


# Pathophysiological Association of Alzheimer's Disease and Hypertension: A Clinical Concern for Elderly Population

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**Abstract:** Alzheimer's disease (AD), the most common cause of dementia and the fifth leading cause of death in the adult population has a complex pathophysiological link with hypertension (HTN). A growing volume of published literature on a parallel elevation of blood pressure (BP), amyloid plaques, and neurofibrillary tangles formation in post-middle of human brain cells has developed new, widely accepting foundations on this association. In particular, HTN in elderly life mediates cerebral blood flow dysfunction, neuronal dysfunction, and significant decline in cognitive impairment, primarily in the late-life populace, governing the onset of AD. Thus, HTN is an established risk factor for AD. Considering the impact of AD, 1.89 million deaths annually, and the failure of palliative therapies to cure AD, the scientific research community is looking to adopt integrated approaches to target early modified risk factors like HTN to reduce AD burden. The current review highlights the significance and impact of HTN-based prevention in lowering the AD burden in the elderly by providing a comprehensive overview of the physiological relationship between AD and HTN with an in-detail explanation of the role and applications of pathological biomarkers in this clinical association. The review will gain worth in presenting new insights and providing inclusive discussion on the correlation between HTN and cognitive impairment. It will increase across a wider scientific audience to expand understanding of this pathophysiological association.

**Keywords:** Alzheimer's disease, hypertension, elderly population, clinical biomarkers

## Introduction

Alzheimer's disease (AD) is one of the leading age-related brain diseases in older adults and imposes a high impact. There are more than 1.89 million deaths annually, with estimated healthcare costs of \$305 billion.<sup>1,2</sup> The high prevalence of this chronic age-related disease is raising clinical concerns in the elderly population. For example, 6.5 million Americans over 65 lived with AD and other dementia-related illnesses, which caused 121,499 deaths in 2019.<sup>3</sup> Unfortunately, this disease has no definitive cure, and the available drugs only relieve the patients from symptoms.<sup>4</sup> This lack of specific treatment and the failure of available palliative therapies for AD have increased the mortality rate among older people, especially in low-income countries.<sup>5</sup> In addition, clinically, there is no obvious mechanism for mid-life AD development.

Despite the many physio-clinical strides made in the past two decades, there is still enough to investigate responsible factors and their mechanism of action in AD development.<sup>6</sup> For most of history, researchers have classified the driving forces in the onset of AD pathology into two main groups: non-modifiable risk factors (aging, sex and genetics) and modifiable risk factors.<sup>7,8</sup> In addition, the educational-learning level, smoking, high body weight, diabetes, and hypertension (HTN) are interlinked with the pathology of the disease.<sup>9</sup>

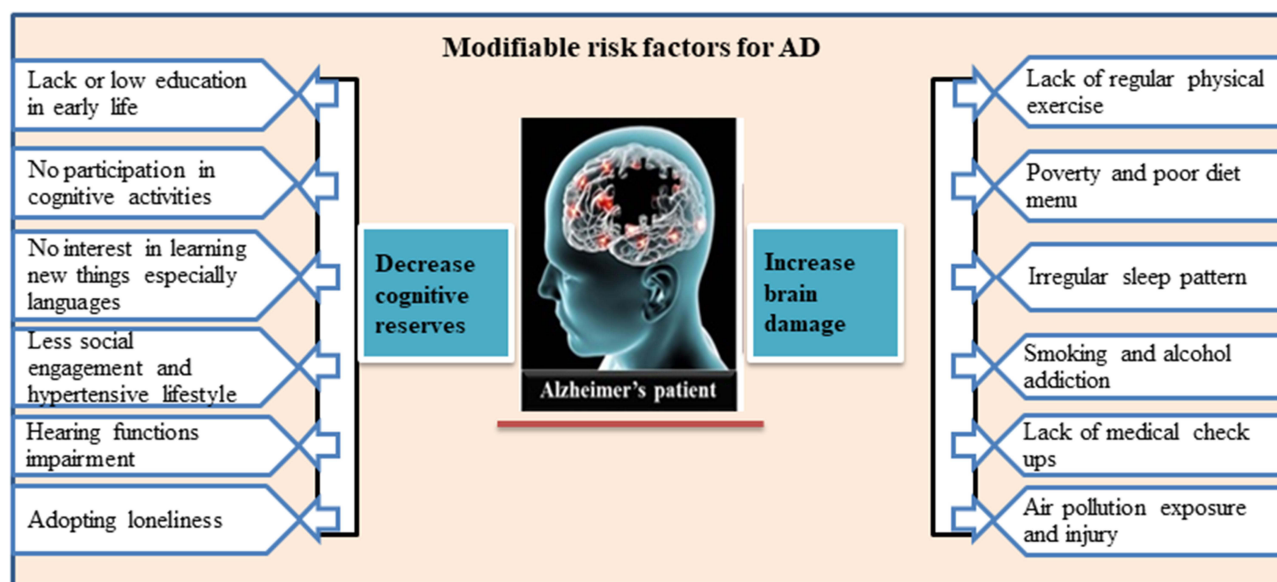
It has been observed that intervention of modifiable risk factors could prevent the up to 35% of AD-related dementia cases.<sup>10</sup> In addition, positive lifestyle changes like diet and exercise can prevent cognitive functioning deterioration.<sup>11</sup> With some limitations, many studies have concluded that strategic preclinical intervention may prevent the onset and development of AD if the risk factor is the cause and slow down the progression of the disease if the risk factor is a symptom.<sup>12,13</sup>

In particular, HTN is the most decisive factor in all modifiable risk factors mediating AD development.<sup>14,15</sup> Targeting HTN has a considerable impact on lowering AD in the elderly population. **Figure 1** explains the modifiable risk factors-treatable medical conditions and lifestyle choices that play a role in AD onset.

Today's population aged 65 and over is expected to grow rapidly, and older people live worldwide. Unfortunately, this rapid population growth has birthed several socioeconomic and psychological issues which impose adverse severe health outcomes on the elderly population.<sup>16–18</sup> With these HTN depression-related risk factors, late-age exacerbates AD and dementia risk in this population segment effectively.<sup>19,20</sup> Furthermore, these conditions develop complex, positively correlated clinical associations between HTN and AD development.<sup>21,22</sup> The relationship between HTN and AD development in older people is an understood research topic. Therefore, this review concentrates on and summarizes the studies on AD development and the mediating role of HTN in this disease with associated risk factors. We aimed to highlight the significance and impact of HTN-based prevention in lowering the AD burden in the elderly. Furthermore, this literature review might encourage and assist researchers and clinicians in collaborating in designing various experimental approaches to explore the clinical links between AD development and HTN.

## Pathological and Molecular Considerations for the Brain in the Alzheimer's Disease State

As previously said, AD is a clinically diagnosed disorder followed by amyloid plaques and neurofibrillary tangles in neurons, ultimately leading to the loss of neurons in patients with AD, presenting various clinical symptoms that change over time.<sup>23,24</sup> Signs and progression from mild to moderate and moderate to severe vary depending on the damage to neurons across multiple brain areas.<sup>25</sup> A healthy adult brain contains 100 trillion synapses.<sup>26</sup> They let impulses traverse swiftly across the brain's neuronal circuits, establishing the cellular basis of memories, thoughts, feelings, emotions, movements, and talents.<sup>27</sup> Clinically, AD is characterized as the accumulation of the proteins fragment, beta-amyloid (referred to as beta-amyloid plaques) outside neurons and forming an aberrant version of the protein tau (referred to as tau tangles) inside neurons.<sup>28</sup> These brain alterations halt the communication process of brain machinery.<sup>29</sup> Beta-amyloid



**Figure 1** Figurative description of a modified risk factor for AD developments.

plaques cause cell death by interfering with neuron-to-neuron transmission at synapses, whereas tau tangles prevent nutrition and other critical chemicals from entering neurons. When beta-amyloid levels reach a threshold level, aberrant tau spreads throughout the brain.<sup>30</sup> These alternations ultimately induce cognitive impairment. Therefore, they are considered the gold standard for pathological AD diagnosis.

The amyloid hypothesis best describes the molecular profile of AD development. It explains that the cleaving of an enzyme called beta-secretase (BACE-1) or amyloid initiates the production of the toxic amyloid  $\beta$  ( $A\beta$ ) of AD-related pathologies.<sup>31,32</sup> In the beginning, the C-terminus of BACE-1 contributes to the breakage of amyloid precursor protein-APP that lead to the amyloidogenic-APP processes to form soluble amyloid precursor protein (sAPP).<sup>33,34</sup> This soluble amyloid penetrates the neuronal membrane and eventually binds with sAPP death receptor-6 (DC-6), further activating caspase (caspase-6) in the cell.<sup>35</sup> Caspases that have been activated then launch apoptotic pathways and cause neuronal death.<sup>36,37</sup>

In this amylogenic pathway, after the breakage of remaining membrane-bound APP, four monomer fragments ranging in length from 40 to 42 amino acids (A40/A42) formed, in which A40 dominates the formation of produced monomers.<sup>38</sup> The aggregation of monomers outside the neuron membrane forms thick, insoluble oligomers or senile plaques.<sup>39</sup> Misfolded peptides are created in a variety of conformations. They are released into the extracellular environment by donor neurons as naked proteins or vesicles called exosomes, which are then picked up by receptor-mediated endocytosis by receiver neurons.<sup>40</sup> A40/A42 binds to several receptors on the neuron's membrane. It influences the synaptic transmission via inhibiting ion channels and leads to a disorder in the tau protein function (a predominant protein of brain cells working as a stabilizer of the internal skeleton of nerve cells). Tau pathology may be produced by independent regulators such as apolipoprotein-E (ApoE), cholesterol metabolism, receptor-mediated endocytosis, and microglial activation.<sup>41-43</sup> The creation of the toxic  $A\beta$  plaques in neurons drives the release of chemokines and cytokines involved in generating reactive oxygen species (ROS).<sup>44,45</sup> This causes mitochondrial oxidative stress and triggers a cascade of apoptotic caspases via the synthesis of p53, Bad, and Bax, resulting in lipid peroxidation, membrane damage, and neuronal death.<sup>46,47</sup>

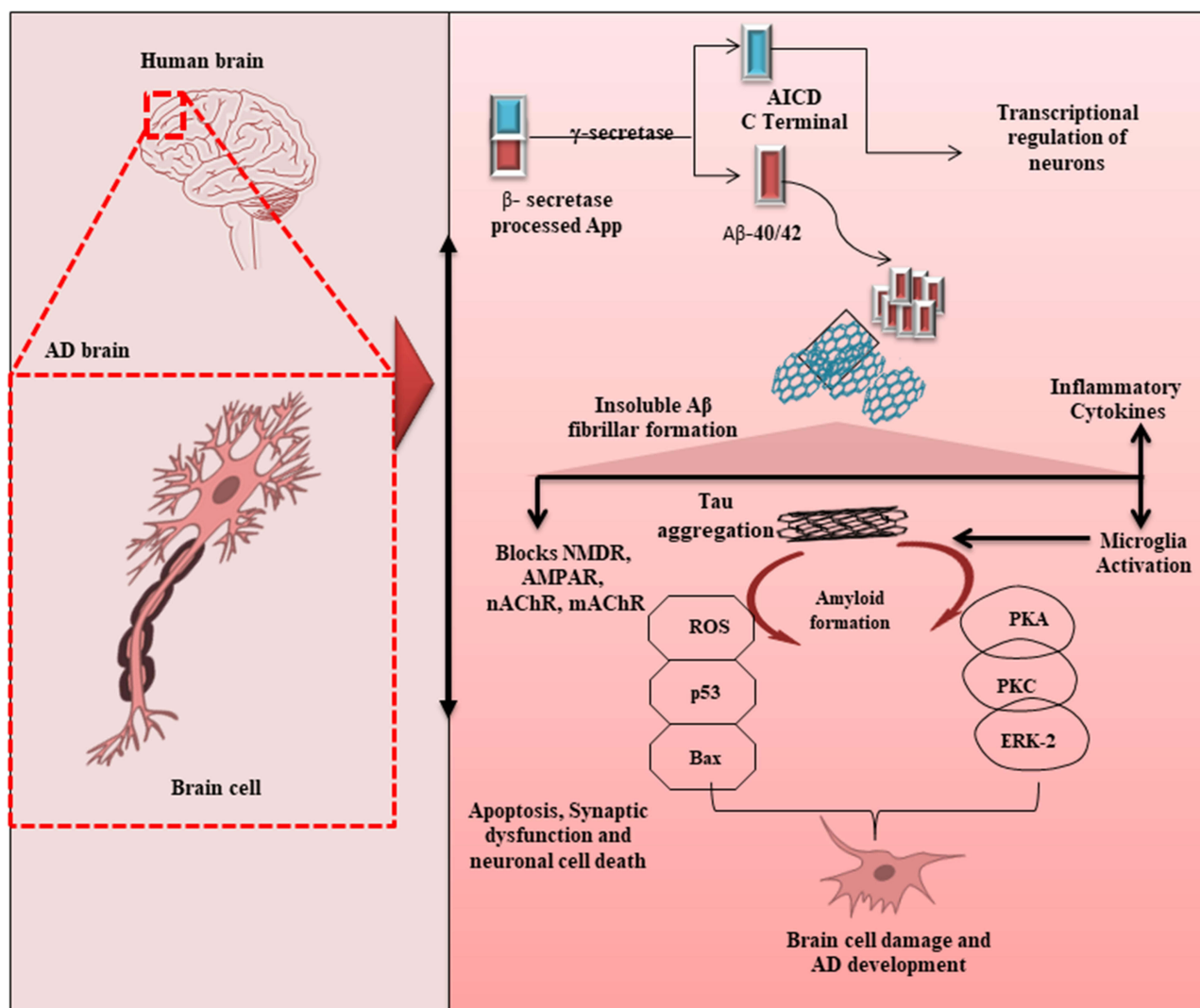
Moreover, amyloid formation stimulates protein kinase C (PKC), protein kinase A (PKA), and Extracellular Signal-Regulated Kinases 2 (ERK2), leading to tau hyperphosphorylation and neurofibrillary tangle development.<sup>48,49</sup> The activation of protein kinase B (PKB) or Akt to activate glycogen synthase kinase-3 (GSK3) causes tau hyperphosphorylation.<sup>50,51</sup> The activation of cyclin-dependent kinases 5 (CDK5) and P25 by P35-calpain increases tau hyperphosphorylation and neuronal death (Figure 2).<sup>51</sup>

Apart from the amyloid hypothesis, other molecular pathways contribute to AD development. Memory and learning are governed by cholinergic neurotransmitters like acetylcholine. It is an essential neurotransmitter for proper synaptic transmission. An enzyme known as acetylcholinesterase (AChE) located in neuromuscular junctions, degrades acetylcholine into choline and acetate, leading to the end of synaptic transmission.<sup>52,53</sup> Cholinergic system deterioration has been observed in AD when AChE activity significantly reduces acetylcholine levels.<sup>54</sup> Anatomically, the limbic lobe regions in the AD brain frequently show mild atrophy.<sup>55</sup> In addition, most AD patients' frontal and temporal cortices display ventricular enlargement and gyri atrophy, although the main motor and somatosensory cortices are intact.<sup>56</sup> Altogether, these molecular and anatomical events are highly relevant in AD-related pathologies. However, we still lack the exact mechanism and driving forces behind the initiation of these molecular cascades.

## Aging-Dementia and AD

Human aging is known to decrease brain weight. It is connected with gyri atrophy, a reduction in the number of neurons and the amount of white matter. In addition, AD-related drivers like the development of amyloid deposits, granulovacuolar degeneration (GVD), and Hirano bodies (Hb) in the hippocampus change with age.<sup>57,58</sup> Furthermore, many amyloid plaques and neurofibrillary tangles, the two most well-known pathological markers of AD, are detected in the aging human brain, even those without dementia.<sup>59</sup>

Clinical observations have shown that in the aging brain, argyrophilic grain disease (AGD) and dementia diseases reflect elderly- AD-like signs.<sup>60</sup> Although depending on many factors, including the patient history of visiting neurology or psychiatry clinics, the clinical patterns of AGD vary, the clinical outcomes at the neuropsychiatric clinic tend to appear



**Figure 2** Molecular levels factors involved in neural death—from  $\beta$ -secretase processing to synaptic dysfunction and neuronal cell death in AD development.

in a front temporal dementia pattern, similar to AD.<sup>61,62</sup> Similarly, memory studies in clinics on elderly GVD brain and primary age-related tauopathy (PART) revealed a clinical characteristic similar to moderate cognitive impairment or AD.<sup>63,64</sup>

These studies on the association of this aging-related dementia (AGD and PART) and AD show enough resemblance to tau protein accumulation and rise with age. However, the pathological results and clinical symptoms are not always correlated with age, dementia, and AD onset. Therefore, new approaches are required to investigate this AD association regarding later-age dementia-related neuropathological issues and the disease itself.

## Hypertension and Its Prevalence

Clinically, HTN is a condition of high systolic blood pressure (BP)  $\geq 140$  mmHg that has affected 1 billion individuals worldwide.<sup>65</sup> HTN prevalence increases with age, and if untreated, it leads to serious health risks, including heart disease and stroke.<sup>17,66</sup> Symptoms of HTN include early morning headache, nose bleeds, irregular rhythms, vision changes and buzzing in the ears.<sup>67</sup> However, lifestyle interventions like a healthier diet with less salt, routine exercise, and taking medication on advice effectively reduce the risk of HTN.<sup>68</sup>

According to current global statistics, approximately 1.13 billion adults had HTN in 2015, predicted to increase to 1.56 billion in 2025.<sup>69,70</sup> The prevalence of HTN is high in low and middle-income countries.<sup>71</sup> Comparative data shows

that there were 333 Million adults with HTN in high-income countries in 2000, while 654 Million were in low-and middle-income countries (LMIC).<sup>71,72</sup> The senior population suffers a disproportionate share of the burden of HTN due to its increasing prevalence and associated morbidity and mortality, which raise a serious concern.<sup>73,74</sup>

In today's society, systemic HTN is a growing public health risk. It is a well-known cause of several potentially deadly outcomes, such as cerebrovascular accidents, coronary artery disease, heart failure, peripheral atrial problems, renal failure, and AD development in the elderly.<sup>75–77</sup> Furthermore, HTN is recognized as a major modifiable risk factor for cardiovascular disease (CVD), accounting for about 45% of global CVD morbidity and mortality in 2010, with 9.4 million deaths documented globally.<sup>78,79</sup>

In addition, HTN is associated with a substantial financial burden. This burden comprises direct healthcare costs related to HTN management, such as medications, laboratory tests, clinical visits, and other expenses. The global financial burden of HTN was projected to be roughly \$ 370 billion, accounting for around 10% of global healthcare expenditure.<sup>80,81</sup> According to the US national database, the average yearly adjusted extra cost for patients with HTN was \$1920 more than those without HTN.<sup>82–84</sup> The American Heart Association estimates that the direct cost of HTN in the United States will exceed \$200 billion by 2030.<sup>85</sup> The rising trends of HTN worldwide and its impact on human healthcare expenditure are challenges for policymakers. They emphasize implementing evidence-based clinical recommendations and public health strategies to lessen HTN's worldwide impact.

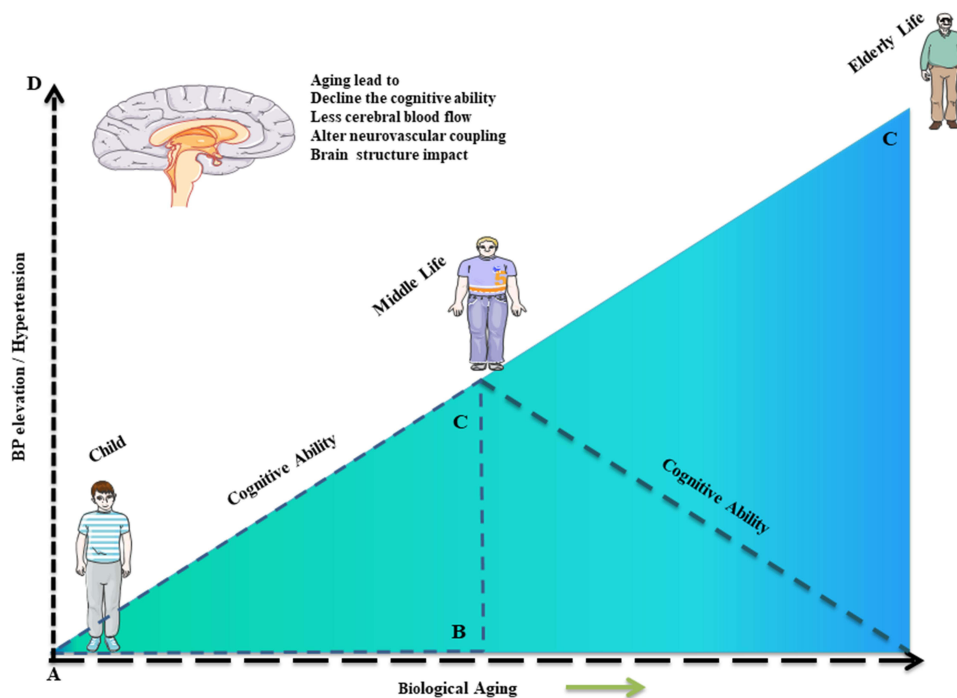
## Chronic Hypertension and Cerebrovasculature Disease

Over the life span, BP and age are connected in somewhat distinct ways: systolic BP tends to grow with age, but diastolic BP peaks around age 50 and then drops. As increasing age causes an elevation in BP through psychological/behavioral interventions of the brain,<sup>86,87</sup> it also determines the HTN.<sup>88</sup> Extending the given viewpoint of growing age and HTN development, it is highly significant to investigate how HTN relates to cerebrovasculature illness and find common risk factors mediating cognition decline in the elderly population.

Chronic HTN positively correlates with a cerebrovasculature state, stroke, cognitive dysfunction and dementia. Given the premise that natural aging raises BP, it has been observed that HTN and aging have comparable effects on the vasculature, including cerebrovasculature and vascular structural alterations.<sup>89,90</sup> Clinical findings reveal that HTN thickens the vascular wall and lowers the number of vessels in the brain. Furthermore, HTN progress leads to the narrowing of pial and intracerebral capillaries in the latter stages of HTN.<sup>91</sup> Chronic exposure to these conditions eventually overwhelms brain defenses and interferes with brain function, leading to primary dementia and cerebrovasculature disease, predominantly stroke.<sup>92,93</sup> With the coexistence of our perspective and described findings, [Figure 3](#) clearly shows that brain functional and structural changes with age are also connected with high BP. These findings suggest that the progression of HTN causes specific apparent aging effects over time and that the condition affects the brain far before consequences such as stroke.

## Chronic Hypertension and Alzheimer's Disease

As mentioned above, HTN is the most decisive modifiable risk factor for cerebrovascular disease, leading to stroke and dementia. Available knowledge on the association between HTN and high BP strongly linked HTN to stroke, vascular dementia and increased risk of AD.<sup>94,95</sup> Pathogenic pathways, including atherosclerosis and arteriolosclerosis with stroke and cerebral ischemia, occur in HTN patients, leading to a significant decline in cognitive function.<sup>96</sup> Based on the clinical outcomes of high BP and cognitive decline, large-scale clinical studies demonstrated a complex link between cognitive function and progressive levels of HTN.<sup>97,98</sup> The severity of HTN to the brain depends on both stage of the disease and the age of the patient; higher risk of dementia at an elderly age as compared to young ones (65–75), and it is not effective at the age of 75–85 or > 85.<sup>99,100</sup> Furthermore, clinical data of AD patients also support this association as a directional cue. Patients in the early stage of AD show high BP values, while late-life AD patients have more severe HTN complications with substantial cognitive decline.<sup>101</sup> These findings further support that HTN-based cognitive decline is lower and slow in late life than young-old age.<sup>102,103</sup> Furthermore, evidence from female reproductive time and HTN studies show females are more prone to HTN-based cognitive decline and AD onset than men.<sup>104–106</sup>



**Figure 3** Depicts the consequences of biological aging and high blood pressure on a person's life over time. Both are linked to cognitive, functional, and structural brain damage (cognitive loss, reduced cerebral blood flow, altered distribution of blood flow in response to the cognitive and physiological challenge, reduced grey matter volume, presence of white matter high intensities, greater diffusion within white matter tracts, more porous blood brain barrier, and presence of reactive oxygen species).

Although some well-established correlations between vascular dementia and HTN are highly relevant to AD development, they have not been thoroughly studied to answer the ambiguous factors, such as severity, type (systolic or diastolic), duration, and age, and these need additional large-scale clinical data validation.

## Pathogenesis of Hypertension and Alzheimer's Disease: Experimental Findings

Given the fast accumulating evidence supporting the vascular hypothesis regarding AD onset, it has been well characterized that the early stage of AD is predominantly a microvascular condition, narrowing of brain arteries.<sup>107,108</sup> Furthermore, according to this theory, cerebrovascular dysfunction may be the first and most aberrant indicator of AD development.<sup>109,110</sup> In line with these findings, several population-based cross-sectional and longitudinal studies have been published depicting the relationships between vascular risk factors, incidence, and AD progression in older people.<sup>111–113</sup> In particular, among all these vascular risk factors, HTN is the most important leading factor in AD development. Furthermore, it is recognized as a critical factor for doubling the risk rate of AD in older adults.<sup>114,115</sup>

Through advancements in experimental procedures evaluating HTN as a risk factor, several modifications and expansions to the original vascular hypothesis of AD have been added. First, it accelerated the HTN-induced microvascular injury in different pathological manifestations of AD ranging from cerebral microhemorrhages to blood-brain barrier disruption and subsequent neuroinflammation.<sup>116,117</sup> It is noted that neuroinflammation plays an essential role in the development of both HTN and AD. For example, chronic neuroinflammation in the paraventricular nucleus of the hypothalamus induced by long-term high salt intake could lead to HTN in the Dahl salt-sensitive rat model.<sup>118,119</sup> On another side, HTN could also induce microvascular inflammation in the brain. So, cerebral microvascular inflammation likely accelerated cognitive impairment in the elderly with AD under HTN.<sup>120</sup>

According to the amyloid cascade hypothesis concerning AD, higher levels of A $\beta$  cause progressive, multidimensional cerebrovascular damage, which plays a role in forming early-stage pre-plaque cognitive dysfunctions and the disease's later progression.<sup>121,122</sup> In particular, A $\beta$  production, processing, and deposition in neurons and cerebral

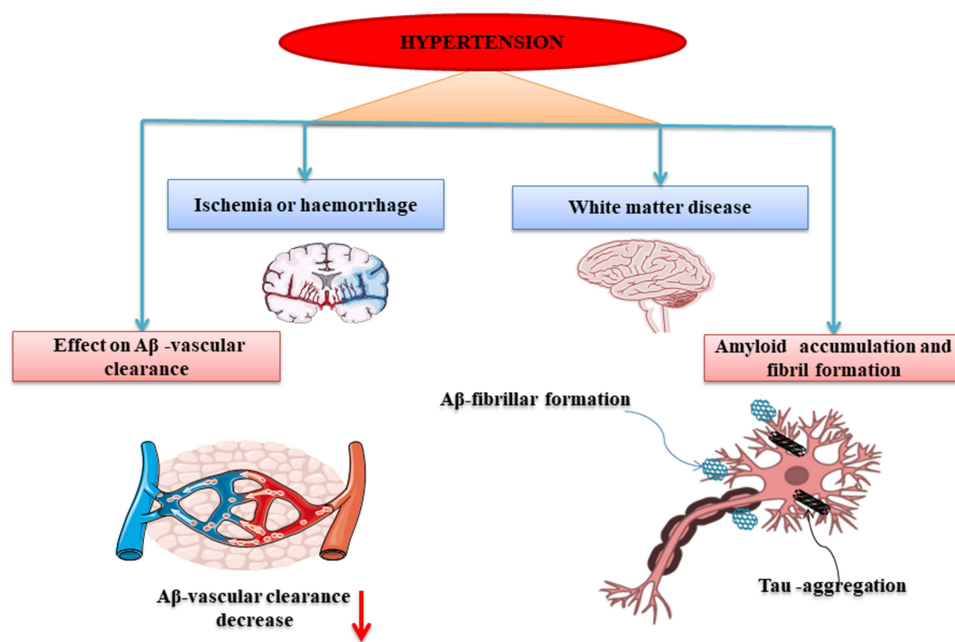
microvessels play a critical role in AD development. A large amount of genetic and biochemical evidence supports this idea.<sup>123,124</sup>

Recapitulating the human clinical data on AD pathy from both the vascular theory and the amyloid hypothesis of AD, it articulately suggests that HTN exacerbates A $\beta$ -induced cerebrovascular damage in AD, worsening the disease and accelerates its progression.<sup>125,126</sup> Recently, critical insights into the pathophysiological mechanism have been provided to explain the links between A $\beta$  deposition, HTN, and AD development.<sup>15,127</sup> According to experimental research in transgenic animal models with angiotensin II infusion, long-term HTN consistently enhances microvascular amyloid deposition in Tg2576 mice and accelerates beta-secretase APP cleavage.<sup>128,129</sup>

Transverse aortic-coarctation mediates the A $\beta$  deposition in the brain. In the mouse model, it has been evaluated that HTN is associated with transverse aortic coarctation in the brain and enhances the A $\beta$  deposition, further promoting cognitive decline. It has also been observed that A $\beta$  deposition was manifested within four weeks after induction of HTN to the brain, suggesting that triggering of the molecular process contributes to the pathogenesis of AD.<sup>130,131</sup> Thus, HTN is enough to trigger cerebrovascular impairment.<sup>132,133</sup> In another novel study, the amyloidogenic gene is over-expressed in the brain of aging and HTN-induced mouse.<sup>134</sup> Furthermore, activating the receptor for advanced glycation end-products (RAGE) in cerebral microvessels is also thought to be a route to the processes of HTN-induced AD development. This idea is similarly important in elucidating how HTN exacerbates AD pathology,<sup>68,69</sup> concluding that blocking one or more of these biological targets might delay the emergence of microvascular-related AD impairments.

Tau pathology, in addition to A $\beta$  pathology, is regarded as a substantial risk factor for AD.<sup>135</sup> Despite significant research still lacking, new studies have revealed vital insights into the molecular link between HTN and tau hyperphosphorylation and miss-folding in AD<sup>136,137</sup> (Figure 4). The A $\beta$  levels in cerebrospinal fluid (CSF) in a cohort of AD Neuroimaging Initiative patients were investigated. Researchers discovered that lobar microbleeds caused by HTN were associated with increased longitudinal cognitive decline and a higher likelihood of having defective CSF levels of phosphorylated tau proteins.<sup>138,139</sup>

It has been observed that A $\beta$  deposition produced intraneuronal tau hyperphosphorylation in hypertensive, non-transgenic, and spontaneously hypertensive stroke-prone mice and rat models. In addition, findings revealed that HTN induces cerebral small vessel disease (CSVD), meaning that CSVD is associated with HTN and causes a rise in brain A $\beta$ .<sup>140</sup> Kurata et al observed that telmisartan treatment decreased the number of A $\beta$  and phospho-tau-positive neurons



**Figure 4** A detailed description of the pathophysiological association between Alzheimer's Disease and hypertension.

and neuro-inflammation markers.<sup>141</sup> Clinical observations in cerebrovascular AD and progressive supranuclear palsy (PSP) patients highlight that aberrantly misfolded tau may accumulate in neurons in AD and tau pathology.<sup>142</sup>

In line with our current review, the cited studies above have provided fundamental key aspects on the association of AD pathy and HTN severity. These notable findings can be considered fingerprints in designing the new integrated approach to recapitulate the clinical and ex vivo data. Given these findings, it could be rightly postulated that HTN in the elderly population works as the progenitor for the onset of AD pathy.

## Clinical Pathological Biomarkers of AD in HTN

Despite the evidence on the fairly established association of HTN and AD, there are limitations. Therefore, biologists are working to understand the processes behind this relationship to determine if this link directly causes AD-related neuropathy or contributes to cognitive impairment.<sup>143</sup>

To explore this association, approaches based on clinical tests (positron emission tomography, PET; Magnetic Resonance Imaging, MRI) and physiological examinations based on BP, systolic BP, and CSF are adopted to understand better the active biological markers involved in HTN-AD associations. Clinical observations from elderly participants with known vascular risk factors like HTN showed higher levels of amyloid bodies in their brains. Authors proposed that HTN in late life might be a possible direct factor for elevated brain amyloid. However, it needs further exploration.<sup>144</sup> In another study, clinical evidence from PET (focusing on both tau and amyloid) and MRI testing of people over 60 years old revealed that increased vascular risk, particularly HTN, is linked to brain cell shrinkage and neurodegeneration rather than brain amyloid formation.<sup>145</sup> Despite the importance of BP monitoring, BP was not associated with brain amyloid in a late-life neuropathological sample; however, systolic BP has been associated with neurofibrillary tangles.<sup>146</sup>

Similarly, CSF biomarkers suggested HTN was not associated with amyloid; however, it has an association with tau in APOE-4 homozygotes and showed a putative relationship between BP and APOE genotype.<sup>147</sup> Furthermore, the associations between HTN and regional brain shrinkage suggest that high BP may play a role in AD's neurodegeneration diagnosis. In addition, MRI has revealed a link between midlife BP and hippocampal atrophy, with the strongest associations reported in untreated HTN patients.<sup>148</sup>

## Antihypertensive Drugs and AD

To overcome the effects of HTN, several anti-hypertension drugs (AHDs) prevent, control and treat HTN.<sup>149</sup> The clinical findings of the study on the relationship between HTN and late-life dementia have provided a rationale for using AHDs to control HTN and reduce the risk of dementia.<sup>150,151</sup> In addition, a large-scale clinical study on the use of AHDs demonstrates that lowering the systolic BP to less than 120 mmHg compared to 140 mmHg exhibits excellent results by reducing the risk of the secondary outcome of mild cognitive impairment and dementia.<sup>152</sup> Similarly, in another study, it has been concluded that antihypertensive medications (AHM) have significant results in neuroprotective treatments.<sup>153</sup> Although studies differ in source populations and the prevalence of confounding factors, the observational data endorsed the potential role of different AHM as the most potent candidate drugs to reduce AD-related pathologies and their prevention.<sup>154,155</sup>

Clinical trials are ongoing using AHM to cure dementia and AD-related pathologies. In addition, investigations are underway regarding the AHM drug's efficacy in reducing AD risks. [Table 1](#). Demonstrates studies on the relationship between AHM drug use and AD therapy. Calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and beta-blockers are the four major groups of AHM drugs.

## Potential Limitations to Using Antihypertensive Drugs for AD

Despite the evidence supporting the effectiveness of AHM in controlling AD, numerous physiological and pharmacological restrictions limit the case for further clinical benefits of this treatment. Age dependence is the biggest obstacle to AHD-based AD therapeutic success. According to neural clinicians, only 40 years and older AD patients showed better cognitive performance.<sup>156,157</sup> The findings of Dalen et al also restricted the efficacy of this treatment. They explained that stopping AHDs in old AD patients between 70 and 80 did not protect cognition and may increase the risk of dementia.<sup>158</sup> The effectiveness of this therapy is seriously hampered by these restrictions, which need to be thoroughly examined.



**Table 1** The Studies on the Relationship Between AHM Drug Use and AD Therapy

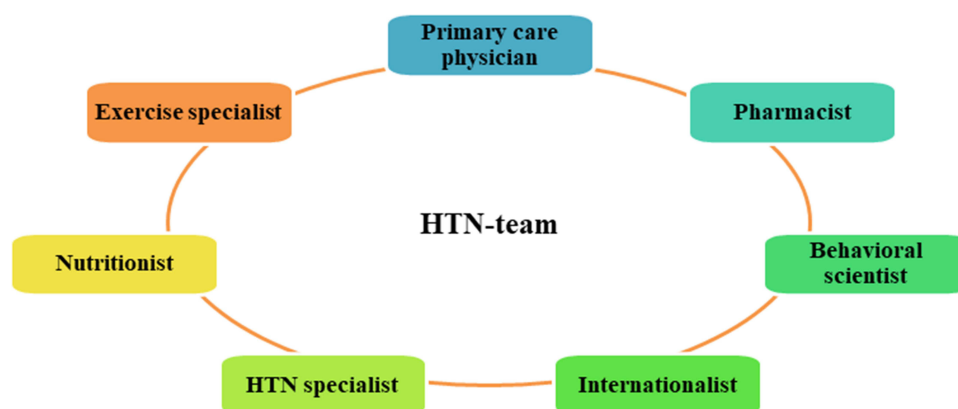
Antihypertensive Class	Antihypertensive Drug	Alzheimer Disease Related Observation	References
Calcium Channel Blockers	<ul style="list-style-type: none"> <li>• Isradipine</li> <li>• Nilvadipine</li> <li>• Nimodipine</li> </ul>	Neuronal malfunction, cell death, and apoptosis are all caused by increased intracellular calcium. Production of amyloid-beta (A $\beta$ ) protein. Clearance by glial and neuronal cells by autophagy.	[165–168]
Angiotensin-Converting Enzyme Inhibitors	<ul style="list-style-type: none"> <li>• Lisinopril</li> <li>• Captopril</li> <li>• Perindopril</li> </ul>	Reduce symptoms of cognitive decline in patients with “Alzheimer”s disease. Decrease levels of the neurotoxic 3-hydroxykynurenine (3-HK). Decrease levels of the reactive oxygen species (ROS) hydrogen peroxide. Attenuation of Human Lysozyme. Amyloid Fibrillation.	[169–171]
Angiotensin Receptor Blockers	<ul style="list-style-type: none"> <li>• Valsartan</li> <li>• Candesartan</li> <li>• Telmisartan</li> <li>• Losartan</li> </ul>	AT4Rs (angiotensin IV receptors) are associated with cognitive, cerebrovascular, and neuro-inflammatory rescue. Reduces dense core A $\beta$ plaques but not diffuse plaques or A $\beta$ species. Decrease level of hyperphosphorylated tau protein.	[172–175]
Beta Blockers	<ul style="list-style-type: none"> <li>• Propranolol</li> <li>• Carvedilol</li> </ul>	Potentiate peripheral inflammation following systemic LPS. Potentiate microglial phagocytosis of synaptosomes.	[176,177]

## Prevention and Awareness of HTN: Public Health Nursing

Low public awareness about HTN also causes mayhem. Despite the significant prevalence of HTN, most people are unaware of its symptoms or presence, which raises the risk of related problems, especially in the elderly population.<sup>159–161</sup> In contrast to its prevalence, awareness of HTN at the time of diagnosis is higher in developed countries (73% among adult Americans) than in developing countries (30% among adult Nigerians).<sup>162,163</sup> Patients’ commitment to dietary changes and medication depends on their understanding of the diagnosis and the risk factors leading to the onset of HTN.<sup>164</sup> Studies have shown that increasing HTN knowledge can reduce the risk of developing HTN. Practical actions are needed to lessen the burden of HTN in the population through collaborative patient care coordination of different domains as a single HTN team, including primary care physicians, pharmacists, behavioral scientists, internationalists, HTN specialists, nutritionists, and exercise specialists (Figure 5).

## Conclusions, Remarks and Future Prospective

Available knowledge supports the link between amyloid deposition in developing AD patients’ brain cells and cerebrovascular impairment as a marker of HTN. Older adults are more likely to have HTN, which is linked to higher AD-related morbidity and mortality rates. The summarized literature on this physiological association is substantial. This review will encourage the preclinical trials to accumulate data on administering antihypertensive drugs to treat AD.

**Figure 5** A coordination of different domains as HTN-team to knowledge the general public about HTN.

Future studies need integrated strides for novel methodological strategies and disease models to recapitulate the association accurately. Doubtlessly, the exploration of this association holds great promise in identifying predictive biomarkers and applied therapeutic targets. Furthermore, the clinicians must also work at the management level to continuously advise policymakers to develop long-term programs that address the incidence of HTN patients and insert awareness about this public health concern, eventually reducing the AD burden in the elderly population.

## Abbreviations

AD, Alzheimer's disease; HTN., hypertension; AHDs, Antihypertensive drugs; CVD, Cardiovascular disease; BP, Blood Pressure; A $\beta$ ,  $\beta$ -peptide; CSF, Cerebral spinal fluid; sAPP, soluble Amyloid Precursor Protein beta; CDK5, Cyclin-Dependent Kinases 5; ERK2, Extracellular Signal-Regulated Kinase 2; ApoE, Apolipoprotein-E; ROS., Reactive Oxygen Species; AHMs, Antihypertensive medications; PSP, Progressive supranuclear palsy; CSVD, Cerebral small vessel disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BBs, beta-blockers (BBs); CCBs, calcium channel blockers; AT1R, angiotensin receptor subtype 1.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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