AD. Moreover, data from these studies reveal a distinct association between vascular risk factors and AD. These include hypertension,⁵ total cholesterol (TC), type II diabetes mellitus (DM),⁶ hypotension, smoking,⁷ and oxidative stress.⁸ Furthermore, dysfunction of the endothelial cells that compose the blood-brain barrier (BBB) has also been demonstrated and correlates with AD severity.⁹ The degree to which these factors contribute to AD may be influenced by genetic factors such as apolipoprotein E (ApoE), which has a role in both AD and vascular disease.

Recent evidence from epidemiological, clinical, pathological, and neuroimaging studies implicates neurovascular dysfunction as an integral part of Alzheimer's disease (AD).

NEUROPATHOLOGY

Vascular pathology in the aging brain and AD includes ischemic infarcts, lacunes, cerebral hemorrhages, white matter lesions, BBB dysfunction, cerebral amyloid angiopathy (CAA), and microvascular degeneration.¹⁰ These pathologies are commonly seen in various vascular diseases and can contribute to cognitive impairment by affecting neuronal networks involved in cognition, memory, behavior, and executive functioning.¹¹

Multi-Infarct Dementia

It was first proposed that dementia occurs only in the presence of cerebral infarcts having a volume larger than 100 ml.¹² However, challenging this view, recent work has suggested that small infarcts and even multiple microscopic infarcts can also lead to dementia.^{13–17} Although the accumulation of macro-infarcts, particularly in the hippocampus and the association neocortex, represents the primary form of VaD, much less is known regarding the contributions of microvascular pathology to cognitive decline leading to AD. Microvascular lesions indeed encompass a broad spectrum of pathologies, are highly heterogeneous, and may present with different patterns of clinical symptoms.¹⁸ Additionally, pathological lesions associated with AD, including an accumulation of $A\beta$ and NFTs, may mask clinically relevant consequences due only to the microvascular pathology itself.^{18–20}

Keeping these confounders in mind, many studies have attempted to elucidate the contributions of multiple micro-infarcts to the pathogenesis of dementia. The Nun study found that cerebrovascular disease determines the severity of AD and that patients with multiple lacunar infarcts had poorer cognitive function and a higher prevalence of dementia, regardless of the NFT load, in comparison with those without infarcts.¹⁵ The Rotterdam Scan study found a similar association: patients with multiple brain infarcts had double the risk for developing dementia and a steeper decline in global cognitive function.²¹ Recently, Kövari *et al.*¹⁸ used postmortem human brain specimens taken from patients ranging in age from 63 to 100 years and found that the presence of micro-infarcts as well as focal cortical gliosis had a significant correlation with the extent of cerebral microvascular pathology and cognitive function.¹⁸

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Lacunes

Lacunes, found in the periventricular white matter and in subcortical structures such as the basal ganglia, internal capsule, thalamus, pons, corona radiata, and centrum semiovale, are small ischemic infarcts surrounded by reactive gliosis and macrophages that have a diameter of less than 15 mm.^{22–24} Such lesions may present clinically as severe dysexecutive syndrome accompanied by deficits in memory, frontal lobe deficits, slowing of motor function, changes in personality, impairment in activities of daily living, parkinsonian features, and other problems associated with deterioration of working memory (such as deficits in the planning, organization, and sequencing of events).²⁵

Studies examining the clinical significance of lacunes as well their effects on cognition have yielded largely mixed results. Although as many as 23% of individuals older than 65 years of age may present with lacunes, up to 25% of these lacunes appear to be clinically silent: they have little or no observable effect on cognitive functioning.²² However, when lacunes are observed in patients presenting with concomitant AD-related alterations, the presence of deep white matter, basal ganglia, and thalamic lacunes significantly affects cognitive function.¹⁵ In a comparative autopsy study, it was found that there was a higher incidence of cerebrovascular lesions in AD patients in comparison with age-matched controls (48.0% versus 32.8%, $P < 0.01$) with a high incidence of minor to moderate lacunar lesions.²⁶ As the emergence of AD-related pathology can complicate the relationship between vascular lesions and dementia, Gold *et al.*²³ controlled for the presence of NFTs by including only those cases that met the criteria for Braak stages I and II and thus ensured that AD-related pathologies would be less likely to mask the contributions of lacunar and microvascular pathologies to clinical dementia rating (CDR) scores. The results showed that cognitive status was significantly predicted by the presence of lacunes in the thalamus and basal ganglia (5% and 6%, respectively). Interestingly, this study also documented significant interactions between A β staging (7% of CDR variability), age (3% of CDR variability), and various microvascular pathologies (23% of CDR variability) and variability in CDR scores.^{22,24}

In a comparative autopsy study, it was found that there was a higher incidence of cerebrovascular lesions in AD patients in comparison with age-matched controls (48.0% versus 32.8%, $P < 0.01$) with a high incidence of minor to moderate lacunar lesions.

MIXED DEMENTIA

Across the lifespan, normal brain aging includes the development of various AD-related pathologies as well as the progressive emergence of lesions associated with a range of vascular pathologies. For the majority of the aging population, the cognitive impact of this combination of pathologies remains essentially silent.²⁷ The emerging concept of mixed dementia refers to a broad spectrum of conditions in which cognitive declines may be attributed to the presence of both AD and vasculature-related alterations.^{11,26} At present, research efforts have been made more difficult as a result of the broad application of this diagnosis; patients presenting with every combination of pathologies from severe AD lesions but sparse vascular pathology to severe vascular pathology with few AD lesions are

eligible for the diagnosis of mixed dementia.²⁸ Additionally, a range of structural alterations of microvessels have been documented in both normal aging and AD. Normal aging has been associated with both microvascular lesions and the presence of amyloid deposition and NFTs in nondemented patients with hypertension, whereas patients with AD exhibit severe vascular modifications, including atrophic or string vessels, glomerular loop formation, twisted vessels, and fragmentation of the microvasculature.^{28,29} Hampering research efforts still further is the lack of well-defined threshold values for both AD and vascular lesions that consistently predict cognitive status and dementia in patients as well as the diffuse nature of the pathological lesions under study. In an effort to develop better thresholds for the diagnosis of mixed dementia, Gold and colleagues²⁷ again used systematic semiquantitative methods both to control for the confounding effects of age and to more reliably identify cutoff values that consistently identify individuals as demented or nondemented on the basis of their burden of AD and vascular pathology.

These authors assessed the relationship between CDR scores of a randomized sample of patients and the presence of the aforementioned previously identified neuropathological features. Following the univariate analysis, these data²⁴ closely matched previous findings^{23,27} and suggested that Braak NFT staging, A β deposition staging, cortical micro-infarct scores, the degree of lacunar pathology in the thalamus and basal ganglia, and age were all significantly related to CDR scores. When the data were further parsed with a multiple regression model, the effect of age was lost, and up to 48.9% of the variability in the CDR scores could be explained by the variations in NFT staging, A β staging, cortical micro-infarcts, and lacunes alone. Among the most important findings of this work, however, was the identification of neuropathological thresholds that the authors were able to use to classify accurately up to 90% of their sample as demented or nondemented. Moreover, the derivation model employed by Gold *et al.*²⁷ resulted in high sensitivity and specificity, a strong positive predictive value, and a high correct rate of classification.

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Cerebral Amyloid Angiopathy

CAA is defined as the deposition of A β peptide within the walls of the leptomeninges and parenchymal arteries, arterioles, and capillaries with a concomitant thickening of arteriole walls and formation of micro-aneurysms. In addition, CAA has been associated with the degeneration of smooth muscle cells, ischemic white matter damage, fibrinoid necrosis, and dementia (reviewed by Jellinger¹¹). The majority of CAA is spontaneous and its incidence increases with age to almost 100% past the age of 80. In AD, CAA can range from 70% to 97.6%.³⁰ The origin of the A β deposited in blood vessels has not been clearly elucidated. One possibility, the drainage hypothesis, suggests that neurons are the main source of vascular amyloid because neurons are the main source of amyloid precursor protein (APP) and A β in the brain.³¹ Normally, A β produced in neurons is transported across the BBB. However, if there is a deficiency in the transport mechanism of A β , A β can build up in the vessel walls. It has been shown that the effect of widespread A β deposition is the degeneration and death of endothelial cells and the obliteration of the capillary lumen.³² Moreover, ultrastructural studies indicate that approximately 32% of fibrillar amyloid plaques are in contact with 1 or more cerebral capillaries³³ and that 77% of plaques in Tg2576 mice and 91% of human plaques are in direct contact with capillaries.³³ Another theory is that A β can be systemic and originate in the circulating bloodstream. Finally, it has also been suggested that smooth muscle cells within the vessel walls or pericytes produce

the A β .³⁴ Regardless of its origins, the A β associated with CAA, causing microscopic bleeding throughout the neocortex and its associated lobar white matter, has been shown to have a pathogenic role in dementia (reviewed by Jellinger¹¹). Many of the mouse models for AD, harboring many different APP mutations associated with AD (ie, Swedish, Dutch, Iowa, and London), have also been shown to exhibit CAA. In addition to the accumulation of parenchymal A β , many of these models have A β deposits within the vessel walls of the leptomeninges and the neocortical, hippocampal, and thalamic vessel walls.^{35–44} Therefore, it would appear that CAA may be an integral cerebrovascular dysfunction in the diagnosis of AD and dementia.

RISK FACTORS

AD is a complex, multifactorial neurodegenerative disorder likely resulting from the contribution of complex gene-gene and gene-environmental interactions. There are many underlying risk factors that contribute to vascular disease and AD, including apolipoprotein genotype, hypertension, hypotension, cholesterol levels, DM, and smoking. These, in addition to environmental risk factors (ie, brain injury, metals, education levels, dietary factors, and smoking), have been studied and implicated as possible risk factors for AD.

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Apolipoprotein E Genotype

Although there are many environmental risk factors that contribute to dementia in AD, genetic risk factors, such as ApoE, play a central role in its pathophysiology. In addition to its association with sporadic AD, ApoE is also related to vascular disease. ApoE is a plasma cholesterol transport molecule found on chromosome 19q13.2, and it occurs in 3 common alleles (ϵ 2, ϵ 3, and ϵ 4).^{45,46} It is a key constituent in very low density lipoproteins and is vital in the transport of cholesterol and other lipids throughout the brain.⁴⁷ ApoE in the central nervous system (CNS) is expressed primarily in astrocytes but can also be found in microglia and neurons. It is thought to act as a neurotrophic factor in growth and repair during CNS development and injury and is regulated by endocytosis with low-density lipoprotein receptor-related protein 1 (LRP1).⁴⁸

Many epidemiological studies have found an association between ApoE ϵ 4 and AD.⁴⁹ ApoE ϵ 4 is known to play a major role in AD and dementia and is associated with a younger age of onset in a dose-dependent manner.⁵⁰ Those homozygous for the ApoE ϵ 4 allele have a 12-fold increase in the risk for AD.⁴⁹ However, ApoE ϵ 4 is neither necessary nor sufficient for the development of AD. ApoE 4 is also known to be associated with coronary heart disease⁵¹ and has been implicated as a risk factor for atherosclerosis⁵² and stroke.^{53,54} ApoE ϵ 4 has also been shown to have a strong association with CAA, and it has been suggested that the contribution of CAA to AD is largely dependent on ϵ 4.⁵⁵ Data from the Honolulu-Asia study and the Rotterdam study indicate that patients who are ϵ 4 carriers have more pronounced vascular risk factors than noncarriers.⁵⁶ Moreover, patients who are ϵ 4 carriers and have atherosclerosis are at increased risk of cognitive decline.⁵⁷ It has also been shown in a different population cohort that patients with mild AD who are 4 carriers have a faster rate of cognitive decline.⁵⁸ Studies in transgenic mice have also demonstrated that ApoE ϵ 4 promotes the formation of CAA.^{44,59}

The mechanisms by which ApoE contributes to AD are not completely understood. Many studies have demonstrated that ApoE has isoform-specific capabilities (ϵ 2 > ϵ 3 > ϵ 4) for

acting as a chaperone molecule for A β and influences A β metabolism, deposition, toxicity, fibril formation, and clearance from the brain.^{60–64} In addition, ApoE could also mediate tau hyperphosphorylation and modulate the distribution and metabolism of cholesterol in neuronal membranes in an isoform-dependent manner.⁴⁶ This is supported by evidence showing that increased plasma cholesterol concentrations correlate with increased A β accumulation in the brains of humans and transgenic mice and may be a result of serum ApoE concentrations.⁶⁵

Hypertension

The relation between high blood pressure, cognitive function, and dementia has been the subject of numerous epidemiological and clinical studies that have generated a rather mixed outcome. Hypertension, currently defined as a systolic blood pressure (SBP) above 140 mm Hg and/or a diastolic blood pressure (DBP) above 90 mm Hg,^{66–67} is a risk factor for many disorders, including AD, stroke, atherosclerosis, myocardial infarction, and cardiovascular disease.⁶⁸ Hypertension is estimated to affect 25% of the general population with a 50% prevalence in people over 70 years of age.⁶⁸ Epidemiologically, it has been shown that hypertension precedes dementia onset by approximately 30 years; however, this relationship is complex and does not follow a linear progression.⁶⁹ Midlife hypertension is particularly associated with an increased risk of developing both AD and VaD, whereas elevated blood pressure late in life does not appear to have the same associated risk. By itself, hypertension has been shown to be an independent risk factor for AD, but it is also associated with other diseases such as cardiovascular disease and stroke, which are known to be important factors leading to the onset of dementia.⁷⁰ Neuropathological and imaging investigations have demonstrated that individuals with high blood pressure often have large areas of white matter hyperintensity (manifested histopathologically as demyelination, arteriolosclerosis, gliosis, and tissue degeneration), ventricular enlargement, and silent infarcts, all of which can lead to cognitive dysfunction and dementia.¹

Many population-based studies, both cross-sectional and longitudinal, have evaluated the link between hypertension and memory impairment and have generated conflicting data. Several longitudinal studies have confirmed that hypertension or elevated blood pressure, occurring in middle age or late in life, plays an important role in the development of cognitive dysfunction and is associated with an increase in the risk for AD and dementia.^{71–74} However, other studies have shown that treatment with antihypertensive drugs has no significant effect on AD. One of the first studies that provided evidence relating blood pressure and cognitive decline was the Framingham study. This study concluded that elevated blood pressure was associated with modest impairment of cognitive function.^{75–76} Following this study, several randomized placebo-controlled clinical trials evaluated the effect of antihypertensive drugs on dementia and AD (summarized in Table 1). The Rotterdam study, the Kungsholmen study, the Honolulu-Asia Aging Study, and the Epidemiology of Vascular Aging Study supported the results observed in the Framingham study.

In addition to the epidemiological studies associating hypertension with the incidence of AD, many studies have found associations between hypertension and AD brain pathology. Data from a brain imaging study found cross-sectional associations between SBP and medial temporal lobe atrophy in patients with AD. Hippocampal atrophy has also been reported in both the Honolulu-Asia study and the Rotterdam study in patients not treated for hypertension. Furthermore, the Honolulu-Asia study also reported an association between midlife SBP, lower brain weight, and an abundance of amyloid plaques in the hippocampus and neocortex. Furthermore, patients with a DBP > 95 mm Hg exhibited higher numbers of NFTs in the hippocampus.⁷⁷ It is thought that the onset of these pathologies occurs prior to the onset of dementia as plaques and NFTs were also present in nondemented, middle-aged

individuals with hypertension.⁷⁷ A few theories about how hypertension can contribute to AD and dementia have been proposed. First, it is thought that hypertension causes vascular alterations that then lead to lacunar or cortical infarcts and leukoaraiosis and ultimately cognitive decline. Second, it has been suggested that hypertension leads to cardiovascular disease, which gives rise to AD.¹⁵ Third, hypertension can have adverse effects on neuronal health and increase the production of $A\beta$ and can thereby lead to neuronal dysfunction, synapse and neuronal loss, and dementia.⁷⁸ Altogether, it seems that hypertension, aging, and cerebrovascular risk factors act synergistically to cause vascular degeneration, oxidative stress, mitochondrial dysfunction, neuronal degeneration, and AD.

Hypotension

Although it has been shown that increased blood pressure is a strong risk factor for AD and VaD, a decrease in blood pressure can also have adverse effects on cognition in old age.^{79–81} Hypotension, defined as having a DBP ≤ 70 mm Hg, is usually associated with increased mortality.⁸² However, recent studies have shown that hypotension is a key factor in conditions such as diabetes and psychosomatic distress,^{83–84} which all can be considered risk factors for AD. The mechanism by which low blood pressure can lead to AD is speculative, but it is thought either to be a result of the dementia process or to accelerate and predispose to cognitive decline.⁸⁵

Many population-based prospective studies have demonstrated an increased prevalence of AD and dementia in persons with low blood pressure (Table 2).^{79–81} Reports from the Honolulu-Asia study found that in a cohort of Japanese-American men, low DBP was associated with an increased risk of developing AD in later life. This risk was particularly significant in subjects that were not treated with antihypertensive drugs.⁷³ Further longitudinal studies of cohorts from Sweden (the Kungsholmen study) and Boston (the East Boston study) found that low DBP (<70 mm Hg) tended to increase the relative risk for AD and dementia.^{81–86} In another population-based cohort, Zhu *et al.*⁸⁰ examined 924 persons who were 75 years old or older and found that there was also a correlation between systolic pressure reduction and cognitive decline in women.⁸⁰ Results from the Kungsholmen project and the Chicago Health and Aging Project corroborated these data and showed that people with an SBP ≤ 140 mm Hg and a DBP < 70 mm Hg or an SBP ≤ 130 mm Hg and a DBP < 70 mm Hg had significantly higher risks of dementia and AD, respectively.^{87–88} Moreover, the risk of AD associated with low blood pressure was particularly pronounced in antihypertensive drugs users.⁸⁶ More recently, Ruitenberg *et al.*⁸⁹ observed that there was a higher prevalence of decreased blood pressure, independent of age and sex, in demented patients in comparison with nondemented patients at follow-up.

How hypotension is associated with the risk for AD remains unclear. It is possible that low blood pressure occurs as a result of brain pathology. Pathological changes, such as the development of $A\beta$ plaques, can lead to a reduction of arterial pressure, which in turn may produce hypoxicischemic changes that would act synergistically with existing pathology to exacerbate the degree of dementia.^{72–79–90}

Alternatively, low blood pressure may predispose people to the risk of AD and dementia and act as an early correlate of the dementia process.^{81–86–89} Aging of the vasculature results in changes in the structural and mechanical properties of the arterial walls that ultimately lead to a dampening of the autoregulatory capabilities of cerebral arteries rendering the brain more vulnerable to ischemia and hypoperfusion.⁹¹ Evidence shows that a decrease in cerebral blood flow (CBF) precedes the neuropathology observed in AD, and it continues to decline during the course of the disease.^{92–93}

Cholesterol

The specific mechanisms underlying the correlation between cholesterol metabolism and AD are controversial.⁴⁷⁻⁹⁴ It has been suggested that cholesterol plays an essential role in regulating the enzyme activity that is involved in the production of A β protein and the metabolism of APP.⁹⁵ In AD, the cleavage of APP occurs within the hydrophobic lipid bilayer and is catalyzed by the activity of the α -secretase, β -secretase, and γ -secretase enzymes. As such, disturbances in the levels of cellular cholesterol, which cause disorganization in the structure of the lipid bilayer, could alter the processing of APP by α -secretase by shifting the proximity of the secretase cleavage sites to the intramembrane domain of APP.⁹⁶ The activity of β -secretase [or β -site amyloid precursor protein cleavage enzyme (BACE)] and γ -secretase appears to be dependent on the composition of lipid rafts in the membrane.⁹⁷⁻⁹⁹ Many in vitro studies have demonstrated that high levels of cholesterol affect α -secretase and BACE activity and result in a decrease in soluble APP levels and an increase in A β ₁₋₄₀ and A β ₁₋₄₂. Conversely, cholesterol depletion can promote α -secretase activity and the production of soluble APP while decreasing the production of A β ₁₋₄₀ and A β ₁₋₄₂.⁹⁷⁻¹⁰⁰⁻¹⁰³ The impact of cholesterol on γ -secretase function is still unresolved. It has been shown that γ -secretase is dependent on lipid rafts but is not cholesterol-dependent,¹⁰³⁻¹⁰⁴ whereas others have shown that cholesterol can indeed modulate enzyme activity.⁹⁸⁻¹⁰⁵⁻¹⁰⁶ It has been proposed that high levels of cholesterol alter the plasma-membrane composition and appear to impede membrane fluidity and thereby prevent the interaction of α -secretase with APP and preclude the production of soluble APP while increasing the number of lipid rafts in the membrane and thereby facilitating the interaction between APP and BACE and the generation of A β .¹⁰⁰ This shift of APP within the membrane and the increase or decrease in lipid rafts in the membrane can lead to neuronal degeneration because soluble APP is neuroprotective and has been shown to act as a trophic factor, reduce intracellular calcium concentrations, and protect against hypoglycemic damage and glutamate toxicity,⁹⁷⁻¹⁰⁷ whereas A β is known to be neurotoxic.

In vivo studies have also demonstrated the effect of cholesterol on the generation of A β . Staining of hippocampal and frontal cortex paraffin sections showed that rabbits given high cholesterol diets had both high-intensity staining and increased levels of brain A β . When the animals were returned to a normal diet, the intensity of staining was significantly reduced, and the levels of brain A β returned to normal.¹⁰⁸⁻¹⁰⁹ Recent findings have suggested that a partial loss of γ -secretase function and an accumulation of γ -secretase substrates impair endocytosis of lipoproteins.¹¹⁰ Refolo *et al.*¹¹¹ showed that diets high in cholesterol, administered to rabbits and AD mouse models, increased A β levels.

Several epidemiological studies analyzing the possible connections between AD and cholesterol levels have conflicting results, but the majority stress an association between high plasma cholesterol in midlife and increased susceptibility to sporadic AD.⁴⁷⁻¹¹²⁻¹¹⁴ Interestingly, there was no significant correlation found when cholesterol levels were analyzed in patients later in life.¹¹⁴⁻¹¹⁵ In an investigation by Kuusisto *et al.*,¹¹⁶ 980 participants between the ages of 69 and 78 years had a positive association between low serum TC and AD. In contrast, another analysis of 1449 elderly participants suggested that there was an inverse relationship between decreased TC and the incidence of AD.¹¹⁷ Furthermore, a study demonstrated that in a group of individuals lacking an ApoE ϵ 4 allele, high TC was associated with AD.¹¹⁸ Other studies looking at the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have shown that the use of statins decreases the incidence and prevalence of AD.¹¹⁹⁻¹²¹ Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, in addition to affecting intracellular cholesterol distribution. Statins have been shown to alter the expression of genes involved in cell growth and signaling with a neuroprotective effect.¹²² Initial studies suggested that the probable risk of AD

development in patients who were taking statins was lower than that in those patients taking other medications.¹²⁰ However, other studies have shown that statins may not have a protective effect against dementia. The Prospective Study of Pravastatin in the Elderly at Risk did not find statins to have a significant effect on the cognitive functions of patients ranging from 70 to 82 years of age.¹²³ The Heart Protection Study, which included 20,536 patients who received either 40 mg of daily statins or a placebo, showed no statistical difference in cognitive decline. However, dementia was determined on the basis of phone interviews, which may have lower reliability in assessing dementia severity.¹²³

The relationship between AD and cholesterol varies; it depends on when in life the levels of cholesterol are measured. High cholesterol in midlife seems to be a high risk factor for developing AD; however, individuals who have high cholesterol in late life do not seem to present with an increased risk of dementia. Statins have been an interesting avenue of research as they are the first line of treatment for hypercholesterolemia and because of evidence that they may prevent neuronal death.⁹⁵ Although the aforementioned studies show that cellular cholesterol levels modulate APP, the exact mechanisms through which this modulation occurs remain elusive.

Diabetes Mellitus

DM is a metabolic disorder that is common in more than 10% of the elderly population in the United States⁹⁵ and is associated with changes in mental cognition and flexibility.¹²⁴ Type 1 DM is characterized by a deficit in the production of insulin by the pancreatic β cells. A review of 33 longitudinal studies suggested that patients with type 1 DM show an increase in cognitive dysfunction and a decrease in the speed of mental processing.¹²⁵ Type 2 DM is characterized by resistance to the effects of insulin. Longitudinal investigations have confirmed that there is a relationship between type 2 DM and a faster rate in the decline of cognition.¹²⁶

Early studies suggested that there is no apparent correlation between type 2 DM and AD.^{127–129} In fact, these studies, showing that patients with AD have a low rate of diabetes, suggest that there may not in fact be a link between diabetes and AD.¹²⁷ In contrast, others have reported that up to 80% of patients with AD also exhibit type 2 DM.^{6,130–132} Longitudinal population-based studies that assessed both diabetes and dementia in late life found that the incidence of dementia was increased by 50% to 100% in diabetic patients.¹²⁴ Furthermore, prospective and cross-sectional analyses have proposed an association between type 2 DM and an increased risk of AD, particularly in poststroke patients; they suggest that diabetes may accelerate the onset of AD, rather than increasing the long-term risk.¹³³

Three pathophysiological mechanisms have been proposed to explain the association between DM and dementia.¹²⁴ First, diabetic individuals have an increased risk of developing dementia through ischemic cerebrovascular disease. Type 2 DM, which is most prevalent in elderly individuals, can develop a cluster of risk factors such as insulin resistance, obesity, and hypertension, which can constitute a metabolic syndrome.^{116,134,135} This combination of risk factors has been established as a predictor of cerebrovascular disease and dementia.¹³⁶

Second, it has been proposed that hyperglycemia has toxic effects on neurons, which can in turn lead to functional or cellular brain deficits through oxidative stress and the accumulation of glycation end products.^{137,138} Advanced glycation end products (AGEs) are sugar-derived substances formed by a nonenzymatic reaction between reducing sugars and free amino groups of proteins, nucleic acids, and lipids. They are normally produced in the body; however, their formation is greatly increased in individuals with diabetes because of the increased glucose availability.¹³⁹ Data have suggested that the primary event

initiating both intracellular and extracellular AGEs is intracellular hyperglycemia.¹⁴⁰ AGEs can come from intracellular auto-oxidation, which forms reactive dicarbonyls such as glyoxal, methylglyoxal, and 3-deoxyglucosone.¹⁴¹⁻¹⁴² There are 3 different mechanisms through which target cells can be damaged by the production of intracellular AGE precursors. First, intracellular proteins have been modified covalently by dicarbonyl AGE precursors, which alter several cellular functions. For example, the basic fibroblast growth factor found in endothelial cells is one of the predominant AGE-modified proteins.¹⁴³ Proteins that play a role in the endocytosis of macromolecules are also modified by AGEs, as overexpression of the methylglyoxal-detoxifying enzyme glyoxalase I prevents the increase in endocytosis caused by hyperglycemia.¹⁴⁴ Also, AGE formation causes abnormal interactions of modified extracellular matrix proteins with other matrix proteins and integrins,¹³⁹ and this results in decreased elasticity of vessels in diabetic rats, even when vascular tone is abolished.¹⁴⁵ Moreover, plasma proteins modified by AGE precursors produce ligands that bind to AGE receptors on endothelial cells.¹⁴⁶ Such binding to the AGE receptor induces the activation of a transcription factor known as nuclear factor kappa B, which causes pathological changes in the expression of several genes, such as the expression of proinflammatory molecules by endothelial cells.¹⁴⁷⁻¹⁴⁸ Furthermore, endothelial AGE receptors that have bound ligands partially result in hyperpermeability of the capillary wall, which is caused by diabetes.¹⁴⁹ Recent evidence has, therefore, suggested that complications caused by diabetes are fueled by glucose and oxidative, proinflammatory AGEs.¹⁵⁰

Lastly, resistance to insulin is associated with hyperinsulinemia, which is a risk factor for dementia.¹¹⁶⁻¹⁵¹ Because insulin has vasoactive effects, this association is at least partly mediated through vascular disease.¹⁵² Furthermore, observations have suggested that insulin may have a direct effect on the brain.¹⁵³⁻¹⁵⁵ Insulin is actively transported across the BBB and may also be locally produced in the brain.¹⁵⁶⁻¹⁵⁷ Insulin receptors are widely present in many regions of the brain, such as the granule cell layer of the olfactory bulb, the cerebellar cortex, and the hippocampal formation.¹⁵⁸ Insulin in the brain is also a modulator of energy homeostasis and intake of food.¹⁵⁹ In fact, patients with AD may have impaired activation of insulin receptors in the brain, and this suggests that AD could in fact be considered an insulin-resistant brain state.¹⁶⁰⁻¹⁶¹ It appears that the metabolism and removal of A β are directly affected by insulin.¹⁶² A β breakdown through the insulin-degrading enzyme is inhibited by insulin.¹⁶³ Insulin stimulates A β intra-cellular trafficking in neuronal cultures and thereby directly increases the secretion of A β and decreases the intracellular levels of A β peptides.¹⁶⁴ Investigations in Tg2576 mice found that diet-induced insulin resistance can increase AD-type amyloidosis in the brain through an impairment of insulin receptor signaling resulting in an increase in γ -secretase activity.¹⁶⁵ These mechanisms may provide a substrate for the apparent association between diabetes and AD. Furthermore, they suggest that vascular disease, changes in glucose blood concentration, and amyloid metabolism are important factors in understanding how diabetes affects brain function, particularly in individuals with AD.

Smoking

The relationship between smoking and neurodegenerative diseases is controversial. Previous predominantly case-controlled studies have proposed that the nicotine in cigarette smoke is inversely correlated with AD and cognitive decline.¹⁶⁶⁻¹⁶⁸ In contrast, it has also been established that smoking causes many deleterious effects through vascular mechanisms, which result in atherosclerosis and thrombosis and increase the risk of AD.¹⁶⁹⁻¹⁷⁰ Furthermore, although some studies have reported weak or negative results,¹⁷¹⁻¹⁷³ others have suggested that former smokers are at a low risk of AD in comparison with nonsmokers¹⁷⁴⁻¹⁷⁵ or are at a higher risk.⁷⁻¹⁷⁶

The neuroprotective effects of smoking have been evaluated by many groups, and it has been found that cigarette smokers are 50% less likely to develop AD than age-matched and gender-matched nonsmokers (reviewed by Fratiglioni and Wang¹⁷⁷). Prospective cohort studies have shown that there is an increased risk^{175,178} or an unchanged risk^{172,173,179} of AD in smokers. When comparing the risk of current smokers and former smokers to the risk of individuals who never smoked, the Chicago Health and Aging Project study found that smokers were 3 times more likely to develop AD than nonsmokers and that former smokers had no difference in risk in comparison with nonsmokers.¹⁸⁰ Studies examining the relationship between smoking and ApoE ϵ 4 found that individuals who were smokers and lacked the ApoE ϵ 4 allele had a greater relative risk of developing AD, whereas those who had ApoE ϵ 4 had an insubstantial relative risk.¹⁸¹

Various possible mechanisms associating smoking history with the onset of AD have been proposed. First, it has been established that exposure to tobacco can lead to the development of atherosclerosis, which in turn leads to an increased risk of ischemic stroke^{169,170} and hence dementia. Second, nicotine has been shown to modulate the neurotoxic effects of A β , can exert potent neuroprotective effects, and may confer resistance to AD. The presence of nicotine from cigarettes causes an up-regulation and activation of nicotinic acetylcholine receptors, which in turn protect against A β cytotoxicity.^{168,182–184} Cholinergic deficits, characterized by reduced levels of acetylcholine nicotinic receptors, are found in AD.¹⁸⁵ Furthermore, Poirier *et al.*¹⁸⁶ found that patients with AD who have an ApoE4 allele have fewer nicotinic receptor binding sites and a depletion of choline. Third, nicotine can also have an effect on oxidative stress. In vitro and in vivo studies have demonstrated that nicotine can act as a scavenger of oxygen free radicals and efficiently scavenge superoxide and hydroxyl radicals in the brain.¹⁸⁷ Other possible roles of nicotine include its ability to inhibit arachidonic acid-induced apoptosis cascades,^{188,189} A β -induced apoptosis,¹⁸⁷ N-methyl-D-aspartate receptor-mediated calcium-dependent excitotoxicity,¹⁹⁰ and A β fibril formation.¹⁹¹ Transgenic mouse studies have also yielded conflicting results. Studies in transgenic mouse models have shown contradictory results: chronic nicotine administration has been shown to be effective in reducing total A β levels in the brain and improving cognition^{35,192–195} or to have no effect at all.^{196,197} Consequently, more mechanistic studies are needed to resolve whether smoking is protective or a detrimental risk factor for AD.

BLOOD-BRAIN BARRIER DYSFUNCTION

Another possible hypothesis that can account for the pathogenesis of AD is the impairment of the BBB.¹⁹⁸ It is known that cerebral blood vessels undergo profound changes with aging. These changes continue and are exacerbated in AD and have led to intensive research into the properties of the BBB. The BBB, found in all vertebrates, prevents the free diffusion of circulating molecules, leukocytes, and red blood cells into the brain interstitial space and is an essential regulator of the neuronal and glial cell environment. The barrier is formed by the presence of epithelial-like, high-resistance tight junctions that fuse brain capillary endothelial cells together into a continuous cellular layer separating the blood and brain.¹⁹⁹ The disruption of tight junctions that are found in endothelial cells results in altered transport of molecules between the blood and brain and the brain and blood, aberrant angiogenesis, vessel regression, brain hypoperfusion, and inflammatory responses, and it can have detrimental effects on synaptic plasticity and neuronal survival. Indeed, reduced microvascular density, increased fragmentation of vessels, increased thickening of basement membranes, increased vessel diameter, and a reduced number of endothelial mitochondria have all been described in AD (reviewed by Zlokovic²⁰⁰).

Disturbances in the BBB have been associated with stroke,¹⁹⁸ cerebrovascular ischemia,¹⁹⁸ hypertension,²⁰¹ and mutations in the ApoE gene.²⁰² The integrity of the BBB in aging and in AD is an area of contention and conflicting results. Given that the majority of AD cases are sporadic and do not have evidence of genetic mutation in APP and thus overproduction of A β , it is thought that the accumulation of A β in AD brains and on blood vessels is due to a deficiency in amyloid clearance from the brain.²⁰³ This can occur because of either deficient efflux of amyloid from the brain or faulty degradation in the CNS that leads to the accumulation of neurotoxic amyloid in the brain (reviewed by Zlokovic²⁰³). There are 2 main receptors that are responsible for amyloid influx and efflux across the BBB. The receptor for advanced glycation end products (RAGE), responsible for the influx of amyloid across the BBB, is a multiligand receptor in the immunoglobulin superfamily found in neurons, microglia, and cerebral endothelial cells. It binds many ligands such as A β , the S100/calgranulin family of proinflammatory cytokine-like mediators, and the high-mobility group of DNA binding protein amphoterin.²⁰⁴⁻²⁰⁵ It is normally expressed at low levels in the brain and is dependent on the presence of its ligands. In AD, RAGE expression is increased several-fold in affected vessels, neurons, and glia.²⁰⁴⁻²⁰⁶ Studies in transgenic mice overexpressing mutated APP as well as RAGE have shown that RAGE is a cofactor for A β -induced neuronal perturbation in AD.²⁰⁷⁻²⁰⁸ RAGE/A β complexes have been shown to decrease CBF²⁰⁷ and initiate oxidative stress by activating microglia.²⁰⁴ In RAGE/APP mice, early abnormalities in spatial learning, accompanied by altered activation of markers of synaptic plasticity and exaggerated neuropathology, were found. These changes were observed approximately 3 to 4 months earlier in comparison with APP mice.²⁰⁸ Moreover, in APP transgenic mice bearing a dominant-negative RAGE construct, there was preservation of spatial learning/memory as well as diminished neuropathological changes.²⁰⁸

Given that the majority of AD cases are sporadic and do not have evidence of genetic mutation in amyloid precursor protein and thus overproduction of amyloid beta, it is thought that the accumulation of amyloid beta in AD brains and on blood vessels is due to a deficiency in amyloid clearance from the brain.

LRP, responsible for the efflux of A β across the BBB, is a member of the low-density lipoprotein receptor family and is a multifunctional scavenger and signaling receptor. Its ligands include biomolecules such as ApoE, APP, A β , α_2 -macroglobulin, tissue plasminogen activator, and lactoferrin.²⁰³ LRP is expressed in brain capillary endothelium and exhibits reduced expression during normal aging and AD.²⁰⁶⁻²⁰⁹ Studies in LRP-deficient mice and AD transgenic mice have demonstrated a significant increase in the cerebral amyloid load and parenchymal plaques in comparison with controls.²⁰⁶⁻²¹⁰⁻²¹¹

Although BBB impairment is more commonly associated with VaD than AD, studies in transgenic mice and in humans raise the possibility that BBB dysfunction may be more prevalent in AD than previously believed. Ujii *et al.*²¹² reported that there was increased permeability in the BBB of Tg2576 AD mice in comparison with age-matched controls at 10 months of age as the signs of the disease became manifest. Moreover, the increase in BBB permeability was evident as early as 4 months of age, prior to disease onset and plaque deposition.²¹² Further evidence supporting the involvement of the BBB in AD pathogenesis can be seen in studies focusing on the immunization of mice and humans with amyloid peptides and antibodies. In many cases, microhemorrhages occurred in mice after immunization²¹³⁻²¹⁴; however, the presence of these lesions was antibody-independent. In another A β immunization study that focused on a more global degree of BBB status, it was reported that immunization with A β appears to repair the damage to the BBB and may even prevent further disease progression.²¹⁵ Human studies have also shown an association

between BBB impairment and AD. In a small cohort of patients diagnosed with probable AD, BBB impairment was a stable characteristic, as determined by cerebrospinal fluid albumin levels and cerebrospinal fluid/plasma immunoglobulin G levels.²¹⁶ Interestingly, this impairment was not associated with vascular factors, ApoE status, or age, and this suggests that BBB impairment in AD may be due to processes distinct from VaD. Recently, Farrall and Wardlaw²¹⁷ performed a systematic review of the literature on human clinical studies and found that BBB permeability increases in normal aging and is even more pronounced in patients with dementia and AD. It is important to note that there is significant heterogeneity between studies, and thus more data are needed to clearly resolve this issue.

Although blood brain barrier impairment is more commonly associated with vascular dementia than AD, studies in transgenic mice and in humans raise the possibility that blood brain barrier dysfunction may be more prevalent in AD than previously believed.

OXIDATIVE STRESS

During normal aging and AD, there is a reduction in resting CBF as well as dysfunction in the mechanism that regulates cerebral circulation. This dysfunction results in part from the loss of endothelial mitochondria and a thickening of the vascular basement membrane.⁸ Growing evidence appears to implicate oxidative stress as the common factor rendering the brain vulnerable to environmental insults, and it has been shown to play an important role in the pathogenesis of AD (reviewed by Mariani *et al.*²¹⁸). Many of the risk factors that play key roles in AD are associated with vascular oxidative stress; however, whether oxidative stress precedes the onset of AD or exacerbates the pathology is controversial. Oxidative stress, manifested by increased protein oxidation, lipid peroxidation, decreased polyunsaturated fatty acids (PUFAs), and the presence of reactive oxygen species (ROS), is a major characteristic of AD. ROS have long been implicated in the pathogenesis of AD and occur in response to inflammation, injury, and exceedingly low CBF, leading to cell injury and death. There are several sources of vascular ROS, but reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is thought to be one of the main enzymes involved in the production of vascular ROS.^{219–221} NADPH is a superoxide-producing enzyme and has been implicated in several oxidative stress conditions including hypertension, and it is significantly activated in AD brains.²¹⁹ It has been shown that the presence of excess superoxide ($O_2^{\cdot-}$) radicals in the brains of APP mice is due to the activity of NADPH oxidase, and the inhibition of NADPH activity by either pharmacological inhibitors or the inhibition of the NADPH oxidase complex assembly blocked the production of ROS and cerebrovascular dysfunction induced by $A\beta$ and aging.^{90,222} Furthermore, a mouse model lacking the catalytic subunit gp91phox (Nox2) of the enzyme showed a decrease in ROS production, did not show signs of oxidative stress, and appeared to be protected from alterations in the vasculature such as endothelial relaxation and hyperemia.^{221,223,224} When APP-overexpressing mice that contained a deletion of Nox2 were compared to APP mice that expressed Nox2, there was no oxidative stress, cerebrovascular dysfunction, or behavioral deficits.²²³

Growing evidence appears to implicate oxidative stress as the common factor rendering the brain vulnerable to environmental insults, and it has been shown to play an important role in the pathogenesis of AD.

Accumulated oxidative stress affects nitric oxide (NO) function to relax endothelial vasculature, increases vascular endothelial permeability, and further reduces CBF.⁸ These are thought to occur because of the reduced bioavailability of NO and the increase in free radicals. When superoxide dismutase (SOD), a potent antioxidant, was incubated in vitro

with endothelial cells from aged APP mice, there was a complete restoration of cerebral vascular function.²²⁵ In vivo, when SOD was applied topically to the cerebral cortex of APP transgenic mice, there were no deficits in endothelial function.²²⁶ Moreover, mice expressing both APP and SOD-1 have no endothelial cell deficits.²²⁶ These pronounced oxidation-induced pathological effects in patients with AD and transgenic mice provide evidence that oxidative stress precedes the onset of AD pathology. On the other hand, brains of postmortem AD patients show increased levels of oxidative stress in comparison with non-AD patients, specifically in vascular lesions and mitochondria,⁸ and they provide evidence that oxidative stress further attenuates the pathology of AD, whereas levels of antioxidants and antioxidant enzymes are decreased in brains of postmortem AD patients. Levels of PUFAs are also decreased in the brains of AD patients.⁸ There is evidence that PUFAs, arachidonic acid, and docosahexaenoic acid are more vulnerable to attack by ROS, and this provides further evidence that oxidative stress exacerbates the pathology of AD. DNA, RNA, and protein oxidation levels are increased in the brains of AD patients, and oxidative stress markers such as AGEs have been found in A β plaques and NFTs.⁸ Oxidative stress in mitochondria leads to several downstream effects, as mitochondria become less efficient at producing adenosine triphosphate and more efficient at producing ROS; this ultimately results in oxidative stress to the nucleus and cell death.⁸

Amyloid peptides and plaques have been linked to degenerative neurons and to areas high in oxidative stress, and it has been suggested that amyloid is able to induce cerebrovascular dysfunction via oxidative stress mechanisms (see Varadarajan *et al.*²²⁷). In vitro studies have shown that the application of A β peptides to endothelial cells results in the generation of large quantities of O₂⁻, enhances the rates of apoptosis and necrosis, and prevents the formation of capillary networks.^{225·228·229} In mice that overexpress mutated forms of APP, signs of oxidative stress in the vasculature are evident even before plaques have formed.²³⁰ The A β -induced oxidative stress impairs cerebrovascular dilatory responses, alters autoregulation and functional hyperemia, and causes cerebral hypometabolism.^{224·226·230} Moreover, cerebral vasculature dysfunction can be rescued in aged APP mice treated with antioxidants.²³¹ Another model names A β peptide bound to redox metal ions as the culprit of neurotoxicity found in AD. Varadarajan *et al.*²²⁷ proposed that small soluble A β aggregates insert into the membranes of neurons or glia and generate oxygenated free radicals that cause protein oxidation and lipid peroxidation. This, in turn, causes membrane disruption, which leads to cellular dysfunction, including perturbation of calcium homeostasis, transporter function, and activation of apoptotic signaling pathways.

Oxidative stress is associated with negative pathology related to a reduction in CBF, detriments to NO and endothelial vasculature, A β plaques, and ultimately cell death. Because of the vast role of oxidative stress in preceding or exacerbating AD pathology, with the help of antioxidants, it can act as a major therapeutic target in the onset and pathology of AD.

CONCLUSION

At first glance, the relationship between vascular risk factors and AD may appear contradictory, as vascular risk factors and the presence of vascular disease were considered exclusion criteria for the clinical diagnosis of AD. However, recent studies have suggested that these co-occurrences, both common in the elderly and believed to occur by chance, have more pathological significance. Studies have suggested that microvascular disorder and dysfunction can contribute to cognitive decline and pathology associated with AD in a synergistic manner and can exacerbate the clinical symptomatology of AD. Although there are still conflicting views on the evidence put forth from the many epidemiological studies, it is agreed that there does indeed appear to be a relationship between many vascular risk

factors, vascular dysfunction, and cognitive decline. These data have led to the vascular hypothesis for AD, which proposes that dysfunction of the neurovasculature and nonneuronal neighboring cells contributes to the pathogenesis of dementia and AD. However, as the exact relationships between (and potentially shared mechanisms of) vascular risk factors, vascular dysfunction, and neuronal degeneration remain poorly understood, it is difficult to state definitive conclusions. More prospective studies on human patients with longer follow-up periods as well as studies in transgenic mice are needed to resolve this issue. Further exploration of the roles of vascular risk factors and vascular dysfunction in the pathogenesis of AD and cognitive decline may provide a better understanding of the molecular mechanisms and sharper therapeutic targets for intervention in the future.

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Abbreviations

Aβ	Amyloid beta protein
ACE	Angiotensin converting enzyme
AD	Alzheimer's disease
AGE	Advanced glycation end product
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
ATI	Angiotensin II type 1
BACE	β -Site amyloid precursor protein cleavage enzyme
BBB	Blood-brain barrier
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CBF	Cerebral blood flow
CDR	Clinical dementia rating
CI	Confidence interval
CNS	Central nervous system
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
LRP	Low-density lipoprotein receptor-related protein
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NFT	Neurofibrillary tangle

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association
NO	Nitric oxide
Nox2	gp91phox
OR	Odds ratio
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PUFA	Polyunsaturated fatty acid
RAGE	Receptor for advanced glycation end products
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SHEP	Systolic Hypertension in the Elderly Program
SOD	Superoxide dismutase
Syst-Eur	Systolic Hypertension in Europe
TC	Total cholesterol
VaD	Vascular dementia

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Table 1

Summary of Hypertensive Therapy Studies in AD.

Reference	Study Setting	Participants and Follow-Up	Treatment	Main Result
232	SHEP	4736 people, ~72 years at baseline, followed up to 4.5 years	Diuretic $\pm$ β -blocker $\pm$ hypertensive drug or placebo	No significant effect of treatment on AD risk
233, 234	MRC trial	2584 people, ~69 years at baseline, followed up to 3.9 years	Diuretic or β -blocker or placebo	No significant effect of treatment on AD risk
235, 236	SCOPE	4964 people, ~76 years at baseline, followed up to 4.5 years	ATI receptor agonist or placebo (candesartan $\pm$ hydrochlorothiazide versus placebo)	Significantly less cognitive decline in the treated group
237	PROGRESS	6105 people, ~64 years at baseline, followed up to 4.5 years	ACE inhibitor $\pm$ diuretic or placebo (perindopril $\pm$ indapamide versus placebo)	Decreased the rates of dementia in actively treated patients
238–240	Syst-Eur study	2418 people, ~68 years at baseline, followed up to 2 years	Calcium channel blocker $\pm$ ACE inhibitor $\pm$ diuretic or placebo (nitrendipine $\pm$ enalapril $\pm$ hydrochlorothiazide versus placebo)	Decreased the risk of dementia by 55%

NOTE: This table is a summary of randomized, double-blind, placebo-controlled studies describing the association between hypertension and antihypertensive therapy in relation to AD and has been adapted from Takeda *et al.*¹ and Poon.²⁴¹

Abbreviations: ACE, angiotensin converting enzyme; AD, Alzheimer's disease; ATI, angiotensin II type 1; MRC, Medical Research Council; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe.

Table 2

Studies Describing the Association Between Hypotension and Dementia.

Reference	Study Setting	Participants and Follow-Up	Outcomes	Main Results
89	Gothenburg H-70 and Rotterdam studies	382 people, 70 years, followed up to 15 years	Dementia, AD; DSM-III, NINCDS-ADRDA	BP was inversely related to the risk of dementia in patients taking antihypertensive drugs.
81	East Boston study	378 people, ≥ 65 years, followed up to 3 years	AD; NINCDS-ADRDA	SBP ≥ 160 mm Hg versus 130–139 mm Hg (OR = 0.3, 95% CI = 0.1–0.9); DBP < 70 mm Hg versus 80–89 mm Hg (OR = 1.8, 95% CI = 0.3–4.3)
79	Kungsholmen study	1642 people, ≥ 75 years	Dementia, AD; DSM-III	People with DBP < 70 mmHg or SBP < 140 mm Hg had a higher risk of dementia and AD.
88	Chicago Health and Aging Project	709 people, ≥ 65 years	AD; NINCDS-ADRDA	People with DBP < 70 mmHg or SBP < 130 mm Hg had a higher risk of dementia and AD.
242	OCTO-Twin study	599 people, ≥ 80 years at baseline, mean follow-up of 4 years	Dementia; DSM-III, MMSE	Lower SBP and DBP were associated with cognitive decline.

Abbreviations: AD, Alzheimer's disease; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; OR, odds ratio; SBP, systolic blood pressure.