Review Article

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Midlife hypertension is a risk factor for some, but not all, domains of cognitive decline in later life: a systematic review and meta-analysis

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Introduction: Management of midlife blood pressure and hypertension status may provide a window of intervention to mitigate cognitive decline with advancing age. The aim of this review was to investigate the relationship between midlife hypertension and cognition in midlife and later life.

Methods: Online electronic databases were searched from their inception to May 2022. Studies assessing midlife (40–65 years) hypertension and cognition at mid and/or later-life were included. A random effects meta-analysis was deemed appropriate.

Results: One hundred forty-nine studies across 26 countries were included. Qualitative synthesis found negative relationships between midlife hypertension and later life cognition in the domains of memory, executive function, and global cognition. Metanalytical evidence revealed midlife hypertension negatively impacts memory, executive function, and global cognition but had no observed effect on attention at midlife.

Discussion: Hypertension at midlife has a significant negative impact on cognition in mid-life and later life, namely memory, executive function, and global cognition.

Keywords: cognition, high blood pressure, hypertension, middle-aged, midlife

Abbreviations: AHA, American Heart Association; AXIS, Appraisal Tool for Cross sectional Studies; BP, Blood Pressure; CI, Confidence Interval; ESC, European Society of Cardiology; MD, Mean Difference; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; SD, Standard Deviation; SE, Standard Error; TBI, Traumatic Brain Injury

BACKGROUND

The worldwide prevalence of age-related cognitive decline is a major public health concern, especially in the context of an ageing population. Globally, the number of people living with dementia and cognitive impairment is expected to rise from 24.3 million in 2001 to 81.1 million in 2040, almost doubling every 20-years [1,2]. Current evidence from the Lancet Commission on dementia prevention, intervention, and care suggests that up to 40% of all dementia cases can be linked to modifiable risk factors [3]. Identification of such risk factors and strategies to modify their negative influence on cognitive function therefore has the potential to protect and improve quality of life for a significant proportion of the global population, now and in the future.

Hypertension, which affects at least 1 billion people globally [4], has emerged as an important risk factor for cognitive deterioration and vascular dementia [5], and age of onset may impact on overall risk to brain health and function later in life [6]. Specifically, there is evidence that hypertension during midlife could accelerate brain ageing [5,7], potentially inducing premature cognitive decline via vascular and structural change [8]. Interestingly, blood pressure (BP) exceeding optimal values even in the absence of a diagnosis of hypertension during young adulthood and midlife has been found to increase the risk of cognitive impairment in later life [9]. Therefore, midlife may be the optimal time point for appropriate treatment and management of BP to mitigate the associated trajectory of cognitive decline with age. Cognitive function can be measured clinically and experimentally across several domains including but not limited to memory, attention, executive function, and global cognition. Different studies have assessed the effects of hypertension on one or more of these functions, yet there is no consensus on the impact of midlife hypertension on any of these domains at midlife or later life; the systematic analysis and meta-analysis presented here aims to address this issue.

As the world's population over the age of 60 years is expected to double by 2050 [10], there is a growing need to investigate the association between midlife hypertension and cognitive decline, including any parallels in the time course of progression of each domain, to help inform public health policy. Although midlife hypertension has the potential to increase risk of later life cognitive decline,

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it is unclear at what point in the lifespan this decline begins and whether it is apparent during midlife. The purpose of this systematic review was to perform an analysis of the published evidence to explore the relationship between midlife hypertension status and cognitive function at both later life and at midlife, and to assess whether any negative impact was evident across different cognitive domains.

MATERIALS AND METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; www.prisma-statement.org) and was recorded in PROSPERO, a registry of systematic reviews. Registration of this review can be found at https://www.crd.york.ac.uk/prospero/ (registration number: CRD42021238293). The present review is a subset analysis of the registered review.

Search strategy

Online electronic databases were searched, and relevant articles retrieved from the following: EMBASE, MEDLINE, PubMed, Web of Science, and CINAHL, from their inception to May 2022. All search strategies were conducted by a medical librarian with methodological experience and the full search strategy can be found in the supplementary file, http://links.lww.com/HJH/C344. The search strategy comprises key words, MeSH terms, common medical terms, and a combination of these including, but not limited to, middle age, midlife, cardiovascular disease, cardiovascular risk, hypertension, high BP, cognition, and cognitive defect. The search strategy focused on the inclusion of longitudinal, prospective, and follow-up studies to ensure later life cognition was captured. No search restrictions for language or publication date were implemented. The search of electronic databases was supplemented by a manual literature search of the reference lists of included studies and appropriate databases to ensure all relevant studies were captured.

The stepwise process of the search methodology can be seen in Fig. 1. All stages of the screening process were conducted independently by two reviewers (O.C.J. and C. McH.), including title and abstract screening and subsequent full text screening. Disagreements between the two reviewers were resolved through discussion. If a consensus was not achieved, a third reviewer (F.W or A.K) was consulted. Titles, abstracts, and full texts of all eligible articles were screened using Covidence (https://www.covidence.org/home).

Eligibility criteria

Studies were deemed eligible based on the following inclusion criteria: human participants, adults between ages of 40–65 years were classified as middle-aged (WHO definition of middle age), hypertension, and/or BP reported as an outcome measure at later life, midlife, or both for determination of the longitudinal association with midlife hypertension and cognition across domains including memory, attention, executive function, intelligence, and global cognitive functioning (see Supplementary file, http://links.lww.com/HJH/C344). Hypertension was considered an outcome of elevated BP where diagnosis by clinician, self-report, and/or by recorded BP metric in line with accepted definitions were considered eligible for inclusion and data analysis. Studies not published in the English language where a translation could not be obtained were excluded. Studies were excluded if cognitive testing was undertaken by a proxy or designated respondent, such

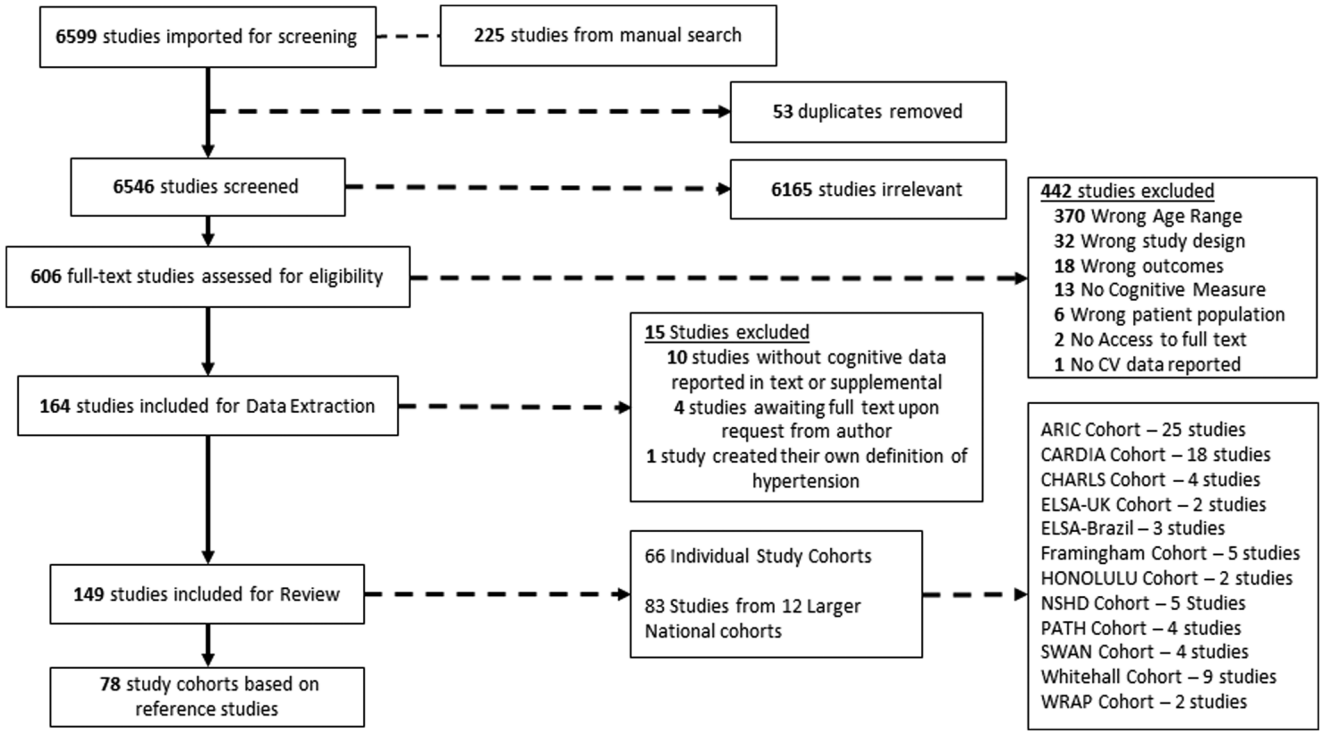

FIGURE 1 Flow chart of the study selection process.

as a friend or family member, if the participant cohorts included those with midlife dementia or any form of pre-existing cognitive impairment and if studies of specific disabilities [traumatic brain injury (TBI), stroke, HIV, spinal cord injury, and so on] were associated with modifiable behavioural risk factors.

Data extraction

Data extraction was carried out in accordance with the STROBE guidelines [11], including study aims, participant characteristics, measures of cognition and cardiovascular risk factors alongside relevant outcome data as group means, standard deviation (SD), standard error (SE) of the mean, statistical significance, and precision estimates. Adults between the ages of 40 and 65 years were considered middle aged in line with the WHO definition and those beyond the age of 65 years were classified as later life participants. To prevent double reporting of data from prospective longitudinal cohorts, the most recent publication relating to each was selected as the reference study for the determination of baseline data (see Supplemental file, http://links.lww.com/HJH/C344). If uncertainties arose, the corresponding authors were contacted for further clarification. Each study was assigned a reference number and separate data collection form. To ensure accurate reporting, the data extraction pro-forma was piloted against a selection of articles. All BP values reported are classified according to the European Society of Cardiology (ESC) classification in order to determine hypertension status [12].

Risk of bias and methodological assessment

The methodological quality of included studies was evaluated using the Appraisal Tool for Cross sectional Studies (AXIS) [13]. This tool employs 20 questions to determine quality of study design and risk of bias with questions being answered as 'Yes', 'No', or 'Unsure'. Using the method outlined by McHugh *et al*. [14], answers were inserted in colour coding to reflect the impact on the text, including green, positive impact on quality of study; red, negative impact on quality of study; and amber, unknown impact on quality of study. Two reviewers (O.C.J. and C.McH.) independently evaluated the included studies. Disagreements between reviewers were resolved through discussion. If a consensus was not achieved, a third reviewer (F.W or A.K) was consulted. Study quality was then classified as either low, moderate, or high.

Statistical analysis

The weighted mean for demographics, cognitive measures (cognitive-specific domains and associated neuropsychological tests), SBP, and DBP values were calculated across studies to better understand the relationship with hypertension diagnosis. Weighted means were calculated using the following formula: $\sum^{n}{}_{i=1}$ (xi∗wi)/$\sum^{n}{}_{i=1}$ wi; where $\sum$ denotes the sum, w denotes the weights, and x is the corresponding value [15].

$$\bar{x} = \frac{\sum_{i=1}^{n}(x_i * w_i)}{\sum_{i=1}^{n} w_i}$$

Cognitive outcome measures were grouped according to cognitive domain. Qualitative analysis assessed the relationship between midlife hypertension status and cognition at later life and midlife; positive, negative, or neutral, across studies.

A random effects meta-analysis was conducted to compare the difference across each cognitive domain between two independent groups, hypertension vs. normotension. This meta-analysis was deemed appropriate to calculate the pooled summary effect of midlife hypertension on cognition at midlife across the domains of memory, attention, executive function, and global cognition. Group mean differences, 95% confidence intervals (95% CIs), and P values were calculated using Review Manager (RevMan) software ([Computer pro-gramme], Version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). Sub-grouping for meta-analyses included study design and quality. The heterogeneity between studies was established using the I^2 statistic. I^2 values of 25, 50, and 75% ($P > 0.05$) correspond to low, moderate, and high degrees of heterogeneity, respectively [16]. Where high levels of heterogeneity ($I^2 > 75\%$) were detected and a sufficient availability of studies was present, sensitivity analyses were applied, and studies were removed one by one to assess their overall influence. Studies that were removed due to the sensitivity analysis are represented by a 0.0% weight in the forest plots.

All remaining studies that were not included in our meta-analysis due to lack of available comparative data between those with and without hypertension were subject to qualitative analysis. This was undertaken based on the findings reported by the respective authors in the studies included in our review. Our intention was to provide a comprehensive synthesis of the available evidence in these areas, even when the number of eligible studies was limited for specific cognitive domains.

RESULTS

Literature search

Figure 1 displays details of the study selection. The initial search and manual search yielded 6824 records. Following the removal of duplicates and title and abstract screening, 606 full texts were screened, and 442 studies were excluded (see Fig. 1). The authors of four studies were contacted for access to full texts and were later recorded as 'studies awaiting classification' due to lack of response. All studies were imported in Endnote version 20 and an appropriate database was created from all extracted data in Microsoft Excel. Overall, 149 studies published between 1992 and 2022 were included.

Methodological and risk of bias assessment

Of the 149 included studies, 35 were deemed low quality, 59 moderate quality, and 55 high quality. Overall, studies were deemed of moderate-to-high quality with negative commonalities arising across several domains (see Supplementary file, http://links.lww.com/HJH/C344). The most common domains that were absent or unclear from studies included sample size justification ($n = 127$), categorization

of nonresponders ($n = 130$), information about nonresponders ($n = 137$), clear determination of statistical significance ($n = 56$), discussion of limitations ($n = 22$), and disclosure of ethical approval or consent ($n = 21$).

Characteristics of included studies

Of all included studies, 131 assessed men and women, 11 assessed men only and seven assessed women only. Eighty-three studies assessed subsets of data from 12 prospective longitudinal cohorts (see Supplementary file, http://links.lww.com/HJH/C344). The remaining 66 studies assessed data from individual study cohorts. Studies were conducted across 26 countries with the top five including USA ($n = 67$), UK ($n = 23$), China ($n = 7$), Australia ($n = 4$), and Brazil ($n = 4$).

Participant characteristics

Studies included in this review incorporated a total of 129 274 participants, who were pooled for analysis. The weighted mean age of participants was 54.5 ± 3.9 years, weighted mean BMI was $27.19 \pm 4.6\,kg/m^2$, and weighted mean height and weight were 171.4 ± 7.1 cm and 78.7 ± 14.6 kg, respectively.

In studies that provided data according to sex ($n = 56$), 39 325 men and 40 678 women were included. Weighted mean BMI for men and women was 25.7 ± 3.4 and $24.5 \pm 4.3\,kg/m^2$, respectively. Weighted mean age for men was 58.9 ± 1.8 and 56.7 ± 1.9 years for women. Mean height and weight were not available.

Blood pressure and hypertension

The pooled weighted mean SBP and DBP for all participants were 130.5 ± 12.1 and 80.8 ± 7.6 mmHg, respectively. Men had a higher SBP (128.2 ± 6.2 vs. 121.8 ± 8.2 mmHg) and DBP (82.7 ± 0 vs. 77.4 ± 1.5 mmHg) compared with women.

Hypertension was most commonly defined using the ESC definition ($n = 30$). Alternative definitions included American Heart Association (AHA) ($n = 8$), use of antihypertensive medication ($n = 12$), and self-reported hypertension ($n = 10$). Seven studies did not provide a working definition (see Tables 2 and 3). A total of 46 706 participants were classified as hypertensive, with 1553 classified as prehypertensive; 3968 were taking antihypertensive medication. More women were identified as hypertensive (8423 individuals compared with 7516 men) and prehypertensive (108 individuals compared with none in the male group). A higher number of men than women reported taking antihypertensive medication (951 vs. 800). A total of 18 931 participants were normotensive, with a higher proportion of women than men reporting normal BP (2849 vs. 2682).

Associations between hypertension status at midlife and measures of cognition at later life

Of the 12 longitudinal study cohorts, 10 evaluated midlife hypertension and cognitive function at later life. A negative relationship was reported by qualitative analysis among domains including, memory ($n = 8$), executive function ($n = 4$), attention ($n = 3$), global cognition ($n = 5$), visuospatial organization ($n = 1$), and psychomotor speed ($n = 1$) (see Table 1).

From the 67 independent study cohorts, 10 evaluated the relationship between midlife hypertension and later life cognition. Three studies reported negative relationships for memory and visuospatial organisation and a further three studies also found a negative relationship for executive function, global cognition, and psychomotor speed. No relationship was found between hypertension and any measure of cognition in four studies.

Findings on the relationship between midlife hypertension and later life cognition did not differ by study quality. Longitudinal studies of moderate-to-high quality reported a negative relationship between midlife hypertension and later life cognition mainly in memory, executive function, and global cognition (see Table 1).

In summary, midlife hypertension was found to negatively impact on cognitive function across multiple domains at later life assessed by qualitative analysis, irrespective of study design or quality.

Associations between hypertension and measures of cognition at midlife

Table 2 details mean pooled weighted outcomes for all measures of cognition and associated BP and hypertension values.

Conflicting findings were reported on the relationships between midlife hypertension and cognitive function at midlife by qualitative analysis (see Tables 2 and 3). A similar number of studies reported no relationship or a negative relationship for cognitive domains, including attention, memory, inductive reasoning, and visuospatial organisation. Reports of no relationship were more common in the case of intelligence ($n = 5$, 83%), global cognition ($n = 17$, 74%), and executive function ($n = 25$, 75%). A negative relationship was more commonly reported for psychomotor speed ($n = 5$, 71%).

There were no discernible differences in reported relationships between midlife hypertension and midlife cognition based on study design (individual cohorts vs. large cohorts) or by study quality (low vs. moderate vs. high) (see Tables 2 and 3).

Meta analyses

All meta-analyses performed reflect the association between midlife hypertension diagnosis and midlife cognition. There were insufficient data available for meta-analyses including later life cognition (Fig. 2). Fifteen studies across four cognitive domains (memory, executive function, attention, and global cognition) were suitable for meta-analysis. A total of 12 919 participants were classified as hypertensive and 21 342 as normotensive. High levels of heterogeneity ($I^2 \geq 75\%$) was identified for all four cognitive domains. Hypertension diagnosis had a negative effect on memory compared to normotension (MD = −0.06; 95% CI = −0.20 to 0.08; $I^2 = 0\%$). Hypertension diagnosis had no effect on attention compared to normotensives (MD = 0.41; 95% CI = 0.26 to 0.56; $I^2 = 18\%$). Hypertension diagnosis had a negative effect on executive function (MD = −0.02; 95% CI = −0.08 to 0.03; $I^2 = 36\%$). Hypertension diagnosis negatively impacted global cognition compared to normotensive status (MD = −0.24; 95% CI = −0.28

TABLE 1. Summary of longitudinal studies with negative or null relationship between hypertension and cognitive measures at later life.

Ref.	Year	Setting	Study quality	Cognitive variables	Relationship
Anstey *et al.*	2014	PATH through Life; Australia	High	Memory, attention, executive function, global cognition, and psychomotor speed	- (Memory, attention, global cognition, psychomotor speed)
Bangen *et al.*	2013	Framingham Study; USA	High	Memory, executive function, global cognition, and visuospatial organisation	(Executive function, attention, visuospatial organization)
Bayes-Marin *et al.*	2020	Edad con Salud; Spain	High	Memory	- (Memory)
Brunner *et al.*	2017	Whitehall II Study; UK	Low	Global Cognition	- (Global Cognition)
de Menezes *et al.*	2021	ELSA Study; Brazil	High	Memory, executive function, and global cognition	- (Memory, executive function, global cognition)
Derby *et al.*	2021	SWAN, USA	Moderate	Memory and executive function	- (Women only: Memory and executive function)
Dixon *et al.*	2021	SWAN, USA	Moderate	Memory and executive function	- (Memory and executive function)
Hajjar *et al.*	2016	USA	Moderate	Memory, executive function, attention, global cognition, and visuospatial organisation	0
Hoffmann *et al.*	2021	Recall Study; Germany	High	Memory, executive function, and visuospatial organization	- (Memory)
Kazlauskaite *et al.*	2020	SWAN; USA	Moderate	Memory and psychomotor speed	- (Memory, executive function)
Kesse-Guyot *et al.*	2015	SU.VI.MAX study; France	High	Memory, attention, executive function, and global cognition	0
Kivipelto *et al.*	2001	North Karelia Project and FINMONICA study; Finland	High	Memory, attention, executive function, and global cognition	- (Global Cognition)
Leong *et al.*	2020	TILDA; Ireland	Moderate	Attention, Global cognition	- (Global cognition)
Lin *et al.*	2020	KALS; Taiwan	High	Global cognition, memory, executive function, visuospatial orientation and attention	0
Lutski *et al.*	2019	BIP Neurocognitive Study; Israel	High	Memory, executive function, attention, global cognition and visuospatial organization	0
Olaya *et al.*	2019	ELSA; UK	High	Memory	- (Memory)
Power *et al.*,	2017	ARIC Study; USA	High	Memory and executive function	- (Memory, global cognition)
Rouch *et al.*	2019	VISAT Cohort Study; France	Moderate	Memory, attention, executive function, global cognition, and psychomotor speed	- (Global cognition)
Swan *et al.*	1998	NHLBI Twin Study; USA	Moderate	Memory, executive function, global cognition, and psychomotor speed	- (Global cognition, psychomotor speed)
Swan *et al.*	1998	Western Collaborative Group Study, USA	Moderate	Memory, executive function, and psychomotor speed	- (Global cognition)
Szoeke *et al.*	2016	WHAP; Australia	Moderate	Memory	(Memory)
Zhang *et al.*	2019	CHARLS; China	Low	Memory, executive function, and global cognition	(Memory, executive function)

0, no association; -, negative association; +, positive association.
ACE, Akershus Cardiac Examination; APAC, Asymptomatic Polyvascular Abnormalities Community; ARIC, Atherosclerosis Risk in Communities; ASCEND, A Study of Cardiovascular Events in Diabetes; Barcelona-AsIA, Asymptomatic Intracranial Atherosclerosis; BHS, Bogalusa Heart Study; BIP, Bezafibrate Infarction Prevention; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CHARLS, China Health and Retirement Longitudinal Study; DBP, diastolic blood pressure; ELSA, Brazilian Longitudinal Study of Adult Health, FINMONICA, Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; ELSA, English Longitudinal Study of Ageing; HAALSI, Health and Aging in Africa; HANDLS, healthy Aging in Neighborhoods of Diversity Across the Life Span; HHP, Honolulu Heart Program; IHDB, Institute of Human Development in Berkeley; KALS, Kaohsiung Atherosclerosis Longitudinal Study; KEEPSCog, Kronos Early Estrogen Prevention cognitive; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; MACS, Multicentre AIDS Cohort Study; MADT, Middle-Aged Danish Twins; MDCS, Malmö Diet and Cancer Study; MORGEN, Monitoring Project on Cardiovascular Disease Risk Factors; MRC, Medical Research Council; NHLBI, National Heart, Lung, and Blood Institute; NSHD, National Survey of Health and Development; PATH, Population Assessment of Tobacco and Health; PURE, prospective Urban and Rural Epidemiological; RECALL, Risk Factors, Evaluation of Coronary Calcium and Lifestyle; SBP, systolic blood pressure; Swan, Study of Women's Health Across the Nation; TILDA, The Irish Longitudinal Study on Ageing; VETSA, Vietnam Era Twin Study of Aging; VISAT, Vieillissement Santé Travail (Aging, Health and Work); WHAP, Women's Health Aging Project.

to −0.21; $I^2 = 12\%$) (see Fig. 3). Study quality or study design had no influence on meta-analyses findings for all four measures (Tables 4 and 5).

DISCUSSION

This review aimed to investigate the relationship between midlife hypertension status and cognitive function at later life and midlife. Using qualitative analysis, our results indicate mixed and inconsistent findings across all cognitive domains, but predominantly favour negative relationships between midlife hypertension and later life cognition in some but not all domains, most notably memory, executive function, and global cognition. No relationship was observed for attention, inductive reasoning, visuospatial organization, or temporal orientation. There was conflicting evidence on the relationship between hypertension and cognitive function at midlife, irrespective of study quality and study design. Though qualitative analysis suggested no relationship between hypertension and memory or global cognition at midlife, findings from our meta-analyses indicate a negative relationship for memory, executive function, and global cognition and no relationship with attention.

The finding in this review that midlife hypertension affects later life cognition is consistent with previous research [17–19], indicating accelerated cognitive decline with midlife hypertension, specifically memory, executive function, and global cognition. Growing evidence highlights the hypertension-cognition relationship is age-dependent [20,21]. Long-term hypertension spanning 25–30 years, initiated during middle-age, increases the likelihood of cognitive impairment in later life [19]. Evidence

TABLE 2. Summary Table of pooled weighted average for all cognitive measures and associated BP metrics at baseline (i.e., midlife).

Cognitive variable	No. of studies	Weighted average (Mean ± SD)	Age (Mean ± SD; years)	S BP (Mean ± SD; mmHg)	SBP category status (ESC)	DBP (Mean ± SD; mmHg)	DBP category status (ESC)
Memory Verbal Memory	Total: *n* = 21 *Immediate*: *n* = 3, *Delayed*: *n* = 11, *STW*: *n* = 1, *EBM*: *n* = 2, *RAVLT (Immediate & Delayed recall, Learning & Summary Score)*: *n* = 2, *SRT*: *n* = 1, *ROCF (Immediate & Delayed)*: *n* = 1, *CERAD (Immediate & Delayed)*: *n* = 1, *CVLT (Immediate & Delayed)*: *n* = 1 *WLL*: *n* = 1	Immediate: Total = 9.9, men = 5.7 ± 1.1, women = 4.6 ± 1.5 Delayed: Total = 6.2 ± 1.5 men = 9.9 ± 2.9, women = 12.7 ± 3.7 STW: Total = 50.5 EBM: Total = 10, Female = 10.2 RAVLT (Immediate & Delayed recall): Total = 7.1 ± 2.7 RAVLT (Learning Score): Total = 36.8 ± 8.3 RAVLT (Summary Score): Total = 8.8 ± 3.2 SRT: Total = 34.3 ROCF (Immediate): Total = 16.1 ± 7.6 ROCF (Delayed): Total = 14.9 ± 7.8 CERAD (Immediate): Total = 7.2 ± 1.1 CERAD (Delayed): Total = 7.7 ± 1.5 CVLT (Immediate): Total = 8.8 ± 2.1 CVLT (Delayed): Total = 8.8 ± 3.2 WLL: Total = 20.5 ± 0.5	Total = 52.7 ± 4.8 men = 53.2 ± 4.9, women = 52.4 ± 4.5	Total = 124.2 ± 16.8, men = 123.7 ± 15.6, females = 120.9 ± 16.8 *Delayed:* Total = 121.6 ± 17.1, males = 123.7 ± 15.6, females: 120.9 ± 16.8 *Immediate:* - *STW:* - *EBM:* - *RAVLT (Immediate & Delayed recall, Learning Score):* Total = 131.2 ± 16.1 *SRT:* Total = 134.1 ± 16.9 *ROCF (Immediate & Delayed):* Total = 131.2 ± 16.1 *CERAD (Immediate & Delayed):* Total = 127.9 ± 20.7 *CVLT (Immediate & Delayed):* Total = 127.9 ± 20.7 *WLL*: Total = 123.7 ± 17.6	Total = Normal, men = Normal, women = Normal *Delayed:* Total = Normal, men = Normal, women = Normal *Immediate:* - *STW:* - *EBM:* - *RAVLT (Immediate & Delayed recall, Learning Score):* Total = High Normal *SRT:* Total = High Normal *ROCF (Immediate & Delayed):* Total = High Normal *CERAD (Immediate & Delayed):* Total = Normal *CVLT (Immediate & Delayed):* Total = Normal *WLL*: Normal	Total = 82.7 ± 10.3 *Delayed:* Total = 74.8 ± 10.5 *Immediate:* - *STW:* - *EBM:* - *RAVLT (Immediate & Delayed recall, Learning Score):* Total = 83.4 ± 10.7 *SRT:* Total = 88.8 ± 10.2 *ROCF (Immediate & Delayed):* Total: 83.4 ± 10.7 *CERAD (Immediate & Delayed):* Total = 88.8 ± 10.6 *CVLT (Immediate & Delayed):* Total = 88.8 ± 10.6 *WLL*: 77.2 ± 8.1	Total = Normal *Delayed:* Total = Optimal *Immediate:* - *STW:* - *EBM:* - *RAVLT (Immediate & Delayed recall, Learning Score):* Total = Normal *SRT:* Total = High Normal *ROCF (Immediate & Delayed):* Total = Normal *CERAD (Immediate & Delayed):* Total = High Normal *CVLT (Immediate & Delayed):* Total = High Normal *WLL*: Optimal
Episodic Memory	*Total:* *n* = 4	*Total* = 5.9 ± 2.3	Total = 51.7 ± 6.1, men = 50.3 ± 8, women = 51 ± 8.1	–	–	–	Total = High Normal
Semantic Memory	*Total*: *n* = 1	*Total* = 15.6 ± 2.9 men = 15.2 ± 3.0, women = 16 ± 2.8	Total = 50.7 ± 8, men = 50.3 ± 8, women = 51 ± 8.1	–	–	–	–
Working Memory	*Total:* *n* = 22 *DSST:* *n* = 8 *Composite Score:* *n* = 1 *CMS Score:* Total: *n* = 1 *DSB Test:* *n* = 7 *McNS:* n = 1 *WDS:* *n* = 1 *MIS (MoCA):* *n* = 1 *VRT*: *n* = 1	*DSST:* Total = 47.8 ± 7.9 *Composite Score:* men = 6.9 ± 2.3, women = 6.9 ± 2.72 *CMS Score:* Total = 76.6 ± 12.9 *DSB Test:* Total = 6.2 ± 1.9, men = 5, women = 5.3 *McNS:* Total = 27.7 ± 1.9 *WDS:* men = 38.6 ± 3.9, women = 38.9 ± 4.7 *MIS (MoCA):* Total = 12.72 ± 2.4 *VRT:* Total = 11.3	Total = 52.3 ± 4.2, males = 54.2 ± 4.9, females = 56 ± 4.9	Total = 123.4 ± 15.9, men = 123.5, women = 121.7 *DSST:* Total = 119.3 ± 15.6 *Composite Score:* men = 123.5, women = 121.7 *CMS Score:* - *DSB Test:* Total = 132.7 ± 14.8 *McNS:* - *WDS:* - *MIS (MoCA):* - *VRT:* Total = 134.1 ± 16.9	Total = Normal, males = Normal, females = Normal *DSST:* Total = Optimal *Composite Score:* men = Normal, women = Normal *CMS Score:* - *DSB Test:* Total = High Normal *McNS:* - *WDS:* - *MIS (MoCA):* Not available *VRT:* Total = High Normal	Total = 77.2 ± 9.9, men = 78.3, women = 75.1 *DSST:* Total = 73.2 ± 9.8 *Composite Score:* male = 78.3, female = 75.1 *CMS Score:* - *DSB Test:* Total = 80.5 ± 9.1 *McNS:* - *WDS:* - *MIS (MoCA):* - *VRT:* Total = 88.8 ± 10.5	Total = Optimal, men = Optimal, women = Optimal *DSST:* Total = Optimal *Composite Score:* men = Optimal, women = Optimal *CMS Score:* - *DSB Test:* Total = High Normal *McNS:* - *WDS:* - *MIS (MoCA):* - *VRT:* Total = High Normal
Attention	*Total:* n = 11 *TMT-A:* *n* = 10 *CRT:* *n* = 4 *SiRT:* *n* = 3 *DSF Test:* *n* = 5 *5-CMT*: *n* = 1	*TMT-A:* Total = 24.8 ± 8.4 *CRT:* Total = 733.4 ± 153.8 *SiRT:* Total = 296.5 ± 64.6 *DSF Test:* Total = 7.5 ± 1.9 *5-CMT:* Total = 370.5	Total = 51.9 ± 4.3, men = 56.1 ± 3.7, women = 56.5 ± 3.6	Total = 130.5 ± 16.13 *TMT-A:* Total = 129.4 ± 15.9 *CRT:* Total = 134.1 ± 15.8 *SiRT:* Total = 134.8 ± 15.7 *DSF Test:* Total = 132.8 ± 17.1 *5-CMT:* Total = 129.4 ± 5.03	Total = High Normal *TMT-A:* Total: = Normal *CRT:* Total = High Normal *SiRT:* Total = High Normal *DSF Test:* Total = High Normal *5-CMT:* Total = High Normal	Total = 81.04 ± 9.4 *TMT-A:* Total = 82.4 ± 9.3 *CRT:* Total = 79.03 ± 8.8 *SiRT:* Total = 78.2 ± 8.4 *DSF Test:* Total = 80.4 ± 10.8 *5-CMT:* Total = 83.4 ± 3.2	Total = Normal *TMT-A:* Total = Normal *CRT:* Total = Optimal *SiRT:* Total = Optimal *DSF Test:* Total = High Normal *5-CMT:* Total = Normal
Intelligence	*Total:* *n* = 6 *WAIS:* *n* = 1 *IQ:* *n* = 2 *MR:* *n* = 1	*WAIS:* Total = 17 ± 3 *IQ:* Total = 104.08 ± 18.5 *MR:* Total = 18.13	Total = 54.7 ± 4.7	Total = 125.7 ± 17.5 *WAIS:* Total = 124 ± 18 *IQ:* Total = 149.9 ± 13.4 *MR:* Total = 126.7 ± 13.7	Total = Normal *WAIS:* Total = Normal *IQ:* Total = Grade 1 Hypertension *MR:* Total = Normal	Total = 84.4 ± 7.3 *WAIS:* - *IQ:* Total = 90.3 ± 6.9 *MR:* Total = 77.3 ± 6.9	Total = High Normal *WAIS:* - *IQ:* Total = Grade 1 Hypertension *MR:* Total = Optimal
Executive Function *Letter Cancellation*	*Total:* *n* = 2 *LSST*: *n* = 1 *LCCS*: n = 1	*LSST:* Total = 282 *LCCS:* Total = 50 ± 7.3	Total = 52.66 ± 2.59	*Total* = 129.7 ± 17.1 *LSST:* Total = 134.8 ± 17.9 *LCCS:* Total: 118.58 ± 15.25	Total = High Normal *LSST:* Total = High Normal *LCCS:* Total = Optimal	Total = 77.2 ± 9.7 *LSST:* Total = 77.2 ± 9.7 *LCCS:* -	Total = Optimal *LSST:* Total = Optimal *LCCS:* -

TABLE 2 (*Continued*)

Cognitive variable	No. of studies	Weighted average (Mean ± SD)	Age (Mean ± SD; years)	S BP (Mean ± SD; mmHg)	SBP category status (ESC)	DBP (Mean ± SD; mmHg)	DBP category status (ESC)
Verbal Fluency	*Total:* n = 15 *WFT:* n = 10 *BNT:* n = 2 *MVT:* n = 2 *PFT:* n = 2 *SFT:* n = 2 *VIS (MoCA):* n = 1 *BeDT:* n = 1 *BuDT:* n = 1	*WFT:* Total = 31.3 ± 8.2, men = 25.7 ± 6.4, women = 24.8 ± 6.2 *BNT:* Total = 27.1 ± 1.9 *MVT:* Men = 25.8 ± 3.7, women = 23.3 ± 5.4 *PFT:* men = 17.1 ± 4.3, women = 16.8 ± 4.8 *SFT:* men = 16.7 ± 3.9, women = 16.02 ± 4.6 *VIS (MoCA):* Total = 6.48 ± 0.92 *BeDT:* men = 12, women: 12 *BuDT:* men = 7, women: 6	Total = 52.9 ± 5.3, men = 51.2 ± 4.9, women = 52.9 ± 4.9	Total = 123.7 ± 16.5, men = 128.7 ± 16.2, women = 122.6 ± 17 *WFT:* Total = 123.7 ± 16.4, men = 128.7 ± 16.2, women = 122.6 ± 17 *BNT:* Total = 123.7 ± 17.6 *MVT:* - *PFT:* - *SFT:* - *VIS (MoCA):* - *BeDT:* Total = 126.7 ± 12.9 *BuDT:* Total = 126.7 ± 12.9	Total: Normal, men: Normal, women: Normal *WFT:* Total = Normal, men = Normal, women = Normal *BNT:* Total = Normal *MVT:* - *PFT:* - *SFT:* - *VIS (MoCA):* - *BeDT:* Total = Normal *BuDT:* Total = Normal	Total = 77.8 ± 12.1 *WFT:* Total = 77.8 ± 12.1 *BNT:* 77.2 ± 8.1 *MVT:* - *PFT:* - *SFT:* - *VIS (MoCA):* - *BeDT:* Total = 77.2 ± 7.8 *BuDT:* Total = 77.2 ± 7.8	Total = Optimal *WFT:* Total = Optimal *BNT:* Optimal *MVT:* - *PFT:* - *SFT:* - *VIS (MoCA):* - *BeDT:* Total = Optimal *BuDT:* Total = Optimal
Processing speed	*Total:* n = 19 *TMT-B:* n = 9 *TrB-A:* n = 1 *STIT:* n = 2 *WMT:* n = 1 *CES:* n = 3 *RVP (CANTAB & Isolated):* n = 1 *SCWT:* n = 1 *EIS (MoCA):* n = 1 *VSS:* n = 1 *LT:* n = 1	*TMT-B:* Total = 93.9 ± 2.7 *TrB-A:* Total = 1.14 *STIT:* Total = 42.9 ± 1.5 *WMT:* Total = 2.25 ± 1.09 *CES:* Total = 57.1 ± 0.1 *RVP (CANTAB):* Total = 0.92, 333.61 ± 88.01 *SCWT:* Total = 19.1 *EIS (MoCA):* Total = 11.64 ± 1.42 *VSS:* male = 302.02 ± 74.5, female = 323.5 ± 74.5 *LT:* men = 39.77 ± 17.8, women = 45.51 ± 26.6	Total = 52.5 ± 5.1, men = 56.9 ± 3.8, women = 54.1 ± 3.5	Total = 130.4 ± 14.6, men = 128.7 ± 16.2, women = 122.7 ± 16.9 *TMT-B:* Total = 131.6 ± 16.9, Female = 123.3 ± 16.3 *TrB-A:* Total = 138.3 ± 8.4 *STIT:* Total = 131.2 ± 16.1, male = 128.7 ± 16.2, female = 122.6 ± 17 *WMT:* Total = 133.3 ± 16.9 *CES:* Total = 121 *RVP (CANTAB):* - *SCWT:* male = 128.7 ± 16.2, female: 122.6 ± 17 *EIS (MoCA):* - *VSS:* Total = 138.3 ± 8.4 *LT:* -	Total = High Normal, men = Normal, women = Normal *TMT-B:* Total = High Normal, female = Normal *TrB-A:* Total = High Normal *STIT:* Total = High Normal, male = Normal, female = Normal *WMT:* Total = High Normal *CES:* Total = Normal *RVP (CANTAB):* - *SCWT:* men = Normal, female = Normal *EIS (MoCA):* - *VSS:* Total = High Normal *LT:* -	Total = 85.7 ± 8.7, women = 77.4 ± 9.34 *TMT-B:* Total = 87.5 ± 10.4, Female = 77.4 ± 9.34 *TrB-A:* Total = 86.1 ± 6.5 *STIT:* Total = 83.3 ± 10.7 *WMT:* Total = 84.1 ± 12.3 *CES:* Total = 76.5 *RVP (CANTAB):* - *SCWT:* - *EIS (MoCA):* - *VSS:* Total = 86.1 ± 6.5 *LT:* -	Total = High Normal, women = Optimal *TMT-B:* Total = High Normal, female = Optimal *TrB-A:* Total = High Normal *STIT:* Total = Normal *WMT:* Total = Normal *CES:* Total = Optimal *RVP (CANTAB):* - *SCWT:* - *EIS (MoCA):* - *VSS:* Total = High Normal *LT:* -
Global Cognition	*Total:* n = 23 *MMSE:* n = 13 *MoCA:* n = 7 *IQCODE:* n = 1 *CAMCOG:* n = 1 *NART:* n = 1 *MINT:* n = 1 *IST:* n = 1 *BPP:* n = 1 *ACE:* n = 1 *HRS-CS:* n = 1 *CERAD:* n = 1	*MMSE:* Total = 27.8 ± 0.6 *MoCA:* Total = 24.9 ± 3.1 *IQCODE:* Total = 43.38 ± 3.01 *CAMCOG:* Total = 90 *NART:* Total = 28, male = 35.13 ± 9.5, female = 35.5 ± 9.1 *MINT:* Total = 30.25 *IST:* Total = 32.4 *BPP:* Total = 46.9 *ACE:* Total = 94.9 *HRS-CS:* Total = 14.31 ± 4.06, male = 14.2 ± 4.15, female = 14.44 ± 3.96 *CERAD:* Total = 81.6 ± 0.9	Total = 54.5 ± 5.3, men = 58.6 ± 2.8, women = 58.2 ± 2.8	Total = 131.5 ± 16.6 *MMSE:* Total = 133.2 ± 16.7 *MoCA:* Total = 118.3 ± 15.03 *IQCODE:* Total = 124.05 ± 15.6 *CAMCOG:* Total = 140.8 ± 19.3 *NART:* Total = 140.8 ± 19.3 *MINT:* Total = 126.7 ± 12.9 *IST:* - *BPP:* - *ACE:* - *HRS-CS:* - *CERAD:* Total = 119.9 ± 11.8	Total = High Normal *MMSE:* Total = High Normal *MoCA:* Total = Optimal *IQCODE:* Total = Normal *CAMCOG:* Total = Grade 1 Hypertension *NART:* Total = Grade 1 Hypertension *MINT:* Total = Normal *IST:* - *BPP:* - *ACE:* - *HRS-CS:* - *CERAD:* Total = Optimal	Total = 81.14 ± 10.08 *MMSE:* Total = 82.6 ± 10.02 *MoCA:* Total = 72.4 ± 10.4 *IQCODE:* Total = 73.9 ± 9.06 *CAMCOG:* Total = 88.7 ± 12.6 *NART:* Total = 88.7 ± 12.6 *MINT:* Total = 77.2 ± 7.8 *IST:* - *BPP:* - *ACE:* - *HRS-CS:* - *CERAD:* Total = 77.2 ± 8.1	Total = Normal *MMSE:* Total = High Normal *MoCA:* Total = Optimal *IQCODE:* Total = Optimal *CAMCOG:* Total = High Normal *NART:* Total = High Normal *MINT:* Total = Optimal *IST:* - *BPP:* - *ACE:* - *HRS-CS:* - *CERAD:* Total = Optimal
Inductive Reasoning	Total: n = 4	*AH-4:* Total = 52.02 ± 8.5. male = 49.2 ± 9.5, female = 42.9 ± 11.6	Total = 52.56 ± 2.95, males = 49.5 ± 5.9, females = 49.86 ± 5.9	Total = 126.6 ± 15.2, male = 122.4 ± 15.5, female = 119.6 ± 16.7	Total = Normal, male = Normal, female = Optimal	Total = 82.4 ± 10.3	Total = Normal
Psychomotor Speed	Total: n = 5	*SDMT:* Total = 56.1 ± 11.2, male = 48.2 ± 13.7, female = 50.5	Total = 52.3 ± 5.2, women = 50.01 ± 2.6	Total = 133.8 [SE: 0.3], Female = 123.3 ± 16.3	Total = High Normal, female = Normal	Total = 82.9 [SE: 0.2], female = 77.4 ± 9.34	Total = Normal, female = Optimal
Visuospatial Organisation	Total: n = 5 *BDT:* n = 2 *VIS MoCA:* n = 1 *CDT:* n = 1	*BDT:* Total = 16.9 ± 0.1 *VIS MoCA:* Total = 6.48 ± 0.92 *CDT:* male = 28 ± 5, female = 55 ± 10	Total = 52.2 ± 5.7	Total = 128.5 ± 16.2 *BDT:* Total = 131.1 ± 15.2 *VIS MoCA:* - *CDT:* -	Total = Normal *BDT:* Total = High Normal *VIS MoCA:* - *CDT:* -	Total = 82.9 ± 9.4 *BDT:* Total = 82.9 ± 9.4 *VIS MoCA:* - *CDT:* -	Total = Normal *BDT:* Total = Normal *VIS MoCA:* - *CDT:* -

5-CMT, Choice Movement Test; ACE, Addenbrooke's cognitive examination; AH-4, Alice Heim 4-I; BDT, Block Design Test; BeDT, Benson Delay Test; BNT, Boston Naming Test; BP, Blood Pressure; BPP, Børge Priens Prøve; BuDT, Buschke Delay Test; CAMCOG, Cambridge Cognition Examination; CANTAB, Cambridge Neuropsychological Test Automated Battery; CDT, Clock Drawing Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CES, Composite Executive Score; CMS, Chinese Clinical Memory Scale; CRT, Choice Reaction Time; CVLT, California Verbal Learning Test DSB, Digit Span Backwards; DSF, Digit Span Forward; DSST, Digit Symbol Substitution Test; EBM, East Boston Memory Test; EIS, Executive Index Score; HRS-CS, U.S. Health and Retirement Study Composite Score; IQ, Intelligence Quotient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IST, Intelligenz-Struktur-Test; LCCS, Letter Cancellation Composite Score; LSST, Letter Search Speed Test; LT, Labyrinth Test; McNS, McNair Survey; MINT, Multilingual Naming Test; MIS, Memory Index Score; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; MR, Mental Rotation Test; MVT, Mill Hill Vocabulary Test; NART, National Adult Reading Test; PFT, Phonemic Fluency Test; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey–Osterreith complex figure; RVP, Rapid Visual Processing; SCWT, Stroop Colour Word Test; SDMT, Symbol Digits Modalities Test; SFT, Semantic Fluency Test; SiRT, Simple Reaction Time; SRT, Selective Reminding Test; STIT, Stroop Test (Interference Time); STW, Spot the Word Test; TMT-A, Trail making Test Part A; TMT-B, Trail making Test Part B; TrB-A, Trail making Test Difference between Part B and A; VIS, Visuospatial Index Score; VRT, Visual Reproduction Test; VSS, Visual Search Speed; WAIS, Wechsler Adult Intelligence Scale; WDS, WAIS-IV Digit Sequencing; WFT, Word Fluency Test; WLL, Word List Learning; WMT, Word Matching Test.

TABLE 3. Summary of all studies with negative relationships between hypertension and cognitive measures at midlife.

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables	Relationship
.	2020	Cross sectional	ELSA; Brazil	High	*n* = 5275 Age = 56.3	Memory, executive function, temporal orientation, and global cognition	- (Executive function and global cognition)
Alves de Moraes	2002	Longitudinal follow-up	ARIC Study; USA	Low	*n* = 8058 Age = 56.7 (5.6)	Memory and executive function	- (Memory and executive function)
Bangen *et al.*	2013	Cross-sectional analysis of longitudinal	Framingham Study; USA	High	*n* = 1436 (men = 660, women = 775) Age = 54 (9)	Memory, executive function, global cognition, and visuospatial organisation	- (Executive function, attention, visuospatial organisation)
Bayes-Marin *et al.*	2020	Longitudinal	Edad con Salud; Spain	High	*n* = 633 (men = 304, women = 329) Age = 56.6	Memory	- (Memory)
Bressler *et al.*	2013	Prospective cohort study	ARIC Study; USA	Low	White: *n* = 8364 (men = 3859, women = 4505); African-American: *n* = 2083 (men = 716, women = 1367) Age: White = 57 (5.6); African-American = 55.8 (5.7)	Memory and executive function	- (Memory and executive function)
Cerhan *et al.*	1998	Longitudinal cohort	ARIC Study; USA	Moderate	*N* = 13913 Aged 45–64	Memory and executive function	- (Women only: Memory and executive function)
Chen *et al.*	2015	Cross-sectional analysis of longitudinal	WHAP Study; Australia	High	*n* = 247 Age = 50.1 (2.6)	Executive function, psychomotor speed, and memory	- (Executive function, psychomotor speed, memory)
Cui *et al.*	2016	Case–control	Guangzhou, China	Moderate	*Hypertensive*: *n* = 278; *Controls* = 155 Age: *Hypertensive* = 54.2 (4.2); *Controls* = 55.8 (5.5)	Intelligence and global cognition	- (Intelligence, global cognition)
de Menezes *et al.*	2021	Longitudinal follow-up	ELSA Study; Brazil	High	*n* = 7063 Age = 58.9 (5.9)	Memory, executive function, and global cognition	- (Memory, executive function, global cognition)
Debette *et al.*	2011	Prospective	Framingham Study; USA	Moderate	*n* = 1352 (men = 6634, women = 718) Age = 54 (9)	Memory and executive function	- (Executive function)
Derby *et al.*	2021	longitudinal study of the menopause transition	SWAN, USA	Moderate	*N* = 1139 Age = 53.4 (2.6)	Memory and executive function	- (Women only: Memory and executive function)
Dixon *et al.*	2021	longitudinal epidemiological study	SWAN, USA	Moderate	European American (*n* = 1000) African-American (*n* = 516) Asian American (*n* = 437) Age: European American = 45.95 (2.73) African American = 45.88 (2.61) Asian American = 46.11 (2.58)	Memory and executive function	- (Memory and executive function)
Elkins *et al.*	2005	Prospective	ARIC Study; USA	High	*n* = 12 096 (men = 12 039, women = 57) Age = 57 (5.7)	Memory and executive function	- (Memory)
Elmassry *et al.*	2015	Cross sectional	Egypt	Moderate	*Patients*: *n* = 85(men = 40, women = 45); *Controls*: *n* = 60 (men = 27, women = 33) Age: *Patient* = 43.9 (6.2); *Control* = 45 (9)	Memory, executive function, and global cognition	- (Memory, executive function, global cognition)
Gerasimenko *et al.*	2017	Cross sectional	Ukraine	Low	*Patients*: *n* = 102; *Controls*: *n* = 20 Age: *Patients* = 49.8 (0.8); *Controls* = 52.2 (1.9)	Memory and global cognition	- (Global cognition)
Giugliano *et al.*	2018	Randomized, control trial	Pozzilli, Italy	Low	*Active Treatment*: *n* = 18 (men = 13, women = 5); *Control*: *n* = 18 (men = 14, women = 4) Age: *Active Treatment* = 58.2 (8); *Control* = 57.9 (6.7)	Executive function, and global cognition	- (Executive function, global cognition)
Gonzalez *et al.*	2018	Prospective, epidemiologic	ARIC Study; USA	Moderate	*n* = 13 720 (men = 5873, women = 7397) Age = 54.1 (5.7)	Memory, executive function, and global cognition	- (Memory, executive function, global cognition)
Gottesman *et al.*	2017	Prospective	ARIC Study; USA	High	*n* = 15 744 (men = 7054, women = 8690) Age = 54.2 (5.8)	Memory, executive function, and global cognition	- (Global cognition)
Gottesman *et al.*	2014	Prospective	ARIC Study; USA	High	Normal BP = 4, 322 + 779 = 5101 (men = 2195, women = 2908) Pre HT = 2274 + 601 = 2,875 (men = 1388, women = 1487) HT = 3651 + 1849 = 5500 (men = 2401, women = 3099) Age: Normal BP = 55(7), Prehypertensive = 56 (8), Hypertensives 57 (8)	Memory, executive function, and global cognition	- (Memory, executive function, global cognition)
Gourley *et al.*	2020	Cross-sectional	Texas; USA	Moderate	*n* = 132 (men = 59, women = 73) Age = 49 (6)	Memory, executive function, intelligence, and attention	- (Memory, executive function)

TABLE 3 (*Continued*)

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables	Relationship
Gupta *et al.*	2008	Cross-sectional	Jaipur; India	Moderate	*n* = 85 (men = 59, women = 26) Age = 52 (7.5)	Memory, executive function, global cognition, and attention	- (Memory, executive function, and global cognition; Systolic hypertension: attention, executive function)
Hajjar *et al.*	2016	Longitudinal,	USA	Moderate	*n* = 291 (men = 191, women = 400) Age = 48.8 (0.4)	Memory, executive function, attention, global cognition, and visuospatial organisation	- (Memory, executive function)
Hoffmann *et al.*	2021	Longitudinal	Recall Study; Germany	High	Normal BP: *n* = 692 (men = 242, women = 450); Incident hypertension T1: *n* = 366 (men = 175, women = 191); Incident hypertension T2: *n* = 245 (men = 109, women = 136); Temporary hypertension: *n* = 329 (men = 183, women = 209); Prevalent hypertension: *n* = 1145 (men = 635, women = 510) Age: Normal BP = 55.2 (6.6); Incident hypertension *T1* = 57.8 (7.1); Incident Hypertension T2: 56.5 (6.6); Temporary hypertension = 57.6 (7.1); Prevalent hypertension = 60.2 (7.1)	Memory, executive function, and visuospatial organization	- (Memory)
Houle *et al.*	2019	Cross-sectional analysis of longitudinal	HAALSI Study; South Africa	Moderate	*n* = 2059 (men = 2345, women = 2714) Age = 40–59	Memory, executive function, attention, global cognition, and temporal orientation	- (Memory, executive function, attention)
Jenkins *et al.*	2021	Longitudinal	CARDIA study; USA	Moderate	*N* = *578* (men = 255, women = 323*)* Age: 55 (4)	Memory, executive function, global cognition, and psychomotor speed	- (Global cognition)
Jia *et al.*	2021	Cross-sectional	China	Moderate	Total: *N* = 4923 Age: 55–64: *N* = 2043	Global Cognition	- (Global Cognition)
Kaffashian *et al.*	2013	Prospective	Whitehall II Study; UK	High	*n* = 4374 (men = 3162, women = 1212) Age = 55.2 (5.1)	Memory, executive function, attention, global cognition, and inductive reasoning	- (Attention, executive function, global cognition, inductive reasoning)
Kaffashian *et al.*	2011	Prospective	Whitehall II Study; UK	High	*n* = 4827 (men = 3486, women = 1341) Age: men = 55.1 (5.9), women = 55.3 (5.9)	Memory, executive function, attention, global cognition, and inductive reasoning	- (Global cognition)
Kivipelto *et al.*	2001	Prospective and cross-sectional analysis of population-based, longitudinal study with a large cohort of individuals	North Karelia Project and FINMONICA study; Finland	High	Total: *N* = 1449; MCI: *N* = 82, Without MCI: *N* = 1270 Age: Midlife: MCI = 51.7 (5.8); Without MCI = 50.1 (6.0) Late life: MCI = 72.8 (4.1), Without MCI = 71.0 (3.9)	Memory, attention, executive function, and global cognition	- (Global Cognition)
Knopman *et al.*	2001	Longitudinal	ARIC Study; USA	Low	*n* = 10 882 (men = 6978, women = 3904) Age = 56.8 (5.7)	Memory and executive function	- (Memory, executive function)
Knopman *et al.*	2018	Longitudinal	ARIC Study; USA	Low	*n* = 10 882 (men = 8723, women = 7137) Age = 51.4 (4.9)	Memory and executive function	- (Memory, executive function)
Knopman *et al.*	2009	Longitudinal	ARIC Study; USA	Moderate	*n* = 1130 (men = 429, women = 701) Age = 59 (4.3)	Memory and executive function	- (Memory, executive function)
Kovacs *et al.*	2014	Cross sectional	Hungary	Moderate	Hypertensive = 72; Controls = 85 Age: Hypertensive = 43.6; Controls = 43.6	Memory, executive function, attention, psychomotor speed, and visuospatial organisation	- (Attention, memory, executive function, psychomotor speed, visuospatial organisation)
Kumar *et al.*	2008	Cross-sectional study	PATH Through Life Project; Australia	Moderate	Diabetic individuals: *N* = 39; Nondiabetic individuals: *N* = 428 Age: Diabetic individuals = 62.62 (1.16) Nondiabetic individuals = 62.55 (1.48)	Memory, attention, global cognition, and psychomotor speed	- (Psychomotor Speed)
Kumari *et al.*	2005	Longitudinal	Whitehall II Study, UK	Moderate	*N: NGT*: men = 3407, women = 1334; *IGT*: males = 405, females = 192; *Diabetes*: males = 208, females = 101 *Age: NGT*: men = 55.1, women = 55.7; *IGT*: men = 58.2, women = 57.8; *Diabetes*: men = 57.9, women = 58.9	Memory, inductive reasoning, and executive function	- (Inductive reasoning, executive function)
Lane *et al.*	2019	Longitudinal	Insight 46; UK	High	*n* = *499* (men = 255, women = 244*)* Age at cognitive testing = 70.7 (0.7)	Memory, executive function, and global cognition	- (Global cognition)

TABLE 3 (*Continued*)

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables	Relationship
Leong *et al.*	2020	Prospective, longitudinal	TILDA; Ireland	Moderate	Non hypertensive: $n=2280$ (men = 848, women = 1432); Hypertensive w/o medication: $n=2823$ (men = 1420, women = 1403); Hypertensive with medication: $n=3070$ (men = 1495, women = 1595) Age: Non hypertensive = 59.5; Hypertensive w/o medication = 62.7; Hypertensive with medication = 68.1	Attention, Global cognition	- (Global cognition)
Mahinrad *et al.*	2020	Longitudinal	CARDIA Study; USA	Moderate	$n=191$ (men = 104, women = 87) Age = 56 (4)	Memory, executive function, and attention	- (Memory, executive function, attention)
Olaya *et al.*	2019	Longitudinal	ELSA; UK	High	$n=4372$ (men = 2023, women = 2349) Age = 56.8 (4.1)	Memory	- (Memory)
Palacios-Mendoza *et al.*	2018	Cross-sectional	Guayaquil, Ecuador	High	Diabetes: $n=142$ (men = 65, women = 76); No diabetes: $n=167$ (men = 116, women = 50) Age: Diabetes = 59.9 (4.2); No Diabetes = 59.9 (3.8)	Memory, executive function, intelligence, and attention	- (Memory)
Pan *et al.*	2018	Longitudinal	CHARLS; China	Low	$n=1825$ (45–54 = 962, 55–64 = 863) Age = 56.9 (8)	Memory and global cognition	- (Memory, global cognition)
Passos *et al.*	2021	Cross-sectional study nested within the PróSaúde cohort study	Pró-Saúde study, Rio de Janeiro, Brazil	Moderate	Total: $N=488$, Male = 235, Female = 253 Age groups: 45–54 = 243 55–64 = 145	Memory, executive function, and global cognition	- (Memory, executive function, and global cognition)
Rose *et al.*	2010	Prospective, epidemiologic	ARIC Study; USA	Low	OH No = 12 050; OH Yes = 652 Age: OH No = 53.9; OH Yes = 57.3	Memory and executive function	- (Memory, executive function)
Rouch *et al.*	2019	Prospective	VISAT Cohort Study; France	Moderate	$n=3201$ Controlled hypertension: $n=83$ (men = 32, women = 51); Uncontrolled hypertension: $n=223$ (men = 140, women = 83); Untreated hypertension: $n=784$ (men = 551, women = 233); No hypertension: $n=2111$ (men = 919, women = 1192) Age: Controlled hypertension = 51.3 (9.3); Uncontrolled hypertension = 54.3 (7.7); Untreated hypertension = 48.6 (10.1); No hypertension = 42.3 (9.4)	Memory, attention, executive function, global cognition, and psychomotor speed	- (Global cognition)
Sands *et al.*	1992	Longitudinal	Intergenerational Studies from IHDB, California; USA	Low	$n=103$ Age: 55.4 (3.41)	Memory, attention, executive function, and visuospatial organisation	- (Attention)
Sha *et al.*	2018	Longitudinal	CHARLS; China	High	$n=9750$	Memory and global cognition	- (Global cognition)
Sierra *et al.*	2004	Cross sectional	Barcelona; Spain	High	Without WML: $n=37$ (men = 24, women = 13); With WML: $n=23$ (men = 14, women = 9) Age: Without WML = 53.9 (3.5); With WML = 55.2 (4.2)	Intelligence, memory, and attention	- (Attention)
Singh-Manoux *et al.*	2005	Cross sectional analysis of longitudinal	Whitehall II Study; UK	Moderate	$n=5838$ Age: men = 43.9 (5.9), women = 44.4 (6)	Memory, executive function, and inductive reasoning	- (Memory, executive function, inductive reasoning)
Suemoto *et al.*	2021	Cross-sectional analysis of longitudinal	ELSA; Brazil	High	$n=12\,271$ Age: 51.3 (8.9) Poor (0–2 metrics) $n=6483$ (men = 3190, women = 3293; Intermediate (3–4 metrics) $n=4757$ (men = 1955, women = 2802); Optimal (5–7 metrics) $n=1031$ (men = 332, women = 699) Age: Poor (0–2 metrics) = 53.4 (8.6); Intermediate (3–4 metrics) = 49.7 (8.7); Optimal (5–7 metrics) = 45.8 (7.4)	Memory, executive function, and global cognition	- (Memory, attention, executive function, global cognition)
Suvila *et al.*	2021	Prospective	CARDIA Study; USA	High	$n=2496$ (men = 534, women = 1689) Age = 55.1 (3.6)	Memory, executive function, psychomotor speed, and global cognition	- (Psychomotor speed, memory, executive function, global cognition)
Swan *et al.*	1998	Prospective, longitudinal	NHLBI Twin Study; USA	Moderate	$n=392$; 71 MZ and 61 DZ intact pairs; 128 singletons	Memory, executive function, global cognition, and psychomotor speed	- (Global cognition, psychomotor speed)

TABLE 3 (*Continued*)

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables	Relationship
Swan *et al.*	1998	Longitudinal	Western Collaborative Group Study, USA	Moderate	$n = 717$ Midlife SBP categorized by Later life SBP (n = Low < 120 mmHg, Medium 120–139 mmHg, High ≥140 mmHg): Low < 120 mmHg: 73, 173, 113 Medium 120–139 mmHg: 20, 119, 165 High ≥140 mmHg: 2, 16, 36 Long-term Change in SBP midlife-to-later life: Normals (n = 553–643) High-High (n = 30–36) Decreased (n = 31–38)	Memory, executive function, and psychomotor speed	- (SBP increase: Memory)
Szczesnia *et al.*	2020	Longitudinal	PURE Study; Poland	High	$n = 547$ (men = 195, women = 352) Age = 56.2 (6.5) [men = 55.1 (6.8), women = 56.9 (6.3)]	Attention, executive function, psychomotor speed, and global cognition	- (Psychomotor speed, executive function, global cognition)
Wang *et al.*	2016	Cross sectional	APAC Study; China	High	$n = 3048$ (men = 1727, women = 1321) Age = 57.9 (11.1)	Global cognition	- (Global cognition)
Wei *et al.*	2018	Cross-sectional	CHARLS; China	High	$n = 6732$	Memory and global cognition	- (Memory, global cognition)
Wod *et al.*	2018	Cross-sectional analysis of longitudinal	MADT; Denmark	High	$n = 4132$ (men = 2120, women = 2012) Age: 56.6 (men = 56.6, women = 56.6)	Memory, executive function, and attention	- (Memory, executive function, attention)
Wolf *et al.*	2007	Observational	Framingham Study; USA	Low	$n = 1814$ (men = 854, women = 960) Age = 52.6 (7.9)	Memory, executive function, and visuospatial orientation	- (Memory, executive function)
Zhang *et al.*	2019	Cross sectional	CHARLS; China	Low	No Diabetes: $n = 7151$; Controlled Diabetes: $n = 232$; Untreated Diabetes = 185; Treated Diabetes = 241 Age: No Diabetes = 59.5 (9.5)	Memory, executive function, and global cognition	- (Memory, executive function)

a, AHA; b, ESC; c, self-report; d, antihypertensive medication use; e, SBP >150 mmHg or DBP >95 mmHg.
0, no association; -, negative association; +, positive association
ACE, Akershus Cardiac Examination; APAC, Asymptomatic Polyvascular Abnormalities Community; ARIC, Atherosclerosis Risk in Communities; ASCEND, A Study of Cardiovascular Events in Diabetes; Barcelona-AsIA, Asymptomatic Intracranial Atherosclerosis; BHS, Bogalusa Heart Study; BIP, Bezafibrate Infarction Prevention; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CHARLS, China Health and Retirement Longitudinal Study; DBP, diastolic blood pressure; ELSA, Brazilian Longitudinal Study of Adult Health; ELSA, English Longitudinal Study of Ageing; HAALSI, Health and Aging in Africa; HANDLS, healthy Aging in Neighborhoods of Diversity Across the Life Span; HHP, Honolulu Heart Program; IHDB, Institute of Human Development in Berkeley; KALS, Kaohsiung Atherosclerosis Longitudinal Study; KEEPSCog, Kronos Early Estrogen Prevention cognitive; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; MACS, Multicentre AIDS Cohort Study; MADT, Middle-Aged Danish Twins; MDCS, Malmö Diet and Cancer Study; MORGEN, Monitoring Project on Cardiovascular Disease Risk Factors; MRC, Medical Research Council; NHLBI, National Heart, Lung, and Blood Institute; NSHD, National Survey of Health and Development; PATH, Population Assessment of Tobacco and Health; PURE, prospective Urban and Rural Epidemiological; RECALL, Risk Factors, Evaluation of Coronary Calcium and Lifestyle; SBP, systolic blood pressure; Swan, Study of Women's Health Across the Nation; TILDA, The Irish Longitudinal Study on Ageing; VETSA, Vietnam Era Twin Study of Aging; VISAT, Vieillissement Santé Travail (Aging, Health and Work); WHAP, Women's Health Aging Project.

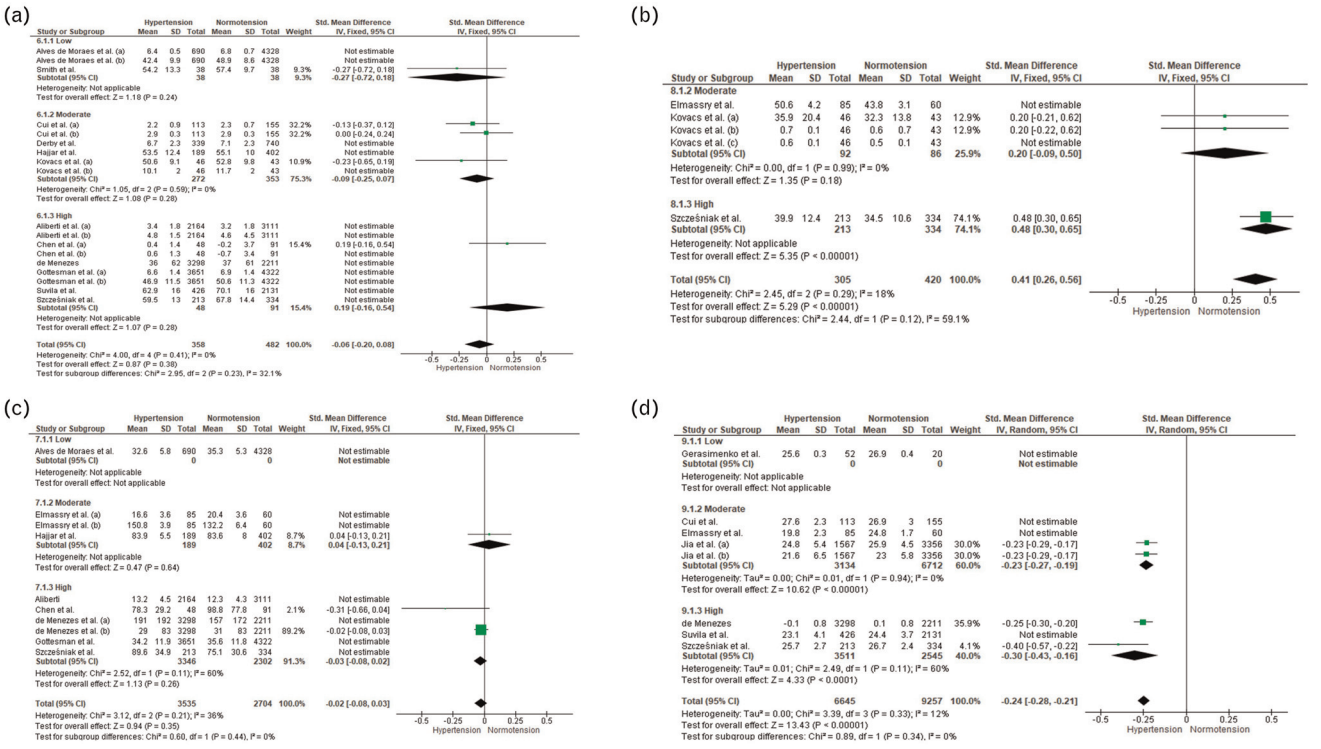

FIGURE 2 Forest plot examining the overall effect of hypertension status vs. normotension status. (a) Memory function. (b) Attention. (c) Executive function. (d) Global cognition.

suggests elevated BP even during young adulthood can have deleterious effects on cognition among middle-aged adults [22]. Ageing plays a key role in functional adaptation to elevated BP, which precedes hypertension-induced microvascular damage and subsequent vascular cognitive impairment. Hypertension and ageing create a state of vulnerability suggested to alter hippocampal gene expression associated with cognitive decline and Alzheimer's Disease [23]. The findings presented here confirm previous reports that midlife hypertension negatively affects cognition in later life. However, our analysis reveals that select domains like memory are more notably affected than others. The hippocampus and entorhinal cortex are structures associated with learning and memory that are vulnerable to pathoanatomical and pathophysiological change in the presence of cardiovascular risk factors such as hypertension [24,25]. Impairments in working memory and the encoding of new long-term memories are reported with age-related cognitive decline [26]. Working memory declines with age are in line with the Baddeley model where processing or central executive components are negatively impacted [27]. Therefore, hypertension may limit attentional capacity, where older adults are less able to inhibit irrelevant information and cognitive correlates of efficiency and arousal become impaired with ageing, beginning as early as midlife [28–32].

Neurocognitive tests can enable subtle detection of cognitive change before observable signs and symptoms develop, acting as robust indicators of pathological ageing. Our results provide evidence of significant consequences of midlife hypertension for the time course and progression of cognitive impairment, and possible neurological comorbidities including dementia and AD [33,34]. Similar to our later life findings, meta-analysis indicated memory, executive function, and global cognition at midlife were negatively affected by hypertension. Hypertension with increasing age primarily affects specific cognitive domains, such as memory and executive function, rather than overall cognitive function. In line with this finding, hypertension status among 207 late middle-aged adults was associated with age-related decline in verbal learning and memory, although hypertension was reported in only 19% of the study population [35]. Various forms of memory are thus subject to age-related and pathological decline with the rates of change highly varied [36]. Moreover, executive function also declines with age and is accelerated in late midlife, that is, after 65 years of age [37]. Decline in executive function is believed to precede reductions in memory by up to 18 years before diagnosis of AD and cognitive impairment [38], with longitudinal evidence from women in midlife showing a mean decline of 2% per year in memory [39]. The specific reasons behind the accelerated regional decline during midlife remain unclear. However, our results are supported by several hypothesized mechanisms, including higher aortic stiffness [40,41], adaptive vascular changes in cerebral blood flow and arterial pressure, and hypertension-induced neurovascular uncoupling [5,42,43]. The precise timing and onset of pathological features and concurrent cognitive decline remain to be adequately determined. However, emphasizing midlife as a focal point for intervention could potentially yield significant benefits.

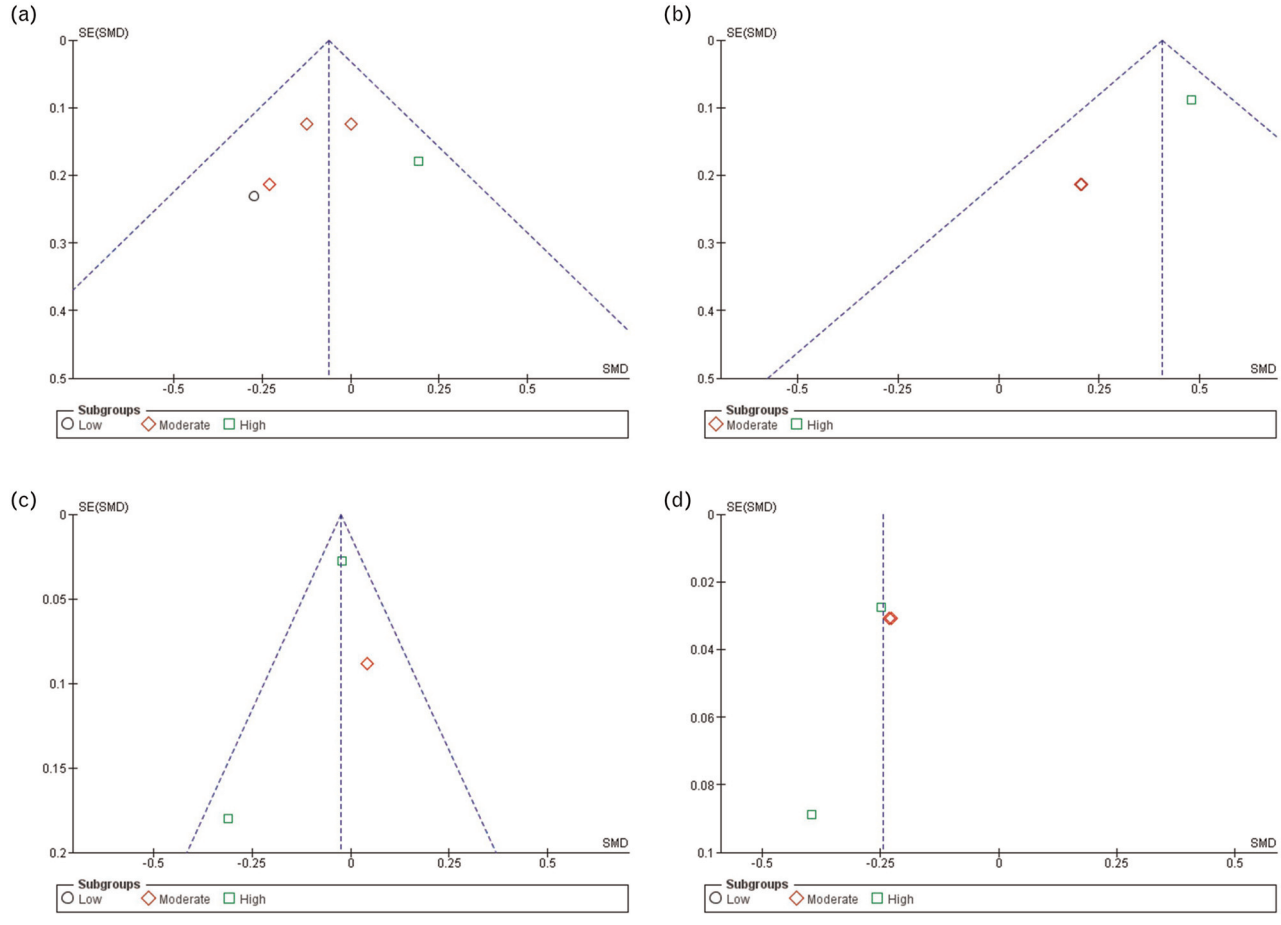

FIGURE 3 Funnel plots representing hypertensive vs. normotensive individuals and their effect on cognition in midlife. (a) Memory; (b) Attention; (c) Executive function; (d) Global cognition. SMD, standardized mean difference; SE, standard error.

Similar to previous research, we found conflicting evidence on the impact of hypertension and cognitive function at midlife [17,18,44]. Notably, our meta-analyses indicated no relationship between hypertension and attention at midlife, contradicting those of Ou *et al.* [17] possibly explained by the lower number of studies included in the previous review (range: 2–4 studies) compared with 15 studies in the present review. It is probable rather than possible that in studies where no relationship was reported, negative implications consequent to hypertension are not identifiable through cognitive testing at midlife. Greater duration of time since onset of hypertension is therefore associated with increased cognitive impairment, independent of age [19,45]. Theories of cognitive ageing and dynamics of neural networks, however, postulate the most basic of cognitive functions, such as attention, are affected by age. Attention at midlife was unaffected by midlife hypertension in our review. The majority of cognitive tests tend to incorporate more than one domain of cognitive function in any given task [46]. Deficits in early processing stages may influence additional co-domains in the later processing cognitive streams ultimately affecting global cognition from midlife into later life as seen in the present review. It is well known that attention is involved in most cognitive processes, therefore any impact on attention potentially causes downstream consequences affecting the ability to complete normal daily tasks. Early evidence reports those with hypertension exhibit deficits in memory and executive function but no apparent decline in continuity of attention, similar to our present findings [47]. A decline in attention in response to a synergy between age and hypertension has been found to increase with age but did not significantly differ between those with hypertension and those without [48]. Deficits in higher order processes, like attention, in the prefrontal cortex can impact memory function in later life with significant impairment in divided attention or switching attentional focus [49–51]. This may be explained by the so-called 'central executive control', which has a role in virtually all cognitive functions from the allocation of attentional resources to the inhibition of irrelevant stimuli [52,53]. However, the stage from midlife onwards when cognitive changes begin to be exacerbated by the presence of hypertension, and how declining trajectories across select domains can be targeted with intervention strategies, remains to be identified at a population or an individual level.

Significant cognitive impairment should not be considered a normal part of the ageing process. As a modifiable risk factor, hypertension represents a key target for the prevention, delayed progression, and reduction of cognitive

TABLE 4. Summary of studies with a null or positive relationship between hypertension and cognitive measures at midlife.

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables
Babaei *et al.*	2013	RCT	Iran	Low	$n = 52$ (28 patients and 24 controls) Age = 57.1 (5.9)	Memory
Backestrom *et al.*	2015	Retrospective, cross-sectional	Betula Prospective Cohort Study, Sweden	Moderate	$n = 291$ (men = 127, women = 164) Age = 50.7 (8) [men = 50.3 (8), women = 51 (8.1)]	Memory
Bahchevanov *et al.*	2021	Cross-sectional	District of Plovdiv, Bulgaria	High	$n = 112$ Without MetS: $n = 67$ (men = 18, women = 49) With MetS: $n = 45$ (men = 24, women = 21) Age: Without MetS = 49.87 (3.36) With MetS = 50.29 (3.26)	+ (lower SBP and DBP: memory, executive function, and global cognition)
Boots *et al.*	2015	Cross-sectional	WRAP; USA	High	$n = 315$ (men = 102, women = 213) Age = 58.58 (6.3)	Memory, executive function, visuospatial organization, and global cognition
Carmichael *et al.*	2019	Community-based cohort study	Bogalusa Heart Study (BHS), USA	Low	$N = 50$ Age = 48.8 (4.7)	Memory, attention, and executive function
Chen *et al.*	2018	Longitudinal	ARIC-NCS Study; USA	High	$n = 12\,515$ (men = 5334, women = 6981) Age = 56.9 (5.7)	Memory and executive function
Christman *et al.*	2011	Prospective	ARIC Study; USA	Moderate	$n = 8958$ (men = 3943, women = 5015) Age = 56.5 (5.6)	Memory and executive function
Cohen-Manheim *et al.*	2016	Cross-sectional	Jerusalem LRC Study; Israel	High	$n = 507$ (men = 343, women = 164) Age = 49.9 (0.8)	Memory, executive function, and attention
Dearborn-Tomazos *et al.*	2019	Longitudinal observational	ARIC Study; USA	Low	$n = 13\,588$ (men = 3000, women = 7588) Age = 54.6 (5.7)	Memory, executive function, and global cognition
Dounavi *et al.*	2022	Cross-sectional analysis of longitudinal multisite study	PREVENT-Dementia study; Ireland & UK	Low	Total: $N = 701$ ($n = 600$ analysable) Age = 51.2 (5.4)	Global cognition
Elbaz *et al.*	2014	Longitudinal	Whitehall II Study; UK	High	$n = 4699$ (men = 3,324, women = 1375) Age = 48.6 (5.8)	Inductive reasoning
Fava *et al.*	2013	Prospective longitudinal	Italy	Low	Total: $n = 96$ (Group A = 48, Group B = 48) Age: Group A = 53 (7), Group B = 54.6 (8.1)	Memory, executive function, global cognition
Ferguson *et al.*	2018	Cross-sectional	CARDIA Study; USA	Moderate	$n = 634$ (men = 305, women = 329) Age = 50.4 (3.5)	Memory and executive function
Ford *et al.*	2010	Longitudinal	SWAN; USA	Moderate	$n = 2003$ Age = 50 (2.6)	Memory and psychomotor speed
Fuh *et al.*	2007	Matched, case–control study from a population-based cohort	Kinmen Women-Health Investigation (KIWI); Kinmen, Taiwan	Low	Normal ($N = 144$) Impaired glucose tolerance ($N = 68$) Diabetes mellitus ($N = 72$) Age: Normal = 47.9 (4.3) Impaired glucose tolerance = 46.8 (4.1) Diabetes mellitus = 47.9 (4.3)	Memory, attention, and executive function
Gerber *et al.*	2021	Multicentre, population-based cohort study	CARDIA study, USA	Low	Overall ($n = 2809$); Liver attenuation: No NAFLD >51 HU ($n = 2136$); Mild NAFLD >40–51 HU ($n = 392$); Severe NAFLD ≤40 HU ($n = 281$) Overall Age = 50.1 (3.6); Liver attenuation: No NAFLD >51 HU = 50.0 (3.7); Mild NAFLD >40–51 HU = 50.3 (3.6); Severe NAFLD ≤40 HU = 50.5 (3.6)	Memory and executive function
Haley *et al.*	2010	Cross-sectional	USA	Moderate	$n = 38$ Age = 50 (6.4)	Global cognition, intelligence, memory, attention, executive function, and psychomotor speed
Hossain *et al.*	2020	Cross-sectional analysis of longitudinal	HANDLS Study; USA	High	$n = 128$ (men = 102, women = 126) Age: men = 57.1 (0.5), women = 56 (0.8)	Memory, attention executive function and global cognition
Ihle-Hansen *et al.*	2019	Prospective	ACE Study; Norway	High	$n = 3413$ (men = 1774, women = 1639) Age = 63.9 (0.65) [men = 63.9 (0.66), women = 63.9 (0.63)]	Global cognition
John *et al.*	2021	Longitudinal cohort	National Child Development Study (NCDS), UK	High	$N = 3730$ Age = 44	Memory, and executive function
Kazlauskaite *et al.*	2020	Longitudinal	SWAN; USA	Moderate	$n = 2149$ (all women); No MetS = 1514, MetS = 635) Age = 50.7 (2.9); No MetS = 50.6 (2.8), MetS = 51.1 (3.2)	Memory and psychomotor speed
Kesse-Guyot *et al.*	2015	Longitudinal (Observational Follow-up)	SU.VI.MAX study; France	High	$n = 2788$ (men = 1480, women = 1308) Age at cognitive evaluation: men = 66.0 (4.5), women = 65.1 (4.6)	Memory, attention, executive function, and global cognition
Kilander *et al.*	2000	Longitudinal	Sweden	Low	$n = 2322$ Age = 50 years $n = 1860$ Age = 60 years	+ (Low DBP: attention, executive function, psychomotor speed, and shifting capacity

TABLE 4 (*Continued*)

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables
Kohde *et al.*	2012	Cross-sectional, case–control	India	Moderate	$n = 120$ (60 patients and 60 controls) Age: patients = 53.7 (6.9), controls = 52.1 (6.2)	Attention
Kumar *et al.*,	2020	Longitudinal	ASCEND; UK	Low	$n = 80$ Age = 59	Global cognition, attention, executive function, memory and global cognition
Launer *et al.*,	2015	Cross-sectional	CARDIA Study; USA	Low	$n = 680$ Age = 50.3 (3.5)	Memory and executive function
Lin *et al.*	2020	Longitudinal	KALS; Taiwan	High	$n = 528$ Age = 53.9 (8.4)	Global cognition, memory, executive function, visuospatial orientation, and attention
Liu *et al.*	2022	Prospective	Neck-Shoulder and Lumbocrural Pain Hospital and the Affiliated Hospital of Shandong University of TCM; China	Moderate	Overall: $n = 156$; Controls = 64, SCI = 92 Age: Controls = 57.1 (6.3); SCI = 57.6 (6.7)	General Cognition
Lopez-Oloriz *et al.*	2014	Population-based	AsIA Neuropsychology Study; Spain	Low	$n = 95$ Age = 59.9 (3.3)	Executive function, psychomotor speed and global cognition
Lutski *et al.*	2019	Longitudinal	BIP Neurocognitive Study; Israel	High	T1: $n = 588$, T2: $n = 337$ Age: T2 = 56.6 (6.4)	Memory, executive function, attention, global cognition and visuospatial organisation
Mefford *et al.*	2021	Multicenter longitudinal, prospective	CARDIA study, USA	Moderate	N = 3328 Time-averaged LDL-C levels over follow-up, mg/dl: <100 ($n = 519$) 100–129 ($n = 1094$) 130–159 ($n = 961$) ≥ 160 ($n = 754$) Age: Time-averaged LDL-C levels over follow-up, mg/dl: <100 = 46.9 (3.2); 100–129 = 49.2 (3.5); 130–159 = 51.1 (3.1); ≥ 160 = 52.6 (2.5)	Memory, attention, and executive function
Meyer *et al.*	2022	Cross-sectional analysis of longitudinal, cohort study	CARDIA study, USA	Moderate	$N = 597$ Age = 55.2 (3.5)	Memory, executive function, and global cognition
Moore *et al.*	2014	Longitudinal	VETSA, Thailand	High	$n = 651$ (all men) Age = 55.3 (3.1)	Executive function, memory, visuospatial organization, and intelligence
Nation *et al.*	2016	Longitudinal	Subset of Framingham Offspring Cohort; USA	High	$n = 549$ (men = 257, women = 292) Age: 59.6 (2.7)	Memory, attention, executive function, and visuospatial organization
Nunley *et al.*	2017	Prospective, observational	Pittsburgh Epidemiology of Diabetes Complications Study; USA	High	$N = 108$ Age = 49.52 (7.04)	Memory, attention, executive function, global cognition, intelligence, and psychomotor speed
Olaya *et al.*	2017	Longitudinal	ELSA; UK	High	$n = 5523$ Age = 50–64	Memory
Palta *et al.*	2019	Prospective	ARIC Study; USA	Moderate	*No PA*: $n = 1996$ (men = 795, women = 1201); Low: $n = 774$ (men = 247, women = 497); Middle: $n = 669$ (men = 295, women = 404); High: $n = 1194$ (men = 733, women = 461) Age: No PA = 59.1 (5.4); Low = 59.4 (5.6) Middle = 60.6 (5.9); High = 60.2 (5.8)	Memory and executive function
Panigrahi *et al.*	2021	Cross-sectional	New Delhi, India	Moderate	$N = 80$ (men = 31, women = 49) Age = 51.71 (7.15)	Global Cognition
Pokharel *et al.*	2019	Prospective	ARIC Study; USA	Moderate	$n = 18\,222$	Memory and executive function
Power *et al.*	2017	Prospective	ARIC Study; USA	High	$n = 15\,792$ Age = 57.5 (5.7)	Memory and executive function
Ravona-Springer *et al.*	2020	Prospective longitudinal	Israel Registry for Alzheimer Prevention (IRAP) study; Israel	Moderate	Total: $N = 483$; FH+ = 379, FH- = 104 Age: FH+ = 54.55 (6.76), FH- = 56.42 (6.19)	Memory, executive function, and global cognition
Rawlings *et al.*	2014	Prospective	ARIC Study; USA	Moderate	$n = 13\,351$ Age = 48–67	Memory, executive function, and global cognition
Reis *et al.*	2013	Cross-sectional	CARDIA study; USA	Moderate	Total: $N = 2510$; Coronary artery calcified plaque: Present = 686, Absent = 1824; Abdominal aortic calcified plaque: Present = 1297, Absent = 1213 Age: Coronary artery calcified plaque: Present = 51.1 (3.3), Absent = 49.6 (3.7); Abdominal aortic calcified plaque: Present = 50.6 (3.6), Absent = 49.5 (3.7)	Memory, attention, and executive function
Richards *et al.*	2005	Longitudinal	MRC NSHD, UK	Low	$n = 1764$ Age = 43 and 53	Memory and executive function

TABLE 4 (*Continued*)

Author	Year	Study design	Setting	Study quality	Participants	Cognitive variables
Ritchie *et al.*	2017	Cross sectional	PREVENT Dementia Program; UK	Low	Non-FH: $n=107$ (men = 35, women = 71); FH: $n=103$ (men = 29, women = 73) Age: Non-FH = 52.7; FH = 53.3	Memory, executive function, visuospatial organization, and attention
Root *et al.*	2015	Prospective, epidemiological	ARIC Study; USA	Moderate	$n=10\,041$ Age = 53.5	Memory and executive function
Salama *et al.*	2019	Cross-sectional study	Egypt	Moderate	Total: $N=186$; MCI: $N=14$, Normal: $N=172$ Age: <50: $N=65$ 50 - <55: $N=64$ 55 - <60: $N=42$ 60–65: $N=15$	Global cognition
Salzwedel *et al.*	2019	Prospective, observational	Germany	High	$n=401$ (men = 321, women = 80) Age = 54.5 (6.3)	Global cognition
Singh-Manoux *et al.*	2003	Longitudinal	Whitehall II Study; UK	Moderate	$n=10\,308$ (men = 6896, women = 3411) Age = 44.45	Memory, executive function, and inductive reasoning
Singh-Manoux *et al.*	2009	Cross-sectional and prospective follow up of longitudinal cohort study	Whitehall II study; UK	High	$n=5292$ (men = 3810, women = 1481) Age: CHD = 59.4 (5.5); No CHD = 55.2 (5.9)	+ (Lower BP Status: memory, attention, and executive function)
Swan *et al.*	1998	Longitudinal	Western Collaborative Group Study, USA	Moderate	*n = 717* Midlife SBP categorized by Later life SBP (n = Low <120 mmHg, Medium 120–139 mmHg, High ≥140 mmHg): Low <120 mmHg: 73, 173, 113 Medium 120–139 mmHg: 20, 119, 165 High ≥140 mmHg: 2, 16, 36 Long-term change in SBP midlife-to-later life: Normals (n = 553–643) High-High (n = 30–36) Decreased (n = 31–38)	+ (SBP decrease: psychomotor speed)
Tufvesson *et al.*	2013	Prospective	MDCS; Sweden	High	$n=933$ (men = 369, women = 564) Age = 57.5 (5.7)	Global cognition
Tuligenga *et al.*	2014	Prospective, longitudinal	Whitehall II study; UK	Moderate	Total: $N=5653$; Normoglycaemia (n = 4703); Prediabetes (n = 648); Newly diagnosed diabetes (n = 115); Known diabetes (n = 187) Age: Total = 54.4; Normoglycaemia = 55.1 (5.9); Prediabetes = 57.5 (6.1); Newly diagnosed diabetes 59.0 (6.1); Known diabetes = 57.4 (6.3)	Memory, executive function, and inductive reasoning
Vadini *et al.*	2020	longitudinal, randomized, controlled, parallel-arm study	Italy	Moderate	Preliraglutide (n = 16) Prelifestyle (n = 16) Age: Preliraglutide = 57 (49–64); Prelifestyle = 53 (52–58)	Memory, attention, executive function
Veugen *et al.*	2018	Observational, prospective	Maastricht Study; Netherlands	High	$n=3011$ (men = 1542, women = 1469 Age = 52 (5)	Memory, executive function and attention
Walker *et al.*	2019	Prospective	ARIC Study; USA	High	$n=3012$ (men = 1382, women = 1630) Age = 55.5 (5.4)	Memory, executive function and psychomotor speed
Wang *et al.*	2018	Prospective epidemiological	ARIC Study; USA	High	$n=13\,720$	Memory, executive function, and global cognition
Ward *et al.*	2005	Cross-sectional	WRAP & UWM; USA	High	$n=114$ (men = 44, women = 73) Age = 54.2 (6.5)	+ (Low DBP: Episodic Learning)
Whitaker *et al.*	2021	Longitudinal Cohort study	CARDIA study	Moderate	$N=1970$ (men = 822, women = 1148) Age = 45.27 (3.56)	Memory and executive function
Wieczorek *et al.*	2016	Prospective study	Poland	Moderate	$n=74$ (men = 44, women = 30) Age = 59 (50–63)	Global cognition
Winkler *et al.*	2014	Population based	RECALL Study; Germany	Moderate	$n=1089$ (men = 515, women = 574) Age = 58.4 (4.1)	Memory, executive function, and visuospatial orientation
Yang *et al.*	2018	Prospective	MACS; USA	Moderate	$n=900$ (all men)	Psychomotor speed, attention, executive function, and memory
Ylilauri *et al.*	2017	Prospective	KIHD; Finland	High	$n=2497$ (all men) Age = 42–60	Global cognition, attention executive function and memory
Young *et al.*	2006	Longitudinal, observational	ARIC Study; USA	Moderate	$n=7148$ (men = 3173, women = 3975) Age = 53.7	Memory and executive function
ZekiAlHazzouri *et al.*	2015	Prospective	CARDIA Study; USA	Moderate	$n=2618$ (men = 1125, women = 1493) Age = 45.3 (3.6)	Memory and executive function

a, AHA; b, ESC; c, self-report; d, antihypertensive medication use.
0, no association; -, negative association; +, positive association
ACE, Akershus Cardiac Examination; APAC, Asymptomatic Polyvascular Abnormalities Community; ARIC, Atherosclerosis Risk in Communities; ASCEND, A Study of Cardiovascular Events in Diabetes; Barcelona-AsIA, Asymptomatic Intracranial Atherosclerosis; BHS, Bogalusa Heart Study; BIP, Bezafibrate Infarction Prevention; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CHARLS, China Health and Retirement Longitudinal Study; DBP, diastolic blood pressure; ELSA, Brazilian Longitudinal Study of Adult Health HAALSI, Health and Aging in Africa; ELSA, English Longitudinal Study of Ageing; HANDLS, healthy Aging in Neighborhoods of Diversity Across the Life Span; HHP, Honolulu Heart Program; KALS, Kaohsiung Atherosclerosis Longitudinal Study; KEEPSCog, Kronos Early Estrogen Prevention cognitive; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; MACS, Multicentre AIDS Cohort Study; MADT, Middle-Aged Danish Twins; MDCS, Malmö Diet and Cancer Study; MORGEN, Monitoring Project on Cardiovascular Disease Risk Factors; MRC, Medical Research Council; NSHD, National Survey of Health and Development; PATH, Population Assessment of Tobacco and Health; PURE, prospective Urban and Rural Epidemiological; .RECALL, Risk Factors, Evaluation of Coronary Calcium and Lifestyle; SBP, systolic blood pressure; SU.VI.MAX, SUpplémentation en VItamines et Minéraux AntioXydants; Swan, Study of Women's Health Across the Nation; TILDA, The Irish Longitudinal Study on Ageing; VETSA, Vietnam Era Twin Study of Aging and; WHAP, Women's Health Aging Project.

TABLE 5. Summary of negative relationships between hypertension and cognition at midlife by study design and quality.

Study design	Memory	Attention	Executive function	Global cognition	Psychomotor speed	Intelligence	Visuospatial organization
Individual Study Cohorts	Bayes-Marin *et al.* (2020), Chen *et al.* (2015), Elmassry *et al.* (2015), Gourley *et al.* (2020), Gupta *et al.* (2008), Hajjar *et al.* (2016), Hoffmann *et al.* (2020), Houle *et al.* (2019), Kovacs *et al.* (2014), Palacios-Mendoza *et al.* (2018), Wod *et al.* (2018)	Houle *et al.* (2019), Kovacs *et al.* (2014), Sierra *et al.* (2004), Wod *et al.* (2018), Sands *et al.* (1992)	Aliberti *et al.* (2020), Chen *et al.* (2015), Elmassry *et al.* (2015), Giugliano *et al.* (2018), Gourley *et al.* (2020), Gupta *et al.* (2008), Hajjar *et al.* (2016), Houle *et al.* (2019), Kovacs *et al.* (2014), Wod *et al.* (2018)	Aliberti *et al.* (2020), Cui *et al.* (2016), Elmassry *et al.* (2015), Gerasimenko *et al.* (2017), Giugliano *et al.* (2018), Gupta *et al.* (2008), Wang *et al.* (2016), Rouch *et al.* (2019)	Chen *et al.* (2015), Kovacs *et al.* (2014)	Cui *et al.* (2016)	Kovacs *et al.* (2014)
Longitudinal Study Cohorts	Olaya *et al.* (2019), Suvila *et al.* (2021), Zhang *et al.* (2019)	-	Suvila *et al.* (2021), Zhang *et al.* (2019	Suvila *et al.* (2021), Leong *et al.* (2020)	Suvila *et al.* (2021)	-	-
Study Quality ($n =$)	Low: 9 Moderate: 12 High: 11	Low: - Moderate: 4 High: 3	Low: 8 Moderate: 13 High: 8	Low: 3 Moderate: 6 High: 10	Low: - Moderate: 1 High: 3	Low: - Moderate: 1 High: -	Low: - Moderate: 1 High: 1

impairment in aging populations [5]. Attention at midlife was not negatively impacted by midlife hypertension as evident by meta-analysis but was affected in later life. Studies of ageing and neurocognition have reported age-related declines in attention [54–57]. Our results highlight an inconsistent relationship between hypertension at midlife and a decline in attention in later life, similar to previous reports [58–60]. Recent evidence from the National Health and Nutrition Examination Survey reports 70% of older adults are living with hypertension in comparison to just 32% of adults aged 40–59 years [61]. Management of previously untreated hypertension later in life cannot correct for the negative impact of decades of uncontrolled hypertension on cognitive function [62,63]. Hypertension may therefore contribute to, and even exacerbate, brain ageing via deterioration of neuroanatomical substrates and modulators among certain cognitive domains from midlife onwards [64–67]. Our results support the hypothesis of significant variation of age-related cognitive trajectories across several domains, which may be exacerbated with long-term exposure to hypertension across the lifespan.

There are several limitations to this study. A range of tools assessing cognitive function were broadly categorized for one or several cognitive domains. Although some tests will incorporate multiple cognitive domains, for the purpose of this review each test was organised according to core cognitive functions. We did not investigate the biological underpinnings of reported cognitive impairments, only examining the qualitative relationship between hypertension status and cognitive function. Studies were of varied design and quality and data reporting limited the ability to perform meta-analysis. Furthermore, different BP values were used across studies for the classification of hypertension. Clearer reporting of data in primary studies will enable better quality systematic analysis in the future.

CONCLUSION

The risks of midlife hypertension to cognition across the adult lifespan are of considerable concern in the context of an ageing population. The variability across cognitive domains is apparent, such that midlife hypertension adversely affected memory, executive function, and global cognition in later life, and negatively affected the same select domains of memory, executive function, and global cognition, but not attention, at midlife. Further longitudinal and prospective studies are required to determine the specific timeframe at which cognitive decline in certain domains begins to manifest from midlife onward. This will help establish a clear window of hypertension duration during which cognitive impairment and the earliest affected cognitive domains become evident.

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manuscript. Kelly ÁM is the project Principal Investigator and final author and contributed to editing the manuscript.

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Consent was not necessary given the nature of this article.

Within this article, all data collected and/or analysed during this review are included throughout and in the supplementary material, http://links.lww.com/HJH/C344.

This research was exempt from local ethical approval as only published data were pooled.

Appendices and supplementary tables in this review article contain extensive data. In line with the guidelines, the authors recommend they be published in the electronic version of the *Journal of Hypertension* and referenced in a footnote in the print edition. A cover letter, highlights, and research in context have also been provided in support of the preliminary review by the editor.

Conflicts of interest

No potential conflict of interest is reported by the author(s).

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