

Review

Effects of Hypertension on Alzheimer's Disease: Updates in Pathophysiological and Neuroimaging Findings

Si-Cheng Yan^{1,†}, Lu Liu^{2,†}, Gao-Li Fang^{3,†}, Shi-Ting Weng¹, Jun-Jun Wang², Lin Cheng², Ye-Jia Mo², Qi-Lun Lai², Yin-Xi Zhang⁴, Tian-Yi Zhang⁵, Pan-Pan Gai⁶, Li-Ying Zhuang^{2,*}, Song Qiao^{2,*}

¹The Second Clinical Medical College, Zhejiang Chinese Medicine University, 310053 Hangzhou, Zhejiang, China

²Department of Neurology, Zhejiang Hospital, 310025 Hangzhou, Zhejiang, China

³Department of Neurology, Zhejiang Chinese Medicine and Western Medicine Integrated Hospital, 310020 Hangzhou, Zhejiang, China

⁴Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, 310027 Hangzhou, Zhejiang, China

⁵Department of Neurology, First Affiliated Hospital, School of Medicine, Zhejiang University, 310027 Hangzhou, Zhejiang, China

⁶Hospital of the Chinese People's Liberation Army Unit 71217, 265200 Laiyang, Shandong, China

*Correspondence: zhuangliying43205409@126.com (Li-Ying Zhuang); qiaosongicu@163.com (Song Qiao)

†These authors contributed equally.

Academic Editor: Gernot Riedel

Submitted: 8 February 2024 Revised: 14 May 2024 Accepted: 30 May 2024 Published: 12 August 2024

Abstract

Alzheimer's disease (AD) is recognized as the leading cause of dementia, imposing a significant economic toll on society. Despite the emergence of novel therapeutic approaches for AD, their efficacy and safety mandates further validation through rigorous clinical trials. In this context, hypertension (HTN) has garnered considerable attention as an amendable risk factor for AD. Research indicates that hypertension during midlife is associated with an elevated risk of AD in later years, influencing both the onset and progression of the disease. Nevertheless, the relationship between AD and hypertension in the later stages of life remains a subject of debate. Moreover, the consequences of blood pressure reduction on cognitive function, along with the optimal pharmacological interventions and therapeutic thresholds for hypertension, have emerged as pivotal areas of inquiry. This review synthesizes findings on epidemiology, neuroimaging, and biomarkers, and the effects of antihypertensive medications to elucidate the link between hypertension and cognitive performance. We particularly investigate how hypertension and AD are related by plasma sulfide dysregulation, offering possible indicators for future diagnosis and therapy.

Keywords: Alzheimer's disease; hypertension; biomarkers; neuroimaging; pathophysiology

1. Introduction

Alzheimer's disease (AD), recognized as the primary cause of dementia, imparts a substantial economic strain on society [1,2]. Extensive research has highlighted several interconnected neurodegenerative processes, leading to the identification of common pathological features in AD, notably beta-amyloid plaques and neurofibrillary tangles (NFT) within nerve cells [3,4]. The accumulation of abnormal forms of amyloid beta ($A\beta$) in the brain gives rise to senile plaques (SP), which can result in physical damage to axons, ultimately leading to profound cytoskeletal alterations. These cytoskeletal changes are the basis of the neurofibrillary pathology and overall neurodegenerative process. NFT are formed by the aggregation of abnormal tau proteins and are thought to be directly linked to neuronal death [5,6]. Notably, NFT and SP are also present in cognitively healthy older adults, but their presence becomes particularly disruptive in AD, causing extensive disruptions in critical cortical circuits. Due to the widespread degradation of these circuits, multiple cognitive domains, including memory and attention, are adversely affected. The persis-

tent development of these changes can lead to escalating behavioral alterations, memory loss, and decreased learning ability [7]. While recent developments in immunotherapeutic strategies for AD have shown promise, their efficacy and safety profiles remain limited [8]. A case in point is the aducanumab antibody, which has been recently approved for the market with the assertion that it diminishes $A\beta$ plaques in the brains of AD in mice models [9]. The safety report underscores the need for further investigation into this therapeutic's efficacy and safety, particularly considering the emergence of amyloid-related imaging abnormalities (ARIA). ARIA encompass imaging findings that suggest the presence of vasogenic edema (ARIA-E) and intracerebral hemorrhage (ARIA-H). Notably, the report draws attention to a possible link between ARIA and the development of malignant hypertension, emphasizing the importance of conducting comprehensive additional clinical trials to thoroughly evaluate the implications of these adverse effects on blood pressure conditions [10].



Hypertension (HTN) is one of the most prevalent chronic diseases, affecting as many as one billion adults. Currently, around 75% to 85% of people over the age of 65 years have hypertension [11,12]. HTN is also the most preventable and modifiable risk factor for cognitive impairment stemming from neurodegenerative diseases, including AD, stroke, Parkinson's disease (PD), and small cerebral vessel disease (SCVD) [2].

Interestingly, AD and HTN are frequent comorbidities among the elderly [11,13]. Current evidence indicates that HTN not only affects neurobiological substrates but also plays a role in the clinical progression of cognitive impairment and dementia. Further investigation into the mechanisms underlying this impact could provide valuable insights for developing more effective strategies to prevent and diagnose AD.

2. Hypertension and AD

2.1 Epidemiological Study of Hypertension and AD

Neuropsychological testing is a potent tool for measuring cognitive functioning and can capture even the most subtle cognitive changes to uncover evidence of cognitive dysfunction [14]. Cognitive decline (cognitive functions such as memory, thinking, and reasoning may decline over years to decades to a greater extent than would be expected due to age alone) is assessed by longitudinally comparing the degree of cognitive decline in a patient. It does not require the patient to meet definitive criteria for dementia or mild cognitive impairment (MCI). Studies on cognitive decline have helped to identify the danger of preclinical cognitive impairment in advance, providing a simpler technique of testing cognitive function and allowing for a more accurate assessment of the relationship between hypertension and cognitive performance [14,15]. However, clinical diagnosis of MCI or dementia is equally crucial, as both diagnoses have far-reaching public health consequences [16]. In the case of hypertension, current evidence from epidemiologic studies has found that hypertension is strongly associated with cognitive decline [14], MCI [17], and dementia [2,18,19].

Prospective cohort studies may be preferable to cross-sectional studies when examining the causal relationship between hypertension and AD, so we focused primarily on evidence from longitudinal cohort studies. While the correlation between hypertension and cognitive impairment was first established in patients with stroke and Vascular Cognitive Impairment (VCI), subsequent investigations have determined that cognitive decline attributed to hypertension could also occur in the absence of stroke [20]. Multiple studies have found that there may be an age-dependent relationship between hypertension and the risk of AD, and that the association between hypertension and AD at different ages of onset is complex and variable [21,22].

Several studies have arrived at more consistent conclusions about the relationship between midlife hyperten-

sion and the risk of AD. In a meta-analysis of prospective cohort studies, middle-aged hypertension was found to be more strongly associated with AD [19]. In the Honolulu-Asia Aging Study, untreated hypertension levels in midlife were found to be associated with an increased risk of AD 25 years later, and it was suggested that hypertension may be an important mediator or pathologic contributor to AD [23]. Another study with 21 years of follow-up found that elevated systolic blood pressure (SBP) in midlife was an independent risk factor for AD in later life [24]. Moreover, the Atherosclerosis Risk in Communities (ARIC) study revealed that hypertension and prehypertension among middle-aged individuals confer a comparable risk of dementia, with both groups displaying a higher risk relative to normotensive individuals [14]. A national cohort study in Korea also found an increased risk of AD with SBP ≥ 160 mmHg in midlife [25]. In conclusion, all the above studies emphasize that control of hypertension in midlife may benefit cognition in later life.

As for the effect of late-life hypertension on AD there is currently inconsistency. A few studies have found late-life hypertension to be associated with AD. In the Kungsholmen Project, a community-based cohort of 75-year-olds followed for 6 years found that subjects with an SBP >180 mmHg had an elevated risk of AD [26]. In Addition, a 15-year follow-up study in 70-year-olds found that participants who developed dementia at age 79–85 years had higher SBP and diastolic blood pressure (DBP) at age 70 years than those who did not, with higher DBP recorded in patients with AD than those who did not develop AD [27]. However, no relative risk assessment for hypertension-related dementia was reported. No other studies have confirmed a strong association between late-life hypertension and AD. In fact, some current studies in older adults (≥ 70 years) have shown a U-shaped relationship between blood pressure and cognitive performance. The inconsistent results seen in older adults may reflect differences in the cognitive domains assessed, differences in study design, including the way in which follow-up time and rates of cognitive change were modeled, differences in the characteristics of the study populations and different age ranges, and adjustments for co-determinants that may confound the hypertension-cognition association. Reverse causality may also contribute to the observed association between blood pressure (BP) and cognition, particularly in studies with cross-sectional designs. Cognitive impairment is a process that lasts for decades, thus posing a challenge in determining temporality. More research is needed to elucidate the causal relationship between BP and cognition and to better understand the role of medications in the observed associations [28–30].

Collectively, the above results highlight the potential detrimental impacts of hypertension acquired during midlife. Nevertheless, due to the absence of a gold standard for stratifying dementia subtypes, the subset of stud-

ies investigating the correlation between hypertension and specific dementia subtypes might inadvertently complicate the assessment of hypertension's role in other forms of dementia and cases with mixed underlying causes. Therefore, more rigorous criteria are needed to aid in the diagnosis of dementia subtypes. Furthermore, age-stratified and long-term follow-up studies focused on hypertension could serve as valuable tools for enhancing our comprehension of the intricate connection between hypertension and AD.

2.2 Hypertension and AD Cognitive Domain Impairment

Research suggests that HTN may have a global impact on cognitive performance and in global cognitive assessments, such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), people with vascular risk including hypertension score lower. Individuals with more factors also score lower, which is largely influenced by difficulties related to attention (in the MMSE assessment) and visuospatial executive functioning (in those with lower MoCA scores) [31]. Broader neuropsychological assessments suggest that hypertension most significantly affects executive function [16], motor speed, and attention [32,33]. These cognitive domains are often associated with subcortical disorders such as common vascular diseases or pure vascular dementia (VaD) [34].

The pattern of cognitive impairment in hypertension-associated dementia is complicated by potential overlapping etiologies and the high prevalence of mixed dementia (MD). Although memory impairment is considered a typical feature of AD compared with VaD [35,36], it has been found that situational memory is significantly affected in cognitively impaired hypertensive participants and is associated with elevated $A\beta$ Pittsburgh Compound-B positron emission tomography (PiB-PET) binding. This suggests that the pathological mechanisms of AD may play an equally prominent role in hypertensive patients. Conversely, patients with MD (i.e., AD coexisting with VaD) exhibit worse global scores as well as worse attention and visuospatial abilities [37].

Studies focusing only on specific cognitive domains are therefore prone to errors in findings due to misdiagnosis or the effect of difficulties in determining the exact cause throughout an individual's lifetime. Further incorporation of biomarkers (including serology, cerebrospinal fluid, and imaging) can help to better characterize the disease [38].

2.3 The Pathophysiological Mechanism of AD Induced by Hypertension

The potential mechanisms linking hypertension and AD are complex and multifaceted. Current evidence suggests that a synergistic interplay among various pathological factors may underlie the cognitive impairments associated with hypertension and there are extensive detailed reviews on this topic [39]. Below, we provide a summary

of the key points and an overview of the current evidence using neuroimaging markers to elucidate the connection between hypertension and AD (Fig. 1) [40].

The relationship between hypertension and brain structure and functions is not completely understood and current evidence suggests that several pathological factors can interact [41]. Hypertension can produce vascular and functional changes in large and small cerebral vessels in the brain, and small cerebral vessels and arterioles are more vulnerable to the mechanical stress associated with hypertension [42]. It is relevant to highlight the strong relationship between arterial hypertension and cerebral small vessel disease (cSVD); the characteristic findings of cSVD in magnetic resonance imaging (MRI) include lacunar infarcts, white matter hyperintensities (WMH), cerebral microbleeds (CMB), enlarged perivascular spaces, and brain atrophy [42]. Conversely, chronic hypertension induces a rightward shift in the autoregulatory curve and, consequently, an increment of vulnerability to sudden changes in blood pressure, resulting in ischemia or increased risk of brain hemorrhage.

The modified structure of the perivascular space, often observed in conditions such as hypertension, heightens the possibility that the perivascular and paravascular clearance systems, which are vital for the removal of waste products from the brain, may be disrupted, potentially contributing to white matter injury [43,44]. Specifically, in hypertension, the perivascular spaces become enlarged and distorted [43,45], a change that could hinder the effective elimination of neurotoxic metabolic byproducts. This is significant as hypertension is also linked to the accumulation of $A\beta$ and tau proteins, indicating a possible reduction in the clearance of these proteins, which are associated with AD pathogenesis. Furthermore, the atherosclerosis of large arteries due to hypertension leads to increased pulsatility in the microvasculature. This increased pulsatility is hypothesized to affect the perivascular space, potentially reducing the clearance of interstitial fluid (ISF) and cerebrospinal fluid (CSF; a colorless, clear fluid found in the ventricles and subarachnoid space of the brain.) [43]. The perivascular space is a critical component of the glymphatic system, which is responsible for the drainage of metabolic waste from the brain. Disruptions to this system can result in the buildup of harmful substances, such as $A\beta$ and tau, which are known to negatively impact brain health.

In conclusion, vascular damage caused by hypertension results in brain dysfunction due to hypoxia-ischemia and increased production of $A\beta$ due to the increased processing of amyloid precursor protein (APP) by secreted enzymes and decreased clearance of AD-related proteins. In turn, $A\beta$ and tau proteins alter vascular function and amplify the deleterious effects of hypertension on the vasculature.

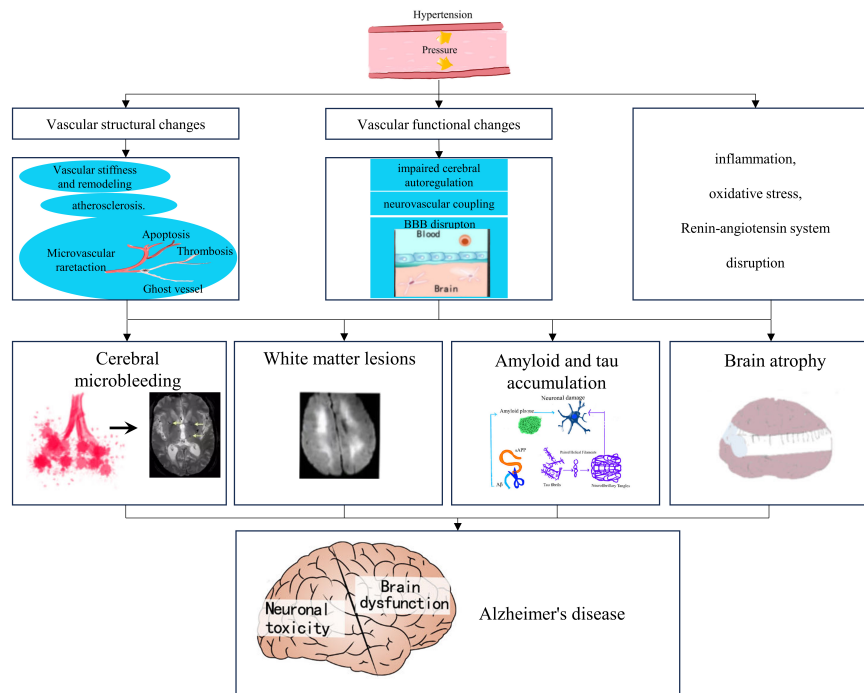


Fig. 1. Common imaging features and potential mechanistic links between hypertension and Alzheimer's disease (AD). Hypertension exerts a multifaceted influence on the brain, manifesting through alterations in the structure and function of the cerebrovasculature, perturbations in the renin-angiotensin system, the emergence of inflammation, and the induction of oxidative stress. Such pathological processes can lead to the development of cerebral white matter lesions, brain atrophy, microhemorrhages, and the accumulation of pathologic proteins associated with AD. These conditions are discernible through neuroimaging technologies and are recognized for their potential to affect the initiation or advancement of AD. BBB, blood-brain barrier; A β , amyloid beta; APP, amyloid precursor protein.

3. Biomarkers of AD in Hypertension

3.1 Hypertension and the Cerebral Microcirculation

Hypertension impairs the structural and functional integrity of the cerebral microcirculation, promoting microvascular thinning, cerebral microvascular endothelial dysfunction, and neurovascular uncoupling, as well as impairing cerebral blood supply [39]. This insufficient blood supply, in turn, triggers metabolic irregularities within the brain parenchyma. Consequently, there is an increased activity of beta-secretase 1, an enzyme responsible for cleaving APP into beta-amyloid, thus promoting the formation of amyloid plaques [46]. HTN also increases the pressure in the lumen of cerebral vessels, leading to increased formation of reactive oxygen species and weakening of the vessel wall, resulting in disruption of the blood-brain barrier (BBB). This allows the contents of the plasma to enter the central nervous system (CNS) thereby triggering neuroinflammation. Mouse model studies have effectively demonstrated that neuroinflammation is a pivotal link connecting hypertension and AD. Additionally, BBB disruption impedes the efficient clearance of beta-amyloid, which further promotes its deposition. Taken together, these series of events significantly contribute to both the onset and progression of AD [20].

3.2 Hypertension and Beta-Amyloid

While the heightened risk of AD associated with hypertensive patients is evident and the impact of hypertension on cognition is relatively well-established, a degree of uncertainty remains regarding whether HTN directly influences AD neuropathology or simply serves as a concurrent factor contributing to cognitive impairment and dementia [47].

An autopsy study reported that midlife hypertension was associated with more senile plaques and NFT pathology at death, showing that the apolipoprotein E (*APOE*) $\epsilon 4$ allele (especially $\epsilon 4$ homozygosity) was associated with hypertension through the elevation of CSF tau and phosphorylated tau levels. However, in that study, hypertension did not interact similarly with the effect of carrying the $\epsilon 4$ allele on CSF A β levels [48]. Other studies have reported that late-life hypertension (BP) is associated only with NFT, if not with both NFT and senile plaques [49,50]. *In vivo* AD biomarker studies based on PET imaging or CSF analysis have produced similarly contradictory results. Although several studies have shown a significant correlation between hypertension and A β deposition in the brains of older adults [51,52], many other studies have not found such a direct relationship [53–61]. However, some of these findings suggest that current hypertension (rather than a his-

tory of hypertension) synergistically modulates the relationship between A β and tau deposition in the brain in later life [61,62].

Several epidemiologic and clinicopathologic studies have reported an association between hypertension and AD. However, a challenge to the interpretation of the relationship between hypertension and AD is the substantial lag in time from the start of hypertension studies to the pathologic diagnosis of AD. The increasing popularity of amyloid PET imaging and structural MRI provides an opportunity to better understand the role of hypertension and brain pathology *in vivo*. In population-based or special (enriched) cohort studies, large sample sizes are needed to distinguish the separate roles of SBP, DBP, pulse pressure, mean arterial pressure, and carotid-femoral pulse wave velocity (PWV) for each imaging feature. Longitudinal studies that prioritize the assessment of perfusion deficit, white matter changes, cortical volume changes, microbleeds, and amyloid accumulation are needed to understand their interrelationships. Future imaging techniques that can detect the involvement of specific targets will be needed to understand which cells or cellular components are the sites of initial pathogenic injury in hypertension. The cell types and endpoints most suitable for treatment remain undetermined.

3.3 Hypertension and Tau

Although most of the current research has concluded that a direct association between hypertension and tau is lacking [60], a recent study from China has introduced a novel perspective. The study reported a noteworthy link between a history of hypertension and elevated systolic blood pressure with tau levels in the CSF, specifically in individuals under the age of 65 years [53]. Furthermore, other studies have suggested that hypertension may influence tau levels under certain conditions. For instance, individuals in the hypertension group who are carriers of the *APOE* ϵ 4 allele demonstrated a pathological correlation with increased levels of mid-tau (including total tau and phosphorylated tau) [55]. Additionally, a significant correlation between tau concentration and the hypertensive group was observed following a decrease in mean pulse pressure [63]. Moreover, a recent study found that although hypertension had no direct relationship with A β and tau deposition, it could synergistically modulate the interaction between cerebral A β load and tau deposition in later stages of life [60,61]. These emerging insights suggest that the development of strategies for blood pressure control in mid- to later life could provide benefits for both the prevention and treatment of AD.

3.4 Hypertension and Plasma Sulfides

Hydrogen sulfide (H₂S) is an important gaseous transmitter that regulates neuronal and vascular homeostasis [64]. It has been shown that the cerebral microvasculature produces H₂S and, in the vascular system, it has a

wide range of inflammatory and immunomodulatory functions [65]. Sulfides protect against vascular disease [66,67], and free sulfides promote cerebral vasodilation [68], protect against systemic and focal cerebral ischemia injury [69,70], and contribute to BBB integrity [71,72]. Lower sulfide levels predict cardiovascular disease risk [72]. In the nervous system, free sulfide acts as a calcium-based neuromodulator [72]. In addition, H₂S preserves cognitive performance in experimental dementia models, possibly by improving antioxidant status, attenuating oxidative stress [73,74], and inflammation *in vivo* and *in vitro* [74]. In AD-related dementia (ADRD), recent studies have found that increased plasma total sulfide toxicity is associated with elevated acidic soluble sulfide and bound sulfide [75]. Cognitive and microvascular disease indicators correlated with H₂S levels. Total plasma sulfide is the strongest indicator of ADRD [75]. It plays a partial role in the relationship between cognitive dysfunction and the volume of cerebral white matter lesions, the latter being an indicator of microvascular disease. Thus, plasma H₂S and sulfide may be potential biomarkers for the link between hypertension and AD [76]. Carrying out further large prospective experiments to explore the causal role of sulfide in microvascular disease and ADRD could help further explore the mechanism of action of AD and HTN.

4. The Relationship between Hypertension and Neuroimaging Features of AD

4.1 Functional Connectivity in Patients with Hypertension and AD

The recent availability of imaging and biochemical biomarkers of AD has provided the opportunity to investigate the relationship between AD pathology and hypertension [77–80]. From the beginning of the 20th century to the present, functional MRI (fMRI) has increased in popularity [81], as it has been shown that brain functional connectivity has been altered in hypertensive patients who show no signs of macroscopic damage on structural MRI [82,83]. At the same time, fMRI signals are generated by neurovascular coupling, making it sensitive to the effects of hypertension and more favorable for observing the effects of hypertension on brain function.

Several studies have highlighted the structural brain alterations that are characteristic of AD, which include diminished hippocampal volume, reduced cortical thickness, and disruptions in the microstructure of white matter fiber tracts [2,82]. These suggest the presence of alterations in functional brain activity as well as in brain network connectivity, particularly within the default network (DMN) [84,85]. Shah *et al.* [86] previously observed distinctive cerebral white matter lesions in hypertensive patients. They further uncovered a significant correlation between cerebral white matter load and DMN regions by studying the relationship between cerebral white matter load and functional cerebral networks in hypertensive patients, revealing that

greater white matter lesion volumes correlated with lower functional connectivity (reflects the functional relationship between brain regions, FC) in the DMN [87]. Moreover, this was accompanied by poorer performance on cognitive tests, suggesting that WMH could be a potential mechanism through which hypertension impacts the progression of cognitive decline in AD.

Another study delved into the interaction between hypertension and individuals carrying the *APOE* $\epsilon 4$ allele. The study demonstrated that the presence of this allele exacerbated brain function impairment, particularly in the frontal and parietal regions of hypertensive patients. While fewer studies directly examined the effect of hypertension on brain function, those that did found disruptions in functional connectivity within the frontal-parietal network, dorsal attention network (DAN), and DMN networks in hypertensive patients. These findings align with the observed decline in executive function and attention in individuals with hypertension [88].

Collectively, these studies underscore the structural and functional transformations that hypertension induces in the brain, although there is currently a lack of convincing large cohort prospective studies exploring the causal relationship between hypertension and cognitive function.

Analyses of structural brain studies conducted on individuals with both AD and hypertension have highlighted distinct patterns of atrophy when compared with AD patients without hypertension. Notably, in the hypertensive group, significant atrophy was observed primarily in the temporal lobe, frontal lobe, and cingulate gyrus [88–90]. These findings imply that hypertension might play a role in the initiation and progression of AD by influencing critical brain regions. While research exploring brain function in individuals with combined AD and hypertension is more limited and currently exhibits some variation due to diverse analytical approaches, it remains crucial to acknowledge the impact of hypertension on resting-state brain function in AD patients, especially the disruption of the DMN region [82,84]. However, some literature has reported enhanced the posterior cingulate cortex (PCC) functional connectivity in AD/MCI patients, with areas such as the ventral medial prefrontal, bilateral dorsolateral frontal, and left middle cingulate gyrus. Moreover, heightened connectivity has been noted between the left inferior parietal lobule and the PCC in AD patients with hypertension [91,92]. These findings are indicative of a potential compensatory mechanism, suggesting that these regions might enhance their function in response to early-stage AD/MCI-associated damage to other brain areas. However, other studies did not identify this compensatory phenomenon. Variations in sample sizes and analytical methodologies are factors that might contribute to these discrepancies. This area of research currently features substantial gaps, and further studies are essential to provide deeper insights and more conclusive findings.

4.2 Multimodal Imaging Techniques in Hypertension and AD

The introduction of multimodal imaging techniques has helped us to better understand the pathogenesis shared in the imaging features of hypertension and AD. Notably, these shared features include WMH, cerebral microhemorrhages, and atrophy. Meanwhile, diffusion tensor imaging is another useful imaging technique developed for assessing the anatomic integrity of white matter [93]. Some parameters of the microstructural abnormalities derived from diffusion tensor imaging (DTI) have been reported to help differentiate between dementias. Some studies have found that compared with conventional MRI, DTI may provide a more objective method for the differential diagnosis of VaD and AD disease patients who have only mild white matter alterations on T2-weighted imaging. Compared with VaD patients, AD patients had lower fractional anisotropy (FA) values in the anterior frontal lobe, temporal lobe, hippocampus, inferior-fronto-occipital fascicles (IFOF), genu of the corpus callosum (GCC), and the cingulate fasciculus (CF); and higher apparent diffusion coefficient (ADC) values in the temporal lobe and hippocampus [94]. Parahippocampal tracts were found to be mainly affected in AD, while VaD showed more spread white matter damages associated with thalamic radiation involvement. The genu of the corpus callosum was predominantly affected in VaD, while the splenium was predominantly affected in AD, revealing the existence of specific patterns of alteration useful in distinguishing between VaD and AD [95]. Based on the above evidence, cerebrovascular dysfunction, including HTN, is associated with the accumulation of AD pathology. The “vascular dysregulation hypothesis” proposes that an imbalance between blood flow-based substrate supply and brain energy demand caused by vascular risk factors such as hypertension exacerbates AD and ADRD [96,97]. The current view is that cerebrovascular dysfunction occurs early in ADRD and therefore may be a potential diagnostic marker and target for intervention. Cerebrovascular dysfunction induces pathophysiology that may contribute to the common symptoms of AD, including cerebral atrophy, cortical thinning, and white matter deterioration. These can be observed by multimodal magnetic resonance, facilitating exploration of the potential link between hypertension and AD [76].

DTI, fMRI, and PET are three imaging techniques widely used in neuroscientific research and clinical diagnostics, and despite their unique advantages, they have some limitations. DTI is primarily used to depict white matter fiber bundles in the brain, but its ability to image grey matter and subcortical structures is limited and it is not sensitive enough for certain types of white matter lesions. fMRI can non-invasively measure brain activity, but its signal can be affected by a variety of physiological and operational factors, such as vascular saturation, the complexity of the task design, and the level of participant cooperation, which can lead to challenges in data interpretation.

PET assesses metabolic and neurochemical activity in the brain using radiotracers, and although it provides detailed information about brain function, it carries radiation risks, is costly, and often requires special radiopharmaceuticals, which limits its use in some situations. The introduction of multimodal imaging techniques has helped us to better understand the pathogenesis shared in the imaging features of hypertension and AD.

4.3 White Matter Hyperintensities (WMH)

The pathology of AD is indeed intricate, encompassing not only the accumulation of A β and tau proteins but also involving a multitude of markers related to vascular pathology and neuroinflammation. For instance, in addition to A β and tau, other biomarkers such as WMH (de Leeuw F-E *et al.*, 2004 [98]) and neurofilament light (NFL) [99] have gained recognition as contributors to AD pathology. While WMH were previously considered a natural outcome of aging and often associated with cerebrovascular diseases (especially hypertension) [100,101], recent advancements have highlighted their association with multiple pathological pathways. Recent evidence suggests that WMH could be linked to tau levels, thus linking them to the incidence of AD [102,103].

NFL, a biomarker associated with significant axonal injury, has gained attention due to its increased levels in the CSF of individuals with AD [91]. Recent studies have facilitated the analysis of NFL not only in the CSF but also in the blood (serum and plasma), offering a more accessible means of monitoring [104]. An intriguing link has been suggested between NFL levels and white matter alterations in AD [87,105,106]. A recent study by Walsh *et al.* [99] found a significant positive correlation between NFL and WMH volume in a population with different cognitive impairments and a large proportion of age-related, independent vascular risk factors (including hypertension). However, further analysis by the same research group found that the combination of hypertension and the *APOE* ϵ 4 allele was associated with increased WMH [98,107]. The authors further hypothesized that the mechanisms behind the WMH observed in AD patients with comorbid hypertension may be more complex. The study did not find an interaction between hypertension and AD pathophysiologic processes in response to WMH loading because the two have a superimposed effect in response to increased WMH loading, which may lead to earlier and more pronounced cognitive decline [98].

4.4 Cerebral Microhemorrhage

Cerebral microhemorrhages have traditionally been attributed to two main causes: cerebral amyloid vascular degeneration and hypertension [98,108]. Hypertension-related microhemorrhages are typically found deep within the brain parenchyma, often localized in regions such as the internal capsule. Notably, microhemorrhages in corti-

cal sites are more often associated with the presence of the *APOE* ϵ 4 allele and elevated levels of A β [108]. A significant correlation between hypertension and increased microhemorrhagic foci has been observed in patients with AD [109,110]. However, the interaction between A β and AD in the formation of microhemorrhages lacks conclusive evidence and requires further investigation for a more comprehensive understanding.

The report found that patients with vascular or MD presented with a more severe load of white (periventricular and deep) and grey matter lesions compared with AD. The high number of juxtacortical microhemorrhages observed in the group with MD suggests that cerebral amyloid angiopathy (CAA) may be a relevant pathological finding within this group [111]. Microhemorrhages may cause cognitive impairment by affecting executive function, information processing, and memory [112]. However, the mechanisms by which microhemorrhages alter cognitive function remain to be determined, and it is currently believed that the direct cognitive effects of microhemorrhages are related to localized damage or dysfunction of adjacent brain tissue. Alternatively, microhemorrhages may be a more general marker of the severity of small-vessel pathology associated with CAA, modulating altered vascular supply and reduced cortical function [113].

Indeed, neuropathological studies have recognized CAA as a major cause of MD in combination with Alzheimer's or Lewy body pathology [114,115]. Furthermore, CAA has been significantly associated with subcortical white matter damage, particularly in *APOE* ϵ 4 carriers [116]. This suggests that CAA can be fully recognized as a prototype of MD, in which AD and cerebrovascular lesions coexist. Therefore, special attention should be paid to microhemorrhages during diagnostic tests for dementia.

4.5 Decreased Brain Volume

Hypertension is currently thought to cause brain atrophy [117,118], but the exact mechanism remains elusive [118]. Part of the reason is that hypertension-mediated WMH leads to a reduction in brain volume due to white matter thinning. Other potential factors include reduced brain volume due to brain tissue destruction caused by cerebral microinfarcts, cerebral atherosclerosis, and impaired clearance of abnormal proteins in AD patients [119].

A greater number of periventricular lesions, deep white matter lesions, deep grey matter lesions, and enlarged perivascular spaces was observed in vascular dementia compared with AD, while MD showed a significantly greater number of periventricular lesions, deep white matter lesions, deep grey matter lesions, and deep and juxtacortical microhemorrhages. Comparing VaD and MD, VD showed a higher number of perivascular spaces in the basal ganglia and centrum semiovale, while MD showed more deep and juxtacortical microhemorrhages. Gray and white matter lesions predominate in vascular and MD, while deep and

juxtacortical microhemorrhages predominate in MD, suggesting that cerebral amyloid angiopathy may be the main underlying pathology in cases of mixed-based cognitive decline.

5. Blood Pressure Control and Dementia

In several observational studies, the use of antihypertensive medication has been correlated with a reduced decline in cognitive abilities. In the ARIC study, participants who were on antihypertensive medications experienced a 20-year cognitive decline equivalent to that of the prehypertensive group (higher than those with normal blood pressure but lower than those with untreated hypertension) [14]. The Northern Manhattan Study found that SBP was negatively associated with cognitive function in the elderly, both cross-sectionally and longitudinally. Antihypertensive treatment eliminated the longitudinal negative correlation between SBP and the functions of processing speed and visual motor integration [120]. In the Epidemiology of Vascular Aging (EVA) study group, treated hypertension was associated with less cognitive decline over a four-year period compared with untreated hypertension [121]. Another study indicated that in patients with various forms of dementia, including AD, who received permanent correction of hypertension, the cognitive decline could be alleviated [122]. The results of the Systolic Blood Pressure Intervention Trial to Reduce Memory and Cognition in Hypertension (SPRINT MIND) study support intensive SBP reduction (goal: <120 mmHg) to maintain cognitive function. However, due to the early termination of the study, SPRINT MIND may be inadequate for the primary endpoint, which may be dementia [123]. The European Systolic Hypertension (systolic - eur) trial concluded that long-acting dihydropyridine calcium channel blockers protect against dementia in elderly patients with systolic hypertension [124]. A similar study of another antihypertensive drug, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), suggests that all patients with cerebrovascular disease may be able to reduce their risk of cognitive decline by lowering their blood pressure through the combined use of perindopril and indapamide [125]. Other studies suggest no link between antihypertensive treatment and cognitive decline [125,126]. For example, the Memory in Diabetes (MIND) Action to Control Cardiovascular Risk in Diabetes (ACCORD) substudy intensified the SBP reduction group and there was no difference in cognitive performance at 40 and 80 months [127,128]. Separation of treatment goals between treatment groups and loss to follow-up may account for the lack of detectable long-term effects [127].

Lowering blood pressure may lead to a lower risk of dementia or cognitive impairment, as suggested by several recent meta-analyses, but there is no evidence that a specific class of antihypertensive drugs is more effective than any other in reducing dementia risk. These findings challenge the hypothesis that renin-angiotensin system blockade may

be more likely to preserve cognition [126,129–131]. The limitations of some of the methods described above are worth noting. Subgroup and meta-regression analyses from systematic evaluations may be prone to ecological bias, and the use of randomized controlled trial (RCT) data rather than observational data may be more appropriate for addressing some challenging and unresolved questions of interest.

The above studies consider the role of antihypertensive drug therapy, although all of them are susceptible to some indication bias: individuals prescribed and taking antihypertensive drugs are different from those not taking antihypertensive drugs; beyond that, many aspects are open to statistical adjustment. Clinical trials would therefore be an ideal forum to answer this question, but given that the evidence reviewed above suggests that consideration of the relationship between hypertension and dementia is strongest in middle age, decades before the development of dementia, and that clinical trials cannot randomize and follow participants for that long, some type of long-term observational study design is needed to take into account these lifespan considerations. These studies would also allow for consideration of age at treatment or duration of treatment, which may be beyond what clinical trials currently allow.

6. Conclusions

Hypertension and AD are two major health concerns within the global aging population, showing high rates of co-morbidity. Hypertension has been shown to increase the risk of AD by two-fold. Moreover, when hypertension and AD co-occur, their combined impact appears to magnify. Structural and functional changes induced by hypertension play a substantial role in elucidating the pathophysiological connection between these two diseases. The integration of multiple biomarkers in scientific research has provided valuable insights into the synergistic effects arising from the interplay of hypertension and AD. While studies investigating brain function within the context of AD and hypertension co-morbidity are relatively scarce, ongoing and future research will likely aim to unravel this relationship in greater detail. In the absence of definitive therapeutic approaches for AD, evidence strongly indicates that achieving treatment targets for hypertension holds significant importance since this not only aids in reducing the incidence of cardiovascular disease but also plays a crucial role in curbing the occurrence of AD.

7. Questions and Challenges

Although the body of knowledge on hypertension and cognitive outcomes, dementia, and AD has expanded considerably in recent years, several key questions remain. The answers to some of the questions listed below are critical to better understand how hypertension affects cognitive function and to best recommend preventive and management strategies, suggesting some possible paths for future

research. (1) Is hypertension-induced neurovascular dysfunction sufficient to cause cognitive impairment? Which are the best surrogate endpoints or biomarkers for measuring brain or cognitive benefit in hypertension treatment? (2) Is lowering blood pressure alone sufficient to maintain cognitive performance? Should other dementia risk factors be considered? When is it necessary to start antihypertensive therapy to reduce the risk of cognitive impairment? Which class of antihypertensive medications is most effective in preventing cognitive impairment?

Author Contributions

SCY, LL and GLF equally contributed to the primary study design of this review. SCY, LYZ, and SQ equally performed the literature search and wrote the manuscript. STW, JJW, QLL, LC, YJM, TYZ, YXZ and PPG were involved in conceptualizing and designing the manuscript, data collection, or data analysis and interpretation, and added important intellectual content to the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by the Zhejiang Science and Technology Project [2023RC120] and Zhejiang Provincial Natural Science Foundation [LQ19H090006] and Zhejiang Provincial Health Commission [NO. 2023KY006].

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007; 69: 2197–2204.
- [2] 2023 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2023; 19: 1598–1695.
- [3] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002; 297: 353–356.
- [4] Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M, *et al.* Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. *The Lancet. Neurology*. 2012; 11: 1048–1056.
- [5] Bloom GS. Amyloid- β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurology*. 2014; 71: 505–508.
- [6] Vickers JC, King AE, Woodhouse A, Kirkcaldie MT, Staal JA, McCormack GH, *et al.* Axonopathy and cytoskeletal disruption in degenerative diseases of the central nervous system. *Brain Research Bulletin*. 2009; 80: 217–223.
- [7] Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, *et al.* Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet. Neurology*. 2013; 12: 357–367.
- [8] Song C, Shi J, Zhang P, Zhang Y, Xu J, Zhao L, *et al.* Immunotherapy for Alzheimer's disease: targeting β -amyloid and beyond. *Translational Neurodegeneration*. 2022; 11: 18.
- [9] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, *et al.* The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature*. 2016; 537: 50–56.
- [10] VandeVrede L, Gibbs DM, Koestler M, La Joie R, Ljubenkov PA, Provost K, *et al.* Symptomatic amyloid-related imaging abnormalities in an APOE ϵ 4/ ϵ 4 patient treated with aducanumab. *Alzheimer's & Dementia*. 2020; 12: e12101.
- [11] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nature Reviews. Nephrology*. 2020; 16: 223–237.
- [12] GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018; 392: 1923–1994.
- [13] McAlse KE, Colloby SJ, Attems J, Thomas AJ, Francis PT. Mixed brain pathologies account for most dementia in the UK's Brains for Dementia Research cohort. *Alzheimer's & Dementia*. 2020; 16: S2.
- [14] Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, *et al.* Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurology*. 2017; 74: 1246–1254.
- [15] Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, *et al.* Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study. *American Journal of Epidemiology*. 2014; 179: 956–966.
- [16] Gottesman RF, Schneider ALC, Albert M, Alonso A, Bandeen-Roche K, Coker L, *et al.* Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurology*. 2014; 71: 1218–1227.
- [17] Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *American Journal of Epidemiology*. 1993; 138: 353–364.
- [18] Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension*. 1998; 31: 780–786.
- [19] Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, *et al.* Blood Pressure and Risks of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of 209 Prospective Studies. *Hypertension*. 2020; 76: 217–225.
- [20] Santisteban MM, Iadecola C, Carnevale D. Hypertension, Neurovascular Dysfunction, and Cognitive Impairment. *Hypertension*. 2023; 80: 22–34.
- [21] Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet. Neurology*. 2005; 4: 487–499.
- [22] Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and dementia - a comprehensive review. *Therapeutic Advances in Neurological Disorders*. 2009; 2: 241–260.
- [23] Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, *et al.* Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiology of Aging*. 2000; 21: 49–55.

- [24] Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, *et al.* Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Annals of Internal Medicine.* 2002; 137: 149–155.
- [25] Cho MH, Han K, Lee S, Jeong SM, Yoo JE, Kim S, *et al.* Blood pressure and dementia risk by physical frailty in the elderly: a nationwide cohort study. *Alzheimer's Research & Therapy.* 2023; 15: 56.
- [26] Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L. Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Archives of Neurology.* 2003; 60: 223–228.
- [27] Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, *et al.* 15-year longitudinal study of blood pressure and dementia. *Lancet.* 1996; 347: 1141–1145.
- [28] Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA.* 1999; 281: 438–445.
- [29] Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, *et al.* Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dementia and Geriatric Cognitive Disorders.* 2001; 12: 33–39.
- [30] Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. *Hypertension.* 2005; 45: 374–379.
- [31] Sikaroodi H, Yadegari S, Miri SR. Cognitive impairments in patients with cerebrovascular risk factors: a comparison of Mini Mental Status Exam and Montreal Cognitive Assessment. *Clinical Neurology and Neurosurgery.* 2013; 115: 1276–1280.
- [32] Goldstein FC, Hajjar IM, Dunn CB, Levey AI, Wharton W. The Relationship Between Cognitive Functioning and the JNC-8 Guidelines for Hypertension in Older Adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences.* 2017; 72: 121–126.
- [33] Goldstein FC, Levey AI, Steenland NK. High blood pressure and cognitive decline in mild cognitive impairment. *Journal of the American Geriatrics Society.* 2013; 61: 67–73.
- [34] Smits LL, van Harten AC, Pijnenburg YAL, Koedam ELGE, Bouwman FH, Sistermans N, *et al.* Trajectories of cognitive decline in different types of dementia. *Psychological Medicine.* 2015; 45: 1051–1059.
- [35] Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine.* 2012; 2: a006171.
- [36] Sokolović L, Hofmann MJ, Mohammad N, Kukulja J. Neuropsychological differential diagnosis of Alzheimer's disease and vascular dementia: a systematic review with meta-regressions. *Frontiers in Aging Neuroscience.* 2023; 15: 1267434.
- [37] Smith EE, Muzikansky A, McCreary CR, Batool S, Viswanathan A, Dickerson BC, *et al.* Impaired memory is more closely associated with brain beta-amyloid than leukoaraiosis in hypertensive patients with cognitive symptoms. *PLoS ONE.* 2018; 13: e0191345.
- [38] Dong Y, Gan DZQ, Tay SZ, Koay WI, Collinson SL, Hilal S, *et al.* Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia. *Journal of the Neurological Sciences.* 2013; 333: 5–8.
- [39] Iadecola C, Gottesman RF. Neurovascular and Cognitive Dysfunction in Hypertension. *Circulation Research.* 2019; 124: 1025–1044.
- [40] Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, *et al.* Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nature Reviews. Nephrology.* 2021; 17: 639–654.
- [41] Mahinrad S, Sorond FA, Gorelick PB. Hypertension and cognitive dysfunction: a review of mechanisms, life-course observational studies and clinical trial results. *Reviews in Cardiovascular Medicine.* 2021; 22: 1429–1449.
- [42] Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *The Lancet. Neurology.* 2019; 18: 684–696.
- [43] Brown R, Benveniste H, Black SE, Charpak S, Dichgans M, Joutel A, *et al.* Understanding the role of the perivascular space in cerebral small vessel disease. *Cardiovascular Research.* 2018; 114: 1462–1473.
- [44] Rastogi A, Weissert R, Bhaskar SMM. Emerging role of white matter lesions in cerebrovascular disease. *The European Journal of Neuroscience.* 2021; 54: 5531–5559.
- [45] Ramaswamy S, Khasiyev F, Gutierrez J. Brain Enlarged Perivascular Spaces as Imaging Biomarkers of Cerebrovascular Disease: A Clinical Narrative Review. *Journal of the American Heart Association.* 2022; 11: e026601.
- [46] Cole SL, Vassar R. Linking vascular disorders and Alzheimer's disease: potential involvement of BACE1. *Neurobiology of Aging.* 2009; 30: 1535–1544.
- [47] Iadecola C, Gottesman RF. Cerebrovascular Alterations in Alzheimer Disease. *Circulation Research.* 2018; 123: 406–408.
- [48] Petrovitch H, White LR, Izmirlian G, Ross GW, Havlik RJ, Markesbery W, *et al.* Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiology of Aging.* 2000; 21: 57–62.
- [49] Arvanitakis Z, Capuano AW, Lamar M, Shah RC, Barnes LL, Bennett DA, *et al.* Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. *Neurology.* 2018; 91: e517–e525.
- [50] Wang LY, Larson EB, Sonnen JA, Shofer JB, McCormick W, Bowen JD, *et al.* Blood pressure and brain injury in older adults: findings from a community-based autopsy study. *Journal of the American Geriatrics Society.* 2009; 57: 1975–1981.
- [51] Toledo JB, Toledo E, Weiner MW, Jack CR, Jr, Jagust W, Lee VMY, *et al.* Cardiovascular risk factors, cortisol, and amyloid- β deposition in Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's & Dementia.* 2012; 8: 483–489.
- [52] Langbaum JBS, Chen K, Launer LJ, Fleisher AS, Lee W, Liu X, *et al.* Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. *Neurobiology of Aging.* 2012; 33: 827.e11–827.e19.
- [53] Hu H, Meng L, Bi YL, Zhang W, Xu W, Shen XN, *et al.* Tau pathologies mediate the association of blood pressure with cognitive impairment in adults without dementia: The CABLE study. *Alzheimer's & Dementia.* 2022; 18: 53–64.
- [54] Glodzik L, Mosconi L, Tsui W, de Santi S, Zinkowski R, Pirraglia E, *et al.* Alzheimer's disease markers, hypertension, and gray matter damage in normal elderly. *Neurobiology of Aging.* 2012; 33: 1215–1227.
- [55] Kester MI, van der Flier WM, Mandic G, Blankenstein MA, Scheltens P, Muller M. Joint effect of hypertension and APOE genotype on CSF biomarkers for Alzheimer's disease. *Journal of Alzheimer's Disease.* 2010; 20: 1083–1090.
- [56] Gottesman RF, Schneider ALC, Zhou Y, Coresh J, Green E, Gupta N, *et al.* Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA.* 2017; 317: 1443–1450.
- [57] Vemuri P, Knopman DS, Lesnick TG, Przybelski SA, Mielke MM, Graff-Radford J, *et al.* Evaluation of Amyloid Protective Factors and Alzheimer Disease Neurodegeneration Protective Factors in Elderly Individuals. *JAMA Neurology.* 2017; 74: 718–726.
- [58] Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Sr, Diaz-

- Arrastia R, Park DC. Risk factors for β -amyloid deposition in healthy aging: vascular and genetic effects. *JAMA Neurology*. 2013; 70: 600–606.
- [59] Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, *et al.* Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *The Lancet. Neurology*. 2019; 18: 942–952.
- [60] Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Lowe VJ, Graff-Radford J, *et al.* Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Annals of Neurology*. 2017; 82: 706–718.
- [61] Kim T, Yi D, Byun MS, Ahn H, Jung JH, Kong N, *et al.* Synergistic interaction of high blood pressure and cerebral beta-amyloid on tau pathology. *Alzheimer's Research & Therapy*. 2022; 14: 193.
- [62] Rabin JS, Yang HS, Schultz AP, Hanseeuw BJ, Hedden T, Viswanathan A, *et al.* Vascular Risk and β -Amyloid Are Synergistically Associated with Cortical Tau. *Annals of Neurology*. 2019; 85: 272–279.
- [63] Glodzik L, Rusinek H, Pirraglia E, McHugh P, Tsui W, Williams S, *et al.* Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. *Neurobiology of Aging*. 2014; 35: 64–71.
- [64] Sun HJ, Wu ZY, Nie XW, Bian JS. Role of Endothelial Dysfunction in Cardiovascular Diseases: The Link Between Inflammation and Hydrogen Sulfide. *Frontiers in Pharmacology*. 2020; 10: 1568.
- [65] Kolluru GK, Shackelford RE, Shen X, Dominic P, Kevil CG. Sulfide regulation of cardiovascular function in health and disease. *Nature Reviews. Cardiology*. 2023; 20: 109–125.
- [66] Gojon G, Morales GA. SG1002 and Catenated Divalent Organic Sulfur Compounds as Promising Hydrogen Sulfide Prodrugs. *Antioxidants & Redox Signaling*. 2020; 33: 1010–1045.
- [67] Kolluru GK, Shen X, Kevil CG. Reactive Sulfur Species: A New Redox Player in Cardiovascular Pathophysiology. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2020; 40: 874–884.
- [68] Hedegaard ER, Gouliaev A, Winther AK, Arcanjo DDR, Aalling M, Renaltan NS, *et al.* Involvement of Potassium Channels and Calcium-Independent Mechanisms in Hydrogen Sulfide-Induced Relaxation of Rat Mesenteric Small Arteries. *The Journal of Pharmacology and Experimental Therapeutics*. 2016; 356: 53–63.
- [69] Yin J, Tu C, Zhao J, Ou D, Chen G, Liu Y, *et al.* Exogenous hydrogen sulfide protects against global cerebral ischemia/reperfusion injury via its anti-oxidative, anti-inflammatory and anti-apoptotic effects in rats. *Brain Research*. 2013; 1491: 188–196.
- [70] Woo CW, Kwon JI, Kim KW, Kim JK, Jeon SB, Jung SC, *et al.* The administration of hydrogen sulphide prior to ischemic reperfusion has neuroprotective effects in an acute stroke model. *PLoS ONE*. 2017; 12: e0187910.
- [71] Wang Y, Jia J, Ao G, Hu L, Liu H, Xiao Y, *et al.* Hydrogen sulfide protects blood-brain barrier integrity following cerebral ischemia. *Journal of Neurochemistry*. 2014; 129: 827–838.
- [72] Jiang Z, Li C, Manuel ML, Yuan S, Kevil CG, McCarter KD, *et al.* Role of hydrogen sulfide in early blood-brain barrier disruption following transient focal cerebral ischemia. *PLoS ONE*. 2015; 10: e0117982.
- [73] Zhong H, Yu H, Chen J, Sun J, Guo L, Huang P, *et al.* Hydrogen Sulfide and Endoplasmic Reticulum Stress: A Potential Therapeutic Target for Central Nervous System Degeneration Diseases. *Frontiers in Pharmacology*. 2020; 11: 702.
- [74] Giovinazzo D, Bursac B, Sbodio JI, Nalluru S, Vignane T, Snowman AM, *et al.* Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulphydrating GSK3 β and inhibiting Tau hyperphosphorylation. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2017225118.
- [75] Disbrow E, Stokes KY, Ledbetter C, Patterson J, Kelley R, Pardue S, *et al.* Plasma hydrogen sulfide: A biomarker of Alzheimer's disease and related dementias. *Alzheimer's & Dementia*. 2021; 17: 1391–1402.
- [76] Reekes TH, Ledbetter CR, Alexander JS, Stokes KY, Pardue S, Bhuiyan MAN, *et al.* Elevated plasma sulfides are associated with cognitive dysfunction and brain atrophy in human Alzheimer's disease and related dementias. *Redox Biology*. 2023; 62: 102633.
- [77] Armario P, Gómez-Choco M. Contributions of neuroimaging to the knowledge of the relationship between arterial hypertension and cognitive decline. *Hypertension Research*. 2023; 46: 1344–1346.
- [78] Duperron MG, Knol MJ, Le Grand Q, Evans TE, Mishra A, Tsuchida A, *et al.* Genomics of perivascular space burden unravels early mechanisms of cerebral small vessel disease. *Nature Medicine*. 2023; 29: 950–962.
- [79] Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, *et al.* Neuroimaging standards for research into small vessel disease—advances since 2013. *The Lancet. Neurology*. 2023; 22: 602–618.
- [80] Thrippleton MJ, Backes WH, Sourbron S, Ingrisch M, van Osch MJP, Dichgans M, *et al.* Quantifying blood-brain barrier leakage in small vessel disease: Review and consensus recommendations. *Alzheimer's & Dementia*. 2019; 15: 840–858.
- [81] Barkhof F, Haller S, Rombouts SARB. Resting-state functional MR imaging: a new window to the brain. *Radiology*. 2014; 272: 29–49.
- [82] Carnevale L, Maffei A, Landolfi A, Grillea G, Carnevale D, Lembo G. Brain Functional Magnetic Resonance Imaging Highlights Altered Connections and Functional Networks in Patients With Hypertension. *Hypertension*. 2020; 76: 1480–1490.
- [83] Sheline YI, Raichle ME. Resting state functional connectivity in preclinical Alzheimer's disease. *Biological Psychiatry*. 2013; 74: 340–347.
- [84] Gu Y, Liu R, Qin R, Chen X, Zou J, Jiang Y, *et al.* Characteristic changes in the default mode network in hypertensive patients with cognitive impairment. *Hypertension Research*. 2019; 42: 530–540.
- [85] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr, Kawas CH, *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011; 7: 263–269.
- [86] Shah C, Srinivasan D, Erus G, Schmitt JE, Agarwal A, Cho ME, *et al.* Changes in brain functional connectivity and cognition related to white matter lesion burden in hypertensive patients from SPRINT. *Neuroradiology*. 2021; 63: 913–924.
- [87] Li X, Liang Y, Chen Y, Zhang J, Wei D, Chen K, *et al.* Disrupted Frontoparietal Network Mediates White Matter Structure Dysfunction Associated with Cognitive Decline in Hypertension Patients. *The Journal of Neuroscience*. 2015; 35: 10015–10024.
- [88] Wang D, Xu C, Wang W, Lu H, Zhang J, Liang F, *et al.* The Effect of APOE ϵ 4 on the Functional Connectivity in Frontoparietal Network in Hypertensive Patients. *Brain Sciences*. 2022; 12: 515.
- [89] Li X, Ma C, Sun X, Zhang J, Chen Y, Chen K, *et al.* Disrupted white matter structure underlies cognitive deficit in hypertensive patients. *European Radiology*. 2016; 26: 2899–2907.
- [90] Luo DH, Tseng WYI, Chang YL. White matter microstructure disruptions mediate the adverse relationships between hypertension and multiple cognitive functions in cognitively intact older

adults. *NeuroImage*. 2019; 197: 109–119.

- [91] Liao D, Guo ZP, Tang LR, Gao Y, Zhang ZQ, Yang MH, *et al*. Alterations in regional homogeneity and functional connectivity associated with cognitive impairment in patients with hypertension: a resting-state functional magnetic resonance imaging study. *Hypertension Research*. 2023; 46: 1311–1325.
- [92] Zhang Bin CJ, Li Y, Li X, Lang X, Li J, *et al*. MRI study of the effects of hypertension on brain structure and function in patients with Alzheimer's disease. *Chongqing Medicine*. 2018; 47: 1105–1108. (In Chinese)
- [93] Skillbäck T, Farahmand B, Bartlett JW, Rosén C, Mattsson N, Nägga K, *et al*. CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. *Neurology*. 2014; 83: 1945–1953.
- [94] Fu JL, Zhang T, Chang C, Zhang YZ, Li WB. The value of diffusion tensor imaging in the differential diagnosis of subcortical ischemic vascular dementia and Alzheimer's disease in patients with only mild white matter alterations on T2-weighted images. *Acta Radiologica*. 2012; 53: 312–317.
- [95] Palesi F, De Rinaldis A, Vitali P, Castellazzi G, Casiraghi L, Germani G, *et al*. Specific Patterns of White Matter Alterations Help Distinguishing Alzheimer's and Vascular Dementia. *Frontiers in Neuroscience*. 2018; 12: 274.
- [96] Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews. Neuroscience*. 2004; 5: 347–360.
- [97] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews. Neuroscience*. 2011; 12: 723–738.
- [98] de Leeuw F-E, Richard F, de Groot JC, van Duijn CM, Hofman A, van Gijn J, *et al*. Interaction Between Hypertension, apoE, and Cerebral White Matter Lesions. *Stroke*. 2004; 35: 1057–1060.
- [99] Walsh P, Sudre CH, Fiford CM, Ryan NS, Lashley T, Frost C, *et al*. The age-dependent associations of white matter hyperintensities and neurofilament light in early- and late-stage Alzheimer's disease. *Neurobiology of Aging*. 2021; 97: 10–17.
- [100] Debette S, Seshadri S, Beiser AS, Au R, Himali JJ, Palumbo C, *et al*. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011; 77: 461–468.
- [101] van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008; 39: 2712–2719.
- [102] McAleese KE, Firbank M, Dey M, Colloby SJ, Walker L, Johnson M, *et al*. Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathologica Communications*. 2015; 3: 60.
- [103] Schneider JA, Boyle PA, Arvanitakis Z, Bienias JL, Bennett DA. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. *Annals of Neurology*. 2007; 62: 59–66.
- [104] Zetterberg H, Blennow K. From Cerebrospinal Fluid to Blood: The Third Wave of Fluid Biomarkers for Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2018; 64: S271–S279.
- [105] Osborn KE, Liu D, Samuels LR, Moore EE, Cambrono FE, Acosta LMY, *et al*. Cerebrospinal fluid β -amyloid₄₂ and neurofilament light relate to white matter hyperintensities. *Neurobiology of Aging*. 2018; 68: 18–25.
- [106] Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, *et al*. Neuropathologic features of amnesic mild cognitive impairment. *Archives of Neurology*. 2006; 63: 665–672.
- [107] Rojas S, Brugulat-Serrat A, Bargalló N, Minguillón C, Turcholka A, Falcon C, *et al*. Higher prevalence of cerebral white matter hyperintensities in homozygous APOE- ϵ 4 allele carriers aged 45–75: Results from the ALFA study. *Journal of Cerebral Blood Flow and Metabolism*. 2018; 38: 250–261.
- [108] Lu D, Liu J, MacKinnon AD, Tozer DJ, Markus HS. Prevalence and Risk Factors of Cerebral Microbleeds: Analysis From the UK Biobank. *Neurology*. 2021; 97: e1493–e1502.
- [109] Gyanwali B, Shaik MA, Venketasubramanian N, Chen C, Hilal S. Mixed-Location Cerebral Microbleeds: An Imaging Biomarker for Cerebrovascular Pathology in Cognitive Impairment and Dementia in a Memory Clinic Population. *Journal of Alzheimer's Disease*. 2019; 71: 1309–1320.
- [110] Lim EY, Ryu SY, Shim YS, Yang DW, Cho AH. Coexistence of Cerebral Microbleeds and Amyloid Pathology in Patients with Cognitive Complaints. *Journal of Clinical Neurology*. 2020; 16: 83–89.
- [111] Ramusino MC, Vitali P, Anzalone N, Melazzini L, Lombardo FP, Farina LM, *et al*. Vascular Lesions and Brain Atrophy in Alzheimer's, Vascular and Mixed Dementia: An Optimized 3T MRI Protocol Reveals Distinctive Radiological Profiles. *Current Alzheimer Research*. 2022; 19: 449–457.
- [112] Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, *et al*. Association of Cerebral Microbleeds With Cognitive Decline and Dementia. *JAMA Neurology*. 2016; 73: 934–943.
- [113] Werring DJ, Gregoire SM, Cipolotti L. Cerebral microbleeds and vascular cognitive impairment. *Journal of the Neurological Sciences*. 2010; 299: 131–135.
- [114] De Reuck JL, Deramecourt V, Auger F, Durieux N, Maurage CA, Pasquier F, *et al*. Cerebrovascular Lesions in Mixed Neurodegenerative Dementia: A Neuropathological and Magnetic Resonance Study. *European Neurology*. 2017; 78: 1–5.
- [115] De Reuck JL, Deramecourt V, Auger F, Durieux N, Cordonnier C, Devos D, *et al*. The significance of cortical cerebellar microbleeds and microinfarcts in neurodegenerative and cerebrovascular diseases. A post-mortem 7.0-tesla magnetic resonance study with neuropathological correlates. *Cerebrovascular Diseases*. 2015; 39: 138–143.
- [116] Esiri M, Chance S, Joachim C, Warden D, Smallwood A, Sloan C, *et al*. Cerebral amyloid angiopathy, subcortical white matter disease and dementia: literature review and study in OPTIMA. *Brain Pathology*. 2015; 25: 51–62.
- [117] Carmelli D, Swan GE, Reed T, Wolf PA, Miller BL, DeCarli C. Midlife cardiovascular risk factors and brain morphology in identical older male twins. *Neurology*. 1999; 52: 1119–1124.
- [118] Turner ST, Fornage M, Jack CR, Jr, Mosley TH, Knopman DS, Kardia SLR, *et al*. Genomic susceptibility Loci for brain atrophy, ventricular volume, and leukoaraiosis in hypertensive sibships. *Archives of Neurology*. 2009; 66: 847–857.
- [119] Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, *et al*. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Science Translational Medicine*. 2012; 4: 147ra111.
- [120] Sun X, Dong C, Levin BE, Caunca M, Zeki Al Hazzourie A, DeRosa JT, *et al*. Systolic Blood Pressure and Cognition in the Elderly: The Northern Manhattan Study. *Journal of Alzheimer's Disease*. 2021; 82: 689–699.
- [121] Tzourio C, Dufouil C, Ducimetière P, Alpérovitch A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. *Epidemiology of Vascular Aging*. 1999; 53: 1948–1952.
- [122] Kujovic M, Lipka T, Zalman M, Baumann L, Jänner M, Baumann B. Treatment of hypertension and obstructive sleep apnea counteracts cognitive decline in common neurocognitive disorders in diagnosis-related patterns. *Scientific Reports*. 2023; 13: 7556.

- [123] SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, *et al.* Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA*. 2019; 321: 553–561.
- [124] Forette F, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, *et al.* Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet*. 1998; 352: 1347–1351.
- [125] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, *et al.* Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Archives of Internal Medicine*. 2003; 163: 1069–1075.
- [126] Peters R, Warwick J, Anstey KJ, Anderson CS. Blood pressure and dementia: What the SPRINT-MIND trial adds and what we still need to know. *Neurology*. 2019; 92: 1017–1018.
- [127] Murray AM, Hsu FC, Williamson JD, Bryan RN, Gerstein HC, Sullivan MD, *et al.* ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia*. 2017; 60: 69–80.
- [128] Williamson JD, Launer LJ, Bryan RN, Coker LH, Lazar RM, Gerstein HC, *et al.* Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Internal Medicine*. 2014; 174: 324–333.
- [129] Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, *et al.* Investigation of antihypertensive class, dementia, and cognitive decline: A meta-analysis. *Neurology*. 2020; 94: e267–e281.
- [130] Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, *et al.* Antihypertensive medications and risk for incident dementia and Alzheimer’s disease: a meta-analysis of individual participant data from prospective cohort studies. *The Lancet. Neurology*. 2020; 19: 61–70.
- [131] Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, *et al.* Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA*. 2020; 323: 1934–1944.