

REVIEW

Neurodegenerative diseases and blood pressure variability: A comprehensive review from HOPE Asia

Yuda Turana MD, PhD^{1,2} | Robert Shen MD^{1,2} | Michael Nathaniel MD¹ |
Yook-Chin Chia MBBS, FRCP^{3,4} | Yan Li MD, PhD⁵ | Kazuomi Kario MD, PhD⁶

¹School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, North Jakarta, Jakarta, Indonesia

²Master Study Program in Biomedical Sciences, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, North Jakarta, Jakarta, Indonesia

³Department of Medical Sciences, School of Medical and Life Sciences, Sunway University, Bandar Sunway, Malaysia

⁴Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁵Department of Cardiovascular Medicine, Shanghai Key Lab of Hypertension, Shanghai Institute of Hypertension, National Research Centre for Translational Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

⁶Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

Correspondence

Yuda Turana MD, PhD, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jl. Pluit Raya No. 2, North Jakarta, Jakarta 14440, Indonesia.
Email: yuda.turana@atmajaya.ac.id

Abstract

Asia has an enormous number of older people and is the primary contributor to the rise in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. The therapy of many neurodegenerative diseases has not yet progressed to the point where it is possible to alter the course of the disease. Mid-life hypertension is an important predictor of later-life cognitive impairment and brain neurodegenerative conditions. These findings highlight the pivotal role of preventing and managing hypertension as a risk factor for neurodegenerative disease. Autonomic dysfunction, neuropsychiatric and sleep disturbances can arise in neurodegenerative diseases, resulting in blood pressure variability (BPV). The BPV itself can worsen the progression of the disease. In older people with neurodegenerative disease and hypertension, it is critical to consider 24-h blood pressure monitoring and personalized blood pressure therapy.

KEYWORDS

Alzheimer's disease, hypertension, neurodegenerative, Parkinson

1 | INTRODUCTION

The problem of population aging occurs globally, but the process in western countries is not as rapidly accelerating as in Asia.¹ As aging is happening worldwide, neurodegenerative disease numbers are increasing in parallel.^{2,3} As Asia has the highest absolute numbers of older people, neurodegenerative disease occurrence in Asia is unavoidable.⁴ Recent data shows that population aging contributes

most to the increase of neurodegenerative diseases in east Asia.⁵ World Alzheimer's report in 2015 also showed that Asia has the highest number of people with dementia (22.9 million) compared to the European region (10.5 million) and the American region (9.4 million).⁶ The trend is also predicted to increase if adequate interventions are not being done.⁷ Parkinson disease (PD), the second most common neurodegenerative disorder after Alzheimer disease (AD), also occurs more commonly with increasing age. It affects more than 1.7% world population aged 65 years or older.^{8,9} In China alone, it is suggested that PD affects about 1.7–2 million (1–2%) population aged 60 years or older.¹⁰

Yuda Turana, Robert Shen, and Michael Nathaniel contributed equally to this work.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *The Journal of Clinical Hypertension* published by Wiley Periodicals LLC.

In the rapid development of neuroscience, the treatment of various degenerative diseases is not yet at the stage of treatment to modify the course of the disease.^{11,12} Controlling neurodegenerative diseases' risk factors, including hypertension, is critical as it is a significant risk factor for target organ damage, including the brain.^{13–15} It strongly correlates with brain aging, increasing AD and PD risk, especially in the Asian population.^{7,16} It is also known that each continent has its risk factor differences regarding blood pressure variability (BPV), which affects the susceptibility toward neurodegenerative diseases, including in Asia.⁷ This paper will discuss further the significance of brain aging and BPV, and its impact on neurodegenerative diseases in Asia.

2 | HYPERTENSION AND OTHER RISK FACTORS OF BRAIN AGING

CDC (Centers for Disease Control and Prevention) defines normal brain aging as a slower processing speed and more trouble multitasking with remaining stable (or just occasionally forgetting) routine memory, skills, and knowledge that may improve with age.¹⁷ In line with that definition, according to the new diagnostic criteria of AD, brain aging is defined as normal if there is the absence of an upstream AD biomarker, the A β in the brain or cerebrospinal fluid, neither the downstream AD biomarker (CSF tau and phosphor-tau, decrease glucose utilization, etc.).¹⁸ Brain aging is known as one of the most relevant biomarkers of neurodegeneration which represents a combination of several homeostatic disruptions, such as protein aggregation, DNA damage, mitochondrial dysfunction, lysosomal dysfunction, and changes in epigenetic regulation. These disruptions of the homeostatic process can result in various diseases depending on their origins in brain locations and the pattern of propagation.¹⁹ Brain tissues are susceptible to aging because they are primarily composed of post-mitotic cells, sensitive to age-dependent changes, such as DNA damage or methylation.^{20,21} However, a recent study suggests that neurodegenerative diseases occurrence are determined by multiple factors such as genetic predisposition, education, lifestyle, exposure to environmental risk factors (trauma, smoking, alcohol, drugs, or toxins), presence of diseases (hypertension, dyslipidemia), early life developmental defects of the brain, and spatiotemporal distribution of the lesions.^{19,22–25} In AD, genetic mutations, epigenetic modifications, cellular senescence, and altered intercellular communications are associated with the production and formation of amyloid-beta plaque, hindering brain synaptic transmission and impairing mitochondrial function, activation of microglia, and production of inflammatory signals. In PD, striatal dopamine deficit is caused by the process of α -synuclein proteostasis, oxidative stress, mitochondrial dysfunction, disrupted axonal transport, and neuroinflammation.²⁶ Missense and loss of function mutations in approximately 20 genes have been associated with the occurrence of PD.²⁷ Together, AD and PD pathophysiology are strongly related to the advancement of age.³

One of the most prevalent and potentially modifiable brain aging risk factors is arterial hypertension (Table 1). As a disease of aging, hypertension is associated with neuroinflammation, disruption of cere-

bral microcirculation's structural and functional integrity, disruption of the blood-brain barrier integrity, and production of protein pathologies such as beta-amyloid.²⁸ It is suggested that vascular damages caused by hypertension in the brain begin earlier in life and gradually become less reversible.²⁹ Initially, cerebral arteries and arterioles can still make structural adaptations, which results in an increased wall-to-lumen ratio that reduces wall stress and increases segmental resistance.^{30,31} Young cerebral vasculature may also have an enhanced pressure-induced myogenic constriction response of segmentally connected cerebral arteries and arterioles, ensuring high arterial pressure is not transmitted to a more distal location, where it would damage the thin-walled arteriolar and capillary microvessels in the brain.^{32,33}

3 | BLOOD PRESSURE VARIABILITY AS RISK FACTOR OR CONSEQUENCE OF AGING

Maintaining normal BP is an important strategy in preventing neurodegenerative diseases and cognitive decline, considering that hypertension is a major modifiable risk factor that is most often found in neurodegenerative diseases such as AD, stroke, PD, cerebral small vessel disease (cSVD) and cognitive impairment due to other vascular causes. Whereas, the problem is 75%–85% of the elderly over 65 years were found to have hypertension.^{22,38–41} Human BP fluctuates widely throughout the day-to-night-time period. Research shows that clinical use of BPV provides an accurate analysis of homeostatic BP control mechanisms under physiological and pathological conditions that affect autonomic control of blood circulation due to cardiovascular and non-cardiovascular disease within 24 h, as well as information on the annual progression of organ damage due to hypertension.⁴² Measurement of BPV provides broader information than mean BP alone because it describes the annual trend of SBP and diastolic blood pressure (DBP) that increases or undergoes biphasic changes with aging, beat-to-beat to yearly variations.⁴³ Age has been calculated to be the determinant factor of BPV, both variability in the calculation of very short-term (beat-to-beat), short-term (24 h), medium-term (daily), long-term (visit-to-visit in 5 years), and very long-term (visit-to-visit more than 5 years).⁴⁴

Large arteries rigidity as the consequence of aging has been found to be significantly related to BPV although not directly in terms of causes relation; In aging, there is an increase in the rigidity of blood vessels which results in a rise in pulse wave velocity due to a faster bloodstream which triggers an increasing central systolic pressure which variably in the short term, indirectly causes BPV in 24 h.^{44–46} There is an interrelation between microcirculation and macrocirculation alterations that affect blood flow resistance resulting in BPV due to an increase in central systolic blood pressure (CSBP) in aging (Figure 1); In aging of microcirculation, there is a decrease in the diameter of the blood vessels lumen due to an increase in the media-to-lumen ratio which disrupts the process of dilation of blood vessels, in the long term there is an increase in vascular resistance which increases BP and BPV, indirectly causing remodeling and rigidity of blood vessels and altering macrocirculation while ultimately increases pulse waves and CSBP

TABLE 1 Study on hypertension as a risk factor for neurodegenerative disease by year order

References	Design	Diseases	Size (n)	Follow-up duration	Key findings
Laurer LJ, and coworkers, 1995. ³⁴	Prospective cohort study (The Honolulu-Asia Aging Study)	Dementia (not specified) and MCI	3735	28 years (baseline in 1965–1968; follow up in 1991–1993)	The midlife SBP is a significant predictor of later-life cognitive impairment.
Swan GE, and coworkers, 1998. ³⁵	Prospective cohort study (The National Heart, Lung, and Blood Institute Twin Study)	MCI, decline in neurobehavioral functioning, and brain atrophy	392	10 years	The midlife SBP can be used as a predictor of cognitive function and brain atrophy in late life.
Igase M, and coworkers, 2012. ²⁹	Comprehensive review on five randomized-controlled trials	Dementia (AD and VaD)	–	–	Conflicting results regarding hypertension treatment benefits in dementia
Gottesman RF, and coworkers, 2017. ³⁶	Prospective cohort study	AD	15,744	25 years	The vascular risk factors (obesity, smoking, diabetes, prehypertension, hypertension, and hypercholesterolemia) and APOE ε4 allele in midlife are associated with an increased risk of dementia.
Wei J, and coworkers, 2018. ³⁷	Cross-sectional study (The China Health and Retirement Longitudinal Study/CHARLS)	MCI	6,732	–	People aged 60 years and over, the SBP and pulse pressure significantly correlated to cognitive function. In this group, untreated hypertension, treated but uncontrolled hypertension, and high SBP become the risk factors for cognitive decline.
Cheng YW, and coworkers, 2020. ²²	Prospective cohort study	AD and MCI	295	2 years	Follow-up for 2 years showed that vascular risk factors were not significantly associated with cognitive outcome.
Wrigglesworth J, and coworkers, 2021. ²⁵	Systematic review	AD	52 papers, 5–31,227 participants	–	Brain aging is associated with genetics, lifestyle, health, and disease, including cardiovascular disease and BP as physical markers.

Abbreviations: AD, Alzheimer's Disease; BP, Blood Pressure; MCI, Mild Cognitive Impairment; SBP, Systolic Blood Pressure; VaD, Vascular Dementia.

with complications of end-organ damage.^{44,47,48} Research shows that aging on blood vessel rigidity affects systolic BPV more, while diastolic BPV through its pathophysiology is influenced by endothelial function and the autonomic nervous system; But aging itself affects both systolic BPV and diastolic BPV.^{49–51}

The effect of aging on BPV, both as a risk factor and as a consequence, still needs more confirmatory research because there are still studies with different results. Adoor and coworkers in explorative research on the healthy group found that aging affects the imbalance of neural regulation on cardiovascular so that there is a significant

difference in BPV with aging and also significantly reduces baroreflex sensitivity (BRS).⁵² Long-term BPV and BRS reduction on aging were also related to poor cardiovascular outcomes and increased mortality.⁵¹ On the other hand, Veerman and coworkers found that there was no effect of aging on BPV because BPV in resting conditions in the normotensive group did not significantly differ between the elderly group compared to the adolescent and adult groups; however, it was found that along with aging, there was a decrease in DBP variation when in standing position and decrease of pulse (R-R) interval variability.⁵³

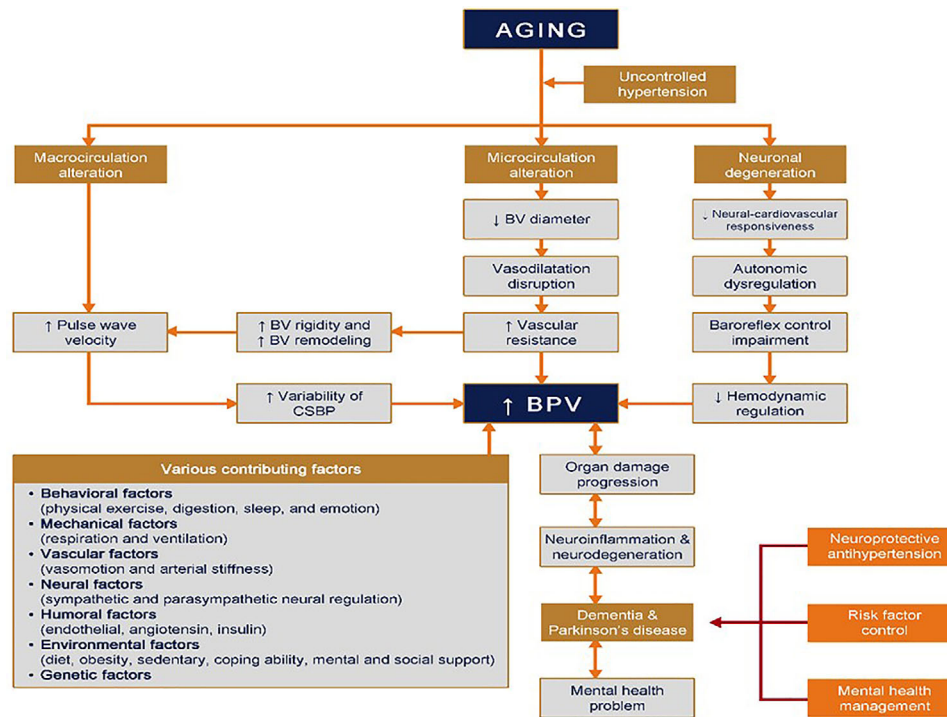


FIGURE 1 Effect of aging on BPV. Notes: BPV (Blood Pressure Variability); BV (Blood Vessels); CSBP (Central Systolic Blood Pressure)

4 | NEURODEGENERATIVE DISEASES IN ASIA ETHNICITY HAS GREATER IMPACT THAN OTHER RACES

Research on neurodegenerative diseases and their relationship to ethnicity still requires population studies with large samples to show multi-ethnic variations of brain maps in various neurodegenerative disorders; The UNITED (Uncovering Neurodegenerative Insights Through Ethnic Diversity) consortium stated that currently neuroimaging samples for the study of their relationship to genetic variants and cohorts data mostly come from Europe and North America, but data from Asia, Africa, and South America are still under-represented.⁵⁴ As the most populous region globally, Asia, with its rapidly increasing aging population, also is the greatest contributor to neurodegenerative diseases, such as dementia. This change in epidemiological status is influenced by various factors such as genetic ethnicity factor, alteration in demographic profile, urbanization, literacy, perception toward aging, environmental factors, and even the development of medical tools and knowledge, including neuroimaging modalities.⁵⁵ In Asia itself, Wong and coworkers found that there were ethnic differences of neurodegenerative diseases neuroimaging markers in three major Asian ethnicities, which are Chinese, Malays, and Indians, with a higher burden of neurodegenerative markers (cognitive performance, intracranial stenosis, and cortical atrophy) in Malays and Indians than in the Chinese.⁵⁶

As a consequence of population aging, it is predicted that in 2050 there will be 2.7 times more dementia cases than in 2019.⁵⁷ Dementia prevalence in Asia has been known previously to be lower than dementia prevalence in Western.⁵⁵ However, the numbers especially in India,

China, and the surrounding Western Pacific and South Asian countries are forecasted to quadruple between 2001 and 2040, compared to just double in developed countries. This issue can be caused by a more massive population aging condition, altered demographic profile, urbanization, environmental changes, and advances in neuroimaging modalities.⁵⁸ And because Asia is more populous, the region with the most dementia will be Asia with 22.9 million while that of Europe is 10.5 million and the America region is 9.4 million.⁶ A recent analysis for the Global Burden of Disease Study 2019 also showed that dementia incidences in North America and Europe are decreasing, potentially due to a better educational system and better management of cardiovascular disease and its risk factors.⁵ Some regions in Asia, including Indonesia, predicted a more rapid increase in dementia prevalence. A dementia study (cognitive decline complained by an individual or a reliable informant, confirmed with an objective cognitive test, which interferes with daily living activities) in Yogyakarta and Jatinangor on elderly aged ≥ 60 showed a higher dementia prevalence than global prevalence with 20.1% and 29.15%, respectively. Both of these study populations are dominated by patients with low education who reside predominantly in rural areas, with lower occupational attainment, less active intellectual and recreational activities, and last but not least take less fruit as a daily diet.^{59,60}

Different from dementia, studies of PD in the relationship with ethnicity yielded mixed results in different time projections. Abbas and coworkers by the descriptive and meta-analysis study using the review papers up to May 2017 showed that the prevalence and incidence rate of PD is slightly lower in Asia compared to Western countries; and this issue could be explained by different environmental and genetic risk factors, although no firm conclusions can be drawn due to the small

number of Asian studies.⁹ However, the meta-analysis by Pringsheim and coworkers and epidemiological studies of prevalence conducted in the USA and New Zealand show that the prevalence rates of PD in Asia are lower than in Western countries only in the 70–79 year age group.^{61–64} This review on prevalence also showed sex differences, where there was a predominance of PD in the males; On the other hand, in Japan and South Korea, the prevalence of PD in females was reported to be higher than in males unlike what is seen in other countries globally.⁶² Due to the large populations in Asian countries and also because populations aging is happening rapidly in Asia, by 2030 the number of PD cases in the Western Pacific Region (Parts of Asia, Oceania, and Pacific countries, including China, Australia, and New Zealand) and China is estimated to be more than half (60%) of the total PD population in the world.^{62,65,66}

5 | BRAIN AGING AND BLOOD PRESSURE VARIABILITY IN DEMENTIA AND PARKINSON'S DISEASE

Three components determine hemodynamic regulation: BP, blood flow, and vascular resistance; The brain receives constant feedback information from these three components to regulate BP.⁶⁷ Constant BP is maintained by the autonomic nervous system that receives BP information by sensory inputs of baroreceptors divided into high-pressure arterial baroreceptors (carotid sinuses and aortic arch) and low-pressure volume receptors that so-called cardiopulmonary receptors (atrium, ventricles, and pulmonary vasculature).^{68–70} These baroreceptors are very sensitive to arterial stretch. In chronic hypertension, the adaptive response of baroreflex is blunted and the resulting inhibitory response fails to maintain arterial pressure and hence impairs cardiovascular function.^{71–73} With aging, baroreflex impairment caused by autonomic dysfunction results in an increase in BPV (Figure 1) (Tables 2).⁷⁴ Aging-associated chronic hypertension may cause blunted cardiovascular baroreflex because of vascular rigidity and decreased neural-cardiovascular responsiveness. Under normal conditions, the activation of the baroreflex to regulate hemostasis depends on changes in BP, but with aging, the blunted baroreflex causes an increase in BPV due to the inability to maintain acute BP changes.⁷⁵ Other studies have found that baroreflex control impairment caused by aging only impairs parasympathetic control, whereas sympathetic control is not impaired and is well maintained even over several decades.^{75,76} BPV is influenced by many factors, including behavioral factors, mechanical factors, vascular factors, neural factors, humoral factors, environmental factors, and genetic factors, which until now are still not conclusive evidence.^{43,77,78} However, the exact mechanism of the relationship between hypertension and neurodegenerative disease is still unclear. Inflammation is speculated to be a pathophysiological mediator between the two based on chronic inflammation both systemically and in the central nervous system (CNS) caused by hypertension resulting in decreased cerebral blood flow (CBF) and blood-brain barriers disruption; As a result, proinflammatory cells and neurotoxins that enter the brain parenchyma chronically cause neu-

roinflammation and ultimately damage brain functions that contribute to an increased risk of neurodegenerative disease during brain aging.³⁹

Hypertension has been found to be one of the modifiable risk factors underlying chronic neuroinflammation, which activation of microglial damaging neuronal and non-neuronal cells in the brain, leading to an increase in dementia incidence that is most commonly caused by AD and PD.^{79,80} Increased day-to-day BPV significantly increases the risk and incidence of all subtypes of dementia and the development of several brain pathologies including white matter hyperintensities, microbleeding and microinfarct, although the use of BPV as an indicator of the success of dementia prevention and intervention still needs further investigation.^{81,82} However, Ninomiya and coworkers stated that BP association with dementia is still inconclusive.⁸³ Those with midlife to late-life hypertension, and those with midlife hypertension followed by late-life hypotension, had a higher risk for dementia incidence than the normotensive group.^{83,84} By exploring the ambulatory BP in AD patients in China, Wang and coworkers found that AD patients are generally characterized by night-time systolic hypertension, day-time diastolic hypotension, and abnormal circadian BP rhythm of reduced and reverse dipping, which refers to a lower decrease of nocturnal BP and has higher night-time BP compared to day-time BP, respectively.⁸⁵ Elevated BPV is associated with neuronal injury due to increased shear stress of blood vessels that leads to small vessel disease and brain hypoperfusion; Dementia development is more related to autonomic dysfunction due to CNS injury caused by CNS BPV compared to absolute blood pressure values.^{81,84,86} A seven-year cohort study in South Korea proved that BPV is an independent predictor and has a linear association with all subtypes of dementia; it concluded that BPV reduction potentially becomes a dementia prevention strategy.⁸⁷ Controlling BPV as early intervention starting from middle age might reduce the risk of cognitive impairment rather than later in life, based on cerebral hemodynamic control to prevent autonomic dysfunction, such as transient cerebral hypoperfusion due to orthostatic hypotension, which affects around 30% of the elderly population, the aim is to prevent brain hypoperfusion implicated in dementia; Although optimal BP range for elderly depends on earlier blood pressure characteristics.^{83,88,89}

PD as a CNS neurodegenerative disease also has autonomic dysfunction due to cardiac sympathetic nerve degeneration, which accounts for about 40% of non-motor symptoms of PD, which can even occur earlier before the onset of motor symptoms, with signs such as changes in BPV from OH and postprandial hypotension to supine hypertension.^{90–92} A meta-analysis of case-control studies by Ng and coworkers in Asian populations, showed that hypertension increases the risk of PD by 1.9 times, but there are genetic and environmental factors that may influence it because, in the Caucasian population, hypertension was found to be a protective factor of PD.¹⁶ Autonomic dysfunction that occurs in PD is caused by a neuropathological process by abnormal deposits of α -synuclein forming neuronal inclusions of Lewy body that are found in autonomic neurons in peripheral nerves and also in CNS, particularly in substantia nigra pars compacta (SNpc) and locus coeruleus (LC) causing neurodegeneration.^{93,94} Shen and coworkers found that the BPV in the advanced stage of the PD group

TABLE 2 Study on association of BPV and neurodegenerative disease by year order

Reference	Design	Diseases	Size (n)	Follow-up duration	Key findings
Senard JM, and coworkers, 1992 ¹¹⁰	Cross sectional study	PD	38	–	Orthostatic hypotension in PD is associated with loss of circadian rhythm of BP, increased diurnal BPV, and post-prandial hypotension.
Plaschke M, and coworkers, 1998 ¹⁰⁸	Cross sectional study	PD and multiple system atrophy	37	–	Nocturnal hypertension is hypothesized to be a risk factor in developing the additional cerebrovascular disease in patients with PD or multiple system atrophy affected by autonomic failure.
Ejaz AA, and coworkers, 2006 ⁹⁵	Cross sectional study	PD	13	–	PD patients have a high tendency for circadian rhythm reversal, postprandial hypotension, and nocturnal hypertension. ABPM better identifies dysregulation of BP than just a one-time measurement.
Schmidt C, and coworkers, 2009 ¹⁰⁹	Cross sectional study	PD, Multiple system atrophy, and supranuclear palsy	99	–	Patients with PD, multiple system atrophy, and supranuclear palsy have a higher tendency of pathological nocturnal BP regulation than the control group. Nocturnal hypertension in multiple system atrophy and PD patients is associated with orthostatic hypotension events.
Guo H, and coworkers, 2010 ¹¹⁶	Cross sectional study (The J-SHIPP Study)	MCI	144	–	An abnormal nocturnal BP profile was a strong indicator of MCI in otherwise healthy community-dwelling elderly persons.
Ninomiya T, and coworkers, 2011 ⁸⁴	Prospective cohort study (The Hisayama Study)	VaD and AD	668	32 years	Midlife hypertension and late-life hypertension are significant risk factors for the late-life onset of vascular dementia but not for that of AD in a general Japanese population. Midlife hypertension is strongly associated with vascular dementia, regardless of late-life blood pressure levels.
Sommer S, and coworkers, 2011 ¹¹¹	Cross sectional study	PD	40	–	There is a high prevalence of non-dipping patterns in PD patients with and without orthostatic hypotension. This result is independent of coexisting arterial hypertension and antihypertensive treatment.
Tarumi T, and coworkers, 2015 ¹¹⁴	Cross sectional study	MCI	40	–	A β burden in the posterior cingulate and altered dynamic CBF regulation strongly correlates with attenuated reductions in sleep BP in patients with amnesic mild cognitive impairment.
Wolters FJ, and coworkers, 2016 ⁸⁹	Population-based prospective cohort study	Dementia	6204	15.3 years	Orthostatic hypotension was associated with an increase in long-term risk of dementia in a population predominantly of European descent.
Oishi E, and coworkers, 2017 ⁸¹	Prospective cohort study (The Hisayama Study)	All-cause dementia	1674	5.3 years	Increased day-to-day BPV is a significant risk factor for developing all-cause dementia, VaD, and AD in the general elderly Japanese population.
Tanaka R, and coworkers, 2018 ¹¹²	Cross sectional study	PD	137	–	A relationship exists between a riser pattern coexisting with orthostatic hypotension and dementia in PD. Thus, investigating whether abnormal nocturnal blood pressure profiles may predict dementia in PD will be helpful.
Walker KA, and coworkers, 2019 ⁸³	Prospective cohort study (The Atherosclerosis Risk in Communities prospective population-based cohort study)	Dementia	4761	30 years	Sustained hypertension in midlife to late-life and a pattern of midlife hypertension and late-life hypotension, compared with midlife and late-life normal BP, are associated with increased risk for subsequent dementia.

(Continues)

TABLE 2 (Continued)

Reference	Design	Diseases	Size (n)	Follow-up duration	Key findings
Arici Duz O, and coworkers, 2020 ⁷¹	Cross sectional study	PD	35	–	PD patients have a high tendency of non-dipping and reverse dipping BP patterns, independent of PD severity, drug dose, vitamin D and the other non-motoric symptoms.
Chen S-W, and coworkers, 2020 ¹¹³	Cross sectional study (SFC BP Multicentre Study in China)	PD	101	–	Orthostatic hypotension can occur in one-fourth of PD patients without abnormal BP history. A reverse dipping pattern is suggested to be helpful in suspecting orthostatic hypotension since it is present in more than half of patients with PD
Yoo JE, and coworkers, 2020 ⁸⁷	Population-based retrospective cohort study	Dementia	7844814	6.2 years	Since BPV is an independent predictor of developing dementia and its subtypes, reducing BPV may prevent dementia in the general population.
Tan X, and coworkers, 2021 ¹¹⁵	Prospective cohort study	Dementia and AD	286	24 years	Reverse systolic BP dipping may represent an independent risk factor for dementia and AD in older men. Thus, investigating whether therapies lowering nocturnal systolic BP below daytime levels have an association with decreased development of dementia will be helpful.
Wang H, and coworkers, 2021 ⁸⁵	Cross sectional study	AD	106	–	AD patients have high nighttime systolic BP, low daytime diastolic BP, and abnormal circadian BP rhythm of reduced and reverse dipping. The AD patients' diastolic BP, especially in the daytime, is adversely correlated with cognitive deterioration.
Shen L, and coworkers, 2022 ⁹⁰	Cross sectional study	PD	75	–	Reverse dipping was more common in PD patients, especially the advanced PD patients. The 24-h ambulatory BP monitoring is an important method to evaluate the BP alterations in PD patients. Thus, clinicians can prevent severe clinical events.

Abbreviations: ABPM, Ambulatory Blood Pressure Monitoring; AD, Alzheimer's Disease; BP, Blood Pressure; BPV, Blood Pressure Variability; CBF, Cerebral Blood Flow; MCI, Mild Cognitive Impairment; PD, Parkinson's Disease; VaD = Vascular Dementia.

was significantly higher than in the early stage of the PD group and the normal group, also the differences between these groups in both BPV and circadian BP rhythm measurements were statistically significant, although there was no significant difference between the groups of PD with predominantly tremor or non-tremor; This can allow BPV examination to detect the progression of a stage of PD or various abnormalities related to BP before other symptoms develop.^{90,95} It is also in line with the findings of high SBP that is significantly associated with a decline of UPDRS III (Unified Parkinson's Disease Rating Scale III) motor scores and becomes a predictor of motor decline in PD because of high SBP as the risk factors for white matter hyperintensities development which increases the rate of motoric disability.^{96–98} However, controlling blood pressure with therapy, especially in PD patients with hypertension, will be more difficult due to BPV caused by fluctuations in BP due to autonomic dysfunction and neuropsychiatric disorders and sleep disorders as complications of PD that disrupt BP stability.⁹⁹ In our clinical observation of 77 years-old male with PD and rapid clinical deterioration with office BP 139/ 85 mm Hg without a history of antihypertensive medication; During 24-h ambulatory BP

measurement, there was a large variation in BP, hypotension during the administration of Levodopa 100 mg/ Benserazide HCl 25 mg, nocturnal hypertension and morning surge (Figure 2).

Aging impacts the 24-h circadian rhythm where dysfunction may further exacerbate the progress of neurodegenerative diseases such as AD and PD.¹⁰⁰ Among many physiological variables, autonomic blood pressure regulation is one of the most studied variables of circadian variation which in turn has a high impact on cerebrovascular and cardiovascular diseases.^{101,102} As there is a complex relationship between circadian, and the widespread distribution of neuropathology that happened in neurodegenerative diseases, it is difficult to conclude any specific cause and effect.¹⁰³ However, the hypothalamus's degeneration of the suprachiasmatic nucleus (SCN), the “master clock”, responsible for anticipating daily environmental changes and adjusting their physiology and behavior, is suggested to be the core cause. It is regarded as the circadian main pacemaker and coordinator that maintains the synchrony of many central and peripheral tissues by using both neuronal and humoral signals.^{104–107} A transcriptional-translational feedback loop consisting of positive transcriptional

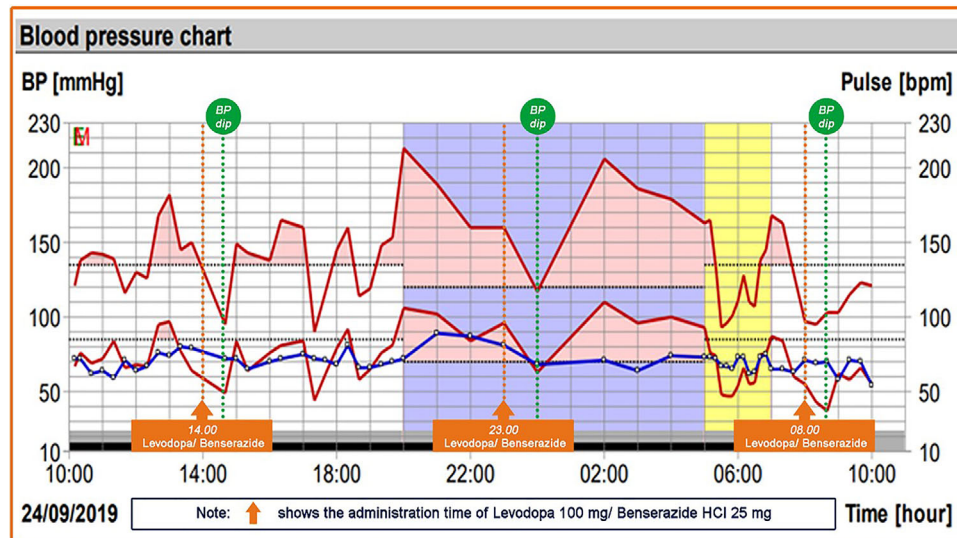


FIGURE 2 BPV in Parkinson's disease patient without antihypertensive medication showed hypotension in 30 min to 1 h after Levodopa 100 mg/ Benserazide HCl 25 mg administration during 24-h ambulatory BP measurement

regulators CLOCK and BMAL1, and their negative feedback inhibitors PERIOD, CYTOCHROME, and REV-ERB proteins are also suggested to play the part in the circadian clock. Together with SCN, it is proposed that circadian clock dysfunction may induce pathological toxic protein aggregation and neurodegeneration, which is also reflected in the abnormal BPV.^{100,101}

Some abnormal BPV characteristic findings in PD patients are reversing circadian rhythm, postprandial hypotension, orthostatic hypotension, and nocturnal hypertension.^{95,108–112} A proposed pathophysiology is sympathetic denervation which may contribute to supine hypertension during the night due to super sensitivity of the vascular α -adrenergic receptors which causes exaggerated vasoconstriction.¹¹¹ Chen and coworkers found that more than half of PD patients present with reverse dipping patterns; One-fourth of PD patients were also found to have orthostatic hypotension even without abnormal BP history, and in this group had a higher nocturnal SBP level significantly and more severe autonomic dysfunction, non-motor symptoms, and cognitive impairment compared to PD patients without orthostatic hypotension.¹¹³ The rise in nocturnal blood pressure was also significantly associated with Dementia.¹¹² A study by Tarumi and coworkers showed that nocturnal BP abnormality is associated with a greater A β burden in the posterior cingulate and altered dynamic CBF regulation in patients with amnesic mild cognitive impairment (aMCI).¹¹⁴ The normal dip in nocturnal BP is proposed to play an essential role in the glymphatic system's efficacy to remove neurotoxic metabolites from the brain. If these toxins are not removed properly, they may aggregate to form plaques and neurofibrillary tangles in the brain.¹¹⁵ All of these BPV abnormalities found in neurodegenerative diseases are in line with the burden of cerebrovascular lesions, cognitive decline, reduced cerebral blood flow, increased electroencephalographic wave velocity, and the high risk of later stroke.^{102,111,112,116,117}

6 | MANAGEMENT OF HYPERTENSION IN NEURODEGENERATIVE DISEASE

A recent meta-analysis consisting of nine randomized controlled trials with 34,994 participants, especially older adults, aged more than 60 years by Gupta and coworkers showed that treatment of hypertension does not worsen cognition as previously feared by many. In fact, it may be associated with a reduction in cognitive decline over time.¹¹⁸ Another meta-analysis by Hou and coworkers and Ng and coworkers suggests that hypertension might increase the risk of PD, specifically in the Asian population.^{8,16} Those studies highlight the importance of early diagnosis and treatment of hypertension, which will be essential and critical for those with preclinical neurodegenerative disease.^{8,118} The blood pressure target must also be personalized, especially in frail and very old patients.¹¹⁹ The largest randomized clinical trial on the evaluation of intensive blood pressure control on risk of dementia by SPRINT (Systolic Blood Pressure Intervention Trial) Research Group for 5 years in 9361 participants aged ≥ 50 years old with hypertension without diabetes or stroke history provided the benefits of intensive blood pressure control (SBP goal less than 120 mm Hg) that significantly reduced the risk of mild cognitive impairment and the combined rate of mild cognitive impairment or probable dementia comparing to standard blood pressure control group (SBP goal less than 140 mm Hg); However, both groups showed that reduction in the risk of probable dementia was insignificant due to the early study termination and fewer dementia cases.⁸⁸

Relationships between lowering blood pressure and dementia risk are less well-understood, particularly in very old age. An interesting result from the Leiden 85 plus study showed that a 10 mm Hg increase in SBP was associated with better cognitive performance in global tests and several domain-specific tests in groups aged 80 or older. This study explored that low BP in this age group may lead to insufficient cerebral

perfusion, particularly in populations that have advanced cerebrovascular damage.¹²⁰ The Vantaa 85 plus study also reported supporting data, where lower SBP increased mortality among people aged 85 or more with no significant relationship between baseline BP and dementia occurrence. Hence, the use of antihypertensive in this special group needs to be evaluated carefully.^{121,122}

Studies suggest that BP decline precedes the onset of mild cognitive impairment and dementia, although it remains unclear if this pattern is the consequence of neurodegeneration or a risk factor for later cognitive decline.^{36,123,124} A study by Stewart and coworkers tried to explain what happens. This study showed that 58% of those diagnosed with dementia had experienced a fall in SBP of at least 10 mm Hg over the previous 6 years compared to 39% of those without dementia, with an odds ratio of 2.10. Thirty-nine percent of dementia patients had also experienced a systolic blood pressure fall of greater than 20 mm Hg compared to 24% of those without dementia, with an odds ratio of 2.09.¹²⁵ Increased arterial stiffness, deterioration in cerebral autoregulation, and general metabolic changes associated with neurodegeneration (weight loss and a fall in total cholesterol prior to the dementia clinical onset) result from untreated midlife hypertension, which all lead to hypotension later in life.¹²⁵⁻¹³⁴

These facts suggest the importance of early prevention of hypertension in modifying the risk of neurodegenerative diseases. It is suggested that vascular damages caused by hypertension in the brain begin earlier in life and gradually become less reversible.²⁹ The effects of midlife hypertension can be seen through arteriosclerosis measurement in the brain.¹³⁵ BP in midlife is potentially a good target since many studies have found an association between degenerative disorders and midlife hypertension. First, midlife hypertension significantly predicts white matter hyperintensity volume progression and worse executive function.^{136,137} Moreover, other interesting studies by Walker and coworkers have also found an association between those with midlife and late-life hypertension and those with midlife hypertension and late-life hypotension had both increased risk of dementia compared with those who remained normotensive.⁸³ An interesting note to be highlighted here is that midlife hypertension is associated with higher dementia risk irrespective of late-life blood pressure.^{83,84,120} These suggest that hypertension at a younger age (significantly closer to midlife) is harmful.³⁶

An accurate BP record, especially 24-h blood pressure monitoring, is significant because it can analyze an individual's short- and long-term BP fluctuations.^{111,138,139} BP measurements must be cautious in PD patients, which might lead to wrong assumptions since the patients are susceptible to dysautonomia manifestations such as orthostatic hypotension, postprandial hypotension, or supine hypertension.¹⁴⁰ The BP decline preceding the onset of mild cognitive impairment and dementia may also lead to wrong assumptions; thus, it states the importance of comprehending the pathophysiology behind the issue.^{36,123,124} As awareness and control are poor in most Asian countries/regions, the highlight must be put on educating about the importance of keeping normal blood pressure and reducing other risk factors related to it, such as reducing obesity and salt intake.¹⁴¹ Mental health problems in the hypertensive Asian elderly

have to be taken seriously whenever antihypertensive therapy is given. It correlates with lower quality of life, lower rate of hypertension treatment adherence, and higher mortality among elderly individuals.¹⁴²

A comprehensive evaluation is a must in choosing medications since different antihypertensive drugs have different effects on the intra- and inter-individual blood pressure fluctuations. The first thing to consider is finding a safe neuroprotective drug. As the nocturnal BP is a big issue to be handled, Kario and coworkers suggested esaxerenone may be a useful treatment option for this abnormality, especially in riser patterns.¹⁰² Esaxerenone is a novel drug for hypertension and diabetic nephropathies that received its first global approval in 2019; It is a non-steroidal selective mineralocorticoid receptor (MR) blocker with high potency and selectivity for MR compared to steroidal MR antagonists and has a renoprotective effect.^{143,144} Middelaar and coworkers showed that calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) have neuroprotective effects as seen by changes in AD pathology, for example, plaques and tangles. Both options are also associated with decreased risk of dementia, although a stronger association was with CCBs.¹⁴⁵ CCBs, especially dihydropyridine, which can penetrate the blood-brain barrier effectively, may regulate calcium influx.^{146,147} The calcium influx regulation by CCBs may have anti-inflammatory effects, inhibit the production of pathological proteins such as amyloid β and neurofibrillary tangles, and may improve cerebral blood flow, which prevents the production of pathological proteins ongoing degenerative neuronal cell death.¹⁴⁶

Choices of antihypertensive that can induce orthostatic hypotension or drug interaction must also be well evaluated so as not to aggravate the symptoms of neurodegenerative disease, as many antihypertensive medicines, as well as drugs used in the treatment of PD, can make blood pressure fluctuate more.¹⁴⁸ As mentioned earlier, patients with PD often have autonomic dysfunction and neuropsychiatric and sleep disorders, which manifest as abnormal BP. These may make PD therapy more complex because clinicians may have wrong assumptions in treating supine hypertension, and antihypertensive may worsen orthostatic hypotension, resulting in falls, physical deconditioning, cognitive decline, and other cardiovascular events. Time to administer antihypertensive should also be considered as some antihypertensives administered in the morning do not have a lasting effect until night. This may prone the patient with night-time high blood pressure uncovered therapeutically.^{99,140}

Other PD therapy, such as L-Dopa, dopamine agonist, or monoamine oxidase inhibitors, may also affect BP fluctuations.¹⁴⁹⁻¹⁵⁴ It is suggested that some options such as levodopa sustained-release tablets, dopamine receptor agonists, continuous infusions of levodopa or dopamine agonists by intra-duodenal administration, or deep brain stimulation may avoid BP fluctuations.^{155,156} But as not all facilities have these modalities available, physicians may adopt the chronotherapy concept, which tries to match the human body's daily rhythms and behavioral patterns such as sleep-wake, rest-activity, and fasting-feeding cycles, by tailoring the timing of doses.¹⁵⁷⁻¹⁶⁰

In this way, drug administration modification may be done by dividing the total daily dose into smaller but multiple doses to increase

beneficial effects and/or minimize any adverse medication effects across the day and night. The administration of sedative and anxiolytic drugs to modify nocturnal- and early-morning hypertension in neuropsychiatric and sleep disorders can also be considered. Short-acting pressor agents to control OH such as midodrine or droxidopa should be preferred over long-acting agents such as fludrocortisone. NSAIDs or SNRIs, which are not primarily used as pressor agents, should be avoided since they can cause significant BP increases in baroreflex dysfunction PD patients. Moreover, non-drugs and more practical methods to treat postprandial and orthostatic hypotension are also suggested since these options provide fewer side effects and costs. The options include body positioning to 10–20° full-body head-up tilt during sleep, eating frequent smaller meals, consuming enough daily water (up to 2,5 L/day) and salt (6–10 g/day), and a careful daily physical exercise.^{99,161–165}

7 | CONCLUSIONS

The predicted prevalence increase of neurodegenerative diseases is strongly related to population aging and hypertension in Asia. Midlife hypertension has been found to be an important predictor of later cognitive impairment and neurodegenerative conditions of the brain; however, the effectiveness of antihypertensive therapy on cognitive improvement is still inconclusive, and further research is needed to make evidence-based recommendations. BPV may cause alterations in the macro-and micro-circulation and this could be one of the pathophysiology mechanisms causing neurodegenerative diseases. It is essential to consider personalized blood pressure therapy in the elderly with neurodegenerative diseases.

AUTHOR CONTRIBUTION

The authors confirm contribution to the paper as follows: study conception and design: Yuda Turana, Robert Shen, Michael Nathaniel, Yook-Chin Chia, Yan Li, Kazuomi Kario; analysis and interpretation of results: Yuda Turana, Robert Shen, Michael Nathaniel; draft manuscript preparation Yuda Turana, Robert Shen, Michael Nathaniel, Yook-Chin Chia, Yan Li, Kazuomi Kario. All authors reviewed the results and approved the final version of the manuscript.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

Yook-Chin Chia has received unrestricted educational grants from Viatrix and Omron and from Medtronic for activities of the Malaysian Society for World Action on Salt, Sugar, and Health (MyWASSH) Yook-Chin Chia also has received speaker honoraria from Medtronic, Astra-Zeneca, Omron, and Xepa-Sol. All other authors report no potential conflicts of interest in relation to this review paper.

REFERENCES

- Westley SB, Mason A. Asia's aging population. *The future of population in Asia*. 2002:85–95.
- Gitler AD, Dhillon P, Shorter J. Neurodegenerative disease: models, mechanisms, and a new hope. *Dis Model Mech*. 2017;10(5):499–502.
- Azam S, Haque ME, Balakrishnan R, et al. The ageing brain: molecular and cellular basis of neurodegeneration. *Front Cell Dev Biol*. 2021;9:683459.
- Economic United Nations Department of Affairs Social, Strengthening the Demographic Evidence Base for the Post-2015 Development Agenda: a Concise Report. United Nations; 2017.
- Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the global burden of disease study 2019. *Lancet Public Health*. 2022;7(2):105–125.
- Prince MJ, Wimo A, Guerchet MM, et al. The global impact of dementia: an analysis of prevalence, incidence, cost and trends. *World Alzheimer Report 2015*. 2015. London: Alzheimer's Disease International. Accessed February 24, 2022. Available on: <http://www.alz.co.uk/research/world-report-2015>
- Turana Y, Tengkawan J, Chia YC, et al. Hypertension and dementia: a comprehensive review from the HOPE Asia Network. *J Clin Hypertens*. 2019;21(8):1091–1098.
- Hou L, Li Q, Jiang L, et al. Hypertension and diagnosis of Parkinson's disease: a meta-analysis of cohort studies. *Front Neurol*. 2018;9: 162
- Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson's disease—east versus west. *Mov Disord Clin Pract*. 2018;5(1):14–28.
- Kizza J, Lewington S, Mappin-Kasirer B, et al. Cardiovascular risk factors and Parkinson's disease in 500,000 Chinese adults. *Ann Clin Transl Neurol*. 2019;6(4):624–632.
- Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312–339.
- Kalia LV, LangAE Parkinson's. Parkinson's disease. *Lancet*. 2015;386(9996):896–912.
- O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388(10046):761–775.
- Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. *Hypertension*. 2016;68(6):e67–e94.
- Fujiwara T, Hoshida S, Kanegae H, et al. Exaggerated blood pressure variability is associated with memory impairment in very elderly patients. *J Clin Hypertens*. 2018;20(4):637–644.
- Ng YF, Ng E, Lim EW, et al. Case-control study of hypertension and Parkinson's disease. *NPJ Parkinsons Dis*. 2021;7(1):1–4.
- Aging The Truth About and Dementia. *Centers for Disease Control and Prevention (CDC)*. 2021. Accessed February 24, 2022. Available on: <https://www.cdc.gov/aging/publications/features/dementia-not-normal-aging.html>
- Swerdlow RH. Alzheimer's disease, and mitochondria. *Biochim Biophys Acta - Mol Basis Dis*. 2011;1812(12):1630–1639.
- Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature*. 2016;539(7628):180–186.
- Jin B, Li Y, Robertson KD. DNA methylation: superior or subordinate in the epigenetic hierarchy? *Genes Cancer*. 2011;2(6):607–617.
- Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14(10):3156.
- Cheng Y-W, Chiu M-J, Chen Y-F, et al. The contribution of vascular risk factors in neurodegenerative disorders: from mild cognitive impairment to Alzheimer's disease. *Alzheimer's Res Ther*. 2020;12(1):91.
- Dean DC, III, Jerskey BA, Chen K, et al. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. *JAMA Neurol*. 2014;71(1):11–22.

24. Schaeffers ATU, Teuchert-Noodt G. Developmental neuroplasticity and the origin of neurodegenerative diseases. *World J Biol Psychiatry*. 2016;17(8):587-599.
25. Wrigglesworth J, Ward P, Harding IH, et al. Factors associated with brain ageing - a systematic review. *BMC Neurol*. 2021;21(1):312.
26. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers*. 2017;3(1):1-21.
27. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. *Lancet Neurol*. 2020;19(2):170-178.
28. Ungvari Z, Toth P, Tarantini S, et al. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol*. 2021;17(10):639-654.
29. Igase M, Kohara K, Miki T. The association between hypertension and dementia in the elderly. *Int J Hypertens*. 2011;2012:e320648.
30. Toth P, Tarantini S, Csiszar A. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol - Heart Circ Physiol*. 2017;312(1):H1-20.
31. Fulop GA, Ramirez-Perez FI, Kiss T, et al. IGF-1 deficiency promotes pathological remodeling of cerebral arteries: a potential mechanism contributing to the pathogenesis of intracerebral hemorrhages in aging. *J Gerontol A Biol Sci*. 2019;74(4):446-454.
32. Toth P, Tucek Z, Sosnowska D, et al. Age-related autoregulatory dysfunction and cerebrovascular injury in mice with angiotensin ii-induced hypertension. *J Cereb Blood Flow Metab*. 2013;33(11):1732-1742.
33. Harder DR, Smeda J, Lombard J. Enhanced myogenic depolarization in hypertensive cerebral arterial muscle. *Circ Res*. 1985;57(2):319-322.
34. Launer LJ, Masaki K, Petrovitch H, et al. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA*. 1995;274(23):1846-1851.
35. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurol*. 1998;51(4):986-993.
36. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol*. 2017;74(10):1246.
37. Wei J, Yin X, Liu Q, et al. Association between hypertension and cognitive function: a cross-sectional study in people over 45 years old in China. *J Clin Hypertens (Greenwich)*. 2018;20(11):1575-1583.
38. Meissner A. Hypertension and the brain: a risk factor for more than heart disease. *Cerebrovasc Dis*. 2016;42(3-4):255-262.
39. Youwakim J, Girouard H. Inflammation: a mediator between hypertension and neurodegenerative diseases. *Am J Hypertens*. 2021;34(10):1014-1030.
40. Qiu C, Hu G, Kivipelto M, et al. Association of blood pressure and hypertension with the risk of parkinson disease. *Hypertension*. 2011;57(6):1094-1100.
41. Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71(6):1269-1324.
42. Mancia G, Grassi G. Mechanisms and clinical implications of blood pressure variability. *J Cardiovasc Pharmacol*. 2000;35:S15.
43. Mancia G. Short- and long-term blood pressure variability. *Hypertension*. 2012;60(2):512-517.
44. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *Eur Heart J Suppl*. 2020;22(Supplement_E):E1-E6.
45. Schillaci G, Bilo G, Pucci G, et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension*. 2012;60(2):369-377.
46. Bilo G, Giglio A, Styczkiewicz K, et al. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J Hypertens*. 2007;25(10):2058-2066.
47. Rizzoni D, Agabiti-Rosei C. Relationships between blood pressure variability and indices of large artery stiffness: does the microvasculature play a role? *Hypertens Res*. 2017;40(4):348-350.
48. Omboni S, Posokhov IN, Rogoza AN. Relationships between 24-h blood pressure variability and 24-h central arterial pressure, pulse wave velocity and augmentation index in hypertensive patients. *Hypertens Res*. 2017;40(4):385-391.
49. Parati G, Stergiou GS, Dolan E, et al. Blood pressure variability: clinical relevance and application. *J Clin Hypertens*. 2018;20(7):1133-1137.
50. Bilo G, Parati G. Blood pressure variability and kidney disease: another vicious circle? *J Hypertens*. 2018;36(5):1019-1021.
51. Lukito AA, Thengker A, Hadi MW, et al. 3 visit-to-visit blood pressure variability varies by age groups. *J Hypertens*. 2017;35:e3.
52. Adoor M, Jaideep SS, Sujana MU, et al. Influence of age and gender on blood pressure variability and baroreflex sensitivity in a healthy population in the Indian sub-continent. *J Basic Clin Physiol Pharmacol*. 2018;29(4):329-337.
53. Veerman DP, Imholz BP, Wieling W, et al. Effects of aging on blood pressure variability in resting conditions. *Hypertension*. 1994;24(1):120-130.
54. Adams HHH, Evans TE, Terzikhan N. The uncovering neurodegenerative insights through ethnic diversity consortium. *Lancet Neurol*. 2019;18(10):915.
55. Catindig J-AS, Venketasubramanian N, Ikram MK, et al. Epidemiology of dementia in Asia: insights on prevalence, trends and novel risk factors. *J Neurol Sci*. 2012;321(1-2):11-16.
56. Wong LCK, Wong MYZ, Tan CS, et al. Interethnic differences in neuroimaging markers and cognition in Asians, a population-based study. *Sci Rep*. 2020;10(1):2655.
57. Schwarzinger M, Dufouil C. Forecasting the prevalence of dementia. *Lancet Public Health*. 2022;7(2):e94-95.
58. Venketasubramanian N, Sahadevan S, Kua EH, et al. Interethnic differences in dementia epidemiology: global and Asia-Pacific perspectives. *Dement Geriatr Cogn Disord*. 2010;30(6):492-498.
59. Ong PA, Annisafitrie FR, Purnamasari N, et al. Dementia prevalence, comorbidities, and lifestyle among Jatinangor elders. *Front Neurol*. 2021;12:643480.
60. Suriastini N, Turana Y, Supraptilah B, et al. Prevalence and risk factors of dementia and caregiver's knowledge of the early symptoms of Alzheimer's disease. *Aging Med Healthc*. 2020;11:60-66.
61. Pringsheim T, Jette N, Frolkis A, et al. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590.
62. Lim S-Y, Tan AH, Ahmad-Annur A, et al. Parkinson's disease in the Western Pacific Region. *Lancet Neurol*. 2019;18(9):865-879.
63. Pitcher TL, Myall DJ, Pearson JF, et al. Parkinson's disease across ethnicities: a nationwide study in New Zealand. *Mov Disord*. 2018;33(9):1440-1448.
64. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Dis*. 2018;4(1):1-7.
65. Li G, Ma J, Cui S, et al. Parkinson's disease in China: a forty-year growing track of bedside work. *Transl Neurodegener*. 2019;8(1):22.
66. Dorsey ER, Elbaz A, Nichols E, et al. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(11):939-953.
67. Julius S, Weder AB. Brain and the regulation of blood pressure: a hemodynamic perspective. *Clin Exp Hypertens*. 1989;11(sup1):1-19.

68. Jennings JR, Christie IC, Muldoon MF, et al. Brain function, cognition, and the blood pressure response to pharmacological treatment. *Psychosom Med.* 2010;72(7):702-711.
69. Armstrong M, Kerndt CC, Moore RA, Physiology, baroreceptors. *StatPearls Publishing*; 2022.
70. Al-Khazraji BK, Shoemaker JK. The human cortical autonomic network and volitional exercise in health and disease. *Appl Physiol Nutr Metab.* 2018;43(11):1122-1130.
71. Mifflin SW. What does the brain know about blood pressure? *Physiol.* 2001;16(6):266-271.
72. Suzuki M, Kuramochi T, Suga T. GABA receptor subtypes involved in the neuronal mechanisms of baroreceptor reflex in the nucleus tractus solitarius of rabbits. *J Auton Nerv Syst.* 1993;43(1):27-35.
73. Vitela M, Mifflin SW. Gamma-Aminobutyric acid(B) receptor-mediated responses in the nucleus tractus solitarius are altered in acute and chronic hypertension. *Hypertension.* 2001;37(2):619-622.
74. Mano J, Saku K, Kinoshita H, et al. Aging steepens the slope of power spectrum density of 30-minute continuous blood pressure recording in healthy human subjects. *PLoS One.* 2021;16(3):e0248428.
75. Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol.* 2007;293(1):R3-R12.
76. Ebert TJ, Morgan BJ, Barney JA, et al. Effects of aging on baroreflex regulation of sympathetic activity in humans. *Am J Physiol.* 1992;263:H798-803.
77. Ulasi II, Anisiuba BC, Ijoma CK. Blood pressure variability and its implications in people of African descent. *Hypertens Res.* 2011;34(10):1076-1077.
78. Hart ECJ, Charkoudian N. Sympathetic neural regulation of blood pressure: influences of sex and aging. *Physiol.* 2014;29(1):8-15.
79. McKenzie JA, Spielman LJ, Pointer CB, et al. Neuroinflammation as a common mechanism associated with the modifiable risk factors for Alzheimer's and Parkinson's diseases. *Curr Aging Sci.* 2017;10(3):158-176.
80. Winklewski PJ, Radkowski M, Wszedybyl-Winklowska M, et al. Brain inflammation and hypertension: the chicken or the egg? *J Neuroinflammation.* 2015;12(1):85.
81. Oishi E, Ohara T, Sakata S, et al. Day-to-day blood pressure variability and risk of dementia in a general Japanese elderly population: the Hisayama study. *Circulation.* 2017;136(6):516-525.
82. Havlik RJ, Foley DJ, Sayer B, et al. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia aging study. *Stroke.* 2002;33(1):26-30.
83. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA.* 2019;322(6):535.
84. Ninomiya T, Ohara T, Hirakawa Y, et al. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension.* 2011;58(1):22-28.
85. Wang H, Xu Y, Ren R, et al. Ambulatory blood pressure characteristics of patients with Alzheimer's disease: a multicenter study from China. *J Alzheimers Dis.* 2021;83(3):1333-1339.
86. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol.* 2010;67(5):564-569.
87. Yoo JE, Shin DW, Han K, et al. Blood pressure variability and the risk of dementia. *Hypertension.* 2020;75(4):982-990.
88. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA.* 2019;321(6):553.
89. Wolters FJ, Mattace-Raso FUS, Koudstaal PJ, et al. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *PLoS Med.* 2016;13(10):e1002143.
90. Shen L, Yang X, Lu W, et al. 24-hour ambulatory blood pressure alterations in patients with Parkinson's disease. *Brain Behav.* 2022;12(1):e2428.
91. Arici Duz O, Helvacı Yılmaz N. Nocturnal blood pressure changes in Parkinson's disease: correlation with autonomic dysfunction and vitamin D levels. *Acta Neurol Belg.* 2020;120(4):915-920.
92. Asahina M, Vichayanrat E, Low DA, et al. Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. *J Neurol Neurosurg Psychiatry.* 2013;84(6):674-680.
93. Biaggioni I. Parkinson's disease: autonomic neuronopathy with impaired cardiovascular regulation. *Hypertension.* 2007;49(1):21-22.
94. Lima MMS, Reksidler ABB, Vital MABF. The neurobiology of the substantia nigra pars compacta: from motor to sleep regulation. *J Neural Transm Suppl.* 2009(73):135-145.
95. Ejaz AA, Sekhon IS, Munjal S. Characteristic findings on 24-h ambulatory blood pressure monitoring in a series of patients with Parkinson's disease. *Eur J Intern Med.* 2006;17(6):417-420.
96. Kotagal V, Albin RL, Müller MLTM, et al. Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease. *Neurol.* 2014;82(17):1514-1520.
97. Lineback C, Albin R, Bohnen N, et al. Elevated systolic blood pressure predicts motor outcomes in Parkinson's disease—a retrospective analysis of the CALM-PD Trial (S5.004). *Neurol.* 2016;86(16S).
98. Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol.* 2009;66(5):563-570.
99. Chen DW, Chen JW, Liu W, et al. An elderly parkinsonian patient with extreme blood pressure fluctuations. *Int J Gerontol.* 2014;8(3):168-170.
100. Leng Y, Musiek ES, Hu K, et al. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* 2019;18(3):307-318.
101. Cortés-Ríos J, Rodríguez-Fernández M. Circadian rhythm of blood pressure of dipper and non-dipper patients with essential hypertension: a mathematical modeling approach. *Frontiers Physiol.* 2020;11:536146.
102. Kario K, Ito S, Itoh H, et al. Effect of esaxerenone on nocturnal blood pressure and natriuretic peptide in different dipping phenotypes. *Hypertens Res.* 2022;45(1):97-105.
103. Hastings MH, Goedert M. Circadian clocks and neurodegenerative diseases: time to aggregate? *Curr Opin Neurobiol.* 2013;23(5):880-887.
104. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol.* 2010;72:517-549.
105. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci.* 2003;4(8):649-661.
106. Bass J, Lazar MA. Circadian time signatures of fitness and disease. *Science.* 2016;354(6315):994-999.
107. Werdann M, Zhang Y. Circadian rhythm and neurodegenerative disorders. *Brain Sci Adv.* 2020;6(2):71-80.
108. Plaschke M, Trenkwalder P, Dahlheim H, et al. Twenty-four-hour blood pressure profile and blood pressure responses to head-up tilt tests in Parkinson's disease and multiple system atrophy. *J Hypertens.* 1998;16(10):1433-1441.
109. Schmidt C, Berg D, et al. Loss of nocturnal blood pressure fall in various extrapyramidal syndromes. *Mov Disord.* 2009;24(14):2136-2142.
110. Senard JM, Chamontin B, Rascol A, et al. Ambulatory blood pressure in patients with Parkinson's disease without and with orthostatic hypotension. *Clin Auton Res.* 1992;2(2):99-104.
111. Sommer S, Aral-Becher B, Jost W. Nondipping in Parkinson's Disease. *Parkinsons Dis.* 2011;2011:897586.
112. Tanaka R, Shimo Y, Yamashiro K, et al. Association between abnormal nocturnal blood pressure profile and dementia in Parkinson's disease. *Parkinsonism Relat Disord.* 2018;46:24-29.
113. Chen S-W, Wang Y-K, Dou R-H, et al. Characteristics of the 24-h ambulatory blood pressure monitoring in patients with Parkinson's

- disease - the SFC BP multicentre study in China. *J Hypertens.* 2020;38(11):2270-2278.
114. Tarumi T, Harris TS, Hill C, et al. Amyloid burden and sleep blood pressure in amnesic mild cognitive impairment. *Neurology.* 2015;85(22):1922-1929.
 115. Tan X, Sundström J, Lind L, et al. Reverse dipping of systolic blood pressure is associated with increased dementia risk in older men. *Hypertension.* 2021;77(4):1383-1390.
 116. Guo H, Tabara Y, Igase M, et al. Abnormal nocturnal blood pressure profile is associated with mild cognitive impairment in the elderly: the J-SHIPP study. *Hypertens Res.* 2010;33(1):32-36.
 117. Kario K, Matsuo T, Kobayashi H, et al. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension.* 1996;27(1):130-135.
 118. Gupta A, Perdomo S, Billinger S, et al. Treatment of hypertension reduces cognitive decline in older adults: a systematic review and meta-analysis. *BMJ Open.* 2020;10(11):e038971.
 119. Turana Y, Tengkawan J, Chia Y-C, et al. High blood pressure in dementia: how low can we go? *J Clin Hypertens.* 2020;22(3):415-422.
 120. Sabayan B, van Vliet P, de Ruijter W, et al. High blood pressure, physical and cognitive function, and risk of stroke in the oldest old: the Leiden 85-Plus study. *Stroke.* 2013;44(1):15-20.
 121. Rastas S, Pirttilä T, Virmo P, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc.* 2006;54(6):912-918.
 122. Rastas S, Pirttilä T, Mattila K, et al. Vascular risk factors and dementia in the general population aged >85 years: prospective population-based study. *Neurobiol Aging.* 2010;31(1):1-7.
 123. Skoog I, Nilsson L, Persson G, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet.* 1996;347(9009):1141-1145.
 124. Qiu C, von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia. *Stroke.* 2004;35(8):1810-1815.
 125. Stewart R, Xue Q-L, Masaki K, et al. Change in blood pressure and incident dementia. *Hypertension.* 2009;54(2):233-240.
 126. Stewart R, Masaki K, Xue Q-L, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia aging study. A 32-year prospective study of change in body weight and incident dementia. *Arch Neurol.* 2005;62(1):55.
 127. Barrett-Connor E, Edelstein SL, Corey-Bloom J, et al. Weight loss precedes dementia in community-dwelling older adults. *J Am Geriatr Soc.* 1996;44(10):1147-1152.
 128. Notkola IL, Sulkava R, Pekkanen J, et al. Serum total cholesterol, apolipoprotein E {FC12}e4 allele, and Alzheimer's disease. *Neuroepidemiology.* 1998;17(1):14-20.
 129. Stewart R, White LR, Xue QL. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia aging study. *Arch Neurol.* 2007;64(1):103.
 130. Waldstein SR, Rice SC, Thayer JF, et al. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore longitudinal study of aging. *Hypertension.* 2008;51(1):99-104.
 131. Matsushita K, Kuriyama Y, Nagatsuka K, et al. Periventricular white matter lucency and cerebral blood flow autoregulation in hypertensive patients. *Hypertension.* 1994;23(5):565-568.
 132. Suter OC, Sunthorn T, Kraftsik R, et al. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke.* 2002;33(8):1986-1992.
 133. Kalback W, Esh C, Castaño EM, et al. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease. *Neurol Res.* 2004;26(5):525-539.
 134. Niwa K, Kazama K, Younkin L, et al. Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein. *Am J Physiol - Heart Circ Physiol.* 2002;283(1):H315-H323.
 135. Hughes TM, Sink KM. Hypertension and its role in cognitive function: current evidence and challenges for the future. *Am J Hypertens.* 2016;29(2):149-157.
 136. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology.* 2011;77(5):461-468.
 137. Gottesman RF, Schneider ALC, Albert M, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol.* 2014;71(10):1218.
 138. Lattanzi S, Vernieri F, Silvestrini M. Blood pressure variability and neurocognitive functioning. *J Clin Hypertens.* 2018;20(4):645-647.
 139. Paganini-Hill A, Bryant N, Corrada MM, et al. Blood pressure circadian variation, cognition and brain imaging in 90+ year-olds. *Front Aging Neurosci.* 2019:11.
 140. Tulbă D, Cozma L, Bălănescu P, et al. Blood pressure patterns in patients with Parkinson's disease: a systematic review. *J Pers Med.* 2021;11(2):129.
 141. Chia Y-C, Buranakitjaroen P, Chen C-H, et al. Current status of home blood pressure monitoring in Asia: statement from the HOPE Asia Network. *J Clin Hypertens.* 2017;19(11):1192-1201.
 142. Turana Y, Tengkawan J, Chia YC, et al. Mental health problems and hypertension in the elderly: review from the HOPE Asia Network. *J Clin Hypertens.* 2021;23(3):504-512.
 143. Wan N, Rahman A, Nishiyama A. Esaxerenone, a novel nonsteroidal mineralocorticoid receptor blocker (MRB) in hypertension and chronic kidney disease. *J Hum Hypertens.* 2021;35(2):148-156.
 144. Duggan S. Esaxerenone: first global approval. *Drugs.* 2019;79(4):477-481.
 145. Van Middelaar T, van Vught LA, van Charante EPM, et al. Lower dementia risk with different classes of antihypertensive medication in older patients. *J Hypertens.* 2010;28(10):2095-2101.
 146. Peters R, Schuchman M, Peters J, et al. Relationship between antihypertensive medications and cognitive impairment: part II. review of physiology and animal studies. *Curr Hypertens Rep.* 2016;18(8):66.
 147. Nimmrich V, Eckert A. Calcium channel blockers and dementia. *Br J Pharmacol.* 2013;169(6):1203-1210.
 148. Jost WH. What are the considerations for anti-hypertensive treatment in patients with Parkinson's disease? *Expert Opin Pharmacother.* 2020;21(10):1127-1230.
 149. Barbeau A. L-Dopa therapy in Parkinson's Disease. *Can Med Assoc J.* 1969;101(13):59-68.
 150. Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1997;63(5):584-589.
 151. Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. *Neurology.* 1997;49(4):1060-1065.
 152. Korchounov A, Kessler KR, Schipper HI. Differential effects of various treatment combinations on cardiovascular dysfunction in patients with Parkinson's disease. *Acta Neurol Scand.* 2004;109(1):45-51.
 153. Churchyard A, Mathias CJ, Lees AJ. Selegiline-induced postural hypotension in Parkinson's disease: a longitudinal study on the effects of drug withdrawal. *Mov Disord.* 1999;14(2):246-251.
 154. Turkka J, Suominen K, Tolonen U, et al. Selegiline diminishes cardiovascular autonomic responses in Parkinson's disease. *Neurology.* 1997;48(3):662-627.
 155. Nutt JG. Pharmacokinetics and pharmacodynamics of levodopa: pharmacokinetics and pharmacodynamics of levodopa. *Mov Disord.* 2008;23(S3):S580-4.
 156. Busk K, Nyholm D. Long-term 24-h levodopa/carbidopa gel infusion in Parkinson's disease. *Parkinsonism Relat Disord.* 2012;18(8):1000-1001.

157. Singh BN. Effects of food on clinical pharmacokinetics. *Clin Pharmacokinet.* 1999;37(3):213-255.
158. Lemmer B. Temporal aspects in the effects of cardiovascular active drugs in man. *Chronopharmacology - Cell Biochem Interactions.* 1989:525-542.
159. Rumble RH, Roberts MS, Denton MJ. Effects of posture and sleep on the pharmacokinetics of paracetamol (acetaminophen) and its metabolites. *Clin Pharmacokinet.* 1991;20(2):167-173.
160. Baraldo M. The influence of circadian rhythms on the kinetics of drugs in humans. *Expert Opin Drug Metab Toxicol.* 2008;4(2):175-192.
161. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. *J Hypertens.* 2019;37(8):1541-1546.
162. Eschlböck S, Wenning G, Fanciulli A. Evidence-based treatment of neurogenic orthostatic hypotension and related symptoms. *J Neural Transm (Vienna).* 2017;124(12):1567-1605.
163. Speelman AD, van Nimwegen M, Bloem BR, et al. Evaluation of implementation of the ParkFit program: a multifaceted intervention aimed to promote physical activity in patients with Parkinson's disease. *Physiotherapy.* 2014;100(2):134-141.
164. Speelman AD, Warrenburg BPVD, Nimwegen MV, et al. How might physical activity benefit patients with Parkinson disease? *Nat Rev Neurol.* 2011;7(9):528-534.
165. Goldstein DS. Dysautonomia in Parkinson's disease: neurocardiological abnormalities. *Compr Physiol.* 2014;4(2):805-826.

How to cite this article: Turana Y, Shen R, Nathaniel M, Chia Y-C, Li Y, Kario K. Neurodegenerative diseases and blood pressure variability: A comprehensive review from HOPE Asia. *J Clin Hypertens.* 2022;24:1204-1217.
<https://doi.org/10.1111/jch.14559>