Blood Pressure, Cognition, and Dementia

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Abstract

This review synthesizes findings from studies that investigate the impact of blood pressure on cognition and the development of Alzheimer’s disease (AD), while highlighting research limitations that add to variability. To properly capture this relationship, we review findings from a neuropsychological perspective, considering the effect of blood pressure on different aspects of cognition (e.g., processing speed, memory, and executive function) rather than cognition as a unitary construct. Hypertension in mid-life is associated with worse cognitive outcomes in later life, particularly in the areas of executive functioning and processing speed. Findings are mixed in late-life studies; however, with several lines of research demonstrating that either high or low blood pressure is associated with worse cognition. Much of this variability may be due to greater incidence of dementia for those with low blood pressure in late-life. The effect of blood pressure levels on attention, visuospatial skills, and language skills is scarcely investigated and requires further examination. The effectiveness of antihypertensive agents for slowing cognitive decline or reducing dementia risk is still debated. There is strong evidence, however, that blood pressure treatment for at least 12 years or for people aged <75 may be effective in preserving cognitive function, reducing risk for AD, and may facilitate clearance of toxic AD-related biomarkers in the brain.

Key words: Alzheimer disease, antihypertensive agents, blood pressure, cognition, dementia

Introduction

Hypertension poses important public health issues, affecting 30% of people worldwide. It is one of several risk factors for cerebrovascular disease and is frequently observed in the context of neurodegenerative diseases such as Alzheimer’s disease (AD) and vascular dementia (VaD). As blood pressure (BP) can be successfully managed and treated in clinical contexts, current investigations have focused on whether (a) hypertension contributes to cognitive impairment and (b) whether treatment for hypertension can slow or halt cognitive decline in aging or in people at risk for dementia. This review will discuss recent perspectives in these two main areas.

Hypertension is generally defined as >90 mm Hg diastolic blood pressure (DBP) or >140 mm Hg systolic blood pressure (SBP). Both SBP and DBP are considered important for clinical outcomes, but systolic hypertension is usually associated with greater stroke risk and mortality. SBP and DBP follow different trajectories across the lifespan, emphasizing the importance of treating them separately. DBP and SBP naturally increase until mid-life, after which DBP typically lowers and SBP continues to rise. This means that SBP hypertension (considered as isolated systolic hypertension) is most common among elderly and frequently the focus of modern hypertension research. The difference between SBP and DBP is termed pulse pressure (PP). Widening of PP caused by increases in SBP and decreases in DBP in late life is considered to be an indirect measure of arterial stiffness and a predictor of adverse vascular outcomes.

Blood Pressure and Cognition

The effects of elevated blood pressure on cognition have been investigated widely, predominantly since the early 1990s.
Many investigations have employed cognitive screeners such as the Mini-Mental State Examination (MMSE), which are relatively brief and easy assessments that amalgamate many aspects of cognition into a unitary measure, and have reported highly variable results. This is not surprising, as vascular risk factors and cerebrovascular disease have greatest impact on attention, processing speed, and executive functions which are not always observable with cognitive screeners. Many advantages are gained, however, by investigating cognition using neuropsychological test batteries instead of cognitive screeners: They are sensitive to subtle changes across cognitive domains, they are less likely to be suffer ceiling effects, and they may correct for age, sex, and education status.

The cognitive areas most extensively investigated in hypertension research include executive function, memory, and processing speed. Executive function is a term used to describe a cluster of high-level cognitive processes associated with inhibitory control, selective attention, cognitive flexibility (set shifting), problem solving, planning, and generation of ideas. In hypertension research, executive function is most frequently assessed with letter and semantic fluency tasks. Processing speed (cognitive efficiency measured in time) is usually assessed using the Digit Symbol-Coding subtest variants from versions of the Wechsler Adult Intelligence Scale or similar tasks. The tools used to assess learning and memory are highly variable, which complicate interpretation and adds to variability in findings, but typically involve list-learning or recall of prose passages.

Overall, it appears that the presence of mid-life (generally < 65 years) hypertension is especially predictive of cognitive impairment later in life, particularly for executive and processing speed tasks. This can be compared with the highly variable findings in late-life studies. This distinction suggests that degree of cognitive impairment is dependent on the duration of elevated blood pressure, an observation which is supported by longitudinal findings with longer follow-up times.

In terms of executive function, there is ample evidence linking mid-life hypertension with worse letter and semantic fluency later in life. The effect of hypertension has also been associated with worse performance in other areas of executive function, such as cognitive flexibility and reasoning. Reduced executive function is generally found even when controlling for the presence of other vascular risk factors. The association is less robust for those with higher blood pressure in late-life, however, and one study found that younger individuals within their sample of older people with high DBP performed better on fluency tasks. For the latter study, as well as several other late-life investigations, cerebrovascular disease, and/or stroke were exclusion criteria for recruitment. As discussed in later sections, hypertension is strongly associated with the development of white matter lesions, stroke, and various other manifestations of cerebrovascular disease. Excluding these participants may, therefore, have biased the sample to include healthier individuals whose hypertension had not yet exacerbated breakdown of cerebral vasculature. As incidence of cerebrovascular disease increases with age, this may not pose an issue for mid-life studies. Similarly, in older age, hypertension is highly comorbid with other vascular risk factors (such as obesity, diabetes, and hypercholesterolemia) which lowers the potential of finding independent hypertension-related effects. This is supported by Elias et al. who found worse cognitive performance in individuals with both hypertension and obesity, than just hypertension alone.

In mid-life studies, hypertension is frequently found to be associated with worse performance on processing speed tasks; however, this has not been demonstrated consistently across studies. One study found a stronger effect for individuals with both diabetes and hypertension, suggesting an additive effect with other vascular risk factors. A 30-year longitudinal study found worse performance on processing speed tasks for individuals who were hypertensive in mid-life and dropped below 139 mm Hg SBP after 30 years. This suggests that late-life decrease in SBP in the context of pre-existing hypertension is especially predictive for reduced processing speed. Findings from late-life hypertension studies are less clear, partly due to the exclusion of processing speed tasks in the selected battery of cognitive tests highlighting the need for further investigation. Nevertheless, there is some evidence that elevated BP is associated with reduced processing speed in late-life.

The effect of hypertension on memory is unclear and requires further investigation. Independent of whether blood pressure was measured in mid- or late-life, findings are mixed with some investigations finding clear associations between hypertension and worse memory performance and others finding no effect. It is also possible that much of this variability is caused by failure to account for individuals who are in preclinical phases of dementia due to illnesses such as AD or VaD. As the presence of hypertension is a risk factor for both dementia subtypes, and AD and VaD together cause 80% of all dementia worldwide, it is probable that a high proportion of participants across all studies will go onto develop either of these illnesses. Individuals who go onto develop AD typically demonstrate greater and earlier memory impairments than those who develop VaD. Therefore, studies with a greater proportion of participants in preclinical phases of AD may observe an effect on memory, producing variability across studies. Merely excluding participants with a diagnosis of dementia is not enough; however, high accumulation of the AD biomarker amyloid-β can be detected 15 years before dementia diagnosis, when memory deficits are prominent. In support of this notion, one study found that hypertensives who experienced decline in BP showed greater levels of CSF p-tau (another AD biomarker) and worsening verbal memory performance.

Future investigations should include amyloid-β or tau as possible moderating variables, especially since hypertension along with other vascular risk factors are thought to play an important role in the pathogenesis of AD.

Another issue with memory research involves the frequent amalgamation of many memory outcome measures into one factor. While this makes sense for statistical reasons (reducing...
the number of comparisons and simplifying the data; individuals who develop VaD are likely to show worse performance on learning and retrieval aspects of memory with good retention, whereas those who develop AD typically score poorly on all aspects of memory, and especially retention. [45] Amalgamating all memory components can hide these differences and produce unaccountable variability.

Other domains that are typically less thoroughly investigated include attention, working memory, language, and visuospatial skills. Attention and working memory are usually investigated together, using digit span tasks. Kilander, Nyman (20) reported an association between elevated blood pressure and impaired digit span performance, although this finding was not robust across other investigations. [26,27,52,54] In terms of language, hypertension has been associated with reduced word knowledge and naming. [25] However, one late-life study observed that verbal skills assessed with a synonym task were better amongst Stage 1 hypertensives (140–159 mm Hg SBP or 90–99 mm Hg DBP) than in normotensives, but not for those with higher levels of hypertension (e.g., > 160 mm Hg SBP). [97] Given that it is at odds with other findings, this could be an artifact. The effect of hypertension on visuospatial skills was either not observed in mid-life studies or associated with better performance in late-life studies. [97]

Some investigations report a nonlinear association between cognition and blood pressure. Waldstein et al. observe that cognition is worst for individuals at the low and high ends of the blood pressure spectrum as opposed to mid-range BP in some areas of cognition. [28] For example, older participants with low education perform worse on executive function tasks at both the higher and lower range of BP as opposed to mid-range BP. Others who find this inverted-U shaped effect usually measured blood pressure and cognition in late-life. [26,46] One likely explanation for this (discussed in greater detail below) involves findings that late-life hypertension in the context of pre-existing hypertension is associated with greater cognitive impairment, higher dementia risk, and greater vulnerability to ischemia. This is complemented by previously discussed findings that conclude greater vulnerability to processing speed deficits for hypertensives that dropped below 139 mm Hg SBP in late-life. This raises a significant methodological flaw with late-life investigations that assume BP is static across the lifespan. Namely, either high or low BP can have deleterious outcomes in the context of pre-existing hypertension.

Another likely cause of heterogeneity in late-life studies in general involves the failure to account for duration of exposure to hypertension, and age first diagnosed. As mid-life studies clearly demonstrate that both are important for predicting cognitive impairment, late-life studies should include at least one proxy measure of hypertension duration in attempt to account for these factors. Pulse pressure partly reflects arterial stiffness and is often considered a better measure of the long-term effects of hypertension when measured in late-life. [47] Some studies now use PP rather than any single BP component separately. [46] Recent studies find that PP is associated with cognitive decline, dementia risk, and greater atrophic changes in the brain. [50] One study observed that increasing PP was associated with decline in verbal learning, visual memory, and working memory. [51] Another study found that arterial stiffness, but not hypertension, was associated with worse performance in executive function, processing speed, and working memory. [32] Hypertension was only associated with worse executive skills when seen in conjunction with arterial stiffness. Therefore, late-life studies should arguably consider including a measure of arterial stiffness to better account for long-term exposure to hypertension.

Alzheimer’s Disease

As mid-life hypertension influences cognitive performance later in life, elevated blood pressure has been investigated for its contribution to the development of dementia. Alzheimer’s disease is the most common form of dementia, with the greatest global burden on resources, impacting a projected 100 million people by 2050. [32] AD is characterized by progressive cognitive decline, brain atrophy, and accumulation of amyloid-β as well as neurofibrillary tangles in the brain. However, vascular contributions to AD are now well recognized, as over 55% of autopsy-confirmed AD brains have at least one type of vascular pathology. [53] With no disease modifying therapy available, current investigations question whether management of blood pressure among other vascular risk factors could reduce dementia risk, slow pathogenesis, or slow AD-related cognitive decline.

In terms of dementia risk, a combination of various vascular risk factors, including hypertension, is often found to be associated with increased risk for AD. [34] Other research suggests the presence of vascular risk factors lowers a clinical threshold for diagnosis, essentially advancing inevitable AD dementia diagnosis earlier in life. [55] In terms of the effect of hypertension specifically, several large studies have observed that mid-life hypertension is associated with higher incidence of AD diagnosis later in life. [56,57] For example, one study found that untreated mid-life hypertension was associated with almost 4.5 times greater risk of AD. [57] Measures relating to late-life hypertension are mixed, with a recent meta-analysis concluding no difference in dementia risk between hypertensives and normotensives. [56] One reason for this finding may be that in late-life, the combination of multiple vascular risk factors, rather than hypertension alone, influences dementia risk.

Individuals who develop AD have a greater rise in BP from mid-life to late-life and a greater decrease in BP in the years before dementia diagnosis. [50,60] This same pattern is comparable to investigations of brain volume, which shows that for individuals with a history of mid-life hypertension, lower late-life BP is associated with smaller medial temporal lobe structures, including hippocampi, than any other pattern of blood pressure change. [61,62] In studies with shorter follow-up periods, a general association between higher blood pressure and greater atrophic changes are observed. [63,64] Interestingly, this deleterious pattern
of blood pressure described above is comparable to cognitive findings discussed previously, as both high and low BP in late life can be associated with worse cognitive outcomes.\textsuperscript{[32]} It is likely that those with low BP and poor cognitive outcomes will later be diagnosed with AD.

There is considerable debate concerning the way changes in BP influence the pathogenesis of AD. One theory that has gained attention recently involves disruption to autoregulatory processes. The brain is dependent on a constant rate of cerebral blood flow. One process by which it protects from ischemic damage is through autoregulation, whereby the natural fluctuations in arterial pressure are corrected by relaxation and constriction of arteries.\textsuperscript{[65]} In AD research, it is understood that prolonged hypertension disrupts cerebrovascular autoregulation so that higher perfusion pressures are necessary to maintain stable cerebral perfusion. The brain is then susceptible to the deleterious effects of ischemia once blood pressure drops in older age, as autoregulatory mechanisms fail to compensate for this change\textsuperscript{[66]} causing vascular insufficiency and ischemia in vulnerable brain areas such as periventricular regions, which are supplied by end arteries.\textsuperscript{[65]} Supporting evidence demonstrates that those who developed AD dementia had more extensive white matter lesions later in life and higher blood pressure in mid-life.\textsuperscript{[60]} In addition, degree of periventricular white matter damage\textsuperscript{[68]} is associated with the degree of autoregulation dysfunction.\textsuperscript{[69]} These ischemic lesions appear to interact with AD pathology to enhance the manifestation of dementia.\textsuperscript{[70]}

Another way the brain regulates cerebral blood flow is through functional hyperemia, diverting cerebral blood flow to areas with increased neural activity\textsuperscript{[65]} and controlling clearance of metabolic by-products to maintain homeostasis of the cerebral microenvironment.\textsuperscript{[51]} The downstream effects of hypertension cause failure of this mechanism to clear toxic amyloid-\(\beta\) deposits during synaptic activity.\textsuperscript{[72]} This leads to amyloid-\(\beta\) accumulation in the brain and blood vessels, a condition termed cerebral amyloid angiopathy (CAA). The degree of either amyloid-\(\beta\) burden or CAA is predictive of cognitive impairment in AD.\textsuperscript{[73,74]}

**Antihypertensive Therapies**

The effect of blood pressure reduction medications on cognition is still debated. Nevertheless, many randomized control studies have found that the use of antihypertensives is protective for cognitive impairment.\textsuperscript{[75,76]} Antihypertensives are especially linked to improved or preserved executive function,\textsuperscript{[73]} processing speed,\textsuperscript{[74]} and memory.\textsuperscript{[77,78]} Treatment of hypertension is also thought to lower the incidence of AD,\textsuperscript{[79,81]} and a postmortem study found that brains of individuals using hypertensive medications had less AD-related neuropathology than normotensive subjects,\textsuperscript{[82]} while the Honolulu Asia Aging Study found that use of antihypertensives lowered risk for hippocampal atrophy.\textsuperscript{[83]} Mouse models have demonstrated that antihypertensives can facilitate amyloid clearance across the blood-brain barrier.\textsuperscript{[84]} These findings provide support for the role of hypertension in cognitive impairment as well as the pathogenesis of AD.

On the other hand, many investigations have not found an effect of blood pressure treatment on cognition or incident dementia.\textsuperscript{[45,47]} A systematic review of randomized, double-blind placebo-controlled studies of participants with no history of cerebrovascular disease found no clear evidence for the effectiveness of antihypertensives.\textsuperscript{[88]} However, this may partly be due to methodological limitations. Namely, the average duration of follow-up was a short 3.3 years and ages of participants ranged between 60 and 89 years. Current evidence suggests that BP treatment for at least 12 years\textsuperscript{[89]} and for people aged <75 years\textsuperscript{[80]} are more likely to be efficacious. This is consistent with prolonged exposure to hypertension in mid-life being associated with cognitive decline, brain atrophy, and white matter lesions. In addition, the effectiveness of antihypertensives is likely dependent on the type of treatment used, as a recent systematic review found that angiotensin II receptor blockers were the most effective for preserving cognitive function, and especially memory, in older adults.\textsuperscript{[90]} Therefore, additional longitudinal investigations with younger populations are required to assess the long-term effectiveness of antihypertensives on cognition and dementia.

**Conclusion**

Effective treatment for hypertension may be important for the preservation of cognition and brain health. Mid-life hypertension is associated with worse cognitive outcomes, particularly in the areas of executive function and processing speed. Mid-life hypertension is also associated with higher incidence of Alzheimer’s disease later in life. Two mechanisms by which hypertension is thought to influence the pathogenesis of AD involve disruption to autoregulatory processes and poor clearance of amyloid deposits. While the effect of late-life hypertension on cognition and incidence of Alzheimer’s disease is less clear, there is some evidence that low BP in late-life is also associated with cognitive impairment and the development of AD, but this requires further investigation. Research on the use of antihypertensive medications partially supports a causal relationship between mid-life hypertension and worse cognition, but variable methodologies, short follow-up periods, and inclusion of older participants complicate findings.

Greater attention needs to be given to the effect of hypertension in specific cognitive areas, using rigorous and consistent neuropsychological tools, particularly in the areas of attention, working memory, language and visuospatial skills, which are scarcely investigated, and can often underpin memory performance. Future late-life studies should include proxy measures of duration of exposure to hypertension (such as PP) to reduce variability.

**References**


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