ESC European Society of Cardiology

Cardiovascular Research (2024) **120**, 2360–2372
https://doi.org/10.1093/cvr/cvaf010

SPOTLIGHT REVIEW

Blood pressure and the brain: the conundrum of hypertension and dementia

Rebecca F. Gottesman [1]*, Marco Egle[1], Renee C. Groechel[1], and Amreen Mughal[1,2]

[1]Stroke Branch, National Institute of Neurological Disorders and Stroke Intramural Research Program, Building 10, 4D37, 10 Center Drive, Bethesda, MD 20814, USA; and [2]Translational Vascular Medicine Branch, National Heart, Lung, and Blood Institute Intramural Research Program, Bethesda, MD 20814, USA

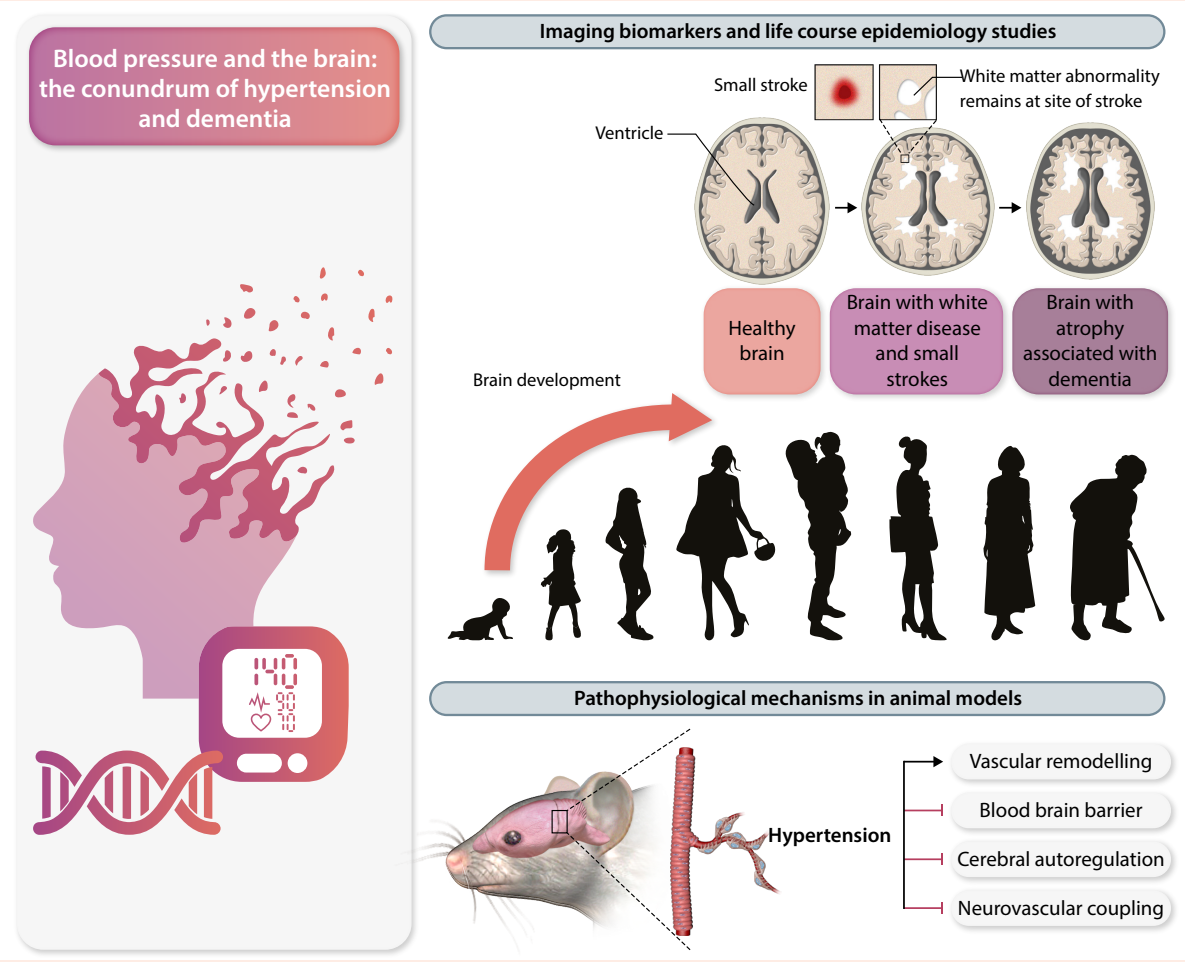
Received 14 June 2024; revised 4 November 2024; accepted 9 December 2024; online publish-ahead-of-print 14 March 2025

Abstract

As the population ages, the anticipated rates of dementia worldwide are likely to increase dramatically, especially in low- and middle-income countries; thus, any opportunity to modify dementia risk is especially critical. Hypertension is one risk factor that is highly prevalent, consistently important for late-life brain health, and which could represent a target for prevention of dementia. Furthermore, hypertension is the most significant modifiable risk factor for stroke. This review will summarize existing literature linking hypertension with dementia and brain health more broadly, will discuss potential mechanisms linking hypertension with brain health, and will consider specific factors that may impact not only the relationship between hypertension and the brain but also the importance of treatment, including different associations over the life course.

* Corresponding author. Tel: +301 435 9321; fax: +301 827 2419, E-mail: Rebecca.gottesman@nih.gov

Graphical Abstract



Keywords Dementia • Stroke • Hypertension • Small vessel disease

This article is part of the Spotlight Issue on Brain, Heart, and Vessels Crosstalk.

1. Epidemiology of the link between hypertension and dementia

Elevated blood pressure (BP) is consistently linked to declines in cognition and incident dementia. This is especially true for the presence of hypertension in midlife, which has stronger associations with cognitive decline than hypertension in late life, as shown in multiple longitudinal studies.[1–3] Furthermore, midlife hypertension is associated with dementia; the Honolulu Asia Aging Study (HAAS) study showed a three- and four-fold elevated dementia risk in individuals with untreated elevated diastolic or systolic BP (SBP).[4] In the Atherosclerosis Risk in Communities (ARIC) study, hypertension was associated with risk of dementia over 25 years, independent of other vascular risk factors and demographics.[5] Thus, based on the body of literature describing these associations, hypertension has been identified as one of the major modifiable risk factors for dementia in the Lancet Commission's report on dementia prevention.[6] Taken together, between a third and a half of dementia cases are likely due to modifiable risk factors.[6]

Whereas hypertension is not associated with as large of an individual-level risk for dementia as other factors, such as diabetes, its high prevalence in the population makes it a major contributor to dementia cases. Further, because hypertension prevalence increases with age, despite a stronger association with dementia when considered in midlife, the proportion of dementia cases felt to be attributable to hypertension increases with age: the population attributable fraction (PAF) for dementia by age 80 was estimated to be 15% for US adults with elevated BP at age 45–54, and up to 20% for US adults with elevated BP at ages 65–74,[7] with larger increases for higher BP.

Different features of BP occur more frequently in individuals with hypertension and are also linked with cognitive decline and dementia. Orthostatic hypotension, for instance, which is more common in individuals with hypertension, has been associated with cognitive decline and dementia,[8] and more visit-to-visit BP variability (BPV) has been associated with dementia risk.[9] Furthermore, dysregulated, abnormal nocturnal BP patterns (either non-dipping, extreme dips, or increases in BP) are associated with worse cognition.[10,11]

Hypertension may also contribute to cognitive decline via stroke or subclinical cerebral small vessel disease (cSVD). Furthermore, there is pathologic evidence linking hypertension with Alzheimer's disease (AD) neuropathology specifically.[12] Because hypertension (along with other vascular risk factors) may act on dementia via various mechanisms, to be

discussed below, the term 'vascular contributions to cognitive impairment and dementia' (VCID)[13] is used in reference to hypertension's impacts on cognition. Although VCID refers to the impact on brain health from a range of vascular risk factors and conditions, this review will focus on the impacts from hypertension in particular.

1.1 Imaging markers related to hypertension

cSVD accounts for around 25% of ischaemic strokes and is also a major risk factor for haemorrhagic strokes.[14] It is a leading cause of VCID and can cause significant cognitive decline, gait and balance problems, and mood disorders. There are several well-defined neuroimaging markers of cSVD that include white matter hyperintensities (WMH) of presumed vascular origin, lacunes, lobar or subcortical cerebral microbleeds (CMB), enlarged perivascular spaces (PVS), cortical cerebral microinfarcts, cortical superficial siderosis, and brain atrophy.[15] These markers are useful in understanding the epidemiology, potential treatment benefits, and mechanisms by which hypertension contributes to cognitive decline and dementia.

1.2 The importance of life course

To better disentangle this complex association between hypertension and dementia, researchers have advocated for the importance of evaluating the time during the life course when hypertension is measured.[16] This approach allows researchers the opportunity to identify how risk varies over time, potentially identifying critical time windows for intervention (*Figure 1*).

1.2.1 Age-dependent risk

SBP and DBP gradually increase through early adulthood, whereas DBP falls in late life (after age 50–60 years old) and SBP concurrently increases.[17] Subsequently, numerous cross-sectional and longitudinal observational studies have shown associations between hypertension and cognitive decline,[18] poor cognitive performance,[3] and ultimately dementia.[5,19] These studies have led to widespread recognition that midlife hypertension (ages 40–65) may be most deleterious in terms of late-life outcomes and cognitive decline.[1,3,5,18,20] Interestingly, studies that examine hypertension in advanced age (75+ years old) have instead shown that low BP, or hypotension, in late life may predispose individuals to worse outcomes whereas hypertension shows a potentially protective effect.[21–23]

1.2.2 Early life sets the stage

Many studies have begun to examine the cumulative burden of hypertension in late life through examination of younger to middle-aged adults. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, every 5 mmHg increment in time-weighted average (TWA) of SBP in young adults is associated with approximately 1-year greater brain age. Likewise, participants with TWA BP over the recommended guidelines (SBP <120 mmHg, DBP <80 mmHg) had on average 3-year greater brain age compared to age peers with healthy BP.[24] Additionally, individuals with moderate to increasing BP trajectories were more likely to have higher abnormal WM volume and/or lower grey matter CBF.[25]

Additional cohort studies have evaluated cardiovascular risk factors as early as childhood and adolescence. In the longitudinal Young Finns study, elevated SBP in children was associated with worse midlife cognitive performance, independent of adulthood exposures to elevated SBP.[26] The Generation R Study also showed an association of BP with brain volume, but associations between other measures of cardiovascular health and white matter (WM) integrity[27] and behaviour and cognition[28] were not significant.

Taken together, these studies highlight the significant need to prevent and treat hypertension and associated vascular risk factors as early as possible. Although cohort studies are generally adjusted for other comorbidities, it is important to consider that other vascular exposures are often comorbid with hypertension and equally as likely to shape brain health through the lifetime[29] and might be more likely in certain individuals. Studies in older adults have repeatedly shown strong associations between social determinants of health and vascular outcomes, particularly in people with lower socioeconomic status (SES). While this by no means provides evidence that vascular risk factors act as mediators between SES and cardiovascular health, it reaffirms that people who have poorly controlled BP as early as childhood are more likely to be at risk for other vascular risks.[30,31] Combinations of vascular comorbidities in the long term are associated with more severe conditions such as cardiovascular disease, stroke, dementia, and other neurological disorders.[32,33] Moreover, many of these studies that have examined risk profiles in varying age groups have shown that the highest associations with adverse outcomes are in individuals who have multiple risk factors at a young age.[32,33] Altogether, the cumulative effect of these risk factors, particularly if left untreated, is likely to manifest in a compounded manner even beyond what is captured in observational studies.

2. Epidemiological studies and clinical trials on BP control and dementia

2.1 Epidemiological studies

In response to population-based studies illustrating a significant association between hypertension and an increased dementia risk,[5,34,35] many have investigated whether improved BP control through anti-hypertensive medication would reduce cognitive decline and dementia risk in late life. The ARIC study showed that individuals taking anti-hypertensive medication showed a similar 20-year cognitive decline as a pre-hypertensive group and significantly less decline than the non-treated hypertensive group.[1] In the Epidemiology of Vascular Aging (EVA) Study Group, high BP controlled by anti-hypertensive therapy was associated with less cognitive decline than untreated hypertension over a 4-year period.[36] A recent meta-analysis has pointed in a similar direction, showing that individuals with treated hypertension had a significantly decreased risk of dementia, an association that was not modified by age.[37] In support of these studies highlighting midlife as a critical window for anti-hypertensive treatment,[1] recent studies using causal inference methods have provided evidence of a causal relationship between anti-hypertensive medication use in midlife and reduced risk of dementia in late life.[38]

2.2 Clinical trials

Several randomized clinical trials investigating anti-hypertensive medications in reducing the risk of dementia in late life have shown conflicting results (*Table 1*). In more recent years, the findings from the SPRINT-MIND trial have received considerable attention showing that intensive BP control (<120 mmHg) did not significantly reduce the risk of probable dementia as compared to standard BP control (<140 mmHg) in individuals with hypertension, but did find that intensive BP treatment reduced the risk of mild cognitive impairment (MCI) and the combined rate of MCI or probable dementia.[44]

More comprehensive evidence came from a recent meta-analysis of 14 clinical trials (96 158 participants), including SPRINT-MIND,[45] which found that BP lowering with anti-hypertensive medication compared to control was associated with a lower risk of dementia or cognitive impairment, although with a very small absolute risk reduction (0.39%).[45] Furthermore, the studies compiled into this meta-analysis had varying degrees of BP control and included different patient populations; SPRINT-MIND had a much larger achieved difference between the two BP arms (as compared to other studies), which was one of the major reasons why it was so successful for its cardiovascular outcome endpoints but also may explain why other studies have had so much heterogeneity.

2.2.1 Class-specific anti-hypertensive drugs on dementia risk

Beyond the broad potential effects of anti-hypertensive medications, it is important to further explore whether certain class-specific anti-hypertensive drugs show a more beneficial effect in reducing dementia risk and if different effects of different drugs might explain the inconsistent trial results (SPRINT-MIND, for instance, allowed all anti-hypertensive

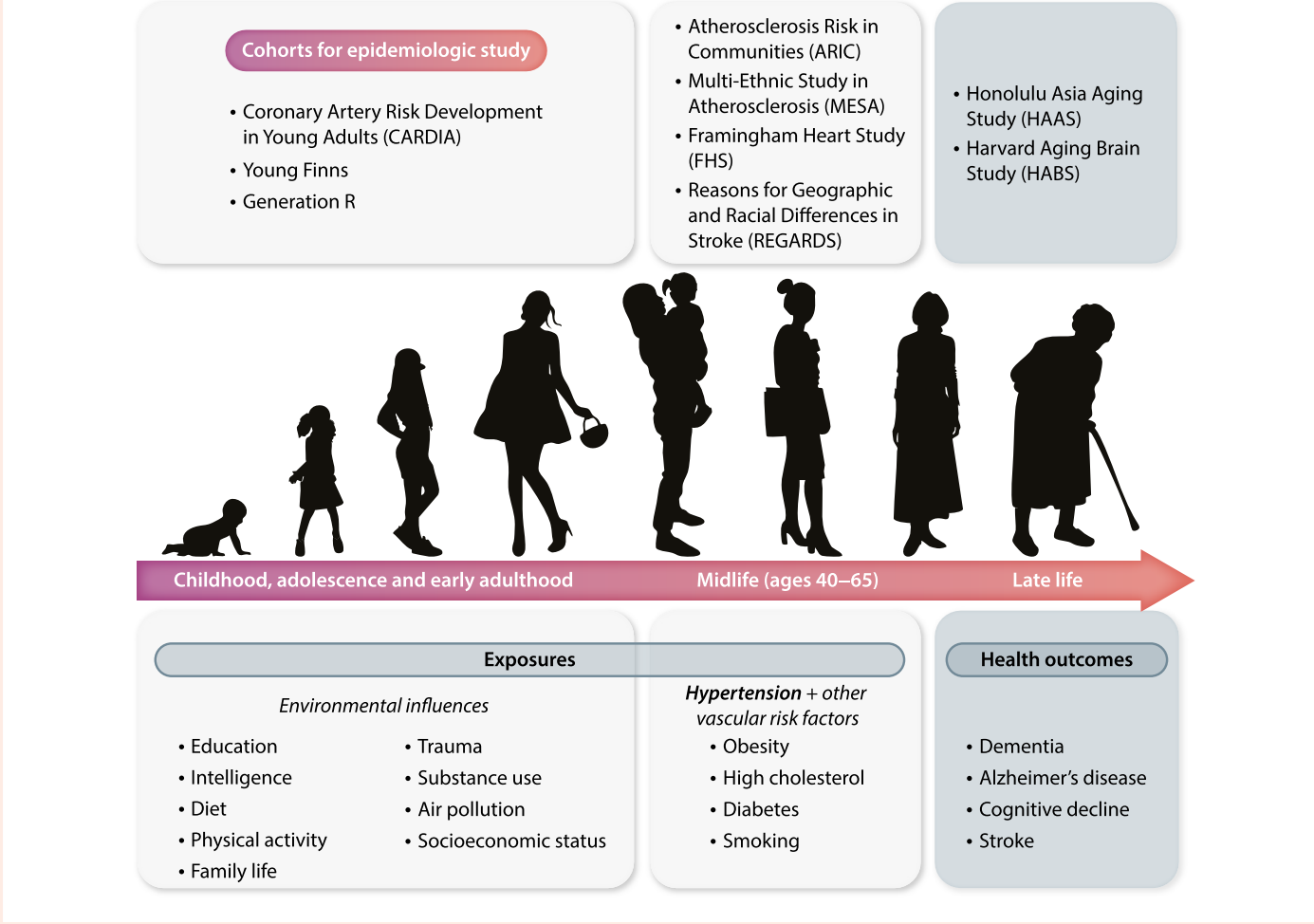


Figure 1 The life course model underlying the association between hypertension and dementia risk.

drugs). Two large meta-analyses (one with over 50 000 participants from 27 observational studies and trials and a second with over 30 000 participants from 6 observational studies) did not find any compelling evidence that would support any one anti-hypertensive drug class for cognitive decline or dementia.[46,47] There has been some evidence, however, that angiotensin II-stimulating anti-hypertensive drugs in particular are specifically neuroprotective: *post hoc* analysis from the PreDIVA trial showed that patients taking angiotensin II-stimulating anti-hypertensive medications had a 45% lower risk of dementia than individuals on angiotensin II-inhibiting anti-hypertensive medications.[48] In a *post hoc* secondary analysis of SPRINT, anti-hypertensive medications that stimulate (vs. inhibit) type 2 and 4 angiotensin II receptors had a 24% reduced risk of amnestic MCI or probable dementia over 4.8 years.[49] Similarly, in a large cohort study of Medicare beneficiaries with incident hypertension, anti-hypertensive medication stimulating type 2 and 4 angiotensin II receptors resulted in a 16% lower risk of incident dementia over a 7-year period.[50] A recent meta-analysis also concluded that angiotensin II receptor blockers, along with calcium channel blockers, could significantly reduce dementia risk.[51] A drug's ability to cross (vs. not cross) the blood–brain barrier (BBB) is also likely to impact its role in reducing cognitive decline: BBB-penetrant renin–angiotensin drugs appear to reduce cognitive decline in older adults with normal cognition more than do drugs that are not BBB penetrant.[52] Future studies should evaluate these class-specific and BBB penetrance effects further and explore mechanisms underlying their potential effect on cognitive decline.[53]

2.2.2 The role of clinical trial design

Methodological aspects likely explain some of the inconsistent findings shown across clinical trials assessing the effect of anti-hypertensive medications on dementia risk (*Figure* 2).[54,55] First, insufficient statistical power may interfere with the ability to detect a difference related to treatment. Beyond the relatively low dementia prevalence of ~10% among individuals of less than 80 years of age,[56] selection bias, particularly in race and ethnic minority groups, precludes many from receiving a timely diagnosis of dementia.[57] Additionally, the way dementia is defined is critical in interpreting trial findings: the use of appropriate normative data, and whether a comprehensive neuropsychological assessment and/or informant interviews are incorporated into study definitions can impact the ascertainment of dementia events. Moreover, dementia incidence is likely to be biased if solely based on medical records or surveillance data.

Precisely determining the onset of MCI and dementia in a clinical trial is difficult as, unlike a cardiovascular emergency event, cognitive function is only periodically assessed which introduces the issue of interval censoring.[55] Likewise, trials that define cognitive status at only a single timepoint are more likely to be confounded, with more bias from educational attainment and/or other social factors.[58] Competing risks of mortality and other clinical events arising from a multimorbid disease state in older age additionally complicate study results; anti-hypertensive therapy may be most effective when combined with other risk control. More comprehensive therapeutic interventions beyond anti-hypertensive treatment may therefore be needed to show a significant reduction in dementia incidence in a

Table 1 Randomized controlled trials (sample size >1000) examining anti-hypertensive therapy and dementia risk

Trial name	Sample size, inclusion	Intervention	Duration	Major findings
Systolic Hypertension in the Elderly Program (SHEP)[39]	4736 adults aged ≥60 years with isolated systolic hypertension (SBP > 160 mmHg)	Chlorthalidone or atenolol vs. placebo	5 years	Reduced stroke and cardiovascular disease, no dementia difference
Systolic Hypertension in Europe (Syst-Eur)[40]	3228 adults aged ≥60 years with sitting systolic hypertension (SBP 160–219 mmHg) but without diastolic hypertension (DBP <95 mmHg)	Nitrendipine with the possible addition of enalapril and hydrochlorothiazide vs. placebo	Median follow-up 3.9 years	Reduced dementia incidence by 55%
Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[41]	6105 adults with prior stroke or transient ischaemic attack	Active treatment: Perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic, vs. placebo	Mean follow-up 3.9 years	Reduced risk of composite dementia with recurrent stroke by 34% and cognitive decline with recurrent stroke by 45% No reduced dementia risk in the absence of recurrent stroke
Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG)[42]	3336 adults with hypertension (SBP 160–200 mmHg; DBP <110 mmHg) aged ≥80 years	Indapamide or perindopril, vs. placebo	Mean follow-up 2.2 years	No dementia difference
Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)[43]	20 332 adults with an ischaemic stroke	2 × 2 factorial design: aspirin and extended-release dipyridamole or clopidogrel, and telmisartan vs. placebo	Median follow-up 2.4 years	No significant difference in cognitive impairment or dementia
Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND)[44]	9361 adults aged ≥50 years with hypertension (SBP 130–180 mm Hg) but without diabetes or stroke	Intensive (SBP <120 mmHg) vs. standard BP treatment: (SBP < 140 mmHg) All major classes of anti-hypertensive medications were included	Median treatment period 3.3 years; follow-up 5.11 years	No significant reduction in probable dementia but reduced MCI and MCI/dementia composite

clinical trial. Finally, the relatively short duration of clinical trials on dementia risk (usually <2–4 years) may impact the likelihood for positive trial results, given the importance of hypertension duration and the life course in dementia risk, and thus the presumed importance of prolonged exposure to appropriate anti-hypertensive medications, starting at a key point in the life course, in order to reduce that risk.

2.2.3 Clinical trials evaluating cSVD

Since hypertension is a major cause of cSVD, the presence and progression of cSVD is also an outcome of interest in clinical trials evaluating anti-hypertensive medication use, as changes in cSVD may precede alterations in cognition, but generally trials in cSVD have yielded mixed results.[59] The SPRINT-MIND MRI sub-study showed that WMH progression was significantly lower in the intensive than in the standard anti-hypertensive treatment group, but with a very small absolute difference (0.54 cm^3).[60] On the other hand, the PRESERVE clinical trial, which randomized 111 hypertensive adults with confirmed cSVD on brain MRI to less divergent BP groups [standard SBP (130–140 mmHg) vs. intensive SBP (SBP < 125 mmHg] did not show a significant difference in WMH progression,[61] but did not reach its goal sample size, so it had limited statistical power. To optimize trial design, recommendations have been made to bolster study populations, choice of clinical endpoints, and the selection of surrogate markers and therapeutic agents.[62]

2.2.4 Inclusiveness in clinical trials of hypertension and dementia

Stroke and cSVD are more common and more severe in minoritized populations, including Black and Hispanic individuals.[63–65] Dementia is also more common in these same groups,[5] as is hypertension[66] (and treatment-resistant hypertension[67]). While risk associated with the diagnosis of hypertension is similar in Black and White adults in the USA,[5] differences in hypertension prevalence and control may explain some of the disparities in dementia rates. In a pooled cohort of nearly 20 000 individuals without stroke or dementia from 5 US-based cohort studies, cumulative mean SBP explained the observed greater cognitive decline in Black compared to White individuals.[68] There was no evidence of a similar explanation for cognitive decline in Hispanic adults when compared to White adults.[69]

Pivotal US-based cardiovascular trials have traditionally included low numbers of women (36% across 35 cardiovascular and diabetes drug trials) and lower numbers of minoritized individuals (4% Black, 11% Hispanic).[70] While more recent trials evaluating the hypertension–dementia association have had improved representativeness (SPRINT-MIND included 30% Black participants and 10.5% Hispanic participants),[44] continued efforts are needed to ensure that studies are representative of the population, as treatment of hypertension to prevent dementia is likely to have larger impacts among Black and Hispanic adults. The PAF of dementia cases in the USA due to 13 modifiable risk factors (including midlife

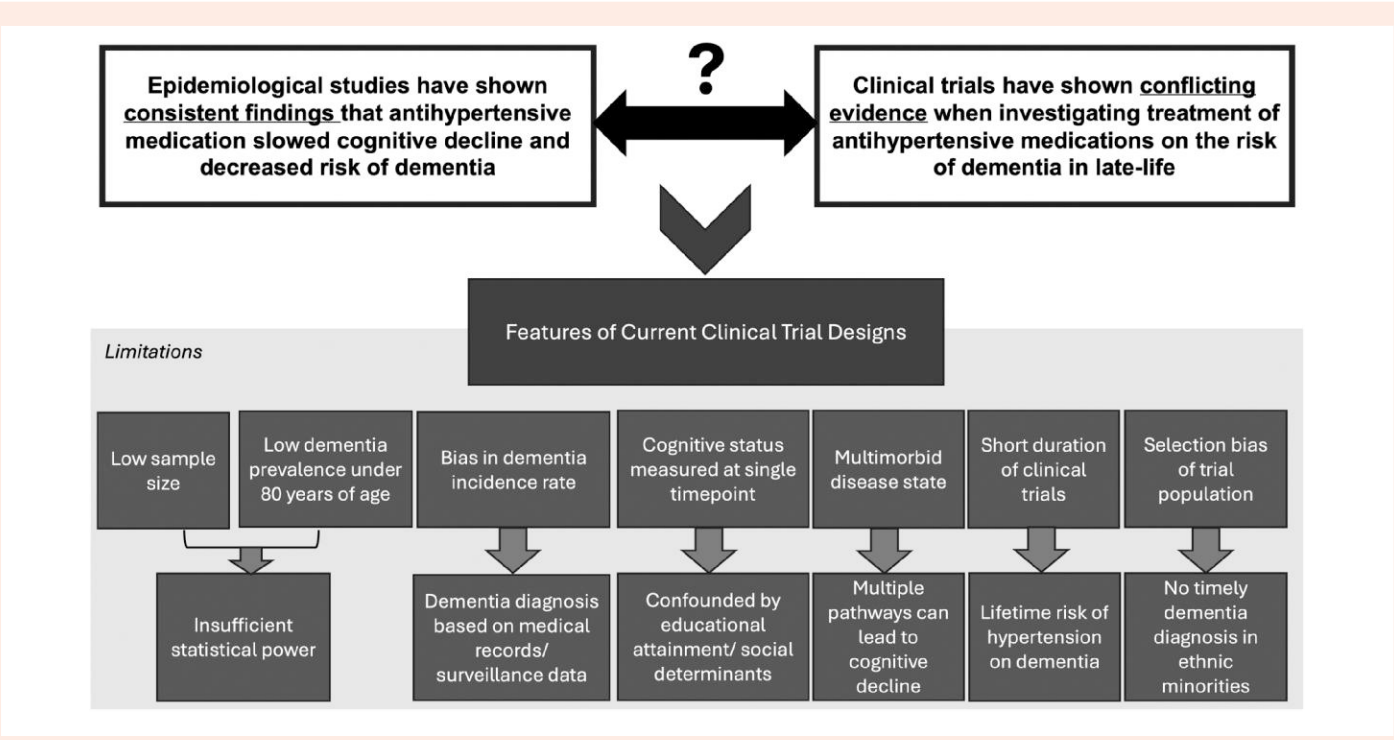


Figure 2 Methodologic differences between clinical trials and epidemiologic studies that may contribute to the inconsistent findings of anti-hypertensive medications on dementia risk.

hypertension[6]) is higher in Black (45.6%) and Hispanic (46.7%) adults than White (39.4%) or Asian adults (35.8%), and the unweighted PAF for hypertension is 26.8% in Black adults (vs. 20.2% in the total population), driven by the high prevalence of hypertension in Black individuals (61% using national survey data).[71]

3. Mechanisms linking hypertension and dementia in humans

3.1 The use of imaging biomarkers to evaluate mechanism

The advent of neuroimaging technologies has allowed for the visualization of vascular changes *in vivo* prior to the onset of clinical symptomology of neurologic disorders such as stroke and dementia. Improvements to magnetic resonance imaging (MRI) technology and ligands used for positron emission tomography (PET) have allowed for the characterization of subtle microvascular changes that are believed to reflect hypertension and related processes before macroscopic signs become apparent.[72] The time-sensitive nature of such biomarkers is advantageous for efforts to monitor age-related changes and potential disease progression in aging adults as well as for means of prevention. Below, we clarify our current understanding of neurodegenerative and AD-specific biomarkers as they relate to hypertension.

3.2 Stroke and cSVD

WMH is one of the most common MRI neuropathological features associated with hypertension and reflects areas of tissue damage that extend into what was previously healthy-appearing surrounding tissue.[15] Such damage may be due to stenosis or occlusion of small vessels, such as arterioles, that penetrate the WM, yet the damage of WMH is not localized to the WM alone.[73] Typically, the presence of WMH affects the volume of surrounding grey matter areas in addition to key structures associated with motor and cognitive control including the motor and premotor cortices, cerebellum, thalamus, and brainstem.[74]

The formation and progression of WMH and lacunes is dynamic and associated with increased age, hypertension, and smoking.[75–77] Hypertension, especially in midlife, has been associated with WMH, reduced WM integrity, microbleeds, lacunes, and brain atrophy.[78–81] It is also a well-established risk factor for clinical stroke (as are cSVD markers[82,83]), and stroke itself has been linked to dementia risk.[84] Given the observed association between hypertension and markers of cSVD, and the associations between cSVD markers and cognitive decline and dementia, it is plausible that the development of cSVD might mediate the association between hypertension and dementia. This is supported by studies showing that composite cardiovascular risk's effect on cognition was mediated by mixed lesions including cSVD markers and brain volumes[85] and WMH mediated part of the hypertension–dementia association, but AD biomarkers did not.[86]

More recent evidence has shown that the radiological SVD features seen on conventional MRI are often only the tip of the iceberg, and that individuals with cSVD also have alterations in microstructural WM which can be assessed using diffusion tensor imaging (DTI). Higher values in mean diffusivity (MD) and lower values of fractional anisotropy (FA) in the WM have been shown to be associated with impaired cognition, cognitive decline, and dementia in cSVD patients.[87] Importantly, these DTI measures, which are abnormal in the setting of hypertension even in early adulthood,[88,89] show significant change over short periods of time which significantly correlate with worse clinical outcomes and hence make them a highly time-sensitive measure to monitor cSVD progression.[90] Furthermore, the effect of elevated SBP on some aspects of cognition appears to be at least partially mediated by DTI-detected alterations in WM integrity.[91] Additional MRI methods such as neurite orientation dispersion and density imaging and multicomponent MR relaxometry have been developed to further understand the aetiology of weakened microstructural WM integrity and its relationship with hypertension.[91,92]

3.3 How hypertension and cSVD may be linked to brain atrophy

The downstream effects of cSVD involve brain atrophy occurring in several brain regions and the combined burden is believed to explain many of the functional deficits that can result from cSVD.[93] In the ARIC study, the effect of cSVD on cognition was partially mediated by brain volumes[94]; similarly, in the Northern Manhattan Study, cSVD was associated with grey matter atrophy and cognitive impairment, particularly among individuals with uncontrolled hypertension.[95]

Anatomical location of the CMB may be the most indicative of whether such features stem from vascular origin or mechanisms related to AD or neurodegeneration. Deep (subcortical) microbleeds have a stronger association with hypertension compared to lobar microbleeds.[81,96] Despite this, lobar microbleeds are more strongly associated with dementia than are subcortical microbleeds.[97,98] Taken together, these findings support the understanding that deep microbleeds are of vascular origin, whereas lobar microbleeds may reflect amyloid-related pathologies characteristic of cerebral amyloid angiopathy (CAA) and even AD.[96]

3.4 Imaging to glimpse changes in cerebrovascular function

Functional modes of MRI, including measures of functional connectivity between brain networks and measures of cerebral blood flow (CBF), are used to study neurodegeneration and AD-specific mechanisms in association with cerebrovascular function. Both are very useful in the context of hypertension as they provide a snapshot of functional hyperaemia and functional network connectivity in living human subjects.[99]

Studies using functional MRI (fMRI) have historically shown that a network of brain regions, termed the default mode network (DMN), may be implicated in cognitive control and the development of AD pathophysiology.[100,101] Using resting-state fMRI, studies have shown altered functional connectivity in regions like the DMN in addition to the broader dorsal attention network in individuals with hypertension relative to those who are normotensive.[102] Likewise, other studies examining CBF through arterial spin labelling MRI have shown a significant negative correlation between BP, age, and CBF, with the lowest CBF values captured in patients with hypertension.[103] In lieu of such, further studies have begun to explore how anti-hypertensive drugs and BP management may confer protection of the brain from chronically reduced perfusion, yet results thus have been mixed.[103–105]

An increasing number of studies have examined how BPV, which can be measured over time frames ranging from seconds to years, may relate to functional connectivity and CBF given the previously established associations shown between BPV with cognitive impairment and cerebrovascular outcomes.[106,107] Such studies have provided additional evidence that greater BPV is associated with lower functional connectivity specific to the DMN[106] and CBF decline in many medial temporal regions.[108]

Other clinical applications used to measure changes in cerebrovascular function include ^{18}F-fluorodeoxyglycose (^{18}F-FDG) PET. [^{18}F]FDG-PET is particularly useful for early diagnosis of AD, as it is believed to capture subtle changes in hypometabolism before more macroscopic changes are apparent on MRI.[109] Strong associations between elevated BP and lower glucose metabolism, particularly in regions such as the frontal and temporal brain regions, have been established,[110] and associations between hypertension and longitudinal decline in glucose metabolism appear particularly strong in APOE ϵ4 carriers.[111] More recent studies are employing machine learning models to build predictive models of AD based upon findings from [^{18}F]FDG-PET scans.[112]

3.5 How hypertension may be linked to AD-specific mechanisms

3.5.1 Biomarkers of AD: amyloid-beta and tau

Population-based autopsy data show that nearly 50% of dementia cases are of mixed aetiology, with vascular pathology being the most predominant pathology co-occurring along with AD.[113] One of the most clear-cut ways in which hypertension can be linked to proteins such as amyloid-beta and tau is through the glymphatic and perivascular systems.[114] Hypertension induces arterial stiffening which increases backflow and, ultimately, reduces the net flow of cerebrospinal fluid (CSF) in PVS.[114] This reduction in CSF flow renders similar decreases in the glymphatic clearance of proteins like amyloid-beta and tau.[115] It has been suggested that the longer these products stay in the PVS, the greater the chance of further amyloid accumulation and tau phosphorylation as a direct result of the oxidative and inflammatory sequelae of hypertension.[115,116]

Several studies have leveraged PET imaging to examine the association, and potential interactions that may exist, between hypertension and amyloid-beta. Findings in the ARIC-PET study showed that greater vascular burden in midlife was associated with late-life amyloid burden on PET in non-demented older adults, yet when measured alone, hypertension did not show an association.[117] Others have shown potential interactions ranging from none[118] to additive,[119] to synergistic or multiplicative.[120,121]

More recently, researchers have built upon these studies by examining the potential interaction between vascular risk and tau. Findings from the Swedish BioFINDER-2 study showed a significant association between microbleeds and amyloid pathology at baseline and with longitudinal tau accumulation, but these findings did not extend to models which included the Framingham Heart Study Cardiovascular Disease (FHS-CVD) risk score as the primary marker of vascular burden or those that included cognitively impaired individuals.[122] In the Harvard Aging Brain Study, there was a significant synergistic interaction between the FHS-CVD score and amyloid on tau accumulation. A closer examination of FHS-CVD factors showed that SBP (adjusted for anti-hypertensive use) and body mass index had persistent significant interactions with amyloid-beta on tau burden over time.[123] While further studies are needed, these findings suggest that hypertension may independently accelerate tau accumulation even in those with subthreshold levels of amyloid.

3.5.2 The eye as a window for studying brain health

Whereas directly imaging the brain's small vessels *in vivo* remains very challenging, retinal vessels are anatomically and physiologically similar to the brain's small vessels and may present as a more feasible alternative for studying cerebral microvascular contributions to AD pathology. For instance, retinal microvascular disease has been strongly associated with cSVD,[124] with cognitive decline,[125] and studies have shown that retinal microvascular disease (often caused by hypertension and diabetes) is associated with increased amyloid burden.[126] However, future well-powered studies are needed to assess the importance of retinal vasculature in relation to hypertension and the microvascular pathogenesis of AD.

4. Mechanisms linking hypertension and dementia in animal models

Impairment in brain structure and function [including BBB integrity, autoregulation, and neurovascular coupling (NVC)] contributes to the pathophysiology of dementia.[127] Multifaceted functional and molecular mechanisms connecting hypertension with dementia can be further dissected using animal models, leveraging the use of pharmacological or genetic approaches to represent the pathophysiology of acute and/or chronic hypertension (see Supplementary material online, *Table S1*).[128]

4.1 Structural modification of the cerebral vasculature with hypertension

Hypertension severely alters brain vasculature at both macroscopic and microscopic levels, causing arterial stiffness, remodelling with excessive deposition of collagen and fibronectin, and increased smooth muscle cell proliferation. Mechanical and neurohumoral factors released with acute and chronic hypertension contribute to decreases in vascular compliance and

changes in the luminal diameter (internal or external remodelling) and vascular wall structure (eutrophic or hypertrophic).[129]

Vascular remodelling is an adaptive response in the brain pial vessels to protect the downstream microvasculature from excessive damage with flow and pressure changes.[130,131] This is supported by evidence showing that pial cerebral arteries in hypertensive rats have higher resistance with a minimum difference in the penetrating arteriolar pressure, compared to their normotensive counterparts.[132] Loss of vascular hypertrophy with denervation of perivascular sympathetic nerves in hypertensive rats promotes cerebrovascular lesions leading to BBB damage, cerebral oedema, and vasoconstriction.[133] Cerebral arterial remodelling is dependent on the renin–angiotensin signalling as tested using spontaneously hypertensive mice, where pathology develops independently of the renin–angiotensin system.[134] These findings support the protective role of arterial remodelling. On the other hand, evidence also suggests that elevated pulse pressure with arterial remodelling increases the risk of stroke, cognitive impairment, and dementia.[135,136] Less collateral vessel formation and increased smooth muscle proliferation are reported in hypertensive rats, making them prone to ischaemic lesions and cerebral hypoperfusion.[137,138] Moreover, an increase in atherosclerotic plaques with hypertension contributes to the development of acute cerebrovascular occlusion and stroke in hypertensive rats.[139]

Hypertension-associated damage is also reported in the microvasculature and neural cells in the brain. Angiotensin (Ang II) hypertensive mice have reduced pericyte numbers and less capillary pericyte coverage in the hippocampus.[140] The reduction in cortical and hippocampal microvasculature with hypertension accelerates the progression of cognitive impairment in an APP/PS1 mouse model of sporadic AD.[141,142] Reactive oxygen species formed with chronic hypertension leads to reduction in number of dendritic spines in the cortex of spontaneous hypertensive rats (SHRs) and renovascular hypertensive rats.[143,144] It remains unclear whether some of the neurodegenerative changes found with hypertension are consequences of the vasculature structural/functional changes or are occurring independent of the vascular pathophysiology.

Hypertensive animal models also present pathology of cSVD. Hypertensive rats have brain atrophy, severe WMH with reduced WM volume, intracerebral haemorrhages (ICH), lacunes, enlarged PVS, blood vessel stenosis, increased BBB permeability, and higher neuroimmune and inflammatory response.[145,146] Although these models represent hypertension-induced cSVDs, combining these with other genetic or sporadic cSVDs and/or AD pathologies might provide further mechanistic insights about resulting cognitive impairment and dementia.

4.2 Hypertension makes the BBB leaky

The BBB, formed by endothelial cells and supported by mural cells, basement membrane, and astrocytic end-feet, is a physical and metabolic barrier between the central nervous system (CNS) and systemic circulation to control the passage of molecules into the CNS. It is critical for protecting and maintaining brain homeostasis, and its disruption leads to the accumulation of toxins in the brain parenchyma, thus contributing to cognitive impairment and dementia. The passage of molecules through the BBB is controlled by tight junctions and numerous transporters. Hypertension-driven increases in neurohumoral and neuroimmune mediators lead to BBB damage by disruption of these tight junctions.[147–149]

One of the outstanding questions in the field is whether hypertension-induced BBB leakage is involved in the initiation of dementia or is a consequence of the complex neurovascular pathology.[150] The answer remains unclear, but many studies have used young hypertensive animals to study this mechanism. Findings have shown a higher BBB leakage in cardiovascular regulatory regions in young hypertensive rats compared to normotensive controls.[151,152] Interestingly, the increased BBB permeability in cardiovascular regulatory regions in the brain preceded BBB permeability in cortical regions in hypertensive rats,[153,154] suggesting that early damage in the cardiovascular regulatory regions of the brain could be involved in the initiation of dementia. Evidence suggests that hypertension-induced BBB leakage may also fast-track the progression of cognitive impairment and dementia when presented with other neurovascular diseases. Chronic hypertension induced with nitro-L-arginine (synthetic endothelial nitric oxide synthase; eNOS inhibitor) exacerbated BBB leakage and the accumulation of amyloid-beta in mouse models of CAA and AD, resulting in cognitive deficits at earlier ages compared to normotensive controls.[155,156]

4.3 Cerebral autoregulation and vascular reactivity

Cerebral autoregulation is the ability of the vasculature to maintain steady blood flow in the brain despite changes in cerebral perfusion pressure. In humans, the usual autoregulatory range is between mean arterial pressure (MAP) of 60 (lower) to 150 (upper) mmHg. When cerebral perfusion pressure fluctuates beyond these autoregulation limits, CBF is altered[157,158]: when MAP goes below the lower autoregulation limit, CBF is reduced and cerebral ischaemia can result, and when MAP reaches above the upper limit, there is forced dilation of cerebral vessels causing increases in intracranial pressure, cerebral blood volume, and ultimately disruption of the BBB, oedema, and haemorrhage.[159]

In some hypertensive animal models, the limits of cerebral autoregulation are extended in early ages (~3–4 months) to provide functional adaptation to the cerebral microcirculation with abrupt changes in flow and pressure.[160–162] However, this functional adaptation towards higher pressure is absent in aged hypertensive mice (~24 months),[140] an age-dependent impairment also associated with loss in insulin-like growth factor (IGF-1) signalling.[163,164]

Myogenic tone of the cerebral arteries is important in autoregulation and controlled by vascular cells (endothelium and mural cells) through the release of vasoactive mediators [e.g. nitric oxide, prostacyclin, 20-hydroxyeicosatrienoic-acid (20-HETE)]. Along with the morphological changes in the vasculature, hypertension also modulates endothelial and smooth muscle cell functions.[165] Endothelial dysfunction and reduced vasodilation in the cerebral arteries and arterioles have been reported in hypertensive models.[166–171] This reduced vasodilation is attributed to reduction in eNOS expression and nitric oxide signalling.[172–174] Conversely, few other studies have shown unchanged eNOS levels, but an upregulation of inducible NOS (iNOS) levels contributing to aberrant nitric oxide signalling.[172,175] Interestingly, vascular reactivity findings using different hypertensive models are not consistent. Some have shown increased myogenic tone,[176,177] while others reported reduced or no change in tone.[161,178] Similarly, different trends in 20-HETE signalling are reported between different studies.[179–182] It remains unclear whether impaired or exacerbated myogenic response contributes to the deterioration of cerebral autoregulation in hypertensive models. The resistant cerebral arteries, unlike peripheral vasculature, constrict to the increases in intraluminal flow.[183,184] This flow-induced myogenic response is exacerbated in cerebral arteries from SHRs,[162,185] suggesting higher chances of microbleeds and ICH with hypertension.

4.4 NVC and CBF regulation

Hypertension leads to a progressive decline in regional CBF,[186] suggesting impairment in local control mechanisms, i.e. NVC. Components of the neurovascular unit [neurons, endothelial cells, mural cells (smooth muscle cells and pericytes), astrocytes, and glial cells][187,188] work in close coordination to regulate blood flow in the brain and are collectively known as NVC. Although NVC is well appreciated in functional hyperaemia,[189] it can have a critical role in other functions, including clearance of metabolic by-products, energy homeostasis, maintenance of pH, and thermal regulation.[190]

Several studies have dissected the functional deficits in NVC with hypertension and identified molecular pathways involved in the development and progression of the NVC deficits.[191–198] Koide *et al.*[191] attributed the loss of functional hyperaemia to the reduction in capillary endothelial cell (cEC) inward-rectifying K+ (Kir2.1) channels. Capillary endothelial Kir2.1 channels are the major players in the capillary to arteriolar communication for the regulation of CBF.[199] Similar impairments in cEC Kir2.1 channel activity and functional hyperaemia are reported in Notch3[200] and Col4A1

mutant mouse models of cSVD,[201] presenting the possibility of a convergent pathology. A group of elegant studies connected the loss of functional hyperaemia with BBB damage, showing the aberrant production of reactive oxygen species in PVMs, and increased interleukin-17 secretion from dura matter T cells, leading to BBB damage and exacerbating Ang II/AT1 signalling.[192,193] Moreover, Ang II/AT1 signalling itself can cause NVC deficits and these changes precede the timeline of hypertension.[194–197] Ang II signalling also potentiates astrocytic Ca^{2+} responses to a level that promotes vasoconstriction over vasodilation, independent of the BP changes.[198]

Overall, hypertension-associated structural and functional changes lead to a complex pathophysiology that can collectively contribute to the initiation and progression of cognitive impairment and dementia. Future studies clarifying some of the differences in the findings and time course, and the importance of comorbid conditions (sporadic or genetic) will expedite the development of therapeutic strategies for the treatment of hypertension-associated VCID.

5. Future directions

While much is understood about the importance of BP for later-life brain health, there is still much more to learn about the specifics of treating elevated BP to prevent dementia or reduce its progression and mechanisms underlying hypertension's impact on neurodegeneration and AD specifically. Given the long duration between hypertension and its maximum impact on the brain in human studies, surrogate endpoints including both fluid-based and imaging-based biomarkers may be critical to understand implications for treatment and prevention. Furthermore, studies should include populations with mixed pathology, or mixed risk (e.g. genetic risk and vascular risk), and need to prioritize recruitment of individuals from diverse communities. This pertains to animal models, as well, where evaluating mixed pathologies, and the importance of hypertension in the setting of other comorbidities or other neurodegenerative or genetic conditions, will help clarify the role of hypertension for brain health in these common co-occurring conditions.

Hypertension represents a major, potentially modifiable, and common condition impacting a large portion of the population. Reducing its prevalence or severity is likely to reduce dementia cases worldwide, and the more that is understood about how and when to treat hypertension and its associated sequelae, the more likelihood of success in improving cognitive outcomes and reducing dementia.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Conflict of interest: none declared.

Funding

All authors are supported by the NINDS Intramural Research Program.

Data availability

This manuscript is a summary of existing published studies and thus does not use new data.

References

1. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, Coresh J, Knopman D, Power MC, Rawlings A. Midlife hypertension and 20-year cognitive change: the Atherosclerosis Risk In Communities Neurocognitive Study. *JAMA Neurol* 2014;**71**:1218–1227.
2. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Cushman M, McClure LA, Safford MM, Wadley VG. Blood pressure and cognitive decline over 8 years in middle-aged and older Black and White Americans. *Hypertension* 2019;**73**:310–318.
3. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 1995;**274**:1846–1851.
4. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ. Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging* 2000;**21**:49–55.
5. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, Schneider ALC, Windham BG, Wruck LM, Knopman DS. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol* 2017;**74**:1246–1254.
6. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimaki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbaek G, Teri L, Mukadem N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;**392**:413–446.
7. Smith JR, Sharrett AR, Pike JR, Gottesman RF, Knopman DS, Lee M, Lutsey PL, Palta P, Windham BG, Coresh J, Deal JA. Dementia occurring over a 32-year follow-up attributable to hypertension observed at different ages: implications for dementia prevention. *Alzheimers Dement* 2023;**19**:3435–3447.
8. Rawlings AM, Juraschek SP, Heiss G, Hughes T, Meyer ML, Selvin E, Sharrett AR, Windham BG, Gottesman RF. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. *Neurology* 2018;**91**:e759–e768.
9. Mahinrad S, Bennett DA, Sorond FA, Gorelick PB. Blood pressure variability, dementia, and role of antihypertensive medications in older adults. *Alzheimer Dement* 2023;**19**:2966–2974.
10. Guo H, Tabara Y, Igase M, Yamamoto M, Ochi N, Kido T, Uetani E, Taguchi K, Miki T, Kohara K. Abnormal noctural blood pressure profile is associated with mild cognitive impairment in the elderly: the J-SHIPP study. *Hypertens Res* 2010;**33**:32–36.
11. Paganini-Hill A, Bryant N, Corrada MM, Greenia DE, Fletcher E, Singh B, Floriolli D, Kawas CH, Fisher MJ. Blood pressure circadian variation, cognition and brain imaging in 90+ year olds. *Front Aging Neurosci* 2019;**11**:54.
12. Abdulrahman H, van Dalen JW, den Brok M, Latimer CS, Larson EB, Richard E. Hypertension and Alzheimer's disease pathology at autopsy: a systematic review. *Alzheimer Dement* 2022;**18**:2308–2326.
13. Corriveau RA, Koroshetz WJ, Gladman JT, Jeon S, Babcock D, Bennett DA, Carmichael ST, Dickinson SL, Dickson DW, Emr M. Alzheimer's Disease-Related Dementias Summit 2016: National research priorities. *Neurology* 2017;**89**:2381–2391.
14. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;**9**:689–701.
15. Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw F-E, Debette S, Frayne R, Jouvent E, Rost NS, Ter Telgte A, Al-Shahi Salman R, Backes WH, Bae H-J, Brown R, Chabriat H, De Luca A, DeCarli C, Dewenter A, Doubal FN, Ewers M, Field TS, Ganesh A, Greenberg S, Helmer KG, Hilal S, Jochems ACC, Jokinen H, Kuijf H, Lam BYK, Ledenberg J, Macintosh BJ, Maillard P, Mok VCT, Pantoni L, Rudilosso S, Satizabal CL, Schirmer MD, Schmidt R, Smith C, Staals J, Thrippleton MJ, van Veluw SJ, Vemuri P, Wang Y, Werring D, Zedde M, Akinyemi RO, Del Brutto OH, Markus HS, Zhu Y-C, Smith EE, Dichgans M, Wardlaw JM. Neuroimaging standards for research into small vessel disease— advances since 2013. *Lancet Neurol* 2023;**22**:602–618.
16. Backhouse EV, Bauermeister S, Wardlaw JM. Lifetime influences on imaging markers of adverse brain health and vascular disease. *Cereb Circ Cogn Behav* 2024;**6**:100194.
17. Franklin SS, Gustin IVW, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* 1997;**96**:308–315.
18. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 1998;**51**:986–993.
19. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;**64**:362–381.
20. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, Seshadri S. Blood pressure from mid- to late life and risk of incident dementia. *Neurology* 2017;**89**:2447–2454.
21. Guo Z, Viitanen M, Winblad B, Fratiglioni L. Low blood pressure and incidence of dementia in a very old sample: dependent on initial cognition. *J Am Geriatr Soc* 1999;**47**:723–726.
22. Kritz-Silverstein D, Laughlin GA, McEvoy LK, Barrett-Connor E. Sex and age differences in the association of blood pressure and hypertension with cognitive function in the elderly: the Rancho Bernardo Study. *J Prev Alzheimers Dis* 2017;**4**:165–173.
23. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, Bandeen-Roche K, Coresh J, Gross A, Windham BG, Knopman DS, Power MC, Rawlings AM, Mosley TH, Gottesman RF. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA* 2019;**322**:535–545.
24. Dintica CS, Habes M, Erus G, Vittinghoff E, Davatzikos C, Nasrallah IM, Launer LJ, Sidney S, Yaffe K. Elevated blood pressure is associated with advanced brain aging in mid-life: a 30-year follow-up of the CARDIA study. *Alzheimers Dement* 2022;**19**:924–932.
25. Hu Y-H, Halstead MR, Bryan RN, Schreiner PJ, Jacobs DR Jr, Sidney S, Lewis CE, Launer LJ. Association of early adulthood 25-year blood pressure trajectories with cerebral lesions and brain structure in midlife. *JAMA Netw Open* 2022;**5**:e221175.
26. Hakala JO, Pahkala K, Juonala M, Salo P, Kahonen M, Hutri-Kahonen N, Lehtimaki T, Laitinen TP, Jokinen E, Taittonen L, Tossavainen P, Vikari JSA, Raitakari OT, Rovio SP. Cardiovascular risk factor trajectories since childhood and cognitive performance in midlife: the cardiovascular risk in Young Finns study. *Circulation* 2021;**143**:1949–1961.
27. Defina S, Silva CCV, Cecil CAM, Tiemeier H, Felix JF, Mutzel RL, Jaddoe VWV. Associations of arterial thickness, stiffness, and blood pressure with brain morphology in early adolescence: a prospective population-based study. *Hypertension* 2024;**81**:162–171.
28. Goncalves R, Gaillard R, Cecil C, Defina S, Steegers EAP, Jaddoe VWV. Arterial health markers in relation to behavior and cognitive outcomes at school age. *J Am Heart Assoc* 2024;**13**:e029771.

29. Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. *J Clin Hypertens (Greenwich)* 2011;**13**:244–251.
30. Schiel R, Beltschikow W, Kramer G, Stein G. Overweight, obesity and elevated blood pressure in children and adolescents. *Eur J Med Res* 2006;**11**:97–101.
31. Short KR, Blackett PR, Gardner AW, Copeland KC. Vascular health in children and adolescents: effects of obesity and diabetes. *Vasc Health Risk Manag* 2009;**5**:973–990.
32. Joundi RA, Patten SB, Williams JV, Smith EE. Vascular risk factors and stroke risk across the life span: a population-representative study of half a million people. *Int J Stroke* 2022;**17**: 1021–1029.
33. Kaneko H, Yano Y, Okada A, Itoh H, Suzuki Y, Yokota I, Morita K, Fujiu K, Michihata N, Jo T, Yamaguchi S, Takeda N, Morita H, Node K, Yamauchi T, Nangaku M, Kadowaki T, McEvoy JW, Lam CSP, Yasunaga H, Komuro I. Age-dependent association between modifiable risk factors and incident cardiovascular disease. *J Am Heart Assoc* 2023;**12**:e027684.
34. Mulligan MD, Murphy R, Reddin C, Judge C, Ferguson J, Alvarez-Iglesias A, McGrath ER, O'Donnell MJ. Population attributable fraction of hypertension for dementia: global, regional, and national estimates for 186 countries. *EClinicalMedicine* 2023;**60**:102012.
35. Kim H, Ang TFA, Thomas RJ, Lyons MJ, Au R. Long-term blood pressure patterns in midlife and dementia in later life: findings from the Framingham Heart Study. *Alzheimers Dement* 2023;**19**:4357–4366.
36. Tzourio C, Dufouil C, Ducimetière P, Alpérovitch A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. *Neurology* 1999;**53**:1948–1952.
37. Lennon MJ, Lam BCP, Lipnicki DM, Crawford JD, Peters R, Schutte AE, Brodaty H, Thalamuthu A, Rydberg-Sterner T, Najar J, Skoog I, Riedel-Heller SG, Rohr S, Pabst A, Lobo A, De-la-Camara C, Lobo E, Bello T, Gureje O, Ojagbemi A, Lipton RB, Katz MJ, Derby CA, Kim KW, Han JW, Oh DJ, Rolandi E, Davin A, Rossi M, Scarmeas N, Yannakoulia M, Dardiotis T, Hendrie HC, Gao S, Carriere I, Ritchie K, Anstey KJ, Cherbuin N, Xiao S, Yue L, Li W, Guerchet MM, Preux PM, Aboyans V, Haan MN, Aiello AE, Ng TP, Nyunt MSZ, Gao Q, Scazufca M, Sachdev PSS. Use of antihypertensives, blood pressure, and estimated risk of dementia in late life: an individual participant data meta-analysis. *JAMA Netw Open* 2023;**6**:e2333353.
38. Wei J, Xu H, Zhang D, Tang H, Wang T, Steck SE, Divers J, Zhang J, Merchant AT. Initiation of antihypertensive medication from midlife on incident dementia: the Health and Retirement Study. *J Alzheimers Dis* 2023;**94**:1431–1441.
39. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;**265**:3255–3264.
40. Forette F, Seux M, Staessen J, Thijs L, Babarskiene M, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhäger W; Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2003;**162**:2046–2052.
41. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;**163**:1069–1075.
42. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C; HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* 2008;**7**:683–689.
43. Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlof B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW; Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study group. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008;**7**: 875–884.
44. SPRINT MIND Investigators for the SPRINT Research Group; Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Erus G, Fine LJ, Gaussoin SA, Harris D, Hsieh MK, Johnson KC, Kimmel PL, Tamura MK, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nasrallah IM, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT, Wright CB. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA* 2019;**321**:553–561.
45. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, Bosch J, O'Donnell MJ, Canavan M. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA* 2020;**323**:1934–1944.
46. Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, Beckett N, Beer JC, Bertens AS, Booth A, van Boxtel M, Brayne C, Brodaty H, Carlson MC, Chalmers J, Corrada M, DeKosky S, Derby C, Dixon RA, Forette F, Ganguli M, van Gool WA, Guaita A, Hever AM, Hogan DB, Jagger C, Katz M, Kawas C, Kehoe PG, Keinanen-Kiukaanniemi S, Kenny RA, Kohler S, Kunutsor SK, Laukkanen J, Maxwell C, McFall GP, van Middelaar T, Moll van Charante EP, Ng TP, Peters J, Rawtaer I, Richard E, Rockwood K, Ryden L, Sachdev PS, Skoog I, Skoog J, Staessen JA, Stephan BCM, Sebert S, Thijs L, Trompet S, Tully PJ, Tzourio C, Vaccaro R, Vaaramo E, Walsh E, Warwick J, Anstey KJ. Investigation of antihypertensive class, dementia, and cognitive decline: a meta-analysis. *Neurology* 2020;**94**:e267–e281.
47. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, Pase MP, Himali JJ, Windham BG, Griswold M, Gottesman R, Mosley TH, White L, Gudnason V, Debette S, Beiser AS, Seshadri S, Ikram MA, Meirelles O, Tzourio C, Launer LJ. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol* 2020;**19**:61–70.
48. van Dalen JW, Marcum ZA, Gray SL, Barthold D, Moll van Charante EP, van Gool WA, Crane PK, Larson EB, Richard E. Association of angiotensin II-stimulating antihypertensive use and dementia risk: post hoc analysis of the PreDIVA trial. *Neurology* 2021;**96**:e67–e80.
49. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, Supiano MA, Sonnen JA, Weintraub WS, Williamson J, Pajewski NM, Bress AP; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Association of antihypertensives that stimulate vs inhibit types 2 and 4 angiotensin II receptors with cognitive impairment. *JAMA Netw Open* 2022;**5**:e2145319.
50. Marcum ZA, Gabriel N, Bress AP, Hernandez I. Association of new use of antihypertensives that stimulate vs inhibit type 2 and 4 angiotensin II receptors with dementia among Medicare beneficiaries. *JAMA Netw Open* 2023;**6**:e2249370.
51. den Brok M, van Dalen JW, Abdulrahman H, Larson EB, van Middelaar T, van Gool WA, van Charante EPM, Richard E. Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis. *J Am Med Dir Assoc* 2021;**22**:1386–1395 e1315.
52. Ho JK, Moriarty F, Manly JJ, Larson EB, Evans DA, Rajan KB, Hudak EM, Hassan L, Liu E, Sato N, Hasebe N, Laurin D, Carmichael PH, Nation DA. Blood-brain barrier crossing renin-angiotensin drugs and cognition in the elderly: a meta-analysis. *Hypertension* 2021; **78**:629–643.
53. Kehoe PG. The coming of age of the angiotensin hypothesis in Alzheimer's disease: progress toward disease prevention and treatment? *J Alzheimers Dis* 2018;**62**:1443–1466.
54. Whiteley WN, Anand S, Bangdiwala SI, Bosch J, Canavan M, Chertkow H, Gerstein HC, Gorelick P, O'Donnell M, Pare G, Pigeyre M, Seshadri S, Sharma M, Smith EE, Williamson J, Cukierman-Yaffe T, Hart RG, Yusuf S. Are large simple trials for dementia prevention possible? *Age Ageing* 2020;**49**:154–160.
55. Pajewski NM, Donohue MC, Raman R, Espeland MA. Ascertainment and statistical issues for randomized trials of cardiovascular interventions for cognitive impairment and dementia. *Hypertension* 2024;**81**:45–53.
56. Licher S, Leening MJG, Yilmaz P, Wolters FJ, Heeringa J, Bindels PJE; Alzheimer's Disease Neuroimaging Initiative, Vernooij MW, Stephan BCM, Steyerberg EW, Ikram MK, Ikram MA. Development and validation of a dementia risk prediction model in the general population: an analysis of three longitudinal studies. *Am J Psychiatry* 2019;**176**:543–551.
57. Tsoy E, Kiekhofer RE, Guterman EL, Tee BL, Windon CC, Dorsman KA, Lanata SC, Rabinovici GD, Miller BL, Kind AJH, Possin KL. Assessment of racial/ethnic disparities in timeliness and comprehensiveness of dementia diagnosis in California. *JAMA Neurol* 2021;**78**:657–665.
58. Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, Coker LH, Coresh J, Couper DJ, Griswold ME, Heiss G, Knopman DS, Patel MD, Penman AD, Power MC, Selnes OA, Schneider AL, Wagenknecht LE, Windham BG, Wruck LM, Mosley TH. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study. *Am J Epidemiol* 2014; **179**:956–966.
59. Smith E, Markus H. New treatment approaches to modify the course of cerebral small vessel diseases. *Stroke* 2020;**51**:38–46.
60. Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Doshi J, Erus G, Fine LJ, Gaussoin SA, Harris D, Johnson KC, Kimmel PL, Kurella Tamura M, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT, Wright CB, Williamson JD, Bryan RN, Outcomes M, Registration T, Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, Cutler JA, Davatzikos C, Desiderio L, Doshi J, Erus G, Fine LJ, Gaussoin SA, Harris D, Johnson KC, Kimmel PL, Kurella Tamura M, Launer LJ, Lerner AJ, Lewis CE, Martindale-Adams J, Moy CS, Nichols LO, Oparil S, Ogrocki PK, Rahman M, Rapp SR, Reboussin DM, Rocco MV, Sachs BC, Sink KM, Still CH, Supiano MA, Snyder JK, Wadley VG, Walker J, Weiner DE, Whelton PK, Wilson VM, Woolard N, Wright JT, Wright CB, Williamson JD, Bryan RN. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA* 2019;**322**:524–534.
61. Markus HS, Egle M, Croall ID, Sari H, Khan U, Hassan A, Harkness K, MacKinnon A, O'Brien JT, Morris RG, Barrick TR, Blamire AM, Tozer DJ, Ford GA. PRESERVE: randomized trial of intensive versus standard blood pressure control in small vessel disease. *Stroke* 2021;**52**: 2484–2493.
62. Markus HS, van Der Flier WM, Smith EE, Bath P, Biessels GJ, Briceno E, Brodtman A, Chabriat H, Chen C, De Leeuw F-E. Framework for clinical trials in cerebral small vessel disease (FINESSE): a review. *JAMA Neurol* 2022;**79**:1187–1198.

63. Gottesman RF, Fornage M, Knopman DS, Mosley TH. Brain aging in African-Americans: the Atherosclerosis Risk in Communities (ARIC) experience. *Curr Alzheimer Res* 2015;**12**: 607–613.
64. Nyquist PA, Bilgel MS, Gottesman R, Yanek LR, Moy TF, Becker LC, Cuzzocreo J, Prince J, Yousem DM, Becker DM, Kral BG, Vaidya D. Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovasc Dis* 2014;**37**:244–250.
65. Skolarus LE, Sharrief A, Gardener H, Jenkins C, Boden-Albala B. Considerations in addressing social determinants of health to reduce racial/ethnic disparities in stroke outcomes in the United States. *Stroke* 2020;**51**:3433–3439.
66. Lackland DT. Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci* 2014;**348**:135–138.
67. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Fleck JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018;**72**:e53–e90.
68. Levine DA, Gross AL, Briceno EM, Tilton N, Kabeto MU, Hingtgen SM, Giordani BJ, Sussman JB, Hayward RA, Burke JF, Elkind MSV, Manly JJ, Moran AE, Kulick ER, Gottesman RF, Walker KA, Yano Y, Gaskin DJ, Sidney S, Yaffe K, Sacco RL, Wright CB, Roger VL, Allen NB, Galecki AT. Association between blood pressure and later-life cognition among black and white individuals. *JAMA Neurol* 2020;**77**:810–819.
69. Levine DA, Gross AL, Briceno EM, Tilton N, Whitney R, Han D, Giordani BJ, Sussman JB, Hayward RA, Burke JF, Elkind MSV, Moran AE, Tom S, Gottesman RF, Gaskin DJ, Sidney S, Yaffe K, Sacco RL, Heckbert SR, Hughes TM, Lopez OL, Allen NB, Galecki AT. Blood pressure and later-life cognition in Hispanic and white adults (BP-COG): a pooled cohort analysis of ARIC, CARDIA, CHS, FOS, MESA, and NOMAS. *J Alzheimers Dis* 2022;**89**: 1103–1117.
70. Khan MS, Shahid I, Siddiqi TJ, Khan SU, Warraich HJ, Greene SJ, Butler J, Michos ED. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc* 2020;**9**:e015594.
71. Lee M, Whitsel E, Avery C, Hughes TM, Griswold ME, Sedaghat S, Gottesman RF, Mosley TH, Heiss G, Lutsey PL. Variation in population attributable fraction of dementia associated with potentially modifiable risk factors by race and ethnicity in the US. *JAMA Netw Open* 2022;**5**:e2219672.
72. de Roos A, van der Grond J, Mitchell G, Westenberg J. Magnetic resonance imaging of cardiovascular function and the brain: is dementia a cardiovascular-driven disease? *Circulation* 2017;**135**:2178–2195.
73. Iadecola C. The pathobiology of vascular dementia. *Neuron* 2013;**80**:844–866.
74. Vangberg TR, Eikenes L, Haberg AK. The effect of white matter hyperintensities on regional brain volumes and white matter microstructure, a population-based study in HUNT. *Neuroimage* 2019;**203**:116158.
75. Das AS, Regenhardt RW, Vernooij MW, Blacker D, Charidimou A, Viswanathan A. Asymptomatic cerebral small vessel disease: insights from population-based studies. *J Stroke* 2019;**21**:121–138.
76. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. *Stroke Vasc Neurol* 2016;**1**:83–92.
77. Van Leijsen EMC, Van Uden IWM, Ghafoorian M, Bergkamp MI, Lohner V, Kooijmans ECM, Van Der Holst HM, Tuladhar AM, Norris DG, Van Dijk EJ, Rutten-Jacobs LCA, Platel B, Klijn CJM, De Leeuw FE. Nonlinear temporal dynamics of cerebral small vessel disease. *Neurology* 2017;**89**:1569–1577.
78. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010;**41**: 3–8.
79. Power MC, Tingle JV, Reid RI, Huang J, Sharrett AR, Coresh J, Griswold M, Kantarci K, Jack CR Jr, Knopman D, Gottesman RF, Mosley TH. Midlife and late-life vascular risk factors and white matter microstructural integrity: the Atherosclerosis Risk in Communities Neurocognitive Study. *J Am Heart Assoc* 2017;**6**:e005608.
80. Power MC, Schneider AL, Wruck L, Griswold M, Coker LH, Alonso A, Jack CR Jr, Knopman D, Mosley TH, Gottesman RF. Life-course blood pressure in relation to brain volumes. *Alzheimers Dement* 2016;**12**:890–899.
81. Jensen PN, Rashid T, Ware JB, Cui Y, Sitlani CM, Austin TR, Longstreth WT Jr, Bertoni AG, Mamourian E, Bryan RN, Nasrallah IM, Habes M, Heckbert SR. Association of brain microbleeds with risk factors, cognition, and MRI markers in MESA. *Alzheimer Dement* 2023;**19**: 4139–4149.
82. Koton S, Schneider ALC, Windham BG, Mosley TH, Gottesman RF, Coresh J. Microvascular brain disease progression and risk of stroke: the ARIC study. *Stroke* 2020; **51**:3264–3270.
83. Windham BG, Deere B, Griswold ME, Wang W, Bezerra DC, Shibata D, Butler K, Knopman DS, Gottesman RF, Heiss G, Mosley TH. Small brain lesions and incident stroke and mortality: a cohort study. *Ann Intern Med* 2015;**163**:22–31.
84. Koton S, Pike JR, Johansen M, Knopman DS, Lakshminarayan K, Mosley T, Patole S, Rosamond WD, Schneider ALC, Sharrett AR, Wruck L, Coresh J, Gottesman RF. Association of ischemic stroke incidence, severity, and recurrence with dementia in the Atherosclerosis Risk in Communities cohort study. *JAMA Neurol* 2022;**79**:271–280.
85. Wang R, Fratiglioni L, Kalpouzos G, Lovden M, Laukka EJ, Bronge L, Wahlund LO, Backman L, Qiu C. Mixed brain lesions mediate the association between cardiovascular risk burden and cognitive decline in older age: a population-based study. *Alzheimers Dement* 2017;**13**: 247–256.
86. Lespinasse J, Chene G, Mangin J-F, Dubois B, Blanc F, Paquet C, Hanon O, Planche V, Gabelle A, Ceccaldi M, Annweiler C, Krolak-Salmon P, Godefroy O, Wallon D, Sauvee M, Bergeret S, Chupin M, Proust-Lima C, Dufouil C; MEMENTO study group. Associations between hypertension, dementia biomarkers, and cognition: the MEMENTO cohort. *Alzheimers and Dementia* 2023;**19**:2332–2342.
87. Egle M, Hilal S, Tuladhar AM, Pirpamer L, Hofer E, Duering M, Wason J, Morris RG, Dichgans M, Schmidt R. Prediction of dementia using diffusion tensor MRI measures: the OPTIMAL collaboration. *J Neurol Neurosurg Psychiatry* 2021;**93**:14–23.
88. Won J, Maillard P, Shan K, Ashley J, Cardim D, Zhu DC, Zhang R. Association of blood pressure with brain white matter microstructural integrity assessed with MRI diffusion tensor imaging in healthy young adults. *Hypertension* 2024;**81**:1145–1155.
89. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, Carmichael O, Wolf PA, DeCarli C. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol* 2012;**11**:1039–1047.
90. Egle M, Hilal S, Tuladhar AM, Pirpamer L, Bell S, Hofer E, Duering M, Wason J, Morris RG, Dichgans M. Determining the OPTIMAL DTI analysis method for application in cerebral small vessel disease. *Neuroimage Clin* 2022;**35**:103114.
91. Acosta JN, Haider SP, Rivier C, Leasure AC, Sheth KN, Falcone GJ, Payabvash S. Blood pressure-related white matter microstructural disintegrity and associated cognitive function impairment in asymptomatic adults. *Stroke Vasc Neurol* 2023;**8**:358–367.
92. Suzuki H, Gao H, Bai W, Evangelou E, Glocker B, O'Regan DP, Elliott P, Matthews PM. Abnormal brain white matter microstructure is associated with both pre-hypertension and hypertension. *PLoS One* 2017;**12**:e0187600.
93. De Guio F, Duering M, Fazekas F, De Leeuw FE, Greenberg SM, Pantoni L, Aghetti A, Smith EE, Wardlaw J, Jouvent E. Brain atrophy in cerebral small vessel diseases: extent, consequences, technical limitations and perspectives: the HARNESS initiative. *J Cereb Blood Flow Metab* 2020;**40**:231–245.
94. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR Jr, Graff-Radford J, Schneider AL, Windham BG. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: Atherosclerosis Risk In Communities-Neurocognitive Study. *Stroke* 2015;**46**:433–440.
95. Kern KC, Wright CB, Bergfield KL, Fitzhugh MC, Chen K, Moeller JR, Nabizadeh N, Elkind MSV, Sacco RL, Stern Y, DeCarli CS, Alexander GE. Blood pressure control in aging predicts cerebral atrophy related to small-vessel white matter lesions. *Front Aging Neurosci* 2017;**9**:132.
96. Park J-H, Seo SW, Kim C, Kim GH, Noh HJ, Kim ST, Kwak K-C, Yoon U, Lee JM, Lee JW, Shin JS, Kim CH, Noh Y, Cho H, Kim HJ, Yoon CW, Oh SJ, Kim JS, Choe YS, Lee K-H, Lee J-H, Ewers M, Weiner MW, Werring DJ, Na DL. Pathogenesis of cerebral microbleeds: in vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. *Ann Neurol* 2013;**73**:584–593.
97. Graff-Radford J, Simino J, Kantarci K, Mosley TH Jr, Griswold ME, Windham BG, Sharrett AR, Albert MS, Gottesman RF, Jack CR Jr, Vemuri P, Knopman DS. Neuroimaging correlates of cerebral microbleeds: the ARIC study (Atherosclerosis Risk in Communities). *Stroke* 2017;**48**:2964–2972.
98. Wu A, Sharrett AR, Gottesman RF, Power MC, Mosley TH Jr, Jack CR Jr, Knopman DS, Windham BG, Gross AL, Coresh J. Association of brain magnetic resonance imaging signs with cognitive outcomes in persons with normal cognition and with mild cognitive impairment. *JAMA Netw Open* 2019;**2**:e193359.
99. Banerjee G, Wilson D, Jager HR, Werring DJ. Novel imaging techniques in cerebral small vessel diseases and vascular cognitive impairment. *Biochim Biophys Acta* 2016;**1862**: 926–938.
100. Haight TJ, Bryan RN, Erus G, Davatzikos C, Jacobs DR, D'Esposito M, Lewis CE, Launer LJ. Vascular risk factors, cerebrovacular reactivity, and the default-mode brain network. *Neuroimage* 2015;**115**:7–16.
101. Hedden T, Van Dijk K, Becker A, Mehta A, Sperling R, Johnson K, Buckner RL. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *J Neurosci* 2009;**29**:12686–12694.
102. Carnevale L, Maffei A, Landolfi A, Grillea G, Carnevale D, Lembo G. Brain functional magnetic resonance imaging highlights altered connections and functional networks in patients with hypertension. *Hypertension* 2020;**76**:1480–1490.
103. Christie IN, Windsor R, Mutsaerts HJ, Tillin T, Sudre CH, Hughes AD, Golay X, Gourine AV, Hosford PS. Cerebral perfusion in untreated, controlled, and uncontrolled hypertension. *J Cereb Blood Flow Metab* 2022;**42**:2188–2190.
104. van Dalen JW, Mutsaerts HJ, Petr J, Caan MW, Moll van Charante EP, Macintosh BJ, van Gool WA, Nederveen AJ, Richard E. Longitudinal relation between blood pressure, antihypertensive use and cerebral blood flow, using arterial spin labelling MRI. *J Cereb Blood Flow Metab* 2021;**41**:1756–1766.
105. van Rijssel AE, Stins BC, Beishon LC, Sanders ML, Quinn TJ, Claassen JA, de Heus RA. Effect of antihypertensive treatment on cerebral blood flow in older adults: a systematic review and meta-analysis. *Hypertension* 2022;**79**:1067–1078.
106. Sible IJ, Yew B, Dutt S, Bangen KJ, Li Y, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults. *Neurobiol Aging* 2021;**205**:57–63.
107. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; **354**:i4098.

108. Sible IJ, Nation DA. Blood pressure variability and cognitive decline: a post hoc analysis of the SPRINT MIND trial. *Am J Hypertens* 2023;**36**:168–175.
109. Wang Y, Rosa-Neto P, Gauthier S. Advanced brain imaging for the diagnosis of Alzheimer disease. *Curr Opin Neurol* 2023;**36**:481–490.
110. Langbaum JBS, Chen K, Launer LJ, Fleisher AS, Lee W, Liu X, Protas HD, Reeder SA, Bandy D, Yu M, Caselli RJ, Reiman EM. Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. *Neurobiol Aging* 2012;**33**:e11–e19.
111. Zhou R, Chen H, Ye F, Huang S, Zhang J; Alzheimer's Disease Neuroimaging Initiative. Influence of hypertension on longitudinal changes in brain glucose metabolism was modified by the APOE4 allele among cognitively normal older individuals. *Front Aging Neurosci* 2020;**12**:85.
112. Ding YS, Sohn JH, Kawczynski MG, Trivedi H, Harnish R, Jenkins NW, Lituiev D, Copeland TP, Aboian MS, Aparici CM, Behr SC, Flavell RR, Huang S-Y, Zalocusky KA, Nardo L, Seo Y, Hawkins RA, Pampaloni MH, Hadley D, Franc BJ. A deep learning model to predict a diagnosis of Alzheimer disease by using 18F-FDG PET of the brain. *Radiology* 2019;**290**: 456–464.
113. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* 2009;**66**:200–208.
114. Mortensen KN, Sanggaard S, Mestre H, Lee H, Kostrikov S, Xavier ALR, Gjedde A, Benveniste H, Nedergaard M. Impaired glymphatic transport in spontaneously hypertensive rats. *J Neurosci* 2019;**39**:6365–6355.
115. Harrison IF, Ismail O, Machhada A, Colgan N, Ohene Y, Nahavandi P, Ahmed Z, Fisher A, Meftah S, Murray TK, Ottersen OP, Nagelhus EA, O'Neill MJ, Wells JA, Lythgoe MF. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain* 2020;**143**:2576–2593.
116. Carnevale D, Mascio G, D'Andrea I, Fardella V, Bell RD, Branchi I, Pallante F, Zlokovic B, Yan SS, Lembo G. Hypertension induces brain B-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension* 2012;**60**:188–197.
117. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, Wagenknecht LE, Wong DF, Mosley TH. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* 2017;**317**: 1443–1450.
118. Marchant NL, Reed BR, Sanossian N, Madison CM, Kriger S, Dhada R, Mack WJ, DeCarli C, Weiner MW, Mungas DM, Chui HC, Jagust WJ. The aging brain and cognition: contribution of vascular injury and aB to mild cognitive dysfunction. *JAMA Neurol* 2013;**70**:488–495.
119. Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Preboske GM, Kantarci K, Raman MR, Machulda MM, Mielke MM, Lowe VJ, Senjem ML, Gunter JL, Rocca WA, Roberts RO, Peterson RC, Jack CR Jr. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain* 2015;**138**:761–771.
120. Lee MJ, Seo SW, Na DL, Kim C, Park JH, Kim GH, Kim CH, Noh Y, Cho H, Kim HJ, Yoon CW, Ye BS, Chin J, Jeon S, Lee J-M, Choe YS, Lee K-H, Kim JS, Kim ST, Lee J-H, Ewers M, Werring DJ, Weiner MW. Synergistic effects of ischemia and B-amyloid burden on cognitive decline in patients with subcortical vascular mild cognitive impairment. *JAMA Psychiatry* 2014;**71**:412–422.
121. Rabin JS, Schultz AP, Hedden T, Viswanathan A, Marshall GA, Kilpatrick E, Klein H, Buckley RF, Yang HS, Properzi M. Interactive associations of vascular risk and ß-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol* 2018;**75**:11241131.
122. Coomans EM, van Westen D, Pichet Binette A, Strandberg O, Spotorno N, Serrano GE, Beach TG, Palmqvist S, Stomrud E, Ossenkoppele R, Hansson O. Interactions between vascular burden and amyloid-B pathology on trajectories of tau accumulation. *Brain* 2024;**147**: 949–960.
123. Yau W-YW, Shirzadi Z, Yang H-S, Ikoba AP, Rabin JS, Properzi MJ, Kim DR, Schultz AP, Rentz DM, Johnson KA, Sperling RA, Chhatwal JP. Tau mediates synergistic influence of vascular risk and AB on cognitive decline. *Ann Neurol* 2022;**92**:745–755.
124. Hanff TC, Sharrett AR, Mosley TH, Shibata D, Knopman DS, Klein R, Klein BE, Gottesman RF. Retinal microvascular abnormalities predict progression of brain microvascular disease: an Atherosclerosis Risk In Communities Magnetic Resonance Imaging study. *Stroke* 2014; **45**:1012–1017.
125. Deal JA, Sharrett AR, Rawlings AM, Gottesman RF, Bandeen-Roche K, Albert M, Knopman D, Selvin E, Wasserman BA, Klein B, Klein R. Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study. *Neurology* 2018;**90**:e1158–e1166.
126. Egle M, Deal JA, Walker KA, Wong DF, Sharrett AR, Gottesman RF. Association between retinal microvascular abnormalities and late-life brain amyloid-beta deposition: the ARIC-PET study. *Alzheimers Res Ther* 2024;**16**:100.
127. Pacholko A, Iadecola C. Hypertension, neurodegeneration, and cognitive decline. *Hypertension* 2024;**81**:991–1007.
128. Lerman LO, Kurtz TW, Touyz RM, Ellison DH, Chade AR, Crowley SD, Mattson DL, Mullins JJ, Osborn J, Eirin A, Reckelhoff JF, Iadecola C, Coffman TM. Animal models of hypertension: a scientific statement from the American Heart Association. *Hypertension* 2019;**73**:e87–e120.
129. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab* 2008; **7**:476–484.
130. Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension* 1989;**13**:968–972.
131. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension* 2005;**45**:1050–1055.
132. Werber AH, Heistad DD. Effects of chronic hypertension and sympathetic nerves on the cerebral microvasculature of stroke-prone spontaneous hypertensive rats. *Circ Res* 1984; **55**:286–294.
133. Sadoshima S, Busija DW, Heistad DD. Mechanisms of protection against stroke in stroke-prone spontaneously hypertensive rats. *Am J Physiol* 1983;**244**:H406–H412.
134. Baumbach GL, Sigmund CD, Faraci FM. Cerebral arteriolar structure in mice overexpressing human renin and angiotensinogen. *Hypertension* 2003;**41**:50–55.
135. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Peterson RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:2672–2713.
136. Henskens LHG, Kroon AA, van Oostenbrugge RJ, Gronenschild EHBM, Fuss-Lejeune MMJJ, Hofman PAM, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension* 2008;**52**: 1120–1126.
137. Henning EC, Warach S, Spatz M. Hypertension-induced vascular remodeling contributes to reduced cerebral perfusion and the development of sopntaneous stroke in aged SHRSP rats. *J Cereb Blood Flow Metab* 2010;**30**:827–836.
138. Coyle P. Dorsal cerebral collaterals of stroke-prone spontaneously hypertensive rats (SHRSP) and Wistar Kyoto rats (WKY). *Anat Rec* 1987;**218**:40–44.
139. Kawashima S, Yamashita T, Miwa Y, Ozaki M, Namiki M, Hirase T, Inoue N, Hirata K-I, Yokoyama M. HMG-CoA reductase inhibitor has protective effects against stroke events in stroke-prone spontaneously hypertensive rats. *Stroke* 2003;**34**:157–163.
140. Toth P, Tucsek Z, Sosnowska D, Gautam T, Mitschelen M, Tarantini S, Deak F, Koller A, Sonntag WE, Csiszar A, Ungvari Z. Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotension II-induced hypertension. *J Cereb Blood Flow Metab* 2013;**33**:1732–1742.
141. de Montgolfier O, Pincon A, Pouliot P, Gillis M-A, Bishop J, Sled JG, Villeneuve L, Ferland G, Levy BI, Lesage F, Thorin-Trescases N, Thorin E. High systolic blood pressure induces cerebral microvascular endothelial dysfunction, neurovascular unit damage, and cognitive decline in mice. *Hypertension* 2019;**73**:217–228.
142. Cifuentes D, Poittevin M, Dere E, Broqueres-You D, Bonnin P, Benessiano J, Pocard M, Mariani J, Kubis N, Merkulova-Rainon T, Levy BI. Hypertension accelerates the progression of Alzheimer-like pathology in a mouse model of the disease. *Hypertension* 2015;**65**: 218–224.
143. Sanchez F, de Jesus Gomez-Villalobos M, Juarez I, Quevedo L, Flores G. Dendritic morphology of neurons in medial prefrontal cortex, hippocampus, and nucleus accumbens in adult SH rats. *Synapse* 2011;**65**:198–206.
144. Vega E, de Jesus Gomez-Villalobos M, Flores G. Alteration in dendritic morphology of pyramidal neurons from the prefrontal cortex of rats with renovascular hypertension. *Brain Res* 2004;**1021**:112–118.
145. Kaiser D, Weise G, Moller K, Scheibe J, Posel C, Baasch S, Gawlitza M, Lobsien D, Diederich K, Minnerup J, Kranz A, Boltze J, Wagner D-C. Spontaneous white matter damage, cognitive decline and neuroinflammation in middle-aged hypertensive hypertensive rats: an animal model of early-stage cerebral small vessel disease. *Acta Neuropathologica Commun* 2014; **2**:169.
146. Guy R, Volkman R, Wilczynski E, Yagil C, Yagil Y, Findler M, Auriel E, Nevo U, Offen D. A novel rodent model of hypertensive cerebral small vessel disease with white matter hyperintensities and peripheral oxidative stress. *Int J Mol Sci* 2022;**23**:5915.
147. Mohammadi MT, Dehghani GA. Acute hypertension induces brain injury and blood-brain barrier disruption through reduction of claudins mRNA expression in rat. *Pathol Res Pract* 2014;**210**:985–990.
148. Hom S, Fleegal MA, Egleton RD, Campos CR, Hawkins BT, Davis TP. Comparative changes in the blood-brain barrier and cerebral infarction of SHR and WKY rats. *Am J Physiol Regul Integr Comp Physiol* 2007;**292**:R1881–R1892.
149. Santisteban MM, Ahn SJ, Lane D, Faraco G, Garcia-Bonilla L, Racchumi G, Poon C, Schaeffer S, Segarra SG, Korbelin J, Anrather J, Iadecola C. Endothelium-macrophage crosstalk mediates blood-brain barrier dysfunction in hypertension. *Hypertension* 2020;**76**:795–807.
150. Wardlaw JM, Sandercock P, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003;**34**:806–812.
151. Biancardi VC, Son SJ, Ahmadi S, Filosa JA, Stern JE. Circulating angiotensin II gains access to the hypothalamus and brain stem during hypertension via breakdown of the blood-brain barrier. *Hypertension* 2014;**63**:572–579.
152. Ueno M, Sakamoto H, Liao Y-J, Onodera M, Huang C-L, Miyanaka H, Nakagawa T. Blood-brain barrier disruption in the hypothalamus of young adult spontaneously hypertensive rats. *Histochem Cell Biol* 2004;**122**:131–137.
153. Fredriksson K, Kalimo H, Westergren I, Kahrstrom J, Johansson BB. Blood-brain barrier leakage and brain edema in stroke-prone spontaneously hypertensive rats. Effect of chronic sympathectomy and low protein/high salt diet. *Acta Neuropathol* 1987;**74**:259–268.
154. Knox CA, Yates RD, Chen I, Klara PM. Effects of aging on the structural and permeability characteristics of cerebrovasculature in normotensive and hypertensive strains of rats. *Acta Neuropathol* 1980;**51**:1–13.

155. Kruyer A, Soplop N, Strickland S, Norris EH. Chronic hypertension leads to neurodegeneration in the TgSwDI mouse model of Alzheimer's disease. *Hypertension* 2015;**66**:175–182.
156. Cifuentes D, Poittevin M, Bonnin P, Ngkleo A, Kubis N, Merkulova-Rainon T, Levy BI. Inactivation of nitric oxide synthesis exacerbates the development of Alzheimer disease pathology in APPPS1 mice (amyloid precursor protein/presenilin-1. *Hypertension* 2017;**70**:613–623.
157. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. *Circ Res* 2019;**124**:1025–1044.
158. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;**2**:161–192.
159. Silverman A, Petersen NH. Physiology, cerebral autoregulation (eds.), *StatPearls*. Treasure Island, FL: National Library of Medicine; 2003.
160. Cipolla MJ. The adaptation of the cerebral circulation to pregnancy: mechanisms and consequences. *J Cereb Blood Flow Metab* 2013;**33**:465–478.
161. Osol G, Halpern W. Myogenic properties of cerebral blood vessels from normotensive and hypertensive rats. *Am J Physiol* 1985;**249**:H914–H921.
162. New DI, Chesser AMS, Thuraisingham RC, Yaqoob MM. Cerebral artery responses to pressure and flow in uremic hypertensive and spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2003;**284**:H1212–H1216.
163. Toth P, Tucsek Z, Tarantini S, Sosnowska D, Gautam T, Mitschelen M, Koller A, Sonntag WE, Csiszar A, Ungvari Z. IGF-1 deficiency impairs cerebral myogenic autoregulation in hypertensive mice. *J Cereb Blood Flow Metab* 2014;**34**:1887–1897.
164. Miller LR, Bickel MA, Tarantini S, Runion ME, Matacchiera Z, Vance ML, Hibbs C, Vaden H, Nagykaldi D, Martin T, Bullen EC, Pinckard J, Kiss T, Howard EW, Yabluchanskiy A, Conley SM. IGF1R deficiency in vascular smooth muscle cells impairs myogenic autoregulation and cognition in mice. *Front Aging Neurosci* 2024;**16**:1320808.
165. Heistad DD, Mayhan WG, Coyle P, Baumbach GL. Impaired dilatation of cerebral arterioles in chronic hypertension. *Blood Vessels* 1990;**27**:258–262.
166. Mayhan WG, Faraci FM, Heistad DD. Impairment of endothelium-dependent responses of cerebral arterioles in chronic hypertension. *Am J physiol* 1987;**253**:H1435–H1440.
167. Matin N, Pires PW, Garver H, Jackson WF, Dorrance AM. DOCA-salt hypertension impairs artery function in rat middle cerebral artery and parenchymal arterioles. *Microcirculation* 2016;**23**:571–579.
168. Pires PW, Girgla SS, McClain JL, Kaminski NE, van Rooijen N, Dorrance AM. Improvement in middle cerebral artery structure and endothelial function in stroke-prone spontaneously hypertensive rats after macrophage depletion. *Microcirculation* 2013;**20**:650–651.
169. Girouard H, Park L, Anrather J, Zhou P, Iadecola C. Cerebrovascular nitrosative stress mediates neurovascular and endothelial dysfunction induced by angiotensin II. *Arterioscler Thromb Vasc Biol* 2007;**27**:303–309.
170. Didion SP, Faraci FM. Angiotensin II produces superoxide-mediated impairment of endothelial function in cerebral arterioles. *Stroke* 2003;**34**:2038–2042.
171. Yang ST, Mayhan WG, Faraci FM, Heistad DD. Endothelium-dependent responses of cerebral blood vessels during chronic hypertension. *Hypertension* 1991;**17**:612–618.
172. Yamakawa H, Jezova M, Ando H, Saavedra JM. Normalization of endothelial and inducible nitric oxide synthase expression in brain microvessels of spontaneously hypertensive rats by angiotensin II AT1 receptor inhibition. *J Cereb Blood Flow Metab* 2003;**23**:371–380.
173. Ando H, Zhou J, Macova M, Imboden H, Saavedra JM. Angiotensin II AT1 receptor blockade reverses pathological hypertrophy and inflammation in brain microvessels of spontaneously hypertensive rats. *Stroke* 2004;**35**:1726–1731.
174. Hojna S, Kadlecova M, Dobesova Z, Valouskova V, Zicha J, Kunes J. The participation of brain NO synthase in blood pressure control of adult spontaneously hypertensive rats. *Mol Cell Biochem* 2007;**297**:21–29.
175. Briones AM, Alonso MJ, Hernanz R, Miguel M, Salaices M. Alterations of the nitric oxide pathway in cerebral arteries from spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 2002;**39**:378–388.
176. Taylor JL, Walsh KR, Mosneag I-E, Danby TGE, Luka N, Chanda B, Schiessl I, Dunne RA, Hill-Eubanks D, Hennig GW, Allan SM, Nelson MT, Greenstein AS, Pritchard HAT. Uncoupling of Ca2+ sparks from BK channels in cerebral arteries underlies hypoperfusion in hypertension-induced vascular dementia. *Proc Natl Acad Sci U S A* 2023;**120**:e230751320.
177. Jarajapu YPR, Knot HJ. Relative contribution of Rho kinase and protein kinase C to myogenic tone in rat cerebral arteries in hypertension. *Am J Physiol Heart Circ Physiol* 2005;**289**:H1917–H1922.
178. Ibrahim J, McGee A, Graham D, McGrath JC, Dominiczak AF. Sex-specific differences in cerebral arterial myogenic tone in hypertensive and normotensive rats. *Am J Physiol Heart Circ Physiol* 2006;**290**:H1081–H1089.
179. Dunn KM, Renic M, Flasch AK, Harder DR, Falck J, Roman RJ. Elevated production of 20-HETE in the cerebral vasculature contributes to severity of ischemic stroke and oxidative stress in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2008;**295**:H2455–H2465.
180. Toth P, Csiszar A, Tucsek Z, Sosnowska D, Gautam T, Koller A, Laniado Schwartzman M, Sonntag WE, Ungvari Z. Role of 20-HETE, TRPC channels, and BKCa in dysregulation of pressure-induced Ca2+ signaling and myogenic constriction of cerebral arteries in aged hypertensive mice. *Am J Physiol Heart Circ Physiol* 2013;**305**:H1698–H1708.
181. Shekhar S, Varghese K, Li M, Fan L, Booz GW, Roman RJ, Fan F. Conflicting roles of 20-HETE in hypertension and stroke. *Int J Mol Sci* 2019;**20**:4500.
182. Fan F, Geurts AM, Murphy SR, Pabbidi MR, Jacob HJ, Roman RJ. Impaired myogenic response and autoregulation of cerebral blood flow is rescued in CYP4A1 transgenic Dahl salt-sensitive rat. *Am J Physiol Regul Integr Comp Physiol* 2015;**308**:R379–R390.
183. Toth P, Rozsa B, Springo Z, Doczi T, Koller A. Isolated human and rat cerebral arteries constrict to increases in flow: role of 20-HETE and TP receptors. *J Cereb Blood Flow Metab* 2011;**31**:2096–2105.
184. Koller A, Toth P. Contribution of flow-dependent vasomotor mechanisms to the autoregulation of cerebral blood flow. *J Vasc Res* 2012;**49**:375–389.
185. Toth P, Csiszar A, Sosnowska D, Tucsek Z, Cseplo P, Springo Z, Tarantini S, Sonntag WE, Ungvari Z, Koller A. Treatment with the cytochrome P450 ω-hydroxylase inhibitor HET0016 attenuates cerebrovascular inflammation, oxidative stress and improves vasomotor function in spontaneously hypertensive rats. *Br J Pharmacol* 2013;**168**:1878–1888.
186. Beason-Held LL, Moghekar A, Zonderman A, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke* 2007;**38**:1766–1773.
187. Mughal A, Nelson MT, Hill-Eubanks D. The post-arteriole transitional zone: a specialized capillary region that regulates blood flow within the CNS microvasculature. *J Physiol* 2023;**601**:889–901.
188. Schaeffer S, Iadecola C. Revisiting the neurovscular unit. *Nat Neurosci* 2021;**24**:1198–1209.
189. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron* 2017;**96**:17–42.
190. Drew PJ. Neurovascular coupling: motive unknown. *Trends Neurosci* 2022;**45**:809–819.
191. Koide M, Harraz OF, Dabertrand F, Longden TA, Ferris HR, Wellman GC, Hill-Eubanks DC, Greenstein AS, Nelson MT. Differential restoration of functional hyperemia by antihypertensive drug classes in hypertension-related cerebral small vessel disease. *J Clin Invest* 2021;**131**:e149029.
192. Faraco G, Sugiyama Y, Lane D, Garcia-Bonilla L, Chang H, Santisteban MM, Racchumi G, Murphy M, Van Rooijen N, Anrather J, Iadecola C. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. *J Clin Invest* 2016;**126**:4674–4689.
193. Santisteban MM, Schaeffer S, Anfray A, Faraco G, Brea D, Wang G, Sobanko MJ, Sciortino R, Facchumi G, Waisman A, Park L, Anrather J, Iadecola C. Meningeal interleukin-17-producing T cells mediate cognitive impairment in a mouse model of salt-sensitive hypertension. *Nat Neurosci* 2024;**27**:63–77.
194. Capone C, Faraco G, Park L, Cao X, Davisson RL, Iadecola C. The cerebrovascular dysfunction induced by slow pressor doses of angiotensin II precedes the development of hypertension. *Am J Physiol Heart Circ Physiol* 2011;**300**:H397–H407.
195. Kazama K, Wang G, Frys K, Anrather J, Iadecola C. Angiotensin II attenuates functional hyperemia in the mouse somatosensory cortex. *Am J Physiol Heart Circ Physiol* 2003;**285**:H1890–H1899.
196. Bloch S, Obari D, Girouard H. Angiotensin and neurovascular coupling: beyond hypertension. *Microcirculation* 2015;**22**:159–167.
197. Iulita MF, Vallerand D, Beauvillier M, Haupert N, Ulysse CA, Gagne A, Vernoux N, Duchemin S, Boily M, Tremblay M-E, Girouard H. Differential effect of angiotensin II and blood pressure on hippocampal inflammation in mice. *J Neuroinflammation* 2018;**15**:62.
198. Boily M, Li L, Vallerand D, Girouard H. Angiotensin II disrupts neurovascular coupling by potentiating calcium increases in astrocytic endfeet. *J Am Heart Assoc* 2021;**10**:e020608.
199. Longden TA, Dabertrand F, Koide M, Gonzales AL, Tykocki NR, Brayden JE, Hill-Eubanks D, Nelson MT. Capillary K+-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. *Nat Neurosci* 2017;**20**:717–726.
200. Dabertrand F, Harraz OF, Koide M, Longden TA, Rosehart AC, Hill-Eubanks DC, Joutel A, Nelson MT. PIP2 corrects cerebral blood flow deficits in small vessel disease by rescuing capillary Kir2.1 activity. *Proc Natl Acad Sci U S A* 2021;**118**:e2025998118.
201. Thakore P, Yamasaki E, Ali S, Sanchez Solano A, Labelle-Dumais C, Gao X, Chaumell MM, Gould DB, Earley S. PI3K block restores age-dependent neurovascular coupling defects associated with cerebral small vessel disease. *Proc Natl Acad Sci U S A* 2023;**120**:e2306479120.