





**REVIEW PAPER**

# Hypertension and Dementia: A comprehensive review from the HOPE Asia Network

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**Abstract**

Approximately 365 million people in Asia were classified as elderly in 2017. This number is rising and expected to reach approximately 520 million by 2030. The risk of hypertension and cognitive impairment/dementia increases with age. Recent data also show that the prevalence of hypertension and age-related dementia are rising in Asian countries. Moreover, not many people in Asian countries are aware of the relationship between hypertension and cognitive impairment/dementia. Furthermore, hypertension control is poorer in Asia than in developed countries. Hypertension is known to be a major risk factor for damage to target organs, including the brain. Decreased cognitive function can indicate the presence of target organ damage in the

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brain. Twenty-four-hour blood pressure profiles and blood pressure variability have been associated with cognitive impairment and/or silent cerebral diseases, such as silent cerebral infarction or white matter lesions, which are predisposing conditions for cognitive impairment and dementia. Hypertension that occurs in midlife also affects the incidence of cognitive impairments in later life. Managing and controlling blood pressure could preserve cognitive functions, such as by reducing the risk of vascular dementia and by reducing the global burden of stroke, which also affects cognitive function.

## 1 | INTRODUCTION

Life expectancy continues to increase globally, resulting in an increasingly elderly population.<sup>1,2</sup> Asia, continent that has world's biggest population (60%), is experiencing a very rapid increase in population aging, compared to Western countries.<sup>3</sup> Approximately 365 million people were over 60 years in Asia and classified as elderly in 2017.<sup>4</sup> This number is expected to reach approximately 520 million by 2030, with Japan having the largest percentage of elderly, estimated at around 37.3%.<sup>4,5</sup> And although such an increase in longevity should ideally be accompanied by improved quality of life, the incidence of dementia and other cognitive impairment also tend to increase with age.<sup>6-8</sup> World Alzheimer Report in 2015 also showed that Asia has the highest number of people suffered from dementia, 22.9 million, compared to Europe region (10.5 million) and America region (9.4 million).<sup>6</sup> Not surprisingly, therefore, data presented by Alzheimer's Disease International predict an increase in dementia in Asia. For example, in 2015, 1 million Indonesians are expected to be affected by dementia, and this number will increase to almost 2 million people by 2030 and nearly 4 million people by 2050. Similarly, in Japan around 3 million people had dementia in 2015, and this number will increase to 4.5 million in 2030 and 5.2 million in 2030.<sup>9</sup> In addition, death from Alzheimer's dementia increased from 3.6 to 9.8 cases per 100 000 people between 2007 and 2017 based on the Annual Report on the Cause of Death Statistics in Korea.<sup>10</sup>

There are important ethnic differences in cardiovascular-renal demographics around the world, and hypertension is one of the most powerful risk factors contributing to these demographic differences. For example, it has been well established that Asians display characteristics that differ markedly from those of whites and blacks.<sup>11,12</sup>

The risk of hypertension increases with age. Data also show that the prevalence of hypertension continues to rise in Asian countries.<sup>13</sup> Many studies have shown that hypertension increases the risk of cognitive disorders, Alzheimer's dementia, and vascular dementia.<sup>14</sup> Data from the INTERSTROKE study show that hypertension is significantly associated with stroke incidence.<sup>15</sup> The data show that hypertension is one of the risk factors that together account for 90.7% of the population-attributable risk (PAR) of stroke worldwide and 97.4% of that in South-East Asia.

The risk of dementia increases 6-fold at 5 years after a stroke event. Moreover, the risk of dementia increases as early as 5 years

before and continues more than 11 years after a stroke event, with the highest risk occurring within 1 year after the stroke event.<sup>16,17</sup> Stroke affects the hippocampus and white matter of the brain, thereby contributing to the pathogenesis of post-stroke cognitive impairment.<sup>18</sup> Reducing the incidence of stroke will thus reduce the incidence of vascular dementia.<sup>14</sup>

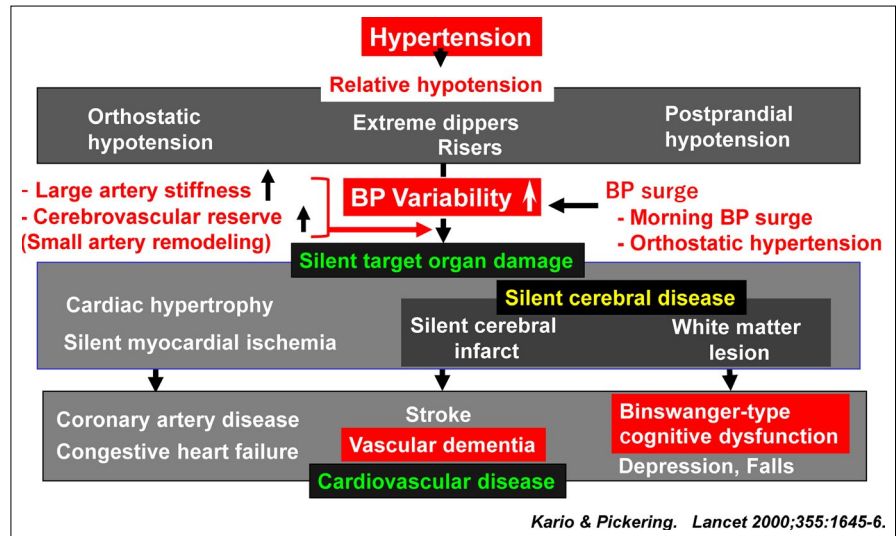
Age-related dementia, which is mostly caused by Alzheimer's disease or cerebrovascular factors (vascular dementia), is a significant public health threat.<sup>19</sup> Previous studies and current research in Asian countries show different trends, such as differences in the ratio of the incidence of Alzheimer's disease and vascular dementia, suggesting that there are trends—particularly trends related to hypertension—that will require further discussion and investigation.<sup>7,20</sup> In addition, not many people in Asian countries are aware of the relationship between hypertension and cognitive impairment/dementia.<sup>21,22</sup>

## 2 | TRENDS OF COGNITIVE IMPAIRMENT AND DEMENTIA IN ASIA

The prevalence of dementia in Asian countries varies from 2% to 13%, with the greatest risk factors being age, female sex, and low education.<sup>20,23</sup> The high epidemiological variation in Asian countries may be attributable to the different diagnostic criteria used. Also, differences in the level of education of respondents can also influence the results, accounting for as much as a twofold difference.<sup>6,20,23</sup> Moreover, the number of dementia and cerebrovascular disease in Asia is higher than the number in Western countries.<sup>24</sup>

The differences in the trends of vascular dementia and Alzheimer's disease are especially apparent when comparing studies conducted before 1990, when the vascular ratio of dementia to Alzheimer's disease was 2:1 in Japan and China, while the reverse ratio was observed in Northern Europe and America. However, since 1990, this trend has changed as the prevalence of Alzheimer's disease has increased in East Asian countries. In Korea, for example, the ratio of Alzheimer's disease to vascular dementia increased to 4.13 in the 2010s from 1.96 in the early 1990s.<sup>25</sup> One of the things that may underlie this trend is changes in lifestyle, such as diet, knowledge of the disease, risk management of vascular disease, and use of imaging such as CT scans.<sup>20,21</sup> Studies in Japan show a higher prevalence

**FIGURE 1** Clinical significance of blood pressure variability in elderly people with hypertension



of vascular dementia compared to studies in China, which have not used CT scans.<sup>20,26,27</sup>

### 3 | TRENDS AND EFFECTS OF HYPERTENSION ON COGNITIVE FUNCTION

Epidemiological data in several Asian countries reveal that hypertension is among the top three chronic diseases and contributes to both elderly morbidity and mortality.<sup>28-31</sup> Studies in India, China, and other Asian countries have also shown that smaller proportions of the population are aware of hypertension and have well-controlled hypertension compared to the corresponding percentages in developed countries.<sup>32-34</sup>

A systematic analysis based on reports from 90 countries comparing data between 2000 and 2010 revealed that both absolute hypertension and the greatest increase in hypertension were observed in East Asia and the Pacific region. An increasing trend in systolic blood pressure for both sexes was also found in the regions of South Asia and South-East Asia.<sup>35</sup>

In relation to race, a study conducted by Du et al<sup>36</sup> on the prevalence of age-adjusted hypertension among Asians living in America found that Filipinos showed the highest prevalence rate (32.7%), while Chinese showed the lowest (20%). In Indonesia, the latest data from the Basic Health Research survey show an increase in prevalence from 25.8% in 2013 to 34.1% in 2018.<sup>30,37</sup> Similar data were found in the May Measurement Month (MMM) study in 2017, which is the most massive screening performed in Indonesia to date; the hypertension prevalence in that survey was found to be 34.5%.<sup>38</sup>

Hypertension is known to be a major risk factor for damage to target organs, including the brain.<sup>15,39-45</sup> Damage to cerebral blood vessels is one of the effects of hypertension. Decreased cognitive function can indicate the presence of target organ damage in the brain, one form of which can be lesions in the white matter.<sup>46,47</sup> The hypertension-induced damage can also include changes to

cerebrovascular structural and function, which in turn can cause the neuropathological abnormalities responsible for cognitive deficits, such as micro-infarcts, microbleeds, silent brain infarcts, and brain atrophy.<sup>39,48</sup> Other structural damages to the brain caused by arterial hypertension include remodeling of the cerebral artery, myogenic reactivity, hypertrophy, and endothelial dysfunction, which cause altered cerebral blood flow (CBF) autoregulation, blood-brain barrier disruption, and cerebrovascular regulatory mechanism impairment.<sup>39,49-51</sup> In addition, clinical manifestation of reduced cognitive function can appear as learning difficulties, lack of focus, gait disorder, and depression.<sup>49,52</sup>

Progressive decrease in BP in the early stages of dementia is likely caused directly by a neurodegenerative process that affects the brain stem and hypothalamic nucleus which regulates arterial pressure and systemic metabolism.<sup>19,53</sup> Godin et al conducted the 3C study in 9294 subjects with an average age of  $72.4 \pm 4.1$  years and analyzed the association between blood pressure and anti-hypertensive treatment in relation to white matter lesions (WML) from the Dijon MRI data. The initiation of anti-hypertensive treatment significantly affected the course of WML evolution only in subjects with a base level of systolic blood pressure higher than 160 mm Hg ( $n = 113$ ); an approximately 85% greater decrease in average WML volume was observed in subjects who started anti-hypertensive treatment compared to those who did not.<sup>54</sup>

### 4 | BLOOD PRESSURE VARIABILITY AND COGNITIVE IMPAIRMENT

The term blood pressure variability (BPV) encompasses a wide range of BP variations, occurring over seconds or minutes (very short term BPV), along 24 hours (short term BPV, usually assessed by ambulatory BP monitoring), and between days (midterm or day to day BPV, assessed with home BP monitoring). Long-term BPV has also been described, including seasonal BP variations and changes between clinic visits over months or years.<sup>55</sup>

Observational studies in elderly subjects  $\geq 60$  years of age in Japan, all of whom lacked dementia at enrollment and were followed for 5 years (2007-2012), showed that daily increase in blood pressure variability led to the development of dementia in the form of either vascular dementia or Alzheimer's disease.<sup>56</sup> Twenty-four-hour blood pressure profiles and blood pressure variability have been shown to be associated with cognitive function and/or silent cerebral diseases, such as silent cerebral infarction or white matter lesions, which are predisposing conditions for cognitive dysfunction (Figure 1).<sup>54,57-61</sup> A previous study by Kario et al<sup>62</sup> showed a relationship between diurnal blood pressure variations and silent cerebrovascular damage, marked by findings of lacunae and advanced periventricular hyperintense lesions on magnetic resonance imaging (MRI) in asymptomatic hypertensive elderly. This silent cerebrovascular damage happens not only to nondippers, but also to extreme dippers (with marked nocturnal fall of blood pressure).

Recently, studies on elderly with high risk of cardiovascular disease showed that exaggerated visit-to-visit BP fluctuations were associated with silent cerebral injury, stroke, and advanced carotid artery remodeling, which lead to cognitive impairment.<sup>60,61</sup> Absolute ambulatory systolic blood pressure level (particularly during sleep) and nocturnal dipping in systolic blood pressure were strong indicators of brain matter volume and cognitive function.<sup>63</sup> In addition, an abnormal circadian blood pressure rhythm, especially the riser pattern, was shown to be clinically significant as a potential indicator of subclinical brain damage and mild cognitive impairment in heart failure patients.<sup>64</sup> Therefore, measuring blood pressure variability by ambulatory monitoring could be considered as one way to detect patients who are at high risk of developing ischemic target organ damage.<sup>59</sup>

## 5 | MIDLIFE HYPERTENSION AND COGNITIVE IMPAIRMENT

Studies in Asia have shown that hypertension is associated with incidence of dementia in the elderly.<sup>65-69</sup> Indeed, not only is hypertension directly related to cognitive function, but hypertension that occurs in midlife (around the age of 45-55 years) also affects the incidence of cognitive impairments in later life.<sup>46,70,71</sup> An analysis conducted in conjunction with the Hisayama study, a prospective cohort study in Japan performed over 32 years (1973-2005), was designed to compare blood pressure in midlife and late life, and to compare these data with dementia output and its subtypes. The results showed that high systolic and diastolic blood pressure in midlife increased the risk of vascular dementia (24% for each 10 mm Hg increase in systolic blood pressure and 37% for each 10 mm Hg increase in diastolic blood pressure).<sup>71</sup> The Coronary Artery Risk Development in Young Adults study (CARDIA) showed that higher SBP from as young as 25 years of age to middle age was associated with worse cognitive functions, including verbal memory and executive function.<sup>39,72</sup> In addition, other studies have shown a significant

association between elevated blood pressure levels in midlife and dementia in later life.<sup>73,74</sup>

Although an increase in late-life blood pressure increases the risk of all cases of dementia, including vascular dementia, the risk is greater for those whose blood pressure was increased in midlife, regardless of blood pressure in late life.<sup>71</sup> Similar studies conducted in Korea show that hypertension is associated with all types of dementia, but especially with vascular dementia. Hypertension in men under 65 years is associated with Alzheimer's disease, which is distinct from the association between hypertension and vascular dementia, which is strong both before and after 65 years of age, and both for men and for women.<sup>75</sup> As to the potential mechanism, it was suggested that chronic hypertension disrupts the blood vessels and impairs the cerebrovascular regulation, which makes the brain, especially the white matter regions that play roles in cognitive function, susceptible to ischemic injury.<sup>39</sup>

## 6 | BLOOD PRESSURE CONTROL, ANTI-HYPERTENSION AGENTS, AND COGNITIVE FUNCTION

The increased incidence of hypertension, especially in Asian populations, and its association with cognitive impairment in old age, suggests that managing and controlling blood pressure would be a potential means of preserving cognitive function, including by reducing the risk of vascular dementia and by reducing the global burden of stroke, which also affects cognitive function.<sup>15,70,75,76</sup> However, aggressive reductions in blood pressure must be carried out carefully in the elderly. In fact, recent findings have revealed that blood pressure-lowering treatment in young adults might eliminate the progression of the detrimental effects related to arterial stiffness, indicating that younger adults may have more favorable outcomes in cognition than their older counterparts if early intervention is conducted at the subclinical stage.<sup>77</sup> Although there was no impact on risk reduction of probable dementia, a recent trial (SPRINT MIND) showed that among ambulatory adults with hypertension who were treated with a goal of SBP  $< 120$  mm Hg, the risk of mild cognitive impairment was significantly reduced, compared to that in those treated with an SBP goal of  $< 140$  mm Hg (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81; 95% CI, 0.69-0.95).<sup>78</sup> A recent review of early morning BP surge (EMBS) showed that EMBS was one form of BP variability associated with the occurrence of strokes and other cardiovascular events. The study also concluded that 24-hour-long-acting anti-hypertensives, such as amlodipine and telmisartan, could control EMBS more effectively than valsartan.<sup>57</sup> Moreover, strict BP control including during sleep may have a neuroprotective effect on the brain, and thereby prevent the incidence of dementia, and vice versa: As an independent marker associated with increased risk of CVD events, cognitive function should always be evaluated in elderly hypertensive patients.<sup>79,80</sup>

A meta-analysis comparing four randomized controlled trials—Syst-Eur, Progress, HYVET-COG, and SHEP—showed that anti-hypertensive medication could significantly reduce the risk of dementia.<sup>81</sup>

Both calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) are suggested to have a more pronounced protective effect than other anti-hypertensives.<sup>82-84</sup> In addition, the Syst-Eur trial also showed that anti-hypertensive medications can reduce stroke morbidity and mortality, and respondents may not be affected by dementia until at least 60 years of age. In that study, a calcium channel blocker (CCB) was used and had a protective effect against dementia, especially Alzheimer's.<sup>85</sup> Another similar study in Kentucky showed that CCBs could reduce dementia progression and minimize amyloid beta peptide formation without changes to cell viability.<sup>82</sup> And in a study conducted on the predominantly male population of the Veterans Healthcare System in the United States, angiotensin receptor blockers achieved a significant reduction in the incidence and progression of AD and dementia compared to other cardiovascular drugs, including angiotensin converting enzyme inhibitors.<sup>83</sup>

A cohort study in China showed similar results—namely although no significant difference in cognitive decline was found between hypertensive subjects who were taking anti-hypertensive medications and subjects without hypertension, greater cognitive decline was seen in the group with untreated hypertension than the group without hypertension.<sup>86</sup> Recent studies also support the idea that the detection of hypertension, and the reduction and control of blood pressure are protective measures against later-life cognitive decline.<sup>87</sup> However, other studies have reported that anti-hypertensive therapy does not reduce the incidence of dementia.<sup>88</sup> Given the continued uncertainty regarding the protective effects of anti-hypertensive therapy on patients with cognitive dysfunction or dementia, further research is needed.<sup>89</sup>

## 7 | CONCLUSIONS

The prevalence of dementia in Asia is expected to increase in the future in accordance with global aging. It has been well established that hypertension is a major risk factor for damage to various target organs, including the brain. Managing and controlling hypertension and blood pressure variability could preserve cognitive functions, such as by reducing the risk of vascular dementia and reducing the global burden of stroke, which also affects cognitive function. The detection of hypertension, and the reduction and control of blood pressure are protective measures against later-life cognitive decline.

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## AUTHOR CONTRIBUTIONS

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## DISCLOSURES

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