Current Hypertension Reports

BLOOD PRESSURE VARIABILITY AND COGNITIVE FUNCTION: A SCOPING REVIEW

--Manuscript Draft--

Manuscript Number:	HYPR-D-21-00018R1
Full Title:	BLOOD PRESSURE VARIABILITY AND COGNITIVE FUNCTION: A SCOPING REVIEW
Article Type:	Review
Section/Category:	Blood Pressure Monitoring and Management
Corresponding Author:	Nur Fazidah Asmuje, MSc University of Malaya Faculty of Medicine Kuala Lumpur, Kuala Lumpur MALAYSIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Malaya Faculty of Medicine
Corresponding Author's Secondary Institution:	
First Author:	Nur Fazidah Asmuje, MSc
First Author Secondary Information:	
Order of Authors:	Nur Fazidah Asmuje, MSc
	Sumaiyah Mat, PhD
	Phyo Kyaw Myint, MD
	Maw Pin Tan, MD
Order of Authors Secondary Information:	
Funding Information:	Universiti Malaya (LRGS/1/2019/UM/01/1) — Maw Pin Tan
Abstract:	Purpose of Review To conduct a scoping review of articles which have evaluated BPV and cognitive function. Articles with keywords, titles or abstracts containing the terms 'cognitive' OR 'cognition' OR 'dementia' AND 'blood pressure variability' were identified from CINAHL, Medline, PMC and Web of Science. Recent Findings Methods of acquisition and analysis of BPV and cognitive measurements and their relationship were extracted from selected articles. Of 656 studies identified, 53 articles were selected. 25 evaluated long-term (LTBPV), nine mid-term (MTBPV), 12 short-term (STBPV) and nine very-short-term BPV (VSTBPV) with conflicting findings on the relationship between BPV and cognition. Variations existed in devices, period and procedure for acquisition. The studies also utilized a wide range of methods of BPV calculation. Thirteen cognitive assessment tools were used to measure global cognition or domain functions which were influenced by the population of interest. Summary The interpretation of available studies was hence limited by heterogeneity. There is an urgent need for standardization of BPV assessments to streamline research on BPV and cognition. Future studies should also establish whether BPV could be a potential modifiable risk factor for cognitive decline, as well as a marker for treatment response. Keywords: Aged; cognition; dementia; blood pressure; blood pressure variability

BLOOD PRESSURE VARIABILITY AND COGNITIVE FUNCTION: A SCOPING REVIEW

Authors

Nur Fazidah, ASMUJE,[1,2] ; Sumaiyah, MAT,[3] ; Phyo Kyaw, MYINT[4,5] ; Maw Pin, TAN, [2,6,7].

[1]Kolej Genius Insan, Universiti Sains Islam Malaysia

[2]Ageing and Age-Associated Disorders Research Group, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur

[3]Physiotherapy Programme and Center of Healthy Ageing and Wellness, Faculty of Health Sciences, Universiti Kebangsaan Malaysia

[4]Ageing Clinical & Experimental Research (ACER) Team, Institute of Applied Health Sciences, University Of Aberdeen, Aberdeen, UK

[5]Department Of Medicine for The Elderly, NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK

[6]Centre for Innovations in Medical Engineering, University of Malaya

[7]Department of Medical Sciences, Faculty of Healthcare and Medical Sciences, Sunway University, Bandar Sunway

Corresponding Author

Maw Pin Tan,

Department of Medicine,

Faculty of Medicine,

University of Malaya,

50603 Kuala Lumpur,

Malaysia.

Email: mptan@ummc.edu.my

Tel: +60 3 79492429 Fax: +60 3 79564613

ABSTRACT

Purpose of Review To conduct a scoping review of articles which have evaluated BPV and cognitive function. Articles with keywords, titles or abstracts containing the terms 'cognitive' OR 'cognition' OR 'dementia' AND 'blood pressure variability' were identified from CINAHL, Medline, PMC and Web of Science.

Recent Findings Methods of acquisition and analysis of BPV and cognitive measurements and their relationship were extracted from selected articles. Of 656 studies identified, 53 articles were selected. 25 evaluated long-term (LTBPV), nine mid-term (MTBPV), 12 short-term (STBPV) and nine very-short-term BPV (VSTBPV) with conflicting findings on the relationship between BPV and cognition. Variations existed in devices, period and procedure for acquisition. The studies also utilized a wide range of methods of BPV calculation. Thirteen cognitive assessment tools were used to measure global cognition or domain functions which were influenced by the population of interest.

Summary The interpretation of available studies was hence limited by heterogeneity. There is an urgent need for standardization of BPV assessments to streamline research on BPV and cognition. Future studies should also establish whether BPV could be a potential modifiable risk factor for cognitive decline, as well as a marker for treatment response.

Keywords: Aged; cognition; dementia; blood pressure; blood pressure variability

.

DECLARATIONS

Funding: The Malaysian Elders Longitudinal Research (MELoR) study is now part of the Transforming Cognitive Frailty into Later Life Self-Sufficiency (AGELESS) longitudinal cohort study, currently funded by the Ministry of Higher Education Long Term Research Grant Scheme (LRGS/1/2019/UM/01/1).

Conflicts of interest: NONE DECLARED

Availability of data and material: NOT APPLICABLE

Code availability: NOT APPLICABLE

Authors' contributions: Study conception by Nur Fazidah, ASMUJE and Maw Pin, TAN. Search strategy developed by Sumaiyah, MAT and Nur Fazidah, ASMUJE. Screening and data extraction performed by Nur Fazidah, ASMUJE; Sumaiyah, MAT and Maw Pin, TAN. Conflicts resolved by Maw Pin, TAN; Phyo Kyaw, MYINT and Nur Fazidah, ASMUJE. Manuscript development led by Maw Pin, TAN with all authors involved in analysis and editing of manuscript.

Consent to participate: NOT APPLICABLE

Consent for publication: NOT APPLICABLE

Introduction

Globally, an estimated 75 million persons will be living with dementia by 2030[1]. Common risk factors for dementia include low educational attainment, diabetes, heart disease and reduced physical activity. Individuals with mild cognitive impairment (MCI) are also at increased risk of developing dementia [2**,3]. Hypertension is now considered an established risk factor for dementia, with optimal blood pressure control linked to reduced risk of developing dementia [4]. However, the measurement of blood pressure (BP) which is required to determine the presence of hypertension usually uses single snapshot measures, despite blood pressure actually varying with each heartbeat [5]. The relevance of variations in the measurements obtained over time in the context of dementia risk remains unclear.

The relationship between increased blood pressure variability (BPV) observed during 24-hour ambulatory blood pressure monitoring and end-organ damage has been investigated for three decades [6]. Some evidence has since become available demonstrating an association between increased blood pressure variability using various measurement methods with cardiovascular outcomes [7*]. In particular, several studies have linked BPV with stroke [8] which is associated with vascular dementia, one of the most common causes of dementia. In contrast, others have suggested that fluctuations in blood pressure observed with posture change are associated with the volume of deep white matter changes within magnetic resonance images of the brain [9].

While evidence supporting a possible link between BPV and cognitive function is emerging within the published literature, numerous factors such as choice of indicators and methods of quantification, appear to lead to the current confusion with regards to whether there is truly a link between BPV and cognition. We, therefore, conducted a scoping review in order to rationalize the methods and results of available studies on BPV and cognitive performance.

Search Strategy and Data Extraction

The Medline, Pubmed Central, CINAHL and Web of Science medical databases were searched for articles published between 2006 and 2020 containing the terms: ‘cognitive’ OR ‘cognition’ OR ‘dementia’ AND ‘blood pressure variability’ within keywords, or within their article titles or abstracts which compared BPV and cognitive impairment determined using validated assessment tools or with clinical diagnoses of minor or major cognitive disorders, mild cognitive impairment (MCI) or dementia. Only English language articles

were included. From the initial 656 titles identified from the database search, a total of 53 articles were selected.

Information extracted from selected articles included methods of calculating variability, BP devices use, BP acquisition methods, period of measurement, as well as cognitive measures. The period of measurement is also known as BPV range[10,11*,12**], and is classified into long-term blood pressure variability (LTBPV), mid-term blood pressure variability (MTBPV), short-term blood pressure (STBPV) and very short-term blood pressure variability (VSTBPV) (Table 1). Whether the selected study evaluated systolic (SBPV) or diastolic BPV (DBPV) was also extracted and are included in Supplementary Tables 1 to 4. All studies evaluated SBPV while some studies also included DBPV. The presence of any significant relationship between any measure of either SBPV or DBPV with cognitive performance was also recorded.

Blood Pressure Variability Indices

Figure 1 summarizes the methods of estimation utilized by the various included studies to estimate each type of BPV. Standard deviation (SD) and coefficient of variance (CV) were the most commonly used methods of calculation for all types of BPV. Both SD and CV are time domain methods of analysis. Other time domain methods are average real variability (ARV), variability independent of mean (VIM), and delta. Variability in the time domain reflects fluctuations in blood pressure that result from defective regulatory processes within the autonomic nervous system and neurohumoral system in addition to arterial stiffness which are associated with hypertension and atherosclerosis, though the role each plays in the different time periods of variability remains unclear [10], [11], [29], [30]. Due to the influence of stressor and day-night differences towards SD index, ARV is a solution to obtain the average of the absolute differences between consecutive measurements and residual BPV [13]**. Time domain analyses are possible with a limited number of observations and hence are usually employed for LTBPV and MTBPV.

Frequency domain analyses require large numbers of observations, and hence are more suitable for VSTBPV, but provide the advantage of differentiating high and low frequency fluctuations, which determine parasympathetic and sympathetic responses respectively [31]*. Frequency domain assessments involve power spectral analyses to determine low and high frequency BPV and low to high frequency ratio. Frequency domain analysis in VSTBPV is more susceptible to the influence of the autonomic nervous system, with high frequency variability attributed to fluctuations in BP associated with respiration and

therefore considered a marker of parasympathetic function [16]. Low frequency variability in VSTBPV is usually linked to sympathetic activation. Therefore, the ratio between low to high frequency VSTBPV is a marker of sympathovagal balance. However, interindividual differences in VSTBPV may also be attributed to arterial stiffness [5]. Spontaneous VSTBPV is also known to occur. The supine rest position is said to provide an accurate estimate of real BPV due to the stability of BP measurements while head-up tilt and active standing is utilized to investigate the presence of orthostatic hypotension due to the decline in venous return leading to reduced cardiac output as blood accumulates in the peripheral vasculature [33].

Measurement Devices

Figure 2 provides a summary of types of blood pressure measurement (BPM) device used according to whether associations were established. Manual measurements obtained using a mercury sphygmomanometer was the most utilized method to measure LTBPV. Oscillometric measurements using automated sphygmomanometers were, however, most commonly used to measure BP for LTBPV to SBPV in the clinic and home settings [18, 19*, 20]. Continuous, non-invasive, beat-to-beat BP monitoring, which provides waveform measurements, were used for VSTBPV in nine studies [21,22**,23-29]. Unlike manual sphygmomanometers which require skilled individuals to obtain measurements using the auscultatory method, and beat-to-beat BP monitoring which requires heavy and expensive equipment which are often only limited to tertiary or specialist centres, the automated oscillometric measurement devices can be operated by unskilled personnel in the clinic or at home, and has hence increased the accessibility of BPV as a clinical measurement. Though determination of VSTBPV remains only accessible to specialist centres at present, rapid advances in monitoring technology would no doubt ensure that this can be obtained more conveniently should the role of this measurement be established.

Duration of Variability

While BPV measurements tend to be categorized, researchers are actually measuring variability within a continuum which has been illustrated in Figure 3. In studies which evaluated differences within one month to 12 months, most studies measured BP every three months, while others reported six monthly or monthly measurements. Blood pressure measured over more than a year used a variable number of visits while other studies stated the minimum number of visits included to determine LTBPV. In studies which looked at

MTBPV, an equal number of studies acquired weekly or four weekly measurements. In studies which evaluated BPV over 24 hours, 35.7% failed to mention measurement intervals, with 10, 20 and 30 minutes intervals with and without reduction to 60 minutes at night employed. Heterogeneity exists in the duration of position of measurement and use of the standing position or head-up tilt for VSTBPV studies which utilized beat-to-beat measurements. Conflicting findings may have resulted from the current observed variations in intervals between BP measurements [44**].

Blood Pressure Variability and Cognition

Table 2 summarizes the findings of our selected studies according to study population, design, geographical location and cognitive assessment tools. Additional information on sample population and strength of association to cognitive performance according to type of BPV are included in Supplementary Tables 1 to 4 [32].

Long-Term Blood-Pressure Variability

Of the 23 articles identified, 20 articles found a negative association between LTBPV and cognition. The presence of a negative association indicates that a reduction in cognitive performance is observed with increased LTBPV. Twenty articles included participants with cardiovascular disease [33,34*,35, 36*], cognitively impairment [37-42] and community dwelling [43,44**,45**, 46-48,49**] populations with single studies evaluating the relationship between LTBPV and cognition in Parkinson's Disease [50], chronic disease [51] and depression [52]*. A longitudinal study among post-menopausal women in North America using manual BP measurements found no association between LTBPV and cognitive impairment. LTBPV may bear clinical importance in the management of hypertension in individuals with increased systolic LTBPV, as hypotensive adverse effects such as falls and syncope may occur during hypotensive events associated with BP troughs, limiting the ability to achieve target blood pressure [13].

Mid-Term Blood Pressure Variability

Of the nine studies which studied MTBPV, eight found a negative association between MTBPV and cognitive function while one found no significant association among individuals with cardiovascular disease. A cross-sectional study conducted in Europe on a newly diagnosed hypertensive population found

no significant association between MTBPV and cognitive function [53]. Other studies found reductions in cognitive performance with increased MTBPV utilizing community-dwelling [54**,55,56,57**], cardiovascular disease [58], or cognitively impaired [59], [60] populations or patients with lacunar infarction [61].

Short-Term Blood Pressure Variability

The 12 studies which evaluated STBPV yielded similar association results. Nine found significant negative associations in community-dwelling [62*,63-65] and people with cardiovascular disease [66-69] or a cognitively impaired [70] population. Three studies found no significant association within a cognitively impaired population [71], [72]. [73]**. Ambulatory blood pressure monitoring conveniently provides repeated measurements under standardized conditions, which makes STBPV a potentially useful clinical tool, in addition to LTBPV and MTBPV, in clinical practice.

Very Short-Term Blood Pressure Variability

Nine articles evaluated the relationship between VSTBPV and cognition. Unlike the other types of BPV measured, six articles found a significant positive association between BPV and cognitive function[21], [23], [27], [74], [75], indicating that lower BPV was associated with poorer cognitive performance. Only one study found a negative association [26]* and two no significant association [28], [29]. Factors which connect variations in BP between each heartbeat and resulting clinical effects remain unclear. Posture change is known to activate central autonomic control due to the baroreceptor reflex, renin angiotensin system, vascular myogenic tone, release of nitric oxide from the endothelium [10], [76], which then influences VSTBPV changes.

Cognitive Assessment Tools

A total of 13 tools have been evaluated with BPV. The most widely used tool was the Mini Mental State Examination (MMSE) followed by the Neuropsychological Assessment Battery (NAB) and the Wechsler Adult Intelligence Scale (WAIS). Typically, cognitive assessment tools measure cognition in a number of domains which are controlled by different areas of the brain. Any pathology arising from pathological increases or reduction in BPV is likely to influence specific domains more than others. Conversely, pathological processes within the brain, which may influence BPV, may also favour specific domains,

which at present have yet to be studied in detail. Furthermore, preferences for cognitive tools should be influenced by the population of interest. Cognitive assessment tools may be selected based on geographical and cultural settings. For instance, the Korean MMSE, and the Chinese and Japan Montreal Cognitive Assessment (MoCA) were utilized for studies involving Korean, Chinese and Japanese populations. Few studies have used consensus diagnosis of dementia or cognitive disorder using accepted definitions. Other methods of determining the effects of BPV on neurological disease associated with cognitive decline, including neuroimaging and post-mortem examination, were not considered in available published studies.

Intervention

The effects of antihypertensive treatment on blood pressure variability has been poorly studied in the literature. Blood pressure variability is known to decrease with antihypertensive use with non-dihydropyridines calcium channel blockers and loop diuretics which correspondingly are known to lower dementia risk [66]. The Systolic Pressure Intervention (SPRINT) study evaluated the effects of blood pressure lowering agents on LTBPV and found that thiazide-type diuretics and non-dihydropyridine calcium channel blockers reduced LTBPV while angiotensin converting enzyme inhibitors and angiotensin receptor blockers increased LTBPV. Cognitive outcomes were not considered within the SPRINT study with respect to LTBPV [66]. Few other studies have actually evaluated the effects of pharmacological agents on BPV and cognition. Non-pharmacological intervention, such as using cognitive behavioural therapy for hostility, has been considered but this did not alter VSTBPV [29]

Recommendations for Future Research

Despite the availability of multiple studies evaluating the relationship between BPV and cognition, the conflicting results found between published studies suggest that far more research is required to gain a better understanding of the implications of the varied findings between the studies. More studies have, however, found a negative association between short to long term BPV indicating that increased BPV within these time periods may adversely influence cognitive performance, though the converse appears to be true for VSTBPV. Further research is required to determine factors that influence BPV which will in turn help inform the management strategies for this potentially modifiable risk factor. Future studies could

also seek to determine whether the alteration of dementia risk associated with some antihypertensive medication classes and not others may be associated with their effect on BPV.

CONCLUSION

The relationship between BPV and cognition has been evaluated in a number of studies. While more studies have found a negative association suggesting that increased BPV, particularly over the long-term, medium-term and short-term, may negatively influence cognition, other studies, very short-term, have also found the opposite effect and the remaining an absence of association. Major differences in methods of BPV calculation, duration of BP monitoring, cognitive assessment tools and sample populations exist between studies. Thus, standardization of definitions and methods of acquisition should be considered in order to obtain more meaningful comparisons between studies in the future.

Acknowledgements

Authors of this study has received funding from a Malaysian Ministry of Higher Education Long Term Research Grant Scheme (LRGS/1/2019/UM//1/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

[1] Jaul E, Barron J. Age-related diseases and clinical and public health implications for the 85 years old and over population. *Front. Public Heal.* 2017; 5:1–7

[2]** Nagai M, Kario K. Visit-to-visit blood pressure variability: A possible marker of cognitive decline in Alzheimer's Disease?. *Neurobiol. Aging*. 2015; 36:1.

[3] Livingston G, Andrew S, Orgeta V, Costafreda SG, Huntley J, Ames D, *et al.*, Dementia prevention, intervention, and care. *The Lancet*. 2017; 390: 2673-2734.

[4] Turana Y, Tengkawan J, Chia YC, Hoshide S, Shin J, Chen CH, *et al.*, Hypertension and dementia: A comprehensive review from the HOPE Asia Network," *J. Clin. Hypertens.* 2019; 21: 1091–1098.

[5] Tan MP, Standing up for frailty: Blood pressure changes do matter. *J. Am. Heart Assoc.*, 2020; 9;7.

[6] Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G, Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J. Hypertens.1987;* 5:93–98

[7]* Smith TO, Sillito JA, Goh CH, Abdel-Fattah AR, Einarsson A, Soiza RL,. *et al.*, Association between different methods of assessing blood pressure variability and incident cardiovascular disease, cardiovascular mortality and all-cause mortality: A systematic review.," *Age Ageing*, 2020; 49:184-192.

[8] Webb AJ, Lawson A, Mazzucco S, Li L, Rothwell PM. Age and sex distribution of beat-to-beat blood pressure variability after transient ischemic attack and minor stroke: A population-based study. *Int. J. Stroke.*2020 10.1177/1747493020971905.

[9] Chen X, Zhu Y, Geng S, Li Q, Jiang H. Association of blood pressure variability and intima-media

thickness with white matter hyperintensities in hypertensive patients. *Frontiers in Aging Neuroscience.2019*; 11:1–8.

[10] Floras JS. Blood pressure variability: A novel and important risk factor, *Can. J. Cardiol.*, 2013; 29:557–563.

[11]* Höcht C.Blood pressure variability : Prognostic value and therapeutic implications. *ISRN Hypertension.* 2013; 1-6

[12]** Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE.Blood pressure variability: Its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens. Res.* 2020; 43: 609–620.

[13]** Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *Eur. Hear. J. Suppl.* 2020; 22:E1–E6.

[14] Saji N. Cerebral small vessel disease and arterial stiffness : Tsunami effect in the brain ?. 2016; 8511:182–189.

[15] Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Setevens RJ, *et al.*, Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ. 2016;* 354:14–16.

[16] Frith J, Zalewski P, Kalwe JJ, Pairman J, Bitner A, Tafil-Klawe M, *et al.* Impaired blood pressure variability in chronic fatigue syndrome-A potential biomarker. *Qjm. 2012;*105:831–838.

[17] Cicolini G, Pizzi C, Palma E, Bucci M, Schioppa F, Mezzeti A, *et al.* Differences in blood pressure by body position (supine, fowler's, and sitting) in hypertensive subjects. *Am. J. Hypertens.* 2011; 24:1073–1079.

[18]** O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: Recommendations of the European Society of Hypertension. *Br. Med. J.* 2001; 322:531–536.

[19]* Muntner P, Shimbo D, Carey Rm, Charleston JB, Gaillard T, Misra S, *et al.*, Measurement of blood pressure in humans: a scientific statement from the american heart association. *Hypertension. 2019;*

73:E35–E66.

[20] Medicines and Healthcare Products Regulatory Agency. Blood pressure measurement devices. *Medicines and Healthcare Products Regulatory Agency*. 2019; 1–13.

[21] Mellingsæter MR, Wyller TB, Ranhoff AH, Bogdanovic N, Wyller VB. Reduced sympathetic response to head-up tilt in subjects with mild cognitive impairment or mild Alzheimer's dementia. *Dement. Geriatr. Cogn. Dis. Extra. 2015;* 5:107–115

[22]** Wolters FJ, Mattace-Raso FUS, Koudstaal PJ, Hofman A, Ikram MA. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *PLoS Med.* 2016; 13:1–15.

[23] Keary TA, Gunstad J, Poppas A, Paul RH, Jefferson AL, Hoth KF, *et al.* Blood pressure variability and dementia ratingy scale performance in older adults with cardiovascular disease. *Cogn. Behav. Neurol.* 2007; 20:73-77.

[24] Gunstad J, Keary TA, Spitznagel MB, Poppas A, Paul RH, Sweet LH, *et al.*, Blood pressure and cognitive function in older adults with cardiovascular disease. *Int. J. Neurosci.* 2009; 119:2228–2242.

[25] Okonkwo OC, Cohen RA, Gunstad J, Poppas A. Cardiac output, blood pressure variability, and cognitive decline in geriatric cardiac patients. *J. Cardiopulm. Rehabil. 2011;* 31:290–297.

[26]* Crichton GE, Elias MF, Dore GA, Torres RV, Robbins MA. Measurement-to-measurement blood pressure variability is related to cognitive performance: The maine syracuse study. *Hypertension. 2014;* 64:1094–1101.

[27] Cohen RA, Poppas A, Forman DE, Hoth KF, Haley AP, Gunstad J, *et al.* Vascular and cognitive functions associated with cardiovascular disease in the elderly. *J. Clin. Exp. Neuropsychol.* 2009; 31:96-110.

[28] Santos WB, Matosa JMD, MAltez M, Gonçalves T, Casanova M, Moreira IFH,*et al.* Spectral analyses of systolic blood pressure and heart rate variability and their association with cognitive performance in elderly hypertensive subjects. *Journal of Human Hypertension*. 2014;29:488–494.

[29] Hajjari P, Mattsson S, McIntyre KM, McKinley PS, Shapiro PA, Gorenstein EE, *et al.* The effect of hostility reduction on autonomic control of the heart and vasculature: A randomized controlled trial. *Psychosom. Med.*, 2016:78:481–491.

[30] B. C. Cardiology Department. *Event Monitoring Methods.* 2017.

[31] Veloudi P, Sharman JE. Methodological factors affecting quantification of blood pressure variability: A scoping review. *J. Hypertens. 2018;*36:711–719.

[32] Borland C. Effect size. *Bmj. 1995;* 310: 672.

[33] Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: New independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *J. Hypertens.*,2012; 30:1556–1563.

[34]* Sabayan B, Wijsman LW, Foster-Dingley JC,Stott DJ, Ford I, Buckley BM, *et al.*, Association of visit-to-visit variability in blood pressure with cognitive function in old age: Prospective cohort study. *BMJ*., 2013; 347:1–11.

[35] Nagai M, Hoshide S, Nishikawa M, Masahisa S, Kario K. Visit-to-visit blood pressure variability in the elderly: Associations with cognitive impairment and carotid artery remodeling. *Atherosclerosis*; 2018; 233:19–26.

[36]* Wijsman LW, De Craen AJM, Muller, M, Sabayan B, Stot D, Ford I, Trompet S, *et al.* Blood pressure lowering medication, visit-to-visit blood pressure variability, and cognitive function in old age. *Am. J. Hypertens.*,2015; 29:311-318.

[37] Epstein NU, Lane KA, Farlow M, Risacher SL, Saykin AJ, Sujuak G, *et al.*, Cognitive dysfunction is associated with increased visit to visit systolic blood pressure variablity. *J. Am. Geriatr. Soc.*, 2013; 61:2168–2173.

[38] Lattanzi S, Brigo F , Vernieri F, Silvestrini M. Visit-to-visit blood pressure variability in alzheimer disease. *Alzheimer Dis. Assoc. Disord.*,2014; 28:347–351

[39] Lattanzi S, Luzzi S, Provinciali L, Silvestrini M. Blood pressure variability in alzheimer's disease and frontotemporal dementia: The effect on the rate of cognitive decline. *J. Alzheimer's Dis.*, 2015; 45:387–394.

[40] Tsang S, Sperling SA, Park MH, Helenius IM, Williams IC, Manning C. Blood pressure variability and cognitive function among older African Americans. *Cogn. Behav. Neurol.*, 2017; 30:90–97.

[41] Lattanzi S, Luzzi S, Provinciali L, SilvestriniM. Blood pressure variability predicts cognitive decline in Alzheimer's disease patients. *Neurobiol. Aging. 2014;* 35:2282–2287.

[42] Lee SH,Han K, Cho H, Park YM, Kwon HS, Kang G, *et al.*, Variability in metabolic parameters and risk of dementia: A nationwide population-based study 11 Medical and Health Sciences 1117 Public Health and Health Services. *Alzheimer's Res. Ther.* 2018;10:1–14.

[43] Alpérovitch A, Blachier M, Soumaré A, Ritchie K, Dartigues JFF, Richard-Harston S, *et al.*, Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimer's Dement.*,2014; 10: S330–S337.

[44]** Qin B, Viera AJ, Muntner P, Plassman BL, Edward LJ, Adair LS, *et al.* Visit-to-visit variability in blood pressure is related to late-life cognitive decline. *Hypertension. 2016;* 68:106–113.

[45]** Yano Y, Griswold M, Wang W, Greenland P, Lloyd -Jones DM, Heiss G, *et al.*, Long- term blood pressure level and variability from midlife to later life and subsequent cognitive change: The ARIC Neurocognitive Study. *J. Am. Heart Assoc.* 2018;7.

[46] Yano Y, Ning H, Allen N, Reis JP, Launer LJ, Liu K, *et al.* Long-term blood pressure variability throughout young adulthood and cognitive function in midlife. *Hypertension. 2014*; 64 983–988.

[47] Sible IJ, Nation DA. Long-term blood pressure variability across the clinical and biomarker spectrum of Alzheimer's Disease. *J. Alzheimer's Dis.*, 2020; 77:655–1669.

[48] Rouch L, Vidak JSS, Hoang T, Cestac P, Hanon O, Yaffe K, *et al.* Systolic blood pressure postural changes variability is associated with greater dementia risk. *Neurology. 2020;* 95:e1932–e1940.

[49]** Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, *et al.*, Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: The SAGES cohort. *Hypertension*. 2020; 76:1280–1288.

[50] Kwon KY, Pyo SJ, Lee HM, Seo WK, Koh SB. Cognition and visit-to-visit variability of blood pressure and heart rate in de novo patients with Parkinson's disease. *J. Mov. Disord. 2016;*9:144–151.

[51] Lande MB, Mendley SR, Matheson MB, Shinnar S, Gerson AC, Samuels JA, *et al.*, Association of blood pressure variability and neurocognition in children with chronic kidney disease. *Pediatr. Nephrol.* 2016; 2137–2144.

[52]* Tully PJ, Debette S, Tzourio C. The association between systolic blood pressure variability with depression, cognitive decline and white matter hyperintensities: The 3C Dijon MRI study. *Psychol. Med.* 2018; 48:1444–1453.

[53] Van Boxtel MPJJ, Henskens LHGG, Kroon AA, Hofman PAMM, Gronenschild EHBMBM, Jolles J, *et al.* Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J. Hum. Hypertens.*2006: 20:5–13.

[54]** Matsumoto A, Satoh M, Kikuya M, Ohkubo T, Hirano M, Inoue R, *et al.*, Day-to-day variability in home blood pressure is associated with cognitive decline: The ohasama study. *Hypertension* 2014; 63:1333–1338.

[55] Liu Z, Zhao Y, Zhang H, Chai Q, Cui Y, Diao Y, *et al.*, Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. *Hypertens. Res.* 2016; 39: 245–253.

[56] Godai K, Kabayama M, Gondo Y, Yasumoto S, Sekiguchi T, Noma T, *et al.* Day-to-day blood pressure variability is associated with lower cognitive performance among the Japanese community-dwelling oldest-old population: The SONIC study. *Hypertens. Res.* Dec; 2019: 43: 404-411.

[57]** Zhou TL, Kroon AA, Van Sloten TT, Van Boxtel MPJ, Verhey FRJ, Scram, Miranda T, *et al.* Greater blood pressure variability is associated with lower cognitive performance. *Hypertension*. 2019; 73:803–811.

[58] Johann AF, Hertenstein E, Feige B, Akram U, Holub F, Baglioni C, *et al.* Cognitive behavioural therapy for insomnia does not appear to have a substantial impact on early markers of cardiovascular disease: A preliminary randomized controlled trial. *J. Sleep Res.*2020; 29: e13102.

[59] Oishi E, Tomoyuki O, Satoka S, Masayo F, Jun H, Daigo Y. *et al.* Day-to-day blood pressure variability and risk of dementia in a general Japanese elderly population. *Circulation.* 2017; 136: 516–525.

[60] De Heus RAAA, Reumers SFII, Van Der Have A, Tumelaire M, Tully, Claassen JAHRHR. Day-to-day home blood pressure variability is associated with cerebral small vessel disease burden in a memory clinic population. *J. Alzheimers. Dis.* 2020; 74:463–472

[61] Lee JHH, Oh E, Oh MS, Kim C, Jung S, Park JHH, *et al.* Highly variable blood pressure as a predictor of poor cognitive outcome in patients with acute lacunar infarction. *Cogn. Behav. Neurol.* 2014; 27:189–198.

[62]* McDonald C, Pearce MS, Kerr SRJ, Newton JL. Blood pressure variability and cognitive decline in older people. *J. Hypertens.* 2017; 35:140–147.

[63] Mossello E, Pieraccioli MC, Zanieri S, Fedeli A, Belladona M, Nesti N, *et al.* Ambulatory blood pressure monitoring in older nursing home residents: diagnostic and prognostic role. *J. Am. Med. Dir. Assoc.* 2012; 13: 760.e1-760.e5.

[64] Tadic M, Cuspidi C, Bombelli M, Facchetti R, Mancia G, Grassi G. Relationships between residual blood pressure variability and cognitive function in the general population of the PAMELA study. *J. Clin. Hypertens.* 2019; 21:39–45.

[65] Cho N, Hoshide S, Nishizawa M, Fujiwara T, Kario K. Relationship Between blood pressure variability and cognitive function in elderly patients with good blood pressure control. *Am. J.*

Hypertens. 2018: 31:293–298.

[66] De La Colina AN, Wu R, Desjardins-Crépeau L, Badji A, Lamarre-Chliche M, Doyon J, *et al.* Diurnal blood pressure loads are associated with lower cognitive performances in controlled-hypertensive elderly individuals. *J. Hypertens.* 2019; 37:2168–2179.

[67] Osovska NY, Mazur YV, Bereziuk OM, Dmytryshyn SP, Velychkoyych MM, Perebetiuk LA, *et al.* Cardiovascular remodeling in patients with hypertension with different degrees of cognitive impairment. *Wiad. Lek.* 2019; 72:670–676.

[68] Baranowski J, Klęczar K, Sołtysiak M, Widecka K. The association between cognitive decline and short-term blood pressure variability in middle-aged patients with primary hypertension - a pilot study. *Arter. Hypertens.* 2018; 22:135–142.

[69] Yıldırım E, Ermis E, Allahyerdiyey S, Ucar H, Yayuzer S, Yayuzer H, *et al.*, Relationship between blood pressure variability and cognitive function in geriatric hypertensive patients with well-controlled blood pressure. *Aging Clin. Exp. Res.* 2019.

[70] Kim JE, Shin JS, Jeong JH, Choi KG, Park KD, Kim S. Relationships between 24-hour blood pressures, subcortical ischemic lesions, and cognitive impairment. *J. Clin. Neurol.2009;* 5:139.

[71] Paganini-Hill A, Bryan N, Corrada MM, Greenia DE, Fletcher E, Singh B, *et al.* Blood pressure circadian variation, cognition and brain imaging in 90+ year-olds. *Front. Aging Neurosci.* 2019; 11:1-9.

[72] Conway KS, Forbang N, Beben T, Criqui MH, Ix JH, Rifkin DE. Relationship between 24-hour ambulatory blood pressure and cognitive function in community-living older adults: The UCSD ambulatory blood pressure study. *Am. J. Hypertens.* 2015; 28:1444–1452.

[73]** Tully PJ, Dartigues JFF, Debette S, Helmer C, Artero S, Tzourio C. Dementia risk with antihypertensive use and blood pressure variability. *Neurology. 2016;* 87:1-8.

[74] Gunstad J, Keary TA, Spitznagel MB, Poppas A, Paul RH, Sweet LH, *et al.*, Blood pressure and cognitive function in older adults with cardiovascular disease. *Int. J. Neurosci.* 2009; 119:2228–

2242.

[75] Okonkwo OC, Cohen RA, Gunstad J, Poppas A. Cardiac output, blood pressure variability, and cognitive decline in geriatric cardiac patients. *J. Cardiopulm. Rehabil. 2011;* 31:290–297.

[76] Chadachan VM, Ye MT, Tay JC, Subramaniam K, Setia S. Understanding short-term blood-pressure-variability phenotypes: From concept to clinical practice. *Int. J. Gen. Med.* 2018; 11:241-254.

FIGURE LEGENDS

Figure 1: Blood Pressure Variability Indices

Stacked column showed the number of BPV indices used in each type of BPV based on significance of association.

Figure 2: Blood Pressure Measuring Devices and Types of Blood Pressure Variability Obtained

Flow chart indicating types of blood pressure measurement devices utilized in included studies. Beneath the textbox of each measurement method, the fraction of studies for each BPV type which indicated an association between BPV and cognition is included. The numerator of each fraction represents the number of studies in which BPV was associated with cognitive performance while the denominator indicates the total number of studies which evaluated the relationship between BPV and cognition.

LTBPV= long-term blood pressure variability; MTBPV= mid-term blood pressure variability, STBPV=short-term blood pressure variability, VSTBPV=very short-term blood pressure variability

Figure 3. Duration of Blood Pressure Monitoring

The horizontal arrow indicates the duration of blood pressure measurements, with the arrowed boxes containing the interval between each BP measurement and the percentage of studies which employed each interval.

FIGURE LEGENDS

Figure 1: Blood Pressure Variability Indices

Stacked column showed the number of BPV indices used in each type of BPV based on significance of association.

Figure 2: Blood Pressure Measuring Devices and Types of Blood Pressure Variability Obtained

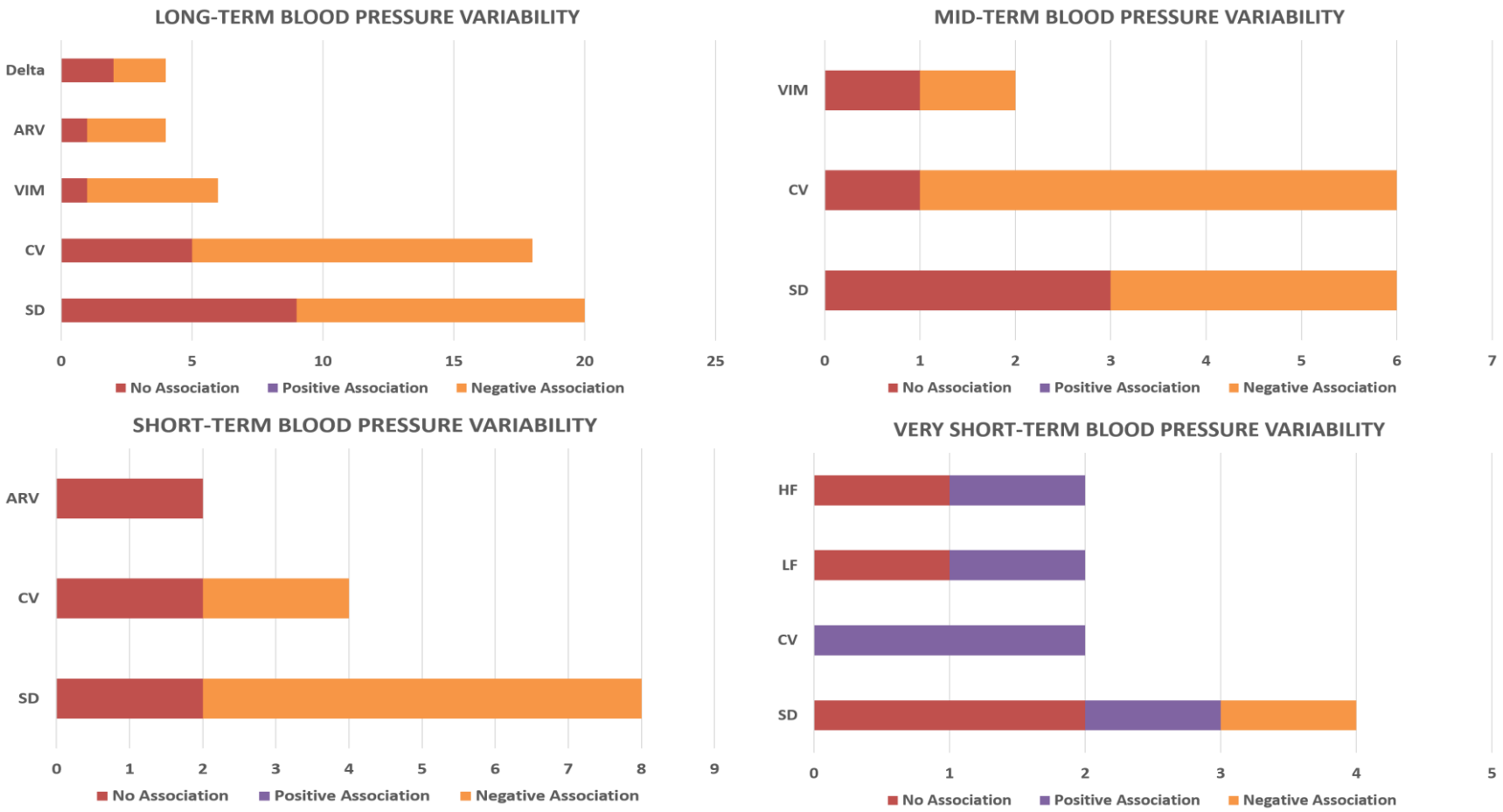
Flow chart indicating types of blood pressure measurement devices utilized in included studies. Beneath the textbox of each measurement method, the fraction of studies for each BPV type which indicated an association between BPV and cognition is included. The numerator of each fraction represents the number of studies in which BPV was associated with cognitive performance while the denominator indicates the total number of studies which evaluated the relationship between BPV and cognition.

LTBPV= long-term blood pressure variability; MTBPV= mid-term blood pressure variability, STBPV=short-term blood pressure variability, VSTBPV=very short-term blood pressure variability

Figure 3. Duration of Blood Pressure Monitoring

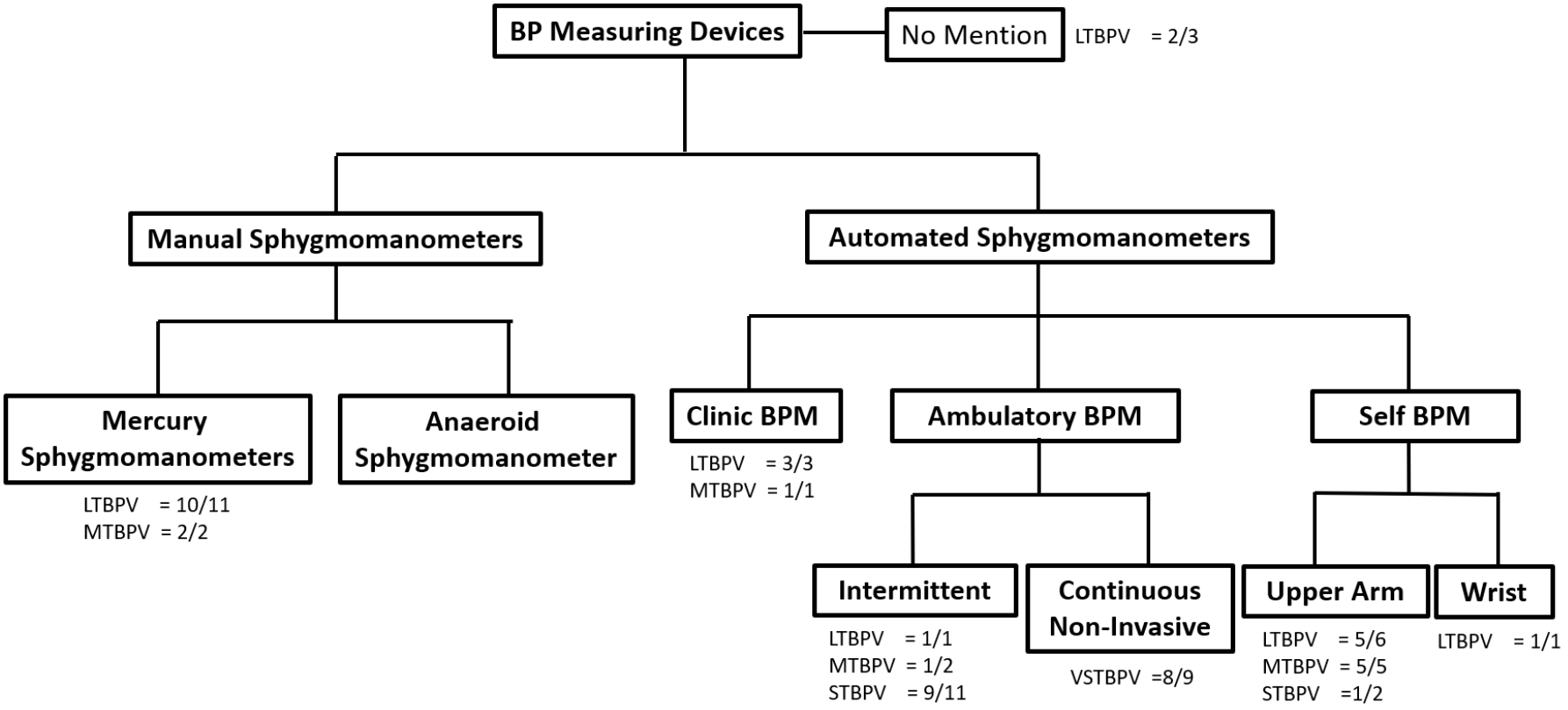
The horizontal arrow indicates the duration of blood pressure measurements, with the arrowed boxes containing the interval between each BP measurement and the percentage of studies which employed each interval.

Figure 1.



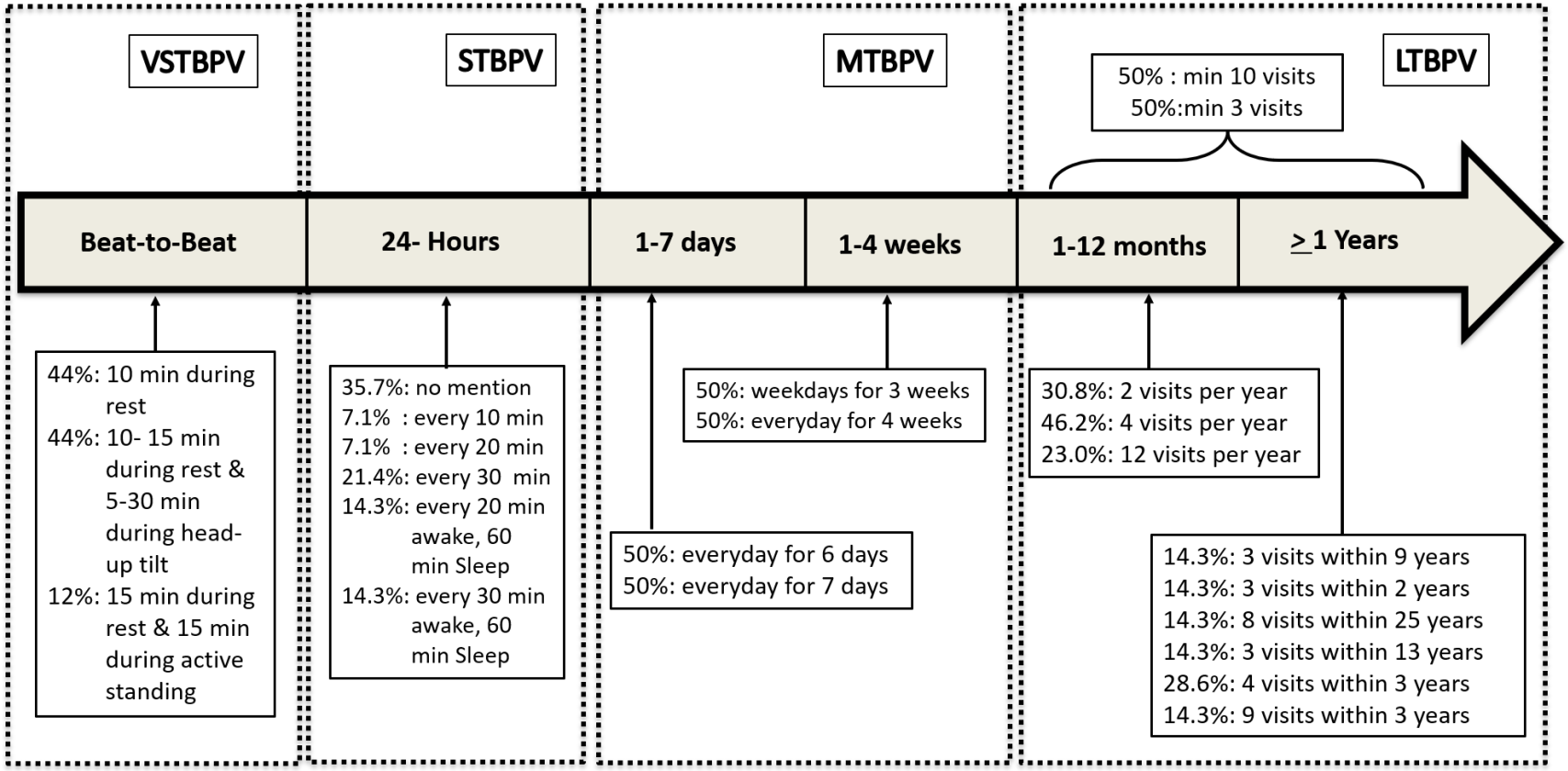
Stacked column shows the number of BPV indices used in each type of BPV based on significant association.

Figure 2: Blood Pressure Measuring Device Used in the Association Between BPV and Cognitive Performance Study



LTBPV = long-term blood pressure variability, MTBPV = mid-term blood pressure variability, STBPV = short-term blood pressure variability, VSTBPV = very short-term blood pressure variability, BPM = blood pressure measurement. Numerator =number of studies in which BPV was associated with cognitive performance; Denominator= total number of studies which evaluated the relationship between BPV and cognition.

Figure 3. Duration of Blood Pressure Monitoring



The horizontal arrow indicates the duration of blood pressure measurements, with the arrowed boxes containing the interval between each BP measurement and the percentage of studies which employed each interval

Table 1: Classification of Blood Pressure Variability

Types of BPV	Period of Measurement
Long Term Blood Pressure Variability (LTBPV) (25 articles)	Visit-to-visit, seasonal measurements
Mid-Term Blood Pressure Variability (MTBPV) (12 articles)	Day-to-day
Short-Term Blood Pressure Variability (STBPV) (11 articles)	24-hour period and discontinuous BP recordings obtained over seconds or minutes
Very Short-Term Blood Pressure Variability (VSTBPV) (8 articles)	Continuous beat-to-beat BP recordings

BPV=blood pressure variability

Table 2. Types of Blood Pressure Variability and Cognitive Function

	LTBPV (n=23)			MTBPV (n=9)			STBPV (n=12)			VSTBPV (n=9)		
	None	+ve	-ve	None	+ve	-ve	None	+ve	-ve	None	+ve	-ve
Population												
Healthy Community Dwellers	1/7	-	6/7	-	-	4/4	1/6	-	4/6	1/3	2/3	-
Cardiovascular Disease	-	-	4/4	1/2	-	1/2	-	-	4/4	1/5	3/5	1/5
Cognitive Impairment	1/8	-	7/8	-	-	2/2	2/2	-	-	-	1/1	-
Parkinson Disease	-	-	1/1	-	-	-	-	-	-	-	-	-
Post-Menopausal Women	1/1	-	-	-	-	-	-	-	-	-	-	-
Depression	-	-	1/1	-	-	-	-	-	-	-	-	-
Other disease specific	-	-	1/1	-	-	1/1	-	-	-	-	-	-
Study Design												
Prospective	3/22		19/22	-	-	5/5	2/6	-	4/6	2/5	3/5	-
Cross Sectional	-	-	1/1	1/4	-	3/4	1/6	-	5/6		3/4	1/4
Geographically Setting												
Asia	-	-	5/5	-	-	6/6	1/2	-	1/2	-	-	-
North America	3/11	-	9/11	-	-	-	1/4	-	3/4	1/7	5/7	1/7
South America	-	-	-	-	-	-	-	-	-	1/1	-	-
Europe	-	-	7/7	1/3	-	2/3	1/6	-	5/6	-	1/1	-
Cognitive Assessment Tools												
MMSE	5/20	-	15/20	-	-	4/4	2/8	-	6/8	-	3/4	1/4
NAB	2/10	-	8/10	1/4	-	3/4	2/4	-	2/4	2/6	3/6	1/6
MoCA	-	-	-	-	-	2/2	2/4	-	2/4	-	-	-
CDR	-	-	3/3	-	-	-	-	-	-	-	1/1	-
WAIS	-	-	2/2	-	-	1/1	-	-	1/1	-	-	-
TICS	-	-	1/1	-	-	-	-	-	-	-	-	-
ADAS-COG	1/2	-	1/2	-	-	1/1	-	-	--	1/8	6/8	1/8
CAMCI	-	-	1/1	-	-	-	-	-	-	-	-	-
Hasegawa	-	-	-	-	-	1/1	-	-	-	-	-	-
HIS	-	-	-	-	-	-	1/1	-	-	-	-	-
CAMDEX	-	-	-	-	-	-	-	-	1/1	-	1/1	-

BPV=blood pressure variability; LTBPV=long term BPV, MTBPV=mid-term BPV, STBPV= short term BPV; VSTBPV=very short term BPV; MMSE=Mini Mental State Examination; NAB= Neuropsychological Assessment Battery; MoCA= Montreal Cognitive Assessment; CDR= Clinical Dementia Rate; WAIS= Weschler Adult Intelligence Scale; TICS= Telephone Interview Cognitive; ADAS-COG= Assessment Scale Cognitive Component; CAMCI= Computer Assessment of Mild Cognitive Impairment; HIS= Hachinski Ischemic Score; CAMDEX = Cambridge Examination of Mental Disorders of the Elderly

None indicates no association; +ve indicates ↑BPV ↑Cognition; -ve indicates ↑BPV ↓cognition. The denominator denotes total number of studies which has evaluated each area, while the numerator indicates in number of studies which fulfil the criteria. E.g. 1/7 in the first cell means 7 studies have evaluated the cognition of healthy community dwellers against LTBPV and 1 found no significant association.

Supplementary Table 1

Supplementary Table 2

Click here to access/download
Supplementary/video
Supplementary Table 2.docx

Supplementary Table 3

Click here to access/download
Supplementary/video
Supplementary Table 3.docx

Supplementary Table 4