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

Herrer Abdulrahman1,2 | Jan Willem van Dalen1,2 | Melina den Brok1,2 | Caitlin S. Latimer3 | Eric B. Larson4 | Edo Richard2,5

1Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands
2Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands
3Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA
4Kaiser Permanente Washington Health Research Institute Seattle, Seattle, Washington, USA
5Department of Public and Occupational Health, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence
Herrer Abdulrahman, Department of Neurology, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
E-mail: h.abdulrahman@amsterdamumc.nl

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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...
the association between hypertension and dementia. 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. 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. 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.

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.

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.
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. Two studies had a poor score (<2), 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...
| 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* | 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* | 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* | 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* | 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* | United States | Retrospectively after death | Residents of nursing homes and elder-living facilities in New York | Extracted from medical records | 291 | 40.2 | Death: 83.4 | Not reported |
| Affleck 2020* | Australia | Retrospectively after death | Community-dwelling older people | Extracted from database | 149 | 40.3 | Death: 88.0 | Not reported |
### 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*  | 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*    | 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    | 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    | 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 | 4 |
| Wang 2009      | 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)
| 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    | 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 | Sri Lanka | Retrospectively after death | Community-dwelling semi-urban population from Colombo | Not reported | – | 50 | 58.0 | BP: 72.1 | Not reported |
| Hooshmand 2018 | 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.25 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 mm² areas in four to six selected brain regions, expressed as counts/ratios per mm².19,20,21 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/mm²) 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 AO–A3) and NFT spread (ranging BO–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/mm²) 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*      | BL 2 FU measurements (2-3 years apart) | Not reported | 61/243 (25%) | Quantitative: NFT/NP counts selected regions (nr/mm²) | Bielschowsky |
| Arvanitakis 2018*    | At BL Annual FU | 134 (8)/ 71 (8) | 1122/1288 (87%) | Quantitative: NFT/NP counts selected regions (nr/mm²) | Modified silver |
| Richardson 2012*     | BL biennial FU (Up to 10 years) | N/a | 146/418 (35%) | Semi-quantitative: CERAD for NP and NFT | Not reported |
| Sparks 1995*         | Not reported | Not reported | Not reported | Quantitative: NFT/NP counts in 3 random cerebral regions (nr/mm²) | Bielschowsky PHF-1 antibody in subsample |
| Hoffman 2009*        | Not reported | Not reported | 77/291 (26.5%) | Quantitative: Mean NP density in 5 cortical regions (nr/mm²). Semi-quantitative: CERAD for NP and NFT | Hematoxylin eosin, modified Bielschowsky modified thioflavin S, anti-B amyloid, anti-tau when necessary |
| Affleck 2020*        | 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*        | 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*          | Not reported | 129 (18.9)/71 (10.7) | Not reported | Semi-quantitative: Braak for NFT, CERAD for NP | Bielschowsky Gallyas Tau immunostain Thioflavin-S |
### 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 thioflavine-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 immunohistochemical 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...
| 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 | Age at death APOE ε4 allele Anti-HT medication | 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 mm² | Hipocampal 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 | 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)
| 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-mediated 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 |
| 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), \( P = 0.03 \). Braak 3/4 vs. Braak 1/2 (ref) OR = 0.36 (0.03–3.43), \( P = 0.42 \) in RAS vs. non-RAS users. Braak 5 vs. Braak 1/2 (ref), OR = 0.18 (0.01–2.56), \( P = 0.21 \) in RAS vs. non-RAS users. CERAD 1 (definite) vs. 4 (no AD), OR = 0.66 (0.18–2.43), \( P = 0.53 \) CERAD 2 (probable) vs. 4, OR = 0.91 (0.24–3.53), \( P = 0.90 \) CERAD 3 (possible) vs. 4, OR = 0.29 (0.03–3.12), \( P = 0.31 \) | 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)
| Source          | Blood pressure operationalization                                      | Neuropathology operationalization                                           | Statistical analysis                          | Adjustments              | Study results                                                | Interpretation study results |
|----------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------|--------------------------|-------------------------------------------------------------|----------------------------|
| Nation 2012    | Use of anti-hypertension medication (yes/no).                          | Braak < VI vs. Braak VI                                                    | Logistic regression:                         | Age                      | No significant associations between BP measures and ADNP after correcting for multiple comparisons |
|                | Mean SBP and DBP (continuous)                                          |                                                                              | Predictor: SBP/DBP                          | Education                |                                                                            |                            |
|                | Pulse pressure (continuous).                                            |                                                                              | Outcome: NFT; low and high Braak stages.   | DRS-score                |                                                                            |                            |
|                | Average of two consecutive BP at one study visit                       |                                                                              | Linear regression:                         | Time-to-death Use of anti-HT APOE ε4 presence ≥ 2 vascular risk factors |
|                |                                                                        |                                                                              | Predictor: BP Outcome: Braak stage severity |                          |                                                                            |                            |
| Besser 2016    | History of hypertension (yes/no)                                       | Dichotomization of NFT/NP: Positive: Braak II–VI and moderate-frequent NP Negative: Braak 0-II and absent-sparse NP. | Logistic regression:                         | Age at death              | No association between late-life PP and ADNP               | No association between late-life PP and ADNP                          |
|                |pulse pressure (continuous)                                             |                                                                              | Predictor: history of hypertension Outcome: presence/absence of NFT/NP | Sex                      |                                                                            |                            |
| Wang 2009      | SBP and DBP (continuous)                                               | NFT: Braak stages (I–II, III–IV, V–VI)                                      | Linear regression:                         | Age at entry              | No significant associations between hypertension and ADNP | No significant association between hypertension and Braak stages or CERAD-score |
|                | Baseline BP measurement                                                | NP: CERAD scores (none/sparse/moderate/frequent)                           | Predictor: NFT/DP                          | Sex                      |                                                                            |                            |
|                |                                                                        |                                                                              | Outcome: SBP/DBP                           | Time-to-death             |                                                                            |                            |
| Zheng 2013     | History of hypertension (yes/no)                                       | NFT: Braak stages (I–II, III–IV, V–VI)                                      | Ordinal regression:                        | Age at death              | No significant associations between hypertension and ADNP | No significant associations between hypertension and NFT/NP             |
|                |                                                                        | NP: CERAD scores (none, sparse moderate frequent)                          | Predictor: history of hypertension Outcome: ordinal Braak stages and CERAD scores | Sex                      |                                                                            |                            |
|                |                                                                        |                                                                              |                                                                              | Ethnicity                |                                                                            |                            |
|                |                                                                        |                                                                              |                                                                              | Years of education        |                                                                            |                            |
| 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:                         | Age                      | No significant associations between hypertension and ADNP | No significant associations between hypertension and NFT/NP             |
|                |                                                                        |                                                                              | Predictor: history of hypertension Outcome: dichotomized Braak stages (I vs. II; III vs. VI; and 0–III vs. IV–VI) and CERAD stages (none vs. CERAD A–C) | Sex                      |                                                                            |                            |

(Continues)
| 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:                  | Age         | No significant associations between hypertension and ADNP                    | No significant associations between hypertension and NFT/NP |
|               |                                  |                                  | Predictor: hypertension Outcome: NP   | Sex         |                                                                              |                              |
|               |                                  |                                  | Linear regression:                    |             |                                                                              |                              |
|               |                                  |                                  | Predictor: hypertension Outcome: 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: | Follow-up time | No significant associations between hypertension and ADNP                    | No associations between BP and AD-neuropathology |
|               |                                  |                                  | Predictor: SBP and DBP outcome: NP/NFT |             |                                                                              |                              |

*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.

3.7 Non-linear relationships

Three studies reported assessing non-linear relationships between BP and ADNC, but only one provided detailed results. This study suggested a potential J-shaped relationship between mid-life SBP 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, and statistical analyses. Selection bias may have influenced our findings. While BP may have been influenced by the time of assessment, BP often declines with cognitive symptoms in late life, or using life-time BP in individuals with cognitive symptoms may have biased our results. Conversely, studies in mainly cognitively healthy older participants may have overestimated the role of hypertension. Interpreting the results of our systematic review is complex.

4 DISCUSSION

Four studies, representing 48% 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.
although this study did significantly associate mid-life hypertension with more ADNC, despite the modest sample size. Only three studies reported evaluating non-linear relationships, and only one fully presented results, 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 assessment.

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. 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, 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. 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

### 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. represent the direct associations for hypertension in a mediation analysis wherein there also was a significant positive relation between hypertension and NFT/NF through cirrhosis. 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.

### FIGURE 3
Potential U-shaped relation for systolic blood pressure and hippocampal neuropathology. Data from Petrovich et al. Count ratios per categories based on midlife systolic blood pressure. NFT, neurofibrillary tangles; NP, neuritic plaques.
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 anti-hypertensive use may protect against the formation of ADNC. Correspondingly, randomized and observational studies suggest that BP lowering reduces dementia risk, and epidemiological studies suggest that AHM may even reduce dementia risk beyond the effects of BP lowering. 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. However, observational biases may also play a role.

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, but subsequent and larger (range n = 256–465) community-based studies did not replicate these findings. 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. Longitudinally, studies found no clear relation between mid-life BP and older age amyloid deposition, and BP in old age also does not predict amyloid deposition development. 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. Studies (range n = 152–430) have reported positive relationships between vascular risk scores and tau levels in non-demented older populations, but others in middle-aged and old-aged (range n = 87–120) cognitively healthy populations did not replicate these findings.

Interpreting CSF biomarkers needs extra care, as their correlations with ADNC may be more precarious, especially in later dementia stages. 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.

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. Other studies in our review also investigated concurrent associations of cerebrovascular pathology with hypertension and/or ADNC, generally finding positive associations specifically with microinfarcts. 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. With regard to hypertension potentially being more related to tau rather than amyloid accumulation, differential relations for hypertension with amyloid and tau pathology did not clearly appear in our results. Studies reported stronger associations with tau, but also amyloid. One suggested that NFT may be particularly associated with DBP, and NP with SBP. 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, particularly NFT. 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

Herrr 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. Edo Richard: concept and design, critical revision of the manuscript, drafting of the manuscript.

ORCID

Herrr Abdulrahman https://orcid.org/0000-0002-1248-2567

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**SUPPORTING INFORMATION**

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