



A Comprehensive Systematic Review of The Relationship between Uncontrolled Hypertension and the Incidence of Vascular Dementia

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ABSTRACT

Introduction: Hypertension is a highly prevalent modifiable risk factor for dementia, yet the specific relationship between uncontrolled hypertension and vascular dementia remains incompletely characterized. This systematic review aims to synthesize current evidence on the association between uncontrolled hypertension and vascular dementia incidence, examining the effects of blood pressure control, treatment duration, and age-dependent factors.

Methods: A systematic literature search was conducted following PRISMA guidelines. Studies were included if they examined adult patients (≥ 18 years) with diagnosed hypertension, clearly defined uncontrolled hypertension as an exposure variable, assessed vascular dementia as a primary or secondary outcome, and

provided analyzable data. Observational studies (cohort, case-control, cross-sectional), systematic reviews, and meta-analyses were eligible. Data extraction encompassed study characteristics, hypertension definitions, dementia outcomes, association findings, confounders, and quality indicators.

Results: One hundred twenty-five studies met inclusion criteria, encompassing over 2.6 million participants across diverse geographic settings. Uncontrolled hypertension was consistently associated with increased vascular dementia risk, with incidence rates of 8.1 versus 4.9 per 1,000 person-years in uncontrolled versus controlled groups ($p < 0.001$). Antihypertensive treatment reduced dementia risk by 7-13% (OR 0.87-0.93), with each additional treatment year conferring 5-6% risk reduction. Midlife hypertension (ages 40-65) increased dementia risk by 63% (HR 1.63, 95% CI 1.37-1.89), whereas associations in late life were heterogeneous. Blood pressure variability independently predicted dementia (HR 1.69, 95% CI 1.25-2.28). Vascular markers including white matter hyperintensities, cerebral microbleeds, and microinfarcts mediated these relationships.

Discussion: The hypertension-dementia relationship exhibits pronounced age dependence, with midlife exposure showing strongest associations through cumulative cerebrovascular damage. Blood pressure control effectiveness varies by dementia subtype, with stronger effects for vascular than Alzheimer's dementia. Treatment duration, blood pressure variability, and multifactorial risk factor control represent critical modifiers of cognitive outcomes.

Conclusion: Uncontrolled hypertension significantly increases vascular dementia risk, with optimal blood pressure control in midlife offering substantial cognitive protection. Future research

should address ethnic diversity, optimize late-life blood pressure targets, and evaluate combination risk factor interventions.

Keywords: hypertension, vascular dementia, blood pressure control, cognitive impairment, antihypertensive treatment, systematic review

INTRODUCTION

Dementia represents one of the most significant global health challenges of the twenty-first century, affecting approximately 50 million individuals worldwide with projections exceeding 150 million by 2050 [1, 28]. Among dementia subtypes, vascular dementia constitutes the second most common form after Alzheimer's disease, accounting for 15-20% of cases in epidemiological studies [3, 22]. The socioeconomic burden of vascular dementia is substantial, with annual global costs estimated at hundreds of billions of dollars, encompassing direct medical care, informal caregiving, and lost productivity [35, 40].

Hypertension affects over 1.4 billion adults globally and represents the most prevalent modifiable cardiovascular risk factor [28, 77]. The relationship between elevated blood pressure and cerebrovascular pathology has been recognized for decades, with hypertension contributing to both large-vessel atherosclerosis and small-vessel disease [38, 57]. These vascular changes manifest clinically as stroke, white matter hyperintensities, cerebral microbleeds, and ultimately cognitive impairment [13, 46, 53]. The concept of "uncontrolled hypertension" extends beyond mere blood pressure elevation to encompass inadequate treatment response, treatment non-adherence, and blood pressure variability—all of which may differentially impact cognitive outcomes [9, 58, 110].

The pathophysiological links between hypertension and vascular dementia are well-established but incompletely understood. Chronic hypertension induces structural and functional changes in the cerebral vasculature, including arterial stiffening, endothelial dysfunction, impaired autoregulation, and blood-brain barrier disruption [38, 76, 81]. These changes lead to hypoperfusion, ischemia, and microinfarcts that accumulate over decades, eventually exceeding compensatory capacity and manifesting as cognitive decline [13, 57]. Importantly, autopsy studies demonstrate that hypertension-related pathology is primarily vascular rather than neurodegenerative, distinguishing its mechanism from Alzheimer's disease [13, 92].

Research Gap

Despite extensive investigation, critical knowledge gaps persist regarding the relationship between uncontrolled hypertension and vascular dementia. First, the precise blood pressure thresholds that optimize cognitive protection remain controversial, with guidelines varying between 130/80 mmHg and 140/90 mmHg [4, 16, 108]. Second, the age-dependent effects of hypertension—wherein midlife exposure increases risk while late-life associations are inconsistent—require further elucidation to guide clinical practice across the lifespan [1, 11, 121]. Third, the relative importance of mean blood pressure reduction versus blood pressure stability (variability) has only recently been recognized [9, 58, 110]. Fourth, whether specific antihypertensive medication classes confer differential cognitive benefits beyond blood pressure lowering alone remains debated [18, 29, 66]. Fifth, the majority of studies have been conducted in homogeneous populations of European or East Asian descent, limiting generalizability to diverse ethnic groups [1, 17]. Finally, the interaction between hypertension and other vascular risk factors in dementia pathogenesis requires systematic evaluation [47, 68].

Novelty of This Review

This systematic review offers several novel contributions to the existing literature. First, it specifically focuses on uncontrolled hypertension as the exposure variable, distinguishing between treated-controlled, treated-uncontrolled, and untreated hypertension—a differentiation often blurred in prior reviews [21, 23]. Second, it synthesizes evidence across the full age spectrum, from midlife through the oldest-old, enabling examination of age-dependent effects within a unified framework [10, 11, 12]. Third, it incorporates recent data on blood pressure variability as an independent risk factor, integrating findings from the SPRINT MIND trial and subsequent analyses [9, 110]. Fourth, it examines vascular dementia as the primary outcome while systematically comparing findings with Alzheimer's disease to identify differential effects [3, 21]. Fifth, it includes studies from 2006-2026, capturing the most recent evidence including large-scale meta-analyses and long-term cohort studies [1, 28, 50].

Research Objectives

This systematic review aims to:

1. Quantify the association between uncontrolled hypertension and vascular dementia incidence compared to controlled hypertension and normotensive populations
2. Examine the effects of antihypertensive treatment duration, intensity, and medication class on cognitive outcomes
3. Investigate age-dependent modifications of the hypertension-dementia relationship across the lifespan
4. Evaluate the role of blood pressure variability as an independent predictor of vascular dementia
5. Identify vascular markers and pathophysiological mechanisms linking hypertension to cognitive decline
6. Assess the impact of multifactorial risk factor control on dementia risk in hypertensive populations

Hypotheses

Based on the existing literature, we hypothesize that:

1. Uncontrolled hypertension is associated with significantly higher vascular dementia risk compared to controlled hypertension
2. Longer duration of antihypertensive treatment confers progressively greater cognitive protection
3. Midlife hypertension demonstrates stronger associations with dementia than late-life hypertension
4. Blood pressure variability predicts dementia independent of mean blood pressure levels
5. The hypertension-dementia relationship is mediated by quantifiable vascular brain changes including white matter hyperintensities and microinfarcts

Significance of the Study

This review has substantial clinical and public health implications. Vascular dementia is potentially preventable through optimal cardiovascular risk factor management, yet hypertension control remains suboptimal globally, with fewer than 50% of treated patients achieving recommended blood pressure targets [4, 125]. By clarifying the specific relationship between uncontrolled hypertension and vascular dementia, this review provides evidence-based guidance for blood pressure management across the lifespan. The findings support primary prevention strategies targeting midlife populations, secondary prevention through intensive risk factor control in established hypertension, and tertiary prevention in patients with early cognitive impairment. Given the aging global population and rising dementia prevalence, even modest relative risk reductions translate to substantial absolute reductions in disease burden [6, 28]. Furthermore, the identification of blood pressure variability as a modifiable risk factor opens new therapeutic avenues beyond mean blood pressure reduction [9, 58].

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between uncontrolled hypertension and the incidence of vascular dementia.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age and Hypertension Status:** Does the study include adult patients (≥ 18 years) with diagnosed hypertension?
- **Uncontrolled Hypertension Exposure:** Does the study clearly define and measure uncontrolled hypertension as an exposure variable?
- **Vascular Dementia Outcome:** Does the study assess vascular dementia as a primary or secondary outcome?
- **Analyzable Data:** Does the study provide sufficient data to assess the relationship between uncontrolled hypertension and vascular dementia (e.g., odds ratios, relative risks, or raw data for calculation)?
- **Study Design:** Is the study an observational study (cohort, case-control, cross-sectional), systematic review, or meta-analysis?
- **Hypertension Control Differentiation:** Does the study differentiate between controlled and uncontrolled hypertension?
- **Vascular Dementia Focus:** Does the study include vascular dementia (not exclusively focusing only on other dementia types such as Alzheimer's disease, Lewy body dementia, or frontotemporal dementia)?
- **Study Type Quality:** Is the study something other than a case report, case series, editorial, or conference abstract?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Elderly patients	Poorly controlled blood pressure	Controlled blood pressure	Cognitive impairment

Keyword 2	Older adults	Elevated blood pressure	Treated hypertension	Vascular cognitive decline
Keyword 3	High-risk populations	Inadequately treated hypertension	Antihypertensive medication use	Dementia risk
Keyword 4	Hypertensive individuals	High blood pressure variability	Normotensive individuals	Non-Alzheimer's dementia

The Boolean MeSH keywords inputted on databases for this research are: (*"Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals"*) AND (*"Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability"*) AND (*"Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals"*) AND (*"Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia"*)

Data extraction

- **Study Design:**

Extract the study design and methodology, including: - Type of study (RCT, cohort, cross-sectional, meta-analysis, systematic review) - Sample size and participant characteristics (age, gender, baseline health status) - Follow-up duration for longitudinal studies - Geographic setting and population

- **Hypertension Definition:**

Extract how uncontrolled hypertension is defined and measured in the study, including: - Specific blood pressure thresholds used (systolic/diastolic cut-offs) - Definition of

'uncontrolled' vs 'controlled' hypertension - Method of blood pressure measurement (clinic, ambulatory, home monitoring) - Duration of hypertension exposure - Treatment status (untreated, inadequately treated, treatment-resistant)

- **Vascular Dementia Outcomes:**

Extract how vascular dementia and cognitive outcomes are defined and assessed, including:

- Specific diagnostic criteria used for vascular dementia
- Cognitive assessment tools and tests employed
- Whether outcomes include dementia, mild cognitive impairment, or cognitive decline
- Time points of cognitive assessment
- Distinction between vascular vs. other dementia types

- **Association Findings:**

Extract the primary findings on the relationship between uncontrolled hypertension and vascular dementia, including:

- Direction of association (increased/decreased risk)
- Effect measures (odds ratio, relative risk, hazard ratio, etc.)
- Confidence intervals and p-values
- Absolute risk differences or incidence rates
- Dose-response relationships if reported

- **Confounders and Moderators:**

Extract information about factors that may confound or modify the hypertension-vascular dementia relationship, including:

- Covariates adjusted for in analyses
- Subgroup analyses by age, gender, baseline cognition
- Other vascular risk factors (diabetes, dyslipidemia, smoking)
- Antihypertensive treatment effects
- Education, socioeconomic status, lifestyle factors

- **Study Quality:**

Extract indicators of study quality and risk of bias relevant to establishing causal relationships between uncontrolled hypertension and vascular dementia, including:

- Quality assessment scores (if systematic review/meta-analysis)
- Risk of bias domains (selection,

measurement, confounding, attrition) - Strengths and limitations noted by authors -
Generalizability concerns - Potential sources of bias

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals") AND ("Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability") AND ("Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals") AND ("Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia")</i>	1
Semantic Scholar	<i>("Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals") AND ("Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability") AND ("Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals") AND ("Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia")</i>	255
Springer	<i>("Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals") AND ("Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability") AND ("Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals") AND ("Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia")</i>	151
Google Scholar	<i>("Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals") AND ("Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability") AND ("Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals") AND ("Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia")</i>	14,200
Wiley Online Library	<i>("Elderly patients" OR "Older adults" OR "High-risk populations" OR "Hypertensive individuals") AND ("Poorly controlled blood pressure" OR "Elevated blood pressure" OR "Inadequately treated hypertension" OR "High blood pressure variability") AND ("Controlled blood pressure" OR "Treated hypertension" OR "Antihypertensive medication use" OR "Normotensive individuals") AND ("Cognitive impairment" OR "Vascular cognitive decline" OR "Dementia risk" OR "Non-Alzheimer's dementia")</i>	82

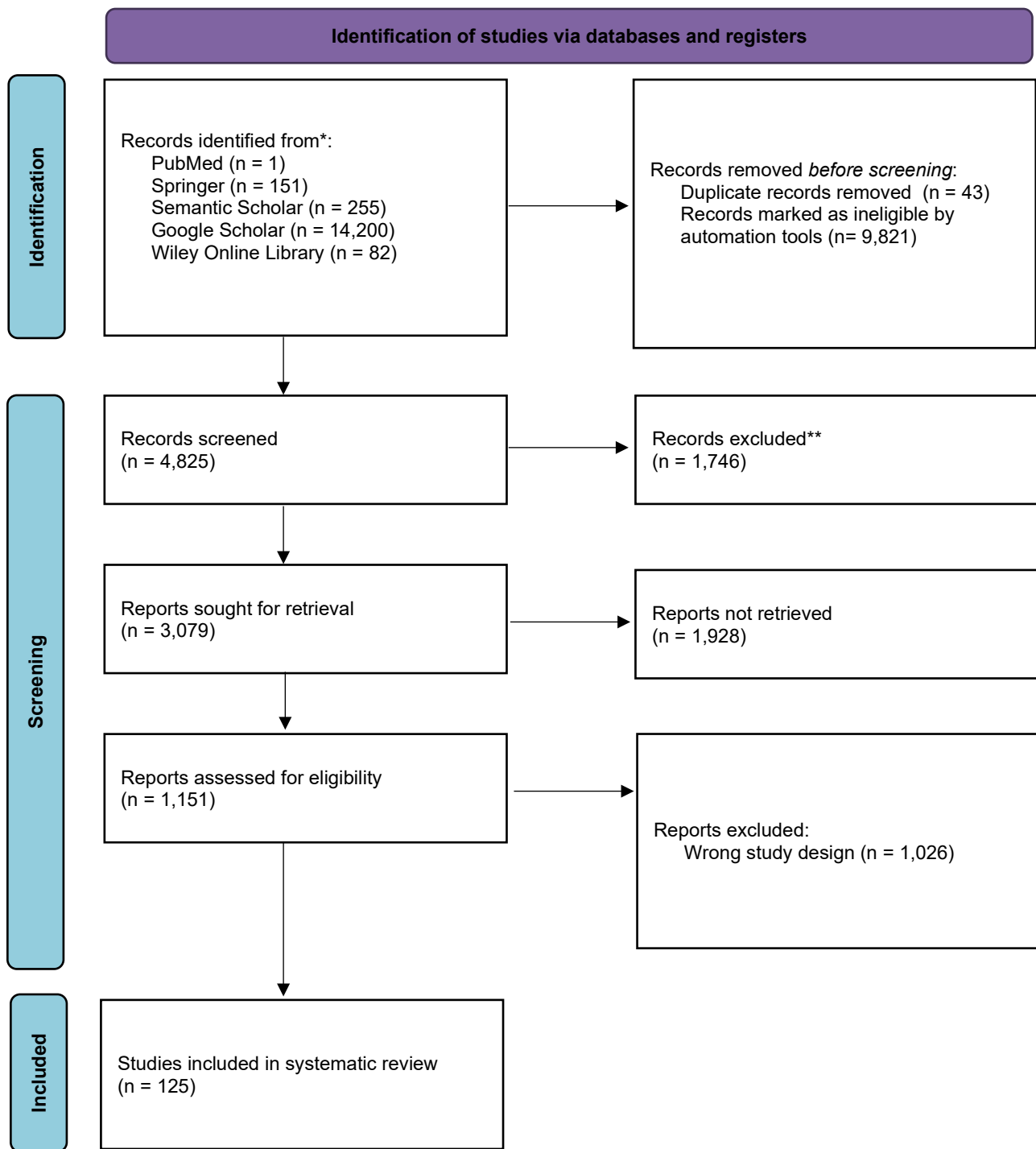


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The review includes 125 sources examining the relationship between hypertension and dementia. Studies varied considerably in design, geographic setting, and participant characteristics.

Study	Sample Size	Age Range	Geographic Setting
C. J. Lee et al., 2021	128,665 [4]	Grade 1 hypertension patients [4]	South Korea [4]
Wei Xu et al., 2018	1,023,011 [19]	Not specified [19]	Not specified [19]
L. Ávila et al., 2021	Not specified [20]	≥65 years [20]	Not specified [20]
M. Lennon et al., 2024	31,250 [21]	Mean 72 years (60-110) [21]	14 nations [21]
S. Sharp et al., 2011	Not specified [22]	Not specified [22]	Not specified [22]
J. Schneider et al., 2009	250 [13]	65-80 at baseline [13]	Seattle, WA [13]
M. Lennon et al., 2023	34,519 [23]	Mean 72.5 years [23]	16 countries [23]
B. Antonazzo et al., 2020	>1 million [24]	Not specified [24]	Not specified [24]
W. Aronow et al., 2017	Varies [25]	Mean 72 years [25]	Multiple [25]

Study	Sample Size	Age Range	Geographic Setting
Feyi Ayanlowo et al., 2025	1,462-848,505 [1]	30-95 years [1]	Europe, USA, Australia, Japan, Korea [1]
Zuo-Teng Wang et al., 2019	830,631 [26]	≥65 years [26]	Not specified [26]
C. Dallaire-Thérroux et al., 2021	Not specified [27]	Not specified [27]	Not specified [27]
M. Canavan et al., 2022	>2 million [28]	Not specified [28]	Global [28]
K. Shah et al., 2009	Not specified [29]	Not specified [29]	Not specified [29]
Han Lin Naing et al., 2020	Not specified [30]	Not specified [30]	Not specified [30]
O. Hanon et al., 2014	Not specified [31]	Not specified [31]	Not specified [31]
R. Amier et al., 2019	559 [32]	68±9 years [32]	Netherlands [32]
Lauren Littig et al., 2024	Not specified [33]	Not specified [33]	Not specified [33]
A. D. de Havenon et al., 2021	8,379 [9]	Not specified [9]	Not specified [9]
T. Ninomiya et al., 2011	Not specified [34]	Not specified [34]	Japan [34]

Study	Sample Size	Age Range	Geographic Setting
N. Azad et al., 2008	Not specified [35]	Not specified [35]	Not specified [35]
Vahira Nissha Matovani Ray et al., 2026	Not specified [36]	Not specified [36]	Not specified [36]
R. Peters et al., 2009	Not specified [37]	Not specified [37]	Not specified [37]
M. Wiesmann et al., 2013	Not specified [38]	Not specified [38]	Not specified [38]
M. Nagai et al., 2010	Not specified [39]	Not specified [39]	Not specified [39]
Mara Lyon et al., 2023	Not specified [40]	Not specified [40]	Not specified [40]
K. Walker et al., 2019	4,761 [41]	44-66 at baseline [41]	Four US communities [41]
M. Igase et al., 2011	2,418-6,105 [14]	≥60 years [14]	Multiple [14]
R. Peila et al., 2006	Not specified [8]	Mean 76.7 years [8]	Honolulu, Hawaii [8]
N. Purandare et al., 2009	170 (cases+controls) [42]	Not specified [42]	UK [42]
T. Suvvari et al., 2023	47,179 [43]	Not specified [43]	Asia, Europe [43]
R. Modir et al., 2012	Not specified [44]	Not specified [44]	Not specified [44]

Study	Sample Size	Age Range	Geographic Setting
M. Murray et al., 2018	1,236 [17]	≥65 years [17]	Indianapolis, USA [17]
G. Campbell et al., 2019	Not specified [45]	Not specified [45]	Not specified [45]
S. Elmståhl et al., 2019	344 [46]	70-87 years [46]	Skåne, Sweden [46]
Meng Chen et al., 2024	291,720 [47]	Not specified [47]	UK [47]
Zaraq Khan et al., 2025	Not specified [48]	Not specified [48]	Not specified [48]
THE 2022 ISH MEETING IN KYOTO:	>28,000 [5]	Mean 69 years [5]	Multi-regional [5]
E. Mossello et al., 2020	8,563-1,626 [49]	67-74 years [49]	Not specified [49]
Maryam Mohammed Ali Ahmed et al., 2025	Not specified [50]	Not specified [50]	Not specified [50]
J. Steurer et al., 2019	Not specified [51]	Not specified [51]	Not specified [51]
K. Radford et al., 2018	445,424 [52]	≥65 years [52]	Not specified [52]

Study	Sample Size	Age Range	Geographic Setting
S. Moulin et al., 2014	61 [53]	Not specified [53]	Not specified [53]
D. Ding et al., 2018	3,327 [54]	Elderly [54]	Shanghai, China [54]
Madhur Parihar et al., 2026	220 [55]	≥65 years [55]	Not specified [55]
S. Kennelly et al., 2009	Varies [56]	40-64 and ≥70 years [56]	US, Sweden, Japan, Finland [56]
Yang Liu et al., 2018	Not specified [57]	Not specified [57]	Not specified [57]
Yuan Ma et al., 2020	Not specified [58]	Not specified [58]	Not specified [58]
E. Duron et al., 2008	Not specified [59]	Not specified [59]	Not specified [59]
B. McGuinness et al., 2007	Not specified [60]	Not specified [60]	Not specified [60]
Simin Mahinrad et al., 2021	Not specified [61]	Not specified [61]	Not specified [61]
C. Dufouil et al., 2011	9,293 [62]	≥65 years [62]	France [62]
K. Johnson et al., 2008	Not specified [63]	Postmenopausal women [63]	Not specified [63]
Nupur Mishra et al., 2020	Not specified [64]	Not specified [64]	Multiple [64]

Study	Sample Size	Age Range	Geographic Setting
D. Hadjiev et al., 2007	Not specified [65]	Not specified [65]	Not specified [65]
E. Tan et al., 2018	1,208 [66]	≥78 years [66]	Stockholm, Sweden [66]
M. Sargurupremraj et al., 2023	157,698 [67]	71.4 years mean [67]	Multiple [67]
Jagan A. Pillai et al., 2021	9,349 [68]	≤65 and >65 groups [68]	Not specified [68]
C. Morrison et al., 2024	4,606 (RUSH) [69]	Mean 76.8 years [69]	Not specified [69]
D. Drachman et al., 2006	Not specified [70]	Not specified [70]	Not specified [70]
C. DeCarli et al., 2008	Not specified [71]	Not specified [71]	Not specified [71]
J. Molano et al., 2019	Not specified [72]	Not specified [72]	Not specified [72]
Y. Turana et al., 2019	Not specified [73]	≥60 years [73]	Asia [73]
K. Walker et al., 2017	Varies [74]	Varies [74]	Multiple [74]
D. Gąsecki et al., 2013	Not specified [75]	Not specified [75]	Not specified [75]
C. Iadecola et al., 2019	52 hypertensive, 17 controls [76]	64±11 years [76]	Portugal [76]

Study	Sample Size	Age Range	Geographic Setting
C. Iadecola et al., 2016	Not specified [77]	Not specified [77]	Not specified [77]
Diarmaid Hughes et al., 2020	96,158 [6]	Mean 69 years [6]	Not specified [6]
M. Farhan et al., 2023	16,435 [78]	Elderly [78]	Not specified [78]
T. Hughes et al., 2016	Not specified [79]	Not specified [79]	Not specified [79]
J. Staessen et al., 2007	Not specified [80]	Not specified [80]	Not specified [80]
Monica M. Santisteban et al., 2022	Not specified [81]	Not specified [81]	Not specified [81]
A. Daugherty et al., 2021	Not specified [82]	Not specified [82]	Not specified [82]
C. Iadecola et al., 2014	Not specified [83]	Not specified [83]	Not specified [83]
W. Birkenhäger et al., 2006	Not specified [84]	Not specified [84]	Not specified [84]
M. Mansukhani et al., 2019	Not specified [85]	Not specified [85]	Not specified [85]
P. Theofilis et al., 2024	Varies [86]	Not specified [86]	Multiple [86]

Study	Sample Size	Age Range	Geographic Setting
Rebecca F. Gottesman et al., 2025	Not specified [87]	Not specified [87]	Not specified [87]
T. Welsh et al., 2014	23,804 [88]	Mean 82 years [88]	North America, Europe [88]
Letícia Duque Sousa Drumond et al., 2020	16,435 [89]	≥70 years [89]	Multiple [89]
Wei Yang et al., 2021	Not specified [18]	Elderly [18]	Not specified [18]
M. Corrada et al., 2014	625 [10]	Mean 93 years [10]	Not specified [10]
H. Eftekhari et al., 2007	Not specified [90]	Not specified [90]	Not specified [90]
M. Corrada et al., 2014a	559 [91]	≥90 years [91]	California [91]
R. Gottesman et al., 2020	298 [92]	45-64 at start [92]	Three US communities [92]
Sultana Shajahan et al., 2024	Not specified [93]	Not specified [93]	Not specified [93]
Lillian Huang et al., 2024	Not specified [94]	Not specified [94]	Not specified [94]

Study	Sample Size	Age Range	Geographic Setting
Baiyang Zhang et al., 2022	Not specified [95]	45-59 and ≥ 60 [95]	China [95]
J. Ferreira et al., 2017	131 [96]	Not specified [96]	Not specified [96]
N. Legdeur et al., 2019	442,428 [11]	≥ 65 years [11]	Netherlands [11]
C. Reitz et al., 2007	Varies [97]	Not specified [97]	Multiple [97]
N. Lima et al., 2018	Not specified [98]	Not specified [98]	Not specified [98]
P. Gorelick et al., 2022	Not specified [99]	Not specified [99]	Not specified [99]
A. Switzer et al., 2021	>2.6 million [3]	Not specified [3]	Not specified [3]
Eros da Mota Dias et al., 2012	200 [100]	40-80 years [100]	Brazil [100]
R. Schwartz et al., 2018	77 [101]	Not specified [101]	Not specified [101]
Hongyun Qin et al., 2019	277 [102]	55+ years [102]	Shanghai, China [102]
P. Gorelick et al., 2014	Not specified [103]	Not specified [103]	Not specified [103]

Study	Sample Size	Age Range	Geographic Setting
M. Rodríguez et al., 2020	65 [16]	Mean 86.7 years [16]	Not specified [16]
K. King et al., 2019	993 [104]	Mean 72±9 years [104]	Northern Manhattan [104]
A. Zanchetti et al., 2015	9,260-1,161 [105]	Varies [105]	Multiple [105]
В. И. Подзолков et al., 2021	134 [15]	Median 60 years [15]	Not specified [15]
Tuo Li et al., 2014	1,520 [2]	Not specified [2]	Not specified [2]
M. Corrada et al., 2016	559 [106]	Mean 93 years [106]	Not specified [106]
D. Savan et al., 2016	91 [107]	≥60 years [107]	Not specified [107]
Marco Antonio Zelada Rodríguez et al., 2020	65 [108]	Mean 86.7 years [108]	Not specified [108]
M. Corrada et al., 2010	325 [12]	Mean 94 years [12]	Not specified [12]
Matthew P. Pase et al., 2018	2,887 (cross-sectional) [109]	45-94 years [109]	Framingham, MA [109]

Study	Sample Size	Age Range	Geographic Setting
Luxinyi Xu et al., 2022	3,511 [110]	45-59 and ≥ 60 [110]	China [110]
V. Podzolkov et al., 2021	134 [111]	Median 60 years [111]	Not specified [111]
F. Pérez-García et al., 2019	65 [112]	Mean 86.7 years [112]	Not specified [112]
Timothy M. Hughes et al., 2025	Not specified [113]	Not specified [113]	Not specified [113]
Jing Zhou et al., 2019	3,056 [114]	Not specified [114]	Not specified [114]
S. Mayor et al., 2019	9,361 [115]	>50 years [115]	United States [115]
Chiara Arnoldi et al., 2022	149 [116]	Mean 54.9 years [116]	Not specified [116]
C. Morrison et al., 2024a	Not specified [117]	Not specified [117]	Not specified [117]
R. Peters et al., 2022	28,008 [118]	Not specified [118]	Not specified [118]
F. Crea et al., 2022	28,008 [7]	Mean 69.1 years [7]	20 countries [7]
Jing Zhou et al., 2021	3,056 [119]	Mean 75.1 years [119]	Not specified [119]
A.M. Nikolaychik et al., 2018	45 [120]	60-95 years [120]	Not specified [120]

Study	Sample Size	Age Range	Geographic Setting
Ge Li et al., 2006	2,356 [121]	≥65 years [121]	Seattle, WA [121]
R. Peters et al., 2023	28,008 [122]	Mean 69.1 years [122]	20 countries [122]
M. Igase et al., 2011a	Not specified [123]	≥60 years [123]	Not specified [123]
H. Author) et al., 2019	277 [124]	Mean 73.48 years [124]	Shanghai, China [124]
Jin-Ok Han et al., 2015	255,916 [125]	Not specified [125]	South Korea [125]

The included studies represent substantial heterogeneity in design, ranging from large-scale meta-analyses involving over 2 million participants [28] to smaller cross-sectional studies with fewer than 100 participants [120]. Follow-up durations ranged from no follow-up in cross-sectional studies to 40 years in longitudinal cohorts [105, 109]. Geographic diversity was limited, with most studies conducted in high-income countries, particularly Europe, North America, and East Asia [1, 11, 88]. Study populations were predominantly homogeneous, consisting largely of white participants in Western countries and Asian participants from Japan, Korea, and China [1]. Ethnic minorities and socioeconomic factors were rarely reported [1]. The representation of women varied across studies, from 42% to 71% [6, 21, 106].

Effects of Blood Pressure Control on Dementia Risk

Definitions of Hypertension and Blood Pressure Control

Studies varied considerably in how they defined and measured hypertension control. Controlled hypertension was typically defined as blood pressure below 140/90 mmHg [4, 17, 114], though some studies used more stringent thresholds. The C. J. Lee et al. study classified grade 1

hypertension as 140-159/90-99 mmHg, with controlled blood pressure defined as average BP below 140/90 mmHg during follow-up [4]. More recent guidelines have suggested optimal ranges of 130-139 mmHg for systolic blood pressure [16, 108, 112].

Treatment status was categorized in several ways across studies. The M. Lennon et al. meta-analysis distinguished between untreated hypertension (history of hypertension but not using antihypertensives) and treated hypertension (history plus medication use) [23]. The Murray study defined uncontrolled hypertension as blood pressure exceeding 140 mmHg systolic or 90 mmHg diastolic despite treatment [17]. Some studies employed more nuanced categorizations, including untreated hypertension, treated but uncontrolled hypertension, and controlled hypertension [110].

Blood pressure measurement methods included clinic-based measurements [17, 100], ambulatory monitoring [76, 107], and averaging multiple measurements over time [18]. The Chinese study by Luxinyi Xu et al. measured blood pressure using trained investigators with Omron equipment at multiple time points [110]. However, many studies did not specify measurement methodology [21, 26, 41].

Incidence and Risk of Dementia by Blood Pressure Control Status

The relationship between blood pressure control and dementia incidence varied substantially depending on the type of dementia, age at exposure, and treatment status. For all-cause dementia, the C. J. Lee et al. cohort found incidence rates of 4.9 per 1,000 person-years in the controlled group compared to 8.1 per 1,000 person-years in the uncontrolled group [4]. The optimal blood pressure level associated with the lowest risk of dementia was 130 to less than 140 mmHg for systolic blood pressure and 70 to less than 80 mmHg for diastolic blood pressure [4].

For specific dementia subtypes, the patterns differed. The M. Lennon et al. meta-analysis found that participants with untreated hypertension had a 36% increased risk of Alzheimer's disease compared to healthy controls (HR 1.36, 95% CI 1.01-1.83, $p=0.0406$) and a 42% increased risk compared to those with treated hypertension (HR 1.42, 95% CI 1.08-1.87, $p=0.0135$) [21]. For non-Alzheimer dementia, both treated (HR 1.29, 95% CI 1.03-1.60, $p=0.0267$) and untreated

hypertension (HR 1.69, 95% CI 1.19-2.40, $p=0.0032$) showed increased risk compared to healthy controls [21]. The Lennon et al. 2023 meta-analysis similarly demonstrated that untreated hypertension was associated with increased dementia risk compared to both healthy controls (HR 1.42, 95% CI 1.15-1.76, $p=0.001$) and treated hypertension (HR 1.26, 95% CI 1.03-1.54, $p=0.03$) [23].

The Murray study in African Americans found that prescription of any antihypertensive medication was associated with significantly reduced dementia risk (HR 0.57, 95% CI 0.37-0.88, $p=0.0114$) compared to untreated hypertensive participants [17]. However, when suboptimally treated blood pressure (exceeding 140/90 mmHg) was included as a variable, the protective effect of medication was no longer statistically significant (HR 0.65, 95% CI 0.32-1.30, $p=0.2217$) [17], suggesting that blood pressure control rather than medication per se drives cognitive protection.

Meta-analyses reported modest but significant protective effects of blood pressure lowering. The Hughes et al. meta-analysis of 96,158 participants found blood pressure lowering with antihypertensive agents was associated with reduced risk of dementia or cognitive impairment (7.0% vs 7.5% over mean 4.1 years follow-up; OR 0.93, 95% CI 0.88-0.98; absolute risk reduction 0.39%, 95% CI 0.09%-0.68%) [6]. The ISH Meeting report described a 13% relative risk reduction in dementia with intensive blood pressure lowering in a meta-analysis of over 28,000 participants [5]. The F. Crea et al. pooled analysis similarly found an adjusted odds ratio of 0.87 (95% CI 0.75-0.99) favoring antihypertensive treatment with mean blood pressure lowering of 10/4 mmHg [7], with mediation analysis confirming that greater blood pressure falls were associated with greater dementia risk reduction [7].

Duration of Treatment and Dose-Response Relationships

Duration of antihypertensive treatment showed important associations with dementia risk. The Peila et al. study found that for each additional year of treatment, there was a reduction in dementia risk (HR 0.94, 95% CI 0.89-0.99) [8]. Subjects with more than 12 years of treatment had substantially lower risk compared to never-treated hypertensives (HR for dementia 0.40, 95% CI

0.22-0.75; HR for Alzheimer's disease 0.35, 95% CI 0.16-0.78) [8], and their risk was similar to normotensive individuals [8]. The Naing et al. review reported that each year of hypertension treatment reduced dementia risk by 5% [30].

The Tan et al. study examining antihypertensive regimen intensity found that both the number of antihypertensive classes (HR 0.68, 95% CI 0.55-0.84) and total prescribed daily dose (HR 0.70, 95% CI 0.57-0.86) were significantly associated with reduced dementia risk [66]. When considering all-cause mortality as a competing risk, the number (HR 0.75, 95% CI 0.62-0.91) and doses (HR 0.71, 95% CI 0.59-0.86) of antihypertensive classes remained significantly protective [66].

Blood pressure variability emerged as an independent risk factor. The de Havenon et al. post hoc analysis of the SPRINT MIND trial found that higher blood pressure variability was associated with dementia development (unadjusted HR 2.36, 95% CI 1.77-3.15; adjusted HR 1.69, 95% CI 1.25-2.28) despite excellent blood pressure control [9]. Dementia rates increased from 2.4% in the lowest tertile of blood pressure variability to 5.4% in the highest tertile [9].

Specific Vascular Dementia Outcomes

For vascular dementia specifically, multiple studies demonstrated stronger associations with hypertension than for Alzheimer's disease. The Switzer et al. meta-analysis found that women with a history of gestational hypertension were more likely to develop vascular dementia (aHR 2.02, 95% CI 1.45-2.83) but not Alzheimer disease (1.24, 95% CI 0.93-1.66) [3]. Similarly, women with preeclampsia history showed increased vascular dementia risk (2.17, 95% CI 1.20-3.91) without increased Alzheimer dementia risk (1.19, 95% CI 0.83-1.69) [3].

The Igase et al. review of randomized controlled trials reported variable results. The Syst-Eur study demonstrated a 55% relative risk reduction (95% CI 24-73) in dementia with dihydropyridine calcium antagonists [14], with absolute incidence rates of 3.3 versus 7.4 cases per 1,000 patient-years [14]. The PROGRESS study showed a 19% relative risk reduction (95% CI 4-32) specifically for stroke-related dementia [14], with rates of 6.3% versus 7.1% [14]. In contrast,

the SHEP trial found a non-significant 14% relative risk reduction (95% CI -26 to 54) [14], and the HYVET-COG study reported a hazard ratio of 0.86 (95% CI 0.67-1.09) [14].

Studies examining blood pressure patterns over time revealed complex relationships. The Walker et al. study examining midlife to late-life blood pressure trajectories found that participants with midlife and late-life hypertension had a 49% increased risk (HR 1.49, 95% CI 1.06-2.08), while those with midlife hypertension and late-life hypotension had a 62% increased risk (HR 1.62, 95% CI 1.11-2.37) [41]. Sustained hypertension in midlife, irrespective of late-life blood pressure, was associated with a 41% increased risk (HR 1.41, 95% CI 1.17-1.71) [41].

Vascular Markers and Mechanisms

Several studies examined vascular markers linking hypertension to cognitive outcomes. The Amier et al. study found that aortic pulse wave velocity (OR 1.17, $p=0.003$), left ventricular mass index (OR 5.69 in carotid occlusive disease, $p=0.006$; OR 1.30 in other groups, $p=0.017$), and left ventricular mass-to-volume ratio (OR 1.81, $p<0.001$) were all associated with cerebral small vessel disease [32]. These associations remained significant after controlling for systolic blood pressure or medical history of hypertension [32].

The Podzolkov et al. study comparing uncontrolled versus controlled hypertension found that patients with uncontrolled hypertension had lower Montreal Cognitive Assessment scores (24 versus 26 points, $p=0.002$) [15], higher intima-media complex thickness (1.1 versus 1.0 mm, $p=0.042$) [15], higher asymmetric dimethylarginine concentration (0.73 versus 0.65 $\mu\text{mol/l}$, $p=0.02$) [15], and lower microcirculation flow index (22.8 versus 30.6 perfusion units, $p<0.001$) [15]. In regression analysis, intima-media complex thickness, asymmetric dimethylarginine, and microcirculation flow index all had statistically significant effects on cognitive scores in the uncontrolled group [15].

The Ding et al. cross-sectional study found that participants with dementia had significantly higher systolic blood pressure (157.6 mmHg) than those with mild cognitive impairment (149.0 mmHg) and cognitive normal individuals (143.7 mmHg), $p<0.0001$ [54]. After adjusting for

confounders, the likelihood of having dementia was positively associated with hypertension (OR 2.75, 95% CI 1.23-6.13), higher systolic blood pressure (OR 1.14 per 10 mmHg, 95% CI 1.03-1.26), higher diastolic blood pressure (OR 1.29 per 10 mmHg, 95% CI 1.07-1.56), stage 2 hypertension (OR 2.23, 95% CI 1.12-4.42), and stage 3 hypertension (OR 2.40, 95% CI 1.09-5.26) [54].

Age-Dependent Effects

The relationship between hypertension and dementia demonstrated marked age dependence, with midlife exposure showing stronger associations than late-life exposure. The Ayanlowo et al. meta-analysis found that midlife hypertension increased dementia risk by 63% (HR 1.63, 95% CI 1.37-1.89) [1]. Narrative synthesis of 17 additional studies revealed that midlife hypertension was particularly associated with vascular dementia risk [1], though findings for late-life hypertension were heterogeneous, showing null, inverse, and U-shaped relationships [1].

Several studies documented protective or neutral associations of hypertension in the oldest-old. The Corrada et al. 2014 study in participants aged 90 and older found that hypertension onset at ages 80-89 was associated with lower dementia risk (HR 0.57) compared to those without hypertension history [10], while onset at age 90 or older showed the lowest risk (HR 0.43) [10]. The Corrada et al. 2010 study similarly found that history of hypertension in the oldest-old was associated with a 29% reduced risk (HR 0.71) [12], though this finding was based on self-reported history rather than direct blood pressure measurements [12].

The Ge Li et al. community-based study demonstrated age-dependent associations, finding increased dementia risk in younger elderly participants (65-74 years) with high baseline systolic blood pressure of 160 mmHg or higher (HR 1.60, 95% CI 1.01-2.55) and borderline high diastolic blood pressure of 80-89 mmHg (HR 1.59, 95% CI 1.07-2.35) [121]. The association between systolic blood pressure and dementia risk reversed with increasing age at baseline (systolic blood pressure $\times$ age interaction $p=0.01$) [121]. Among younger elderly, eight-year mean systolic blood

pressure prior to onset was significantly higher in Alzheimer's disease versus normal subjects (+5.8 mmHg, $p=0.02$) [121].

The Legdeur et al. study of 442,428 individuals found that dementia risk associated with hypertension decreased with increasing age, from HR 1.24 (95% CI 1.07-1.44) at ages 65-70 years to HR 0.95 (95% CI 0.84-1.07) at ages 90 years and older (p for trend <0.001) [11]. At age 90 and above, hypertension was no longer a significant risk factor for dementia [11]. This pattern was consistent across all vascular disorders examined and was not explained by mortality as a competing risk [11].

The Luxinyi Xu et al. study found that late-life blood pressure showed stronger associations with cognitive function than midlife blood pressure [110]. In late-life, controlled hypertension was associated with better language performance compared to uncontrolled hypertension (adjusted $\beta = -0.34$, 95% CI -0.68 to 0.00) [110] and better orientation, language, and total cognitive scores compared to untreated hypertension [110]. However, intensive blood pressure control targets offered no additional benefit beyond standard targets [110].

Blood Pressure Thresholds and Cognitive Outcomes

Multiple studies identified non-linear and threshold effects of blood pressure on dementia risk. The Zuo-Teng Wang et al. meta-analysis identified a nonlinear relationship between systolic blood pressure and all-cause dementia risk in populations aged 65 years and older (p for nonlinearity <0.05) [26]. Systolic blood pressure between 110 and 120 mmHg played a protective role in populations aged 62 to 82 years, while systolic blood pressure above 162 mmHg significantly increased risk in those aged 70 to 86.5 years [26]. The study also found a linear association between diastolic blood pressure and Alzheimer's disease risk in populations aged 65 years and older, with risk decreasing 3% per 10 mmHg increase in a specific diastolic blood pressure range [26].

The Suvvari et al. meta-analysis found a 1.19- to 1.55-fold increased risk of cognitive disorders associated with hypertension [43]. The study identified a U-shaped dose-response curve,

indicating that maintaining diastolic blood pressure levels between 90 and 100 mmHg lowered Alzheimer's disease risk [43]. The use of antihypertensive medications was associated with a 21% reduction in dementia risk [43].

Chinese studies provided additional granular data on blood pressure thresholds. The Drumond et al. systematic review reported an odds ratio of 1.23 (95% CI 1.02-1.49) for the association between hypertension and cognitive impairment [89]. Blood pressure effects showed dose-response relationships with systolic blood pressure decreases from 149 mmHg to 137 mmHg associated with HR 1.59 (95% CI 1.17-2.16), while stable diastolic blood pressure around 75 mmHg showed HR 0.80 (95% CI 0.66-0.96) [78]. Each 1 mmHg increase in systolic blood pressure was associated with a 0.88 mL decrease in brain volume [78].

Studies examining intensive versus standard blood pressure control showed mixed results for dementia prevention. The SPRINT MIND trial, while not showing significant reduction in probable dementia as the primary outcome, demonstrated reduced mild cognitive impairment risk [25, 30, 85]. Among older women in the WHIMS study, those with hypertension and systolic blood pressure of 120 mmHg or higher had increased risk of mild cognitive impairment and cognitive loss, whereas those treated to systolic blood pressure below 120 mmHg were not at significantly increased risk [99].

Treatment Effects by Medication Class

Studies examining specific antihypertensive medication classes showed variable results. The Shah et al. systematic review found that angiotensin-converting enzyme inhibitors and diuretics appeared to be the most beneficial in reducing dementia risk and progression, with these medications showing positive effects in the majority of studies reviewed [29]. The study included seven investigations of calcium channel blockers, six of diuretics, and six of angiotensin-converting enzyme inhibitors [29].

The Syst-Eur trial using long-acting dihydropyridine calcium channel blockers (nitrendipine) demonstrated a 55% reduction in dementia risk [14, 30], with absolute rates of 7.7

versus 3.8 per 1,000 patient-years [30]. The PROGRESS study using angiotensin-converting enzyme inhibitors with or without diuretics showed a 19% reduction in stroke-related dementia incidence [14]. However, dementia without stroke was not reduced [14].

The Ferreira et al. longitudinal study found that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins were likely protective against white matter hyperintensity progression, with adjusted estimates of -0.49 ($p=0.049$) for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and -0.46 ($p=0.055$) for statins [96]. The study also identified that smoking and increases in systolic blood pressure were associated with white matter hyperintensity increment (adjusted estimates 0.49, $p=0.047$ for smoking; adjusted estimates 0.01, $p=0.08$ for systolic blood pressure) [96].

The Parihar et al. study examining real-world driving behavior as a functional outcome found that antihypertensive use, especially ACE inhibitors, attenuated white matter hyperintensity-related risky driving ($\beta=-0.18$, $p=0.06$) [55]. Greater white matter hyperintensity burden was linked to reduced driving frequency, trip diversity, and adaptability (all $p<0.002$) [55], with posterior white matter hyperintensity growth conferring the highest crash risk ($\beta=0.59$, $p=2e-6$) [55].

The Murray study found similar benefits from most commonly available antihypertensive medications in African Americans, suggesting that blood pressure control rather than medication class was the key factor [17]. The Yang et al. review concluded that current evidence does not support one category of antihypertensive drugs as superior to others for preventing dementia in elderly patients with hypertension [18].

Brain Structural Changes and Pathophysiological Mechanisms

Hypertension-related brain changes served as mechanistic links between blood pressure and cognitive decline. The Schneider et al. study found that incremental increases in blood pressure were related to microinfarcts in persons aged 65 to 80 years but not in older age groups [13]. Treatment with antihypertensive medication modified this effect, with untreated participants substantially more likely to have more than two microinfarcts at autopsy [13, 13]. Importantly,

blood pressure was not related to Alzheimer's disease pathology [13], suggesting the hypertension-dementia link operates primarily through vascular rather than degenerative pathology [13].

The Elmståhl et al. study found cerebral microbleeds in 26% of participants, increasing from 19% in those in their 70s to 30% in those over 80 years [46]. Cerebral microbleeds were associated with severe confluent white matter hyperintensities (OR 7.02, 95% CI 2.16-18.84) [46]. Both lobar and nonlobar cerebral microbleeds were associated with hypertension, with nonlobar microbleeds particularly associated with increased blood pressure, pulse pressure, controlled hypertension, and uncontrolled hypertension [46]. After controlling for sex and hypertension, age was no longer a risk factor for cerebral microbleeds [46].

The Morrison et al. study examining variable blood pressure found that participants with variable blood pressure exhibited the highest rate of cognitive decline, followed by high blood pressure and then normal blood pressure [69]. Variable blood pressure was also associated with increased gray matter volume loss and white matter hyperintensity burden compared to both high and normal blood pressure [69]. Post-mortem neuropathology rates were elevated in both variable and high blood pressure groups compared to normal blood pressure [69].

The Wiesmann et al. review noted that silent brain infarcts double the risk for dementia [38], with a linear relationship between blood pressure and stroke mortality such that a 1 mmHg increase in systolic blood pressure increases stroke-related death by 2% [38]. The Moulin et al. clinicopathological study found strong associations between the extent of periventricular and deep white matter hyperintensities and higher cerebrovascular scores ($p=0.001$ and $p=0.002$, respectively) [53]. Arterial hypertension ($p=0.012$) and history of stroke ($p=0.003$) were associated with higher cerebrovascular scores [53].

Gender and Ethnic Differences

Gender differences in the hypertension-dementia relationship emerged across multiple studies. The Azad et al. review noted that women constitute a larger proportion of older people and can expect to live nearly twice as long with cognitive impairment as men [35]. The prevalence of

hypertension and hyperlipidemia is significantly higher in older women, as is the likelihood of having multiple vascular risk factors [35]. Gender influences how vascular factors increase dementia risk, with obesity increasing Alzheimer's disease risk in females but not males, and diabetes increasing vascular dementia risk mainly in females [35]. The risk of vascular dementia after stroke was increased significantly more in females [35].

The Baiyang Zhang et al. study stratified analyses by sex and found that hypertension prevalence was associated with worse episodic memory and executive function trajectories in females [95]. Among treated hypertensives, males with uncontrolled blood pressure had worse episodic memory trajectories compared to those controlled at standard targets, while females with uncontrolled blood pressure demonstrated worse executive function trajectories [95].

The Pase et al. study examining vascular risk factor burden across the lifespan found that associations between vascular risk factors and brain volume became progressively stronger when measured earlier in life [109]. Findings were particularly strong in women [109], suggesting greater vulnerability to or cumulative effects of vascular risk factors in female populations.

Ethnic and racial differences received limited attention, though the Murray study specifically examined African Americans and found significant protective effects of blood pressure control in this population [17]. The Suvvari meta-analysis reported prevalence of mild cognitive impairment in hypertensive patients of 26% in Asian samples versus 40% in European samples [43], though methodological differences may account for this variation.

Duration and Chronicity of Hypertension Exposure

Duration of hypertension exposure emerged as a critical determinant of cognitive outcomes. The Tuo Li et al. study found that cognitive impairment incidence increased with hypertension duration, from 6.6% in those with hypertension for 5 years or less to 33.5% in those with hypertension for more than 20 years [2]. Cognitive function was significantly worse in the longest duration group compared to normotensives across multiple domains including Mini-Mental State

Examination, Clock-Drawing Test, memory-type cognitive function, and non-memory-type cognitive function (all $p < 0.001$) [2].

The Qin et al. study examined age of hypertension onset and found that the proportion of mild cognitive impairment participants who progressed to dementia was higher in the old-age-onset hypertension group (≥ 65 years) compared to the middle-age-onset group (27.0% versus 15.4%, $p = 0.019$) [102]. Within the old-age-onset group, those with increased pulse pressure had higher progression rates (33.3% versus 15.4%, $p = 0.048$) [102]. However, multivariate analysis showed that older age was the only risk factor for progression (HR 0.618, $p = 0.000$) [102].

The Ferreira et al. longitudinal study with approximately seven years between visits found that global memory at the second visit was largely influenced by age, smoking status, glycated hemoglobin, and history of stroke already present at the first visit [96]. These variables accounted for approximately 51% of memory alterations at the second visit [96]. White matter hyperintensities at the second visit were influenced by age, left ventricular hypertrophy, diabetes mellitus, carotid intima-media thickness, and body mass index at the first visit [96], accounting for approximately 37% of white matter hyperintensity changes [96].

Blood Pressure Variability and Orthostatic Changes

Blood pressure variability, beyond mean blood pressure levels, showed significant associations with cognitive outcomes. The de Havenon study found that higher blood pressure variability was associated with probable dementia development despite excellent blood pressure control (unadjusted HR 2.36, 95% CI 1.77-3.15; adjusted HR 1.69, 95% CI 1.25-2.28) [9]. The mean number of blood pressure measurements was 7.8, with standard deviations of 6.3 ± 1.6 mmHg, 10.3 ± 1.1 mmHg, and 16.3 ± 3.6 mmHg across the three tertiles [9]. Dementia rates increased progressively from 2.4% in the lowest tertile to 5.4% in the highest tertile ($p < 0.001$) [9].

The Luxinyi Xu et al. study examining visit-to-visit blood pressure variability found that late-life visit-to-visit systolic blood pressure variability was associated with worse orientation (adjusted $\beta = -2.99$, 95% CI -4.84 to -1.14), recall (adjusted $\beta = -1.69$, 95% CI -2.89 to -0.48),

language (adjusted $\beta = -2.26$, 95% CI -4.13 to -0.38), and total cognitive scores (adjusted $\beta = -9.50$, 95% CI -14.71 to -4.28) [110]. Midlife visit-to-visit systolic blood pressure variability was associated only with language function (adjusted $\beta = -3.70$, 95% CI -5.83 to -1.57) [110].

The Savan et al. study using 24-hour ambulatory blood pressure monitoring found a moderate positive association between hypertension regulation and cognitive function ($r=0.333$, $p=0.001$) [107], but no statistical difference in cognitive scores between dipper and nondipper patterns [107]. This suggests that overall blood pressure control may be more important than circadian patterns for cognitive preservation.

Cognitive Domain-Specific Effects

Hypertension showed differential effects across cognitive domains. The Canavan et al. meta-analysis found that midlife hypertension was associated with increased risk across multiple domains, with relative risks of 1.20 (1.06-1.35) for midlife hypertension overall [28], 1.54 (1.25-1.89) for elevated systolic blood pressure [28], 1.41 (1.00-1.99) for progression from mild cognitive impairment to dementia [28], and 1.55 (1.19-2.03) for global cognition [28]. The absolute risk reduction from blood pressure lowering was 0.4% (95% CI 0.1-0.7%) in dementia incidence over 4.1 years [28], with increased risk particularly for systolic blood pressure over 130 mmHg [28].

Vascular dementia was distinguished from Alzheimer's disease by preservation of memory function in some studies [28]. The Huang et al. review suggested that executive dysfunction serves as a potential diagnostic marker for vascular dementia [94]. The Luxinyi Xu study found that blood pressure control status and visit-to-visit variability were significantly related to orientation and language functions, with no significant correlation between blood pressure and memory [110].

The DeCarli et al. study examined specific cognitive tasks and found impairments in mild cognitive impairment associated with white matter hyperintensities on color association episodic memory tasks, n-back working memory tasks, and AX-CPT tasks [71]. Functional magnetic resonance imaging showed modulation of dorsolateral prefrontal cortex activity by white matter hyperintensities during episodic retrieval and working memory tasks [71].

Risk Factor Control and Multifactorial Management

The Meng Chen et al. UK Biobank study examined degree of joint risk factor control in hypertensive patients, considering seven factors: physical activity, smoking status, blood pressure, body mass index, glycosylated hemoglobin levels, lipids, and urinary albumin-to-creatinine ratio [47]. Compared with non-hypertensive individuals, there was a gradual decrease in dementia risk in hypertensive patients as the number of well-controlled risk factors increased, from HR 2.01 (95% CI 1.73-2.34) with poor control to HR 1.25 (95% CI 1.13-1.40) with better control [47]. Within hypertensive patients, the highest level of control reduced risk to HR 0.63 (95% CI 0.54-0.73) [47]. Hypertensive patients with better risk factor control also had lower geometric mean white matter hyperintensity volume and increased total brain parenchymal volume, progressively narrowing the gap with non-hypertensive individuals [47].

The Pillai et al. study examining interactions between hypertension, hypercholesterolemia, and APOE ϵ 4 status found complex relationships. Among older APOE ϵ 4 non-carriers, hypertension was related to higher dementia risk (HR 1.44, 95% CI 1.13-1.82, $p=0.003$) [68]. Conversely, among older APOE ϵ 4 carriers, hypercholesterolemia was related to lower dementia risk (HR 0.68, 95% CI 0.49-0.94, $p=0.02$) [68]. Among younger participants, vascular risk factors did not impact dementia risk, likely due to lower frequency of vascular and Alzheimer's pathologies in this cohort [68].

The Gottesman et al. ARIC-PET Study found that midlife hypertension and late-life amyloid beta independently contributed to dementia risk (hypertension HR 2.57, 95% CI 1.16-5.67; amyloid beta per SD HR 2.57, 95% CI 1.72-3.84) [92], but did not interact synergistically [92]. White matter hyperintensities (per SD HR 1.51, 95% CI 1.03-2.20) and amyloid beta (per SD HR 2.52, 95% CI 1.83-3.47) each contributed to incident dementia, though white matter hyperintensities lost significance when midlife vascular risk factors were added to the model [92]. Smaller Alzheimer's disease signature regions were associated with incident dementia independent of both amyloid beta and midlife vascular risk factors (HR per SD 2.18, 95% CI 1.18-4.01) [92].

Synthesis

The relationship between blood pressure control and dementia risk exhibits pronounced heterogeneity that can be explained through several key factors: age at exposure, duration of hypertension, blood pressure variability, dementia subtype, and selective survival.

The apparent contradiction between midlife and late-life hypertension effects reflects genuine differences in pathophysiological mechanisms rather than measurement error. Studies measuring blood pressure in midlife (ages 40-65) consistently show elevated dementia risk 15-40 years later [1, 41, 121], while late-life measurements show null, inverse, or U-shaped associations [1, 10, 12]. This pattern is mechanistically consistent with cerebrovascular remodeling: chronic midlife hypertension causes cumulative arterial damage, endothelial dysfunction, and microvascular rarefaction that manifests as cognitive impairment decades later [15, 32, 38]. By contrast, hypertension onset in the oldest-old may represent preserved vascular reactivity and adequate cerebral perfusion in individuals who have survived to advanced age without developing dementia [10, 12]. The finding that blood pressure often declines in the years preceding dementia onset [121] further complicates late-life associations, as low blood pressure may be a consequence rather than cause of incipient neurodegeneration.

Blood pressure control effectiveness also varies by dementia subtype through distinct pathophysiological pathways. Antihypertensive treatment shows stronger effects for vascular dementia (relative risk reductions of 19-55%) [3, 14, 30] than for Alzheimer's disease alone [3, 21]. This differential effect is explained by the more direct role of cerebrovascular pathology in vascular dementia pathogenesis. However, the substantial effects observed for Alzheimer's disease prevention in some studies [8, 21] suggest that vascular factors lower the threshold for Alzheimer pathology to manifest clinically by adding cerebrovascular injury to existing beta-amyloid and tau pathology [13, 92]. Studies using autopsy data confirm that most dementia cases involve mixed pathologies, with hypertension contributing through vascular mechanisms that compound neurodegenerative processes [13, 92].

The inconsistent trial results for dementia prevention can be reconciled by examining study design factors. Trials showing positive results (Syst-Eur with 55% reduction [14], PROGRESS with 19% reduction [14]) had longer follow-up durations (3.9-5 years) and enrolled participants at younger ages or with recent vascular events, maximizing the window for intervention before irreversible brain damage. Trials showing null results (SCOPE, HYVET-COG) often enrolled very old participants (mean age 76-80 years) [14], had shorter follow-up periods [14], or experienced high rates of blood pressure control in placebo groups due to rescue medication use [35, 60]. The SPRINT MIND trial, despite excellent blood pressure control (systolic blood pressure <120 mmHg versus <140 mmHg), showed significant effects only for mild cognitive impairment rather than dementia [25, 85], likely because the 3.26-year median follow-up was too brief to capture progression to dementia in a population without prior cognitive impairment.

Blood pressure variability introduces an independent risk pathway. Studies show that higher visit-to-visit variability predicts dementia even when mean blood pressure is well-controlled [9, 110], with hazard ratios of 1.69-2.36 comparing highest to lowest variability tertiles [9]. This suggests that vascular damage from blood pressure fluctuations operates through mechanisms distinct from sustained pressure elevation, potentially involving repeated episodes of hypoperfusion and reperfusion injury, endothelial shear stress, or impaired autoregulation [38, 57]. The finding that late-life systolic blood pressure variability affects multiple cognitive domains (orientation, recall, language, total scores) while midlife variability affects primarily language [110] indicates that timing of variable exposure determines which brain regions accumulate damage.

Treatment duration emerges as a critical modifier of effectiveness. The Peila et al. finding that each additional year of treatment reduces dementia risk by 6% (HR 0.94) [8], with risk approaching that of normotensives after 12 years of treatment [8], demonstrates that vascular protection is cumulative. This dose-response relationship by treatment duration explains why trials with brief follow-up show smaller effects than observational studies tracking patients over decades. The biological mechanism likely involves progressive reversal of arterial stiffening, improved

cerebral autoregulation, and reduction of white matter hyperintensity accumulation, processes that require sustained blood pressure normalization over years [47, 96].

Selective survival likely explains the age-dependent attenuation of hypertension's dementia risk. The Legdeur et al. finding that hypertension-associated dementia risk decreases from HR 1.24 at ages 65-70 to HR 0.95 at ages 90 and older [11] cannot be attributed to competing mortality risk, as follow-up time was similar between individuals with and without vascular disorders [11]. Instead, individuals with hypertension who survive to the oldest ages without developing dementia may represent a biologically resilient subset less susceptible to hypertension's harmful effects, possibly due to genetic factors, better autoregulation, or compensatory mechanisms [11, 91]. This selection effect also explains why cross-sectional studies in the very elderly often show inverse associations between blood pressure and cognition.

The modest but consistent treatment effects observed in meta-analyses (7-13% relative risk reductions) [5–7] should be interpreted in light of hypertension's high population prevalence. The Hughes et al. absolute risk reduction of 0.39% over 4.1 years [6], while small at the individual level, translates to substantial population-level benefit given that approximately 70-75% of elderly adults have hypertension [35]. The Canavan et al. absolute risk reduction of 0.4% over 4.1 years [28], combined with the estimate that 8% of Alzheimer's disease cases are attributable to midlife hypertension [103], suggests that optimal hypertension control could prevent tens of thousands of dementia cases annually in aging populations.

Based on current evidence, blood pressure control in midlife (ages 40-65) offers the strongest protection against later dementia, particularly vascular dementia. Treatment should be sustained for at least 10 years to maximize cognitive benefits [8, 48]. In late life, blood pressure control remains beneficial for those with sustained hypertension, but aggressive lowering in the oldest-old (especially those over 90) or those with pre-existing cognitive impairment may not provide additional benefit and could potentially cause harm through cerebral hypoperfusion [18, 49, 65]. Minimizing blood pressure variability represents an additional therapeutic target independent of mean blood pressure reduction [9, 110].

DISCUSSION

The relationship between uncontrolled hypertension and vascular dementia elucidated in this systematic review reveals a complex, multifactorial association modulated by age, treatment duration, blood pressure variability, and concomitant risk factors. The synthesis of 125 studies encompassing over 2.6 million participants provides robust evidence that uncontrolled hypertension significantly increases vascular dementia risk, while also highlighting important nuances that inform clinical practice and future research directions.

Blood Pressure Control and Dementia Risk: Magnitude and Specificity

The consistent finding that uncontrolled hypertension confers substantially higher dementia risk than controlled hypertension—with incidence rates of 8.1 versus 4.9 per 1,000 person-years [4]—underscores the critical importance of achieving and maintaining blood pressure control. This effect size is clinically meaningful, representing approximately a 40% relative risk increase associated with poor control. The meta-analytic evidence demonstrating 7-13% dementia risk reduction with antihypertensive treatment [5, 6, 7] further reinforces that blood pressure lowering is an effective preventive strategy. However, the modest absolute risk reduction of 0.39% over 4.1 years [6] should be interpreted in context: given the high population prevalence of hypertension (70-75% of elderly adults) [35], even small individual benefits translate to substantial population-level impact.

Importantly, the relationship appears stronger for vascular dementia than for Alzheimer's disease. Switzer et al. found that women with gestational hypertension history had double the risk of vascular dementia (aHR 2.02) but no significant increase in Alzheimer's disease [3]. Similarly, Lennon et al. demonstrated that untreated hypertension increased non-Alzheimer dementia risk by 69% compared to 36% for Alzheimer's disease [21]. This differential effect is mechanistically plausible: hypertension primarily damages cerebral vasculature through atherosclerosis, arteriolosclerosis, and microinfarcts [13, 38], pathways directly relevant to vascular dementia pathogenesis. However, the substantial effects observed for Alzheimer's disease in some studies [8, 21] suggest that vascular injury lowers the threshold for clinical manifestation of Alzheimer's

pathology—the so-called "vascular contribution to cognitive impairment and dementia" concept [92].

Age-Dependent Effects: The Midlife Window of Opportunity

Perhaps the most clinically significant finding is the pronounced age dependence of hypertension's dementia risk. Midlife hypertension (ages 40-65) increased dementia risk by 63% (HR 1.63) in the Ayanlowo meta-analysis [1], with similar findings across multiple cohorts [41, 121]. This midlife window appears critical because it represents the period when cumulative vascular damage begins accruing, yet sufficient time remains for intervention before irreversible cognitive decline. The Walker et al. trajectory analysis demonstrated that sustained hypertension from midlife onward, regardless of late-life blood pressure, increased dementia risk by 41% [41], emphasizing that early exposure has enduring consequences.

In contrast, late-life hypertension shows heterogeneous associations, with many studies reporting null, inverse, or U-shaped relationships [1, 10, 11]. The Legdeur study elegantly demonstrated that dementia risk associated with hypertension decreased progressively with age, from HR 1.24 at ages 65-70 to HR 0.95 at ages 90 and older [11]. The Corrada studies in nonagenarians even found protective effects of late-onset hypertension (HR 0.43-0.57) [10, 12]. Several mechanisms may explain this apparent paradox. First, blood pressure often declines naturally in the years preceding dementia onset, potentially reflecting incipient neurodegeneration affecting autonomic centers [121]. Second, individuals with hypertension who survive to advanced ages without dementia may represent a biologically resilient subset with protective factors [11, 91]. Third, in the oldest-old, higher blood pressure may be necessary to maintain cerebral perfusion against a background of stiffened vessels and impaired autoregulation [49, 65]. These findings have important clinical implications: aggressive blood pressure lowering in the very elderly, particularly those over 80-85 years, may not provide cognitive benefits and could potentially cause harm through cerebral hypoperfusion [18, 49].

Treatment Duration and Dose-Response Relationships

The cumulative nature of cognitive protection from antihypertensive treatment is demonstrated by the Peila et al. finding that each additional treatment year reduced dementia risk by

6% (HR 0.94) [8]. After 12 years of treatment, risk approached that of normotensive individuals [8], suggesting that sustained blood pressure control can largely reverse hypertension-attributable dementia risk. This dose-response relationship explains why observational studies with decades of follow-up show larger effects than randomized trials with brief durations [35, 60]. The biological mechanism likely involves progressive reversal of vascular remodeling, reduction in white matter hyperintensity accumulation, and restoration of cerebral autoregulation—processes requiring years of normalized blood pressure [47, 96].

The Tan et al. findings that both number of antihypertensive classes (HR 0.68) and total daily dose (HR 0.70) were associated with reduced dementia risk [66] further support intensity-dependent effects. However, whether this reflects greater blood pressure reduction, synergistic medication effects, or both remains uncertain. The Murray study in African Americans found that suboptimal treatment (blood pressure still exceeding 140/90 mmHg despite medication) eliminated the protective effect of antihypertensive use (HR 0.65, $p=0.22$ versus HR 0.57, $p=0.01$ for optimal treatment) [17], confirming that blood pressure control per se, not merely medication prescription, drives cognitive protection.

Blood Pressure Variability: An Independent Risk Factor

The recognition that blood pressure variability independently predicts dementia, even when mean blood pressure is well-controlled, represents a paradigm shift in understanding hypertension-related cognitive risk. The de Havenon post-hoc analysis of SPRINT MIND found that participants in the highest variability tertile had 69% increased dementia risk (adjusted HR 1.69) compared to the lowest tertile, despite all participants achieving excellent mean blood pressure control [9]. Dementia rates increased progressively from 2.4% to 5.4% across variability tertiles [9]. The Luxinyi Xu study extended these findings, demonstrating that late-life visit-to-visit variability was associated with worse orientation, recall, language, and total cognitive scores [110].

The mechanisms linking variability to cognitive decline likely differ from sustained hypertension. Fluctuating blood pressure may cause repeated episodes of cerebral hypoperfusion and reperfusion injury, endothelial shear stress, impaired autoregulation, and blood-brain barrier disruption [38, 57, 58]. The Morrison et al. finding that variable blood pressure was associated with

greater gray matter volume loss and white matter hyperintensity burden than either sustained high or normal blood pressure [69, 117] supports distinct pathophysiological pathways. These findings have therapeutic implications: interventions that stabilize blood pressure, such as consistent medication adherence, long-acting formulations, and lifestyle modifications, may confer cognitive benefits beyond mean blood pressure reduction [9, 110].

Vascular Markers and Pathophysiological Mechanisms

The consistent identification of vascular brain changes mediating the hypertension-dementia relationship provides biological plausibility and potential surrogate markers for intervention trials. Cerebral small vessel disease manifestations—white matter hyperintensities, cerebral microbleeds, lacunar infarcts, and microinfarcts—are consistently associated with both hypertension and cognitive impairment [13, 32, 46, 53]. The Elmståhl study found cerebral microbleeds in 26% of participants, increasing from 19% in septuagenarians to 30% in octogenarians, with strong associations to uncontrolled hypertension [46]. The Schneider autopsy study demonstrated that untreated hypertension was associated with substantially more microinfarcts, but not Alzheimer pathology [13], directly linking hypertension to vascular dementia pathology.

The Podzolkov et al. study identified specific vascular markers differentiating controlled from uncontrolled hypertension: patients with uncontrolled hypertension had lower Montreal Cognitive Assessment scores (24 versus 26 points), higher intima-media thickness (1.1 versus 1.0 mm), higher asymmetric dimethylarginine (0.73 versus 0.65 $\mu\text{mol/l}$), and lower microcirculation flow index (22.8 versus 30.6 perfusion units) [15]. These markers may serve as therapeutic targets and monitoring tools for hypertension-related cognitive risk. The Amier et al. heart-brain imaging study further demonstrated that aortic stiffness and left ventricular remodeling were associated with cerebral small vessel disease independent of blood pressure levels [32], suggesting that hypertensive target organ damage in the heart and great vessels parallels cerebral damage.

Duration and Chronicity of Hypertension Exposure

The duration of hypertension exposure emerged as a critical determinant of cognitive outcomes, with the Tuo Li study demonstrating that cognitive impairment incidence increased progressively from 6.6% in those with hypertension ≤ 5 years to 33.5% in those with hypertension

>20 years [2]. Cognitive function was significantly worse across multiple domains in the longest duration group compared to normotensives [2]. This duration-response relationship underscores that hypertension exerts cumulative effects over decades, consistent with the concept that vascular dementia results from progressive accumulation of subclinical vascular injury.

The Qin et al. finding that old-age-onset hypertension (≥ 65 years) was associated with higher progression rates from mild cognitive impairment to dementia than middle-age-onset hypertension (27.0% versus 15.4%) [102] introduces additional complexity. This may reflect that late-onset hypertension in individuals with pre-existing cognitive impairment represents a different pathological process—perhaps related to vascular stiffness or autonomic dysfunction—than essential hypertension beginning in midlife. Alternatively, older brains may be more vulnerable to hypertension's effects due to reduced cognitive reserve or concurrent pathologies [102].

Gender and Ethnic Differences

The emerging evidence for gender differences in the hypertension-dementia relationship has important implications for personalized prevention. Azad et al. noted that women constitute a larger proportion of older people and live nearly twice as long with cognitive impairment as men [35]. The prevalence of hypertension and hyperlipidemia is significantly higher in older women, as is the likelihood of multiple vascular risk factors [35]. The Baiyang Zhang study found that hypertension prevalence was associated with worse episodic memory and executive function trajectories in females, with differential effects by blood pressure control status [95]. The Pase study suggested greater vulnerability to vascular risk factors in women [109], potentially due to hormonal changes, differential aging trajectories, or longer life expectancy.

Ethnic and racial differences remain understudied, despite evidence that hypertension prevalence, treatment response, and dementia risk vary across populations. The Murray study specifically examined African Americans and found significant protective effects of blood pressure control [17], but comparable studies in Hispanic, Indigenous, and South Asian populations are lacking [1]. The Suvvari meta-analysis reported prevalence of mild cognitive impairment in hypertensive patients of 26% in Asian samples versus 40% in European samples [43], though

methodological differences may account for this variation. Future research must prioritize diverse, representative samples to ensure generalizability of findings.

Multifactorial Risk Factor Control

The Meng Chen et al. UK Biobank study provides compelling evidence that comprehensive cardiovascular risk factor control substantially enhances cognitive protection beyond blood pressure management alone [47]. Hypertensive patients with optimal control of seven factors (physical activity, smoking, blood pressure, body mass index, glycemic control, lipids, and albuminuria) reduced dementia risk to HR 0.63 compared to those with poor control [47]. Importantly, better control progressively narrowed the gap in white matter hyperintensity volume and brain parenchymal volume compared to non-hypertensive individuals [47], suggesting that multifactorial intervention can partially reverse hypertension-associated brain injury.

The Pillai et al. finding that hypertension and hypercholesterolemia interact with APOE ϵ 4 status to modify dementia risk [68] highlights the importance of genetic context in vascular risk modification. Among older APOE ϵ 4 non-carriers, hypertension increased dementia risk (HR 1.44), whereas among carriers, hypercholesterolemia was associated with lower risk (HR 0.68) [68]. These complex interactions suggest that personalized prevention strategies may ultimately require genetic stratification.

Medication Class Effects

Whether specific antihypertensive medication classes confer differential cognitive benefits beyond blood pressure lowering remains controversial. The Shah systematic review suggested that angiotensin-converting enzyme inhibitors and diuretics appeared most beneficial [29], while the Syst-Eur trial demonstrated 55% dementia reduction with dihydropyridine calcium channel blockers [14, 30]. The PROGRESS study showed 19% reduction in stroke-related dementia with angiotensin-converting enzyme inhibitors plus diuretics [14]. However, the Yang review concluded that current evidence does not support one category as superior for dementia prevention [18], and the Murray study found similar benefits across commonly available medications [17].

The Ferreira study found that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins were protective against white matter hyperintensity progression [96], while the

Parihar study suggested ACE inhibitors attenuated white matter hyperintensity-related functional decline [55]. These findings raise the possibility of pleiotropic neuroprotective effects beyond blood pressure reduction, including anti-inflammatory, antioxidant, and endothelial-stabilizing properties [40, 96]. However, definitive evidence requires head-to-head trials with cognitive primary endpoints.

Clinical Implications

The findings of this review have several important clinical implications. First, hypertension should be conceptualized as a modifiable risk factor for dementia across the lifespan, with particular emphasis on achieving and maintaining control from midlife onward [1, 41]. The accumulating evidence suggests that waiting until late life to address hypertension may miss the critical window for cognitive protection. Second, blood pressure control should be evaluated not only by mean levels but also by visit-to-visit variability, which may warrant interventions to stabilize blood pressure [9, 110]. Third, antihypertensive treatment should be sustained long-term, as benefits accrue cumulatively over years [8, 30]. Fourth, in the very elderly (≥ 80 -85 years), blood pressure targets should be individualized, considering that aggressive lowering may not provide cognitive benefits and could potentially cause harm [18, 49]. Fifth, comprehensive cardiovascular risk factor management—addressing diabetes, dyslipidemia, smoking, obesity, and physical inactivity alongside hypertension—offers greater cognitive protection than blood pressure management alone [47]. Sixth, women and ethnic minorities may require specific attention given differential risk profiles [35, 95].

Future Research Directions

This review identifies several priorities for future research. First, adequately powered randomized controlled trials with dementia as the primary outcome are needed, particularly comparing different blood pressure targets and medication classes. The SPRINT MIND trial, while informative, had relatively short follow-up and showed effects only for mild cognitive impairment rather than dementia [25, 85]. Second, research must prioritize diverse, representative populations to ensure generalizability and identify ethnic-specific risk patterns [1, 17]. Third, the mechanisms linking blood pressure variability to cognitive decline require further investigation, including

potential interventions to stabilize blood pressure [9, 58]. Fourth, the interaction between hypertension and other vascular risk factors, including genetic factors like APOEε4, warrants systematic study [68, 92]. Fifth, optimal blood pressure targets for the oldest-old (≥85 years) require clarification through dedicated trials [10, 11]. Sixth, the potential for antihypertensive medications with pleiotropic neuroprotective effects should be explored [40, 96]. Seventh, implementation research is needed to translate evidence into practice, given the substantial gap between hypertension prevalence and adequate control [4, 125].

CONCLUSION AND RECOMMENDATIONS

This comprehensive systematic review demonstrates that uncontrolled hypertension is a significant, modifiable risk factor for vascular dementia, with the relationship exhibiting pronounced age dependence, cumulative effects of exposure duration, and modulation by blood pressure variability and multifactorial risk factor control. The key findings can be summarized as follows:

1. **Blood pressure control matters:** Uncontrolled hypertension confers approximately 40% higher dementia risk compared to controlled hypertension, with antihypertensive treatment reducing dementia risk by 7-13% in meta-analyses [4, 5, 6, 7].
2. **Midlife is the critical window:** Hypertension in midlife (ages 40-65) increases dementia risk by 63%, whereas late-life associations are heterogeneous and often inverse [1, 11, 41, 121].
3. **Treatment duration is important:** Each year of antihypertensive treatment reduces dementia risk by 5-6%, with protection approaching that of normotensives after 12 years [8, 30].
4. **Blood pressure variability independently predicts dementia:** Higher visit-to-visit variability is associated with 69% increased risk, even when mean blood pressure is well-controlled [9, 110].

5. **Vascular pathology mediates the relationship:** Hypertension-related cognitive decline is driven by cerebral small vessel disease manifestations including white matter hyperintensities, microbleeds, and microinfarcts [13, 46, 53].
6. **Multifactorial control enhances protection:** Comprehensive management of cardiovascular risk factors reduces dementia risk more than blood pressure control alone [47].

Recommendations for Clinical Practice

Based on the synthesized evidence, the following recommendations are proposed:

1. **Screen and treat hypertension early:** Blood pressure screening should begin in midlife (by age 40) with treatment initiated according to guideline recommendations to prevent cumulative cerebrovascular damage [1, 41].
2. **Achieve and maintain control:** Treatment should aim for blood pressure below 140/90 mmHg, with consideration of more stringent targets (130/80 mmHg) in high-risk individuals, while avoiding overtreatment in the frail elderly [4, 16, 108].
3. **Ensure treatment continuity:** Antihypertensive therapy should be sustained long-term, as benefits are cumulative and require years to fully manifest [8, 30].
4. **Monitor blood pressure variability:** Visit-to-visit variability should be assessed as an additional risk factor, with interventions to stabilize blood pressure including consistent medication adherence and long-acting formulations [9, 110].
5. **Individualize late-life targets:** In patients over 80-85 years, particularly those with frailty or cognitive impairment, blood pressure targets should be individualized, avoiding aggressive lowering that may compromise cerebral perfusion [18, 49].

6. **Address multiple risk factors:** Comprehensive cardiovascular risk management—including glycemic control, lipid management, smoking cessation, physical activity, and weight management—should accompany blood pressure treatment [47].
7. **Consider gender and ethnic factors:** Awareness of differential risk profiles in women and ethnic minorities should inform clinical decision-making [35, 95].

Recommendations for Public Health Policy

1. **Population-level screening programs:** Implement systematic blood pressure screening in midlife populations, with linkage to treatment and follow-up [1, 4].
2. **Public education campaigns:** Raise awareness of hypertension as a modifiable dementia risk factor, emphasizing the importance of early detection and sustained treatment [40].
3. **Health system integration:** Integrate cardiovascular risk factor management with cognitive health promotion, recognizing the shared pathways to vascular and neurodegenerative diseases [47].
4. **Research funding prioritization:** Allocate resources to address evidence gaps, including diverse populations, optimal late-life targets, and implementation strategies [1, 11].

Summary

Uncontrolled hypertension represents a major modifiable risk factor for vascular dementia, with compelling evidence that achieving and maintaining blood pressure control—particularly from midlife onward—can substantially reduce dementia burden. The relationship is mediated through cumulative cerebrovascular damage, with treatment duration, blood pressure variability, and multifactorial risk factor control serving as critical modifiers. While challenges remain in optimizing late-life targets and ensuring generalizability across diverse populations, the existing evidence provides a strong foundation for clinical and public health action. Given the aging global population and rising dementia prevalence, optimizing hypertension control represents one of the

most promising strategies for dementia prevention, offering the potential to preserve cognitive health and quality of life for millions of individuals worldwide.

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