The relationship between blood pressure and cognitive function

Vera Novak and Ihab Hajjar

Abstract | The relationship between blood pressure (BP) and cognitive outcomes in elderly adults has implications for global health care. Both hypertension and hypotension affect brain perfusion and worsen cognitive outcomes. The presence of hypertension and other vascular risk factors has been associated with decreased performance in executive function and attention tests. Cerebrovascular reserve has emerged as a potential biomarker for monitoring pressure–perfusion–cognition relationships. A decline in vascular reserve capacity can lead to impaired neurovascular coupling and decreased cognitive ability. Endothelial dysfunction, microvascular disease, and mascrovascular disease in midlife could also have an important role in the manifestations and severity of multiple medical conditions underlying cognitive decline late in life. However, questions remain about the role of antihypertensive therapies for long-term prevention of cognitive decline. In this Review, we address the underlying pathophysiology and the existing evidence supporting the role of vascular factors in late-life cognitive decline.

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Introduction

The relationship between blood pressure (BP) and cognitive outcomes in the elderly has gained attention because of its implications for global health care. Hypertension affects more than a third of the population worldwide,[1] especially those older than 65 years, of whom 65–75% report having hypertension.[2] The prevalence of asymptomatic hypotension in this age group is 16.2%.[3] Both high and low BP have been linked with cognitive decline and dementia. The pathophysiology of the relationship between BP and cognition is unclear, but hypoperfusion and neurodegeneration have emerged as possible underlying mechanisms.[4–7] The BP levels that should be targeted to achieve optimal perfusion while preventing cognitive decline are still being debated.

In this Review, we summarize the evidence indicating that decline in vascular reserve capacity, which is associated with impaired neurovascular coupling, is one of the main pathways linking BP to cognitive decline. We also discuss physiological monitoring and MRI studies that improve our understanding of the pathophysiology linking abnormalities in brain vascular reserve and cognitive decline, and present supporting clinical evidence for the BP–cognition relationship from epidemiological studies and clinical trials of antihypertensive therapies.

BP and cognition

Both hypertension and hypotension are associated with disruptions in neurovascular coupling, which lead to a decrease in vascular reserve capacity and can cause microvascular disease, stroke, cognitive decline, and dementia. Factors other than perfusion, such as genetic predisposition, autonomic failure, and neurodegeneration associated with diabetes mellitus, Alzheimer disease, Parkinson disease, and Lewy body disease, have also been proposed to contribute to the progression of dementia, although the mechanisms underlying these associations are still unclear.

BP and brain perfusion

Neurovascular coupling is a concept that refers to the interactions between neurons, vessels and other cells of

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The authors, the journal Chief Editor B. Mearns and the CME questions author C. P. Vega declare no competing interests.

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Key points

- Hypertension and hypotension affect neurovascular coupling, leading to a decrease in perfusion, oxygenation, and vascular reserve capacity, and are associated with microvascular disease, stroke, cognitive function decline, and dementia
- Risk factors for vascular disease accelerate age-related decline in perfusion and brain tissue volumes and have additive effects in worsening cognitive outcomes late in life
- Hypertension and other vascular risk factors are linked to poorer performance in executive function and attention tests than in memory or language scores
- Results of antihypertensive treatment in trials for prevention of dementia in the elderly remain inconclusive, but some studies indicate that single-drug or combined antihypertensive therapies have protective effects on cognition
- More research is needed to determine which blood pressure values should be targeted to optimize perfusion and to prevent cognitive decline in the elderly

the nervous system (such as astrocytes and other glial cells), considered as the basis of the relationship between neuronal activity, hemodynamic factors, and cell-to-cell signaling.[8] These interactions synchronize increases in neuronal activity with perfusion and thus facilitate communication within the functional networks of the brain. Neurovascular coupling enables redistribution of cerebral blood flow (CBF) to areas of increased activity and metabolic demand, as well as allowing adjustments in response to beat-to-beat changes in transmural pressure and central autonomic nervous system activity. The three main components of neurovascular regulation are neurogenic, metabolic (mediated by molecules such as O_2, CO_2, ATP, and glucose, among others), and myogenic regulation. Neurogenic regulation refers to tonic and phasic activity within the network of the central autonomic nervous system, which includes noradrenergic, serotoninergic, cholinergic, and dopaminergic neuronal activity, and also modulates endothelial function and signaling among neuronal networks. These regulatory systems, which converge in associative cortical areas, are widely involved in numerous cognitive and motor functions.

Changes in BP are associated with changes in brain perfusion and metabolism. The capacity of the neurovascular units within vascular territories and of the whole brain to respond to variation in BP and increased metabolic demands is referred to as the brain vascular reserve. Endothelial dysfunction associated with advanced age and risk factors such as hypertension and diabetes set the stage for altered neurovascular coupling and regional decline in vasomotor reserve capacity.[9] In this setting, increased oxidative stress and inflammation lower the intrinsic threshold for cell survival.[10]

Integration of multiple pathways

The combination of advanced age with hypertension and other risk factors provides a background for multifaceted interactions in pathophysiological pathways that lead to cognitive decline and dementia. Examples of these pathways are those involved in small vessel disease, altered regulation of blood flow, presence of white matter hyperintensities (WMHs), deposition of amyloid β A4 protein and neurofibrillary tangles, altered cholinergic transmission, and autonomic failure, as well as those resulting from genetic predisposition (such the *APOEε4* genotype). These pathways interact in a complex pattern. For example, clearance of amyloid β A4 protein from the brain is dependent on vascular reactivity, which in turn is affected by small vessel disease, whereas the presence of comorbidities associated with small vessel disease may contribute to the pathology of Alzheimer disease. Interactions between multiple pathophysiological pathways result in neuronal death, cortical and subcortical white matter disconnection, and functional decline,[11] primarily in the associative areas of frontal and temporal cortices, which are involved in complex functions such as decision-making and memory.

BP has been increasingly linked not only with the pathophysiology of Alzheimer dementia and vascular dementia (the second most common form of dementia, in which several vascular mechanisms, such as those associated with stroke, lacunar infarcts, small vessel disease, or chronic cardiovascular disease, are linked with severe cognitive impairment), but also with mild cognitive impairment (MCI) and mild cognitive disorders (MCDs). MCI is as a state of cognitive deterioration in which the affected person does not have either normal cognitive function or dementia; objective or subjective evidence of cognitive deterioration is present, but activities of daily living are preserved and complex functions are intact or minimally impaired. Subcategories of this classification are single or multidomain MCI with or without memory involvement (amnestic or nonamnestic MCI, respectively).[12] MCDs are a broader spectrum of preclinical cognitive (including neurodegenerative) pathologies.[13] The relationship between BP and these pathologies emphasizes the importance of altered neurovascular coupling in all of these settings.[14] Nevertheless, the relationship between BP and cognition throughout life is still not well understood, with some studies showing a strong association between cognitive decline and hypertension, others showing an association with declining BP, and others showing no such associations. The actual relationship between BP and cognition might be predictable over the course of a lifespan if neurovascular coupling is considered as a hidden variable and the duration of exposure of neurons and cerebral perfusion to fluctuations in BP is assessed. Mounting evidence suggests that the associations between endothelial dysfunction, microvascular disease, and macrovascular disease could have an important role in the manifestations and severity of multiple medical conditions that underlie cognitive decline late in life.

Assessment of vascular reserve

Two biomarkers of vascular reserve are clinically relevant —pressure autoregulation and CO_2 vasoreactivity.[15] Conditions affecting BP regulation are associated with alterations in these markers, which can be assessed with several MRI techniques (Table 1).

Autoregulation

BP autoregulation maintains a fairly stable perfusion over the range of mean systemic pressures 60–150 mmHg.

Table 1 | Modalities for assessment of vascular reserve

Method	Measured variable	Advantages	Limitations
Transcranial Doppler utrasonography	Ultrasound frequency shift reflecting flow velocity in large arteries	Temporal resolution (beat-to-beat ~1 s) Independent of body position	Insonation window, angle, and signal quality Constant artery diameter assumption
Three-dimensional continuous arterial spin labeling MRI	Arterial H^+ spin tagging to measure blood flow	Spatial resolution Noninvasive measurements of regional perfusion	Standard template Signal averaging (~30 s per whole brain) T1 time prolongation by hematocrit Magnetic resonance field inhomogeneities
Blood-oxygen-level-dependent MRI	T2*-weighted imaging to detect differences in oxygenated and deoxygenated hemoglobin	Coupling between regional neuronal activity and blood flow, with a basis on changes of blood oxygenation	Indirect measure of blood flow and activity Signal averaging (~5 s) Standard template Magnetic resonance field inhomogeneities
Single photon emission computed tomography	Technetium-99	Spatial resolution	Signal averaging (~30 s per projection, typically 64 projections) Invasive

Static autoregulation refers to long-term 'steady-state' control, whereas dynamic autoregulation refers to the adaptation of perfusion to beat-to-beat variations in intracranial pressure and BP.[16] Numerous conditions, such as hypertension,[17] hypotension,[18] diabetes,[19] vascular disease, and stroke,[20–22] as well as smoking, impair autoregulation. With impaired autoregulation, the sigmoid autoregulation curve that expresses the relationship between CBF and mean BP becomes more linear and perfusion becomes pressure-dependent (Figure 1). Hypertension and hypotension alter CBF regulation, and the lower limits of the autoregulation window are shifted toward higher BP values. Therefore, the autoregulation range is narrowed and the slope of the CBF–BP curve becomes steeper. In this setting, vasodilatation in response to low BP can be reduced and vasoconstriction in response to high BP can be increased.

Orthostatic and postprandial hypotension are defined as a ≥20 mmHg decline in systolic BP when in an upright position, or within 1 h after a meal, respectively.[23] In hypotension syndromes, altered BP regulation leads to supine hypertension. In individuals with hypotension syndromes, the mean BP can thus vary with postural change, from 80 mmHg in the upright position to >180 mmHg in the supine position. Accordingly, in these individuals the autoregulated range can be narrowed to ≈20 mmHg[24] when in the upright position, or expanded over a wide range of pressures (mean BP 110–180 mmHg), and the lower autoregulation threshold can be shifted toward high BP values.[18] Therefore, in the setting of hypotension syndromes, the upright-position BP might be below the range of effective regulation, leading to perfusion decline. In these patients, daily living activities can induce hypoperfusion[25] and lead to syncope,[26] falls, or ischemia and cognitive changes.[27]

Transcranial Doppler ultrasonography (TCD) enables noninvasive assessment of dynamic autoregulation from spontaneous fluctuations in BP and CBF velocity[28] at baseline and during postural interventions, such as standing up or head-up tilt.[15,29] CBF fluctuations at 0.01–0.03 Hz have been linked with intracranial pressure,[30] central sympathetic activity,[31] microcirculation, and cerebral oxygenation.[32]

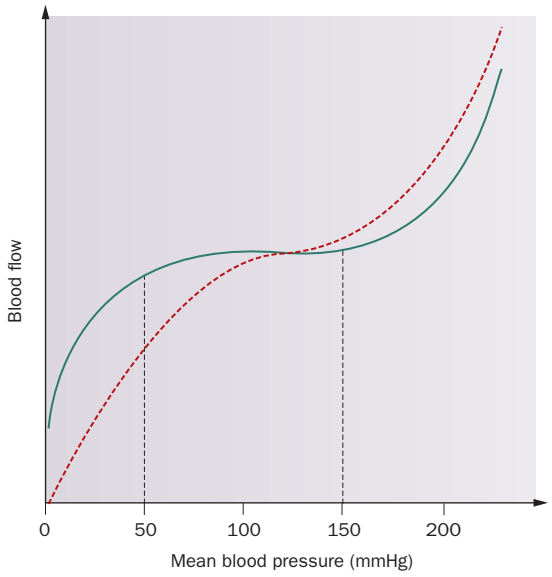

Figure 1 | Normal cerebral autoregulation curve with its lower (50 mmHg) and upper (150 mmHg) limits of mean arterial pressure (green line), and a narrowed range with a steeper curve (red dashed line).

Autoregulation is quantified using mathematical modeling, Fourier transform analysis, coherence function, and more-recently developed nonlinear methods.[19,33–35] A substantial phase lead of CBF velocities with respect to the peripheral BP indicates intact autoregulation.[28,36,37] Nonlinear approaches, such as multiple coherence[15] and multimodal pressure-flow (MMPF), enable assessment of autoregulation at multiple timescales and have greater sensitivity and specificity for detection of autoregulation defects than linear methods.[19,35] The MMPF method demonstrates, for example, that hypertension and diabetes substantially impair autoregulation to an observable degree after ischemic stroke (Figure 2).[35]

CO_2 vasoreactivity

CO_2 vasoreactivity is measured from CBF responses to vasoconstrictor (such as hypocapnia or hyperventilation) and vasodilatating (such as CO_2 rebreathing, breath

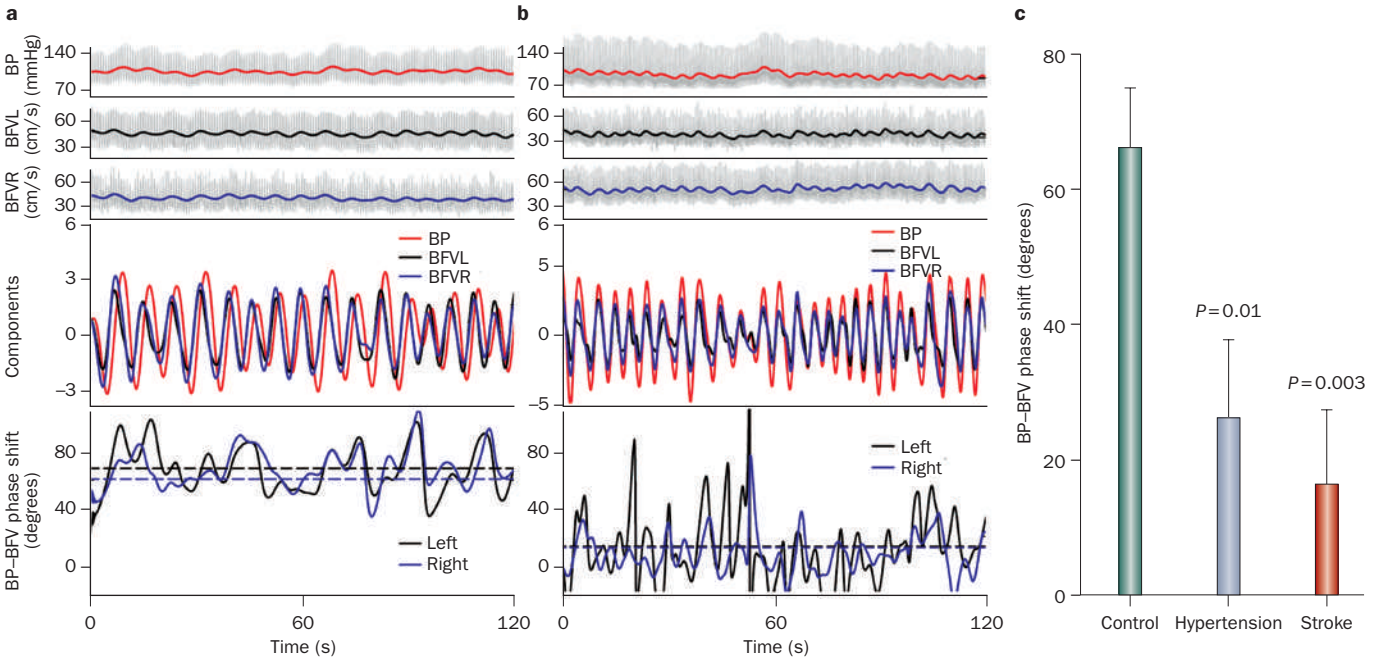

Figure 2 | Relationship between arterial BP and BFV in the middle cerebral artery. **a** | Dominant spontaneous oscillations of BP and BFV in a 72-year-old healthy control woman. **b** | Dominant spontaneous oscillations of BP and BFV in a 68-year-old man with type 2 diabetes mellitus, in the supine position. BP, BFVL and BFVR were decomposed into different modes, each mode corresponding to fluctuations at a different timescale. BP and BFV fluctuations exhibit continuous and dominant oscillations at frequencies 0.07–0.4 Hz. Instantaneous phases of BP and BFV oscillations (solid lines, bottom graphs) and the mean BP–BFV phase shift (dashed lines) were obtained. **c** | Phase shift between arterial BP and BFV. Results were obtained from 12 healthy controls, 10 patients with hypertension, and 10 patients with history of stroke, by calculating the instantaneous phase shift during the Valsalva maneuver. Dynamic autoregulation in controls was characterized by specific BP–BFV phase shifts. The reduction of the phase shifts observed in participants with hypertension who had never had a stroke and patients with history of stroke indicates impaired autoregulation. Abbreviations: BFV, blood flow velocity; BFVL, left BFV; BFVR, right BFVR; BP, blood pressure. Parts a and b modified with permission from Hu *et al.*[19] Part c reprinted with permission from Hu *et al.*[35]

holding, or acetazolamide administration) stimuli.[38] Vasoreactivity is calculated as the percent flow change per CO_2 change. TCD-based assessment of vasoreactivity is restricted to CBF velocity measurements in one or two vascular territories. Advances in imaging techniques based on three-dimensional continuous arterial spin labeling (3D CASL) MRI, blood-oxygen-level-dependent (BOLD) MRI, and single photon emission computed tomography (SPECT) imaging, however, enable the assessment of vasoreactivity in anatomical regions and vascular territories (Table 1).[39] These techniques have advantages over TCD by providing a better assessment of the regional distribution of vasoreactivity, but lack temporal resolution and values need to be averaged over a period of time (a few minutes). Aging, hypertension, diabetes, or stroke reduce vasodilatation[40,41] in multiple vascular territories, whereas vasoconstriction can be preserved.[42] The variability of CBF responses to pathogenic stimuli underscores the importance of underlying small and large vessel disease that can lead to chronic hypoperfusion in numerous brain regions.

Assessment of microvascular disease

Cerebromicrovascular disease associated with hypertension and other cardiovascular risk factors, including age, is linked with regional hypoperfusion and brain volume loss (Figure 3), as well as with neuronal degeneration and cognitive decline in elderly people.[43–48] Cerebromicrovascular disease accelerates CBF decline with age[49–52] and is associated with regional differences in vasoregulation and reserve capacity.[9]

MRI has enabled the visualization of microvascular disease (that is, lacunar infarctions, microinfarctions, microbleeds, iron deposits, and diffused WMHs) with unprecedented resolution (Figure 4). Of note, microinfarcts and iron deposits in patients with hypertension can be visible at ultrahigh-field MRI at 8 T, but not at lower resolutions (Figure 4).[53] WMHs are associated with global and regional brain atrophy, including hippocampal atrophy;[51] reduced functional neuronal mass, which indicates that an active neurodegenerative process has taken place;[54] lower perfusion[55] and metabolism[56] in the white matter, which affect preferentially frontal, parietal, and temporal cortices; lower oxygenation in the frontal lobes;[57] slower CBF velocities;[58] cognitive decline and executive dysfunction;[59] vascular dementia;[60–62] motor impairment;[63] and depression.[64] The presence of WMHs was also associated with a 24-year increase in diastolic BP (>10 mmHg; odds ratio [OR] 2.6, 95% CI 1.3–5.1), systolic BP (>40 mmHg; OR 2.0, 95% CI 1.2–3.4), pulse pressure (>24 mmHg; OR 1.8, 95% CI 1.1–2.7), and mean arterial pressure (>6 mmHg; OR 2.2, 95% CI 1.4–3.4).[65]

BP, cognitive decline, and dementia

Epidemiological studies (Tables 2–5) support the evidence for an age-dependent association between BP and decline in cognitive function and/or dementia. Specifically, high BP (especially high systolic BP) in middle age is consistently associated with late-life cognitive impairment and dementia.[58] Therefore, treatment of high sytolic BP during midlife might be an effective strategy to reduce the risk of late-life dementia and cognitive impairment.[66] By contrast, the association between low BP and cognitive dysfunction is more complicated, and is, therefore, less well understood. Orthostatic hypotension in middle age can indicate autonomic failure (a failure in BP regulation causing fluctuations in BP and perfusion during daily living activities), but is a sign of frailty (onset of rapid decline) in old age.

Hypertension and risk of cognitive decline

Hypertension in middle age and cognition

A combination of hypertension and other vascular risk factors in the middle-aged population could accelerate worsening of cognitive performance late in life (Table 2). Data from a prospective study of a population 40–69 years old with a 12-year follow-up showed that individuals with either central obesity (the uppermost quartile) or hypertension had poorer performance on executive functioning and visual–motor skills tests (Trail Making Test Part B, and Visual Reproduction Immediate and Delayed Recall tests) than other individuals in the population.[67] This association was not observed, however, in leaner individuals with hypertension, and neither hypertension nor obesity was individually or synergistically related to verbal memory (immediate or delayed recall). In another study, obesity was related to increased cerebroascular resistance, slowed CBF velocities, increased systolic BP, and male sex.[68] Hypertension and diabetes were associated with a decline in the ability to perform executive function tasks (Delayed Word Recall Test, Digit Symbol Substitution Test, and Word Fluency Test) in the ARIC study.[69] In the NHANES III study,[62] stroke and the *APOEε4* genotype were independent predictors of verbal memory decline assessed by the Delayed Word Recall Test. Metabolic syndrome, hypertension, and stroke were independently associated with cognitive decline as assessed by the Word Fluency Test. Furthermore, the combination of hypertension and diabetes was associated with decreased cognitive ability as assessed by three measures of cognitive function (Simple Reaction Time Test, Symbol Digit Substitution Test, and Serial Digit Learning Test).[70] These findings indicate that a complex composed of several aspects of vascular disease (such as stroke, lacunar infarcts, and WMHs) is linked to deficits in attention and executive function, rather than to a decline in memory (a feature clinically linked with Alzheimer disease). In the REGARDS cross-sectional study,[71] the odds of experiencing a stroke symptom increased by 35% with each of the following factors: hypertension, diabetes, smoking, lack of exercise, and depressive symptoms; the odds of cognitive impairment increased by 12% with each modifiable factor, in an additive manner.[71] A subsequent analysis of the REGARDS study showed that an increment of 10 mmHg in diastolic BP, but not systolic BP, was associated with an increased risk (7%) of cognitive impairment.[72] Findings of an inverse association between diastolic or systolic BP and cognitive performance (assessed by a wide range of memory, semantic, and fluency tests) that was independent of age, education, employment grade, smoking status, alcohol consumption, use of antihypertensive medication, diagnosis of diabetes, and cardiovascular disease support the existence of a negative relationship between high BP and cognition.[73]

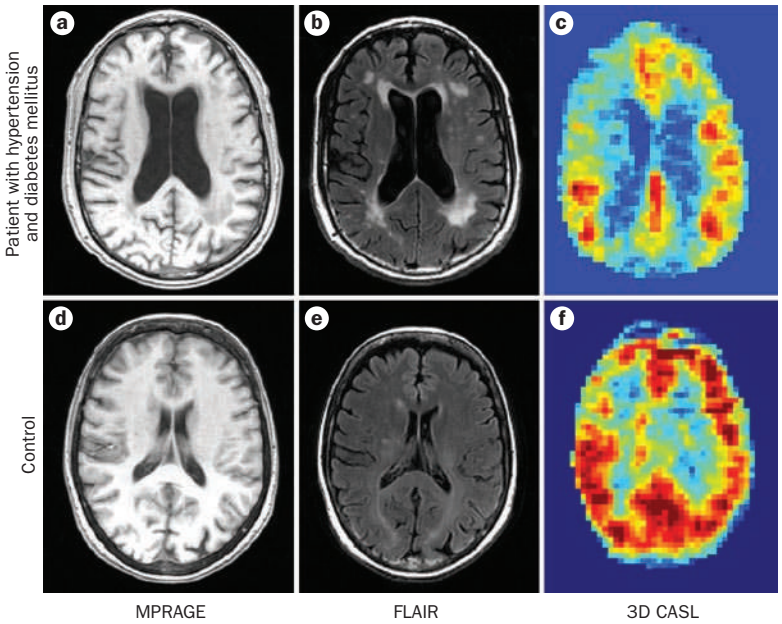

Figure 3 | Anatomical and perfusion images from a patient with hypertension and diabetes mellitus and an age-matched healthy control. **a** | Brain volume loss. **b** | Extensive periventricular white matter hyperintensities. **c** | Reduced perfusion in the frontal and temporal regions. **d** | Normal brain volume. **e** | Absence of white matter hyperintensities. **f** | Normal perfusion throughout the brain. Abbreviations: 3D CASL, three-dimensional continuous arterial spin labeling; FLAIR, fluid attenuated inversion recovery; MPRAGE, T1-weighted magnetization-prepared rapid acquisition with gradient echography.

In a study of individuals aged 60–64 years, a large proportion (71%) of those diagnosed as having MCI reverted to a non-MCI status 4 years later, whereas only 11% of individuals with any MCD reverted to a non-MCD status.[13] Participants with a history of smoking or harmful levels of alcohol consumption, diagnosed but not medically treated hypertension, anxiety, or depression, were at increased risk of transitioning to MCI or any MCD.[13] These findings support the notion that modifiable risk factors may contribute to late-life cognitive decline. Of note, decreased CBF in middle-aged individuals has been linked with worse cognition later in life among patients with hypertension, which indicates that hypoperfusion in middle age might mediate late-life cognitive decline in these individuals.[74]

Hypertension and cognition in the elderly

HYVET[75] and HYVET-COG[76-78] enrolled people older than 80 years with uncontrolled hypertension (systolic BP 160–199 mmHg and diastolic BP <110 mmHg; Table 3).

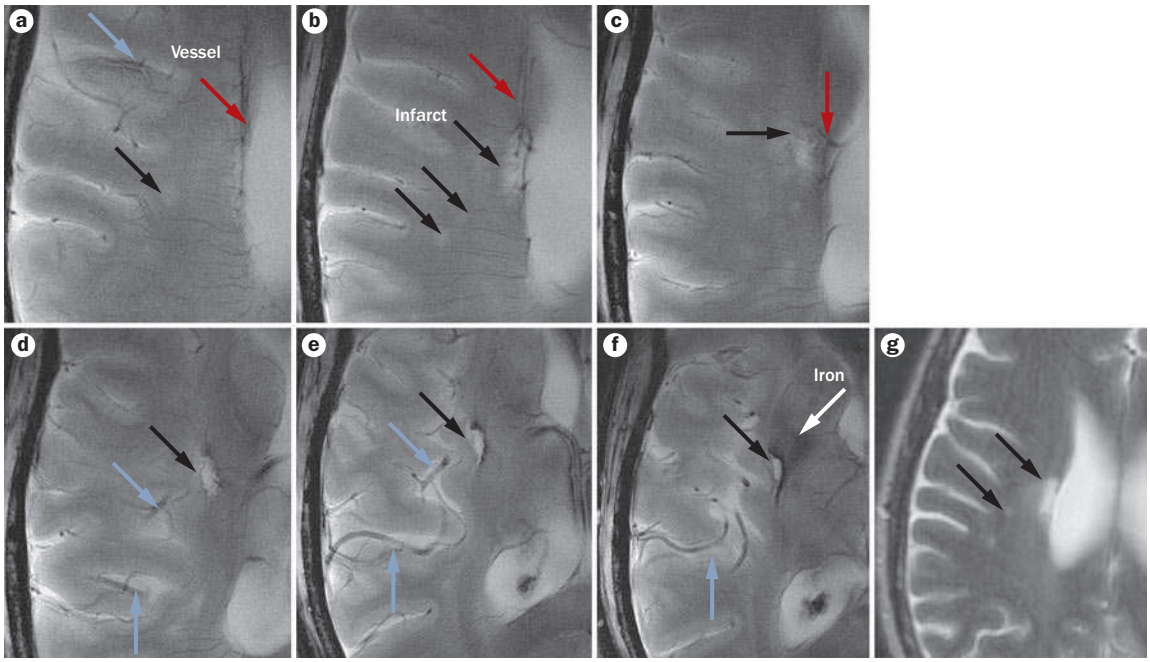

Figure 4 | High resolution 8-T gradient gadolinium-enhanced echography slices (in-plane pixel size 195 μm). **a**–**f** | Vascular supply to the lacunar infarctions and vascular patterns in the infarcted region. Black arrows, infarct sites. Red arrows, small vessel ending within low signal intensity foci in the lacunar infarction. Blue arrows, branches of the cerebral artery supplying infarcted areas. White arrow, larger area of low signal intensity suggestive of iron deposits that extends beyond infarction into the basal ganglia. Iron deposition in brain parenchyma may represent blood–brain-barrier breakdown associated with microvascular disease and microinfarcts. **g** | Clinical T2-weighted image of the infarcted area (indicated by black arrows), obtained with 1.5-T MRI. Modified with permission from Novak *et al.*[53]

The median minimental state examination (MMSE) score was 26 (maximum 30); the MMSE score was higher at younger age, with male sex, higher educational level, higher creatinine and total-cholesterol levels, and lower HDL-cholesterol levels. Being either underweight or obese was shown to contribute to decline in MMSE scores and was also associated with increased incidence of dementia.[77] Of note, lower MMSE scores have been associated with higher systolic and lower diastolic BP during sitting and standing in another study.[79]

In the HYVET study,[75] antihypertensive treatment in elderly patients did not statistically reduce the incidence of dementia. However, this negative finding might have been due to a short follow-up, owing to the early termination of the trial after reductions in mortality and incidence of stroke were demonstrated in association with antihypertensive therapy.

In COGNIPRES, a cross-sectional study of 1,579 patients,[80] the prevalence of cognitive impairment defined by low MMSE scores was 12.3%. Low MMSE scores were associated with age >80 years, uncontrolled BP, and poor compliance to antihypertensive treatment, in addition to history of anxiety, stroke, or transient ischemic attack, and other comorbidities. Overall, BP was controlled only in 28.3% of participants, and 33.6% showed poor adherence to antihypertensive treatment. In a prospective community-based cohort of individuals aged >65 years residing in Northern Manhattan, USA, hypertension was associated with an increased risk of all-cause MCI and nonamnestic MCI, but not with amnestic MCI.[81] Hypertension was related to worse executive ability scores, but not to worse memory or language scores, which confirms the specific link between high BP and executive function and attention.

Hypotension and risk of cognitive decline

Orthostatic hypotension affects about 7% of the normotensive elderly population and >30% of those aged >75 years who have other conditions such as diabetes, cardiac diseases, or Parkinson disease.[82] Orthostatic hypotension increases the risk of stroke, falls, and cognitive decline,[82] regardless of whether the BP drop is systolic or diastolic and regardless of baseline BP (Table 4).[83,84] In the ARIC study,[84] the effect of orthostatic hypotension on several cognitive domains was assessed in a cohort of 12,702 participants over 12 years of follow-up. Participants with orthostatic hypotension were more likely to be in the lowest quartile of the Digit Symbol Substitution Test and the Word Fluency Test scores. However, this association was not independent of other cardiovascular and socioeconomic factors.

With orthostatic hypotension, the maintenance of adequate cerebral perfusion at low BP levels depends on autoregulation. Hypoperfusion can develop with impaired autoregulation, or when BP is low, or when BP falls below the autoregulation range, and can lead to cognitive decline. Among patients with BP in the lower-normal range or hypotension (systolic BP <120 mmHg, diastolic BP <70 mmHg), orthostatic hypotension increases the odds of cognitive impairment (measured as >1 MMSE

Table 2 | Epidemiological studies of hypertension in middle age and cognition

Study name	*n*, age (years)	Study period	Outcomes	BP measures	Covariates	Associations with cognitive tasks
PATH[13]	2,082, 60–64	4 years follow-up	MCI, MCD	Systolic BP 140.77 ± 24.8 43% receiving antihypertensive medication	D, RF, DM, alcohol	Progression from MCI to MCD associated with HTN, harmful alcohol consumption, anxiety, and depression
Framingham Heart Study[67]	1,814, 40–69	8–12 years follow-up	Neuropsychological tests	HTN Antihypertensive medication	Obesity	HTN and midlife obesity associated with worse executive function and visual motor skills, but not memory
ARIC[69]	1,130, ~60	14 years follow-up	Neuropsychological tests	HTN	D	HTN and DM associated with worse executive function (Word Fluency and Delayed Word Recall tests); metabolic syndrome, stroke, and *APOEε4* genotype associated with decline in Delayed Word Recall test scores
NHANES III[70]	3,385 enrolled, 3,270 analyzed, 30–59	Cross-sectional	Neuropsychological tests Short-questionnaire survey	HTN Antihypertensive medication	D, SES	HTN and DM associated with worse cognition (Simple Reaction Time, Digit Symbol Substitution, and Serial Digit Learning tests)
REGARDS[71]	14,566, >45	Cross-sectional	Six-item screening test for cognition and stroke	HTN Antihypertensive medication	D, DM	HTN, DM, depression, smoking, and lack of exercise associated with increased risk of cognitive impairment
Whitehall II[73]	5,838, 46–68	12 years follow-up	Neuropsychological tests	HTN	D, RF	HTN associated with worse memory, semantic, and fluency tests
REGARDS[72]	19,836, 55–74	Cross-sectional	Six-item screening test based on MMSE	HTN Antihypertensive medication	D, RF, depression	High diastolic BP, but not high systolic BP, associated with impaired cognition

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BP, blood pressure; D, demographic variables; DM, diabetes mellitus; HTN, hypertension (>140/90 mmHg); MCD, mild cognitive disorder; MCI, mild cognitive impairment; MMSE, minimental state examination; NHANES III, National Health and Nutrition Examination Survey III; PATH, Personality and Total Health through Life; REGARDS, REasons for Geographic and Racial Differences in Stroke; RF, risk factors (BMI, DM, HTN, cholesterol, smoking); SES, socioeconomic status.

score decline; OR = 4.1, 95% CI 1.11–15.1).[81] This effect might be explained by the fact that, in patients with hypotension, perfusion could decline as BP falls below the autoregulated range. By contrast, among patients with hypertension (systolic BP >140 mmHg, diastolic BP >90 mmHg), the presence of orthostatic hypotension reduces the odds of cognitive impairment (OR = 0.48, 95% CI 0.26–0.90).[85] In patients with hypertension, perfusion can remain within the autoregulated range, or even increase, owing to compensatory vasodilation in response to orthostatic hypotension. Of note, patients with orthostatic hypotension typically have hypertension when in the supine position.

In the Malmö Preventive Project (MPP),[86] the relationship between orthostatic hypotension and long-term morbidity was assessed in 722 men aged 52.6 ± 3.6 years over a follow-up period of 19 ± 5.3 years. 5 years after enrollment, 9.9% of participants had orthostatic hypotension; in 64.5% of the cases of orthostatic hypotension, a decline in systolic BP, but not in diastolic BP, was observed. Orthostatic hypotension was independently associated with age, low BMI, hypertension, increased heart rate, antihypertensive treatment, diabetes, and current smoking. Men with orthostatic hypotension had an increased risk of coronary events, stroke, and all-cause mortality, as shown in a multivariate adjusted Cox proportional hazard model. Furthermore, participants with orthostatic hypotension, both at baseline and during follow-up, were at the highest risk of any adverse event among the study population (OR = 1.76, 95% CI 1.28–2.43).[86] The Helsinki Aging Study,[87] which involved 650 people aged 75–85 years, also found that participants with low general BP had low MMSE scores (<24), whereas hypertension was found to be unrelated to cognitive impairment. In this study, baseline assessments showed that participants with dementia had lower BP than those without dementia and also had signs of left ventricular dysfunction.

BP changes late in life could be the consequence of brain degeneration, or might also be its cause. Declining BP and orthostatic hypotension late in life are markers of general frailty, as they indicate underlying autonomic failure associated with diabetes, Alzheimer disease, Parkinson disease with dementia, Lewy body dementia, and other disorders. The loss of central autonomic regulation and perfusion regulation in late age, which alter the BP–perfusion relationship in the setting of hypotension, might have a broad impact on cognitive networks and, ultimately, on morbidity and mortality. The link between these factors, however, remains unclear.

Table 3 | Epidemiological studies of hypertension in the elderly and cognition

Study name	*n*, age (years)	Study period	Outcomes	BP measures	Covariates	Associations with cognitive tasks
HYVET[75] and HYVET-COG[76–78]	3,763, >80	32 years follow up	Dementia, Hachinski ischemic scale, CT scan	Systolic BP 160–200 mmHg	D, RF, creatinine	Lower MMSE score associated with HTN, female sex, lower education, and comorbidities
COGNIPRES[80]	1,579, >60	Cross-sectional	MMSE, 12.3% MCI	HTN Antihypertensive medication	D	Lower MMSE score associated with HTN and poor compliance with antihypertensive therapy
Northern Manhattan[81]	918, >75–80	4.7 years follow-up	MCI	HTN Antihypertensive medication	D, RF, stroke	HTN associated with increased risk of all-cause MCI and nonamnestic MCI, but not associated with amnestic MCI

Abbreviations: BP, blood pressure; COGNIPRES, Cognitive function and blood pressure control; D, demographic variables; HTN, hypertension (>140/90 mmHg); HYVET, Hypertension in the Very Elderly Trial; HYVET-COG, HYVET cognitive function assessment; MCI, mild cognitive impairment; MMSE, minimental state examination; RF, risk factors (BMI, diabetes mellitus, HTN, cholesterol, smoking).

Table 4 | Epidemiological studies of hypotension and cognitive decline

Study name	*n*, age (years)	Follow-up (years)	Outcomes	BP measures	Covariates	Associations with cognitive tasks
ARIC[84]	12,702, 50–60	12	Neuropsychological tests	OH, HTN	D, E, RF	OH associated with worse cognition (Digit Symbol Substitution and Word Fluency tests)
MPP[86]	722 men, 50–55	20	Cardiac disease stroke, mortality	OH, HTN	D, RF	OH associated with increased age, low body mass, HTN, antihypertensive treatment, DM, smoking, coronary events, stroke, and all-cause mortality
Helsinki Ageing Study[87]	650, 75–85	10	MMSE	OH, HTN	D, RF	Low BP associated with MMSE <24; HTN unrelated to cognition

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BP, blood pressure; D, demographic variables; DM, diabetes mellitus; E, education; HTN, hypertension; OH, orthostatic hypotension; MPP, Malmö Preventive Project; MMSE, minimental state examination; RF, risk factors (BMI, DM, HTN, cholesterol, smoking).

The influence of BP on dementia

Studies evaluating the relationship between BP, vascular dementia, and Alzheimer dementia have yielded inconsistent results (Table 5). Whether low BP leads to Alzheimer disease or whether Alzheimer disease triggers hypotension is still debated. Cross-sectional and longitudinal data of a bi-racial population aged 60–96 years supported a nonlinear, U-shape relationship between low scores on neuropsychological tests and BP values <140 mmHg and >180 mmHg.[43,88] The prevalence of Alzheimer disease was higher among people with systolic BP <130 mmHg and diastolic BP <70 mmHg than in the reference group (systolic BP 130–139 mmHg).[43,88]

The Honolulu Aging study showed that high systolic BP (the group with 120–140 mmHg and the group with >140 mmHg) in midlife increases the risk of late-life dementia.[89] Men who developed dementia had an additional age-adjusted increase in systolic BP of 0.26 mmHg (95% CI 0.01–0.51 mmHg) from midlife to late life and a greater decrease in systolic BP in late life. Up to 58% of those with dementia experienced a systolic BP decrease of ≥10 mmHg in late life. The risk ratio [RR] for dementia was lower in patients treated for hypertension than in untreated patients (RR = 0.76, 95% CI 0.65–0.93 and RR = 1.05, 95% CI 0.86–1.27, respectively).[66]

In the OPTIMA study,[90] cognitive function was prospectively evaluated using the Cambridge Cognitive Examination (CAMCOG) tool in 235 cognitively healthy participants, 42 with MCI, 141 with Alzheimer disease, and 59 with other dementia syndrome. In patients with Alzheimer disease, the rate of decline of CAMCOG scores showed a nonlinear, inverted U-shaped dependence on diastolic BP. Both low and high diastolic BP levels (<60 mmHg and >110 mmHg) were related to faster cognitive decline over 5 years of follow-up ($z = -2.51$, $P = 0.012$). CAMCOG scores also showed an inverted U-shaped relationship between pulse pressure and faster progression of Alzheimer disease ($z = -2.29$, $P = 0.022$). In another study,[90] low diastolic BP (<70 mmHg) was associated with a multi-adjusted hazard ratio (HR) of 2.13 (95% CI 1.05–4.32) for incidence of dementia and 2.16 (95% CI 0.98–4.73) for incidence of Alzheimer disease in people aged >80 years over 9–16 years of follow-up, when compared with normal diastolic BP (70–89 mmHg). By contrast, higher diastolic BP (≥90 mmHg) was only marginally related to a decreased risk of dementia (HR 0.58, 95% CI 0.33–1.02) and of Alzheimer disease (HR 0.57, 95% CI 0.30–1.09). Systolic pressure was not significantly related to dementia risk.[90] Some studies suggest that BP decline could precede the onset of dementia by at least 3 years,[4] supporting a link between abnormalities in autonomic regulation of BP and dementia risk. In addition, other vascular risk factors—especially high BMI—might interact with BP to increase the risk of dementia.[91]

Antihypertensive therapy and cognition

Clinical trials in which the impact of antihypertensive therapy on cognitive outcomes was assessed have had

Table 5 | Epidemiological studies of BP and dementia

Study name	*n*, age (years)	Study period	Outcomes	BP and other outcome measures	Covariates	Associations with cognitive tasks
Baltimore[43,88]	101, 53–84	Cross-sectional	Neuropsychological tests Memory	BP	D, E	AD prevalence associated with SBP <130 mmHg and DBP <70 mmHg
Honolulu Heart Program/ Honolulu-Asia Aging[89]	1,890, 45–65 at enrollment, 83±3.8 at follow-up	32 years follow-up	Dementia, AD, VaD	SBP, DBP	D, HTN	SBP and DBP increased from midlife to late life, but decreased again in late life; dementia associated with SBP rise from midlife to late life, and with a greater SBP decrease (≥10 mmHg) in late life
OPTIMA[90]	477, >60	5 years follow-up	CAMCOG	BP	D	AD progression associated in a U-shape curve with DBP >110 mmHg and <60 mmHg; SBP not related to AD progression
US Veteran Affairs database[111]	819 enrolled, 491 men with CVD, >65	4 years follow-up	Dementia	BP control with ARBs, lisinopril, or other CVD drugs	D, CVD, DM	ARBs associated with lower incidence of AD and any dementia compared with lisinopril and other CVD drugs

Abreviations: AD, Alzheimer disease; ARB, angiotensin-receptor blocker; BP, blood pressure; CAMCOG, Cambridge cognitive examination questionnaire; CVD, cardiovascular disease; D, demographic variables; DBP, diastolic blood pressure; DM, diabetes mellitus; E, education; HTN, hypertension; OPTIMA, Oxford Project to Investigate Memory and Aging; MCD, mild cognitive disorder; MCI, mild cognitive impairment; RF, risk factors (BMI, DM, HTN, cholesterol, smoking); SBP, systolic blood pressure; VaD, vascular dementia.

conflicting results (Table 6). In the earliest trials, such as the SHEP (Systolic Hypertension in the Elderly Program)[92] and the Medical Research Council study,[93] no difference in cognitive function was observed between participants who were treated with antihypertensives and those who were untreated. Later, the Syst-Eur (Systolic Hypertension in Europe) trial showed that hypertension treatment with a calcium-channel blocker was associated with a 50% reduction in the risk of developing dementia.[94,95]

More recently, the PROGRESS (Perindopril Protection Against Recurrent Stroke Study)[96–97] indicated that treatment of hypertension with angiotensin-converting enzyme (ACE) inhibitors in patients with previous cerebrovascular disease reduced the risk of dementia and reduced progression of microvascular disease. Patients who were randomly assigned to receive the ACE inhibitor had a 34% relative risk reduction of the composite outcome of dementia with recurrent strokes (95% CI 3–55%, $P=0.03$). Similarly, the HOPE (Heart Outcomes Prevention Evaluation) trial[98,99] found that ACE inhibitors were associated with a 41% reduction in cognitive decline related to stroke. The SCOPE (Study on Cognition and Prognosis in the Elderly) trial,[100,101] which used the MMSE to assess cognitive outcome, did not, however, demonstrate a difference between the cognitive function of participants randomly assigned to receive an angiotensin-receptor blocker (ARB) and those not given an ARB. In this study, the group receiving candersartan showed less decline in attention than the group not receiving an ARB, but no differences in working memory were observed.[102] A major concern related to this trial is that many patients assigned to the 'control' group were already receiving antihypertensive therapy, including ARBs.

In the very elderly (>75 years old), the effect of antihypertensive therapy is even more inconclusive. In HYVET-COG,[76,77] treatment with an ACE inhibitor had no effect on dementia risk or cognitive decline. However, the median follow-up of this study was only 2 years; the trial was terminated prematurely, because treatment resulted in a 41% decrease in the primary end point of fatal or nonfatal stroke. Of 4,695 randomly assigned patients, 2,418 participated in the substudy on dementia. No other study has been designed to address this issue in very elderly individuals.

The combined results of these trials are also not conclusive A pooled analysis of the PROGRESS, SCOPE, SHEP, and Syst-Eur trials, whose participants in the treatment group total 11,794 and those in the control group total 11,711, revealed a nonsignificant association between antihypertensive treatment and the risk of developing dementia (OR 0.89, 95% CI 0.75–1.04).[103] The heterogeneity measure in this analysis was high, however, and the results were not robust. A meta-analysis of published trials, including HYVET,[75] demonstrated that, when combined, these studies point to a protective effect of antihypertensive therapy on cognition.[75,77] However, more recently published trials do not corroborate these findings. For example, in the PRoFESS trial,[104] which used a 2×2 factorial design, ARB therapy did not provide cognitive protection after stroke. In addition, results from the ONTARGET trial[105] suggest that systolic BP lowering below the 130–150 mmHg range using ramipril and telmisartan does not improve outcomes.

The inconsistencies in the results of these trials, individually or when combined in meta-analyses, are likely to be related to differences in the age and, more importantly, in the baseline cognitive function of the populations studied. The cognitive domain being measured is also likely to be an important cause of the observed heterogeneity. Furthermore, many of the trials have used MMSE, a fairly insensitive and nonspecific measure of cognitive change.[106] Hypertension, however, is more likely

Table 6 | Clinical trials investigating effects of antihypertensive therapy on cognitive function

Trial	Follow-up period	*n*	Mean age (years)	% women	Antihypertensive therapies studied	Effect of treatment on outcomes
HYVET-COG[77]	2.2 years	3,336	84	60	Indapamide or perindopril vs placebo	No effect
SHEP[92]	14 years	455	74	NA	Chlortalidone, atenolol, reserpine	No effect
MRC[93]	5.8 years	2,584	69.5	58	Diuretic vs BB vs placebo	No effect
Syst-Eur[94]	2 years	2,418	70	65–66	Nitrendipine with possibility to add enalapril and HCTZ vs placebo	Positive
PROGRESS[96]	4 years	6,105	64	30	ACE inhibitor ± diuretic vs placebo	Positive in those with stroke
HOPE[98]	4.5 years	9,297	66 ± 7	27	ACE inhibitor vs placebo	Positive
SCOPE[100]	3.7 years	4,964	76	66	ARB vs placebo	No effect
PRoFESS[104]	2.4 years	20,332	66	36	ARB vs placebo	No effect
Fogari *et al.*[112]	24 weeks	120	81	55	Losartan vs atenolol	Positive
Tedesco *et al.*[114]	2 years	69	52	48	Losartan vs HCTZ	Positive
Syst-Eur follow-up[116]	4 years	2,902	68	66	Nitrendipine with possibility to add enalapril and HCTZ vs placebo	Positive
Muldoon *et al.*[117]	6 weeks	88	43	0	BB vs diuretic vs ACE inhibitor vs CCB vs centrally acting sympatholytic agent	Positive
Fogari *et al.*[118]	16 weeks	144	70	55	ARB vs ACE inhibitor	Positive

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BB, β-blocker; CCB, calcium-channel blocker; HCTZ, hydrochlorothiazide; HOPE, Heart Outcomes Prevention Evaluation; HYVET-COG, Hypertension in the Very Elderly Trial cognitive function assessment; MRC, Medical Research Council; NA, not available; PROGRESS, Perindopril Protection against Recurrent Stroke Study; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe.

to be related to executive function than to overall cognitive performance.[107–109] Pharmacogenetic variation in cognitive responses, pharmacokinetic characteristics of antihypertensive agents, and study duration are additional factors that lead to heterogeneity in studies of hypertension therapy and cognitive function. A meta-analysis of randomized controlled trials of antihypertensive therapy in the elderly indicated that BP reduction lowers the risk of stroke (35%), cardiovascular events (27%), and heart failure (50%), but does not affect mortality.[110] By contrast, small BP reductions and low intensity of therapy were associated with decreased mortality.[110]

Some studies have compared the outcomes achieved with different classes of antihypertensive therapy. The US Veteran Affairs study[111] determined prospectively that ARBs are more effective in lowering the risk of Alzheimer disease and any dementia compared with the ACE inhibitor lisinopril or other classes of cardiovascular medications. Other trials that assessed the impact of ARBs on cognitive function demonstrated a superior effect of this class of drugs in comparison with the β-blocker atenolol,[112] and with the combination of hydrochlorothiazide and lisinopril.[113] Antihypertensive drugs such as ACE inhibitors (perindopril, captopril), ARBs (losartan),[112,114] and calcium-channel blockers (nitrendipine) possibly have class-specific effects, and combination therapy might increase cognitive protection. Pharmacokinetic differences within a drug class might also explain this heterogeneity. For example, in the Cardiovascular Health Study,[115] ACE inhibitors that cross the blood–brain barrier provide cognitive protection, which is not observed with ACE inhibitors that do not cross the blood–brain barrier. Studies of antihypertensive therapy suggest that antihypertensive treatment might be protective against vascular diseases and some of their consequences in the brain. The BP targets that would be protective against cognitive decline remain to be determined in future trials.

Conclusions

Substantial evidence exists supporting the link between BP and cognition. This relationship might be mediated by impairment of vascular reserve and microvascular disease. Both hypertension and hypotension contribute to cognitive decline, and a combination of vascular risk factors during an individual's lifetime could accelerate functional cognitive loss later in life. Combined antihypertensive therapy could have protective effects on vascular disease and cognition. Effective approaches for prevention of cognitive decline, risk reduction, and extension of survival are needed for treatment of hypertension in old age.

Review criteria

This article is based on a comprehensive search in the PubMed database for full-text articles published in English between 2005 and 2010. Search terms included "hypertension and cognition", "cognition", "white matter hyperintensities", "hypotension and cognition", "blood pressure and dementia", and "antihypertensive therapy". The reference lists of the articles identified during this search were checked for additional articles published since January 2005.

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Author contributions

V. Novak and I. Hajjar contributed to discussion of content for the article, researched data to include in the manuscript, reviewed and edited the manuscript before submission, and revised the manuscript in response to the peer-reviewers' comments.