The Association between Blood Pressure Variability and Dementia and Cognitive Impairment: A Meta-Analysis

Umama Aamir

This thesis is submitted in partial fulfilment of an Honours Degree of Bachelor of Psychological Science

School of Psychology

The University of Adelaide

November 2018

Word Count: 7,294

Table of Contents

Tables and Figures **4**

Abstract **5**

Declaration **6**

Acknowledgements **7**

1. Introduction **8**

1.1 Dementia and Cognitive Impairment: Aetiology, Epidemiology, Incidence, Prevalence 8

1.2 Hypertension as a risk factor 10

1.3 Types of Blood Pressure Measurements 11

1.3.1 Blood Pressure Monitoring 11

1.3.2 Limitations of the usual BP hypothesis 12

1.3.3 Blood Pressure Variability 14

1.4 Dementia, cognitive decline, and vascular disease 15

1.5 Current study 15

1.5.1 Problem statement 15

1.5.2 Aims 16

2. Methods **17**

2.1 Literature search 17

2.2 Study eligibility 17

2.3 Data extraction 20

2.4 Data preparation 20

2.5 Risk of bias assessment 21

2.6 Statistical analyses....21

3. Results....23

3.1 Study and sample characteristics....23

3.2 Risk of bias....24

3.3 Results of Individual studies....24

3.4 Relationships between BPV and Dementia and Cognitive Impairment....24

3.4.1 Dementia....25

3.4.2 Cognitive Impairment....27

3.4.3 Combined Results....27

3.5 Heterogeneity....32

3.6 Publication Bias....32

4. Discussion....34

4.1 Key Findings....34

4.1.1 Dementia, Cognitive Impairment, and Overall Cognitive Decline....34

4.1.2 BPV and mean BP....35

4.2 Clinical Implications....37

4.3 Limitations....38

4.4 Conclusion....39

References....40

Appendices....52

Tables and Figures

1. Introduction

Table 1: Neurocognitive Disorders as Diagnosed in DSM-5

2. Method

Figure 1: PRISMA flow chart of article selection

3. Results

Figure 2: Risk of bias graph

Table 2: Association between systolic BPV and SBP and dementia

Table 3: Association between diastolic BPV and DBP and dementia

Table 4: Association between systolic BPV and SBP and cognitive impairment

Table 5: Association between diastolic BPV and DBP and cognitive impairment

Table 6: Association between systolic BPV and SBP and overall cognitive decline

Table 7: Association between diastolic BPV and DBP and overall cognitive decline

Figure 3: Funnel plot of systolic BPV and SBP associated with overall cognitive decline

Abstract

Background: Blood pressure irregularities are the precursor to all vascular diseases. Elevated systolic blood pressure (BP) is the leading cause of death and disability worldwide. Similarly, the burden of dementia is on the rise. BP variability (BPV) has been suggested to be able to predict dementia and cognitive impairment more accurately than mean BP. A body of literature has shown the link between increased BPV, a high average BP, cognitive impairment, and incident dementia. However, the extent of this association is controversial, and remains unknown.

Aim: To identify the magnitude of the association between BPV, cognitive impairment, and incident dementia.

Meta-Analysis: Eleven studies, comprised of 52, 784 individuals, were identified after a comprehensive search of the Embase, PsychINFO, PubMed, and Scopus databases. Data was extracted and prepared to calculate risk ratios with 95% confidence intervals. Forest plots were created. Heterogeneity was identified and publication bias was assessed.

Results: Systolic BPV was significantly associated with cognitive impairment [RR: 1.29; 95% CI 1.06 – 1.57; p = 0.01] and overall cognitive decline [RR: 1.23; 95% CI 1.08 – 1.40; p = 0.001].

Conclusion: This meta-analysis has clinical implications on potential clinical interventions and treatments for dementia and cognitive impairment. It may also aid in healthcare policy regarding patient BP monitoring and modulation. We live in a world with an increasingly ageing population, which makes the present a critical time to uncover the relationship between BPV and dementia and cognitive impairment.

Keywords: blood pressure variability, dementia, cognitive impairment, cognitive decline

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

Student (Umama Aamir)

9th November 2018

Acknowledgements

First, I would like to thank my supervisors, Dr. Phillip Tully and Professor Deborah Turnbull, for their guidance, support, and encouragement, without which this research would not have been possible. I would also like to thank Ms. Maureen Bell, a research librarian, for her aid with the electronic database searches. Lastly, I would like to acknowledge my family and friends, who supported and encouraged me through this venture.

1. Introduction

1.1 Dementia and cognitive impairment: aetiology, epidemiology, incidence, prevalence

Dementia is a chronic syndrome which deteriorates cognitive function beyond the extent of normal ageing (Dementia Australia, 2018). It can result from a variety of diseases or injuries that affect the brain, such as stroke. The onset is gradual, which often leads to the early stage of dementia being overlooked. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), dementia is classified as a neurocognitive disorder as it relates to brain disease and disrupts cognitive function (American Psychiatric Association, 2013). The diagnosis of dementia usually occurs when cognitive impairment becomes severe enough to compromise daily life (Hugo & Ganguli, 2014). Mild cognitive impairment (MCI) is a state wherein the individual is functional, but is more cognitively impaired than can be explained by age. Table 1 shows the DSM-5 diagnosis criteria for dementia. The cognitive domains that the diagnosis refers to are complex attention, executive ability, learning and memory, language, motor-visual perception, and social cognition (Hugo & Ganguli, 2014).

Dementia is a major public health issue being the second leading cause of death in Australia, and the leading cause of death in females, contributing to 5.4% of all deaths in males and 10.6% in females each year (Australian Bureau of Statistics, 2017). In Australia in 2016, more than 1 in 7 people were over 65 years old. Without a medical breakthrough, the incidence of dementia will be greater than half a million by 2028 and more than one million by 2058 (Dementia Australia, 2018). There are approximately 250 new cases every day, and in 2018, dementia has had a burden of $15 billion dollars on the Australian government (Dementia Australia, 2018). On a global level, there are 50 million cases now, and it has been projected that by 2050, more than 130 million people worldwide will be diagnosed with dementia (Dementia Australia, 2018).

Table 1

Neurocognitive Disorders as Diagnosed in DSM-5

Diagnostic Criteria	**Major Neurocognitive Disorder/Dementia**	**Mild Neurocognitive Disorder/Dementia**
A	Significant cognitive decline in one or more cognitive domains, based on:	Modest cognitive decline in one or more cognitive domains, based on:
	1. Concern about significant decline, expressed by individual or reliable informant, or observed by clinician.	1. Concern about mild decline, expressed by individual or reliable informant, or observed by clinician.
	2. Substantial impairment, documented by objective cognitive assessment.	2. Modest impairment, documented by objective cognitive assessment.
B	Interference with independence in everyday activities.	No interference with independence in everyday activities, although these activities may require more time and effort, accommodation, or compensatory strategies
C	Not exclusively during delirium.	
D	Not better explained by another mental disorder.	
E	Specify one or more etiologic subtypes, "due to"	
	• Alzheimer's disease • Cerebrovascular disease (Vascular Neurocognitive Disorder) • Frontotemporal Lobar Degeneration (Frontotemporal Neurocognitive Disorder) • Dementia with Lewy Bodies (Neurocognitive Disorder with Lewy Bodies) • Parkinson's disease • Huntington's disease • Traumatic Brain Injury • HIV Infection • Prion Disease • Another medical condition • Multiple etiologies	

Adapted from: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. (as cited in Hugo, J., & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clinics in geriatric medicine, 30*(3), 421-442. doi:10.1016/j.cger.2014.04.001)

Currently treatments are ineffective at reducing the development and progression of the disorder (Lattanzi, Luzzi, Provinciali, & Silvestrini, 2014; Williams, 2009). Therefore it is critical to identify the risk factors of dementia and MCI to reduce and prevent dementia in the long-term, as this would have significant practical implications, such as a clinical approach that focuses on mitigating the onset of the disorder.

One major risk factor for dementia is elevated blood pressure (BP) and hypertension (Bermejo-Pareja et al., 2010; Kececi Savan et al., 2016), while another is cerebral small vessel disease (CSVD), a type of cerebrovascular disease (Hollocks, Brookes, Morris, & Markus, 2016) that is the cause of nearly half of all cases of vascular dementia (Prabhakar et al., 2015). The main risk factor of CSVD is also hypertension (Kececi Savan et al., 2016).

1.2 Hypertension as a risk factor

Elevated systolic blood pressure (SBP) is a leading cause of death and disability worldwide (Lancet, 2017). Hypertension, in itself, is a major public health problem, especially for older adults, and is a risk factor for cardiovascular diseases, such as heart failure, stroke, and dementia (Gifford et al., 2013). The Heart Foundation (2016) describes hypertension as a condition in which an individual's BP is consistently ≥140/90 mmHg. Increased and variable levels of BP play major roles in furthering organ damage and triggering subsequent vascular events (Rothwell, 2010). It should be noted that the cognitive systems associated with BP flow are allegedly connected to neuroanatomical zones affected by dementia and CSVD (Gifford et al., 2013), so cognitive decline may be triggered by BP irregularities in these areas.

However, although hypertension is a risk factor for dementia (Bermejo-Pareja et al., 2010; Kececi Savan et al., 2016), anti-hypertensive treatments have not shown a significant reduction in the incidence and risk of dementia (McGuinness, Todd, Passmore, & Bullock,

2006; Peters et al., 2008; Qiu, Winblad, & Fratiglioni, 2005) and cognitive decline (Plassman et al., 2010).

1.3 Types of BP measurements

There are four ways in which BP can be measured. The first of these is the usual BP, which refers to the hypothetical exact underlying level of BP, which can never be measured with complete accuracy, but remains to be the most central component of BP. This is because it is used to determine the adverse effects depending on the level of BP. The second is the mean BP, which is measured as the average of multiple readings of SBP or diastolic blood pressure (DBP). Third is blood pressure variability (BPV), which refers to how BP varies over time (Rothwell et al., 2010). Lastly, BP instability refers to the fleeting variations in BP, usually as a reaction to a stimulus, such as postural change, pain, or emotional strain. Instability plays a part in overall BPV, but it differs from BPV in that it refers to abrupt changes in BP, which may have different consequences than the more gradual shifts of BPV (Rothwell, 2010).

1.3.1 Blood pressure monitoring

BP can be measured in many ways. The review, which is the focus for the current study, will include all types, including clinic visit-to-visit BP, ambulatory BP monitoring (ABPM), and home BP monitoring, so long as there is sufficient data to calculate BPV. ABPM is now the gold standard for hypertension diagnosis (Linden, 2011). This is because it allows improved accuracy in mean BP calculation (Linden, 2011), and excludes interference from the white coat effect (Parati et al., 2008). The mean BP calculated from the ABPM has also been found to predict vascular disease and cognitive decline better than clinic visit BP (Burr, Dolan, O'Brien, O'Brien, & McCormack, 2008; Salles, Cardoso, & Muxfeldt, 2008), although visit-to-visit BP is still a significant risk factor for vascular events, leading on to cognitive decline (Qin et al., 2016). Still, patients are not always willing to accept the

apparatus that comes with automated ABPM, as cuff inflation may disrupt their daily routines and sleep. In these cases, home BP monitoring is a suitable alternative as measurements can be taken under consistent conditions over several days (Oishi et al., 2017; Parati et al., 2008).

1.3.2 Limitations of the usual BP hypothesis

Hypertension is the most prevalent vascular risk factor and is linked with cognitive decline, impairment, and dementia (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013; Luzzi, Vella, Bartolini, Provinciali, & Silvestrini, 2010; Novak & Hajjar, 2010; Sharp, Aarsland, Day, Sønnesyn, & Ballard, 2011). However, this is subject to the limitations of the usual BP hypothesis which suggests that the underlying usual BP can account for all related risks, and has a beneficial correlation with antihypertensive treatments (Rothwell, 2010).

The limits of the hypothesis can be described as thus. First, the precision of usual BP to be able to predict vascular events declines with age, while the incidence of these events, particularly stroke, increases with age (Colandrea, Friedman, Nichaman, & Lynd, 1970; Hypertension Detection and Follow-up Program Cooperative Group, 1978; Rothwell et al., 2004). Second, it should be noted that the majority of studies on usual BP and vascular risk were conducted on healthy samples, excluding those with a medical history of vascular events (Prospective Studies Collaboration, 2002). This is despite the fact that individuals undergoing antihypertensive treatment are those that have vascular risk factors, or have presented them in the past. The samples of these at-risk individuals have shown a discrepancy between the predictive mean SBP and BP reduction effects (Rothwell et al., 2010).

Third, with consideration to the strong predictive association of the morning surge in BP and incidence of stroke, the predictive value of mean BP is irrelevant (Kario, Shimada, & Pickering, 2003; Wizner et al., 2008). Fourth, the mean BP does not account for temporary surges in BP which can trigger vascular events. These surges can be caused by orthostatic

hypertension, sympathetic over-activity, and increased blood pressure reactivity due to personality traits like anger (Brondolo et al., 2009; Koton et al., 2004). Fifth, orthostatic hypotension, the complete opposite of BP instability, is also a significant risk factor for vascular events (Fedorowski et al., 2010), and is also affected by antihypertensive treatments (Kamaruzzaman, Watt, Carson, & Ebrahim, 2010).

Sixth, in the majority of studies, there is no known baseline of SBP that would result in a decrease of vascular risk (Prospective Studies Collaboration, 2002). Currently the optimal BP range is still unknown (Iadecola et al., 2016); however research has shown that individuals with high BPV are at increased risk, despite their mean SBP being considered normal (Rothwell et al., 2010). Seventh, situational BPV caused by the white coat effect has been linked with increased vascular risk and target-organ damage independent of mean BP (Mancia et al., 2009; Mancia, Facchetti, Bombelli, Grassi, & Sega, 2006). This form of masked hypertension is also a display of BPV. Eighth, antihypertensive treatments have not shown a reduction in dementia risk, as mentioned above (Peters et al., 2008; Skoog et al., 1996), which suggests that lowering the mean BP is not sufficient to combat and prevent the progression of cognitive decline.

Ninth, specific between group differences, such as gender and ethnicity, cannot be accounted for by mean BP with regards to their increased risk of stroke. However, BPV may explain the higher incidence of stroke in females (Rothwell et al., 2010) and black people (Heuschmann, Grieve, Toschke, Rudd, & Wolfe, 2008). Lastly, the surge in BP post-stroke is suggestive of BP instability, and could be a result of similar surges in the past (Rothwell, 2010).

All of these lead to the conclusion that usual BP and mean BP are insufficient as the sole predictive factors for vascular events, cognitive impairment and the incidence of

dementia. However, recent research has shown that measuring BPV seems to be a much more significant predictor for all of these cases (Alpérovitch et al., 2014; Rothwell, 2010; Sabayan et al., 2013).

1.3.3 Blood pressure variability

In recent studies, BPV, as a measure, has been found to be a potential predictor of cognitive decline (Conway et al., 2015; Rothwell, 2010), but the extent of this significance is unknown. The extent of variability is usually positively associated with mean BP, but can also be independent. It is measured as either the overall variability during a set time limit (calculated with standard deviation (SD), a coefficient of variation (CV)), or as the mean absolute difference between adjacent readings (Rothwell, 2010). Variability can be studied over periods of hours on ambulatory monitoring, over minutes during a clinic visit, and over days, weeks, months, and years with home BP monitoring or repeated clinic visits (Rothwell et al., 2010).

BPV can be divided into short-term BPV (e.g. a 24 hour cycle with home monitoring or ABPM) and long-term BPV (e.g. clinic visit-to-visit BPV over weeks, months, or years), both of which are associated with negative outcomes when fluctuations are high. Mechanisms of short-term BPV have been attributed to humoral (e.g. viscosity of blood), neural (increased sympathetic drive and reduced cardiopulmonary reflexes), and environmental factors (e.g. psychological stress, sleep, changes in posture, and physical activity)(Parati, Ochoa, Lombardi, & Bilo, 2013). Conversely, knowledge on the mechanisms of long-term BPV is still limited to concepts such as increased arterial stiffness, poor BP control of long time patients of elevated BP, and seasonal changes (Parati et al., 2013). Negative outcomes of these fluctuations involve depression (Scuteri et al., 2009), anxiety, and hostility (Virtanen et al., 2003) in the short-term, and cognitive impairment in the long-term (Yano et al., 2014). Both are also independently associated with cognitive decline, dementia (Alpérovitch et al.,

2014; Oishi et al., 2017; Yano et al., 2014), and vascular events (Parati et al., 2013; Rothwell, 2010).

1.4 Dementia, cognitive decline, and vascular disease

Longitudinal studies have demonstrated that BPV increases with age, and has a positive correlation with the volume of white matter hyperintensity, which is an indicator for CSVD (Brickman, Reitz, Luchsinger, & et al., 2010). CSVD and many other cardiovascular events are risk factors for cognitive decline, especially when measured with the CV (Au, Massaro, Wolf, & et al., 2006; Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2012).

Emerging literature considers BPV to have potential value, both in predicting impending cognitive decline and vascular events, as well as a possible target for clinical intervention and modulation in the treatment of irregular BP.

1.5 Current study

1.5.1 Problem statement

Current literature has demonstrated that there is a link between increased BPV, cognitive impairment, and incident dementia (Alpérovitch et al., 2014). BP is the precursor to all vascular diseases. It is the main risk factor that can be modified to reduce organ damage, especially in the brain following a stroke. Despite this knowledge, standard antihypertensive treatments have not yet lead to a decline in the risk of dementia and other cognitive impairment (Lattanzi et al., 2014; Williams, 2009). There is also no known optimal BP range for brain health. Hence, our current understanding of how to mitigate dementia onset and progression is sorely lacking.

Although BPV and cognitive impairment have been researched expansively, there is no consensus, to date, on the clinical relevance of this association (Dolan & O'Brien, 2015). This review will attempt to clarify this via a meta-analysis, which will involve a systematic review of all existing literature based on specific inclusion and exclusion criteria. The outcomes of all included studies will be compiled, integrated, and then summarized into a standard effect size. This will allow for an increase in collective precision and power, when compared to any single primary study (Gopalakrishnan & Ganeshkumar, 2013). This review may have clinical implications for the diagnosis, prevention, and treatment of vascular diseases (e.g. hypertension) and injuries (e.g. stroke), as well as dementia and cognitive impairment. We live in an increasingly ageing population, and this is true on a global level. This means that the burden of disease, both dementia and vascular, is only going to increase. Thus, it is critical to investigate BPV, and its relationship with dementia and cognitive impairment.

1.5.2 Aims

Recent studies have explored the link between BPV and dementia and cognitive impairment. However, the exact extent and magnitude of this association, regarding the SBP and DBP and their individual and collective influences on the incidence and rate of dementia and cognitive impairment remains is controversial. This review will strive to compile existing literature into a cohesive argument, following the standards set by a meta-analysis.

The primary aims of this review are (1) to assimilate and investigate all available literature concerning the relationship between BPV and dementia and cognitive impairment, (2) to investigate and identify the magnitude of the relationships of dementia and cognitive impairment with BPV, in the forms of SBP and DBP associations of both binary (dementia and cognitive impairment) outcomes, and (3) to identify the heterogeneity of the studies.

2. Methods

2.1 Literature search

The review protocol was registered on PROSPERO (CRD42017081977). Four electronic databases (Embase, PsychINFO, PubMed, and Scopus) were searched from inception to June 2018 to source relevant studies examining BPV, dementia, and cognitive impairment in an adult population. A research librarian was consulted prior to conducting this search to refine search terms and to ensure accuracy. Key terms related to BPV (e.g. 'blood pressure variability', 'ambulatory blood pressure monitoring'), dementia and cognitive impairment ('dementia', 'cognitive impairment', 'cognitive decline'), and neuropsychological assessments to identify mental deterioration ('neuropsychological test', 'neuropsychological assessment', 'MMSE'). A search term logic grid was devised for each database tailored to their specific indexing term systems (for full logic grids, see Appendix A).

To ensure thorough reporting, no restrictions were set on the date of publication and the search terms were kept fairly broad, including both 'blood pressure variability' and 'hypertension' more generally to account for alternate labels for BPV and cognitive impairment measures. Automatic email alerts for each database were set up to ensure new studies published between June and August 2018 meeting the key terms were also covered.

2.2 Study eligibility

Studies were included if they recruited individuals that (a) were adults (defined as ≥ 18 years), (b) had a measure of incident dementia, cognitive impairment, or cognitive decline (c) if they had a BPV metric, or sufficient data to calculate a BPV metric, (d) and were published in a peer-reviewed journal, to ensure methodological thoroughness and consistency. Studies were excluded if they were (a) case studies, (b) reviews, (c) editorials, (d)

commentaries, (e) animal studies, or (f) on an underage population, as all of these would lack useable data. They were also excluded if they were (g) not published in English, (h) cancer studies, (i) gene or genetic studies, (j) surgical intervention studies (e.g. renal denervation), (k) had a history of sub-acute stroke in the past four weeks, (l) or had been diagnosed with Alzheimer's at baseline.

The literature search yielded 6800 publications (Embase = 3961; PsychINFO = 322; PubMed = 980; Scopus = 1537), of which 1723 duplicates were removed, leaving 5077 publications for screening (see figure flowchart). One additional study was added, which met criteria, but was not available through the search. Titles and abstracts were evaluated on previously defined inclusion and exclusion criteria, and a further 5039 publications were removed. A set of 38 full-text articles were reviewed for eligibility based on the availability of sufficient data to calculate BPV. A total of 13 studies were identified for inclusion through this process. To ensure that there was no confounding due to the overlapping of samples, eligible studies were checked to make certain that only studies, with the same samples, which reported different outcomes, were included. Two authors were contacted to provide additional results for inclusion. These inclusion and exclusion criteria assessments were conducted by the research author, in discussion with a senior researcher, for a final sample which consisted of 11 studies.

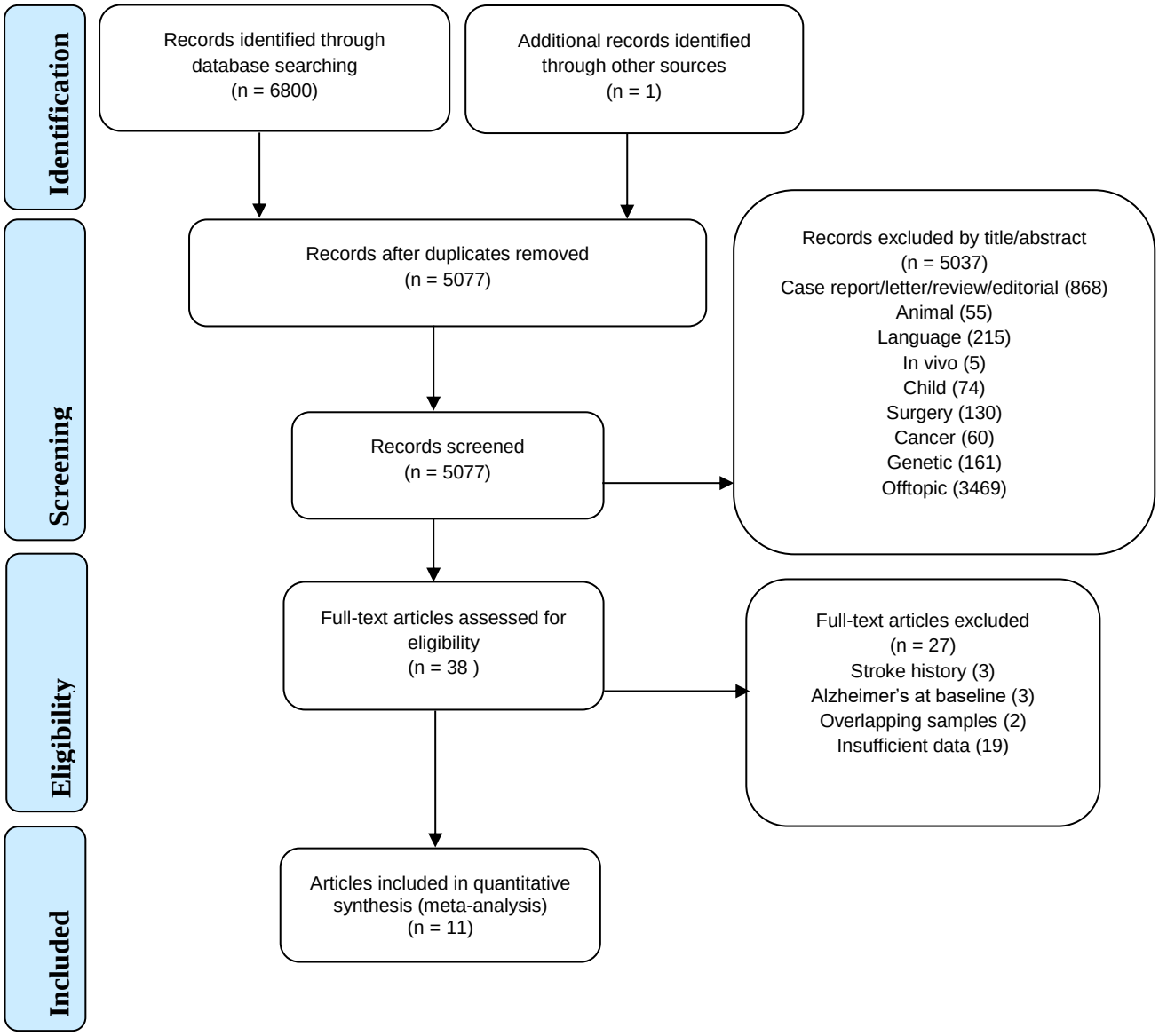


Figure 1. PRISMA flow chart of article selection

2.3 Data extraction

In keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, a data extraction spreadsheet was created to compile data for each study (Liberati, Altman, Tetzlaff, & et al., 2009). The data obtained for each study, as much as possible, included:

a. Study characteristics: Country; Study design; Sample size; Types of neuropsychological assessments used.
b. Sample demographic characteristics: Mean age (SD); Gender ratio; Percentage treated with antihypertensive drugs.
c. BPV specific information: Method of BP measurement; Interval between consecutive measurements; Total duration of consecutive measures; BPV calculation method
d. Follow-up information: Length of follow-up; Number, or %, of participants who completed the follow-up.

2.4 Data preparation

Data were prepared in several steps. First, BP data, both SBP and DBP, associated with dementia and cognitive impairment was extracted from the studies, and standardized so that there would be internal consistency. These data included SDs of BP, CVs, hazard ratios, risk ratios, and odds ratios, and 95% confidence intervals (CI). In the case of mean SBP and DBP, the ratios were standardized to 10mmHg for SBP and 5mmHg for DBP. In the circumstances of the absence of these particular formats of results, BPV metrics were calculated from the raw data available in the paper.

2.5 Risk of bias assessment

According to the PRISMA guidelines, the risk of bias of individual studies needs to be assessed to gauge the strength and validity of the evidence (Liberati et al., 2009). This is due to the varying methodology between studies, as well as different reporting styles. The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias of each individual study. This tool is recommended by Cochrane for evaluating the risk of bias in studies that did not use randomisation. It assesses bias in confounding, participant selection, interventions, deviation, missing data, measurement of outcomes, and reporting bias (Sterne et al., 2016). The judgments range from low, moderate, serious, critical risk of bias, and no information (Sterne et al., 2016).

A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used to self-assess the risk of bias and quality of this review. It consists of 16 items, which can be answered as ‘Yes’, ‘Partial yes’, or ‘No’. There is no quantitative score generated. Instead, the AMSTAR gives an overall confidence rating of the review from the following: high, moderate, low, and critically low. This rating suggests the overall confidence in the results of the review (Shea et al., 2017).

2.6 Statistical analyses

All effect size analyses were conducted using Review Manager (RevMan), version 5.3. A random effects model was used, to reach a relative risk estimate of the magnitude of the association between dementia and cognitive impairment, with the two BP subgroups. The estimates were weighted based on the inverse variance, to allow for the overall effect estimate to account for the higher variability in data that comes with smaller samples. The 95% CIs of the effect estimates of each study were also calculated, to accurately indicate the certainty and precision of each estimate. This is because narrower CIs represent higher accuracy. Forest plots were produced to represent the distribution of effect estimates for all

the studies, as well as to reach a pooled estimate. This would also allow a scaled representation of each study, based off their sample size and power (Borenstein, Hedges, Higgins, & Rothstein, 2009).

This review used three measures of heterogeneity to test for variation in outcomes between studies. The tau squared statistic estimates the variation in true effect sizes, and also assigns weighting to the studies (Borenstein et al., 2009). The chi-squared statistic, also known as Cochran's Q or the Q statistic, tests the significance of heterogeneity by comparing the variation to error in the studies (Borenstein et al., 2009). Lastly, the I^2 statistic is a relative measure for the extent heterogeneity, which is useful for determining the value of further subgroup analyses. It describes the variation percentage that is due to heterogeneity, and not chance (Borenstein et al., 2009). For this review, the I^2 >25% was considered an adequate value of heterogeneity (Fletcher, 2007).

Publication bias may be possible due to the issue of non-significant results having lower chances of being published, as well as the exclusion of non-English studies. To reflect this, a funnel plot was produced to detect bias, which can be indicated by an asymmetrical graphic (Sedgwick, 2013).

3. Results

3.1 Study and sample characteristics

Ten journal articles and one conference abstract, published between 2007 and 2018, were included in this meta-analysis. The primary countries of recruitment were Japan ($N_{studies}$=5) (Fujiwara, Hoshide, Kanegae, Eguchi, & Kario, 2018; Matsumoto et al., 2014; Nagai et al., 2012; Oishi et al., 2017; Sakakura, Ishikawa, Okuno, Shimada, & Kario, 2007), France ($N_{studies}$=2) (Alpérovitch et al., 2014; Tully, Debette, & Tzourio, 2018), and the Netherlands ($N_{studies}$=2)(van Middelaar, van Dalen, van Gool, Moll van Charante, & Richard, 2016; van Middelaar et al., 2018), alongside a single study from the United Kingdom (McDonald, Pearce, Kerr, & Newton, 2017). Böhm et al. (2015)'s multinational study involved recruitment from 40 countries. Apart from a cross-sectional study by Sakakura et al. (2007), all other studies had a cohort design.

Cognitive impairment and decline were measured most commonly by the Mini Mental State Examination (MMSE), which was used as a screening tool in all the studies. Other measures included the Cambridge Cognition Examination (CAMCOG), Isaac's Set Test, Global Deterioration Scale (GDS), Revised Hasegawa Dementia Scale (HSD-R), Trail Making Test, Benton Visual Retention test, and Finger-tapping test. Fujiwara et al. (2018)'s study focused specifically on the working memory assessment subsection of the MMSE. Complete data extraction results on study and sample demographics can be found in Appendix B.

3.2 Risk of bias

The risk of bias of this review was assessed by AMSTAR, and reported to be a moderate quality review. The risk of bias of the individual studies was assessed by ROBINS-I. All of the studies classified as low risk of bias, except for van Middelaar et al. (2016), which was an abstract and lacked sufficient data. Figure 2 shows a summary of the risk of bias classifications, in which each item is presented as a percentage across all included studies.

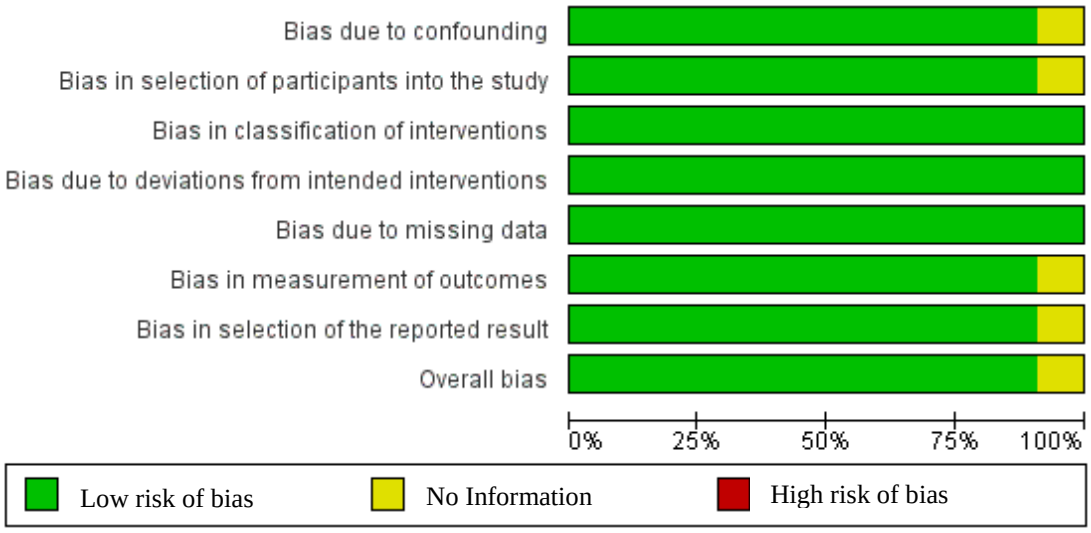


Figure 2. Risk of bias graph.

3.3 Results of individual studies

The included studies can be divided into two subsets based on the outcomes they are measuring: (1) dementia, and (2) cognitive impairment. Alpérovitch et al. (2014) stated that individuals, who had suffered high BPV for 4 years or more, were at significantly higher risk for dementia, whereas the mean BP was not significantly predictive of this association. Oishi et al. (2017) also found results supporting the significance of BPV's incident dementia predictive ability. van Middelaar et al. (2018) reported BPV as a noteworthy predictor of cognitive decline, but were unable to find significant associations with incident dementia. Of

the eight studies that measured cognitive impairment as an outcome, all showed a significant relationship between higher BPV and cognitive decline, except for van Middelaar et al. (2016).

3.4 Relationships between BPV, dementia and cognitive impairment

3.4.1 Dementia

The relationship between BPV and dementia can be seen in Tables 2 and 3. There is no significant association between BPV, both systolic ($p = 0.15$) and diastolic ($p = 0.1$), and dementia. The same can also be seen in the association between mean BP and incident dementia. There is also no significant difference in predictive power of incident dementia between BPV and mean BP (systolic: $p = 0.11$, diastolic: $p = 0.18$). However, there may be some imprecision in these pooled estimates considering the few contributing studies.

Table 2

Association between systolic BPV and SBP and dementia

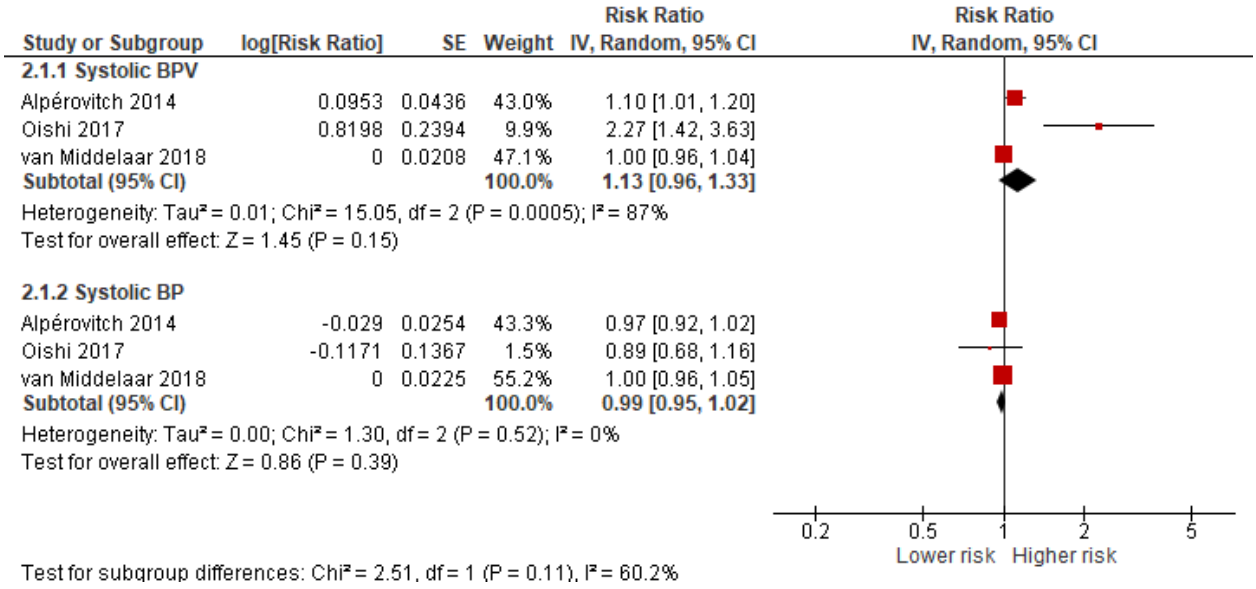
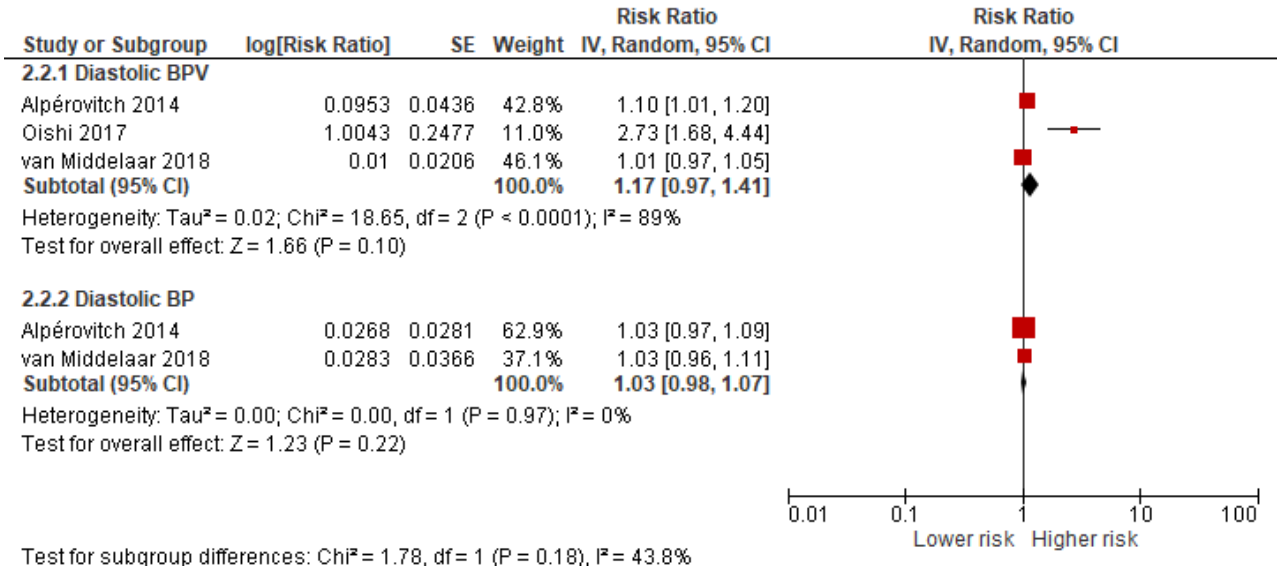


Table 3

Association between diastolic BPV and DBP and dementia



3.4.2 Cognitive impairment

The relationship between BPV and cognitive impairment can be seen in Table 4 and 5. There is a significant association between systolic BPV and cognitive impairment ($p = 0.01$), but not diastolic BPV ($p = 0.39$). Neither systolic nor diastolic mean BP have significant associations with cognitive impairment. Although systolic BPV has significant predictive power, there is no statistically significant difference between BPV and mean BP (systolic: $p = 0.39$, diastolic: $p = 0.91$).

3.4.3 Combined results

The relationship between BPV and overall cognitive decline (combines outcomes of dementia and cognitive impairment) can be seen in Table 6 and 7. There is a significant association between systolic BPV and cognitive decline ($p = 0.001$), but not diastolic BPV ($p = 0.09$). Neither systolic nor diastolic mean BP have significant associations with cognitive decline. There is also no statistically significant difference in the predictive abilities of diastolic BPV and mean DBP. However, systolic BPV has significantly better predictive power over cognitive decline than mean SBP ($p = 0.006$).

No data could be extracted or calculated for the following values: (1) Böhm et al. (2015)'s SBP and DBP values, (2) McDonald et al. (2017)'s SBP and DBP values, (3) Oishi et al. (2017)'s DBP values, (4) Sakakura et al. (2007)'s DBP and DBPV values, and (5) van Middelaar et al. (2016)'s SBP, DBP, and DBPV values. Therefore, these were not represented in the forest plots.

Table 4

Association between systolic BPV and SBP and cognitive impairment

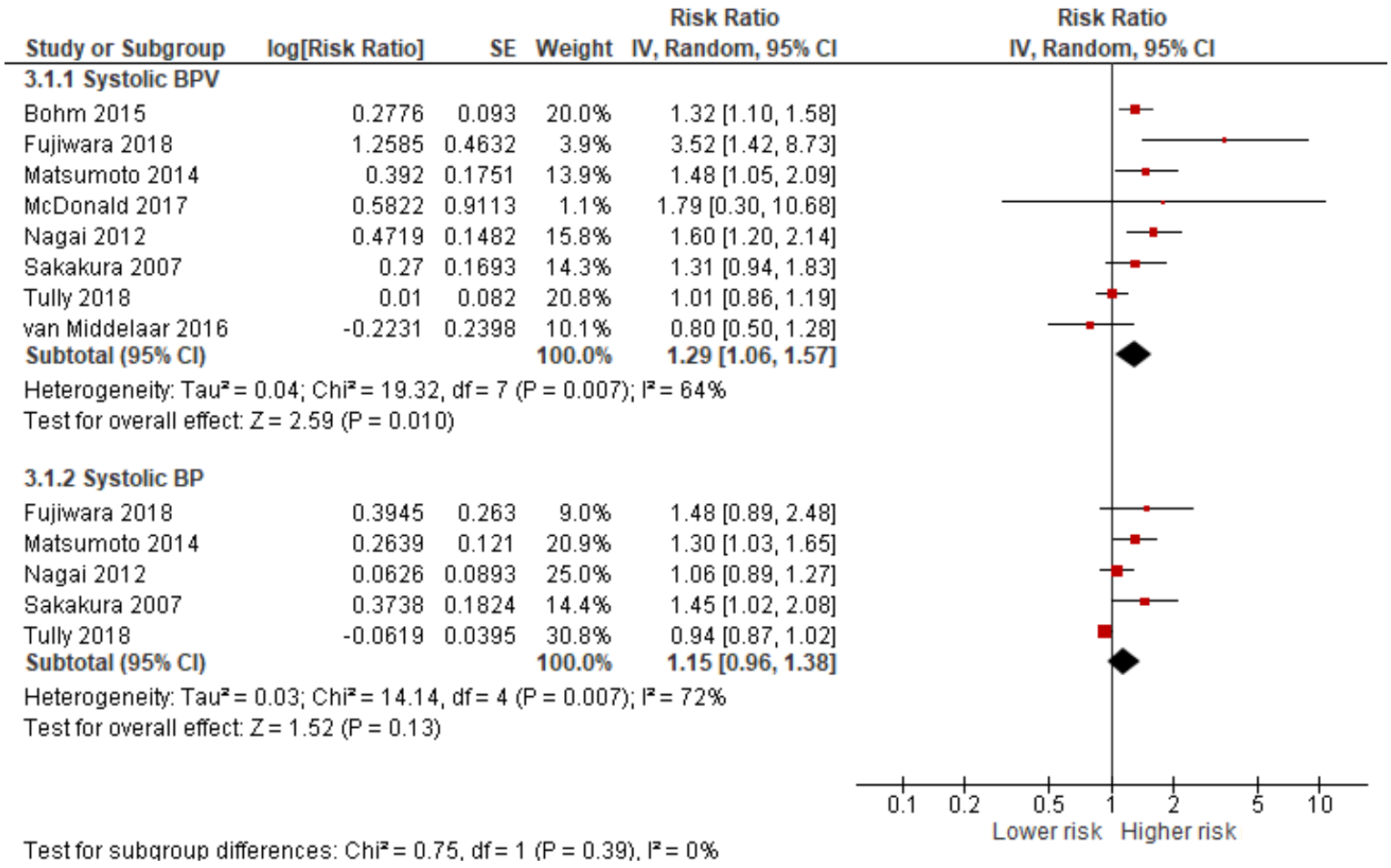


Table 5

Association between diastolic BPV and DBP and cognitive impairment

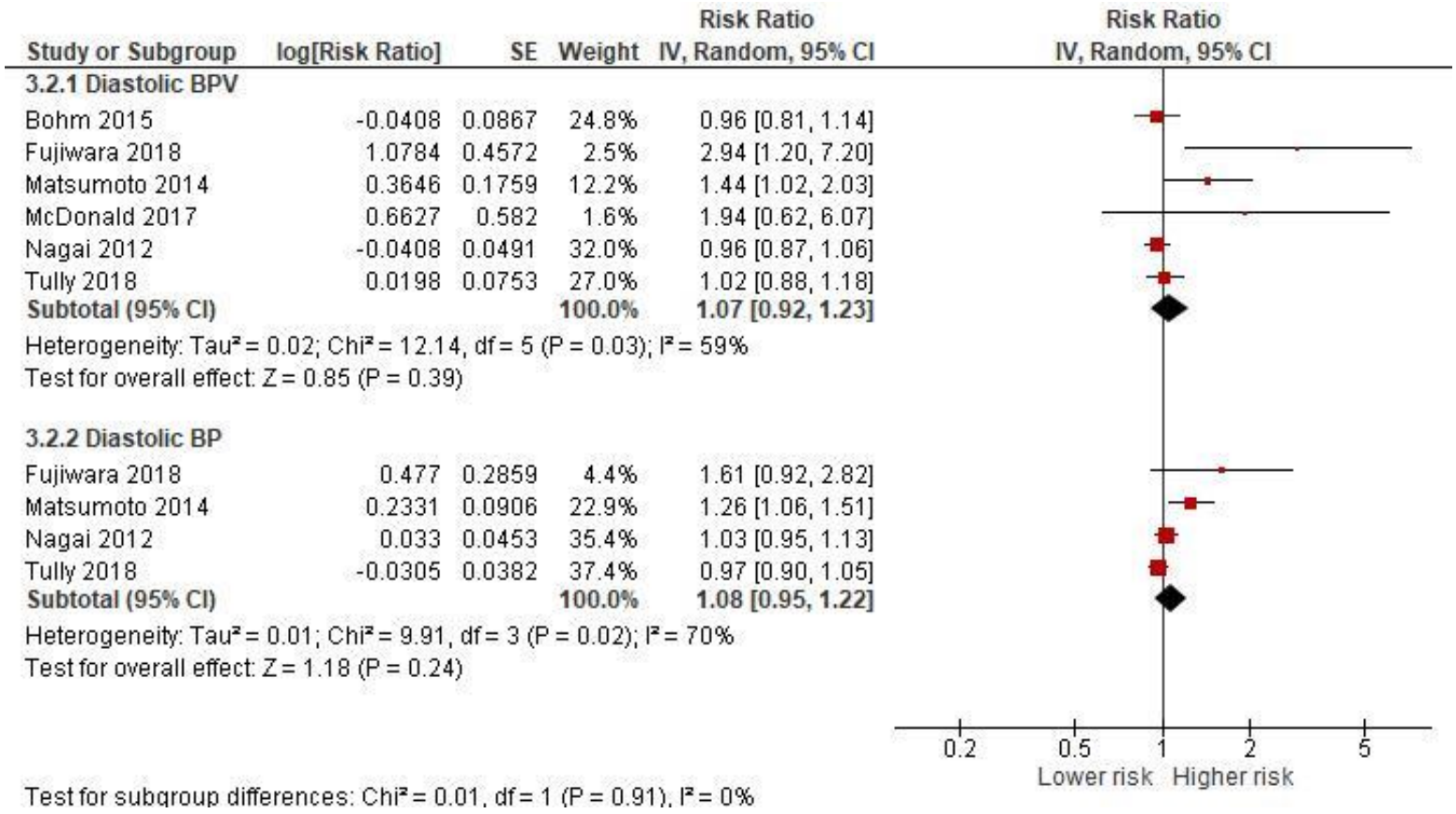


Table 6

Association between systolic BPV and SBP and overall cognitive decline

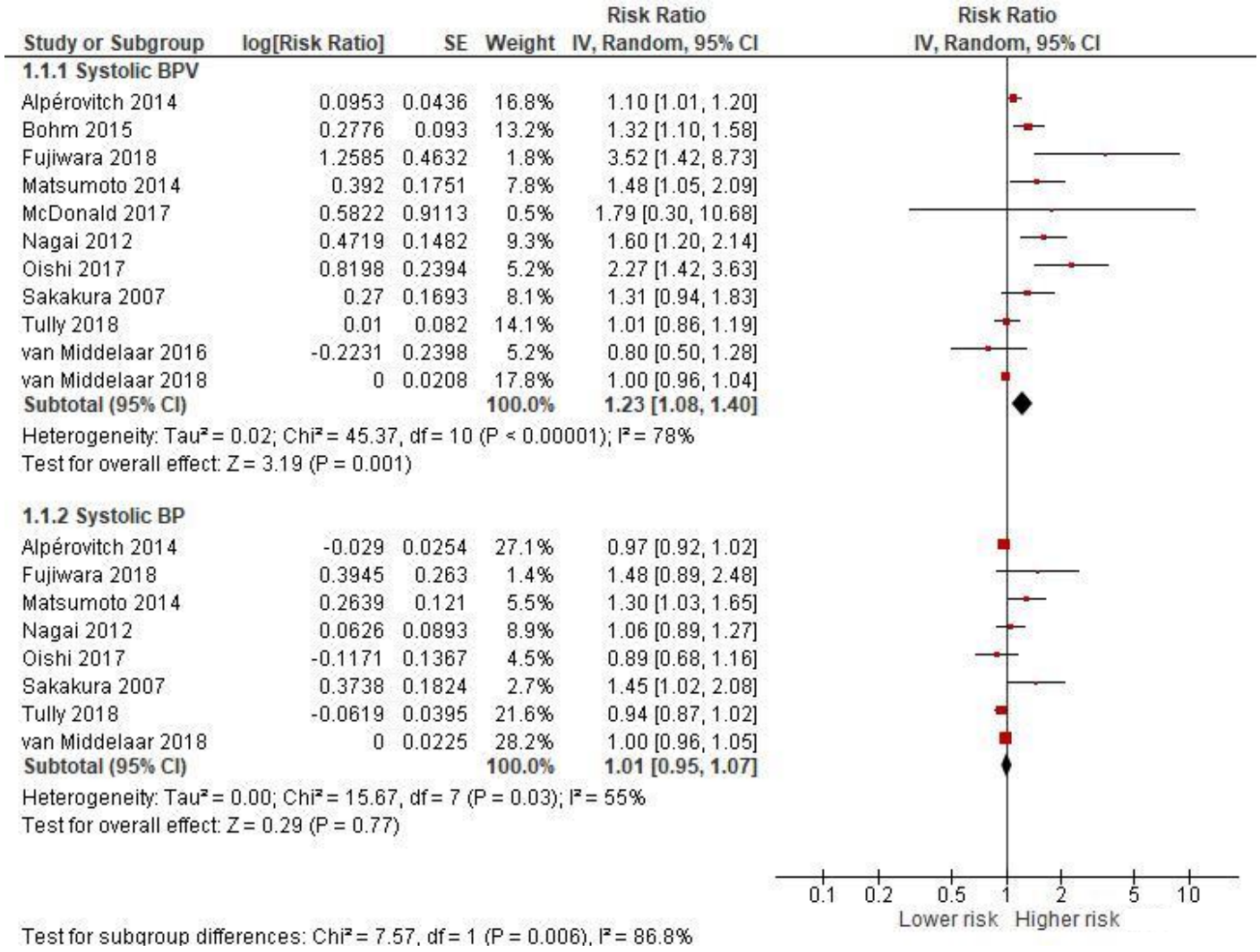
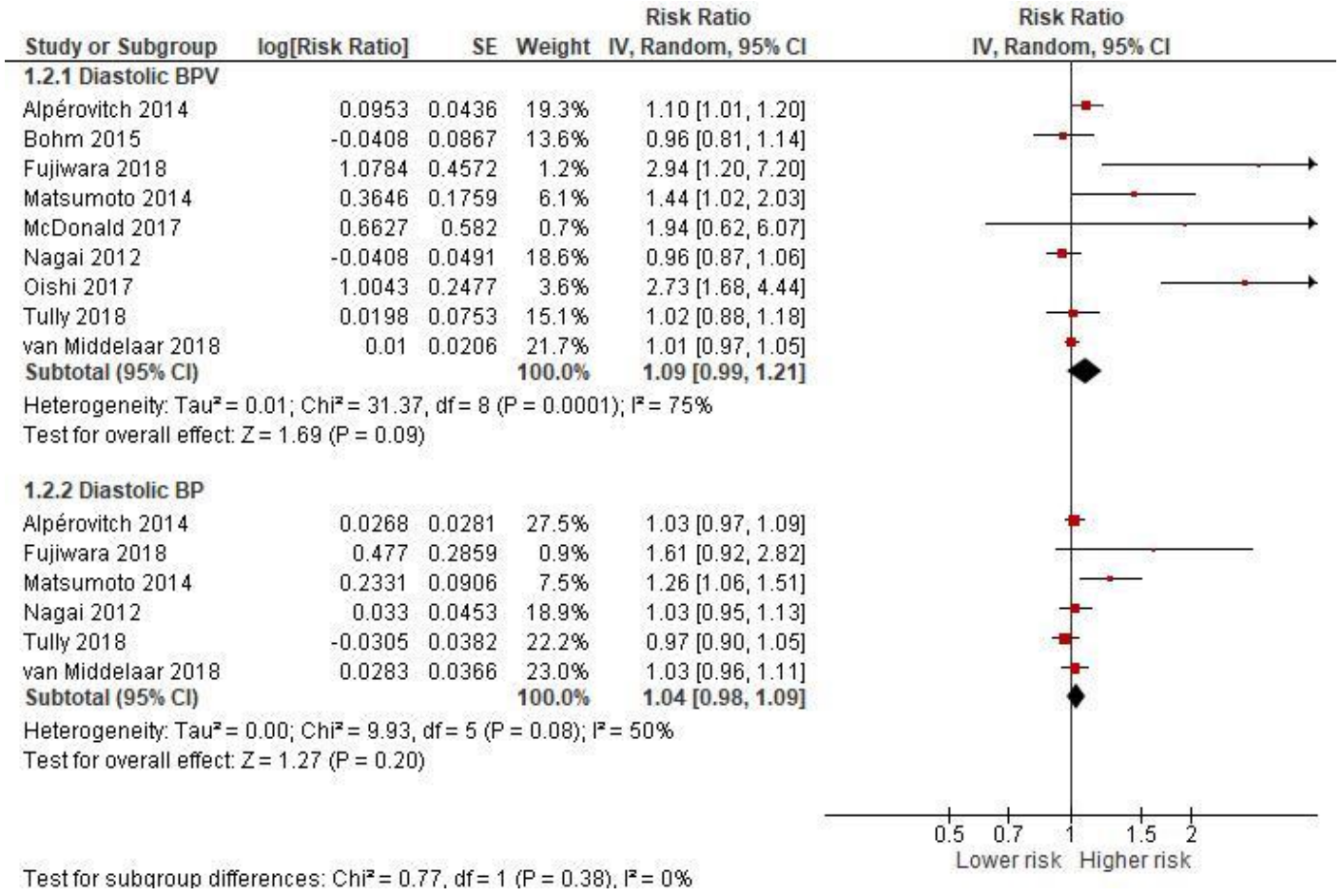


Table 7

Association between diastolic BPV and DBP and overall cognitive decline



3.5 Heterogeneity

Significant heterogeneity, by means of the Q statistic (chi-squared statistic), was observed for all aspects of BPV in relation to dementia, cognitive impairment, and overall cognitive decline, which suggests that the true effect sizes varied across studies. However, results for the mean BP were a little more diverse. Overall, mean SBP had significant heterogeneity ($p = 0.03$), but DBP did not ($p = 0.08$). With incident dementia as an outcome, there was no significant heterogeneity between groups. However, with the outcome of cognitive impairment, both SBP and DBP displayed significant heterogeneity ($p = 0.007$, $p = 0.02$ respectively). This is supported by the corresponding I^2 statistics, which were high (i.e. $I^2 > 50\%$) when the Q statistic was significant. The tau squared statistic estimates the variation in true effect sizes (Borenstein et al., 2009), was the largest for mean SBP ($Tau^2 = 0.03$) and SBPV ($Tau^2 = 0.04$) against cognitive impairment outcome (Table 4).

3.6 Publication bias

Figures 3 shows the funnel plot for SBPV and SBP in overall cognitive decline. This plot was created as the SBPV section consists of more than 10 studies, which is the minimum recommended by Cochrane. Figure 3 shows slight asymmetry which suggests that publication bias is present. However, it should be noted that there is a possibility of this being superficial asymmetry due to the small number of studies.

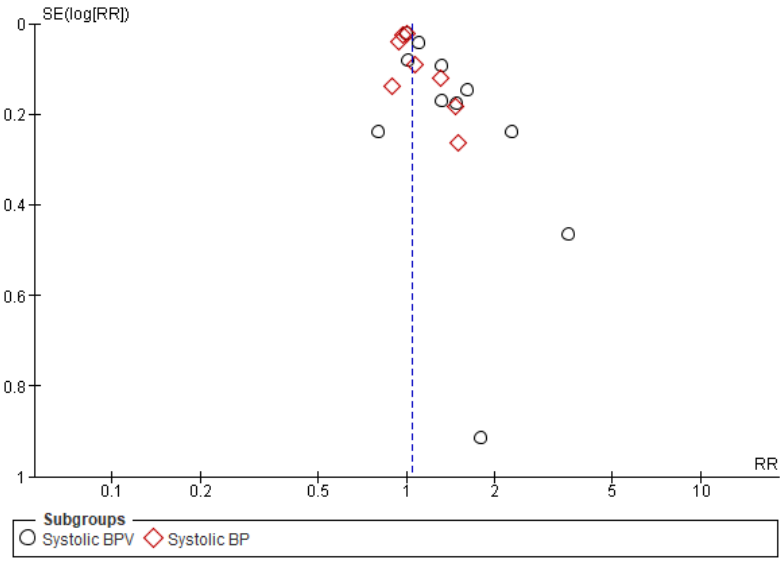


Figure 3. Funnel plot of systolic BPV and SBP associated with overall cognitive decline.

Note: Risk ratio (RR), standard error (SE),

4. Discussion

4.1 Key findings

Eleven studies, comprising a pooled sample of 52,784 participants, were identified to undergo a systematic review and meta-analysis on the association between BPV and dementia and cognitive impairment. The objective of the present review was to collate existing literature and identify the magnitude of the links of dementia and cognitive impairment with BPV, in the forms of SBP and DBP associations of both binary (dementia and cognitive impairment) outcomes. The main results of this meta-analysis show that there is a significant association between systolic BPV and cognitive impairment, as well as overall cognitive decline. However, this association cannot be found with diastolic BPV. These findings will be discussed in detail below, along with the clinical implications and future research directions.

4.1.1 Dementia, cognitive impairment, and overall cognitive decline

The results show that there is no significant association between BPV and incident dementia. This is contrary to the literature which suggests that these two variables do have a relationship (Alpérovitch et al., 2014; Rothwell, 2010; Sabayan et al., 2013). However, these may be imprecise due to a lack of studies, as there were very few studies focusing on the influence BPV has on dementia only ($N_{studies} = 3$).

With the outcome of cognitive impairment ($N_{studies} = 8$), a significant association was found between systolic BPV and cognitive impairment, which supports concepts currently in existing literature (Rothwell, 2010; Sabayan et al., 2013). A potential explanation for finding significance with this outcome and not incident dementia is the large difference in pooled sample sizes.

When systolic BPV was evaluated against the combined outcomes of dementia and cognitive impairment, the relationship was significant. This is consistent with the current literature on the predictive power of systolic BPV as a risk factor of cognitive decline and impairment (Conway et al., 2015; Rothwell, 2010; Sakakura et al., 2007). However, this finding may also mirror a potentially higher rate of neurocognitive disorders due to participant samples having other risk factors for cognitive decline. Naismith, Norrie, Mowszowski, and Hickie (2012) have discussed how late life depression and cerebrovascular diseases are associated, as well as how they are both risk factors for cognitive decline.

In this review, systolic BPV was found to have a significant association with cognitive decline, but diastolic BPV was not. This is also consistent with previous studies, which suggests that while diastolic BPV may be associated with cognitive decline, it is not as significant a predictor as systolic BPV (Tully et al., 2018)

4.1.2 BPV and mean BP

With emerging research on the increasing predictive power of BPV, mean BP may not be the sole indicator of vascular events and irregular BP in future clinical settings. This review compared the systolic and diastolic aspects of BPV and mean BP to clarify their associations with incident dementia and cognitive impairment.

Regarding the heterogeneity of the studies, all aspects of BPV were significant in relation to incident dementia, cognitive impairment, and overall cognitive decline. This showed that there was no overlapping of samples. However, with regards to mean BP, DBP only displayed significant heterogeneity with cognitive impairment as an outcome, while SBP did the same with cognitive impairment and overall cognitive decline. The lack of significant values of heterogeneity could be attributed to the small number of studies in this analysis, rather than proving homogeneity of the samples.

Considering publication bias (Figure 3), the majority of studies are clustered at the tip of the funnel plot, which is a nod at the large sample sizes of the studies. This is due to larger sample sizes having higher power and precision. Asymmetry of a funnel plot can be attributed to chance, reporting bias, methodology, and heterogeneity (Sterne et al., 2011). In this case, the heterogeneity is high, with significance reported by the Q statistic and $I^2 > 75\%$, which may have influenced asymmetry. However, it is also understood that the stringent inclusion and exclusion criteria may also have played a part in contributing to publication bias (i.e. peer-reviewed, English).

There was no significant difference in the associations of mean BP and BPV with incident dementia or cognitive impairment, despite systolic BPV being a significant risk factor of the latter. However, when it came to overall cognitive decline, the difference between systolic BPV and mean SBP was statistically significant ($p = 0.006$). Matsumoto et al. (2014) have also demonstrated that while all of their SBP readings were associated with cognitive decline, the association only reached significance when the systolic BPV was used. This has some interesting implications for clinical settings that will be discussed in the section below.

Interestingly, standalone BP means (systolic and diastolic) have shown no significant association with any of the outcomes. This is strange as a wealth of literature on elevated BP and hypertension has earmarked mean SBP as a significant risk factor for vascular events, cognitive impairment, and cognitive decline (Bermejo-Pareja et al., 2010; Gifford et al., 2013; Kececi Savan et al., 2016). From this, it can be tentatively assumed that mean BP will be joined by BPV in future clinical diagnosis, screening, and intervention.

4.2 Clinical implications

The results of this analysis have some key clinical implications. BP is the precursor to all vascular diseases, as well as the main modifiable risk factor. If correctly modulated, it can reduce organ damage, especially in the brain following a stroke. Despite this knowledge, clinical and pharmaceutical treatments have not been able to prevent or mitigate dementia onset and cognitive decline progression (Lattanzi et al., 2014; Williams, 2009). An optimal BP range for brain health, in which the risk or rate of cognitive decline decreases, is still unknown (Iadecola et al., 2016).

Some studies have suggested that a high BPV, specifically systolic BPV, increases the risk of stroke and other vascular events, despite an individual's mean SBP being in the normal range (Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2011; Ogliari et al., 2016; Rothwell et al., 2010). As mentioned earlier, BPV increases with age and is positively linked with CSVD (Brickman et al., 2010) which, in turn, along with other cardiovascular events are risk factors for cognitive decline (Au et al., 2006; Nagai et al., 2012).

The rate of cognitive decline, for people already afflicted with dementia and cognitive impairment, is also faster for those who have higher BPV(Lattanzi et al., 2014), which can be seen on cognitive tests assessing attention, processing speed, and memory (Sabayan et al., 2013).

In general, this is relevant to both clinicians and researchers. The extent of the knowledge on this topic is not sufficient to keep up with an increasingly ageing population, which will increase the prevalence and incidence of cognitive impairment and dementia. In the future, mean BP will not be the sole assessment of irregular BP. BP monitoring systems, such as ABPM or home BP monitoring may become more popular as research has already shown that they result in a more accurate representation of a patient's BP level and

fluctuations which, in turn, allow for better diagnosis (Matsumoto et al., 2014; Oishi et al., 2017).

In particular, it is important to understand the relationship between mean BP and BPV, to allow for modulation interventions of the latter. Currently, antihypertensive treatments have been known to have no significant influence or control over BPV, both short-term and long-term (Lattanzi et al., 2014; Williams, 2009). Answering this question would enable further clinical progress not only in the neurocognitive and neurodegenerative disorders, but also in the field of cardiovascular health.

4.3 Limitations

Several limitations were evident in this review. First, there is the possibility that not all relevant studies may have been included. Every effort was taken to ensure maximal coverage (i.e. broad search terms, search strategies, multiple databases). Nevertheless, the rigorous inclusion (i.e. peer-reviewed journals) and exclusion (i.e. non-English studies) criteria mean that fewer studies were included. Recently, Jackson and Turner (2017) stated that a meta-analysis with less than five studies in a random-effects model might not have any more power than the original studies. As a result, the sub-analysis of incident dementia against BPV ($N_{studies} = 3$) does not have a strong foundation.

Second, moderator analyses were not conducted to clarify the sources of heterogeneity. This is partly related to the lack of studies identified. The Cochrane Collaboration has set a standard for subgroup analysis, which suggests a minimum of ten studies required to detect true differences between groups (Fu et al., 2011), and to avoid the pitfall of being underpowered. However, recently it has been demonstrated that a minimum of twenty studies may be required (Rubio-Aparicio, Sánchez-Meca, López-López, Botella, &

Marín-Martínez, 2017) to achieve a reliable and satisfactory power level to detect between group differences.

Third, all of the studies used the MMSE as a screening tool. While there are many advantages to it, such as its extensive usage and prominent evidence base, the disadvantages are starting to outweigh them. Some of these are its lack of standardisation, expense, unsuitability for individuals who are illiterate, and most importantly, its limited effectiveness in detecting cognitive impairment and dementia (Carnero-Pardo, 2014; Devenney & Hodges, 2017; Scazufca, Almeida, Vallada, Tasse, & Menezes, 2009). There is a need for a more developed and insightful neurocognitive tool to replace the MMSE in both research and practice.

4.4 Conclusion

BP is inextricably linked with cognition and the health of the brain. It is the most easily modifiable risk factor to prevent further triggers to organ damage after a stroke. The key finding of this study is a significant association between systolic BPV and cognitive impairment and decline.

The discoveries in this review are valuable for health professionals seeking to improve diagnosis, prevention, and treatment of vascular diseases (e.g. hypertension) and injuries (e.g. stroke), as well as dementia and cognitive impairment. It may also aid in healthcare policy regarding patient BP monitoring and modulation. For the general population, this review can serve as a motivation to home monitor BP for irregular fluctuations, as this is easy to implement even on an individual level. This can also serve as a stepping stone for informing future research on clinical treatments and interventions to mitigate dementia onset and slow cognitive decline, as well as to bring an important vascular risk factor under control.

References

Alpérovitch, A., Blachier, M., Soumaré, A., Ritchie, K., Dartigues, J.-F., Richard-Harston, S., & Tzourio, C. (2014). Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimer's & Dementia, 10*(5, Supplement), S330-S337. doi:https://doi.org/10.1016/j.jalz.2013.05.1777

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed ed.). Arlington, VA: American Psychiatric Association.

Au, R., Massaro, J. M., Wolf, P. A., & et al. (2006). Association of white matter hyperintensity volume with decreased cognitive functioning: The framingham heart study. *Archives of Neurology, 63*(2), 246-250. doi:10.1001/archneur.63.2.246

Australian Bureau of Statistics. (2017). Causes of Death, Australia, 2016. Retrieved from http://www.abs.gov.au/ausstats/abs@.nsf/mf/3303.0

Bermejo-Pareja, F., Benito-León, J., Louis, E. D., Trincado, R., Carro, E., Villarejo, A., & de la Cámara, A. G. (2010). Risk of Incident Dementia in Drug-Untreated Arterial Hypertension: A Population-Based Study. *Journal of Alzheimer's Disease, 22*(3), 949-958. doi:10.3233/JAD2010101110

Böhm, M., Schumacher, H., Leong, D., Mancia, G., Unger, T., Schmieder, R., . . . Yusuf, S. (2015). Systolic blood pressure variation and mean heart rate is associated with cognitive dysfunction in patients with high cardiovascular risk. *Hypertension (Dallas, Tex. : 1979), 65*(3), 651. doi:10.1161/HYPERTENSIONAHA.114.04568

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to Meta-Analysis*. Chichester, UK: Chichester, UK: John Wiley & Sons, Ltd.

Brickman, A. M., Reitz, C., Luchsinger, J. A., & et al. (2010). Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Archives of Neurology, 67*(5), 564-569. doi:10.1001/archneurol.2010.70

Brondolo, E., Grantham, K., Karlin, W., Taravella, J., Mencia-Ripley, A., Schwartz, J., . . . Contrada, R. (2009). Trait Hostility and Ambulatory Blood Pressure Among Traffic Enforcement Agents: The Effects of Stressful Social Interactions. *J Occup Health Psychol, 14*(2), 110-121. doi:10.1037/a0014768

Burr, M. L., Dolan, E., O'Brien, E. W., O'Brien, E. T., & McCormack, P. (2008). The value of ambulatory blood pressure in older adults: the Dublin outcome study. *Age and Ageing, 37*(2), 201-206. doi:10.1093/ageing/afm193

Carnero-Pardo, C. (2014). Should the Mini-Mental State Examination be retired? *Neurología (English Edition), 29*(8), 473-481. doi:https://doi.org/10.1016/j.nrleng.2013.07.005

Colandrea, M. A., Friedman, G. D., Nichaman, M. Z., & Lynd, C. N. (1970). Systolic Hypertension in the Elderly: An Epidemiologic Assessment. *Circulation, 41*(2), 239-245.

Conway, K. S., Forbang, N., Beben, T., Criqui, M. H., Ix, J. H., & Rifkin, D. E. (2015). Relationship Between 24-Hour Ambulatory Blood Pressure and Cognitive Function in Community-Living Older Adults: The UCSD Ambulatory Blood Pressure Study. *American Journal of Hypertension, 28*(12), 1444-1452. doi:10.1093/ajh/hpv042

Dementia Australia. (2018, September 2018). Dementia Statistics. *About Dementia.* Retrieved from https://www.dementia.org.au/statistics

Devenney, E., & Hodges, J. R. (2017). The Mini-Mental State Examination: pitfalls and limitations. *Practical Neurology, 17*(1), 79.

Dolan, E., & O'Brien, E. (2015). Is It Daily, Monthly, or Yearly Blood Pressure Variability that Enhances Cardiovascular Risk? *Current Cardiology Reports, 17*(11), 93. doi:10.1007/s11886-015-0649-x

Fedorowski, A., Stavenow, L., Hedblad, B., Berglund, G., Nilsson, P. M., & Melander, O. (2010). Orthostatic hypotension predicts all-cause mortality and coronary events in

middle-aged individuals (The Malmö Preventive Project). *European Heart Journal, 31*(1), 85-91. doi:10.1093/eurheartj/ehp329

Fletcher, J. (2007). What is heterogeneity and is it important? *BMJ (Clinical research ed.), 334*(7584), 94-96. doi:10.1136/bmj.39057.406644.68

Fu, R., Gartlehner, G., Grant, M., Shamliyan, T., Sedrakyan, A., Wilt, T. J., . . . Trikalinos, T. A. (2011). Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *Journal of Clinical Epidemiology, 64*(11), 1187-1197. doi:10.1016/j.jclinepi.2010.08.010

Fujiwara, T., Hoshide, S., Kanegae, H., Eguchi, K., & Kario, K. (2018). Exaggerated blood pressure variability is associated with memory impairment in very elderly patients. *Journal of Clinical Hypertension, 20*(4), 637-644. doi:10.1111/jch.13231

Gąsecki, D., Kwarciany, M., Nyka, W., & Narkiewicz, K. (2013). Hypertension, Brain Damage and Cognitive Decline. *Current Hypertension Reports, 15*(6), 547-558. doi:10.1007/s11906-013-0398-4

Gifford, K. A., Badaracco, M., Liu, D., Tripodis, Y., Gentile, A., Lu, Z., . . . Jefferson, A. L. (2013). Blood Pressure and Cognition Among Older Adults: A Meta-Analysis. *Archives of Clinical Neuropsychology, 28*(7), 649-664. doi:10.1093/arclin/act046

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic reviews and meta-analysis: Understanding the best evidence in primary healthcare. *Journal of Family Medicine and Primary Care, 2*(1), 9-14. doi:10.4103/2249-4863.109934

Heuschmann, P. U. M. D. M. P. H., Grieve, A. P. P. D., Toschke, A. M. M. D. M. P. H. M., Rudd, A. G. F., & Wolfe, C. D. A. M. D. F. (2008). Ethnic Group Disparities in 10-Year Trends in Stroke Incidence and Vascular Risk Factors: The South London Stroke Register (SLSR). *Stroke, 39*(8), 2204-2210.

Hollocks, M. J., Brookes, R., Morris, R. G., & Markus, H. S. (2016). Associations between the Brief Memory and Executive Test (BMET), Activities of Daily Living, and Quality of Life in Patients with Cerebral Small Vessel Disease. *Journal of the International Neuropsychological Society, 22*(5), 561-569. doi:10.1017/S1355617716000187

Hugo, J., & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clinics in geriatric medicine, 30*(3), 421-442. doi:10.1016/j.cger.2014.04.001

Hypertension Detection and Follow-up Program Cooperative Group. (1978). Variability of blood pressure and the results of screening in the Hypertension Detection and Follow-up Program. *Journal of Chronic Diseases, 31*(11), 651-667. doi:https://doi.org/10.1016/0021-9681(78)90069-3

Iadecola, C., Yaffe, K., Biller, J., Bratzke, L. C., Faraci, F. M., Gorelick, P. B., . . . Zeki Al Hazzouri, A. (2016). Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension (Dallas, Tex. : 1979), 68*(6), e67. doi:10.1161/HYP.0000000000000053

Jackson, D., & Turner, R. (2017). Power analysis for random-effects meta-analysis. *Research Synthesis Methods, 8*(3), 290-302. doi:10.1002/jrsm.1240

Kamaruzzaman, S., Watt, H., Carson, C., & Ebrahim, S. (2010). The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study. *Age and Ageing, 39*(1), 51-56. doi:10.1093/ageing/afp192

Kario, K., Shimada, K., & Pickering, T. (2003). Clinical Implication of Morning Blood Pressure Surge in Hypertension. *J Cardiovasc Pharmacol, 42*, S87-S91.

Kececi Savan, D., Cengiz, M., Yavuzer, H., Yavuzer, S., Sulu, C., Doventas, A., & Beger, T. (2016). Relation of ambulatory blood pressure measurement and cognitive functions

in hypertensive elderly patients. *Aging Clinical and Experimental Research, 28*(4), 699-704. doi:10.1007/s40520-015-0477-2

Koton, S., PhD, M., Tanne, D., Bornstein, N., Green, M., & Md, P. (2004). Triggering risk factors for ischemic stroke: A case-crossover study. *Neurology, 63*(11), 2006-2010. doi:10.1212/01.WNL.0000145842.25520.A2

Lancet. (2017). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet, 390*, 1345-1422.

Lattanzi, S., Luzzi, S., Provinciali, L., & Silvestrini, M. (2014). Blood pressure variability predicts cognitive decline in Alzheimer's disease patients. *Neurobiology of Aging, 35*(10), 2282-2287. doi:https://doi.org/10.1016/j.neurobiolaging.2014.04.023

Liberati, A., Altman, D. G., Tetzlaff, J., & et al. (2009). The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Annals of Internal Medicine, 151*(4), W-65-W-94. doi:10.7326/0003-4819-151-4-200908180-00136

Linden, B. (2011). NICE guidance on primary hypertension. *British Journal of Cardiac Nursing, 6*(12), 582-584. doi:10.12968/bjca.2011.6.12.582

Luzzi, S., Vella, L., Bartolini, M., Provinciali, L., & Silvestrini, M. (2010). Atherosclerosis in the Evolution of Alzheimer's Disease: Can Treatment Reduce Cognitive Decline? *Journal of Alzheimer's Disease, 20*(3), 893-901. doi:10.3233/JAD-2010-091378

Mancia, G., Bombelli, M., Facchetti, R., Madotto, F., Quarti-Trevano, F., Friz, H. P., . . . Sega, R. (2009). Long-Term Risk of Sustained Hypertension in White-Coat or Masked Hypertension. *Hypertension, 54*(2), 226–232.

Mancia, G., Facchetti, R., Bombelli, M., Grassi, G., & Sega, R. (2006). Long-Term Risk of Mortality Associated With Selective and Combined Elevation in Office, Home, and Ambulatory Blood Pressure. *Hypertension, 47*(5), 846-853.

Matsumoto, A., Satoh, M., Kikuya, M., Ohkubo, T., Hirano, M., Inoue, R., . . . Imai, Y. (2014). Day-to-day variability in home blood pressure is associated with cognitive decline: the Ohasama study. *Hypertension (Dallas, Tex. : 1979), 63*(6), 1333. doi:10.1161/HYPERTENSIONAHA.113.01819

McDonald, C., Pearce, M. S., Kerr, S. R. J., & Newton, J. L. (2017). Blood pressure variability and cognitive decline in older people: a 5-year longitudinal study. *Journal of hypertension, 35*(1), 140. doi:10.1097/HJH.0000000000001120

McGuinness, B., Todd, S., Passmore, P., & Bullock, R. (2006). Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database of Systematic Reviews*(2). doi:10.1002/14651858.CD004034.pub2

Nagai, M., Hoshide, S., Ishikawa, J., Shimada, K., & Kario, K. (2011). Visit-to-visit blood pressure variations: New independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. *Journal of the American Society of Hypertension, 5*(3), 184-192. doi:https://doi.org/10.1016/j.jash.2011.03.001

Nagai, M., Hoshide, S., Ishikawa, J., Shimada, K., & Kario, K. (2012). Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *Journal of hypertension, 30*(8), 1556. doi:10.1097/HJH.0b013e3283552735

Naismith, S. L., Norrie, L. M., Mowszowski, L., & Hickie, I. B. (2012). The neurobiology of depression in later-life: Clinical, neuropsychological, neuroimaging and

pathophysiological features. *Progress in Neurobiology*, *98*(1), 99-143. doi:https://doi.org/10.1016/j.pneurobio.2012.05.009

Novak, V., & Hajjar, I. (2010). The relationship between blood pressure and cognitive function. *Nature Reviews Cardiology*, *7*, 686. doi:10.1038/nrcardio.2010.161

Ogliari, G., Smit, R. A. J., Westendorp, R. G. J., Jukema, J. W., de Craen, A. J. M., & Sabayan, B. (2016). Visit-to-visit blood pressure variability and future functional decline in old age. *Journal of hypertension*, *34*(8), 1544. doi:10.1097/HJH.0000000000000979

Oishi, E., Ohara, T., Sakata, S., Fukuhara, M., Hata, J., Yoshida, D., . . . Ninomiya, T. (2017). Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study. *Circulation*, *136*(6), 516. doi:10.1161/CIRCULATIONAHA.116.025667

Parati, G., Ochoa, J. E., Lombardi, C., & Bilo, G. (2013). Assessment and management of blood-pressure variability.(Report). *Nature Reviews Cardiology*, *10*(3), 143. doi:10.1038/nrcardio.2013.1

Parati, G., Stergiou, G. S. b., Asmar, R. c., Bilo, G. a., de Leeuw, P. d., Imai, Y. e., . . . on behalf of the, E. S. H. W. G. o. B. P. M. (2008). European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *Journal of hypertension*, *26*(8), 1505-1526.

Peters, R., Beckett, N., Forette, F., Tuomilehto, J., Clarke, R., Ritchie, C., . . . Bulpitt, C. (2008). Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *The Lancet Neurology*, *7*(8), 683-689. doi:https://doi.org/10.1016/S1474-4422(08)70143-1

Plassman, B. L., Williams, J. W., Jr, Burke, J. R., Holsinger, T., & Benjamin, S. (2010). Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine, 153*(3), 182-193. doi:10.7326/0003-4819-153-3-201008030-00258

Prabhakar, P., Chandra, S. R., Supriya, M., Issac, T. G., Prasad, C., & Christopher, R. (2015). Vitamin D status and vascular dementia due to cerebral small vessel disease in the elderly Asian Indian population. *Journal of the Neurological Sciences, 359*(1), 108-111. doi:https://doi.org/10.1016/j.jns.2015.10.050

Prospective Studies Collaboration. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet, 360*(9349), 1903-1913. doi:https://doi.org/10.1016/S0140-6736(02)11911-8

Qin, B., Viera, A. J., Muntner, P., Plassman, B. L., Edwards, L. J., Adair, L. S., . . . Mendez, M. A. (2016). Visit-to-Visit Variability in Blood Pressure Is Related to Late-Life Cognitive Decline. *Hypertension (Dallas, Tex. : 1979), 68*(1), 106. doi:10.1161/HYPERTENSIONAHA.116.07494

Qiu, C., Winblad, B., & Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology, 4*(8), 487-499. doi:https://doi.org/10.1016/S1474-4422(05)70141-1

Rothwell, P. M. (2010). Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *The Lancet, 375*(9718), 938-948. doi:https://doi.org/10.1016/S0140-6736(10)60309-1

Rothwell, P. M., Coull, A. J., Giles, M. F., Howard, S. C., Silver, L. E., Bull, L. M., . . . Anslow, P. (2004). Change in stroke incidence, mortality, case-fatality, severity, and

risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *The Lancet, 363*(9425), 1925-1933. doi:https://doi.org/10.1016/S0140-6736(04)16405-2

Rothwell, P. M., Howard, S. C., Dolan, E., O'Brien, E., Dobson, J. E., Dahlöf, B., . . . Poulter, N. R. (2010). Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lancet, 375*(9718), 895-905. doi:https://doi.org/10.1016/S0140-6736(10)60308-X

Rubio-Aparicio, M., Sánchez-Meca, J., López-López, J. A., Botella, J., & Marín-Martínez, F. (2017). Analysis of categorical moderators in mixed-effects meta-analysis: Consequences of using pooled versus separate estimates of the residual between-studies variances. *British Journal of Mathematical and Statistical Psychology, 70*(3), 439-456. doi:10.1111/bmsp.12092

Sabayan, B., Wijsman, L. W., Foster-Dingley, J. C., Stott, D. J., Ford, I., Buckley, B. M., . . . Mooijaart, S. P. (2013). Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. *BMJ : British Medical Journal, 347*(7919). doi:10.1136/bmj.f4600

Sakakura, K., Ishikawa, J., Okuno, M., Shimada, K., & Kario, K. (2007). Exaggerated Ambulatory Blood Pressure Variability Is Associated with Cognitive Dysfunction in the Very Elderly and Quality of Life in the Younger Elderly. *American Journal of Hypertension, 20*(7), 720-727. doi:10.1016/j.amjhyper.2007.02.001

Salles, G. F., Cardoso, C. L., & Muxfeldt, E. S. (2008). Prognostic influence of office and ambulatory blood pressures in resistant hypertension. *Archives of Internal Medicine, 168*(21), 2340-2346. doi:10.1001/archinte.168.21.2340

Scazufca, M., Almeida, O. P., Vallada, H. P., Tasse, W. A., & Menezes, P. R. (2009). Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the Sao Paulo Ageing &

Health Study. *Eur Arch Psychiatry Clin Neurosci*, *259*(1), 8-15. doi:10.1007/s00406-008-0827-6

Scuteri, A., Spalletta, G., Cangelosi, M., Gianni, W., Assisi, A., Brancati, A. M., . . . Volpe, M. (2009). Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging Clinical and Experimental Research*, *21*(4), 292-297. doi:10.1007/BF03324918

Sedgwick, P. (2013). Meta-analyses: how to read a funnel plot. *BMJ : British Medical Journal*, *346*. doi:10.1136/bmj.f1342

Sharp, S. I., Aarsland, D., Day, S., Sønnesyn, H., & Ballard, C. (2011). Hypertension is a potential risk factor for vascular dementia: systematic review. *International Journal of Geriatric Psychiatry*, *26*(7), 661-669. doi:doi:10.1002/gps.2572

Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., . . . Henry, D. A. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*, *358*. doi:10.1136/bmj.j4008

Skoog, I., Nilsson, L., Persson, G., Lernfelt, B., Landahl, S., Palmertz, B., . . . Svanborg, A. (1996). 15-year longitudinal study of blood pressure and dementia. *The Lancet*, *347*(9009), 1141-1145. doi:https://doi.org/10.1016/S0140-6736(96)90608-X

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., . . . Higgins, J. P. T. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*, *355*.

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., . . . Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, *343*.

The Cochrane Collaboration. (2014). Review Manager (RevMan) (Version 5.3). Copenhagen: The Cochrane Collaboration.

The Heart Foundation. (2016). Hypertension. *Clinical Information.* Retrieved from https://www.heartfoundation.org.au/for-professionals/clinical-information/hypertension

Tully, P. J., Debette, S., & Tzourio, C. (2018). The association between systolic blood pressure variability with depression, cognitive decline and white matter hyperintensities: the 3C Dijon MRI study. *48*(9), 1444-1453. doi:10.1017/S0033291717002756

van Middelaar, T., van Dalen, J. W., van Gool, W. A., Moll van Charante, E. P., & Richard, E. (2016). The association between visit-to-visit blood pressure variability and cognitive impairment in older people. *European Stroke Journal, 1*(1), 242. doi:10.1177/2396987316642909

van Middelaar, T., van Dalen, J. W., van Gool, W. A., van Den Born, B.-J. H., van Vught, L. A., Moll van Charante, E. P., & Richard, E. (2018). Visit-To-Visit Blood Pressure Variability and the Risk of Dementia in Older People. *Journal of Alzheimer's disease : JAD, 62*(2), 727. doi:10.3233/JAD-170757

Virtanen, R., Jula, A., Salminen, J. K., Voipio-Pulkki, L.-M., Helenius, H., Kuusela, T., & Airaksinen, J. (2003). Anxiety and Hostility Are Associated With Reduced Baroreflex Sensitivity and Increased Beat-to-Beat Blood Pressure Variability. *Psychosomatic Medicine, 65*(5), 751-756. doi:10.1097/01.PSY.0000088760.65046.CF

Williams, M. (2009). Progress in Alzheimer's disease drug discovery: an update. *Current opinion in investigational drugs (London, England : 2000), 10*(1), 23-34.

Wizner, B., Dechering, D., Thijs, L., Atkins, N., Fagard, R., O'Brien, E., . . . Staessen, J. (2008). Short-term and long-term repeatability of the morning blood pressure in older

patients with isolated systolic hypertension. *J Hypertens*, *26*(7), 1328-1335. doi:10.1097/HJH.0b013e3283013b59

Yano, Y., Ning, H., Allen, N., Reis, J. P., Launer, L. J., Liu, K., . . . Lloyd-Jones, D. M. (2014). Long-term blood pressure variability throughout young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Hypertension (Dallas, Tex. : 1979), 64*(5), 983. doi:10.1161/HYPERTENSIONAHA.114.03978

Appendices

Appendix A

Logic grids for each database

PUBMED	EMBASE	PsycINFO	SCOPUS
(“blood pressure variability” [tiab] OR “visit-to-visit blood pressure” [tiab] OR “ambulatory blood pressure monitoring”[tiab] OR “24-hour blood pressure monitoring” [tiab] OR “home blood pressure monitoring” [tiab] OR "BPV" [tiab] OR "blood pressure"[mh] OR "hypertension"[mh:noexp] OR "ABPM" [tiab] OR “variable blood pressure” [tiab]) AND (“dementia”[mh] OR “dementia” [tiab] OR cognitive impairment*[tiab] OR cognitive function* [tiab] OR “memory” [tiab] OR memory [mh] OR cognitive dysfunc* [mh] OR cognitive dysfunc* [tiab] OR “mental deterioration” [tiab] OR “cognitive decline” [tiab])	('blood pressure'/exp OR 'blood pressure monitoring'/exp OR ‘blood pressure monitoring’:ti,ab OR 'home blood pressure monitoring'/exp OR 'home blood pressure monitoring':ti,ab OR ‘blood pressure variability’:ti,ab OR ‘BPV’:ti,ab OR 'visit to visit blood pressure variability'/exp OR 'visit to visit blood pressure variability':ti,ab OR ‘hypertension’/de) AND ('dementia'/de OR 'dementia':ti,ab OR 'cognitive defect'/exp OR 'cognitive defect':ti,ab OR ‘cognition’/exp OR 'cognitive decline':ti,ab OR 'cognitive decline'/exp)	(Blood pressure.sh OR hypertension.sh. or hypertension.ti,ab. OR blood pressure variability.tw OR BPV.tw OR variable blood pressure.tw OR visit to visit blood pressure.tw. OR ambulatory blood pressure monitoring.tw. OR ABPM.tw OR 24-hour blood pressure monitoring.tw. OR home blood pressure monitoring.tw.) AND (exp dementia/ OR dementia.ti,ab. OR exp cognitive impairment/ OR cognitive impairment.ti,ab. OR exp cognitive ability OR cognitive ability.ti,ab OR memory.sh OR memory.ti,ab OR mental deterioration.tw. OR cognitive decline.tw.)	TITLE-ABS-KEY ("blood pressure variability" OR "visit-to-visit blood pressure" OR "ambulatory blood pressure monitoring" OR "24-hour blood pressure monitoring" OR "home blood pressure monitoring" OR "BPV" OR "blood pressure" OR "blood pressure monitoring") AND TITLE-ABS-KEY ("dementia" OR "cognitive impairment" OR "cognitive function" OR memory OR "cognitive dysfunction" OR "mental deterioration" OR "cognitive decline" OR "cognitive defect")

AND (“Mini Mental State” [tiab] OR “MMSE” [tiab] OR cognitive test* [tiab] OR neuropsychological test* [mh] OR neuropsychological test* [tiab])	AND ('dementia assessment'/exp OR 'dementia assessment':ti,ab OR 'mini mental state examination':ti,ab OR 'neuropsychological test'/exp OR 'neuropsychological test':ti,ab OR 'neuropsychological assessment'/exp OR 'neuropsychological assessment':ti,ab OR 'cognitive test'/exp OR 'cognitive test':ti,ab)	AND (exp cognitive assessment OR cognitive assessment.ti,ab OR exp neuropsychological assessment OR neuropsychological assessment.ti,ab OR MMSE.tw OR mini mental state examination.ti,ab)	AND TITLE-ABS-KEY ("Mini Mental State" OR "MMSE" OR "cognitive test" OR "neuropsychological test" OR "dementia test" OR "cognitive assessment" OR " neuropsychological assessment" OR "dementia assessment")

Note: Last search was conducted on 29 May 2018, and automatic email alerts were set up for each database.

Appendix B

Table 1: Data extraction summary (study characteristics and sample demographics)

Study reference	Country	Cohort name	Study design	N	Age [M(SD) or Median (IQR)]	Sex ratio (%females)	N(%) antihypertensive drug
Alpertovich 2014	France	The Three-City (3C) Study	Cohort	9294	73.7 (5.2)	62.0%	50.5%
Bohm 2015	Intl*	ONTARGET, TRANSCEND	Cohort	31546	88.0(7.0)	27.5%	NR*
Fujiwara 2018	Japan	SEARCH	Cohort	525	83.2 (3.2)	55.7%	NR*
Matsumoto 2014	Japan	Ohasama Study	Cohort	485	63.3(4.7)	72.0%	31.0%
McDonald 2017	UK	NR	Cohort	302	72(68-77)	42.0%	NR
Nagai 2012	Japan	Shobara City/Soryo Town Cohort Study	Cohort	206	79.9(6.4)	75.0%	71.2%
Oishi 2017	Japan	Hisayama Study	Cohort	1674	71.0(7.0)	55.9%	43.3%
Sakakura 2007	Japan	NR	Cross-sectional	202	84(3.9)	81.2%	73.3%
Tully 2018	France	The Three-City (3C) Study	Cohort	2812	72(69-76)	63.6%	NR**
van Middelaar 2016	Netherlands	preDIVA	Cohort	2212	74(2.4)	NR	NR
van Middelaar 2018	Netherlands	preDIVA	Cohort	3526	74.2(2.5)	55.20%	54.1%

Intl: International Sample; N: sample size; NR: not reported; M(SD): mean (standard deviation); IQR: interquartile range

NR* Antihypertensive medication percentages are given by specific medication types

NR** Antihypertensive medication percentages are given by specific sub sample

Study reference	Cognitive tests	Method of BP measurement	Interval between consecutive BP measures	Total duration of consecutive measures	BPV calculation method	Duration of f/up years	(% completed f/up)
Alpertovich 2014	MMSE, IST	Clinic visit-to-visit	2 years	8 years	CV	8	70%
Bohm 2015	MMSE	Clinic visit-to-visit	initial 6 weeks, 6 months	4.4 years	CV	5.4	78%
Fujiwara 2018	MMSE*	ABPM, Clinic visit-to-visit	30 minutes	24 hours	SD, CV	1	94.7%
Matsumoto 2014	MMSE	Home	24 hours	4 weeks	SD	7.8	NR
McDonald 2017	MMSE, CAMCOG	ABPM	30 minutes (day), 60 minutes (night)	24 hours	CV	5	67.9%
Nagai 2012	MMSE, GDS	Clinic visit-to-visit	1 month	12 months	CV	1	97.6%
Oishi 2017	MMSE; HDS; HDSR	Home	24 hours	28 days	CV	5.3	61.5%
Sakakura 2007	MMSE	ABPM	30 minutes	24 hours	SD	n/a	n/a
Tully 2018	TRAILS, IST, BVRT, MMSE, FTT	Clinic visit-to-visit	2 years	4 years	CV	10	NR
van Middelaar 2016	MMSE	Clinic visit-to-visit	2 years	4-8 years	CV	8	NR
van Middelaar 2018	MMSE	Clinic visit-to-visit	2 years	6-8 years	CV	8	65.4%

MMSE: Mini Mental State Examination; IST: Isaac's Set Test; GDS: Global Deterioration Scale; HSD: Hasegawa's Dementia Scale; HDSR: Hasegawa's Dementia Scale Revised; TRAILS: The Trail Making Test; BVRT: Benton Visual Retention Test; FTT: Finger-tapping test; BP: blood pressure; ABPM: ambulatory blood pressure monitoring; BPV: blood pressure variability; CV: coefficient of variation; SD: standard deviation; f/up: follow-up

MMSE* refers to the specific working memory assessment subsection.