Review

Critical Review of the Methodological Shortcomings of Ambulatory Blood Pressure Monitoring and Cognitive Function Studies

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Abstract: Growing evidence suggests that abnormal diurnal blood pressure rhythms may be associated with many adverse health outcomes including increased risk of cognitive impairment and dementia. This study evaluates methodological aspects of research on bidirectional associations between ambulatory blood pressure monitoring (ABPM) patterns and cognitive function. By examining the 28 recent studies included in a recent systematic review on association between ABPM patterns with cognitive function and risk of dementia, our review revealed several significant limitations in the current studies of ABPM and cognition in terms of study

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design, sample characteristics, ABPM protocol, cognitive assessment, and data analysis. The major concerns include lack of diversity in study populations with underrepresentation of Blacks and Latinos, a predominant focus on Alzheimer's disease or all-cause dementia without distinguishing other dementia subtypes, different and not standardized measures of cognition or dementia, the prevalent use of 24-hour monitoring without considering the adaption effect, inconsistent definitions of dipping status, and ignorance of individual differences in timings of daily activities such as bed and awakening times. In addition, confounding variables such as class, dose, and timing of antihypertensive medication are inadequately controlled or considered. Additionally, longitudinal studies were scarce examining the bidirectional relationship between ABPM patterns and cognitive decline over time. Collectively, these deficiencies undermine the reliability and generalizability of current findings. Addressing these methodological challenges is crucial for more comprehensive understanding of diurnal blood pressure rhythms in diverse populations and for developing an evidence-based guideline of ambulatory monitoring and control of blood pressure across the sleep-wake cycle to prevent cognitive decline and dementia.

Keywords: Ambulatory blood pressure monitoring; Dementia; Hypertension; Cognitive decline

Introduction

Hypertension is a major risk factor for cognitive decline and dementia. The relationship between blood pressure (BP) and cognitive function is complex and bidirectional. Chronic hypertension can lead to cerebrovascular damage, disruption of blood-brain barrier, and alterations of cerebral blood flow autoregulation, all of which can contribute to cognitive impairment [1]. Conversely, cognitive decline and dementia can affect BP control through changes in autonomic regulation and also medication adherence [2].

Around-the-clock ambulatory BP monitoring (ABPM) provides a more comprehensive assessment of BP patterning throughout 24 hours compared to conventional single daytime office BP measurement (OBPM), capturing diurnal variations and nocturnal dipping status [3]. In normal healthy, day-active persons, systolic and diastolic blood pressure (SBP, DBP) vary in a rather predictable-in-time fashion during the daily cycle of activity and rest. They are usually lowest during mid-sleep, rise before awakening and progressively continue to do so until midday/early afternoon, when they undergo minor decline and increase to peak values late afternoon/early evening before again declining to lowest levels during sleep [4]. Growing evidence suggests non-dipping and reverse dipping BP patterns are associated with increased risk for cognitive impairment and dementia [5]. The mechanisms underlying this association likely involve chronic cerebral hypoperfusion, increased blood-brain barrier permeability, and accelerated neurodegeneration [6].

In recent years, there has been growing interest in understanding the complex relationship between diurnal blood pressure patterns and cognitive function [7–12]. A recent systematic review and meta-analysis conducted by Gavriilaki et al. [5] examined the relationship between features of ABPM-derived BP patterns and cognitive function across 28 studies involving 7,595 participants. They reported individuals exhibiting normal nocturnal BP dipping had 51% lower risk of cognitive impairment or dementia compared to non-dippers. Furthermore, reverse dippers had up to a 6-fold higher risk of cognitive impairment compared to dippers. These findings highlight the potential prognostic value of features of the BP 24-hour pattern in identifying individuals at elevated risk for cognitive decline.

However, important methodological considerations impact the interpretation and generalizability of the results, which will hinder the application of ABPM in health care and clinical practice. Variability in protocol design, definition of dipping status, cognitive assessments, and control for confounding factors across studies introduces heterogeneity that warrants careful evaluation. Additionally, the predominance of cross-sectional protocols limits causal inference of the relationship between BP patterning and cognitive outcomes.

Herein, we critically evaluate the methods of those studies included in the systematic review conducted by Gavriilaki et al. [5] We aim to identify critical limitations and areas for improvement in

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research examining the bidirectional association between 24-hour BP rhythms and cognitive function. By highlighting shortcomings of past investigations, we intend to inform more rigorous study designs that more reliably elucidate the complex reciprocal relationship between BP dysregulation and cognitive decline. Addressing the shortcomings of methods of past investigations is crucial for developing evidence-based strategies to not only preserve cognitive health through optimized BP diagnosis and management but also to maintain cardiovascular health and retard the rate of decline of cognition in patients with dementia.

Methods

We systematically evaluated the methods utilized in each of the 28 investigations comprising the systematic review and meta-analysis by Gavriilaki et al. (2023) [5] about the association between ABPM-derived BP patterns and cognitive function or risk of dementia. These original studies, identified through a comprehensive search of PubMed, Embase, and Cochrane databases, involved studies of ≥ 10 participants (each study) and reported on all-cause dementia, cognitive impairment—based on validated cognitive tests, and features of ABPM-derived 24-hour BP patterning. Study design was different among these studies, including randomized controlled, case-control, and cross-sectional designs. Investigations were excluded if they examined the effect of an intervention on BP dipping and cognitive function.

To evaluate the methodological aspects of these studies, we extracted relevant information from each of the reviewed articles using a pre-determined list of relevant elements to capture key aspects of study design and execution that could impact the validity and reliability of findings. The pre-determined list of extracted data/information encompassed study design, sample size, and subject characteristics, duration of ABPM, frequency of BP measurements, definition of BP dipping patterns, criteria for determining validity of ABPM measurements, method of determining daytime wake and nighttime sleep periods, inclusion of follow-up ABPM and cognitive assessments (where applicable), report of sample size/effect size calculation, statement of participant dropout rate, control for confounding factors, and listing or control of the timing of BP medication. Initial data extraction was performed using Claude AI (Claude 3.5 Sonnet, developed by Anthropic), an artificial intelligence language model. Two of the authors (SH, MJG) thoroughly and separately reviewed and revised the extracted information to ensure its accuracy and completeness.

Results

Our comprehensive analysis of 28 studies revealed significant heterogeneity of investigative methods (Tables 1 and 2). Most studies [7,8,10,12–33] (25/28, 89.3%) were cross-sectional in design, and only a small proportion (3/28, 10.7%) were longitudinal [9,11,34]. There were considerable variations in sample size (range: 30 - 1,608; median: 174) and participants' age (mean age range: 54.3-93.2 years). Gender distribution across studies was additionally inconsistent, with male participation ranging from 10% to 100% (median: 53.7%). The study populations lacked diversity, with only 2 studies [9,30] (7.1%) explicitly reporting inclusion of Black or Latino participants.

Methods of cognitive assessments varied between investigations with the Mini-Mental State Examination (MMSE) most frequently utilized (16/28, 57.1%) [10,12,14–16,20,22–25,27,29,30,32,33]. Other common cognitive assessments included the Montreal Cognitive Assessment (MoCA) [16,21,33] (3/28, 10.7%), Trail Making Test [16,25,30] (3/28, 10.7%), and various other neuropsychological tests. The definition of cognitive impairment and dementia lacked standardization across studies, with criteria ranging from specific cut-off scores on cognitive tests to clinical diagnoses based on established criteria. The majority of studies did not specify dementia subtypes, instead focusing on cognitive impairment, mild cognitive impairment (MCI), or using general cognitive assessments. AD was specifically investigated in 4 studies [8,10,13,23] (14.3%) and Vascular dementia (VaD) was examined in 2 studies [8,19] (7.1%), while others focused on cognitive impairment without specifying dementia subtypes.

All studies (28/28, 100%) conducted ABPM solely for 24 hours with BP typically sampled every 15-30 min during daytime hours and every 30-60 min during nighttime hours. Data quality control

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measures for ABPM measurements varied widely, ranging from stringent criteria to unreported procedures (18 or 64.3% studies [7,8,10,12,13,15,16,18,19,22,24,26,27,29,31–34]). None of the studies reported ABPM acceptance rates by participants or addressed the challenges of extended monitoring in cognitively impaired individuals.

The majority of studies [7–19,21–25,27,29–32,34] (24/28, 85.7%) relied on fixed time periods to define the sleep and wake spans of participants when analyzing the around-the-clock ABPM-derived measures. Only one study [20] (1/28, 3.6%) reported using a sleep diary to determine individual sleep-wake cycles, while three studies [26,28,33] (3/28, 10.7%) did not specify their method for determining these periods. No appropriate consideration of sleep/wake schedules potentially gives rise to non-representative daytime/awake and nighttime/asleep BP means from which dipping status was calculated. In addition, the definition of dipping pattern was inconsistent across studies. While several studies [8,9,11,12,16,17,20,23,26,31,34] (11/28, 39.3%) used systolic blood pressure (SBP) to define dipping status, some used both SBP and DBP [7,13–15,24,25,28] (7/28, 25.0%), or mean arterial pressure [18] (1/28, 3.6%). Nine studies [10,19,21,22,27,29,30,32,33] (32.1%) did not specify which blood pressure measurement they used for dipping status. The threshold for defining dipping status also varied, with most studies using a 10% nocturnal decrease.

Control for confounding factors was inconsistent; only 13 studies [8,9,11,17,18,20,23,24,29–32,34] (46.4%) reported adjustment of potentially influential variables such as age, sex, education level, and comorbidities. Notably, none of the studies controlled for antihypertensive medication timing/administration schedule. Statistical reporting was often incomplete, e.g. only 15 studies [9,11,12,17,19–24,29–32,34] (53.6%) reported effect size while many solely provided p-values.

Table 1. Characteristics of studies examining ABPM patterns and cognitive function.

First Author (Year)	Study Question	Study Type	Sample Size (% female)	Age (year)	Race	Cognitive Status at Recruitment	Cognitive Assessment[a]	Blood Pressure Status at Recruitment
Cani I (2022) [7]	Describe cognitive profile in patients with idiopathic autonomic failure	Cross-sectional	23 (30%)	Not specified	Not specified	Not in criteria	CI[b] was defined as an abnormal score on at least one test of the NPS without specifying cognitive domains	Not in criteria
Chen HF (2013) [13]	Examine circadian rhythm of arterial BP[b] in AD[b] patients without hypertension	Cross-sectional	318 (46%)	76[c]	Not specified	AD[b] patients and healthy controls	NINCDS-ADRDA[b] criteria	Without hypertension[d]
Cicconetti P (2003) [14]	Investigate relationship between non-dipping BP[b] pattern and cognitive function in early hypertension	Cross-sectional	40 (65%)	62.9[c]	Not specified	No neurological diseases	MMSE[b] and ERPs[b] (N2, P300 latencies)	Newly diagnosed grade 1 and 2 hypertension[d]
Cicconetti P (2004) [15]	Investigate relationship between circadian BP[b] pattern and cognitive function in elderly with recently diagnosed hypertension	Cross-sectional	30 (90.0%)	68.3[c]	Not specified	No dementia	MMSE[b] and ERPs[b] (N2, P300 latencies)	Recently diagnosed grade 1 or 2 hypertension[d]
Daniela M (2023) [8]	Evaluate BP using 24h ABPM[b] in AD[b] and VaD[b] patients compared to healthy controls	Cross-sectional	90 (51.1%)	74.7	Not specified	30 AD[a], 30 VaD[a], 30 healthy controls	AD[b]: NINCDS-ADRDA[b] criteria; VaD: NINDS-AIREN[b] criteria, Hachinski score, CT[b]/MRI[b]	Not in criteria
Ghazi L (2020) [9]	Determine association between ABPM[b], cognitive function, physical function, and frailty in CKD[b] patients	Longitudinal (Cognitive follow-up after 4 years)	1,502 (44%)	63±10	45% non-Hispanic white, 39% non-Hispanic black, 12% Hispanic	Not in criteria	3MS[b]	Not in criteria

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Gregory MA (2016) [16]	Determine if differences in cognitive and gait performance exist between older adults with normal vs. reduced BP[b] dipping status	Cross-sectional	115 (63%)	71.7±6.9	96% Caucasian	Without dementia	MoCA[b], MMSE[b], TMT[b], DSST[b], verbal fluency tasks, and AVLT[b]	> 180/100 mmHg or < 100/60 mmHg excluded
Guo H (2010) [17]	Investigate association of circadian BP[b] variation with MCI[b] in community-dwelling persons	Cross-sectional	144 (66%)	68 ± 7	Not specified	No definitive dementia	MCIS[b]	Without antihypertensive
Kececi Savan D (2016) [18]	Determine relationship between ABPM[b] and cognitive functions in elderly hypertensive patients	Cross-sectional	91 (77%)	71.9[c]	Not specified	Without antidemential medication	sMMT[b]<24=MCI/early dementia)	Hypertensive[d]
Kim JE (2009) [19]	Examine relationships between ABPM[b] patterns, subcortical ischemic lesions, and cognitive impairment	Cross-sectional	109 (42.2%)	69.9±4.12	Not specified	SvMCI[b], SVaD[b], or healthy controls	DSM[b]-IV, neuropsychological tests, CDR[b], I-ADL[b], Hachinski score, MRI[b] evidence of subcortical lesions	Some with hypertension[d]
Komori T (2016) [20]	Examine if abnormal circadian BP[b] rhythm is associated with MCI[b] in heart failure patients	Cross-sectional	444 (38.5%)	68±13	Not specified	Excluded those with documented dementia	MMSE[b]<26=MCI[b]	Not in criteria
Li XF (2017) [21]	Analyze correlation between cognitive impairment and ABPM[b] in patients with cerebral small vessel disease	Cross-sectional	108 (47.2%)	67.7[c]	Not specified	Healthy and cognitive impairment	MoCA[b]<23=CI[b]	Refractory hypertensions were excluded
Mahmoud KS (2014) [22]	To test the correlation of ABPM[b] to cognitive function in elderly hypertensive patients	Cross-sectional	77 (46.8%)	69	Not specified	No neurological disorders	MMSE[b], MRI[b]	With history of hypertension and control group
Ohya Y (2001) [23]	Study the relationship among activity of daily living, cognitive function, and ABPM[b] in the elderly	Cross-sectional	99 (78%)	79.8±10.1	Not specified	AD[b] and neuronal degenerative disease were excluded	MMSE[b]	Without antihypertensive

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Okuno J (2003) [24]	Investigate association between fall of nocturnal BP[b] and cognitive impairment in elderly subjects	Cross-sectional	204 (69.1%)	75.2±7.2	Not specified	People with severely impaired cognition were excluded	MMSE[b]≤23=CI[b]	Not in criteria
Paganini-Hill A (2019) [25]	Analyze relationship between BP[b] variables and cognition in 90+ year-olds	Cross-sectional	121 (63%)	93	All Caucasian except one Asian	Not in criteria	VFT[b] (Animal, Letter F), BNT[b], CVLT[b], TMT[b], Clock Drawing, CERAD[b] Construction, Digit Span, MMSE[b], 3MS[b], CDR[b], MRI[b]	Not in criteria
Shim YS (2022) [10]	Investigate ABPM[b] profiles and MRI[b] findings of cerebral small-vessel disease in older adults with cognitive complaints	Cross-sectional	174 (68.4%)	75.36±7.13	Not specified	SCD[b], MCI[b], or AD[b]	MMSE[b], CDR[b], CDR-SB[b], SNSB[b], MRI[b]	Not in criteria
Sierra C (2015) [26]	Investigate relationship between circadian BP[b] pattern and cognitive function in middle-aged essential hypertensive patients	Cross-sectional	56 (34%)	54.3±3.1	Not specified	Not in criteria	attention/working memory (Digit Span), logical/visual memory (WMS[b])	Never-treated essential hypertensive[d]
Suzuki R (2011) [27]	Investigate relationships between sleep disturbance, ADL[b], and ABPM[b] patterns in institutionalized dementia patients	Cross-sectional	107 (70.1%)	76.3±9.2	Not specified	Institutionalized dementia patients	DSM-III R, Hachinski Score, MMSE	Not in criteria
Tadic M (2019) [28]	Assess relationships between absolute and individual residual BP[b] variability and cognitive function in general population	Cross-sectional	471 (47%)	63±5.7	Not specified	Not in criteria	MMSE[b]	Not in criteria
Tan X (2021) [11]	Examine if nocturnal dipping pattern of systolic BP[b] was associated with risk of dementia (AD[b], VaD[b], any dementia) in older Swedish men	Longitudinal (Cognitive and ABPM[a] follow-up after 4 years)	997 (0%)	71 at first exam, 77.6 at second	Swedish men	No dementia at baseline	DSM[b]-IV (dementia); NINCDS-ADRDA[b] (AD[b]); ADDTC[b] (VaD[b])	Not in criteria

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Tanaka R (2018) [29]	To assess the relationship between abnormal nocturnal blood pressure profiles and dementia in Parkinson's disease	Cross-sectional	137 (54.0%)	64.1±10.5	Not specified	Not in criteria	Movement Disorder Society Task Force criteria for PDD[b], MMSE[b], HDS-R[b]	Not in criteria
White WB (2018) [30]	Evaluate relationships of clinic, ambulatory, and home BP measurements with WMH[b] burden and mobility/cognitive outcomes in older persons with hypertension	Cross-sectional	199 (54.3%)	81.2±4.1	87.4% Caucasian, 6.5% Black, 4.5% Hispanic/Latino, 1.5% Asian	No dementia	MMSE[b], TMT A&B, Stroop Color and Word Test, Simple Reaction Time, MRI[b]	24h mean systolic hypertension
Xing Y (2021) [12]	To investigate the relationship between ABPM[b] and cognitive impairment in elderly patients and explore the effect on mortality	Cross-sectional	305 (31%)	80.6±7.6	Not specified	Not in criteria	MMSE[b]<27=MCI[b]	Not in criteria
Yamamoto Y (2002) [34]	How ABPM[b] values and MRI[b] findings can predict subsequent development of dementia and vascular events in lacunar infarct patients	Longitudinal (Cognitive follow-up after ~8.9 years)	177 (37.9%)	69.1±8.6	Not specified	Without dementia at baseline	CDR[b], HDSR[b], MRI[b]	Without administration of antihypertensive for >4 weeks
Yamamoto Y (2005) [31]	Investigate relationships between ABPM[b] readings, lacunar infarcts/white matter lesions, and cognitive impairment/VaD[b]	Cross-sectional	200 (39%)	68.8±9.3	Not specified	Without strategic dementia	CDR[b] and HDSR[b]	Without administration of antihypertensive for 2-4 weeks
Yamamoto Y (2011) [32]	Elucidate associations between ABPM[b], cerebral small vessel disease, CKD[b] and cognitive impairment in patients with lacunar infarcts	Cross-sectional	224 (40.2%)	69.8[c]	Not specified	Not in criteria	MMSE[b] ≤24=CI[b], MMSE[b] of 25-27=MCI[b], MRI[b]	Without administration of antihypertensive for >2 weeks

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Yaneva-Sirakova T (2016) [33]	Investigate correlation between dipping status and mild cognitive impairment in hypertensive patients	Cross-sectional	439 (63.6%)	64.65±10.15	Not specified	Not in criteria	MoCA[b], MMSE[b]	Hypertensive[d]

[a] Tests listed in the "Cognitive Assessment" column represent only those cognitive assessments that were specifically analyzed in relation to ABPM findings in each study. Additional cognitive or neuroimaging tests may have been conducted in the studies but are not included here if their results were not directly examined in association with ABPM. [b] Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; AD: Alzheimer's Disease; ADL: Activities of Daily Living; ADDTC: Alzheimer's Disease Diagnostic and Treatment Centers; AVLT: Auditory Verbal Learning Test; BNT: Boston Naming Test; BP: Blood Pressure; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating Sum of Boxes; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CI: Cognitive Impairment; CKD: Chronic Kidney Disease; CT: Computed Tomography; CVLT: California Verbal Learning Test; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSST: Digit Symbol Substitution Test; ERP: Event-Related Potential; HDS-R: Hasegawa Dementia Scale-Revised; I-ADL: Instrumental Activities of Daily Living; MCI: Mild Cognitive Impairment; MCIS: Mild Cognitive Impairment Screen; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: Magnetic Resonance Imaging; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NPS: Neuropsychological Test; PDD: Parkinson's Disease Dementia; SCD: Subjective Cognitive Decline; sMMT: Short Mini-Mental Test; SNSB: Seoul Neuropsychological Screening Battery; SVaD: Subcortical Vascular Dementia; svMCI: Subcortical Vascular Mild Cognitive Impairment; TMT: Trail Making Test; VaD: Vascular Dementia; VFT: Verbal Fluency Test; WMH: White Matter Hyperintensities; WMS: Wechsler Memory Scale; 3MS: Modified Mini-Mental State Examination. [c] calculated from the information in the paper. [d] Diagnosis of hypertension at baseline was not based on ABPM.

Table 2. Methodological characteristics of ambulatory blood pressure monitoring (ABPM) studies examining cognitive function.

First Author (Year)	ABPM Duration (sampling Intervals)	Dipping Definition	ABPM Quality Control	Sleep/Wake Classification	Effect Size Calculation	Report of Dropout or Completion %	Control for Confounding variables	Control for Timing of BP[a] Medication
Cani I (2022) [7]	24h (Not specified)	SBP[a] and DBP[a]	No	Fixed time	No	No	No	No
Chen HF (2013) [13]	24h (30-min)	SBP[a] or DBP[a]	No	Fixed time	No	No	No	N/A (no medication)
Cicconetti P (2003) [14]	24h (Day:15-min, Night: 20-min)	SBP[a] and DBP[a]	SBP[a] > 260 and <70, DBP[a] > 150 and <20 mmHg values excluded	Fixed time	No	No	No	N/A (no medication)

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Cicconetti P (2004) [15]	24h (Day: 15-min, Night: 20-min)	SBP[a] and DBP[a]	No	Fixed time	No	No	No	N/A (no medication)
Daniela M (2023) [8]	24h (Day: 15-min, Night: 30-min)	SBP[a]	No	Fixed time	No	No	sex	No
Ghazi L (2020) [9]	24h (Not specified)	SBP[a]	Excluded if <14 daytime readings or <6 readings nighttime readings	Fixed time	Yes (HR[a])	No	clinic site, year, age, race, sex, education, marital status, income, smoking, alcohol use, illicit drug use, BMI[a], use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR[a]	No
Gregory MA (2016) [16]	24h (Day: 30-min, Night: 60-min)	SBP[a]	No	Fixed time	No	93.5% completion	No	No
Guo H (2010) [17]	24h (Day: 15-min, Night: 30-min)	SBP[a]	Excluded BP[a] readings if beyond specified range	Fixed time	Yes (OR[a])	No	age, sex, clinic SBP[a], hypnotic treatment, type II diabetes, brachial-ankle pulse wave velocity, Apolipoprotein E ε4 allele	N/A (no medication)
Kececi Savan D (2016) [18]	24h (Not specified)	MAP[a]	No	Fixed time	No	No	Stratified by sex	No
Kim JE (2009) [19]	24h (60-min)	Not specified	No	Fixed time	Yes (OR[a])	No	No	No
Komori T (2016) [20]	24h (30-min)	SBP[a]	<20 valid awake readings and <6 valid	Sleep diary	Yes (OR[a])	87% completion	Age, sex	No

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			sleep readings excluded after					
Li XF (2017) [21]	24h (Day: 30-min, Night: 60-min)	Not specified	omitted all presumed erroneous readings	Fixed time	Yes (Correlation)	No	No	No
Mahmoud KS (2014) [22]	24h (Day: 30-min, Night: 60-min)	Not specified	No	Fixed time	Yes (Correlation)	No	No	No
Ohya Y (2001) [23]	24h (30-min)	SBP[a]	Omitted all presumed erroneous readings	Fixed time	Yes (Correlation)	No	age, Barthel Index, hematocrit, previous stroke	N/A (no medication)
Okuno J (2003) [24]	24h (Day: 30-min, Night: 60-min)	SBP[a] and DBP[a], separately	No	Fixed time	Yes (OR[a])	<1% not completed	age, sex, education level, diabetes mellitus, heart disease, hypercholesterolemia, current alcohol intake, Current smoking, benzodiazepine use, BMI≥25. Antihypertensive drug use	No
Paganini-Hill A (2019) [25]	24h (60-min)	SBP[a] and DBP[a], separately	Omitted all presumed erroneous-readings; <6 valid daytime or nighttime readings excluded	Fixed time	No	81.2% completion	No	No
Shim YS (2022) [10]	24h (Day: 30-min, Night: 60-min)	Not specified	No	Fixed time	Yes (Regression)	No	No	No
Sierra C (2015) [26]	24h (Not specified)	SBP[a]	No	Not specified	No	No	No	N/A (no medication)

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Suzuki R (2011) [27]	24h (60-min)	Not specified	No	Fixed time	No	No	No	No
Tadic M (2019) [28]	24h (20-min)	SBP[a] and DBP[a], separately	Edited for artifact (no detail)	Not specified	No	No	No	No
Tan X (2021) [11]	24h (Day: 20 or 30-min, Night: 20 or 60-min)	SBP[a]	Omitted all presumed erroneous readings	Fixed time	Yes (HR[a])	No	BP[a] dipping status; age; BMI[a]; education; daytime SBP[a]; treatment of hypertension; diabetes; hyperlipidemia; physical activity level; smoking habit; living status	No
Tanaka R (2018) [29]	24h (Day: 30-min, Night: 60-min)	Not specified	No	Fixed time	Yes (OR[a])	97.9% completion	age, sex, Hoehn and Yahr Scale, diabetes, history of stroke, cerebrovascular lesions, and orthostatic hypotension	No
White WB (2018) [30]	24h (Day: 15-min, Night: 30-min)	Not specified	>80% of programmed values; < 2h of missing data required	Fixed time	Regression coefficients	No	age, sex, LDL cholesterol, BMI[a]	No
Xing Y (2021) [12]	24h (Day: 30-min, Night: 60-min)	SBP[a]	No	Fixed time	Yes (Correlation)	71.7% completion	No	No
Yamamoto Y (2002) [34]	24h (30-min)	SBP[a,b]	No	Fixed time	Yes (HR[a])	No	age and sex	N/A (4-week washout)
Yamamoto Y (2005) [31]	24h (30-min)	SBP[a]	No	Fixed time	Yes (OR[a])	No	age, sex, PVH[a], and nighttime SBP[a]	N/A (2-4 weeks washout)
Yamamoto Y (2011) [32]	24h (30-min)	Not specified	No	Fixed time	Yes (OR[a])	No	age, sex, 24h SBP[a], estimated GFR[a], white matter lesion grade, lacunar infarct grade	N/A (>2 weeks washout)
Yaneva-Sirakova T (2016) [33]	Not specified (Not specified)	Not specified	No	Not specified	No	No	No	No

[a]Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BMI: Body Mass Index; BP: Blood Pressure; DBP: Diastolic Blood Pressure; GFR: Glomerular Filtration Rate; HR: Hazard Ratio; LDL: Low-Density Lipoprotein; MAP: Mean Arterial Pressure; N/A: Not Applicable; OR: Odds Ratio; PVH: Periventricular Hyperintensities; SBP: Systolic Blood Pressure. [b] This study, unlike others, considered 5% as threshold for dipper/non-dipper definition

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Discussion

Our critical analysis of methodological approaches in the studies of the relationship between ABPM patterns and cognitive function aimed to identify key limitations and areas for improvement in this important field of research. Our review of 28 studies revealed several significant methodological shortcomings that potentially compromise the reliability and generalizability of current findings. These limitations include a lack of diversity in study populations, inconsistent ABPM protocols, inadequate control for confounding variables, and a scarcity of longitudinal studies.

A significant concern is the lack of diversity in study populations, particularly the underrepresentation of Blacks and Latinos. It's important to note that this gap is not a result of our review's inclusion/exclusion criteria because race was not a factor in study selection. Rather, this underrepresentation appears to be a pervasive issue in the broader field of ABPM and cognitive function research. This gap is particularly troubling given the well-documented disparities in the prevalence and outcomes of hypertension among these groups. For instance, Lackland (2014) [35] reported African Americans exhibit a significantly higher prevalence of hypertension compared to other racial groups, with earlier onset and more severe consequences. The limited inclusion of diverse populations in ABPM and cognitive function studies may lead to findings that do not accurately represent the full spectrum of the relationship between BP patterning and cognitive outcomes across different racial and ethnic groups.

Past studies predominantly focused on all-cause dementia or Alzheimer's disease and there was only limited investigation into other subtypes of dementia. It's important to note that this narrow focus is not a result of our review's inclusion/exclusion criteria, as we did not restrict studies based on dementia subtype. Given that different subtypes of dementia have distinct pathophysiological mechanisms, it is plausible their relationships with diurnal BP patterns may vary. For example, vascular contributions to FTLD have been increasingly recognized [36], suggesting the nature of the ABPM pattern might have unique associations with this subtype of dementia. Consideration of different types of dementia will help identify the potential differences in the association between ABPM patterning and specific forms of cognitive decline.

The heterogeneity and limitations of cognitive assessment methodologies employed across studies significantly hinder our understanding of the nuanced relationship between ABPM patterns and cognitive function. The prevalent use of brief screening tools, such as the MMSE, while practical, may obscure subtle cognitive changes associated with blood pressure variability. These global measures often lack the sensitivity to detect domain-specific impairments that could be differentially affected by ABPM patterns. For instance, various cognitive domains may be impacted by blood pressure variations, but these nuanced effects might be overlooked by general cognitive screens. Moreover, the reliance on simple cut-off scores to define cognitive impairment potentially misses individuals in preclinical stages of decline, precisely when ABPM patterns might be most informative. To address these shortcomings, future research should employ comprehensive neuropsychological batteries assessing multiple cognitive domains independently, alongside more sensitive measures designed to detect early cognitive changes. This approach would not only provide a more accurate picture of the ABPM-cognition relationship but also help identify subtle impairments that could be crucial for early intervention strategies.

A methodological issue of concern in several studies is the use of OBPM, rather than ABPM, to define hypertension for satisfaction of inclusion/exclusion criteria. This approach may lead to misclassification of hypertensive status, with the risk for biasing study populations and reported findings of studies. The superiority of ABPM over OBPM in predicting health outcomes is well-established [37–41], suggesting ABPM should be the gold standard for defining hypertension in these studies [42].

All of the 28 studies included in our review relied on 24-hour ABPM, despite compelling evidence 48-hour ABPM provides more representative and reliable data. Hermida et al. (2013) [43] demonstrated that 48-hour, compared to 24-hour, ABPM significantly improves the accuracy of diagnosis and risk for cardiovascular disease events. The first day of ABPM may be slightly unstable

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due to an "ABPM effect"— BP values are somewhat higher than actual values during the initial hours of measurement. This effect can persist for up to 9 hours and result in an average increase of 7 and 5 mm Hg in SBP and DBP, respectively, during the first 4 hours of monitoring [44]. This phenomenon is distinct from white coat hypertension and can lead to misclassification of patients' dipping status. Importantly, Hermida et al. (2002) [44] found that one-third of patients classified as dippers based on the first 24 hours of the 48-hour monitoring became non-dippers when assessed over 48 hours. Our review of the 28 studies of the Gavriilaki et al. (2023) publication [5] additionally revealed considerable variability in ABPM sampling rates. Most studies used a sampling frequency of every 15-30 minutes during the day and 30-60 minutes at night. However, the reproducibility of ABPM-derived parameters depends more on the duration of monitoring than on the frequency of sampling[43]. BP means estimated from data sampled every 1-2 hours over 48 hours were more reproducible than those estimated from data sampled every 20-30 minutes for only 24 hours. This suggests that extending ABPM duration to 48 hours, even with a reduced sampling frequency, could provide more reliable and clinically valuable information than the current standard of frequent measurements of just 24-hour monitoring and also improve tolerance to ABPM, a vital consideration when applied to cognitively impaired persons.

Another critical aspect of the methods of ABPMs that warrants attention is the necessity for rigorous data quality control, which encompasses both the elimination of erroneous values and the establishment of thresholds for missing or invalid data to qualify BP profiles as acceptable for analysis. The integrity and reliability of ABPM data are paramount for accurately assessing BP patterns and their relationship to cognitive outcomes. Our review observed heterogeneity in data preprocessing approaches, with some studies failing to report any data cleaning procedures. This variability may contribute to inconsistencies in findings across studies. One exemplary study [30] stipulated that >80% of programmed values with no more than 2 hours of missing data were required for a profile to be considered valid and to ensure a minimum density of correct measurements. Such criteria are especially crucial for nighttime measurements, where a paucity of readings could lead to misclassification of dipping status or inaccurate estimation of nocturnal BP.

Inconsistencies in dipping definitions across studies present another challenge. While some studies used SBP, others used DBP, both, or mean arterial pressure to define dipping status. This inconsistency may lead to discrepancies in results across studies. Standardization of dipping definitions is crucial for comparability and meta-analysis of findings. In addition, daily rhythms of behaviors such as sleep/wake status and physical activity can also affect the quantification of BP dipping. Hermida et al. (2019) [45] emphasize this point, highlighting the distinction between "night-time" BP and "sleep-time" BP. They argue that daily rhythms in neuroendocrine, endothelial, vasoactive peptide, opioid, and hemodynamic parameters – including renin, angiotensin, and aldosterone – that are primary determinants of the BP 24-hour pattern, are all affected by or aligned to the 24-hour rest/activity cycle. In the other words, the timings of these rhythms in term of clock time can be different for different individuals with different sleep/wake schedules. Reliance on arbitrary fixed clock hours as conventionally done in most of the 28 reviewed studies, are unlikely to be representative of the individualized rest/activity patterns and constitutes a major shortcoming in the calculation of BP dipping. These investigations derived non-biological relevant "daytime/nighttime" BP means, rather than biologically meaningful awake and asleep BP means, constituting a significant limitation of past studies. This fixed-time approach leads to misclassification of sleep and wake periods, potentially affecting the reported association between features of the 24-hour BP profile and cognitive outcomes. The use of more precise methods to determine individual sleep-wake cycles and sleep/wake status, such as actigraphy or detailed sleep diaries, enables accurate determination of the awake and asleep periods and the calculation of BP means and consequently dipping status to properly assess the relationship between diurnal BP patterns and cognitive function.

Inadequate control for confounding variables was observed in many studies. Factors such as age, sex, education level, body mass index, smoking status, alcohol consumption, and comorbidities of diabetes and cardiovascular disease can significantly influence both BP 24-hour patterning and

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cognitive function[1]. Future studies should consistently control for these variables to isolate the specific relationship between features of the 24-hour BP pattern and cognitive outcomes. Additionally, none of the studies reported controlling for the timing/schedule of antihypertensive medication administration. Given the large amount of existing knowledge that the timing of medication can significantly affect ABPM patterns [46–54], this is a crucial factor to consider in future studies. The potential timing effect of medication on the relationship between ABPM patterns and cognitive function remains an important area for investigation.

Another notable limitation observed across most studies in our review was the lack of reporting on ABPM acceptance rates by participants. This omission represents a significant gap in our understanding of the feasibility and acceptability of ABPM, particularly in populations with cognitive impairment or dementia. The successful acceptance and completion of ABPM protocols is crucial for obtaining reliable and representative data, yet the challenges associated with extended monitoring periods in cognitively vulnerable individuals remain largely unexplored. This paucity of information is particularly concerning given the potential impact of cognitive status on adherence to ABPM protocols. Individuals with dementia may experience increased distress or confusion during monitoring, resulting in a high rate of rejection or incomplete or invalid ABPM profiles. Furthermore, the absence of completion rate data precludes a comprehensive assessment of potential selection bias, as those unable to complete ABPM might systematically differ in their BP profiles or cognitive characteristics. Future research should prioritize the explicit reporting of ABPM acceptance and completion rates, stratified by cognitive status where applicable, to elucidate the practical challenges and limitations of applying this method to assess BP in diverse populations. Such data would not only inform the interpretation of study results but also guide the development of more inclusive and adaptable ABPM protocols for individuals across the cognitive spectrum.

Furthermore, several studies relied solely on p-values without reporting effect sizes, limiting the interpretation of the clinical significance of findings and hindering comparison across studies. This practice goes against current statistical reporting recommendations [55], making it challenging to assess the magnitude and practical importance of observed associations.

Finally, another significant limitation is the scarcity of longitudinal studies examining the bidirectional relationship between features of the 24-hour BP pattern and cognitive decline. This gap restricts our understanding of how changes over time in ABPM patterns might precede or follow cognitive decline and vice versa. Longitudinal studies are crucial for establishing temporal relationships and inferring causality.

Conclusion

Herein, we critically revealed the methods of certain key studies that investigated the relationship between ABPM-determined 24-hour patterning and cognitive function. Several significant limitations and areas for improvement were identified. They include a lack of diversity in study populations, insufficient representation of various dementia subtypes, inconsistencies of ABPM protocols, disparity of definition of BP dipping, inadequate control for confounding variables, and a scarcity of longitudinal studies. Future research in this field should prioritize the following: (1) Inclusion of more diverse populations, particularly underrepresented racial and ethnic groups; (2) Investigation of various dementia subtypes beyond those of Alzheimer's disease and all-cause dementia; (3) Implementation of more precise methods for determining individual sleep-wake cycles, such as actigraphy or detailed sleep diaries; (4) Standardization of ABPM protocols, including use of 48-hour monitoring periods and consistent definition of actual awake and sleep of each study participant, as opposed to non-representative arbitrary fixed clock-time daytime and nighttime spans, to correctly derive dipping status; (5) Comprehensive control for confounding variables, including the class, dose, and especially timing of antihypertensive medication administration; (6) Consistent reporting of effect sizes alongside p-values to facilitate interpretation and comparison across studies; (7) Conduct of longitudinal studies to elucidate the bidirectional relationship between ABPM patterns and cognitive decline over time.

Future studies can provide more robust, reliable, and generalizable evidence by addressing the identified shortcomings of past investigations. This improved evidence base will be crucial for informing clinical practice, guiding preventive strategies, and ultimately enhancing understanding of the complex relationship between features of BP patterning and cognitive function. Researchers in this field must collaborate to establish standardized protocols and reporting guidelines to ensure the collective body of research effectively contributes to improved patient outcomes and public health strategies.

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