Title: Effects of Blood Pressure Variability and its Association with Dementia and Cognitive Impairment: A Systematic Review

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ABSTRACT

Background

This systematic review aimed to assess the relationship between blood pressure variability, cognitive function, and the potential for dementia in individuals with hypertension. Hypertension has been increasingly associated with cognitive impairment, with studies suggesting it may lead to structural and functional changes in the brain. This association involves damage to the blood-brain barrier, white matter lesions, and microvascular abnormalities, highlighting the importance of managing blood pressure to preserve cognitive health."

Methods

The review adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A comprehensive search was conducted in databases, including PubMed, Research Gate, Google Scholar, and Science Direct. The inclusion criteria required studies that examined the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Two independent reviewers evaluated each study's quality and potential bias using study-specific tools before inclusion.

Results

There were 17 studies, including four systematic reviews and meta-analyses, four randomized controlled trials, and nine observational studies, with 16,985,492 participants. The findings indicated that late-life blood pressure had a stronger association with cognitive function than midlife blood pressure. Hypertension was linked to an increased risk of all-cause dementia, Alzheimer's disease, and vascular dementia. Anti-hypertensive medications could reduce the risk of dementia or cognitive impairment, although the specific type of medication did not significantly affect overall cognitive performance. A significant limitation of this review was the heterogeneity in diagnostic criteria, cognitive assessment tools, and imaging techniques used among the studies, which limited direct comparisons and conclusive findings.

Conclusion

Blood pressure variability emerged as a potential predictor for cognitive impairment. Implementing strategies to reduce blood pressure variability may help mitigate the risk of dementia and improve cognitive outcomes in vulnerable populations.

Key Words: Dementia, Hypertension, Alzheimer’s Disease, cognitive impairment, Blood Pressure

INTRODUCTION

The number of older people with dementia is rising. Worldwide, dementia affects around 50 million people and this number is projected to increase thrice by 2050. Dementia affects the economy with global costs estimated at United State $1 trillion annually. According to the 2017 Lancet Commission on dementia prevention, intervention, and care, the nine potentially modifiable risk factors for dementia include less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact. The 2020 report of the Lancet Commission included three more risk factors for dementia: excessive alcohol consumption, traumatic brain injury, and air pollution. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed.[1]

Hypertension is a leading cause of age-related cognitive impairment. Hypertension was previously associated primarily with vascular dementia but has recently been linked to Alzheimer's disease as well.[2] It is well-established that midlife (40-65years age) hypertension is a modifiable risk factor for late-life dementia (>65 years if age).[3] One meta-analysis found that blood pressure lowering with antihypertensive agents was significantly associated with a lower risk of dementia or cognitive impairment.[4] Another study concluded that visit-to-visit blood pressure variability (BPV) independent of average blood pressure is associated with higher cardiovascular risk in older adults and that older subjects with higher levels of blood pressure variability have worse cognitive function.[5] Mechanisms by which high Systolic Blood Pressure (SBP) and BPV are thought to contribute to cognitive impairment include endothelial dysfunction, microemboli, and oxidative stress, promoting cerebral atherosclerosis.[6] Another study found that a large variation in blood pressure, rather than the direction of the variation, increases the risk of dementia.[7] Another study added that having both higher Systolic Blood Pressure Variability (SBPV) and Diastolic Blood Pressure Variability (DBPV) additively increased the risk of dementia and its subtypes in a general population.[8]

Multiple studies have been carried out to find the exact association between hypertension, BPV, and cognitive impairment. However, we still don't know the exact mechanisms through which hypertension and BPV lead to cognitive impairment and ultimately to dementia. If we do find the mechanisms responsible, it would help us further to prevent dementia in later stages of life. Moreover, the role of anti-hypertensives in the prevention of dementia is unclear. This review aims to further explore the correlation between high blood pressure, blood pressure variability, and cognitive impairment, and to examine the role of antihypertensives in preventing cognitive impairment.

This systematic review addresses several key questions regarding the association between hypertension, dementia and cognitive impairment. Firstly, the age and gender composition of participants in these studies contribute to our understanding of the relationships between blood pressure, cognitive function, and the risk of dementia. Secondly, the findings regarding the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Thirdly, the diverse diagnostic and testing methods employed in these studies contribute to our understanding of the impact of blood pressure on cognitive function and the risk of dementia. Furthermore, the effects of anti-hypertensive medications on the development and progression of dementia and cognitive impairment. Additionally, the prognostic value of SBPV or DBPV for cognitive impairment and the risk of dementia. Lastly, long-term SBPVs and mean heart

rate levels affect cognitive function in high-risk individuals. This systematic review assesses the correlation between BPV and dementia, particularly the role of hypertension in cognitive impairment, stratified by age and gender, while examining the effects of anti-hypertensive treatment. Despite existing research, the precise mechanisms connecting BPV to cognitive decline remain underexplored, necessitating a systematic review to better elucidate these associations and potential therapeutic implications.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[9]

Search Strategy

A comprehensive literature search was performed using PubMed, ResearchGate, Google Scholar, and ScienceDirect databases. The following filters were applied while considering the studies for the identification process for the review: Studies in the English language, free full-text, and Human studies. Keywords and Medical Subject Headings (MeSH) terms were used to identify 12 studies about our discussion. The search was generated using keywords such as "anti-hypertensives," "dementia," "hypertension," "Alzheimer's disease," "cerebrovascular disease/stroke," "neurovascular dysfunction," and combining them using the BOOLEANs "AND" and "OR." *Table 1* summarizes the search strategy used for the identification process in this systematic review. The search strategy for this review concluded in November 2023.

Eligibility criteria for considering studies under this review

Inclusion criteria

The studies were chosen for inclusion based on the following participant, intervention, and outcome characteristics. Population: Adults without specific medical conditions, diagnosed with or at risk for hypertension, Intervention: Blood pressure variability, Comparison: Consistent blood pressure levels or low blood pressure variability, Outcome: Association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment.

The following study characteristics were considered for inclusion: studies written and published in the English language, focusing on a population age over 50 years, involving only human participants, available as free full text, published within the last 30 years (1993-2023). The studies were required to investigate the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Diagnostic and testing methods for dementia and cognitive impairment needed to be clearly described and appropriate cognitive assessment tools with standardized outcome measures were required. The studies were required to have an adequate sample size and report the duration of blood pressure follow-up for cognitive performance. Study designs including systematic reviews, meta-analyses, randomized controlled trials, and observational studies were considered for inclusion.

Exclusion criteria

To ensure the relevance and quality of the included studies, certain exclusion criteria were applied: Animal participants, studies published before 1993, patients aged less than 50 years, Non-English language studies, paid articles, Gray literature, Studies with incomplete or insufficient data, Case reports, editorials, reviews, and conference abstracts, Studies without specific mention of blood pressure variability, Studies lacking relevant outcomes related to dementia and cognitive impairment, Studies using cognitive assessment tools that are not standardized, Studies without clear diagnostic and testing methods for dementia and cognitive impairment.

By applying the above inclusion and exclusion criteria, the systematic review aims to include relevant studies that provide valuable insights into the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment in adults with hypertension or at risk for hypertension.

Selection of studies for inclusion in the review

The screening of the articles was carried out by AJ and VB, who independently reviewed the titles and abstracts of the identified studies. Any disagreements were resolved through discussion and consensus between the two reviewers. In cases where a consensus could not be reached, a third reviewer, AP, was involved in providing a final decision. This ensured a thorough evaluation of all potentially relevant records and minimized bias. Throughout the screening process, detailed notes were taken to record the specific reasons for excluding research studies from the review.

Assessment of the Methodological Quality and Risk of Bias

The remaining studies were individually evaluated for quality by two independent authors using study-specific techniques. Each assessment tool has its scoring system, and studies with a score of more than 70% were accepted for inclusion in this study. The quality assessment of the studies, as well as the tools utilized, are summarized in *Tables 2 and 3*.[10-12]

RESULTS

A systematic search yielded a total of 11,690 records from various sources, including PubMed (n=3,112), Research Gate (n=100), Science Direct (n=8,310), and Google Scholar (n=168). After removing duplicates (n=8,096) and conducting an initial screening based on titles and abstracts leaving 125 studies for full-text screening. Among these, 106 studies were excluded during full-text screening, resulting in 19 studies that underwent quality assessment. Ultimately, two studies were excluded, leaving 17 studies with a total of 16,985,492 participants for inclusion in the systematic review.[3-8, 13-23,] Based on the assessment tools employed, the studies' quality scores exceeded 70%. Data collection concluded on December 3, 2023. For a visual representation of the selection process, refer to Figure 1, which presents the PRISMA flow chart detailing the identification and screening process used to select the final articles for review.

The studies on hypertension and late-life dementia involved participants aged 54 to 84.4 years, with some studies having a majority of male participants and others with more balanced gender distribution. The duration of blood pressure follow-up for cognitive performance and the mean blood pressure values varied across the studies, providing valuable insights into the relationship between blood pressure and cognitive outcomes in different contexts. Each of these studies contributed to our understanding of the relationship between blood pressure and cognitive function by considering different follow-up durations and mean blood pressure values in their respective populations.

The diagnosis and testing methods employed in the studies varied, reflecting the diverse approaches to assessing cognitive function and dementia. Several studies relied on comprehensive neuropsychological assessments to evaluate cognitive performance. Hughes et al, in their meta-analysis, utilized various cognitive

tests, including the Mini-Mental State Examination (MMSE), to assess cognitive impairment.[4] Similarly, Yano et al employed cognitive function tests, including the Digit Symbol Substitution Test and the Word Recall Test, to evaluate cognitive function.[18] Other studies, such as Chiu et al, focused on the diagnosis of dementia as an outcome.[20] These studies incorporated clinical diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), to identify cases of dementia. Additionally, imaging techniques, such as magnetic resonance imaging (MRI), were used to assess structural brain changes associated with cognitive impairment.[19] Therefore, a comprehensive understanding of the diagnostic and testing methodologies used is essential for accurately evaluating the impact of blood pressure on cognitive function and dementia risk.

Data extraction and management

Table 3 includes a summary of the included studies. The data was extracted in a Microsoft Excel spreadsheet by MK, SSV, and Ad.P to include authors, year of publication, mean age and % sex of the patients, sample size, type of study, duration of blood pressure follow-up for cognitive performance, mean BP, outcomes, diagnosis and testing, and conclusions. The data extraction concluded on Nov 2023. We did not use any statistical analysis to interpret results because of the heterogeneity of data and qualitatively analyzed the included studies.

DISCUSSION

Hypertension and Late-life Dementia and cognitive impairment

Midlife hypertension is significantly associated with a 1.19- to 1.55-fold excess risk of cognitive disorders, with potential benefits of a 21% reduction in dementia risk through antihypertensive medications.[19] Chiu et al indicated a higher dementia risk among the elderly subgroup, suggesting a potential association between hypertension and late-life dementia.[20] Similarly, the study conducted by Ya Nan and colleagues suggests a potential association between BPV, specifically SBPV or DBPV, and the risk of developing all-cause dementia in later life.[24] The research findings indicate that fluctuations in blood pressure may be linked to an increased likelihood of developing dementia.[13] Xu et al found that late-life blood pressure had stronger associations with cognitive function than mid-life blood pressure.[21] Furthermore, among late-life blood pressure control groups, those with controlled hypertension had higher cognitive scores. However, no significant correlation was found between midlife blood pressure control, late-life visit-to-visit DBPV, visit-to-visit pulse pressure (PP) variability, and cognitive scores. These results suggest that late-life blood pressure control and variability may have a more significant impact on cognitive function than midlife blood pressure.[21] The findings are in agreement with the results reported by Rouch et al. And Dregan et al.[14, 25]

Yano et al showed that higher midlife SBP levels were associated with lower cognitive function in later life.[18] Consistent research findings indicate that individuals with higher SBP levels during midlife tend to experience lower cognitive function as they age. These studies have consistently demonstrated an association between elevated SBP in middle age and subsequent cognitive impairment or impairment in later life. The link between midlife SBP and cognitive function suggests that maintaining optimal blood pressure levels during midlife may

play a crucial role in preserving cognitive abilities and reducing the risk of cognitive impairment as individuals grow older.[26-28] This suggests that elevated blood pressure during midlife may have long-term implications for cognitive health.

Association of Blood pressure variability with Dementia and cognitive impairment

Elevated SBPV and DBPV independently associated with a higher risk of dementia and cognitive impairment, surpassing the impact of mean blood pressure.[3] Chiu et al observed insignificant results regarding the incidence of cognitive impairment and no significant association between all-cause dementia risk and SBP.[20] In contrast, Ma et al. indicated that a large variation in both SBP and diastolic blood pressure (DBP) was associated with an increased risk of dementia.[7] This association became more pronounced with longer intervals between the assessment of blood pressure variation and the diagnosis of dementia. Similarly, Yoo et al focused on the relationship between hypertension and the risk of all-cause dementia, AD, and VaD. The findings demonstrated that hypertension increased the risk of all-cause dementia, AD, and VaD. Furthermore, there was an incrementally higher risk of these outcomes with SBPV and DBPV.[8]

Rouch et al. examined the association between blood pressure variability and cognition and found that higher systolic and DBPV were independently associated with poorer cognition, even when controlling for baseline SBP and DBP, respectively. In line with previous research, this study found that while SBPV was associated with poorer cognitive performance and an increased risk of developing dementia, the strongest associations were observed for DBP and mean arterial pressure (MAP).[17,22,23,29-31] This suggests that blood pressure variability, regardless of baseline blood pressure levels, may contribute to cognitive impairment.

Effects of Anti-hypertensives on Dementia and cognitive impairment

Hughes et al performed a meta-analysis and demonstrated that blood pressure lowering with anti-hypertensive agents compared to control was significantly associated with a reduction in dementia or cognitive impairment.[4] Additionally, they found a significant association between blood pressure lowering and a reduction in cognitive impairment. However, no significant correlation was observed between blood pressure lowering and the standardized mean cognitive score.[4] These findings suggest that anti-hypertensive treatment may benefit dementia and cognitive impairment, but it may not directly affect overall cognitive performance. Similarly, Wijsman et al's trial focused on the association between blood pressure-lowering medication (BPLM) and cognitive function/decline. Interestingly, they found no significant association between BPLM and cognitive function or decline, despite investigating different combinations of blood pressure-lowering medication.[5] This suggests that the specific medications used for blood pressure control may not have a direct impact on cognitive outcomes. Prince et al compared the effects of different treatments (diuretics, beta-blockers, and placebo) on cognitive function. The study found no significant difference in the mean learning test coefficients and trail-making coefficients between the three treatment groups.[16] These results suggest that the specific type of anti-hypertensive medication may not significantly impact cognitive function.

Prognostic value of SBPV or DBPV for cognitive impairment

The prognostic value of BPV with cognitive impairment and dementia has been a subject of interest in various studies. Several researchers have explored the association between BPV and cognitive outcomes, shedding light on its potential as an independent predictor and its implications for dementia prevention.

Yoo et al. conducted a study emphasizing that BPV is an independent predictor for developing dementia and its subtypes.[8] Their findings suggest that reducing BPV could be a target for preventing dementia in the general population. Recent research has demonstrated a correlation between the occurrence of dementia and elevated day-to-day or visit-to-visit BPV, as measured by the CV index.[28,31] This highlights the importance of considering BPV as a potential risk factor and the need to control blood pressure fluctuations to mitigate cognitive impairment. Chiu et al examined the association between SBPV and dementia risk and revealed that higher SBPV was significantly associated with an increased risk of all-cause dementia.[20] The significant association between higher SBPV and increased risk of all-cause dementia underscores the potential prognostic significance of SBPV as a predictor for dementia development.

Böhm et al conducted a study focusing on the long-term effects of SBP variations and mean heart rate (HR) levels on cognitive function in high-risk patients and demonstrated that these fluctuations were associated with the development of cognitive impairment, decline, and deterioration in these individuals.[6] These findings highlight the prognostic significance of long-term SBP variations and mean HR levels as potential indicators for identifying high-risk patients prone to cognitive impairment and decline.[22] In contrast, one study revealed the prognostic significance of excessive BPV for the progression of cognitive impairment.[32]

Collectively, these studies contribute to our understanding of the prognostic value of BPV for cognitive impairment. While there is evidence suggesting that BPV is an independent predictor of dementia and its subtypes, further research is needed to elucidate the specific associations and underlying mechanisms. Reducing BPV and maintaining stable blood pressure levels may hold promise as potential preventive strategies for cognitive impairment and dementia. Continued investigation into the role of BPV in cognitive health will be crucial for developing targeted interventions and improving overall cognitive outcomes.

STRENGTHS

The systematic review has notable strengths that enhance the reliability and comprehensiveness of our findings. By including studies with different durations of blood pressure follow-up, we could better understand how blood pressure affects cognitive performance over time. These studies ranged from a few months to several years, allowing us to examine short-term and long-term effects. As a result, our review offers significant insights into how blood pressure fluctuations may impact cognitive abilities.

LIMITATIONS

The main limitation of our review is the differences in diagnostic criteria, cognitive assessment tools, and imaging techniques employed across the studies that may contribute to variations in the reported results. These discrepancies may have contributed to heterogeneity in the reported results and limited the ability to make direct comparisons and draw generalizable conclusions. The use of different diagnostic criteria for dementia introduces variability in case identification and classification, potentially impacting the synthesis of findings. Additionally, the inclusion of specific populations, such as older adults or individuals with cardiovascular diseases, may restrict the generalizability of the observed associations between blood pressure variability and cognitive outcomes. Furthermore, despite our comprehensive search strategies to minimize publication bias, its potential influence on the results cannot be completely ruled out.

CONCLUSION

In conclusion, the systematic review explored the effects of BPV and its association with dementia and cognitive impairment. After an in-depth analysis, we were able to derive significant findings. In addition to using cognitive tests like the MMSE, Digit Symbol Substitution Test, and the Word Recall Test to assess cognitive changes, we also measure the diagnosis of dementia in the patient set.

Firstly, the studies indicate a high risk in the elderly subgroup, a stronger association of late-life blood pressure with cognitive impairment, and long-term implications of midlife blood pressure. Secondly, we emphasize the association between blood pressure variability and poor cognition suggesting the need for early intervention and continuous monitoring of blood pressure fluctuations. We share the impact of anti-hypertensive treatment on cognitive performance. Lastly, we cover the potential of using BPV as a predictor for dementia and its implications for preventing cognitive impairment.

In terms of future research recommendations, we propose investigating the specific mechanisms underlying this relationship to better understand the pathophysiology and develop targeted interventions. Conducting longitudinal studies to establish a causal relationship between BPV and cognitive impairment and exploring the potential moderating factors, such as age, gender, and comorbidities, could provide a more comprehensive understanding of the relationship. Implementing strategies to reduce BPV may help mitigate the risk and improve cognitive outcomes in susceptible populations. By emphasizing the need for further research and highlighting potential interventions, we hope to provide valuable insights for healthcare professionals, policymakers, and individuals seeking to maintain cognitive health.

SUMMARY - ACCELERATING TRANSLATION

Introduction: Dementia's global prevalence is surging, affecting about 50 million people, with projections indicating a threefold increase by 2050. Beyond the significant public health impact, the economic burden is substantial, with annual global costs estimated at $1 trillion. Hypertension, once primarily linked to vascular dementia, is now associated with Alzheimer's disease. Midlife hypertension is identified as a modifiable risk factor for late-life dementia. However, the precise mechanisms connecting hypertension, blood pressure variability (BPV), and cognitive impairment leading to dementia remain unclear.

Aim of Study: This systematic review aims to investigate the correlation between high blood pressure, BPV, and cognitive impairment, along with exploring the potential preventive role of anti-hypertensives. Key questions include the age and gender composition of study participants, the impact of BPV on dementia risk, diagnostic methods used, and the effects of anti-hypertensive medications.

Methodology: Following the PRISMA 2020 guidelines, a thorough literature search identified 12 relevant studies from sources like PubMed, Research Gate, Google Scholar, and ScienceDirect. Inclusion criteria focused on English language studies, human participants over 50 years, and a clear investigation into the association between BPV and dementia. After screening, 17 studies, involving 16,985,492 participants, were included in the review.

Results: Midlife hypertension consistently showed an increased risk of cognitive disorders. The duration of blood pressure follow-up and mean blood pressure values varied across studies, providing insights into the relationship between blood pressure and cognitive outcomes. Elevated SBPV and DBPV were independently linked to a higher risk of dementia and cognitive impairment, surpassing the impact of mean blood pressure. Anti-hypertensive medications were associated with a reduction in dementia risk, although the impact on overall cognitive performance was inconclusive. Different types of medications did not show significant differences in cognitive function outcomes. Studies highlighted the prognostic significance of BPV for cognitive impairment. Elevated day-to-day or visit-to-visit BPV was identified as an independent predictor for developing dementia, emphasizing the need to control blood pressure fluctuations. Long-term SBP variations and mean heart rate levels were associated with cognitive decline, indicating their potential as indicators for identifying high-risk patients prone to cognitive impairment.

Conclusion: In summary, the intricate connection between high blood pressure, BPV, and cognitive impairment leading to dementia is a global health challenge. Evidence suggests that midlife hypertension poses a significant risk, and controlling blood pressure in later life may help reduce the likelihood of cognitive decline. Anti-hypertensive medications show promise in lowering dementia risk, but their impact on overall cognitive function requires further investigation.

The findings reveals the importance of managing blood pressure variability, maintaining stable blood pressure levels, and considering personalized interventions for individuals at risk. This research provides valuable insights into the global concern of dementia, laying the groundwork for targeted preventive strategies and

improved cognitive outcomes. Continued research in this field is crucial to unravel the specific mechanisms and optimize interventions for a healthier aging population worldwide.

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32. Chen KH, Henderson VW, Stolwyk RJ, Dennerstein L, Szoeke C. Prehypertension in midlife is associated with worse cognition a decade later in middle-aged and older women. Age Ageing. 2015;44:439–445.

FIGURES AND TABLES.

Figure 1. The PRISMA Flow Chart Detailing the Identification and Screening Process Used to Select the Final Articles for this Review.

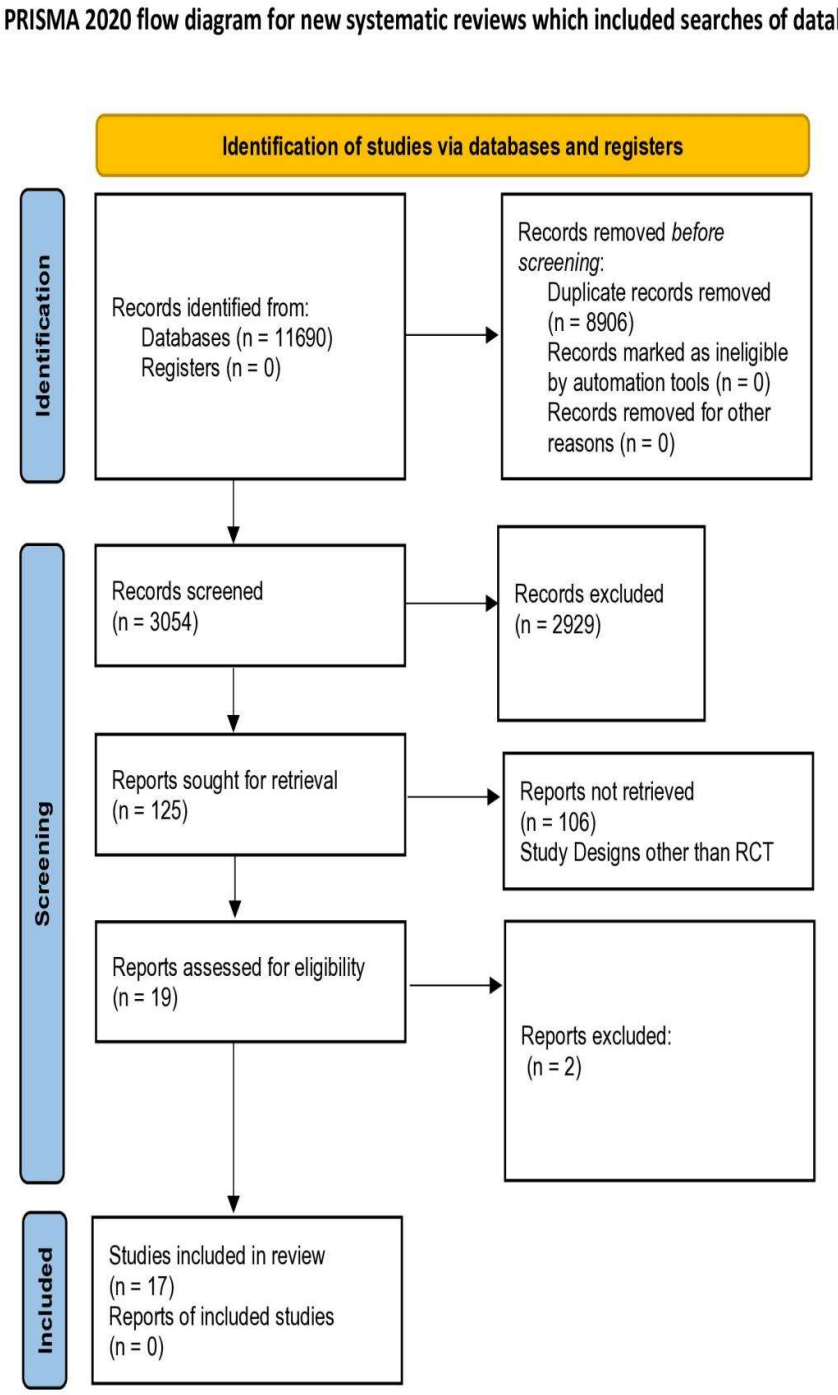

Table 1. **Details of the Search Strategy Used in This Systematic Review**

Serial No.	Database	MeSH terms	Filters applied	Results
1.	PubMed	((((("Blood Pressure"[Mesh] OR "Hypotension"[Mesh] OR "Hypertension"[Mesh]) OR "Blood Pressure Monitoring, Ambulatory"[Mesh]) AND "Dementia"[Mesh]) OR ("Frontotemporal Dementia"[Mesh] OR "Dementia, Multi-Infarct"[Mesh] OR "Dementia, Vascular"[Mesh] OR "Alzheimer Disease"[Mesh] OR "Mixed Dementias"[Mesh])) OR "cognitive impairment"[Mesh]	Free full text, published within the last 30 years (1993-2023), systematic reviews, meta-analyses, randomized controlled trials	3112
2.	Research Gate	("Blood pressure" OR "Hypertension") AND ("Dementia" OR "Alzheimers")	-	100
3.	Science Direct	Keywords: Dementia, Anti-hypertensives, Hypertension, Blood pressure	1993- 2023; Open access and Open archive	8,310
4.	Google Scholar	Keywords: Hypertension, Dementia, cognitive impairment, Anti-hypertensives, cerebrovascular disease/stroke	Full text	168

1

2 **Table 2. Quality Assessment of the Included Studies (Except RCTs)**

Author	Publication year	Report type	Quality assessment tool used	Score
De Heus, RAA et al.[3]	2021	Systematic review and Meta Analysis	AMSTAR	10
Hughes, D et al.[4]	2020	Systematic review and Meta Analysis	AMSTAR	9
Ya-Nan Ou et al.[19]	2020	Systematic review and Meta Analysis	AMSTAR	9
Tzu-Jung Chiu et al. [20]	2015	Systematic review and Meta Analysis	AMSTAR	8
Ozioma C. Okonkwo et al.[13]	2011	Non-randomised controlled trial	Newcastle Ottawa scale	8
Laure Rouch et al.[14]	2020	Cohort study	Newcastle Ottawa scale	8
Bo Qin et al.[17]	2016	Cohort study	Newcastle Ottawa scale	7
Yuan Ma et al.[7]	2019	Cohort study	Newcastle Ottawa scale	8
Jung Eun Yoo et al.[8]	2020	Cohort study	Newcastle Ottawa scale	8
Xu Liu et al.[22]	2016	Observational study	Newcastle Ottawa scale	7

Yuichiro Yano et al.[18]	2018	Cohort study	Newcastle Ottawa scale	8
Luxinyi Xu et al. [21]	2022	Cohort study	Newcastle Ottawa scale	6
Isabel J. Sible et al. [23]	2022	Cross sectional Study	Newcastle Ottawa scale	9

Newcastle Ottawa scale accepted score (>=70%): Minimum score 6 out of 9;[10] AMSTAR checklist accepted score (>=70%): Minimum score 8 out of 11.[11]

Table 3. Cochrane Risk of Bias Assessment for Randomized Controlled Trials[12]

Author	Publication year	Overall risk of bias	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other sources of Bias	Blinding	Blinding Outcome assessment	Incomplete outcome data
Wijsman et al.[5]	2015	Low-risk	Moderate risk	Low-risk	Low- risk	Low- ris	Low-risk	Low-risk	Low-risk
Böhm et al. [6]	2015	Moderate risk	Low-risk	Low-risk	Moderate risk	Moderate risk	Low-risk	Low-risk	Low-risk
Williamson et al.[15]	2019	Low-risk	Low-risk	Moderate risk	Low- risk	Low-risk	Low-risk	Low-risk	Low-risk
Prince et al.[16]	1996	Moderate risk	Moderate risk	Low-risk	Low- risk	Low-risk	Moderate risk	Low-risk	Low-risk

1 **Table 4. Characteristics of Included Studies in this Systematic Review**

2

ID	Author name and year	Mean age and % sex of patients	Sample size	Type of Study	Duration of Blood pressure(BP)follow-up for cognitive performance	Mean BP	Outcomes	Diagnosis and testing	Conclusion
1.	Tzu-Jung Chiu et al. (August 2021) [20]	54.3–84.4 years; 52.4% male, 47.6% female	7924168 (20 cohort studies)	Systematic review and meta-analysis	3 months to 22 years	-	Higher dementia risk among the elderly subgroup.No significance was found between the risk of all-cause dementia and SBP.	MMSE, MoCA, CAMCOG, non-global cognitive test (eg, Trail Making Test (parts A and B, TMT-A&B), Letter Cancellation test, Stroop test, COWA test, Telephone Interview for Cognitive Status-modified, global composite cognitive score, Letter-Digit Coding test, non-global cognitive test (eg, DWRT, DSST, WFT),	Higher SBPV was significantly associated with higher all-cause dementia risk but was not specifically associated with the dementia sub-types.]

								ICD, ADAS-COG, CDR, MSE, DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	
2.	Diarmaid Hughes et al (May 2020) [4]	69 (5.4) years,57.8% male, 42.2% female	92135 (16 randomzied controlled trials)	Meta analysis	4.1 years	SBP: 154 (14.9) mmHg; DBP: 83.3 (9.9) mmHg	The primary outcome was blood pressure lowering with anti-hypertensive agents compared with control was significantly associated with a reduction in dementia or cognitive impairment. The secondary outcome was Blood pressure lowering with anti-hypertensive agents compared with control was significantly associated with a reduction in cognitive impairment	Short-care instrument, MMSE, MoCA, DSCT, LMF II, DSST, TMT Part B, CASI z score, PALT	Lowering blood pressure may be associated with a lower risk of dementia or cognitive impairment.

							and was not significantly associated with a difference in the standardized mean cognitive score.		
3.	Liselotte W. Wijsman et al (March 2016) [5]	70–82 years	5,606	Randomized, double blind, placebo-controlled trial (PROSPER)	Every 3 months for 3.2 years	-	There was no significant association of BPLM and cognitive function.	MMSE	The association between BP variability and cognitive impairment was not mediated by BPLM.
4.	Michael Böhm Et al (Jan 2015) [6]	>55 years	24593	RCT	56 months	SBP: 130-240 mmHg DBP: 80-90 mmHg	cognitive impairment was observed in 1857 patients (7.6%) and cognitive impairment in 1176 patients (4.8%) and incident cognitive impairment in high risk cardiovascular patients.	MMSE	Long-term SBP variations and mean HR levels are associated with the development of cognitive

									impairment, decline, and deterioration in high risk patients.
5.	Ozioma C. Okonkwo et al (Sept 2012) [13]	55-85 years	172	Prospective multicenter cohort study	Baseline, 12 and 36 months	-	Reduced variability in systolic BP was associated with a faster rate of decline in Attention-Executive-Psychomotor function and vice versa.	MMSE, DRS-2, DSST, TMT Part A and B, COWA, Letter Cancellation Test, the Stroop test. WAIS-III	Decline in frontal-subcortical cognitive functions is mediated by variability in blood pressure.
6.	Laure Rouch et al (August 2020) [14]	76.9 (7.8) years old; 43% male, 57% female	3319	Cohort study	Every 6 months for 3 years.	SBP: 133.7 (11.8) mmHg, DBP: 76.9	Higher systolic and diastolic BPV was associated with poorer cognition independently.	MMSE, DSM-III-R. NINCDS-ADRDA, NINDS-AIREN	BPV is a major clinical predictor of cognitive impairment and dementia.
7.	Luxinyi Xu et al. (August 2022) [21]	61.5 years	3511	Prospective study	four waves for 7-year	-	Late-life BP showed stronger associations	MMSE	BP variation and visit-to-

					follow-up		with cognitive function than midlife BP.		visit BP variability were significantly related to cognitive function among the Chinese elderly. Receiving effective late-life anti-hypertensive treatment and keeping SBP stable might contribute to prevent the development of cognitive impairment and dementia.
8.	Yuan Ma et al.	67.6 years;	5273	Prospective	14.6 years	-	A large SBP and DBP	MMSE, GMS	A large blood

	(Nov 2019) [7]	58.1% women, 21.9% male		cohort study			variation was associated with an increased dementia risk, which became more pronounced with longer intervals between the assessment of SBP variation and the diagnosis of dementia.		pressure variation over a period of years was associated with an increased long-term risk of dementia.
9.	Jung En Yo et al. (March 2020) [8]	55.5 years; 52.5% male, 47.5% female	7844814	Retrospective cohort study	6.2 years	SBP: 127 (15.2) mmHg; DBP: 78 (10) mmHg	There were 200 574 new cases of all-cause dementia (2.8%), 165 112 cases of AD (2.1%), and 27 443 cases of VaD (0.3%). Hypertension increases the risk of all-cause dementia, AD, and VaD.	-	BPV is an independent predictor for developing dementia and its sub types.
10.	Yuichiro Yano et al. (July 2018) [18]	54 years; 56% female, 44% male	11408	Retrospective cohort study	25 years	SBP: 123 (11) mmHg; DBP 72 (7)	Lower cognitive performance in later life has been consistently associated to higher midlife	Global cognitive z score	From midlife on, SBP or DBP variability is mildly associat

						mmHg	SBP levels.		ed with lower cognitive function, whereas higher mean SBP and lower DBP levels from midlife to later life are modestly associated with cognitive impairment in later life.
11.	Jeff Williamson et al. (January 2019) [15]	67.9 years; 64.4% male, 35.6% female	9361	Randomized controlled trial	5. 11 years	SBP: 139.7 (15.6) mmHg, DBP: 80 mmHg	The primary outcome in the intensive treatment group, 149 participants dementic com- pared with 176 participants (8.6 per 1000 person-years) in the standard treatment group.	MoCA, Wechsler Memory scale, Wechsler Adult Intelligence scale	Treatment to a systolic blood pressure goal of fewer than 120 mm Hg versus a goal of less

									than 140 mm Hg did not result in a meaningful reduction in the incidence of probable dementia in ambulatory persons with hypertension.
12.	MJ Prince et al. (March 1996) [16]	70. 3 years; 58% female, 42% male	4396	Randomized placebo controlled single blinded trial	54 months	SBP: 160-209 mmHg, DBP: <115 mmHg	The mean learning test coefficients (rate of change of score over time) and trail-making coefficients of the three treatments, diuretics, beta-blockers, and placebo, did not vary.	PALT, TMT Part A	It's doubtful that treating moderate hypertension in elderly persons will have an impact on their subsequent cognitive function

									, either favorably or unfavorably.
13.	De Heus, RAA et al. (November 2021) [3]	73±7 years; 58±13% women	7915 9 46	Systematic review and Meta-analysis	-	-	Elevated systolic and DBPV were independently associated with a higher risk of dementia and cognitive impairment not mean BP	MMSE, MoCA, CDR	Both an elevated average blood pressure and increased blood pressure variability were correlated with higher odds of experiencing dementia or cognitive impairment.

14.	Ya-Nan Ou et al. (May 2020) [19]	35.3 to 93.2 years,; 46% women	2214 8 14	Systematic review and meta analysis	1 month to 5years	-	The analysis revealed stronger associations in midlife compared to late-life. The findings emphasized midlife hypertension's significant association with a 1.19- to 1.55-fold excess risk of cognitive disorders and the potential benefits of antihypertensive medications, which demonstrated a 21% reduction in dementia risk.	Variable	The associations between blood pressure (BP) factors and cognitive disorders vary based on age and the type of blood pressure. The use of antihypertensive medications was linked to a lowered risk of dementia.

15.	Bo Qin et al. (July 2016) [17]	63.1 (6.9); 52% female	976	Cohort study	5.3 years	SBP: 122 mmHg; DBP: 78mmHg	Higher visit-to-visit variability in diastolic BP was associated with a faster decline of cognitive function, independent of mean diastolic BP amongst elderly.	MMSE, Telephone Interview for Cognitive Status – modified (TICS-m)	Higher long-term BP visit-to-visit variability is associated with a faster rate of cognitive impairment among older adults.
16.	Zhendong Liu et al. (July 2016) [27]	74.5% female	232	Cohort study	2.3 years	-	In the oldest old, higher variability in self-measured systolic high blood pressure, as indicated by tertiles of the coefficient of variation at baseline, was significantly associated with greater declines in MMSEscores and increased progression of periventricular and deep white matter hyperintensitie	MMSE	Excessive variability in self-measured systolic HBP exacerbates the progression of cognitive impairment and brain white matter lesions in the oldest

							s.		old.
17.	Isabel J. Sible et al. (October 2022) [23]	69.9 (8.2); 37% female and 63% male	54	Cross-sectional study	-	SBP: 131 mmHg; DBP: 74 mmHg	Elevated blood pressure variability over a 5-minute period was associated with lower levels of plasma Aβ1–42 and Aβ1–42: Aβ1–40 ratio, as well as higher levels of total tau and Ptau181:Aβ1–42 ratio in the study population.	-	Increased variability in blood pressure is correlated with elevated plasma biomarkers indicative of heightened Alzheimer's disease pathophysiology.

MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, CAMCOG: Cambridge Cognition Examination, ADAS-COG: Alzheimer's Disease Assessment Scale-Cognitive Subscale, CDR: Clinical Dementia Rating Scale, MSE: Modified Mini-Mental State Examination, DSM: The Diagnostic and Statistical Manual of Mental Disorders, NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association, NINDS-AIREN: International Workshop of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences, COWA: Controlled Oral Word Association, DWRT: delayed Word Recall Test, DSCT: Digital Symbol Coding Test, DSST: Digit Symbol Substitution Test, WFT: Word Fluency Test, ICD: International Classification of Disease, ADAS-COG: Alzheimer's Disease Assessment Scale–Cognitive Subscale, LMF: Logical Memory form, TMT: Trail making test, CASI: Cognitive Ability Screening Instrument, PALT: Paired Associate Learning Test, BP: Blood pressure, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure, BPLM: Blood pressure lowering medication, RCT: Randomized controlled trial, DRS-2: Dementia Rating Scale-2,WAIS: Wechsler Adult Intelligence Scale, CVD: Cardiovascular disease, BPV: Blood Pressure Variability, GMS: Geriatric Mental Schedule, SBPV: Systolic Blood pressure Variability, DBPV: Diastolic Blood pressure Variability, TICS-m: Telephone Interview for Cognitive Status –modified