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REVIEW ARTICLE

Hypertension and Alzheimer's disease pathology at autopsy: A systematic review

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Abstract

Hypertension is an important risk factor for Alzheimer's disease (AD) and all-cause dementia. The mechanisms underlying this association are unclear. Hypertension may be associated with AD neuropathological changes (ADNC), but reports are sparse and inconsistent. This systematic review included 15 autopsy studies (n = 5879) from observational cohorts. Studies were highly heterogeneous regarding populations, follow-up duration, hypertension operationalization, neuropathological methods, and statistical analyses. Hypertension seems associated with higher plaque and tangle burden, but results are inconsistent. Four studies (n = 3993/5879; 68%), reported clear associations between hypertension and ADNC. Another four suggested that antihypertensive medication may protect against ADNC. Larger studies with longer follow-up reported the strongest relationships. Our findings suggest a positive association between hypertension and ADNC, but effects may be modest, and possibly attenuate with higher hypertension age and antihypertensive medication use. Investigating interactions among plaques, tangles, cerebrovascular pathology, and dementia may be key in better understanding hypertension's role in dementia development.

KEYWORDS
Alzheimer's disease, blood pressure, hypertension, neuritic plaques, neurofibrillary tangles, neuropathology, systematic review

1 | INTRODUCTION

The global prevalence of dementia is expected to increase exponentially to an estimated 150 million by 2050.[1] The pathophysiology of dementia in old age remains unclear but likely involves multiple underlying pathologic processes.[2] Clinically, attempts can be made to distinguish Alzheimer's disease (AD) and vascular dementia, but in late-life dementia, often both AD neuropathologic change (ADNC) and vascular brain injury are seen at autopsy.[3–5]

Hypertension, particularly in midlife, is an important risk factor for late-life dementia, both for vascular dementia and AD.[6–9] In later life, this relation may become negative or U-shaped, with both a low and high blood pressure (BP) indicating elevated dementia risk.[10] The mechanisms by which hypertension and BP may increase dementia risk remain unknown. A history of hypertension is associated with cerebrovascular pathological changes, but this does not fully explain

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the association between hypertension and dementia.[11] A more direct association between hypertension and ADNC could provide a missing link in this complex association, but whether this link exists is currently unclear.[12,13] Although some studies have assessed the relation between hypertension or BP and neuropathology in late life, these differ widely in populations and methods, probably contributing to inconsistent results and conclusions.[14,15] Careful weighing of their results is paramount to interpret the evidence on the relationships of mid- and late-life BP with ADNC. In this systematic review we focus on whether ADNC are associated with hypertension during life, to better understand the relationship between hypertension and dementia.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed the literature using Medline and Embase to evaluate the relation between hypertension and Alzheimer's dementia neuropathological changes (ADNC) at autopsy. Studies were very heterogeneous with respect to study populations and methodological approaches, which may have contributed to the inconsistent results across studies. Overall, findings suggest a positive association between hypertension and ADNC, but effects may be modest, and possibly attenuate with higher hypertension age and antihypertensive use.
2. **Interpretation**: The relation between hypertension and ADNC is not well understood. ADNC may follow cerebrovascular damage, particularly atherosclerosis or microvascular lesions, caused by hypertension. Alternatively, hypertension and ADNC may increase dementia risk through distinct pathways, possibly synergistically.
3. **Future Directions**: More well-powered studies are warranted, aligning statistical analyses, evaluating effects of antihypertensives, non-linear relationships, and age/cognition at hypertension diagnosis and death. Investigating interactions among plaques, tangles, cerebrovascular pathology, and dementia may be key in understanding hypertension's role in dementia development.

Highlights

- We systematically reviewed the literature on hypertension and Alzheimer's disease pathology.
- Studies are sparse and highly heterogeneous in populations, methods, and results.
- Findings suggest a modest association between hypertension and more pathology.
- Associations may attenuate with higher hypertension age and antihypertensive use.
- More knowledge on interactions among amyloid, tau, and vascular damage may be key.

2 | METHODS

2.1 | Inclusion and exclusion criteria

We included prospective and retrospective longitudinal cohort studies in individuals from the general and memory clinic populations. Case-control studies, animal studies, and studies specifically examining patients with neurodegenerative disease other than late-onset cognitive decline and dementia were excluded.

2.2 | Exposure and outcome

The main exposure was hypertension, including any definition. Diagnosis could be based on clinical/study assessments or medical history. The latter includes self-report of hypertension and/or antihypertensive medication (AHM) use during study interviews, as well as previous clinical assessments documented in medical files. These data could be collected prospectively at clinical evaluations or retrospectively from medical records *post mortem*.

ADNC were the primary outcome. This included (1) extracellular neuritic/amyloid plaques (NP), measured according to plaque density or to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD); and (2) neurofibrillary tangles (NFT), measured according to tangle density or Braak staging.[16,17]

2.3 | Search and extraction

Medline and Embase were searched through the OVID platform from inception up until April 2021. Search terms included (synonyms for) dementia and AD, cross-referenced with terms related to hypertension, autopsy, obduction, and neuropathology (supporting information 1). All search terms were exploded to their subject heading if possible. Two reviewers with a medical background (HA, MB), screened titles and abstracts independently. Full-text articles were later hand-searched for additional potentially relevant articles. Two reviewers extracted and double-checked the extracted data (HA, JWvD) using a piloted data-extraction sheet, including study/population characteristics; measures of hypertension/neuropathology; statistical analyses/results; and (influence of) potential moderators including years with hypertension, time of BP assessment (mid life/late life), and AHM use.

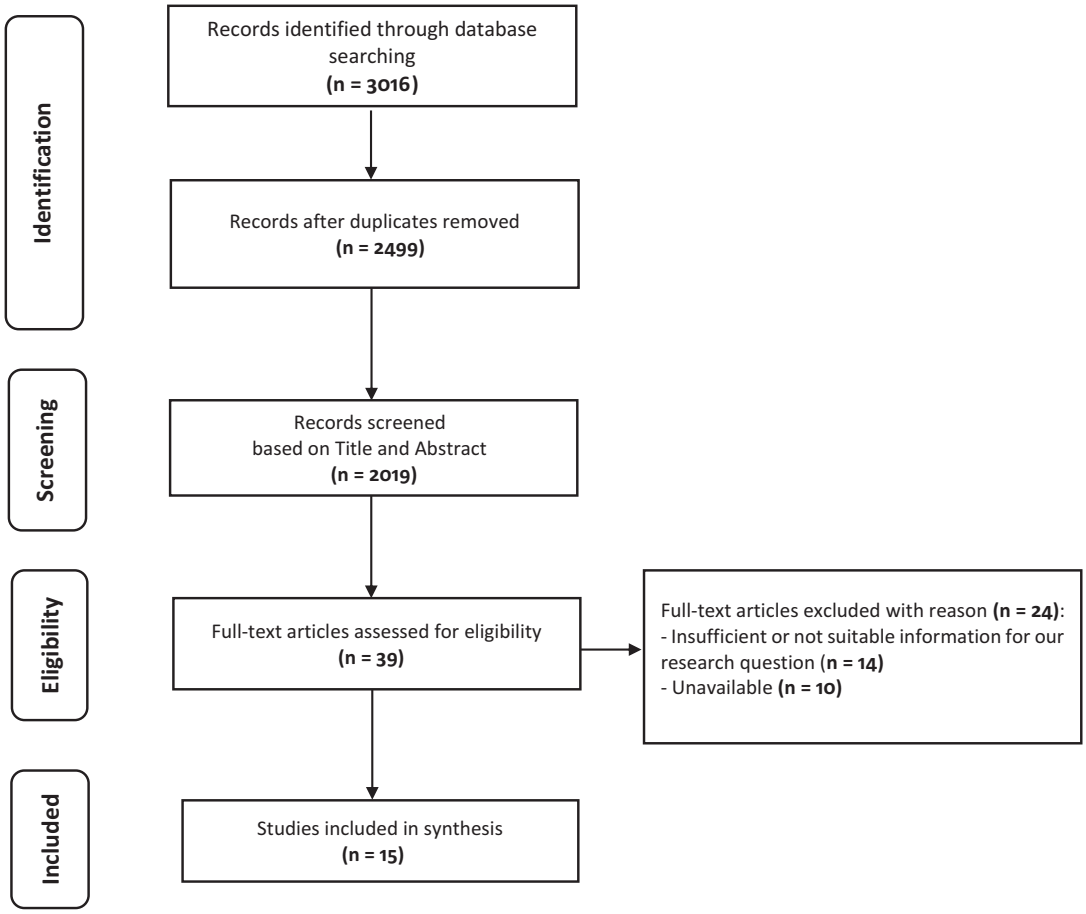

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of selected studies for inclusion

2.4 | Statistical analysis

We considered the methodological differences between the included studies too large to allow pooling of the individual study effect estimates. Instead, we provide a narrative overview of the studies' analyses and results. In addition, we provide a visual overview, using forest plots collating point estimates for NP and NFT including 95% confidence intervals, from studies that used similar statistical methods, comparable methods for hypertension/BP assessment, and comparable measures for ADNC. The methods used to collate and recalculate the studies' findings for this purpose are described in the supporting information Methods 1.

3 | RESULTS

From 2499 abstracts, 39 full exts were evaluated, and 15 studies found eligible (Figure 1). Hand searching references of included papers did not yield additional results.

Table S1 in supporting information lists the quality assessment score according to the Newcastle–Ottawa Scale for Cohort Studies.[18] Two studies had a poor score (<2),[21,30] due to poor population representativeness, assessment of outcome, and adequacy of follow-up.

3.1 | Study design and participant characteristics

Table 1 lists an overview of designs and population characteristics of the 15 included studies. Studies were published between 1995 and 2020. Ten were from the United States,[19–28] three from Europe,[29–31] one from Australia,[32] and one from Asia (Sri Lanka).[33] Ten collected clinical data prospectively before death,[19,20,22,23,25–29,31] four retrospectively after death,[24,30,32,33] and one before and after death.[21]

Ten studies included community-dwelling older people, recruited from the general population and/or retirement homes. Some examined specific subpopulations, including Japanese American older men living in Hawaii;[19] semi-urban older adults from Colombo, Sri Lanka;[33] members of a Catholic clergy;[20] and the oldest old (≥85 years) from a town in Finland.[31] Three studies recruited their study cohort from forensic and hospital morgue databases, which included community-dwelling older people and individuals diagnosed with dementia.[21,22,30] The two remaining studies combined data from various sources, including participants recruited from the general community, memory clinics, and participant referrals.[23,26]

Sample sizes ranged from 50 to 2198 (median 193), with 18.8% to 100% (median 42.8%) of participants being men. The mean age at BP assessment ranged from 45 to 92.8 years (median 83.4). The mean time

TABLE 1 Study design and population characteristics

	Cohort name(s)	Country	Clinical data collection	Population	Cognitive status assessment	Exclusion criteria for cohort population	Autopsy cases (*n*)	Men (%)	Mean age BP assessment/age of death (years)	Time between BP assessment and autopsy (mean years)
Petrovich 2000*	HAAS	United States	Prospectively before death	Community-dwelling Japanese American older men living in Hawaii	Evaluated at FU visit 25+ years after BP assessment		243	100	BP: 45–65	36
Arvanitakis 2018*	Religious Order Study; Rush Memory and Aging project; MARS	United States	Prospectively before death	Catholic clergy from across United States; community-dwelling older people from Illinois; community-dwelling (sub)urban Blacks	Evaluated along with BP assessments		1288	35.0	Death: 88.6 (6.7SD)	8
Richardson 2012*	MRC CFAS	UK	Prospectively before death	Community-dwelling older people	Evaluated during screening interviews for health status		422	41.0	Death: 87.0	6–10
Sparks 1995*	Hospital forensic data and ADRC University of Kentucky	United States	Retrospectively after death in individuals with no dementia. Prospectively before death in individuals with dementia	Individuals with no dementia: Forensic or hospital pathology service University of Kentucky. Individuals with dementia: University of Kentucky ADRC	Extracted from database in individuals with no dementia		264	–	–	Not reported
Hoffman 2009*	Mount Sinai School of Medicine Department of Psychiatry Brain Bank	United States	Retrospectively after death	Residents of nursing homes and elder-living facilities in New York	Extracted from medical records	Mortality age <60 years Primary neuropathology non-AD related	291	40.2	Death: 83.4	Not reported
Affleck 2020*	New South Wales Brain Banks database	Australia	Retrospectively after death	Community-dwelling older people	Extracted from database	Pre-existing neurological or neuropsychiatric disease, mortality age <75, cerebrovascular disease with lobar infarction >50 mL	149	40.3	Death: 88.0	Not reported

(Continues)

TABLE 1 (Continued)

	Cohort name(s)	Country	Clinical data collection	Population	Cognitive status assessment	Exclusion criteria for cohort population	Autopsy cases (*n*)	Men (%)	Mean age BP assessment/age of death (years)	Time between BP assessment and autopsy (mean years)
Wharton 2019*	Rush Clinical Core; Religious Orders Study; Rush MAP	United States	Prospectively before death	African Americans without dementia; Catholic clergy from across USA; Retirement community from Illinois;	Evaluated along with BP assessments	Normotension (SBP ≥140 mmHg/DBP ≥90 mmHg), Untreated hypertension	83	31	BP: 83.1	4.2
Eglit 2019*	NACC ADC	United States	Prospectively before death	Community dwelling older people from referral-based or volunteer case series	Extracted from database	History of clinical stroke, clinical diagnosis other than normal cognition, MCI or AD	2198	52.9	BP: 80.5	Not reported
Nation 2012	University of San Diego ADRC	United States	Prospectively before death	Dementia patients from University Hospital Alzheimer Research Center	Evaluated along with BP assessment	Extensive cerebrovascular disease at autopsy (vascular dementia, mixed dementia)	65	47.7	BP: 74.2	6
Besser 2016	NACC UDS and NDS data for ADC	United States	Prospectively before death	Participants recruited from population-based samples, clinics, public recruitment efforts, participant referrals, and other ongoing studies	Cognition at most recent study visit before death	Individuals with MCI or dementia	193	43.5	BP: 80.2 Death: 84.6	4
Wang 2009	ACT	United States	Prospectively before death	Community-dwelling older people recruited from health maintenance organization	Evaluated along with BP assessments	<65 years	250	42.0	BP: 80.1 Death: 87.0	Not reported

(Continues)

TABLE 1 (Continued)

	Cohort name(s)	Country	Clinical data collection	Population	Cognitive status assessment	Exclusion criteria for cohort population	Autopsy cases (*n*)	Men (%)	Mean age BP assessment/age of death (years)	Time between BP assessment and autopsy (mean years)
Zheng 2013	University affiliated memory clinics or community	United States	Prospectively before death	Individuals with cognitive impairment or dementia recruited from university affiliated memory clinics. Cognitively unaffected individuals recruited from community	Cognitive status prespecified in subsamples	History of cerebral hemorrhage or cortical infarction at study entry	163	55.8	Death: 84.0	Not reported
Wijesinghe 2016	Colombo Teaching Hospital	Sri Lanka	Retrospectively after death	Community-dwelling semi-urban population from Colombo	Not reported	–	50	58.0	BP: 72.1	Not reported
Gerth 2018	Brain Bank Laboratory Neuropathology University of Ulm	Belgium, Germany	Retrospectively after death	Hospital based autopsy cases	Not reported	–	71	45	–	Not reported
Hooshmand 2018	VANTAA 85+	Sweden, Finland	Prospectively before death	Community-dwelling Finnish population ≥85 years	Evaluated along with BP assessments	<85 years	149	18.8	BP: 88.1 Death: 92.8	4.7

Abbreviation: ACT, Adult Changes in Thought; AD, Alzheimer's disease; ADCC, Alzheimer's Disease Core Center; ADRC, Alzheimer's disease Research Center; ADNP, Alzheimer's disease neuropathology; anti-HT, antihypertensive; BP, blood pressure; CVD, cerebrovascular disease; FU, follow-up; HAAS, Honolulu-Asia Aging Study; HR, heart rate; MAP, Memory and Aging Project; MARS, Minority Aging Research study; MCI, mild cognitive impairment; MRC CFAS, Medical Research Council Cognitive Function and Ageing Study; NACC, National Alzheimer's Coordinating Center; Rush MAP, Religious Orders Study Memory and Aging Project; UCSD ADRC, University of California San Diego; UDS, Uniform Data Set; VsD, vascular dementia.

*Reports significant associations between blood pressure and AD-related neuropathology.

from (last) BP assessment to death was reported in seven studies and ranged from 1 month to 7.1 years (median 1.3 years).[22,23,25,27–30]

3.2 | Blood pressure and hypertension assessment

Table 2 depicts an overview of the BP assessment methods used. One study assessed BP in mid life; all others in late life.

Three studies based BP assessment solely on pre-existing medical records.[21,24,30] Four others based BP assessments on study setting BP measurements only,[19,22,25,31] hand-measured by health professionals (clinician/nurse) using a mercury sphygmomanometer. Assessment frequency ranged between annually to once during study follow-up. Two studies used BP data from questionnaires, inquiring about history of hypertension and use of anti-hypertensive drug use: one from participants' self-report collected biennially for up to 10 years of follow-up,[28] the other from relatives' reports *post mortem*.[33] One study performed extensive medical assessments, systematically collected in the clinical setting, and included inquiry on hypertension status.[26] The five remaining studies used a combination of the above-mentioned methods to assess BP and/or hypertension status.

AHM use was reported in nine studies and ranged from 5% to 87% (median 35%).[19,20,22–25,27,29,32]

3.3 | Neuropathological assessment

Six studies exclusively used semi-quantitative staging methods to assess ADNC (Table 2).[23,25,26,28–30] Of these, five staged NP according to CERAD and NFT according to Braak; two staged ADNC according to the 2012 National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines.[30,32] Three studies assessed ADNC exclusively by counting NP and NFT in 1 mm^2 areas in four to six selected brain regions, expressed as counts/ratios per mm^2.[19,20,21] The remaining six studies assessed Braak stage, CERAD score, and counts of NPs and NFTs.[22,24,27,31,32,33]

Histological staining methods varied greatly among the studies. Most neuropathological assessments included Bielschowsky, hematoxylin, and eosin staining methods. Six studies performed additional immunohistochemical staining methods. Three did not report the staining methods used.

Four studies reported that neuropathologists were blinded to clinical data.[20,24–26]

3.4 | Statistical analysis methods used

Table 3 provides an overview of statistical analyses used. To analyze BP, nine studies only used dichotomous measures of hypertension status and/or use of AHM (yes/no),[21,24,26–30,32,33] two only used BP as continuous measure,[25,31] and one used systolic BP (SBP) and diastolic BP (DBP) categories (low/normal/borderline/high/mixed).[19] The remaining three studies used both dichotomous measures for hypertension (yes/no) and continuous BP measures.[20,22,23] Of these, two analyzed pulse pressure instead of SBP and DBP.[22,23]

To analyze neuropathology, three studies only used NP and NFT mean density (counts/mm^2) continuously.[19–21] Three used both NP and NFT counts continuously and Braak and CERAD semi-quantitative staging.[24,27,31] Five studies only used Braak for NFT and CERAD for NP without modifications.[25,26,28,30,32] Of these, two used NIA-AA criteria to illustrate NP spread (ranging A0–A3) and NFT spread (ranging B0–B3).[30,32] The remaining four studies used semi-quantitative staging, categorized specifically for their analyses: one compared CERAD score absent/mild versus moderate/severe;[29] another Braak 0 to V versus VI;[22] another ADNC "positive" (Braak III–V with CERAD moderate-frequent) versus "negative" (Braak 0–II with CERAD absent-sparse);[23] and the final CERAD none versus higher and Braak 0 versus I to VI, 0 to II versus III to VI, and 0 to III versus IV to VI.[33]

For the statistical methods, two studies used descriptive statistics only. Of these, one compared NP and NFT counts between individuals with/without hypertension and with/without clinical AD using analysis of variance (ANOVA), and NP and NFT proportions across these groups using chi-square tests.[21] The other compared CERAD scores of NP and NFT between those with medicated hypertension, non-medicated hypertension, and without hypertension, using ANOVA.[24]

Six studies used linear regression. Four of these used NFT and NP as continuous outcomes (count/mm^2) predicted: by categorized midlife SBP and DBP (as ratio compared to reference category),[19] mean and change in SBP and DBP over three measurements,[20] or (history of) hypertension and/or AHM use (yes/no).[27,30] The other two used continuous measures of late-life SBP and DBP, as predictors with Braak stage as outcome,[22] or as outcomes predicted by CERAD and Braak categories.[25]

Eight studies (also) performed logistic regression analysis, with (history of) hypertension, AHM use, or SBP and DBP as continuous predictors, and dichotomized NP and NFT or Braak and CERAD as outcomes.[22,23,27,29,30–33]

Another four studies (also) performed ordinal regression analysis, predicting categorical measures of NP and NFT with continuous measures of BP, history of hypertension, and/or AHM use.[20,26–28]

3.5 | Study results

Tables 1–3 provide a detailed overview of the study characteristics and results. Of the 15 studies, eight reported an association between higher BP and more severe ADNC, one of which assessed BP in midlife.[19] Five of these operationalized hypertension based on AHM use (yes/no).[21,24,27,29,32] Compared to studies that did not report any associations between BP and ADNC, those that did had almost twice as long study follow-up periods (median 8, range 4.2–36, vs. 4.7 years range 4.0–6.0 years) and greater sample sizes (median 278, range 83–2198, vs. median 149, range 50–250).

Regarding immunohistochemistry staining methods, four of these eight studies performed additional methods next to Bielschowsky/eosin/hematoxylin staining, versus two of seven studies

TABLE 2 Blood pressure and neuropathological assessments

	Method BP assessment	Number of BP assessments	Mean SBP/DBP mm Hg (SD)	Anti-HT medication users (%)	Neuropathological assessments	Histological staining method
Petrovich 2000*	Study setting BP measurement	BL 2 FU measurements (2–3 years apart)	Not reported	61/243 (25%)	Quantitative: NFT/NP counts selected regions (nr/mm^2)	Bielschowsky
Arvanitakis 2018*	Study setting BP measurement Self-reported history of hypertension and use of anti-hypertension medication Both conducted by trained research nurse in participants' residence.	At BL Annual FU	134 (8)/ 71 (8)	1122/1288 (87%)	Quantitative: NFT/NP counts selected regions (nr/mm^2)	Modified silver
Richardson 2012*	Health status questionnaires: Self-reported hypertension diagnosis, use of anti-hypertension medication, conducted in participants' residence.	BL biennial FU (Up to 10 years)	N/a	146/418 (35%)	Semi-quantitative: CERAD for NP and NFT	Not reported
Sparks 1995*	Medical records: BP measurements and/or prescription of antihypertensive medication	Not reported	Not reported	Not reported	Quantitative: NFT/NP counts in 3 random cerebral regions (nr/mm^2)	Bielschowsky PHF-1 antibody in subsample
Hoffman 2009*	Pre-existing medical records: BP measurements and/or prescription of antihypertensive medication	Not reported	Not reported	77/291 (26.5%)	Quantitative: Mean NP density in 5 cortical regions (nr/mm^2). Semi-quantitative: CERAD for NP and NFT	Hematoxylin eosin, modified Bielschowsky modified thioflavin S, anti-B amyloid, anti-tau when necessary
Affleck 2020*	Pre-existing medical records: GP health status summaries, specialist reports, and annual self-report survey responses on hypertension diagnosis, antihypertensive medication use and hypertension status	Not reported	Not reported	57/73 (79%)	Quantitative: NFT/NP counts. Semi-quantitative: Braak for NFT, CERAD for NP (According to NIA-AA guidelines)	Hematoxylin, immunohistochemistry
Wharton 2019*	Study setting BP measurement Conducted by trained research nurse in participants' residence.	BL and annual FU measurements	139 (19)/ 72 (5.3)	388/937 (41.4%)	Quantitative: NFT/NP counts. Semi-quantitative: Braak for NFT, CERAD for NP (According to NIA-AA guidelines)	Not reported
Eglit 2019*	Medical records: self-reported hypertension and/or prescription of antihypertensive medication. Continuous BP measures: Available in subsample of NACC-UDS participants	Not reported	129 (18.9)/71 (10.7)	Not reported	Semi-quantitative: Braak for NFT, CERAD for NP	Bielschowsky Gallyas Tau immunostain Thioflavin-S

(Continues)

TABLE 2 (Continued)

	Method BP assessment	Number of BP assessments	Mean SBP/DBP mm Hg (SD)	Anti-HT medication users (%)	Neuropathological assessments	Histological staining method
Nation 2012	Study setting BP measurement, self-reported use of anti-hypertensive medication	Once	Not reported	18/65 (27.7%)	Quantitative: NFT/NP counts in selected cerebral regions. Semi-quantitative: Only for NFT	Hematoxylin eosin thioflavin-S
Besser 2016	Medical records, health status questionnaires: self-reported hypertension diagnosis, use of anti-hypertension medication	Annual	135 (17.8)/ 71 (9.2)	103/93 (53.3%)	Semi-quantitative: Braak for NFT, CERAD for NP	Not reported
Wang 2009	Study setting BP measurement. Conducted by trained research nurse	BL and biennial FU	Not reported	77/250 (30.8%)	Semi-quantitative: Braak for NFT, CERAD for NP	Formalin fixation
Zheng 2013	Medical assessment: hypertension status, systematically collected in clinical setting	Annual	Not reported	Not reported	Semi-quantitative: Braak for NFT, CERAD for NP	Hematoxylin eosin cresyl violet Congo red Bielschowsky silver
Wijesinghe 2016	Health status questionnaires filled in by family *post mortem*	Not reported	N/a	Not reported	Quantitative: NFT/NP counts Semi-quantitative: None/moderate/ frequent	Hematoxylin eosin immunostaining (immunoperoxidase) antigen retrieval
Gerth 2018	Pre-existing medical records: BP measurements and/or prescription of antihypertensive medication	Not reported	Not reported	Not reported	Semi-quantitative: Braak for NFT, CERAD for NP (According to NIA-AA guidelines)	Formalin Gallyas silver immune-histochemical staining
Hooshmand 2018	Study setting BP measurement. Conducted by physician	Once	154.5 (23.8) /84.5 (12.2)	Not reported	Quantitative counts of NFT/NP; Semi-quantitative Braak for NFT, CERAD for NP	Paraffin methenamine silver Bielschowsky Gallyas

Abbreviations: ADCC, Alzheimer's Disease Core Center; anti-HT, antihypertensive; BP, blood pressure; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DBP, diastolic blood pressure; GP, general practitioner; NACC, National Alzheimer's Coordinating Center; NDS, Neuropathology Data Set; NFT, neurofibrillary tangles; NIA-AA, National Institute on Aging–Alzheimer's Association; NP, neuritic plaques; SBP, systolic blood pressure; UDS, Uniform Data Set.

*Reports significant associations between blood pressure and AD-related neuropathology.

that did not report associations between BP and ADNC (Table 2). There was a great variety, and no consistent pattern, in adjustments made for the statistical analyses between studies.

A summary of the study results is depicted in Figure 2, illustrating the large heterogeneity between study methodologies and results, which impeded pooling the effect estimates. The forest plots show that the direction between hypertension and NPs and NFTs is highly inconsistent.

Three studies are not listed in this overview, because they used predictors and/or outcomes that could not be grouped with the other studies.[22,27,33] One compared immunopositive amyloid beta (Aβ) phase according to Thal between participants with and without hypertension, wherein hypertension was associated with a 62% (non-significant) greater chance of having Aβ phase 0 versus phase ≥1 (odds ratio: 0.28, 95% confidence interval 0.06–1.39, $P = .12$).[33] Another study compared ADNC in AD patients with and without elevated pulse pressure, reporting no significant differences.[22] The remaining study compared renin angiotensin system (RAS) acting AHM users versus non-RAS users, reporting that RAS-users had less severe ADNC.[27]

3.6 | Neuritic plaques versus neurofibrillary tangles

Three of the eight studies that reported significant associations showed both plaques and tangles associated with high BP.[19,21,28] Another showed that late-life higher mean SBP was particularly associated with more NFT ($P = .038$), relations with diffuse NP being non-significant ($P = .063$).[20] The remaining four reported associations

TABLE 3 Statistical analyses and study outcomes

Source	Blood pressure operationalization	Neuropathology operationalization	Statistical analysis	Adjustments	Study results	Interpretation study results
Petrovich 2000*	5 categories of SBP/DBP: Low: <110 mmHg /<80 mmHg Normal: 110–139 mmHg/ 80–89 mmHg Borderline: 140–159 mmHg/ 90–94 mmHg High: ≥160 mmHg/ ≥95 mmHg Mixed: individuals in >1 of these categories for the different measurements. Based on mean BP from 3 measurements, conducted over 9 years (at BL; after 4.5 years; after 9 years)	NFT/NP ratios per mm2 (continuous) Groups with low/borderline/high BP compared to reference group (normal BP)	**Linear regression** Predictor: 5 SBP/DBP categories Outcome: NFT/NP count ratios per mm^2 in four areas from neocortex and two areas from hippocampus compared to reference group with normal BP	Age at death *APOE ε*4 allele Anti-HT medication	Hippocampal NFT count ratio 2.39 (1.34–4.26) with high DBP compared to normal BP Hippocampal NP count ratio 2.18 (1.07–4.46) with high SBP compared to normal BP Neocortical NP count ratio 2.05 (1.00–4.20) with high SBP compared to normal BP	Potential U-shaped relation between densities of NP, NFT and BP Highest midlife DBP (>100 mm Hg) associated with increased density hippocampal NFT. Significant relation between NP-density in group of highest SBP
Arvanitakis 2018*	Mean SBP and DBP measurements (continuous). Annual BP assessments over mean follow-up of 8.0 years (SD = 4.8). History of hypertension (yes/no) Anti-hypertension medication (yes/no)	NFT/NP counts (continuous) and categorized in quartiles	**Linear regression**: Predictor: person specific mean SBP and DBP over time, and slope of change in SBP and DBP over time Outcome: NFT/NP counts per mm^2. **Ordinal regression**: Predictor: person specific mean SBP and DBP over time, and slope of change in SBP and DBP over time Outcome: NFT/NP categorized into 4 groups (quartiles)	Age at death Sex Education Years in study	Counts of NFT associated with higher mean SBP; person-specific mean of NFT 0.037, (SE 0.018), $P = .038$	Higher mean SBP associated with significantly higher number of tangles. No association between mean or slope change in BP and ADNP

(Continues)

TABLE 3 (Continued)

Source	Blood pressure operationalization	Neuropathology operationalization	Statistical analysis	Adjustments	Study results	Interpretation study results
Richardson 2012*	History of hypertension (yes/no) Anti-HT medication (yes/no)	CERAD scoring (none, sparse moderate frequent) dichotomized as absent/mild vs. moderate/severe	**Logistic regression**: Predictor: anti-HT medication status Outcome: CERAD scores for NFT and NP	Age Sex	Medicated hypertension and neocortical NFT association: OR 0.5 (0.3–0.8), $P = .01$	Medicated hypertension associated with fewer moderate/severe NFT
Sparks 1995*	Hypertension (yes/no) Anti-hypertension medication (yes/no)	NFT/NP proportions based on mean numerical densities (continuous)	**Chi-square**: Comparison NFT/NP between groups with/without AD and with/without HT. **ANOVA**: Mean NFT/NP density compared between groups with/without AD and with/without HT. **Pearson's correlation coefficient**: Correlations between NFT and NP between groups with/without AD and with/without HT	Not reported		Highest density of NFT and NP in AD and secondly in group of HT alone
Hoffman 2009*	History of hypertension (yes/no) Anti-HT medication (yes/no)	NFT/NP sums from seven regions in neocortex (continuous) Means of NP (continuous) and CERAD scores (none, sparse moderate, frequent) for both NP/NFT	**ANOVA**: Comparisons of NFT/NP CERAD ratings between three participating groups: those with medicated HT; non-medicated HT, and no HT	Age at death Educational level Sex Race *APOE* ε4 allele BMI	Medicated hypertension least mean average neuropathology compared to those with no hypertension (mean average of 4.83 vs. 17.09, respectively)	Hypertension-medicated group significantly less neuropathology than no hypertension group. Highest CERAD score found in subjects without documented history of hypertension
Affleck 2020*	Anti-HT medication (yes/no)	NFT: NIA-AA B0-B3 NP: NIA-AA A0-A3	**Univariate analysis**: Groups with/without medicated hypertension and A- and B-stages. **Logistic regression**: Predictor: anti-HT medication Outcome: NFT/NP	Age Sex *Post mortem* delay Cerebrovascular disease Hypertensive status	Anti-HT medication: less extensive spread of NP/NFT. Medicated participants have OR of 7.4 to have less severe neuropathology (A0 or A1) than more severe category (A3) compared to participants with no anti-HT medication.	No difference in amounts of NFT/NP in the frontal cortex between medication users. Antihypertensive medication associated with less extensive spread of AD proteins in brain

(Continues)

TABLE 3 (Continued)

Source	Blood pressure operationalization	Neuropathology operationalization	Statistical analysis	Adjustments	Study results	Interpretation study results
Wharton 2019*	History of hypertension (yes/no)	Average of NP/NFT counts (continuous) and NFT: Braak stages (I–II, III–IV, V–VI) NP: CERAD scores (none, sparse moderate, frequent)	**Linear and logistic regression**: Predictor: anti-HT medication status Outcome: change in NP/NFT	Sex Baseline age Race Education Systolic BP Diabetes mellitus Depression	RAS medication users less likely to progress to AD than non-RAS users. Users of RAS exhibit fewer NFT than non-RAS users in certain cerebral regions. Conversion rate to AD in RAS versus non-RAS users: OR = 0.12 (0.02–0.80), $P = .03$. Braak 3/4 vs. Braak 1/2 (ref) OR = 0.36 (0.03–3.43), $P = .42$ in RAS vs. non-RAS users. Braak 5 vs. Braak 1/2 (ref), OR = 0.18 (0.01–2.56), $P = .21$ in RAS vs. non-RAS users. CERAD 1 (definite) vs. 4 (no AD), OR = 0.66 (0.18–2.43), $P = .53$ CERAD 2 (probable) vs. 4, OR = 0.91 (0.24–3.53), $P = .90$ CERAD 3 (possible) vs. 4, OR = 0.29 (0.03–3.12), $P = .31$	RAS medication users less likely to progress to AD than non-RAS users Users of RAS exhibit fewer NFT than non-RAS users in certain cerebral regions
Eglit 2019*	History of hypertension (yes/no) Anti-HT medication (yes/no)	NFT: Braak stages (I–II, III–IV, V–VI) NP: CERAD scores none, sparse moderate frequent)	**Ordinal regression**: Associations between hypertension and AD neuropathology (according to ordinal Braak stages and CERAD scores), expressed as ORs	Age at last visit Sex Non-White race *APOE* ε4 positivity Vascular risk factors	Hypertension indirectly associated with NP (OR: 1.01,95% CI = 1.001–1.00) and NFT (1.003, 95%CI = 1.001–1.00)	Hypertension associated with increased NP and NFT mediated through circle of Willis atherosclerosis

(Continues)

TABLE 3 (Continued)

Source	Blood pressure operationalization	Neuropathology operationalization	Statistical analysis	Adjustments	Study results	Interpretation study results
Nation 2012	Use of anti-hypertension medication (yes/no). Mean SBP and DBP (continuous) Pulse pressure (continuous). Average of two consecutive BP at one study visit	Braak <VI vs. Braak VI	**Logistic regression**: Predictor: SBP/DBP Outcome: NFT, low and high Braak stages. **Linear regression**: Predictor: BP Outcome: Braak stage severity	Age Education DRS-score Time-to-death Use of anti-HT *APOE* ε4 presence ≥2 vascular risk factors	No significant associations between BP measures and ADNP after correcting for multiple comparisons	No significant associations between BP measures and ADNP after correcting for multiple comparisons
Besser 2016	History of hypertension (yes/no) Pulse pressure (continuous)	Dichotomization of NFT/NP: Positive: Braak II-VI and moderate-frequent NP Negative: Braak 0-II and absent-sparse NP.	**Logistic regression**: Predictor: history of hypertension Outcome: presence/absence of NFT/NP	Age at death Sex Education *APOE* ε4 allele Education	No association between late-life PP and ADNP	No association between late-life PP and ADNP
Wang 2009	SBP and DBP (continuous) Baseline BP measurement	NFT: Braak stages (I-II, III-IV, V-VI) NP: CERAD-scores stages (none/sparse/moderate/frequent)	**Linear regression**: Predictor: NFT/NP Outcome: SBP/DBP	Age-at-entry Sex Time-to-death	No significant associations between hypertension and ADNP	No significant association between hypertension and Braak stages or CERAD-score
Zheng 2013	History of hypertension (yes/no)	NFT: Braak stages (I–II, III–IV, V–VI) NP: CERAD scores (none, sparse moderate frequent)	**Ordinal regression**: Predictor: history of hypertension Outcome: ordinal Braak-stages and CERAD scores	Age at death Sex Ethnicity Years of education	No significant associations between hypertension and ADNP	No significant associations between hypertension and NFT/NP
Wijesinghe 2016	History of hypertension (yes/no)	CERAD none vs. CERAD sparse/moderate/frequent. Braak none vs. stages I-VI/stages 0-II vs. II-VI/and stages 0-III versus IV-VI	**Logistic regression**: Predictor: history of hypertension Outcome: dichotomized Braak stages (0 vs. II; III vs. VI; and 0-III vs. IV–VI) and CERAD stages (none vs. CERAD A-C)	Age Sex	No significant associations between hypertension and ADNP	No significant associations between hypertension and NFT/NP

(Continues)

TABLE 3 (Continued)

Source	Blood pressure operationalization	Neuropathology operationalization	Statistical analysis	Adjustments	Study results	Interpretation study results
Gerth 2018	History of hypertension (yes/no)	NP: NIA-AA A0-A3	**Logistic regression:** Predictor: hypertension Outcome: NP **Linear regression:** Predictor: hypertension Outcome: NP	Age Sex	No significant associations between hypertension and ADNP	No significant associations between hypertension and NFT/NP
Hooshmand 2018	SBP and DBP (continuous)	NP/NFT counts (continuous) and NFT: Braak stages (I–II, III–IV, V–VI) NP: CERAD scores (none, sparse moderate frequent)	**Ordinal and logistic regression analyses:** Predictor: SBP and DBP outcome: NP/NFT	Follow-up time	No significant associations between hypertension and ADNP	No associations between BP and AD-neuropathology

*Reports significant associations between blood pressure and AD-related neuropathology.
Abbreviations: AD, Alzheimer's disease; ADNP, Alzheimer's disease neuropathology; anti-HT, antihypertensive; *APOE*, apolipoprotein E; BMI, body mass index; BP, blood pressure; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; DBP, diastolic blood pressure; NFT, neurofibrillary tangles; NIA-AA, National Institute on Aging–Alzheimer's Association; NP, neuritic plaques; OR, odds ratio; PP, pulse pressure; RAS, renin angiotensin system; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

between AHM use and fewer NFTs,[27,29] or both NPs and NFTs,[24,32] compared to non-users.

3.7 | Non-linear relationships

Three studies reported assessing non-linear relationships between BP and ADNC,[19,20,30] but only one provided detailed results.[19] This study suggested a potential J-shaped relationship between midlife SBP and late-life ADNC (Figure 3). The highest densities of NFT and NP were observed in the highest (>160 mm Hg) and lowest (<110 mmHg) SBP groups.

4 | DISCUSSION

Four studies, representing 68% of total persons included, reported a direct association between hypertension and ADNC. Four other studies (16.1% of total) reported an association between AHM use and ADNC. Methods of assessment and analyses varied widely, precluding pooling of effect estimates. Point estimates did not consistently favor an association between hypertension and more ADNC. Significant positive associations were more often reported in studies with longer follow-up and larger sample sizes. All but one study assessed late-life BP, whereas epidemiological studies most consistently report associations between mid-life hypertension and late-life dementia.

4.1 | Methodological considerations

Interpreting the results of our systematic review is complex. Studies varied widely in populations, operationalization of hypertension, neuropathological assessment, and statistical analyses. Selection bias likely occurred, particularly in populations selected on cognitive status (e.g., memory clinic populations). Dementia patients may more often have (mid-life) hypertension and ADNC than healthy controls. When analyzed as a single population without accounting for time with dementia, this may have inflated results: the specific mix of demented and cognitively healthy individuals determining the overall association. Conversely, studies in mainly cognitively healthy older participants may have overrepresented people relatively insusceptible to ADNC caused by hypertension.

The variety in BP assessment may also have impacted results. Studies with longer follow-up more often reported significant associations. This may have been influenced by the time of assessment. While BP rises and hypertension becomes common with older age,[34] BP often declines preceding dementia.[35] In studies assessing BP in individuals with cognitive symptoms, in late life, or using life-time hypertension, this might obscure associations. Also, in late life, negative or U-shaped relationships are often found, potentially leading to divergent results in older populations.[36] Only one study evaluated (late) mid-life BP, so we could not adequately compare mid-life versus late-life results,

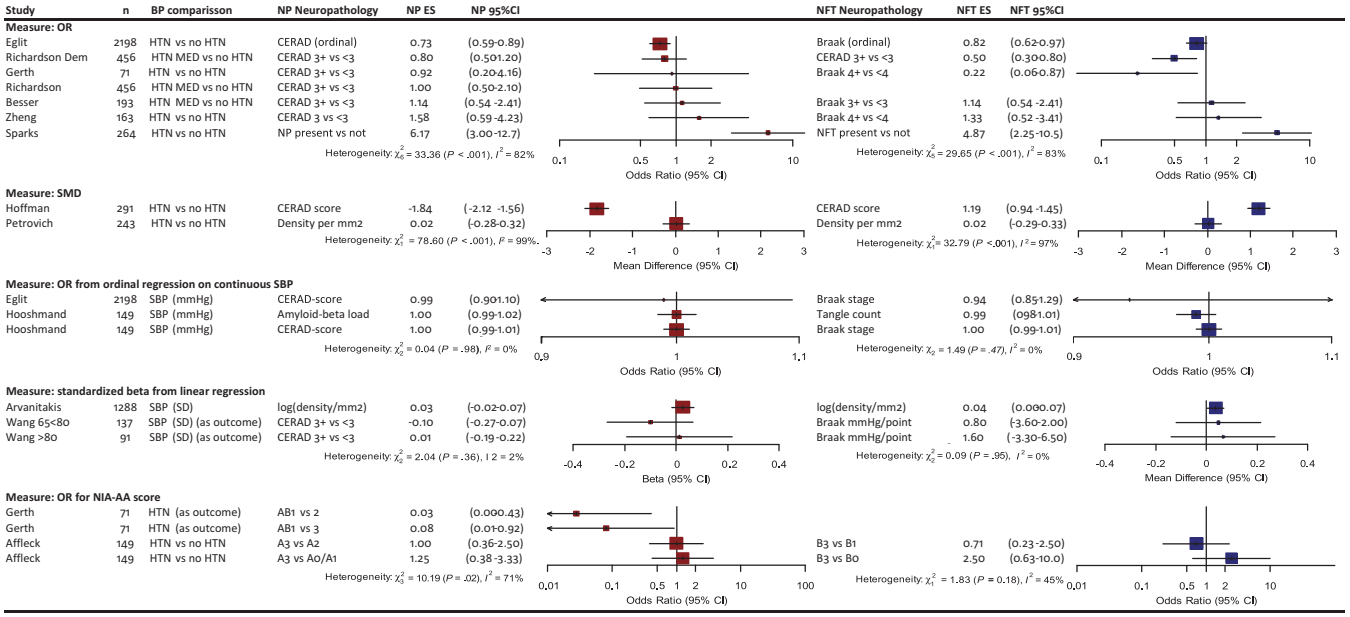

FIGURE 2 Associations for the estimated risk of NP and NFT. Studies were grouped based on the statistical methods used. Point estimates for Eglit et al.[28] represent the direct associations for hypertension in a mediation analysis wherein there also was a significant positive relation between hypertension and NP/NFT trough circle of Willis atherosclerosis. BP, blood pressure; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; DBP, diastolic blood pressure; ES, effect size; HTN, hypertension; HTN MED, medicated hypertension; NFT, neurofibrillary tangles; NP, neuritic plaques; SD, standard deviation; SMD, standardized mean difference; SBP, systolic blood pressure

although this study did significantly associate mid-life hypertension with more ADNC, despite the modest sample size.[19] Only three studies reported evaluating non-linear relationships,[19,20,28] and only one fully presented results,[19] which suggested that both low and high BP were associated with more ADNC than moderately elevated levels. Foremost, studies may have established and analyzed hypertension and BP suboptimally, possibly diluting associations. One-third only used self-reported or retrospectively collected hypertension diagnoses from medical records, possibly obtaining inaccurate exposure data. Sixty percent only analyzed hypertension dichotomously and/or based on antihypertensive use, which may have diminished power and the ability to disentangle the potentially counteractive effects of BP and antihypertensive use. Two-thirds did not evaluate SBP and DBP separately, and only two studies assessed pulse pressure. None reported associations in different age categories and/or multiple time points separately, although one study did evaluate both mean and longitudinal slope of BP measurements over 8 years in old age,[20] finding potential differential associations with ADNC (positive and negative, respectively).

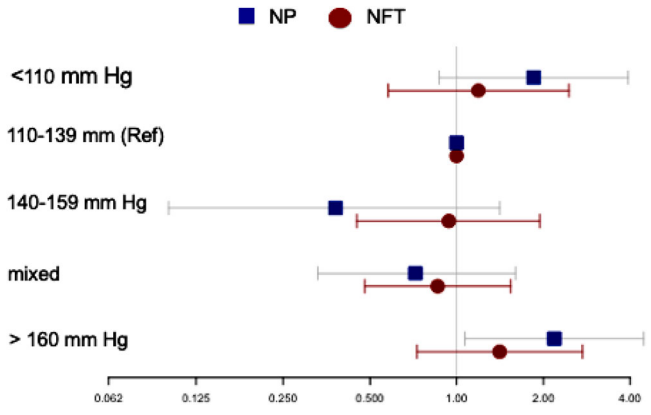

FIGURE 3 Potential U-shaped relation for systolic blood pressure and hippocampal neuropathology. Data from Petrovich et al.[19] Count ratios per categories based on midlife systolic blood pressure. NFT, neurofibrillary tangles; NP, neuritic plaques

The varying methods of assessing neuropathology may also have contributed to the heterogeneous findings. These have evolved with time, and analyzing neuropathology has particular challenges.[36] Most studies assessed NP and NFT density continuously, which is likely optimal for statistical power. Many additionally analyzed CERAD and Braak scores, which may be important, both because of their ubiquitous use and the step-wise implication of different cerebral regions in the neurodegenerative process. Their semi-continuous nature makes them less suitable as linear regression outcomes,[37] and studies mostly used group comparisons or logistic regression with dichotomized scores as outcome. This may have less power than alternative methods such as ordinal/Poisson regression, which can also analyze ordinal categorizations, although requiring a dose-response–like relationship. Alternatively, BP can be used as outcome predicted by neuropathological measures, as done in one study.[25] This has the advantage that BP is generally normally distributed and therefore more suitable as outcome in linear regression, and that neuropathological data can easily be analyzed both as categorical or continuous dose-response–type predictor. However, this does make interpretation and

comparison to other study results, which generally used NP as outcome, challenging.

4.2 | Literature comparison

Our findings suggested that AHM use was associated with less ADNC, seemingly irrespective of BP levels, and that long-term antihypertensive use may protect against the formation of ADNC.[24] Correspondingly, randomized and observational studies suggests that BP lowering reduces dementia risk,[38,39] and epidemiological studies suggest that AHM may even reduce dementia risk beyond the effects of BP lowering.[39–42] The mechanisms explaining these associations are unknown. Studies suggest that reducing BP (variability), influencing the renin–angiotensin system, and/or modulating intracellular calcium homeostasis, may protect against neural damage caused by vascular changes, increased blood–brain barrier permeability, inflammation, or ischemia, potentially through specific AHM class effects.[39–44] However, observational biases may also play a role.[39–44]

Next to gold-standard neuropathological data, in vivo ADNC-related biomarkers obtained from imaging and cerebrospinal fluid (CSF) may provide valuable context, because they allow investigating the relation between BP and ADNC during life, before the effects of old age and dementia. Cross-sectionally, early studies in cognitively healthy people (range n = 32–118) reported significant positive relations between hypertension and positron emission tomography amyloid burden,[45,46] but subsequent and larger (range n = 256–465) community-based studies did not replicate these findings.[47–49] The relation seems particularly absent in mid life and cognitively healthy individuals, despite associations of hypertension with atrophy and small vessel disease (SVD) already being manifest.[47,50] Longitudinally, studies found no clear relation between mid-life BP and older age amyloid deposition,[48–50] and BP in old age also does not predict amyloid deposition development.[51] Tau imaging is relatively novel. One cross-sectional analysis of 120 cognitively healthy older individuals reported no relationships between BP nor antihypertensive medication with tau deposition.[52] Studies (range n = 152–430) have reported positive relationships between vascular risk scores and tau levels in non-demented older populations,[48,53] but others in middle-aged and old-aged (range n = 87–120) cognitively healthy populations did not replicate these findings.[52,54]

Interpreting CSF biomarkers needs extra care, as their correlations with ADNC may be more precarious, especially in later dementia stages.[55] However, they might provide clues regarding the mechanism linking hypertension to neurodegeneration through cerebrovascular damage. Studies in cognitively healthy older individuals and memory clinic populations (n = 391–618) suggest that hypertension and cerebrovascular damage are associated with tau but not isolated amyloid accumulation, and that tau in combination with cerebrovascular damage mediates the relation between vascular risk and cognitive impairment.[55–57]

This would fit results of the single mediation study in our review, which found that a positive relation between hypertension and (particularly) NFT was mediated by (circle of Willis) atherosclerosis, also suggesting that cerebrovascular damage may precede ADNC.[28] Other studies in our review also investigated concurrent associations of cerebrovascular pathology with hypertension and/or ADNC, generally finding positive associations specifically with microinfarcts.[19,22,25,26,29,31,33] Microinfarcts were also the most consistently associated with concomitant ADNC. The association of hypertension and atherosclerosis with ADNC was reported relatively inconsistently, and possibly mostly appeared in dementia patients.[26,28,33] With regard to hypertension potentially being more related to tau rather than amyloid accumulation,[55–57] differential relations for hypertension with amyloid and tau pathology did not clearly appear in our results. Studies reported stronger associations with tau,[19,20] but also amyloid.[21,28,33] One suggested that NFT may be particularly associated with DBP, and NP with SBP.[19] But other studies distinguishing SBP and DBP did not find indications for such differences. ADNC were generally less common in individuals with coronary artery disease,[21,23,24] particularly NFT.[21] Together with findings on microinfarctions, this might suggest a distinction between individuals who have hypertension affecting the greater vessels versus those who develop cerebral microvascular pathology.

4.3 | Recommendations for future studies

Although our review tenuously suggests a relationship between hypertension and ADNC, possibly preceded/mediated by cerebrovascular disease, the extensive methodological heterogeneity impedes strong inferences. More aligned statistical approaches would facilitate comparability. Regarding hypertension, we recommend modeling SBP and DBP as continuous variables to optimize statistical power, in distinct age subgroups, possibly at multiple time points to assess change/slope. The influence of AHM (including class effects) and potential non-linear relationships (e.g., using quartiles or plots) warrants more investigation.

Statistically analyzing neuropathology measures is challenging, and consensus on optimal methods and brain areas to include is seemingly needed. Until then, analyzing both overall continuous NFT/NP density and Braak/CERAD staging as outcomes appears optimal for statistical power and comparability to previous literature.

Assessing interactions among hypertension, cerebrovascular pathology, NP, and NFT may provide clues about the mechanisms relating hypertension to dementia. Path analyses may clarify how cerebrovascular pathology, NP, and NFT mediate the relationship between hypertension and dementia in more detail.

Regarding population, attention needs to be paid to interactions/differences depending on cognitive status—both at BP measurement and the time of death—and the time lived with dementia. Also, the influence of age at death needs examination, as NP and NFT accumulate with aging, and hypertension may decrease life expectancy. Finally, all but one (small) study were performed in relatively ethnically homogeneous high-income country populations, with access to advanced health-care systems. This may limit generalizability of results

to low- and middle-income countries, and more diverse populations, with less access to cardiovascular care during life.

5 | CONCLUSION

Our findings suggest a positive association between hypertension and ADNC, but effects may be modest, and possibly attenuate with higher BP age. Overviewing the literature, the hypothesis emerges that hypertension-related ADNC form subsequently to cerebrovascular damage, particularly atherosclerosis or microvascular lesions. An alternative is that hypertension and ADNC increase dementia risk through distinct pathways, possibly synergically, which could also explain their association.[58,59] More well-powered studies need to disentangle these possibilities. Attention should be paid to differences between BP in mid life and at later age stages; potential non-linear relationships; cognitive status at BP measurement and death; potential modifying effects of AHM; and mediation/interaction effects among cerebrovascular disease, NFT, NP, and dementia.[59,60] Investigating (longitudinal) interactions among vascular damage, NFT, and NP may be key in understanding hypertension's role in dementia development.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Herrer Abdulrahman: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Jan Willem van Dalen: acquisition of data, analysis and interpretation of data, drafting of the manuscript. Melina den Brok: analysis and interpretation of data and critical revision of the manuscript. Caitlin S. Latimer: analysis and interpretation of data and critical revision of the manuscript. Eric B. Larson: analysis and interpretation of data, and critical revision of the manuscript. Edo Richard: concept and design, critical revision of the manuscript, drafting of the manuscript.

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REFERENCES

1. Fratiglioni L, De Ronchi D, Agüero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging*. 1999;15:365-375. https://doi.org/10.2165/00002512-199915050-00004
2. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol Rep*. 2015;67(2):195-203. https://doi.org/10.1016/j.pharep.2014.09.004
3. James BD, Wilson RS, Boyle PA, Trojanowski JQ, Bennett DA, Schneider JA. TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia. *Brain*. 2016;139(11):2983-2993. https://doi.org/10.1093/brain/aww224
4. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, Corrada MM. Multiple pathologies are common and related to dementia in the oldest-old: the 90+ Study. *Neurology*. 2015;85(6):535-542. https://doi.org/10.1212/WNL.0000000000001831
5. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol*. 2007;62(4):406-413. https://doi.org/10.1002/ana.21208
6. Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimers Res Ther*. 2015;7(1):21. https://doi.org/10.1186/s13195-015-0104-7
7. Iadecola C, Hypertension and dementia. *Hypertension*. 2014;64(1):3-5. https://doi.org/10.1161/HYPERTENSIONAHA.114.03040
8. Nagai M, Hoshide S, Kario K. Hypertension and dementia. *Am J Hypertens*. 2010;23(2):116-124. https://doi.org/10.1038/ajh.2009.212
9. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA*. 2019;322(6):535-545. https://doi.org/10.1001/jama.2019.10575
10. van Dalen JW, Brayne C, Crane PK, et al. Association of systolic blood pressure with dementia risk and the role of age, u-shaped associations, and mortality. *JAMA Intern Med*. 2022;182(2):142-152. https://doi.org/10.1001/jamainternmed.2021.7009
11. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487-499, ISSN 1474-4422. https://doi.org/10.1016/S1474-4422(05)70141-1
12. Sharp SI, Aarsland D, Day S, Sønnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry*. 2011;26(7):661-669. https://doi.org/10.1002/gps.2572
13. Skoog I, Gustafson D. Hypertension and related factors in the etiology of Alzheimer's disease. *Ann N Y Acad Sci*. 2002;977:29-36. https://doi.org/10.1111/j.1749-6632.2002.tb04796.x
14. Chui HC, Zheng L, Reed BR, et al. Vascular risk factors and Alzheimer's disease: are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. *Alz Res Therapy*. 2012;4(1):1. https://doi.org/10.1186/alzrt98
15. Lv YB, Zhu PF, Yin ZX, et al. A U-shaped association between blood pressure and cognitive impairment in Chinese elderly. *J Am Med Dir Assoc*. 2017;18(2):193.e7-193.e13. https://doi.org/10.1016/j.jamda.2016.11.011
16. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165. https://doi.org/10.1212/wnl.39.9.1159
17. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging*. 1995;16(3):271-278; discussion 278-84. https://doi.org/10.1016/0197-4580(95)00021-6
18. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011] Higgins JPT, Green S eds. [http://www.cochrane-handbook.org]
19. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging*. 2000;21(1):57-62. https://doi.org/10.1016/s0197-4580(00)00106-8
20. Arvanitakis Z, Capuano AW, Lamar M, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease

pathology. *Neurology*. 2018;91(6):e517-e525. https://doi.org/10.1212/WNL.0000000000005951
21. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *J Neurol Sci*. 1995;131(2):162-169. https://doi.org/10.1016/0022-510x(95)00105-b
22. Nation DA, Delano-Wood L, Bangen KJ, et al. Pulse pressure elevation predicts cerebrovascular disease in autopsy-confirmed Alzheimer's disease. *J Alzheimers Dis*. 2012;30(3):595-603. https://doi.org/10.3233/JAD-2012-111697
23. Besser LM, Alosco ML, Ramirez Gomez L, et al. Late-life vascular risk factors and Alzheimer disease neuropathology in individuals with normal cognition. *J Neuropathol Exp Neurol*. 2016;75(10):955-962. https://doi.org/10.1093/jnen/nlw072
24. Hoffman LB, Schmeidler J, Lesser GT, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. *Neurology*. 2009;72(20):1720-1726. https://doi.org/10.1212/01.wnl.0000345881.82856.d5
25. Wang LY, Larson EB, Sonnen JA, et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study. *J Am Geriatr Soc*. 2009;57(11):1975-1981. https://doi.org/10.1111/j.1532-5415.2009.02493.x
26. Zheng L, Vinters HV, Mack WJ, et al. Cerebral atherosclerosis is associated with cystic infarcts and microinfarcts but not Alzheimer pathologic changes. *Stroke*. 2013;44(10):2835-2841. https://doi.org/10.1161/STROKEAHA.113.0019450
27. Wharton W, Zhao L, Steenland K, et al. Neurofibrillary tangles and conversion to mild cognitive impairment with certain antihypertensives. *J Alzheimers Dis*. 2019;70(1):153-161. https://doi.org/10.3233/JAD-190011
28. Eglit GrahamML, Weigand AlexandraJ, et al. Hypertension and Alzheimer's disease: indirect effects through circle of Willis atherosclerosis. *Brain Commun*. 2020;2(2):fcaa114. https://doi.org/10.1093/braincomms/fcaa114
29. Richardson K, Stephan BC, Ince PG, et al. The neuropathology of vascular disease in the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Curr Alzheimer Res*. 2012;9(6):687-696. https://doi.org/10.2174/156720512801322654
30. Gerth J, Kumar S, et al. Modified amyloid variants in pathological subgroups of β-amyloidosis. *Ann Clin Transl Neurol*. 2018;5(7):815-831. https://doi.org/10.1002/acn3.577
31. Hooshmand B, Polvikoski T, Kivipelto M, et al. CAIDE dementia risk score, Alzheimer and cerebrovascular pathology: a population-based autopsy study. *J Intern Med*. 2018;283(6):597-603. https://doi.org/10.1111/joim.127360/bib>
32. Affleck AJ, Sachdev PS, Stevens J, Halliday GM. Antihypertensive medications ameliorate Alzheimer's disease pathology by slowing its propagation. *Alzheimers Dement (N Y)*. 2020;6(1):e12060. https://doi.org/10.1002/trc2.12060
33. Wijesinghe P, Shankar SK, Yasha TC, et al. Vascular contributions in Alzheimer's disease-related neuropathological changes: first autopsy evidence from a South Asian Aging Population. *J Alzheimers Dis*. 2016;54(4):1607-1618. https://doi.org/10.3233/JAD-160425
34. Buford TW. Hypertension and aging. *Ageing Res Rev*. 2016;26:96-111. https://doi.org/10.1016/j.arr.2016.01.007
35. Peters R, Peters J, Booth A, Anstey KJ. Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review. *Br J Psychiatry*. 2020;216(1):16-28. https://doi.org/10.1192/bjp.2019.156
36. van Dalen JW, Brayne C, Crane PK, et al. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. *JAMA Intern Med*. 2022;182(2):142-152. https://doi.org/10.1001/jamainternmed.2021.7009
37. Malek-Ahmadi M, Mufson EJ, Perez SE, Chen K. Statistical considerations for assessing cognition and neuropathology associations in preclinical Alzheimer's disease. *Biostat Epidemiol*. 2017;1(1):92-104. https://doi.org/10.1080/24709360.2017.1342186
38. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, et al, Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321(6):553-561. https://doi.org/10.1001/jama.2018.21442
39. Hughes D, Judge C, Murphy R, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323(19):1934-1944. https://doi.org/10.1001/jama.2020.4249
40. den Brok MGHE, van Dalen JW, Abdulrahman H, et al. Antihypertensive medication classes and the risk of dementia: a systematic review and network meta-analysis. *J Am Med Dir Assoc*. 2021;22(7):1386-1395.e15. https://doi.org/10.1016/j.jamda.2020.12.019
41. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19(1):61-70. https://doi.org/10.1016/S1474-4422(19)30393-X
42. Peters R, Yasar S, Anderson CS, et al. Investigation of antihypertensive class, dementia, and cognitive decline: a meta-analysis. *Neurology*. 2020;94(3):e267-e281. https://doi.org/10.1212/WNL.0000000000008732
43. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs*. 2015;29(2):113-130. https://doi.org/10.1007/s40263-015-0230-6
44. Yang W, Luo H, Ma Y, Si S, Zhao H. Effects of antihypertensive drugs on cognitive function in elderly patients with hypertension: a review. *Aging Dis*. 2021;12(3):841-851. Published 2021 Jun 1. https://doi.org/10.14336/AD.2020.1111
45. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Diaz-Arrastia R, Park DC. Risk factors for β-amyloid deposition in healthy aging: vascular and genetic effects. *JAMA Neurol*. 2013;70(5):600-606. https://doi.org/10.1001/jamaneurol.2013.1342
46. Langbaum JB, Chen K, Launer LJ, et al. Blood pressure is associated with higher brain amyloid burden and lower glucose metabolism in healthy late middle-age persons. *Neurobiol Aging*. 2012;33(4):827.e11-827.e8.27E19. https://doi.org/10.1016/j.neurobiolaging.2011.06.020
47. Jeon SY, Byun MS, Yi D, et al. Influence of hypertension on brain amyloid deposition and Alzheimer's disease signature neurodegeneration. *Neurobiol Aging*. 2019;75:62-70. https://doi.org/10.1016/j.neurobiolaging.2018.11.001
48. Vemuri P, Lesnick TG, Przybelski SA, et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann Neurol*. 2017;82:706-718. https://doi.org/10.1002/ana.25071
49. Gottesman RF, Schneider ALC, Zhou Y, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA*. 2017;317(14):1443-1450. https://jamanetwork.com/journals/jama/fullarticle/2616396. https://doi.org/10.1001/jama.2017.3090
50. Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study [published correction appears in Lancet Neurol. 2020 Jul;19(7):e6]. *Lancet Neurol*. 2019;18(10):942-952. https://doi.org/10.1016/S1474-4422(19)30228-5
51. Kemppainen N, Johansson J, Teuho J, et al. Brain amyloid load and its associations with cognition and vascular risk factors in FINGER Study. *Neurology*. 2018;90(3):e206-e213. https://doi.org/10.1212/WNL.0000000000004827
52. Köbe T, Gonneaud J, et al. Association of vascular risk factors with β-amyloid peptide and tau burdens in cognitively unimpaired individuals and its interaction with vascular medication use. *JAMA*

Netw Open. 2020;3(2):e1920780. Published 2020 Feb 5. https://doi.org/10.1001/jamanetworkopen.2019.20780

53. Rabin JS, Yang HS, Schultz AP, et al. Vascular risk and β-amyloid are synergistically associated with cortical tau. *Ann Neurol*. 2019;85(2):272-279. https://doi.org/10.1002/ana.25399
54. Bilgel M, Bannerjee A, Shafer A, An Y, Resnick SM. Vascular risk is not associated with PET measures of Alzheimer's disease neuropathology among cognitively normal older adults. *Neuroimage Rep*. 2021;1(4):100068. https://doi.org/10.1016/j.ynirp.2021.100068
55. Bos I, Vos SJB, Schindler SE, et al. Vascular risk factors are associated with longitudinal changes in cerebrospinal fluid tau markers and cognition in preclinical Alzheimer's disease. *Alzheimers Dement*. 2019;15(9):1149-1159. https://doi.org/10.1016/j.jalz.2019.04.015
56. Yu GX, Ou YN, Bi YL, et al. Tau pathologies mediate the associations of vascular risk burden with cognitive impairments in non-demented elders: the CABLE Study. *J Prev Alzheimers Dis*. 2022;9(1):136-143. https://doi.org/10.14283/jpad.2021.55
57. Laing KK, Simoes S, Baena-Caldas GP, et al. Cerebrovascular disease promotes tau pathology in Alzheimer's disease. *Brain Commun*. 2020;2(2):fcaa132. Published 2020 Aug 19. https://doi.org/10.1093/braincomms/fcaa132
58. Rabin JS, Schultz AP, Hedden T, et al. Interactive associations of vascular risk and β-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol*. 2018;75(9):1124-1131. https://doi.org/10.1001/jamaneurol.2018.1123
59. Mahinrad S, Sorond FA, Gorelick PB. Hypertension and cognitive dysfunction: a review of mechanisms, life-course observational studies and clinical trial results. *Rev Cardiovasc Med*. 2021;22(4):1429-1449. https://doi.org/10.31083/j.rcm2204148
60. Busche MA, Hyman BT. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat Neurosci*. 2020;23(10):1183-1193. https://doi.org/10.1038/s41593-020-0687-6

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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