



# Association Between Blood Pressure Variability With Dementia and Cognitive Impairment: A Systematic Review and Meta-Analysis

Rianne A.A. de Heus, Christophe Tzourio<sup>1</sup>, Emily Jo Lynn Lee<sup>2</sup>, Melissa Opozda, Andrew D. Vincent, Kaarin J. Anstey, Albert Hofman, Kazuomi Kario<sup>3</sup>, Simona Lattanzi<sup>4</sup>, Lenore J. Launer<sup>5</sup>, Yuan Ma<sup>6</sup>, Rajiv Mahajan<sup>7</sup>, Simon P. Mooijaart<sup>8</sup>, Michiaki Nagai, Ruth Peters<sup>9</sup>, Deborah Turnbull, Yuichiro Yano<sup>10</sup>; the VARIABLE BRAIN Consortium; Jurgen A.H.R. Claassen, Phillip J. Tully<sup>11</sup>

**ABSTRACT:** Research links high blood pressure variability (BPV) with stroke and cerebrovascular disease, however, its association with cognition remains unclear. Moreover, it remains uncertain which BP-derived parameter (ie, variability or mean) holds more significance in understanding vascular contributions to cognitive impairment. We searched PubMed, Embase, PsycINFO, and Scopus and performed a meta-analysis of studies that quantified the association between resting BPV with dementia or cognitive impairment in adults. Two authors independently reviewed all titles, abstracts, and full-texts and extracted data, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines. Study quality was assessed using the (modified) Newcastle-Ottawa Scale. A multilevel meta-analysis was used, which included effect sizes for both BPV and mean BP, with a combined end point of dementia or cognitive impairment as primary outcome. In the primary analysis, 54 effect sizes were extracted from 20 studies, with a total analytical sample of  $n=7\,899\,697$ . Higher systolic BPV (odds ratio [OR], 1.25 [95% CI, 1.16–1.35]), mean systolic pressure (OR, 1.12 [95% CI, 1.02–1.29]), diastolic BPV (OR, 1.20 [95% CI, 1.12–1.29]), and mean diastolic pressure (OR, 1.16 [95% CI, 1.04–1.29]) were associated with dementia and cognitive impairment. A direct comparison showed that mean BP effect sizes were less strong than BPV effect sizes (OR, 0.92 [95% CI, 0.87–0.97],  $P<0.01$ ), indicating that the relative contribution of BPV exceeded that of mean BP. Methodological and statistical heterogeneity was high. Secondary analyses were less consistent as to whether BPV and mean BP were differentially associated with dementia subtypes and cognitive domains. Future studies are required to investigate BPV as a target for dementia prevention. (*Hypertension*. 2021;78:1478–1489. DOI: 10.1161/HYPERTENSIONAHA.121.17797.) • [Data Supplement](#)

**Key Words:** Alzheimer disease ■ blood pressure ■ cerebrovascular disorders ■ dementia ■ hemodynamics ■ meta-analysis ■ stroke

High blood pressure (BP) during mid-life is widely recognized as a modifiable risk factor for late-life dementia.<sup>1,2</sup> Subsequently, lowering high BP with antihypertensive medication during mid-life is a recommended strategy to prevent dementia.<sup>3,4</sup> Yet, several uncertainties remain that hamper clinical guidelines for the management of BP to maintain brain health, including optimal BP targets in mid- to late-life and the choice

of antihypertensive drug(s).<sup>5</sup> The inconsistency in findings raises the possibility that BP-related factors beyond absolute BP level or treat-to-target BP could be important for dementia prevention and early intervention.

A body of empirical work indicates that oscillations in BP between consecutive measures hold additional prognostic significance, alongside mean BP level, for the risk of cardiovascular diseases and subclinical target

Correspondence to: Phillip J. Tully, Freemasons Centre for Male Health and Wellbeing, Adelaide Medical School, Level 6 AHMS Bldg, The University of Adelaide, Adelaide SA 5005. Email [phillip.tully@adelaide.edu.au](mailto:phillip.tully@adelaide.edu.au)

A list of all VARIABLE BRAIN Consortium participants is given in the [Data Supplement](#).

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## Novelty and Significance

### What Is New?

- High blood pressure variability may be a predictor for the risk of dementia or cognitive impairment.
- The relative contribution of variability in blood pressure exceeded that of mean blood pressure.

### What Is Relevant?

- Variability might be a novel blood pressure-derived parameter to be taken into account in hypertension management.

- Blood pressure variability might be a future target to prevent dementia.

### Summary

In this meta-analysis, that included 20 studies for the primary outcome, both a higher mean level of blood pressure as well as a higher degree of blood pressure variability were associated with greater odds for dementia or cognitive impairment. Effect sizes for blood pressure variability were larger than effect sizes for mean blood pressure.

## Nonstandard Abbreviations and Acronyms

<b>BP</b>	blood pressure
<b>CSVD</b>	cerebral small vessel disease
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>OR</b>	odds ratio

organ damage.<sup>6,7</sup> Previous meta-analyses have reported associations of high BP variability (BPV) with stroke and cerebral small vessel disease (CSVD), underscoring the importance of BPV to brain health.<sup>8-10</sup> An association between BPV with dementia and cognitive impairment was reported as part of a larger meta-analysis on BP and cognition but was limited to only 2 studies.<sup>11</sup>

Evaluating the current evidence regarding BPV and cognitive function may inform evidence-based clinical practice regarding BP management to preserve brain health. Therefore, the objective of this review is to quantify the association between intraindividual BPV with the risk of dementia or cognitive impairment. A second objective is to compare the magnitude of the association between BPV and cognitive outcomes with the effect sizes for mean BP.

## METHODS

The authors declare that all supporting data are available within the article and its [Data Supplement](#). The protocol of this systematic review was registered with the International Prospective Register of Systematic Reviews (CRD42017081977) and published.<sup>12</sup> The study followed the Meta-Analysis of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>13,14</sup>

### Sources and Search Strategy

A comprehensive search of PubMed (Medline), Embase, PsycINFO, and Scopus without language restriction was

performed from database inception to April 20, 2021 ([Data Supplement](#)). Two reviewers (R.A.A. de Heus and M. Opozda) independently screened titles and abstracts to assess eligibility. Full text was evaluated if eligibility was not clear from the abstract. Inconsistencies were resolved by consulting a third reviewer (P.J. Tully). Articles and conference abstracts of case-control studies, prospective cohorts, database registries, cross-sectional studies, and (secondary analyses of) randomized controlled trials were eligible for inclusion. A hand-search was performed of the articles selected for full-text review and of narrative reviews,<sup>15,16</sup> supplementing the electronic search. Where necessary, we contacted authors of relevant articles to request additional data.

### Eligibility Criteria

Studies were considered eligible if they investigated an adult sample ( $\geq 18$  years), examined BPV using repeated measurements of BP at rest, assessed a prespecified cognitive outcome (see below), and reported the association between BPV and study outcome(s), or could provide additional analyses. No restriction was placed on sample size or length of follow-up. Reporting the association between mean BP and study outcome(s) was not a prespecified inclusion criterion. Because the field is lacking a gold standard for quantifying intraindividual BPV, all common metrics were eligible, prioritizing the coefficient of variation where studies reported multiple metrics ([Data Supplement](#)).<sup>17</sup> Studies including persons with baseline dementia were excluded if they did not report the association of BPV with cognition separately for those without dementia. Studies in patients with recent stroke, Parkinson disease, receiving hemodialysis or renal denervation, revascularization, or facing orthostatic challenge were ineligible.

### Outcomes

The primary outcome was the odds for dementia or cognitive impairment attributable to BPV or mean BP. Studies that reported incident dementia, cognitive impairment, a composite of dementia or cognitive impairment, or compared dementia and nondementia groups were included. This approach was chosen to maximize the number of studies in the primary analysis and because dementia and cognitive impairment

represent a continuum of the same syndrome. The definition of dementia was criterion-referenced and was based on *International Classification of Disease* criteria, *Diagnostic and Statistical Manual of Mental Disorders* criteria, an adjudicated expert panel or the prescription of antidementia drugs, inclusive of any dementia, Alzheimer disease, Vascular dementia, or mixed cause. The definition of cognitive impairment was any of the following definitions that were standardized within studies: criterion-referenced diagnosis of mild cognitive impairment,<sup>18,19</sup> a cognitive test score below a predefined, clinical cutoff point, a predefined between-assessment decline, or a score below age and sex appropriate normative data, all based on standardized tests of global cognitive function or assessing specific cognitive domains. Studies using self-reported measures were ineligible.

The secondary outcomes were other effect sizes reporting on the association between BPV and cognition. This included (standardized) mean cognitive function scores in the lowest versus highest group of BPV or mean BP (eg, quartiles) and conversely (standardized) mean differences in BPV and mean BP when grouped by cognitive function. Furthermore, effect sizes of  $\beta/r$  family reporting the correlation between BPV and cognition on a continuous scale were extracted for analyses.

### Data Extraction

Data were independently extracted by 3 reviewers (R.A.A. de Heus, M. Opozda, and E.J.L. Lee) and verified by a fourth reviewer (P.J. Tully). We extracted information pertaining to study identification (first author, year, country, and study name), design characteristics (design, population, sample size, and follow-up), population characteristics (age, sex, education, use of antihypertensive medication, and comorbidities), characteristics of BP(V) (measurements, timing, interval, setting, device, and metrics), dementia adjudication (criteria, subtypes, consensus panel, and number of end points), cognitive testing (tests used, domains assessed, and criteria for impairment or decline), effect sizes (most adjusted effect sizes), and list of adjusted covariates. When studies reported multiple metrics of BPV, we prioritized the methods that adjusted for mean BP level (eg, coefficient of variation instead of SD). The association of mean BP with study outcomes was extracted when available. Effect sizes of mean BP for dementia or cognitive impairment were standardized to 10/5 mmHg increase as not all studies reported the SD of mean BP. In instances where different levels of adjustment were made for mean and BPV data, we prioritized data from the same model to ensure equivalence in covariate adjustment.

### Quality Assessment

The risk of bias within each study was assessed independently by 2 reviewers (R.A.A. de Heus and M. Opozda) using modified versions of the Newcastle-Ottawa Scale, for cross-sectional, case-control, and cohort designs.<sup>20</sup> Discrepancies were resolved by consulting a third reviewer (P.J. Tully). Adjudication of the strength of evidence for the hypothesis that high BPV increases the risk for dementia or cognitive impairment was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, with GRADE Profiler 3.6.1.<sup>21</sup>

### Deviations From Protocol

Based on preliminary data extraction and performing a parallel review on BPV and CSVD, several changes were instigated from the published protocol.<sup>10,12</sup> Our adjudication of the primary outcome was expanded, combining dementia and cognitive impairment together, opting to analyze the categories separately in ancillary analysis. Second, we included cross-sectional studies to estimate the association between BPV with dementia or cognitive impairment, opting to analyze different study designs separately in ancillary analysis. Also, we excluded studies assessing beat-to-beat BPV, as this metric likely represents a different physiological mechanism compared with 24-hour, day-to-day, and visit-to-visit BPV.<sup>22,23</sup>

### Statistical Analysis

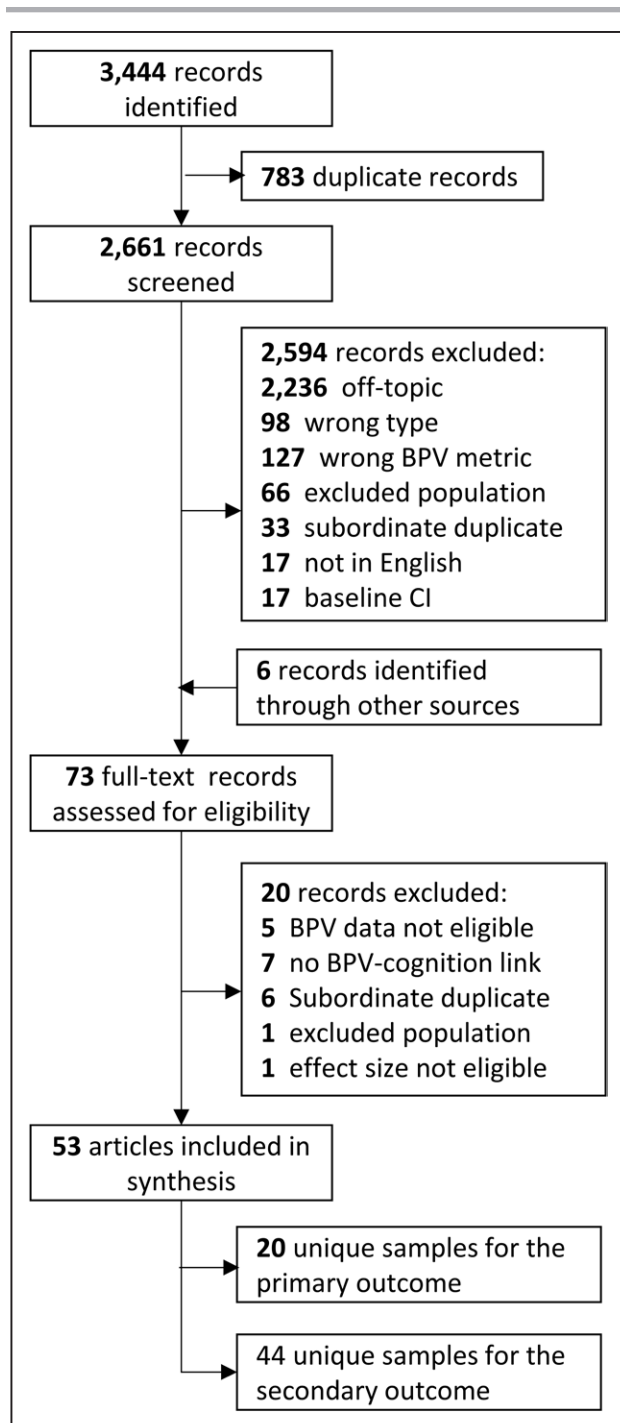
Data pertaining to the likelihood of dementia or cognitive impairment were pooled as odds ratio (OR) with 95% CIs. A multilevel meta-analysis was used using the metafor package in R version 3.5.2.<sup>24</sup> Compared with a traditional meta-analysis, a multilevel meta-analysis accounts for the dependence in effect sizes within a study (eg, between BPV and mean BP from which BPV is often calculated; and dependence of systolic and diastolic BP).<sup>10</sup> Thus a single study could contribute up to 4 effect sizes for each analysis (systolic BP and BPV, diastolic BP and BPV). A mixed-effects model, with a random intercept per study, tested fixed effect moderators for BP type (diastolic versus systolic) and measure (mean versus variability). Random-effects models (inverse-variance method) were used under the assumption of high sampling variability between studies, different BPV metrics, and cognitive function outcomes.<sup>25</sup> Statistical heterogeneity was evaluated with the  $I^2$  statistic and methodological heterogeneity was explored with meta-regression in Comprehensive Meta-Analysis software.<sup>26</sup> The presence of publication bias was evaluated with the test of Egger,<sup>27</sup> Begg-Mazumdar,<sup>28</sup> and the Duval and Tweedie trim-and-fill funnel plot.<sup>29</sup>

Separate analyses considered key methodological and descriptive characteristics that might modulate the association between BP and dementia cognitive impairment and the different dementia subtypes ([Data Supplement](#)). The standardized mean difference between groups of BPV or cognitive impairment groups (dementia or impairment versus no dementia or impairment) were modeled with RevMan 5.3, analyzing cognitive function or BPV, respectively.<sup>30</sup> Comprehensive Meta-Analysis software was used for the analysis of  $r$  family effect sizes showing the linear association between BP(V) measures and cognitive function.<sup>26,31</sup>

## RESULTS

### Study Selection and Characteristics

After duplicate removal, 2661 records were screened, from which 53 were retained (Figure 1). Reasons for exclusion after full-text review are described in Table S1 in the [Data Supplement](#).<sup>32–51</sup> Twenty unique studies samples met the inclusion criteria for the primary outcome (analytical  $n=7\ 899\ 679$ ).<sup>52–71</sup> These comprised 8 cohort studies ( $n=18\ 067$ ), 2 nested cohort studies ( $n=698$ ),



**Figure 1. Flow diagram of included studies.**

BPV indicates blood pressure variability; and CI, cognitive impairment.

one nationwide registry database ( $n=7\,844\,814$ ), 4 randomized controlled trials analyzed as a cohort ( $n=32\,684$ ), 3 cross-sectional studies ( $n=3006$ ), and 2 case-control studies ( $n=410$ ). The timing and interval of exposure and outcome assessment are depicted in Figure 2. Studies' participants had a mean age of  $73\pm 7$  years and  $58\pm 13\%$  women. Two study samples comprised a population of type II diabetes patients and 3 studies comprised patients with high CVD risk or hypertension.

Eleven studies assessed visit-to-visit office BPV, 4 studies 24-hour ambulatory BPV, 4 studies day-to-day home BPV, and 1 study intravisit office BPV. Characteristics are presented in the Table and additional information in Tables S2 through S4.

Forty-seven records, comprising 43 unique study samples (analytical  $n=7\,915\,946$ ) reported any of the secondary outcomes.<sup>52–59,61,63–65,68–72,76–107</sup> Seventeen studies reported standardized mean difference in BPV between groups of cognitive function, 17 studies reported standardized mean difference in cognitive function between groups of BPV, and 23 studies reported the linear association between BPV with cognitive function. Characteristics are presented in Tables S4 and S5.

### Study Quality and GRADE Rating

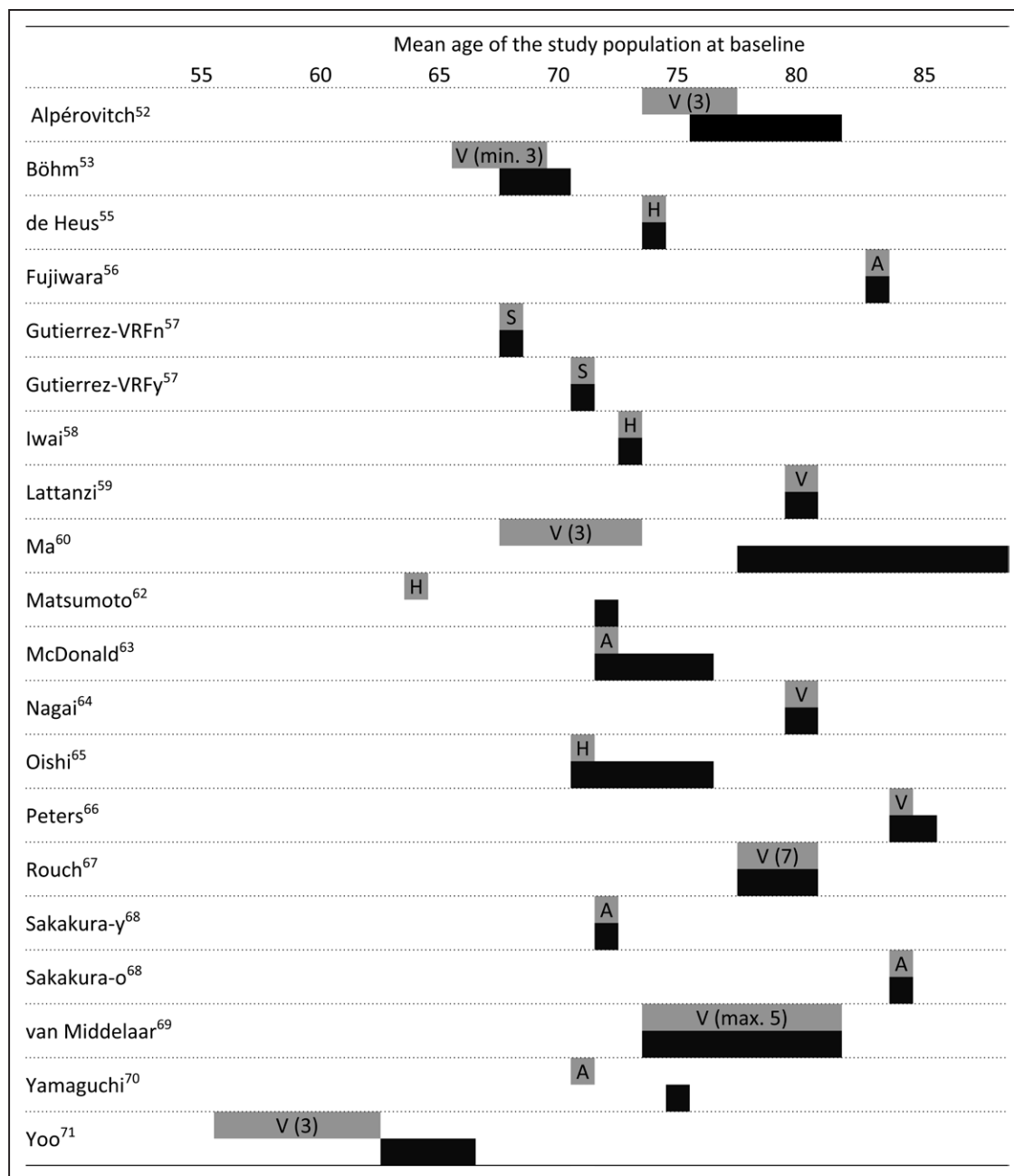
Quality assessment is presented in Tables S6 through S8. Overall quality was deemed good in 16 studies, fair in one study and poor in 3 studies. In all studies, BP was assessed with reliable methods. Eight studies did not adjust their analyses of BPV for mean BP. There was evidence of publication bias for systolic BPV, based on funnel plot asymmetry and Egger test ( $P=0.023$ ; Table S9 and Figure S1). GRADE rating of the quality of evidence was very low (Table S10).

### BPV and Dementia or Cognitive Impairment

Fifty-four effect sizes retrieved from 20 studies were included in the multilevel model (Figure 3). The model included 21 systolic BPV, 11 mean systolic BP, 15 diastolic BPV, and 7 mean diastolic BP effect sizes. Higher systolic BPV was significantly associated with an increase in dementia/cognitive impairment (OR, 1.25 [95% CI, 1.16–1.35];  $P=87\%$ ), as was mean systolic BP (OR, 1.12 [95% CI, 1.02–1.29];  $P=82\%$ ). Similar results were found for diastolic BPV (OR, 1.20 [95% CI, 1.12–1.29];  $P=83\%$ ) and mean diastolic BP (OR, 1.16 [95% CI, 1.04–1.29];  $P=3\%$ ). When effect sizes were directly compared in the multilevel meta-analysis, the association of mean BP with the primary outcome was less strong compared with the association of BPV with the primary outcome (OR, 0.92 [95% CI, 0.87–0.97];  $P<0.01$  for comparison). Diastolic effect sizes were also less strong than systolic effect sizes in a direct comparison including both BPV and mean BP (OR, 0.96 [95% CI, 0.95–0.98];  $P<0.001$  for comparison). Overall, heterogeneity was high.

### Meta-Regression and Subgroup Analyses

Results of the meta-regression on the primary outcomes are presented in Table S11. Higher mean BP of the study population was associated with an attenuation in association, and thus lower effect sizes, for both systolic



**Figure 2. Schematic overview of included studies for the primary analysis.**

X axis represents time in years and each study is presented at the mean age of the study population at baseline. Chuang et al<sup>64</sup> (2016) and Matsumoto et al<sup>62</sup> (2018) are missing from this overview because these studies (abstract only) did not report the mean age of the study population. A indicates ambulatory blood pressure measurements (24-h); H, home blood pressure measurements; S, single-visit (within-visit BP variability); and V, visit-to-visit variability (number presents number of visits).

BPV (coefficient,  $-0.003$  [95% CI,  $-0.005$  to  $-0.001$ ]) and diastolic BPV (coefficient,  $-0.030$  [95% CI,  $-0.039$  to  $-0.021$ ]; Figure 4). In addition, effect sizes for BPV were associated with lower age, female sex, low education, shorter interval between consecutive BP measures, shorter total interval of BP measurements, lower body mass index, and diabetes.

Subgroup analyses by methodological characteristics are presented in Figures S2 and S3. Systolic BPV analyses indicated heterogeneity for study quality, follow-up

length, BP measurement (oscillometric versus other), BP measurement interval, and study region. Studies including only patients with hypertension were heterogeneous for systolic BPV compared with other studies. For diastolic BPV, there was evidence of heterogeneity between study designs and type of BPV metric.

The analysis stratified by subtypes of the primary outcome supported the main findings, indicating an association between BPV and risk of dementia (any type), Alzheimer disease, vascular dementia, cognitive

**Table. Characteristics of Included Studies for the Primary Analysis**

First author	Year	Country	Name of study	Design	Study sample	Sample size	Primary outcome criteria	Type of BP measurement	Length of follow-up
Alpérovitch <sup>52</sup>	2014	France	Three-City	Cohort	Community-dwelling elderly (65+)	6506	DSM-IV criteria, expert panel	Visit-to-visit	6.8 y (MED)
Böhm <sup>53</sup>	2015	Multi-national	ONTARGET/TRANSCEND	RCT	Patients with high CVD risk (55+)	24 593	MMSE <24 at follow-up	Visit-to-visit	4.7 y (MED)
Chuang, <sup>54*</sup>	2016	Taiwan	CVDFACTS	Cohort	Community-dwelling elderly	320	MMSE <24	Visit-to-visit	13 y
de Heus <sup>55†</sup>	2020	The Netherlands	NA	Case-control	Outpatients with and without dementia	200	DSM-IV criteria, expert panel	Day-to-day	...
Fujiiwara <sup>56</sup>	2018	Japan	SEARCH	Nested cohort	Outpatients (80+)	497	MMSE recall score ≤1 (out of 3)	24-h ABPM	1 y
Gutierrez <sup>57</sup>	2015	United States	NHANES	Cross-sectional	Community-dwelling adults (60+)	2573	Digit Symbol Substitution Test	Intravital	...
Iwai <sup>58</sup>	2019	Japan	KAMOGAWA-HBP	Cross-sectional	Outpatients with type 2 diabetes (65+)	231	Mini-Cog ≤2	Day-to-day	...
Lattanzi <sup>59</sup>	2014	Italy	NA	Case-control	Outpatients with and without AD	210	NINCDS-ADRDA criteria, expert panel	Visit-to-visit	6 mo
Ma <sup>60</sup>	2019	The Netherlands	Rotterdam	Cohort	General population (55+)	5273	DSM-III-R criteria, expert panel	Visit-to-visit	14.6 y (MED)
Matsumoto <sup>61*</sup>	2014	Japan	Ohasama	Cohort	General population (55+)	485	MMSE <24 at follow-up	Day-to-day	7.8 y (MED)
Matsumoto <sup>62</sup>	2018	Japan	JPAD2	RCT	Patients with diabetes (30-85)	2450	Prescription of antedementia drugs or dementia admission	Visit-to-visit	9 y
McDonald <sup>63</sup>	2017	England	NA	Cohort	Community-dwelling elderly (65+)	302	change in MMSE after 5 y	24-h ABPM	5 y
Nagai <sup>64</sup>	2012	Japan	Shobara City Soryo Town	Nested cohort	Outpatients with CVD factor(s) (70+)	201	MMSE ≤24	Visit-to-visit	3 mo
Oishi <sup>65</sup>	2017	Japan	Hisayama	Cohort	General population (60+)	1674	DSM-III criteria, expert panel	Day-to-day	5 y
Peters <sup>66†</sup>	2008	Multi-national	HYVET-COG	RCT	Hypertensive elderly (80+)	3336	DSM-IV criteria, expert panel	Visit-to-visit	2.2 y (M)
Rouch <sup>67</sup>	2019	France	S.AGES	Cohort	Community-dwelling elderly (65+)	3319	DSM-IV criteria	Visit-to-visit	2.6 y (M)
Sakakura <sup>68</sup>	2007	Japan	NA	Cross-sectional	Outpatients with chronic diseases (60+)	202	lowest tertile of MMSE	24-h ABPM	...
van Middelaar <sup>69,72</sup>	2018 and 2016	The Netherlands	Pre-DIVA	RCT	Community-dwelling elderly	2305	DSM-IV criteria, expert panel	Visit-to-visit	6.4 y (M)
Yamaguchi <sup>70</sup>	2014	Japan	NA	Cohort	General population (70-72)	188	≥1 point MMSE decrease after 4 y	24-h ABPM	4 y
Yoo <sup>71</sup>	2020	Korea	Korean NHIS	Retrospective registry	General population (40+)	7 844 814	ICD codes/prescription of antedementia drugs	Visit-to-visit	6.2 y (MED)

ABPM, ambulatory blood pressure monitoring; AD, Alzheimer disease; BPV, blood pressure variability; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, *International Classification of Diseases*; M, mean; MED, median; MMSE, Mini-Mental State Examination; NA, not applicable; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; and RCT, randomized controlled trial.

\*Conference abstract only. Additional information for quality assessment was retrieved from Ogawa et al<sup>72</sup> (2008), Chuang et al<sup>74</sup> 2013, and Matsumoto et al<sup>75</sup> 2020.

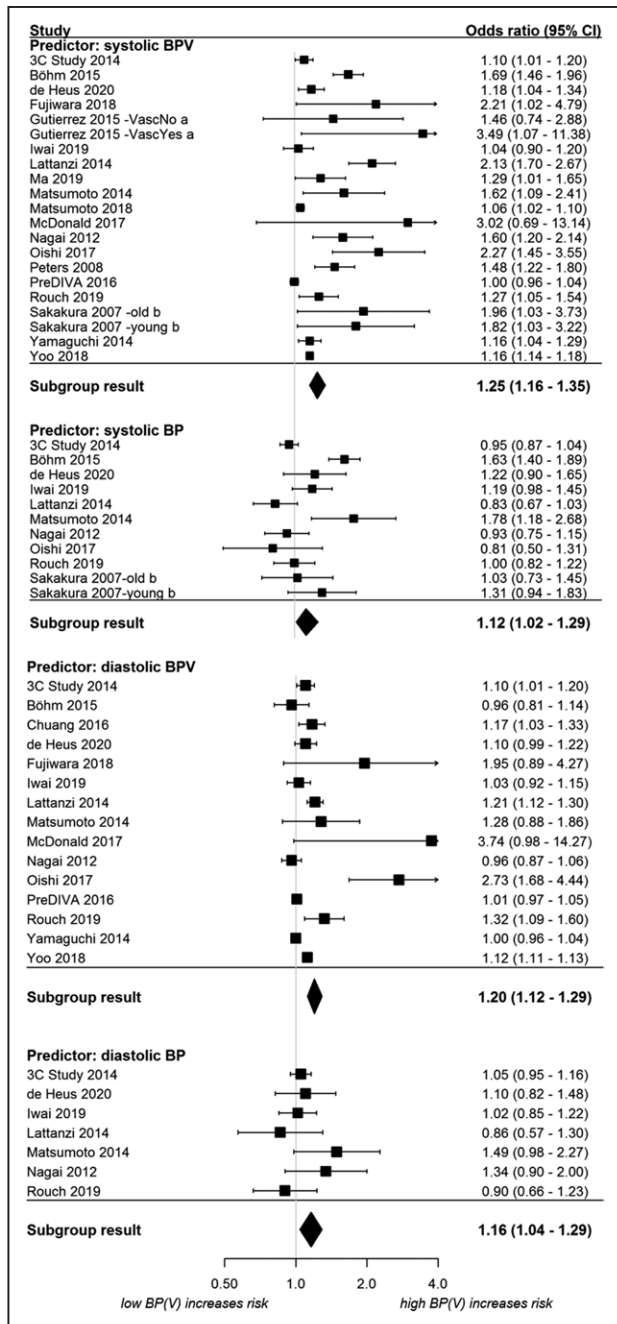
†Authors performed additional analysis on request.

impairment, and cognitive decline (Figure S4). However, the main finding of stronger effect sizes for BPV compared with mean BP was not supported in these subtypes, with the exception of Alzheimer disease ( $P < 0.01$ ).

## Secondary Outcomes

Results of the secondary outcomes analyses were generally consistent with the primary outcome analysis (Figures S5–S7), although evidence was sparse. Comparing BP(V) between groups of cognitive function

indicated higher systolic BPV in those with cognitive impairment, with no difference observed for mean BP. Conversely, we observed lower general cognitive function in those with high BPV compared with low BPV. In addition, general cognitive function and BPV were associated in studies reporting  $\beta/r$  effect sizes, although for diastolic BPV this was only a trend. Associations between cognition and mean BP in secondary analyses were inconsistent, with mean systolic BP associated with improved memory and attention/executive/psychomotor indices.

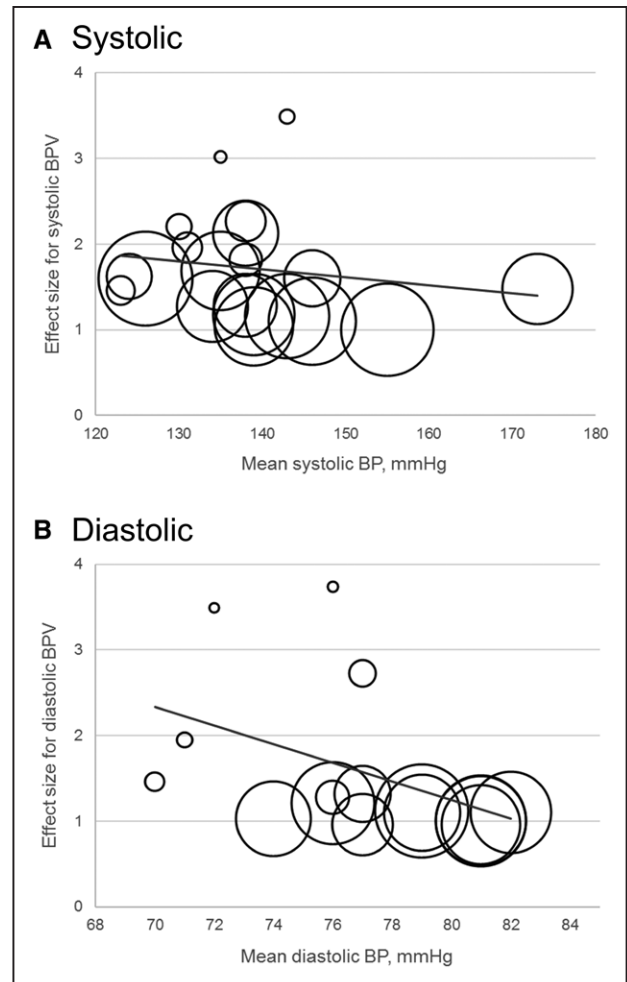


**Figure 3. Association of blood pressure(variability) (BP(V)) with dementia and cognitive impairment following multilevel meta-analysis.**

Odds ratio (OR) for mean blood pressure is presented by 10 (systolic) or 5 (diastolic) mmHg. OR for BPV is presented per 1-unit change in the BPV metric. <sup>a</sup>Effect size reported separately for group with and without vascular risk factors or disease. <sup>b</sup>Effect sizes reported separately for young and old group.

## DISCUSSION

This systematic review and meta-analysis showed that elevated BPV is associated with a higher risk of dementia and cognitive impairment. Findings were generally consistent across dementia subtypes and general cognitive



**Figure 4. Bubble plots of meta-regression result for mean blood pressure (BP) as covariate.**

The size of the bubble reflects the weight of the study. Line represents fitted meta-regression line. BPV indicates BP variability.

impairment, although published data were sparse for secondary outcomes. These findings are derived from observational outcomes. These findings are derived from generally good quality but with high heterogeneity and evidence of publication bias in the retained articles. As such, the GRADE rating and strength of evidence were very low for the primary outcome, which tempers the conclusions that can be drawn.

Our findings emerge in the context of past research documenting associations between cognitive function and impaired BP regulation, such as circadian variation and orthostatic hypotension,<sup>95,108</sup> as well as previous systematic reviews relating BPV to neurological outcomes, including acute stroke, transient ischemic attack, CSVD, and dementia.<sup>8-11</sup> Here, multilevel meta-analysis modeling demonstrated that dementia and cognitive impairment were more consistently associated with BPV than with mean BP. This contrasts with our previous finding showing BPV contributes to CSVD risk but no more than mean BP.<sup>10</sup> Besides methodological differences, this discrepancy can be partly explained by the timing of BP

and outcome assessment. CSVD is known to be primarily induced by hypertension,<sup>109</sup> whereas the link between cardiovascular risk and cognitive impairment is strongest in mid-life, becoming more ambiguous at late-life.<sup>110</sup> In addition, it is likely that the association between BPV and cognitive impairment is only partly attributable to CSVD, involving other pathways such as Alzheimer pathology, hypoxia and blood-brain barrier dysfunction. Conversely, neurodegeneration in brain regions involved in autonomic control might lead to high BPV,<sup>111</sup> as indicated by heterogeneity in effect sizes for diastolic but not systolic BPV when study designs were compared. However, this is not supported by evidence demonstrating intact baroreflex function in early dementia, hinting towards normal BP regulation.<sup>112</sup> Indeed, definitive answers on the direction of causality between BP regulation and dementia are currently lacking.<sup>35</sup>

Our review analyzed an extensive spectrum of cognitive outcomes. There were sparse published data for vascular dementia, mixed dementia, cognitive decline, and domain-specific cognitive function. As such, the association between BPV and secondary outcomes was less clear. The putative association between BP with dementia appears strongest for vascular dementia often as a result of cerebrovascular disease.<sup>5</sup> Yet brain imaging studies indicate that the majority of dementia cases, including Alzheimer disease, have a mix of neurodegenerative and vascular-type pathology evident (eg, amyloid- $\beta$ , lacunes of vascular origin).<sup>113</sup> The combination of neurodegenerative and vascular pathologies further underscores how BP only partly explains the neurodegenerative processes preceding dementia and that BP may work in concert with other nonvascular and vascular risk factors. Previously, we raised the possibility that the interaction between BPV and white matter hyperintensities leads to impairments in processing speed and executive function,<sup>102</sup> with BPV especially impacting periventricular white matter pathways.<sup>10</sup>

The lack of consensus on BPV measurement and quantification contributes substantial heterogeneity between studies.<sup>17</sup> Different BPV metrics were pooled separately in ancillary analyses and demonstrated generally consistent results. Likewise, there was no evidence of heterogeneity between intravital, 24-hour ambulatory BP monitoring, home BP, and visit-to-visit variability. BP measurement intervals of 6 months or less conferred a higher risk for the primary outcome than did BP intervals greater than 6 months. Short- and long-term BPV are hypothesized to both reflect arterial reflex and compliance and dosing/titration of antihypertensive medications.<sup>114</sup> Previously meta-analytic findings indicate that both short- and long-term BPV are associated with cardiovascular outcomes and mortality.<sup>7</sup>

Strengths of this study include the multilevel approach, the large pooled analytical sample, and extensive ancillary analyses. Several limitations temper the

results of this review including evidence of publication bias. The retained studies were primarily undertaken in older aged adults (mean age 55–84 years) which may explain the difference in effect sizes observed for BPV and mean BP. Inclusion of such wide-ranging age groups may introduce other biases in the analyses, such as selection and attrition bias.<sup>115</sup> In addition, our review was marked by significant heterogeneity even when limiting analyses to high-quality studies, implicating methodological and population characteristics as a source of between study heterogeneity.

Another limitation is that several studies defined visit-to-visit BPV using BP measurements that were taken during follow-up, introducing bias due to informative censoring.<sup>109</sup> Likewise, some studies adjusted BPV analyses for mean BP, which may lead to an attenuation of effect sizes due to over-adjustment or multicollinearity. These are inherent limitations of the original studies, which were not designed to prospectively assess BPV independent of mean BP. Pooled analyses are prone to aggregation of study-level biases, and therefore, an individual participant data meta-analysis might reduce methodological heterogeneity and offer new insights on the role of BPV in dementia risk.

## Perspectives

In summary, this systematic review and meta-analysis showed that high BPV was associated with an increased risk of dementia and cognitive impairment, although the strength of evidence was low. The relative contribution of BPV to the risk of dementia and cognitive impairment exceeded that of mean BP in primarily older adult samples. Further investigation is warranted concerning the mechanisms through which BPV may confer heightened dementia risk over mean BP, and the potential of BPV as a target for dementia prevention.

## ARTICLE INFORMATION

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### Affiliations

Radboud University Medical Center, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute for Brain, Cognition, and Behaviour, Nijmegen, the Netherlands (R.A.A.d.H., J.A.H.R.C.). Bordeaux Population Health, University of Bordeaux, Inserm, Team Healthy, UMR 1219, CHU Bordeaux, France (C.T.). Adelaide Medical School (E.J.L.L., M.O., A.D.V., P.J.T.) and School of Psychology (D.T.), Freemasons Centre for Male Health and Wellbeing, The University of Adelaide, Australia. Centre for Nutrition and Gastrointestinal Research (M.O.) and University of Adelaide, Lyell McEwin Hospital (R.M.), South Australian Health and Medical Research Institute, Australia. School of Psychology (K.J.A.), Neuroscience Research Australia (K.J.A.), and Neuroscience Research Australia (R.P.), University of New South Wales, Sydney, Australia. Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA (A.H., Y.M.). Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan (K.K.). Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy (S.L.). Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD (L.J.L.). Department of Gerontology and Geriatrics, Leiden University Medical Center, Institute for Evidence-Based Medicine



in Old Age, the Netherlands (S.P.M.). Department of Cardiology, Hiroshima City Asa Hospital, Japan (M.N.). Imperial College London, United Kingdom (R.P.). Yokohama City University Center for Novel and Exploratory Clinical Trials, Yokohama City University Hospital, Japan (Y.Y.). The Department of Family Medicine and Community Health, Duke University, Durham, NC (Y.Y.).

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### Disclosures

None.

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