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Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review

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Abstract Hypertension is a highly prevalent condition which has been established as a risk factor for cardiovascular and cerebrovascular disease. Although the understanding of the relationship between cardiocirculatory dysfunction and brain health has improved significantly over the last several decades, it is still unclear whether hypertension constitutes a potentially treatable risk factor for cognitive decline and dementia. While it is clear that hypertension can affect brain structure and function, recent findings suggest that the associations between blood pressure and brain health are complex and, in many cases, dependent on factors such as age, hypertension chronicity, and antihypertensive medication use. Whereas large epidemiological studies have demonstrated a consistent association between high midlife BP and late-life cognitive decline and incident dementia, associations between late-life blood pressure and cognition have been less consistent. Recent evidence suggests that hypertension may promote alterations in brain structure and function through a process of cerebral vessel remodeling, which can lead to disruptions in cerebral autoregulation, reductions in cerebral perfusion, and limit the brain's ability to clear potentially harmful proteins such as β-amyloid. The purpose of the current review is to synthesize recent findings from epidemiological, neuroimaging, physiological, genetic, and translational research to provide an overview of what is currently known about the association between blood pressure and cognitive function across the lifespan. In doing so, the current review also discusses the results of recent randomized controlled trials of antihypertensive therapy to reduce cognitive decline, highlights several methodological limitations, and provides recommendations for future clinical trial design.

Keywords Hypertension · Hypotension · Blood pressure · Cognition · Cognitive impairment · Dementia

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Introduction

Hypertension is a highly prevalent condition, occurring in one third of the world's adults and two thirds of adults over age 65 [1, 2]. Already an established risk factor for cardiovascular and cerebrovascular disease [3–6], emerging evidence suggests that hypertension may also play an important role in the development of cognitive decline, Alzheimer's disease, and vascular dementia [7–9]. Because hypertension is a modifiable risk factor, it represents a potentially important mechanism through which the prevention or delay of age-related cognitive disorders may be possible. For this reason, understanding hypertension's role in the development and progression of age-related cognitive decline and dementia has been a research priority over the last two decades. Although a great deal has been learned from epidemiological studies, there is still little consensus about the effectiveness of treating hypertension to prevent or slow cognitive decline. What is clear, however, is that the connection between blood pressure (BP) and cognitive function is biologically complex and still not fully understood.

The goal of this review is to provide an overview of the research that has contributed to the understanding of the connection between BP and cognitive function, paying particular attention to recent findings. In doing so, this review will first provide an overview of what is known about the connection between hypertension, cognitive function, Alzheimer's disease, and vascular dementia. Second, the neurobiological changes associated with hypertension will be described, and the research that demonstrates how these biological processes influence neuronal function will be highlighted. Lastly, the findings from clinical trials designed to assess the effectiveness of antihypertensive agents for the prevention or delay of cognitive decline will be summarized. Methodological considerations and specific recommendations for future research will also be discussed. Although this review focuses on the topic of hypertension and cognitive function, the link between low BP and cognition will also be discussed.

Hypertension and Cognitive Function

Cross-Sectional and Longitudinal Observational Studies

Over the last several decades, the link between hypertension and cognitive function has been examined across many age groups. Although much of this research has focused on understanding the relationship between BP and cognition in older adults, the group most likely to experience cognitive decline, studies which assess BP starting in middle-age and follow participants forward until they reach older ages have also been especially informative. Multiple epidemiological studies have demonstrated that elevated BP in the 4th and 5th decades of life, particularly untreated hypertension, increases the risk for cognitive impairment 20–30 years later (see Table 1) [13•, 24, 25]. These findings have been further supported by longitudinal studies which show that high midlife BP is associated with increased cognitive decline over time [12, 21, 22•]. Because confounding variables, such as education and socioeconomic status, are less likely to affect cognitive change (compared to baseline cognitive abilities) [28], studies which show an increased rate of cognitive decline over time among hypertensive adults provide especially strong evidence for the deleterious effects of high BP. As will be discussed below, several studies have also identified hypertension duration and the trajectory of BP levels over time as important determinants of cognitive function later in life [11••, 23•].

Hypertension in the 6th and 7th decades has been associated with poorer overall cognitive function and cognitive decline (see Table 2) [29, 32, 35, 47, 48]. Hypertension among individuals in their 70s has also been identified as a risk factor for mild cognitive impairment (MCI)—a state of subtle cognitive decline that is believed to precede the onset of dementia [34, 49]. In contrast, studies that include individuals in their 8th, 9th, and 10th decades of life have largely either failed to find such an association [36, 46] or have found high BP to be protective against cognitive impairment [38, 39]. Together, these results suggest that the relationship between cognition and BP in late-life may be age dependent [14]. Inverted U- or J-shaped curves may most accurately represent the relationship between BP and cognition among octogenarians and nonagenarians, as both low BP and extremely high BP (systolic blood pressure (SBP) >160 mmHg) have been linked to cognitive impairment in this age group [39, 44, 45, 50].

While individuals who develop hypertension earlier in life are likely to be subjected to the deleterious neurological effects of hypertension for many decades, this is not the case for individuals who develop hypertension much later. The strong associations found between midlife hypertension and late-life cognitive abilities support the notion that hypertension duration and chronicity in adulthood may be especially important determinants of cognitive impairment in elderly individuals. Perhaps the strongest support for this hypothesis comes from a longitudinal study which found that a longer duration of time between hypertension initiation and cognitive testing is associated with reduced cognitive abilities independent of age [11••]. In particular, longitudinal studies suggest that middle-aged adults with prolonged hypertension and elevated systolic blood pressure (SBP) over a period of 25–30 years are at an exceptionally high risk for cognitive impairment later in life [11••, 23•]. Thus, studies with a longer period between the initiation of BP monitoring and subsequent cognitive assessment may be better able to detect the effects of high BP on neurocognitive outcomes. The trajectory of blood pressure changes from midlife into older age may also be important, as the combination of hypertension in midlife and low diastolic blood pressure (DBP) in late-life has been associated with smaller brain volumes and poorer cognitive outcomes among older adults [51••]. Individuals who develop hypertension before middle adulthood may also be at particularly high risk for cognitive impairment, as a number of studies have found associations between high BP, cognitive deficits, and reduced academic functioning in children, adolescents, and young adults [10, 52–56]. Irrespective of age, the cognitive domains that appear most vulnerable to hypertension are executive functioning and information processing speed. Both cognitive processes rely heavily on the integrity of frontal and subcortical brain structures which may be most vulnerable to the effects of hypertension.

Blood Pressure Variability

BP fluctuates substantially over a 24-h period as a result of factors such as postural change, circadian rhythm, and general physiologic variability [57, 58]. Fluctuations in BP associated with autonomic dysfunction, such as orthostatic hypotension, become more prevalent with increasing age and may be

Table 1 Epidemiologic studies of early- and midlife hypertension and cognition

Study	Study design duration *n*	Age at BP assessment	BP measure	Age at cognitive assessment	Cognitive domains assessed	Major findings
NHANES III, USA [10]	Cross-sectional *n* = 5077	6–16	SBP, DBP	6–16	Arithmetic reading Visuospatial Working memory	Elevated SBP, but not DBP, was associated with poorer working memory.
Normative Aging Study, USA [11••]	Cross-temporal[a] 29 years *n* = 758	37 (5) (BP measured every 3–5 years for up to 44 years)	HTN	66 (5)	Multi-domain composite score	HTN at any point during follow-up and greater duration since onset of HTN were associated with lower cognitive functioning later in life, independent of age at onset.
NHLBI Twin Study, USA [12]	Cross-temporal[a] 25 years Longitudinal 10 years *n* = 392	43–53	SBP, DBP	T1: 59–69 T2: 68–79	MMSE Processing speed Verbal fluency Visual memory	Elevated SBP at baseline was associated with declines in processing speed over a period of 10 years.
Honolulu-Asia Aging Study, USA [13•]	Cross-temporal[a] 25 years *n* = 3735	53 (5)	SBP, DBP	78 (5)	Cognitive Abilities Screening Instrument (CASI)	Elevated SBP at baseline was associated with poorer cognitive functioning in late-life.
Xi'an, China [14]	Cross-sectional *n* = 1799	40–85	SBP, DBP, MAP	40–85	MMSE	Elevated SBP, DBP, and MAP were associated with cognitive impairment among 40–60-year-olds, but this was not the case for older participants.
Whitehall II, UK [15]	Cross-temporal[a] 12 years *n* = 5838	44 (6)	SBP, DBP	56	Memory Reasoning Verbal fluency Vocabulary	Elevated SBP at baseline was associated with poorer baseline memory and reduced verbal fluency at follow-up, especially among women.
REGARDS, USA [16]	Cross-temporal[a] 3 years *n* = 17,630	64 (9)	HTN	67	Multi-domain composite score	HTN was not associated with the development of cognitive impairment over a span of 40 months.
Framingham Heart Study, USA [17]	Cross-temporal[a] 12 years *n* = 1814	40–69	HTN	T1: 52 (8) T2: 64	Executive function Memory Visuospatial	HTN was associated with worse performance on measures of executive functioning and visual memory.
NHANES III, USA [18]	Cross-sectional *n* = 3270	30–59	HTN	30–59	Processing speed reaction time Working memory	HTN and DM, but not HTN alone, was associated with worse reaction time, processing speed, and working memory.
EVA Study Group, France [19]	Longitudinal 4 years *n* = 1373	59–71	HTN	T1: 59–71 T2: 63–75	MMSE	Baseline HTN was associated greater MMSE declines over 4 years. This relationship was stronger among participants who were untreated for hypertension.
ARIC, USA [20]	Longitudinal 6 years *n* = 10,963	47–70	HTN	T1: 47–70 T2: 53–76	Memory Processing speed Verbal fluency	Baseline HTN was associated with greater decline in processing speed over a 6-year period.
ARIC, USA [21]	Longitudinal	59 (4)	HTN	T1: 59 (4)	Memory	

Table 1 (continued)

Study	Study design duration *n*	Age at BP assessment	BP measure	Age at cognitive assessment	Cognitive domains assessed	Major findings
	14 years *n* = 12,702			T2: 62 T3: 65 T4: 73	Processing speed Verbal fluency	Baseline HTN was associated with greater declines in verbal fluency over a 14-year period.
ARIC, USA [22•]	Longitudinal 20 years *n* = 13,476	45–64	Pre-HTN, HTN	T1: 48–67 T2: 54–73 T3: 70–89	Processing speed Verbal fluency Verbal memory	Baseline HTN was associated with greater declines in processing speed, verbal fluency, and a global composite score of cognitive functioning over a 20-year period.
Western Collaborative Group Study, USA [23•]	Cross-temporal[a] 25–30 years *n* = 717	39–59 (BP measured approximately 10 times over 30 years)	SBP	75 (4)	Executive function Memory Processing speed	Compared to participants who maintained a normal SBP over 30 years, participants who had persistently high SBP had poorer verbal memory in late-life. Participants who displayed a significant decrease in SBP over 30 years performed more poorly on measure of processing speed.
Male Cohort in Uppsala, Sweden [24]	Cross-temporal[a] 20 years *n* = 999	50	SBP, DBP	72	Multi-domain composite score	Elevated DBP at baseline was associated with reduced cognitive functioning in late-life. This relationship was stronger among participants who were untreated for hypertension.
Male Cohort in Uppsala, Sweden [25]	Cross-temporal[a] 20 years *n* = 502	50	SBP, DBP	72 (1)	Memory Processing speed Verbal fluency Visuospatial Working memory	Elevated DBP at baseline was associated with poorer performance on measures of working memory, processing speed, and verbal fluency in late-life. Participants with DBP $\leq$ 70 mg Hg at baseline demonstrated highest levels cognitive functioning in late-life.
Framingham, USA [26]	Cross-temporal[a] 28 years *n* = 1993	27–87 (BP measured biennially over 28 years)	HTN, SBP, DBP	55–89	Attention Language Memory Visuospatial	Among participants untreated for hypertension, the proportion of visits during which HTN was present and the average SBP and DBP were inversely associated with cognitive functioning.
ARIC, USA [27]	Cross-sectional *n* = 13,840	45–69	HTN	45–69	Processing speed Verbal fluency Verbal memory	HTN among women, but not men, was associated with poorer performance on all cognitive measures.

ARIC Atherosclerosis Risk in Communities, *BP* blood pressure, *DBP* diastolic blood pressure, *EVA* epidemiology of vascular aging, *HTN* hypertension, *MAP* mean arterial pressure, *MMSE* Mini-Mental Status Exam, *NHANES III* National Health and Nutrition Examination Survey, *NHLBI* National Heart, Lung, and Blood Institute, *REGARDS* Reasons for Geographic and Racial Differences in Stroke, *SBP* systolic blood pressure

[a] Cross-temporal: a study design in which the exposure variable (e.g., hypertension) and the outcome variable (e.g., cognition) are measured in distinct time points

Table 2 Epidemiologic studies of late-life hypertension and cognition

Study	Study design duration *n*	Age at BP assessment	BP measure	Age at cognitive assessment	Cognitive domains assessed	Major findings
COGNIPRES, Spain [29]	Cross-sectional *n* = 1579	71 (7)	HTN, SBP, DBP, PP, MAP	71 (7)	MMSE	HTN and antihypertensive medication noncompliance were associated with lower MMSE scores.
Kungsholmen Project, Sweden [30]	Longitudinal 3 years *n* = 1736	75–101	SBP, DBP	T1: 75–101 T2: 78–104	MMSE	Higher SBP and DBP at baseline were associated with better MMSE score at baseline and 3-year follow-up. Baseline SBP < 130 mmHg was associated with increased risk of cognitive impairment at follow-up.
REGARDS, USA [31]	Cross-sectional *n* = 14,566	65 (9)	HTN	65 (9)	Six-item screener	HTN was not associated with risk of cognitive impairment.
Framingham Heart Study, USA [32]	Cross-temporal[a] 13 years *n* = 1702	67 (8)	HTN	80	Abstract reasoning Language Memory Verbal fluency Working memory	Baseline HTN was associated with poorer working memory, visual memory, and verbal memory at follow-up among participants not on antihypertensive medication.
Framingham Heart Study, USA [33]	Cross-temporal[a] 4–6 years *n* = 1423	66 (7)	HTN	71	Abstract reasoning Executive function Memory	Baseline HTN was associated with greater memory impairment 4–6 years later in men, but not in women.
Northern Manhattan Study, USA [34]	Longitudinal 6 years *n* = 4337	76 (6)	HTN	T1: 78 T2: 80 T3: 81	Executive function Language Memory	Baseline HTN was associated with declines in executive functioning, but not memory or language.
REGARDS USA [35]	Cross-sectional *n* = 19,836	65 (10)	SBP, DBP, PP	65 (10)	Six-item Screener	Higher DBP was associated with greater risk of cognitive impairment.
Indo-US Cross National Dementia Epidemiology Study, India/USA [36]	Cross-sectional *n* = 4810 *n* = 636	67 (7) 82 (4)	SBP, DBP	67 (7) 82 (4)	MMSE	Higher SBP and DBP were associated with increased risk for cognitive impairment in the younger Indian cohort. No association between BP and cognitive impairment was found in the older American cohort.
Osservatorio Geriatrico Regione Campania, Italy [37]	Cross-sectional *n* = 1229	74 (6)	SBP, DBP	74 (6)	MMSE	Higher DBP, but not SBP, was associated with cognitive impairment in participants >75, but not in participants 65–74 years of age.
Baltimore Longitudinal Study of Aging, USA [38]	Longitudinal 11 years *n* = 847	71 (9)	SBP, DBP	82	Attention Executive function Memory Naming Processing speed	High SBP was associated with memory declines among older participants. Cross-sectional analyses demonstrated that both high and low diastolic BP were associated with poorer executive functioning, processing speed, and naming among participant groups.
	Cross-sectional	65–104	SBP, DBP	65–104	MMSE	

Table 2 (continued)

Study	Study design duration *n*	Age at BP assessment	BP measure	Age at cognitive assessment	Cognitive domains assessed	Major findings
Chicago Health and Aging, USA [39]	*n* = 5816					Participants with SBP < 100 mmHg and SBP > 140 mmHg had lower MMSE scores.
Chicago Health and Aging, USA [40]	Longitudinal 6 years *n* = 4284	74 (6)	SBP, DBP	80	MMSE Memory Processing speed	BP was not associated with cognitive change over the span of 6 years.
The Italian Longitudinal Study on Aging, Italy [41]	Cross-sectional *n* = 3425	65–84	HTN	65–84	MMSE	Hypertension was not associated with MMSE score.
Men Born in 1914, Sweden [42]	Cross-sectional *n* = 500	68	HTN	68	Processing speed Verbal abilities Visual memory Visuospatial	HTN (SBP 140–159 mmHg) was associated with better visuospatial and verbal abilities. Severe HTN (SBP ≥ 180 mmHg) was associated with poorer performance on measures of memory and processing speed.
Cardiovascular Health Study, USA [43]	Longitudinal 7 years *n* = 5888	≥65	SBP	≥72	Modified MMSE Processing speed	SBP Elevated SBP was associated with a decline in MMSE and processing speed over a period of 7 years.
East Boston cohort study, USA [44]	Longitudinal 9 years *n* = 3657	74 (6)	SBP, DBP	83	Memory SPMSQ	A U-shaped relationship between SBP and cognition was found whereby SBP < 130 mmHg or ≥160 mmHg was associated with a higher rate of errors on a mental status questionnaire (SPMSQ).
Duke Population Studies of the Elderly, USA [45]	Longitudinal 3 years *n* = 3202	73 (6)	SBP, DBP	76	SPMSQ	Among white participants, a U-shaped relationship between SBP cognitive decline was found whereby SBP < 110 mmHg and SBP > 165 mmHg was associated with 3-year cognitive decline. No association between BP and cognition was found in black participants.
East Boston Study, USA [46]	Cross-sectional *n* = 3627	≥ 65	SBP, DBP, HTN	≥ 65	Attention Memory	BP was not associated with cognitive functioning.

BP blood pressure, *COGNIPRES* cognitive function and blood pressure control, *DBP* diastolic blood pressure, *HTN* hypertension, *MAP* mean arterial presure, *MMSE* Mini-Mental Status Exam, *PP* pulse pressure, *REGARDS* Reasons for Geographic and Racial Differences in Stroke, *SBP* systolic blood pressure, *SPMSQ* Short Portable Mental Status Questionnaire

[a] Cross-temporal: a study design in which the exposure variable (e.g., hypertension) and the outcome variable (e.g., cognition) are measured in distinct time points

associated with cognitive deficits [57, 59, 60]. Although a number of studies have demonstrated a connection between orthostatic hypotension and cognitive function, with worse performance in the setting of orthostasis [61–64], others have failed to replicate this finding [65–67]. Ambulatory blood pressure measurement (ABPM) has been used in a number of studies to more accurately capture short-term, daily BP variability, which may reflect autonomic dysfunction or increased arterial stiffness, among other etiologies. Using ABPM, elevated 24-h mean BP, 24-h BP variability, and reduced nocturnal dipping (a natural reduction of night-time BP) have each been identified as potential risk factors for cognitive impairment [24, 68–70]. Because autonomic dysfunction occurs in the early phase of several neurodegenerative disorders [71], it is difficult to determine whether cognitive deficits found in individuals with potential sequelae of autonomic dysfunction (e.g., BP variability and orthostatic hypotension) are the result of underlying neurodegenerative changes or the direct effect of transient drops in BP.

Genetic Factors

Additional insights into the relationship between hypertension and cognition have emerged through genetic studies. A polymorphism in the *ACE* gene, a gene which regulates BP through its effects on angiotensin-converting enzyme (ACE) activity [72], has been linked to both cognitive function [73] and the presence of neuroimaging abnormalities [74, 75]. Middle-aged and older adults who carry an allele that codes for the high-activity variant (D) of the ACE I/D polymorphism show greater levels of cognitive impairment and cognitive decline [73, 76, 77•, 78]. Unexpectedly, other studies have found the low-activity allele (I) of the ACE I/D polymorphism to confer increased risk for dementia [79, 80]. Polymorphisms in another gene, *AGTR1*, which codes for the angiotensin-II type 1 receptor, also an important part of the regulation of BP, have been associated with reduced prefrontal and hippocampal volume [81], reductions in hippocampal volume over time, and poorer memory in older adults [82]. Additional evidence suggests that specific genetic variants may interact with hypertension to promote or buffer against the effects of elevated BP on cognitive function and brain structural integrity. Two Alzheimer's disease risk genes that have also been associated with cognitive function in nondemented individuals, *Apolipoprotein E* (APOE) and *Clusterin* (CLU), appear to modify the effect of hypertension on cognitive function [83]. For example, multiple studies have found that hypertension is only associated with cognitive deficits in individuals who possess a copy of the ε4 allele of the APOE gene [84, 85].

Dementia Risk and Hypertension

Alzheimer's Disease

Several forms of cardiovascular disease have been identified as risk factors for both Alzheimer's disease and vascular dementia [86–89], which together account for the majority of dementia cases worldwide [90, 91]. Alzheimer's disease, cerebrovascular disease, and cardiovascular disease have shared genetic contributions [92, 93], and approximately 50% of individuals diagnosed with Alzheimer's disease display significant cerebrovascular pathology on autopsy [94, 95]. Together, these findings suggest that cardiovascular disease, Alzheimer's disease, and vascular dementia may have an overlapping pathophysiology [96–98].

Despite significant evidence for the role of cardiovascular disease in the pathogenesis and progression of Alzheimer's disease, the association between hypertension and Alzheimer's disease is still not well understood. Although a consistent relationship between elevated DBP at midlife and incident Alzheimer's disease has been demonstrated [7, 99•, 100], evidence for an association between midlife SBP and incident Alzheimer's disease has been conflicting [100–104]. What is clear is that late-life hypertension does not appear to be a risk factor for incident Alzheimer's disease [88, 104, 105, 106•, 107–109]. In fact, multiple studies suggest that abnormally low DBP in late-life may increase one's risk for Alzheimer's disease [107, 110–114]. Some, but not all, have argued that this inverse relationship between late-life DBP and Alzheimer's disease risk results from a tendency for BP to decline concurrently with the onset and progression of dementia [106, 115, 116]. Together, previous findings suggest that the combination of high BP in midlife followed by low BP in late-life may place individuals at especially high risk of developing Alzheimer's disease. However, few studies have examined this hypothesis directly [117].

Vascular Dementia

Because hypertension is a known risk factor for cerebral small vessel disease [118] and stroke [4], hypertension is often considered a risk factor for vascular dementia, a form of cognitive decline resulting from small- or large-vessel cerebrovascular disease [9, 119]. However, only a handful of studies have directly examined the relationship between hypertension and vascular dementia. Although previous research supports the relationship between midlife hypertension and the development of vascular dementia [8, 99•, 101, 120–122], it is unclear whether there is an association between late-life hypertension and vascular dementia, as findings have thus far been conflicting [88, 105, 107, 123]. Compared to the associations between midlife hypertension and incident Alzheimer's disease, the associations found between midlife hypertension and incident

vascular dementia tend to be more robust and consistent [8, 101, 120]. However, because patients are more likely to develop mixed Alzheimer's and vascular dementia than pure forms of one or the other, this distinction may not be meaningful.

Pathophysiology of Hypertension as It Relates to Cognitive Decline

Evidence from Neuroimaging and Biomarker Studies

Neuroimaging has played a pivotal role in advancing the understanding of how BP influences cognitive function and underlying brain structure. Results from studies that have examined the relationship between BP and brain volume are largely consistent with findings from the BP and cognition studies. High SBP has been associated with smaller regional and total brain volumes [124–128] and reductions in brain volume over time [129]. The relationship between high DBP and brain volume is less consistent, however [125, 127, 128, 130]. In elderly populations, low SBP [131, 132] and low DBP [132, 133] have been associated with reduced brain volume and cortical thickness, suggesting that the relationship between BP and brain volume may be age dependent [12, 134, 135]. A pattern of hypertension in midlife followed by hypotension in late-life appears to be especially harmful [51••], particularly in brain regions affected in the earliest phase of Alzheimer's disease [136•].

An association between hypertension and the development of Alzheimer's disease has also been supported by research that examines Alzheimer's disease biomarkers directly. Compared to the brains of normotensive individuals, the brains of individuals with a history of hypertension show greater levels of β-amyloid plaques, atrophy, and neurofibrillary tangles [102, 137]. Similarly, hypertension has been identified as a risk factor for cortical fibrillar β-amyloid deposits [97, 138, 139] and reduced glucose metabolism in Alzheimer's disease-specific brain regions [138, 140] using positron emission tomography (PET) in the brains of cognitively normal middle-aged and older adults. Consistent with these findings, one study found that individuals with abnormal plasma β-amyloid levels and elevated BP at midlife have an especially high risk of developing Alzheimer's disease later in life [7].

Hypertension has also been associated with several defining features of vascular dementia and cerebral small vessel disease, including WMH volume [12, 118], WMH progression [141•, 142], lacunar infarction, and cerebral microbleeds [5, 143–145]. Supporting the relationship between high BP and white matter pathology, findings from observational studies [142] and clinical trials [128, 146] suggest that treatment of hypertension reduces WMH progression. Even before the development of overt neuroimaging abnormalities, hypertension appears to be associated with reduced white matter microstructural integrity in both young and old individuals, suggesting white matter may be especially vulnerable to the deleterious effects of hypertension [147–150].

Hypertension and Vascular Remodeling

Emerging evidence suggests that sustained elevations in BP may cause cerebral vessel remodeling in a manner which promotes pathological brain changes and subsequent cognitive decline. To preserve the steady low-pressure blood supply to the periphery and protect end-organ microcirculation from pulsatile stress associated with hypertension, a rearrangement in vessel wall material in the form of hypertrophic remodeling of the media and vascular smooth muscle cells occurs [151–153]. This enlargement in media size causes a reduction in lumen diameter, leading to increased vascular resistance and vessel wall stiffening [154]. Arterial stiffening, in turn, increases arterial pulse wave velocity and pulsatile pressure, which over time causes rarefaction of downstream capillaries and further inward remodeling of vessel walls [155–157]. Hypertension promotes intracranial atherosclerosis in large intracranial arteries [157, 158] and arteriolosclerosis in smaller arterioles supplying subcortical white matter and deep gray matter brain structures [159]. Arteriolosclerosis is a process characterized by a loss of tunica media smooth muscle cells, fibro-hyaline deposits, and thickening of the vessel wall, resulting in increased microvascular resistance. Because the brain requires high levels of continuous perfusion throughout systole and diastole [160], increases in vascular resistance leave cerebral arterioles vulnerable to hypoperfusion when systemic BP is reduced [154, 159]. As described below, hypoperfusion has been associated with several neurovascular changes [98], which together may disrupt cognition [161].

Autoregulation and Cerebral Perfusion

The brain requires a high volume of consistent blood flow to sustain adequate perfusion. However, the brain's ability to maintain steady low-pressure blood flow in the context of changing systemic BP—a process known as cerebral autoregulation—can be disrupted as a result of chronic hypertension [162, 163•]. After prolonged exposure to high BP and elevated pulsatility, a shift occurs in the brain's autoregulatory capacity whereby higher systemic BP is required to maintain the same level of cerebral perfusion [164]. Hypertension is believed to alter cerebral autoregulation by inducing changes in arteriole endothelial and vascular smooth muscle cells that diminish cerebrovascular reactivity [165] and increase myogenic tone, respectively [166]. Not only do these vascular changes shift the cerebral autoregulatory curve in a manner which reduces resting cerebral blood flow, but the brain also becomes more susceptible to hypoperfusion during periods of low systemic BP [167] or during periods of normal BP in chronically hypertensive individuals [168]. These

hypertension-induced changes to cerebral autoregulation and perfusion may explain why individuals with chronic hypertension in midlife and low BP in late-life show significant reductions in brain volume [51••, 136•] and greater levels of cognitive deficits [117].

While ischemia may occur in some cases, the brain is more likely to be subjected to chronic oligemia (i.e., mild reductions in blood flow) as a result of hypertension. Chronic oligemia may, in turn, lead to endothelial dysfunction, acidosis, oxidative stress, and unmet metabolic energy demands that can impair neuronal function [98, 169, 170]. Oligemia may also downregulate the synthesis of proteins necessary for synaptic plasticity and memory formation [170], and promote neuronal tau phosphorylation, β-amyloid oligomerization, and the upregulation of amyloidogenic APP [171–175]. Each of these neurophysiological changes likely contributes to the development of Alzheimer's disease and cerebral amyloid angiopathy (CAA). Evidence suggests that β-amyloid accumulation may also occur as a result of hypertension-induced upregulation of the receptor for advanced glycation end products (RAGE), which controls the shuttling of β-amyloid from the blood across the endothelial barrier into the brain [176•].

Endothelial Dysfunction, Altered Functional Hyperemia, and Oxidative Stress

By promoting endothelial dysfunction, hypertension is also believed to disrupt the coordinated coupling among neurons, glia, and cerebral blood flow in the microvasculature [177]. Uncoupling of this system, known collectively as the neurovascular unit, can impair the homeostatic process of functional hyperemia, whereby increases in CBF occur in coordination with increases in neuronal activity to ensure the delivery of adequate levels of oxygen and glucose and facilitate the removal of metabolites [178–180]. Support for these findings comes from animal research, which has demonstrated that hypertension-induced vascular oxidative stress resulting from upregulation of reactive oxygen species (ROS)-producing enzyme NADPH oxidase impairs the endothelium-dependent expression of vasodilators and vasoconstrictors necessary to maintain neurovascular coupling [165, 181, 182].

Antihypertensive Clinical Trials to Improve Cognition

Given the apparent association between BP and cognitive function, efforts have been made to determine whether improved BP control can be used to delay cognitive decline and reduce dementia risk. To date, evidence from large placebo-controlled, randomized clinical trials (RCTs) has been conflicting [183, 184••]. A 2009 Cochrane Review of randomized, double-blind, placebo-controlled trials concluded that there is currently no convincing evidence for the neuroprotective effects of antihypertensive use in late-life [184••]. Although several large placebo-controlled RCTs, such as the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [185], the Systolic Hypertension in Europe (SYST-EUR study) [186], and the Heart Outcomes Prevention Evaluation (HOPE) study [187] have found antihypertensive agents to be protective against cognitive decline and dementia, just as many trials have failed to replicate this finding [188–192]. Thus, it is unknown whether BP control alone is enough to reduce the risk of cognitive decline. It is possible that the neuroprotective effects of antihypertensive agents may result from drug-specific neurobiological changes as opposed to (or in addition to) BP lowering [193, 194]. In support of this idea, a meta-analysis of RCTs which compared the neuroprotective properties of different antihypertensive drug classes found angiotensin receptor blockers (ARBs) to be superior to β-blockers, diuretics, and ACE inhibitors for preventing cognitive decline [195].

The ability to draw conclusions about the effectiveness of BP interventions for the reduction of cognitive decline has been limited by brief study durations and insufficient power to detect effects. Cognitive decline, even in the course of neurodegenerative disease, is a relatively gradual process, and as described above, elevated BP in midlife may be the most important determinant of risk for subsequent cognitive and decline and dementia. Thus, midlife may be the most critical window during which BP control must begin. Extended treatment and follow-up periods and larger sample sizes will likely be needed to reliably detect the effects of BP lowering on cognitive measures. By comparison, neurodegenerative and dementia-specific biomarkers (e.g., hippocampal atrophy and CSF-tau) may be more sensitive to treatment-related effects, but their validity as intermediate endpoints remains a subject of debate [196, 197]. Future studies may also benefit from making use of a more comprehensive cognitive battery. The Mini-Mental State Examination (MMSE), which has been used to assess cognitive abilities in the majority of previous trials, is notoriously insensitive to cognitive change, especially in domains of executive functioning and processing speed, making it an especially poor choice for detecting cognitive change in this context [198, 199]. Additionally, effect sizes in previous BP-lowering trials may have been attenuated because participants receiving antihypertensive medication often saw only minor reductions in BP compared to participants given placebo. This limitation is addressed in an ongoing trial (SPRINT-MIND) to evaluate the neuroprotective effects of reducing BP to below a specific level (i.e., below 120 mmHg) using one or more antihypertensive agents [200•]. The parent trial to this study (SPRINT) has already demonstrated improved cardiovascular outcomes in the setting of this tighter blood pressure control [201]. However, the ability of this trial to show benefit in cognitive outcomes will be limited by short follow-up.

Conclusions and Future Directions

It is clear that hypertension can affect brain structure and function in a manner that increases one's risk of cognitive decline and dementia. Hypertension, high SBP, and high DBP during midlife have been most consistently linked to late-life cognitive decline and incident dementia. However, hypertension has been associated with early-life and midlife cognitive deficits as well. Although the association between late-life hypertension and cognitive function is less clear, particularly among octogenarians and nonagenarians, limited evidence suggests that mildly elevated BP in late-life may be protective against cognitive decline, especially for individuals with a history of longstanding hypertension. Hypertension duration may be an especially important determinant of cognitive decline, as evidence suggests that the damaging neurological effects of hypertension may be cumulative. Few studies have assessed BP longitudinally, and even fewer have attempted to retrospectively determine how lifetime duration of hypertension relates to cognitive function. Given the increasing prevalence of hypertension among younger individuals [202], assessing the cumulative effects of elevated BP over the lifespan will be especially important to understanding how BP may influence neurodevelopment and neurodegeneration [203].

Recent advances in neuroimaging and physiologic and hemodynamic monitoring have allowed for an improved understanding of the mechanisms through which hypertension affects neurocognitive function. Hypertension, especially in midlife, has been identified as a risk factor for cerebral atrophy, white matter microstructural damage, and cerebral small vessel disease. Evidence suggests that hypertension contributes to the development and progression of such neurological changes by promoting vessel wall remodeling and endothelial dysfunction, which results in autoregulatory deficits. These changes to the neurovascular unit leave the brain vulnerable to hypoperfusion resulting from drops in systemic BP. Although evidence exists to support this model of hypertension-induced cerebrovascular changes, much is still unknown about how these pathophysiological processes directly influence cognitive function and promote Alzheimer's and vascular dementia in humans.

Additional insights into the role circulatory changes play in cognitive decline will likely come from the study of other markers of vessel function. For example, pulse pressure, a measure of arterial stiffening, which increases with age and exposure to hypertension [160], can be used as an additional method to quantify the effects of vascular pathology resulting from chronic hypertension. Elevations in pulse pressure have been associated with cognitive impairment [204, 205], cognitive decline [205], cerebral small vessel disease [142, 206], and Alzheimer's disease biomarkers [207]. Compared to BP, pulse pressure is believed to more precisely quantify the exposure of target organs such as the brain to potentially harmful pulsatile energy resulting from arterial stiffening [208].

A more nuanced understanding of the relationship between BP and neural function will likely be needed before antihypertensive therapies can be effectively employed as an intervention to reduce cognitive decline. Given that many individuals who develop hypertension do so before late-life and experience the harmful effects of hypertension for decades, it is unclear whether specific antihypertensive agents will be able to modify the trajectory of cognitive decline within the span of a multi-year trial. If the effects of hypertension on the brain are cumulative, interindividual differences in the duration and severity of previous hypertension must be considered in future trial design. Because the effects of BP on cognition appear to differ with age, future clinical trials may also benefit from limiting enrollment to specific age groups. Other factors such as race, sex, genetics, and the presence of cerebrovascular morbidity have each been identified as effect modifiers in observational studies and should, therefore, be considered when designing future antihypertensive trials.

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Compliance with Ethical Standards

Conflict of Interest Drs. Walker and Power declare no conflicts of interest relevant to this manuscript. Dr. Gottesman reports personal fees from American Academy of Neurology, outside the submitted work, as an Associate Editor for the journal *Neurology*.

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