Chapter 2
Hypertension and Age-Related Cognitive Decline

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Abstract As the population is aging rapidly worldwide, there is an increasing need to better understand chronic conditions associated with aging such as vascular and metabolic diseases, and cognitive decline. Hypertension is one of the most prevalent chronic conditions associated with age and its impact on cognitive decline has often been put forth. Overall, both longitudinal and cross-sectional investigations suggest that hypertension can increase the risk of cognitive decline, and that the negative impact is more salient in processing speed and executive control tests. However, memory deficits associated with hypertension can also be observed. While hypertension has consistently been shown to increase the risk of dementia in middle-aged or young-old adults, some studies suggest that it could have a protective effect on cognition in very old populations. Studies looking at the effect of antihypertensive drug treatments report diverging results, but tend to suggest that treatment might be effective in preventing cognitive decline associated with age. Together, findings summarized here suggest that hypertension is an important factor that has a worsening effect on cognition as people age, and that antihypertensive approaches could help control or alleviate the impact of elevated blood pressure on cognition. Future studies will help identify effective ways to control hypertension and potentially emphasize preventive approaches as complementary avenues to the more traditional pharmacological approach.

Keywords Hypertension • Blood pressure • Cognition • Aging • Antihypertensive treatment • Dementia
1 Introduction

Modern societies are facing challenges of a rapidly aging population. Statistics Canada estimations reveal that by 2026, 20% of Canadians will be over 65. In 2056, over a quarter of the Canadian population will fall in this age group. Reports from the World Health Organization (WHO) state that the proportion of adults aged over 60 years will double from 2000 to 2050, absolute numbers rising from 605 million to 2 billion people worldwide. These demographic changes have a significant impact on the economic and health system as chronological aging is often accompanied by physiological changes that may lead to the development of various diseases. In particular, cognitive impairment associated with aging is the leading cause of disability and institutionalization among older adults. However, it is worth noting that cognitive aging is heterogeneous in many ways. Firstly, not all cognitive functions are impacted by age or altered at the same time or rate in the aging process. While language and crystallized cognitive abilities related to general knowledge remain virtually unchanged or may even improve with increasing age, functions based on fluid cognitive processes such as attention, memory, and processing speed, usually show a greater age-related decline [1, 2]. Among these, executive functions seem to be particularly sensitive to the effects of normal aging [3]. These high-level, frontally mediated cognitive functions are especially useful in inhibiting an automatic behavior, updating information in working memory, coordinating multiple tasks and switching between tasks [4]. They are involved in complex behaviors of everyday life and contribute to the effectiveness of other cognitive functions, such as memory. Neuroimaging evidence show that frontal regions of the cortex, which support executive functioning, are primarily affected during normal aging [5]. Recent studies also suggest that even within a single cognitive domain (e.g., memory or executive functions), some basic mechanisms (e.g., switching) might be more sensitive to normal aging than others (e.g., inhibition) [6]. In addition to this heterogeneous picture of cognitive aging, interindividual differences in cognitive aging profiles bring additional challenges, and hope, in our understanding of how we can cope with age-related changes in cognition and brain functions.

Interindividual variability is a very important feature of cognitive aging, with some individuals showing early cognitive decline while others seem to be immunized against aging. A recent case report revealed the remarkable case of a 115-year-old woman whose brain showed almost no pathological changes at death and whose cognitive performance at age 112–113 was above average of healthy adults of 60–75 years [7]. Several recent studies and reviews support the notion that the level of cognitive functioning and the rate of decline among older adults are affected by lifestyle and medical factors. Indeed, a large proportion of older individuals maintain a high level of cognitive functioning throughout life, and differences in engagement in cognitively stimulating activities and physical activity [8–10], as well as physical functioning [11] seem to partly account for individual heterogeneity in age-related cognitive decline. Moreover, a large body of evidence has shown that vascular risk factors can negatively influence the trajectories of cognitive aging by
weakening brain structures and functions [12, 13] and among those, hypertension has been put forth as having a major impact on cognition as we age. However, not all studies lead to this conclusion and future studies could help understand the profile of cognitive changes associated with hypertension.

Hypertension is the most prevalent cardiovascular risk factor in the elderly population, affecting nearly half of people aged 65 and over in Canada. It has been referred to as the silent killer because it is usually not associated with specific and salient symptoms or morbidity. However, hypertension can be associated with serious complications, including heart diseases, kidney failure, and stroke. According to the WHO, hypertension is responsible for nearly 50% of deaths from stroke or heart disease. The risk of stroke may act as a mediator in the relationship between blood pressure (BP) and cognition, as hypertension is a major risk factor for stroke, and tissue damage associated with stroke is a leading cause for cognitive disability [14]. Nevertheless, regardless of its effect on the risk of stroke, hypertension also exerts a direct impact on cognitive performance [15, 16] and is associated with an increased risk of dementia [17, 18]. Several functional and structural mechanisms may be responsible for this deleterious effect of high BP on cognitive function and the risk of dementia. Among those, endothelial dysfunction and its associated changes in the autoregulation of cerebral blood flow compromises adequate perfusion and renders the brain more vulnerable to ischemic insults. Moreover, chronic hypertension is associated with white matter lesions, lacunar infarcts, neurotic plaques and neurofibrillary tangles, all pathological features of Alzheimer’s disease (AD) [19–21].

In this chapter, we will briefly discuss methodological and measurement issues in the field of cognitive aging and hypertension. We will then review evidence for the relationship between hypertension and cognitive functioning in older adults without dementia and discuss the age-dependent relationship between hypertension and cognition. Finally, we will review recent research on antihypertensive treatment for preventing cognitive decline and dementia in the older adults population.

2 Measuring Cognition and Hypertension in Older Adults and Other Methodological Concerns

Cognition refers to a wide range of various mental processes by which sensory input is transformed into meaningful information, allowing us to interact with our environment. It encompasses many functions, such as attention, memory, working memory, language, problem solving, reasoning, decision making, etc. Neuropsychological testing is a widely used, standardized, and validated way to assess cognition. Tests can target specific functions (e.g., attention) and mechanisms (e.g., switching), or more global functioning summarized in a unique score (e.g., general mental ability). Most studies in the medical field, especially epidemiological and longitudinal studies, usually employ broad measures of cognition that target
general mental functioning and that are faster to administer, and more easily applicable to large cohorts. The most wildly used test is the Mini-mental state evaluation (MMSE [22]). It is used to assess the general mental state in older adults and it can be administered rather quickly. It has thus become a gold standard measure of cognition in studies that examine the link between medical conditions and cognition in large cohorts of elderly population. The use of a single measure of general cognition is certainly convenient and cost-effective but does not allow to identify specific functions that are affected in a targeted population, or to differentiate between various processes included in one broad measure. Yet, the existence of relationships between certain cognitive functions and hypertension may help identifying cerebral regions that are particularly sensitive to pathophysiological effects of hypertension on the brain and may lead to a better understanding of the mechanisms responsible of selective cognitive decline. Few studies have used more comprehensive neuropsychological assessments to represent the variety and the specificity of cognitive functions that may differentially be associated with hypertension, thus evidence for BP-related alterations in specific cognitive domains still remain scarce.

Hypertension status and its various indexes greatly vary among studies as well, standing from a self-reported question to specific and accurate measurements of BP with a sphygmomanometer. Some studies have used medical history and the use of antihypertensive medication to classify participants in the hypertensive or normotensive group, whereas others have made one or several measurements of BP during the same session, or across different sessions. Furthermore, although most studies have used the most recent guidelines to determine BP criteria for hypertensive status (systolic BP [SBP] ≥ 140 mmHg and diastolic BP [DBP] ≥ 90 mmHg), some of them have used other cut-off points.

The variability of inclusion and exclusion criteria across studies may also have an important impact on the observed associations. Age range of participants, inclusion of individuals with untreated or uncontrolled hypertension, exclusion of participants with conditions that are related to cognition, such as history of stroke, cardiovascular diseases, neurological and/or psychiatric conditions, depression, thyroid problems, etc., are all methodological choices that can partly explain and account for discrepant results among studies.

3 Hypertension and Normal Cognitive Aging

Paying attention to cognitive decline without dementia is not a trivial issue since neuropsychological performance within the normal range can predict functional outcomes in aging [23–25] as well as future cognition [26]. Longitudinal investigations of cognitive performance allow assessing the effect of chronic hypertension on cognition thus they appear more enlightening than most cross-sectional studies. However, the use of a cross-sectional design sometimes permits to include a larger amount of cognitive tests in the assessment, therefore leading to a more detailed picture of the impact of hypertension on different cognitive functions and mechanisms. Results from both study designs are presented in the following sections.
3.1 **Longitudinal and Prospective Studies**

The first studies linking hypertension and greater risk of cognitive decline in older adults date back from the early nineties. One of the first carefully designed and controlled study was the Framingham study that showed a negative correlation between untreated BP in middle age adults and cognitive functioning 12–14 years later [16]. Cognitive functions were measured using several standardized neuropsychological tests from the Wechsler adult intelligence and memory scales. Results showed that averaged blood pressure and chronicity of hypertension were associated with verbal and visual memory, as well as working memory performances. The association between BP and cognitive state has also been observed within a shorter follow-up period. Indeed, in the Epidemiology of vascular aging (EVA) study [27], 1373 individuals aged between 59 and 71 years were followed for only 4 years. Authors observed that those showing high BP were 4.3 times more likely to show cognitive decline, as determined by a decrease of four points on the MMSE. The risk of cognitive decline decreased to 1.9 times in individuals who were taking antihypertensive medication.

Other studies further explored the temporal relationship between BP and cognitive decline, while taking into account the severity of hypertension, as to whether it was controlled or not. Alves de Moraes and collaborators followed 8058 participants from the Atherosclerosis Risk in Communities (ARIC) study [28]. BP and cognitive functions were measured at two different time points, 6 years apart. Cognitive testing targeted memory, processing speed, and verbal fluency. Participants were classified in one of the following BP categories: (a) normal BP, defined as having no prevalent hypertension and normal BP at both visits; (b) incident hypertension, defined as having normal BP at the first visit, but hypertension at the second visit; (c) controlled hypertension, defined as having prevalent hypertension but normal BP at both visits; (d) partially controlled hypertension, defined as having prevalent hypertension, and abnormal BP at one of the two visits; and (e) uncontrolled hypertension, defined as having prevalent hypertension with high BP at both visits. Results showed that, at baseline, normotensive participants had higher scores for processing speed than those in the three other groups. Verbal fluency performance was also higher in normotensive individuals when compared to subjects with partially controlled hypertension. Among the hypertensive groups, processing speed and verbal fluency were lower in partially controlled and uncontrolled hypertension categories. Longitudinal analyses on a sample of 10,963 adults from the same cohort revealed that after controlling for demographic factors, hypertension at baseline was associated with decline on a measure of processing speed over 6 years (Digit Symbol Substitution test of the Wechsler adult intelligence scale), but not in memory or word fluency performance [29]. Analysis of change between time 1 and time 2 yielded only one significant difference between normotensives and uncontrolled hypertensive patients, observed in processing speed score. Further, this difference was limited for older participants. These results suggest that the temporal change in cognition is not perfectly related to changes in BP and may be age-dependent. These results also suggest that some domains of cognition are more sensitive to differences in hypertension status than others.
Other studies reporting on longer follow-up periods also support the notion that high BP is associated with cognitive decline in older adults. For instance, an ambitious study examined the longitudinal association between BP and cognition in a large Sweden population-based cohort of 999 men followed over 20 years [30]. Ambulatory 24-h BP monitoring was recorded at the beginning of the study, when participants were 50 years of age, and then 20 years later. Cognitive function was measured only at 70 years with a composite score that included the MMSE and the Trail-making test, a test that taps psychomotor speed and executive control (i.e., switching). Longitudinal analyses revealed that men with DBP ≤ 70 mmHg showed the highest cognitive performance, whereas men with DBP ≥ 105 mmHg had the lowest cognitive performance. SBP was not related to cognition in this sample. Cross-sectional analyses at age 70 also revealed a significant inverse relationship between DBP and cognitive score, with stronger associations in untreated men. In fact, an increase of 1 SD of 24-h DBP raised the risk of cognitive impairment (i.e., being in the lowest quintile of cognitive performance) by 1.45. The composite score precludes conclusion as to whether decline was general or impacted more specific cognitive functions.

In a secondary analysis of the data from the ACTIVE intervention trial, impacts of BP and diabetes mellitus on cognitive performance was investigated in 2802 participants aged 65–94 [31]. Cognitive functioning was assessed yearly over 3 years using a collection of neuropsychological tests that targeted global cognitive function, memory, reasoning, and speed of processing. Using BP at baseline, participants were classified into four BP groups: normal BP (< 120/80 mmHg), prehypertension (120–139/80–89 mmHg), Stage 1 hypertension (140–159/90–99 mmHg), or Stage 2 hypertension (> 160/100 mmHg). Cross-sectional results showed that high BP was specifically associated with reasoning abilities but not memory performance. In longitudinal analyses, although a test–retest improvement of cognitive performance was observed from baseline to time 2, individuals with Stage 1 and Stage 2 hypertension had a faster decrease in reasoning performance than normotensive participants from time 2 to time 3. Interestingly, the acceleration of cognitive decline associated with high BP was specific to frontally-mediated cognitive functions.

Other studies suggest however that verbal episodic memory could also be negatively affected by hypertension. In fact, in Swan, Carmelli, and Larue’s report from the Western Collaborative Group Study [32], SBP was tracked over 30 years to examine if its change was associated with neuropsychological performance after adjustment for age, education, depression, stroke, and use of antihypertensive medication. They found that subjects whose SBP remained high (≥ 140 mmHg) from midlife to follow-up, had lower scores on a composite measure of verbal memory than those whose SBP had a normal trajectory, defined as being low (< 120 mmHg) or medium (120–139 mmHg) throughout life, or showing an increase from low to medium or medium to high over the follow-up period (average increase of 20.1 %). Subjects whose SBP decreased over the life span (average change of −6.7 %) performed less well on a composite measure of processing speed than subjects from the normal group. Participants from the decliners’ group also showed higher prevalence of depression and coronary heart disease, which both have been related to cognition [33, 34].
Some studies have demonstrated a more complex relationship between BP and cognition throughout life span. For instance, a longitudinal population-based study on 2068 men and women aged 65–102 years showed that BP had a U-shaped association with performance on a mental status questionnaire, meaning that subjects with low SBP (< 130 mmHg) and high SBP (≥ 160 mmHg) made more errors than participants with optimal SBP (130–159 mmHg) [35] (see also [36] and [37]). It thus seems that several longitudinal studies support the notion that hypertension, most commonly indexed by abnormal BP, is associated with lower cognitive performance compared to normotensive state and with higher risk of further cognitive decline over relatively short period of time, sometimes as early as 4 years follow-up. A definitive conclusion as to whether this longitudinal observation holds for global cognitive status or is more specific to some cognitive domains can only be supported by a limited number of studies, but it seems that executive control and controlled attention are more sensitive to hypertension status than other functions, although some studies also identified episodic memory as being negatively affected by hypertension. Moreover, it is worth mentioning that not all studies support a relationship between BP and cognitive changes. For instance, in the Chicago Health and Aging Project, BP at baseline was not associated with the 6-year change in cognitive function in the large community-based sample of 4284 older adults [38]. Further studies could certainly help clarify the link between BP and change in BP over years and the profile of cognitive decline.

3.2 Cross-Sectional Studies

Results from cross-sectional studies provide valuable data in order to better understand how hypertension and BP status impacts cognition globally or differentially according to the cognitive domains that are being investigated. In a large population-based cohort of 19,836 individuals aged 45 and older (mean age: 64.6 ± 9.5), a linear relationship between higher DBP and impaired cognition (measured by the 6-item screener, derived from the MMSE) was observed [39]. Each 10 mmHg increase in DBP was associated with a 7% augmentation in odds ratio for cognitive impairment. In this study, SBP was also related to cognitive performance, but adjustment for confounding variables, such as demographic characteristics, vascular risk factors, depressive symptoms, and antihypertensive medication suppressed the significance of the association. Using a more comprehensive battery of cognitive tests (six subtests of the Wechsler Adult Intelligence Scale [WAIS]), Robbins and collaborators [40] assessed the relationship between blood pressure and cognitive performance in a sample of 1563 participants aged 18–79 years (mean age: 49.1 ± 15.0). The results showed that both SBP and DBP were associated with performance in all tests, but regression coefficients indicated that performance at the Digit Symbol Substitution test, a measure of psychomotor speed, was more strongly and consistently related to SBP and DBP than any other cognitive outcome. Performance at the Similarities subtest, a test of abstract reasoning capacities, was also strongly
predicted by BP (SBP and DBP) but to a lesser extent. It could thus be the case that
to some extent BP would have a more specific impact on speed of processing and/
or tests that require controlled and effortful attention, but definitive conclusion
requires further observation with a broader variety of cognitive tests. Interestingly
in this study, the negative effect of high BP level on cognition was independent of
age but not race, as significant interactions of race with SBP and DBP were observed
in most cognitive outcomes. In fact, although African–American sometimes showed
greater impact of high BP on cognition, the relation between BP and cognitive per-
formance was observed in both racial groups. Moreover, the specificity of the cog-
nitive domains altered, with speed of processing and abstract reasoning being more
impaired than other cognitive tests, holds for all participants independently of age
and racial groups.

Vicario et al.’s study [41] further explored the impact of hypertension on execu-
tive functions by using more than one test of attention and executive control. They
observed that 46 % of hypertensive patients were unable to complete Part B of the
Trail-making test within the time limit, whereas only 13 % of normotensives failed
to do so. This suggests a negative impact of hypertension on cognitive flexibility or
attentional switching. The authors also observed significant differences between
groups in the Stroop task, which targets inhibition, as well as delayed recall, a mea-
sure of long-term episodic memory. However, they did not reproduce the effect of
hypertension on MMSE scores that was observed in other studies. Saxby and col-
leagues employed a comprehensive neuropsychological battery to evaluate the
effect of hypertension on attention, memory, and executive functioning in a sample
of 223 individuals aged 70–89 [42], and used factor analysis techniques to reduce
the number of cognitive dimensions studied. When compared to the normotensive
group, hypertensive participants showed lower performance on composite mea-
sures of speed of cognition, executive functions, episodic memory, and working
memory, but not continuity of attention. Hypertension appeared to affect many cog-
nitive functions, sparing only measures of vigilance and task accuracy that were
included in the continuity of attention score.

Overall, cross-sectional studies suggest that older adults with hypertension tend
to show lower cognitive performances than those without hypertension. However,
not all cross-sectional studies support this claim. In DiCarlo et al.’s study, that
involved a large sample of 3425 participants aged 65–84 years, hypertension was
not related to cognitive impairment (measured with the MMSE) [43]. Another study
with 936 adults ranging from 24 to 81 years of age, showed that BP was not a sig-
nificant predictor of cognitive performance, measured with five cognitive tests,
even in participants that were not taking antihypertensive medication [44]. Analysis
with participants stratified for age also did not yield significant results. Nevertheless,
given the number of studies reporting a significant link between hypertension or BP
level on cognition, overall findings support the notion that hypertension and ele-
vated BP can negatively impact cognition. Several cognitive domains have been
pointed out as showing vulnerability to high BP, especially processing speed and
executive functions (e.g., abstract reasoning, cognitive flexibility), but memory may
also be affected.
3.3 Age-Dependent Relation between Hypertension and Cognition

Given the well-established age-dependent effect on cognition and the high prevalence of hypertension in older adults, the potential interaction effect of age on the association between hypertension and/or BP and cognition has been investigated, but studies have led to mixed results. In 357 older men, Brady et al. [45] showed an age-related decline in most neuropsychological measures, but did not find the expected main effect of BP category (normotensive, controlled hypertensive, uncontrolled hypertensive, and untreated hypertensive) on cognitive functioning. Interestingly, their results revealed an interaction between BP and age on performance in tests of verbal fluency and immediate recall. Only older uncontrolled hypertensive men performed less well than normotensive men. The authors suggested that deficits in episodic memory recall and verbal fluency may be due to deficits in the strategies used for information retrieval, which depend on the effectiveness of executive functions. In the same line, Bucur and Madden [46] showed a selective BP-related decline in executive functions only in their oldest group (60–79 years) of participants. In this study, speed of processing was not influenced by BP nor by the interactive effects of age and BP. Thus, it has been hypothesized that elevated BP may exacerbate age-related cognitive decline in frontally mediated functions, namely executive control. However, some studies that tested the interaction of age and BP on various cognitive functions did not yield significant results [39, 47], or showed the inverse pattern. In Suhr, Stewart, and France [48], there was an interaction between SBP and age on performance in a verbal learning/attention measure, where only participants younger than 40 years showed the significant association between SBP and cognition. However, the sample did not include adults older than 59 years.

While some studies shed light on the possible age-accelerating effect of BP on cognition, another body of evidence showed what resembles to a protective effect of high BP in the oldest portion of the older population. For instance, a prospective investigation from the Rotterdam study and the Leiden 85-plus study showed that elevated baseline BP was associated with a greater risk of cognitive decline 11 years later, but only in 65–74-year-old participants, whereas younger (< 65) did not show any significant relationship between BP and future cognition [49]. However, in the oldest group (≥ 75), higher BP was associated with better cognitive functioning a decade later. In Obisesan et al.’s study [50], hypertension was associated with impaired performance in the short-portable MMSE, but not in the oldest group. Indeed, hypertensive subjects aged 80 years and older showed better cognitive performance than their normotensive counterparts. Interestingly, while hypertension has consistently been shown to increase the risk of dementia in middle-aged or young-old adults, this relationship is not observed in the oldest old for whom the inverse association is sometimes observed [51–55]. Further, in Sabayan et al. [56], participants aged 85 and older with high BP had less cognitive and physical disability (measured with the MMSE and assessment of activities of daily living [ADL])
than those with low BP. Longitudinal analyses from this cohort also showed that high BP was associated with less cognitive and physical decline, especially among participants who had preexisting physical disability. Together, these results support the idea that mild hypertension may have a protective effect on cognitive functioning in the oldest portion of older adults. In their exhaustive review of cross-sectional and longitudinal studies on the effect of low and high BP on cognitive functioning and dementia across different age groups, Qiu et al. [18] conclude that elevated BP in midlife is an important risk factor for developing late-life cognitive impairment and dementia. Among older adults, very high SBP (> 180 mmHg) is also associated with an increased risk of dementia, but low DBP (< 70 mmHg) augments the risk as well. The authors go further and suggest that high BP in middle age coupled with low BP in old age may be a marker of AD (see also [17]). Several explanations may account for the potential protective effect of high BP on cognition in the oldest-old. The most largely admitted hypothesis state that higher BP is necessary to overcome age-related arterial stiffness or vascular damage and maintain adequate perfusion in the brain [57], hence the protective effect of mild hypertension on cognition.

4 Effect of Pharmacological Interventions to Lower BP on the Risk of Cognitive Decline and Dementia

The beneficial effect of BP-lowering pharmacological treatments in reducing cardiovascular morbidity and mortality has been widely recognized [58]. However, the positive impact of antihypertensive medications on the risk of cognitive decline and dementia in older adults population has not yet reached scientific consensus. Current evidence on the cerebroprotective effect of antihypertensive drugs stems from both prospective cohort studies and randomized double-blind placebo-controlled trials.

4.1 Prospective Cohort Studies

Results from the Honolulu-Asia Aging Study [59] provided evidence for the relationship between increasing midlife BP and greater risk for cognitive impairment in a cohort of 3703 Japanese-American men. In this study, each 10-mmHg increase in SBP was associated with a 9 \% augmentation in the risk of poor cognitive functioning. Interestingly, in this cohort, every additional year of treatment led to a decreased risk of incident dementia to the point where men who received antihypertensive medication for 12 years and more showed similar risk for dementia than their normotensive counterparts [60] (but see also [61]). After 2.2 years of follow-up, patients from the Rotterdam study who were taking antihypertensive medication at baseline showed a reduced incidence of vascular dementia [62], but the protective effect of pharmacological treatment was not observed on the risk of AD. In a sample of 1617 African Americans aged 65 years and older followed for 5 years, a 38 \%
reduced risk of cognitive dysfunction was found in participants treated with antihypertensive medication [63]. Similarly, in the aforementioned EVA study, the 4-year risk of cognitive decline was reduced in patients treated for hypertension compared to untreated hypertensive patients [27]. The population-based Cache County study provided significant results in AD-risk reduction for patients taking antihypertensive drugs, after adjustments for age, education, sex, apolipoprotein E4 status, stroke, hypercholesterolemia, diabetes, and myocardial infarction [64].

Even in patients already suffering from cognitive impairment and dementia, controlling hypertension can lead to beneficial impacts on cognition. In fact, Hajjar et al. [65] studied 350 patients from a primary care geriatric practice for 2 years. They found that among patients with dementia (vascular dementia and AD), those who were taking BP-lowering medications had a lower rate of decline in MMSE scores than those who were not taking antihypertensive drugs.

Conversely, some studies did not yield evidence for a protective effect of BP-lowering pharmacological agents on the risk of cognitive impairment or dementia in longitudinal investigations. For instance, Yasar and collaborators [66] prospectively examined the association between use of calcium-channel blocker (CCB) and risk of developing AD over 19 years. No significant relationship was found between CCB use and dementia risk after adjustments for BP, sex, education, smoking, and history of heart disease. It thus seems that, although some positive results suggest that pharmacological treatment to lower BP and hypertension might help reduce the risk of cognitive decline and dementia, additional studies are required to further support this claim and help better understand the mechanisms by which hypertension impact cognition in older adult populations. Certainly, intervention studies are valuable here to better control for numerous confounding factors that can come into play.

### 4.2 Randomized, Placebo-Controlled Trials

The Medical Research Council’s project (MRC) [67] was among the first studies to examine the effect of blood pressure reduction on the incidence of cognitive decline. A group of 2584 adults aged 65–74 was followed for 54 months. The active-treatment group received a β-blocker or a diuretic as active agents. Cognitive screening measures included paired-associate learning (memory) and trail-making test (cognitive flexibility). Results showed no difference in cognitive scores between the treatment and placebo groups.

The Systolic Hypertension Study in Europe (Syst-Eur) [68] involved 2418 patients aged 60 and older with systolic hypertension, randomly assigned to two conditions: a calcium-channel blocker (nitrindipine) with or without an angiotensin-converting enzyme (ACE) inhibitor (enalapril), and/or a diuretic (hydrochlorothiazine); or a placebo condition. Cognition was measured with the MMSE, and the dementia diagnostic procedure using DSM-III-TR criteria was conducted for patients with MMSE < 23. Results showed that the incidence of dementia was
reduced by 50% among treated individuals in the 2-year follow-up. Further investigation in this sample (additional follow-up of 2 years among patients withdrawing from double-blind) indicated a 55% reduction in incidence of both AD and vascular dementia [69]. Authors highlighted that the use of a CCB in 1000 patients for 5 years can prevent 20 cases of all-type dementia.

In the Study of Cognition and Prognosis in the Elderly (SCOPE) [70], 4964 adults aged 70–89 years with a MMSE score ≥ 24 received an angiotensin-II receptor blocker (ARB) (candesartan) with or without a diuretic. MMSE scores and proportion of patients with dementia were equivalent in both treatment and placebo groups after 3.7 years of follow-up. However, further analysis comparing cognitive scores at baseline showed that among individuals with lower cognitive function (MMSE scores ranging from 24 to 28 at baseline), MMSE scores declined less in the active-treatment group than in the placebo group during the follow-up period [71]. It is worth mentioning that a fairly large proportion of patients within the placebo group (66%) were taking other antihypertensive drugs, and thus may have benefited from cognitive protection.

The Systolic Hypertension in the Elderly Program (SHEP) examined 4736 patients 60 years and older with systolic hypertension. The mean follow-up period was 4.5 years. The active-treatment group was taking a β-blocker (chlorthalidone) with or without another β-blocker (atenolol) or reserpine. The difference between groups in the incidence of dementia (measured using the Short-CARE) was not significant. However, a large proportion of participants did not complete the cognitive assessment, and this dropout was biased towards older, less-educated and non-Caucasian individuals. Interestingly, when 20–30% of dropouts were assumed to be cognitively impaired, assignment to the active-treatment group in the overall sample was associated with a reduced risk of cognitive impairment [72]. This protective effect was not observed in the Hypertension in the Very Elderly Trial Assessing Cognitive Decline and Dementia Incidence (HYVET-COG). In this study, 3336 participants aged 80 and over were randomly assigned to a treatment group receiving a diuretic (indapamide) with or without an ACE inhibitor (perindopril) or to a matching-placebo group. The follow-up period was 2.2 years. The rate of dementia in the active-treatment group was not significantly different from the placebo group.

Overall, pharmacological treatment seems to have a protective effect against cognitive decline and to lower the risk of dementia in patients with more severe adverse outcomes related to vascular conditions such as those who experienced recurrent strokes. For instance, in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [73], 6105 patients with a previous history of stroke or transient ischemic attack received an active treatment consisted of an ACE inhibitor (perindopril) with or without a diuretic (indapamide). Treatment yielded a nonsignificant 12% overall reduction in the risk of dementia (according to DSM-IV criteria) after the 4-year follow-up. However, among patients with recurrent stroke, a significant diminution of 34% in the risk of dementia in the active-treatment group was observed. As for cognitive decline (defined as 3-point or more decline on MMSE score), active treatment was associated with a 19% reduction in the whole
sample, and with a 45% reduction among participants with recurrent stroke. Furthermore, results showed a superior effect of combination therapy in reducing the risk of dementia when compared to monotherapy.

Recent meta-analyses attempted to draw an overview of the pooled effects of BP-lowering therapy on cognitive function and dementia. McGuiness et al. [74] published a Cochrane review incorporating the SCOPE, SHEP, and Syst-Eur trials. They found a nonsignificant 11% reduction of the risk of dementia in treated patients. Another meta-analysis with patients suffering from cardiovascular disease (from PROGRESS, SCOPE, Syst-Eur, and SHEP trials) revealed a borderline-significant 20% diminution of dementia in patients receiving antihypertensive medication [75]. Finally, the meta-analysis by Birns et al. [76] looked at the effect of BP-lowering on different cognitive functions. Sixteen studies were included in the analysis. They concluded that MMSE was modestly but significantly improved by diminution of BP. A reduction of BP was also associated with better memory performance (immediate and delayed recall). However, processing speed and executive functioning were not improved in treated individuals. It is important to note that BP reduction was not equivalent in each study and that further investigation of differential effects of treatment on several cognitive functions with larger and more carefully designed studies is still warranted.

4.3 Differential Effects of Antihypertensive Classes on Cognition

One concern unaddressed in the studies reported so far is the potential difference amongst subclasses of antihypertensive drugs. Some studies aimed at examining the differential effect of diverse classes of medications in the risk of cognitive decline and dementia. In their network meta-analysis that included 17 randomized-controlled trials, Levi-Marpillat et al. [77] compared the effects of different antihypertensive classes on overall cognition. They found a superior protective effect for ARBs, followed by β-blockers, diuretics, and ACE inhibitors. The effect of reducing BP on cognition was equivalent for each class of medication, therefore the beneficial effect of certain drugs over others was not caused by differences in the extent of BP reduction. Amenta et al. [78] also reviewed evidence for differential effects of antihypertensive classes on the risk for cognitive decline and found diverging results. They stated that CCBs and ACE inhibitors have shown more convincing evidence for cerebroprotective effects than diuretics and β-blockers. Furthermore, it appears that ACE inhibitors that cross the blood–brain barrier (BBB) have a larger beneficial effect on cognition than non-BBB-crossing ACE inhibitors and CCBs [79]. Conversely, Hanon et al. argue for a specific neuroprotective action of CCBs over other classes of drugs via its prevention for age-related disruption in intracellular calcium regulation [80]. This suggests that part of the variability across studies in the extent of risk reduction for cognitive impairment and dementia in treated patients may stem from differential drug-class mechanisms, some of which may not
be related to BP reduction alone. It thus seems that the effects of antihypertensive pharmacological treatment on the incidence of cognitive impairment and dementia would vary depending upon drug classes due to different biophysiological pathways. However, such conclusion is based on a very scarce number of studies and further investigation is required to support it.

5 Conclusion

Hypertension is the most prevalent cardiovascular risk factor in the elderly population as it affects close to 50% of older adults. Often considered a silent killer due to the fact that symptoms are virtually absent, hypertension effect on cognition and the risk of dementia is nevertheless well supported. In this review, we addressed the methodological concerns and differences among study that sometimes precludes clear conclusion on the effect that hypertension might have on the aging brain. Our review allowed to emphasize that hypertension is associated with greater cognitive decline and risk of dementia in longitudinal studies, and larger age-related deficits in cross-sectional studies. While antihypertensive drug treatments are improving, their potential beneficial effects on cognition remain hard to demonstrate without reserves.

Several open issues call for further investigations. Among those, the optimal BP-target to maintain adequate cognitive functioning in older adults, especially among the oldest old, is still to be determined. Along the same line, some studies suggest an age-dependent relationship between BP and cognition. While this must await confirmatory studies, a potential age-dependent effect of BP-lowering pharmacological therapy on cognitive functioning has also been proposed. Furthermore, the exact mechanisms by which hypertension affects cognitive functions would worth being studied extensively with brain imaging techniques. In fact, while most studies support the notion that hypertension comes with higher risk of cognitive decline, it has also been suggested that age-related changes in the central nervous system that leads to cognitive impairment may itself be the cause of BP dysregulation [81]. Moreover, there is a need to better understand the class-specific effects of antihypertensive agents on the risk of cognitive decline and dementia. Finally, whether some specific cognitive functions are preferentially impacted by elevated BP warrants further studies involving a large range of cognitive tests.

The quest for moderators of cognitive decline and ways to prevent disability and promote healthy and independent living in aging will still be a matter of scientific interest in the years to come. As our knowledge on the beneficial effect cognitive intervention [82] and physical exercise [83] on brain structure and functions and their moderating effect on age-related cognitive decline is improving, it would be worth exploring the combination of lifestyle intervention and antihypertensive drug treatment on cognition and brain functions as people age. Recent studies have shown that physical training can lead to structural and functional changes in the brain [84] and can improve cognitive performance, especially executive functioning.
Given that cardiovascular training can also help reducing BP in normotensive and hypertensive populations [86], it would be interesting to look at the additive or interactive effects of physical exercise and antihypertensive treatment on both BP and age-related cognitive decline among hypertensive patients. Perhaps a more comprehensive and holistic approach would lead to better lifestyle management that will in turn enhance hypertension control and reduce its negative impact on the aging brain.

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