

# BRAIN COMMUNICATIONS

## Hypertension and Alzheimer's disease: indirect effects through circle of Willis atherosclerosis

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Hypertension is common among older adults and is believed to increase susceptibility to Alzheimer's disease, but mechanisms underlying this relationship are unclear. Hypertension also promotes circle of Willis atherosclerosis, which contributes to cerebral hypoperfusion and arterial wall stiffening, two potential mechanisms linking hypertension to Alzheimer's disease. To examine the role of circle of Willis atherosclerosis in the association between hypertension and Alzheimer's disease neuropathology, we analysed post-mortem neuropathological data on 2198 decedents from the National Alzheimer's Coordinating Center database [mean (standard deviation) age at last visit 80.51 (1.95) and 47.1% female] using joint simultaneous (i.e. mediation) modelling. Within the overall sample and among Alzheimer's dementia decedents, hypertension was indirectly associated with increased neuritic plaques and neurofibrillary tangles through its association with circle of Willis atherosclerosis. Similar indirect effects were observed for continuous measures of systolic and diastolic blood pressure. These results suggest that hypertension may promote Alzheimer's disease pathology indirectly through intracranial atherosclerosis by limiting cerebral blood flow and/or dampening perivascular clearance. Circle of Willis atherosclerosis may be an important point of convergence between vascular risk factors, cerebrovascular changes and Alzheimer's disease neuropathology.

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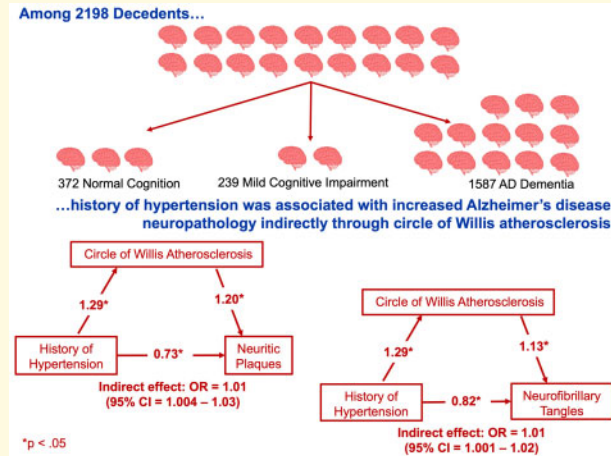
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**Keywords:** Alzheimer's disease; blood pressure; atherosclerosis; neuropathology; dementia

**Abbreviations:**  $A\beta$  = amyloid- $\beta$ ; ADC = Alzheimer's Disease Center; APOE  $\epsilon 4$  = apolipoprotein epsilon 4 allele; CI = confidence interval; MCI = mild cognitive impairment; NACC = National Alzheimer's Coordinating Center; NFT = neurofibrillary tangle; OR = odds ratio; UDS = Uniform Data Set

## Graphical Abstract



## Introduction

Hypertension is believed to increase susceptibility to Alzheimer's dementia (Skoog *et al.*, 1996; Launer *et al.*, 2000; Walker *et al.*, 2017). However, the role of vascular risk factors in Alzheimer's dementia pathophysiology remains unclear. Specifically, there is ongoing debate as to whether vascular risk factors contribute to the deposition of the neuritic plaques and neurofibrillary tangles (NFTs) that represent the pathological hallmarks of Alzheimer's dementia (Hyman *et al.*, 2012), lead to cerebrovascular changes that in turn lower the threshold for the clinical expression of Alzheimer's dementia pathology, or operate through both mechanisms (Zlokovic, 2011; Chui *et al.*, 2012).

Hypertension is among the most prevalent of these vascular risk factors, occurring in nearly one-third of adults and two-thirds of older adults worldwide (Mills *et al.*, 2016). Hypertension is a risk factor for Alzheimer's dementia (Walker *et al.*, 2017) and has been linked to increased amyloid- $\beta$  ( $A\beta$ ) plaque burden (Sparks *et al.*, 1995; Ashby *et al.*, 2016), parahippocampal NFT density (Sparks *et al.*, 1995) and *in vivo* brain imaging markers of  $A\beta$  deposition (Rodrigue *et al.*, 2013). In addition, elevated systolic and diastolic blood pressures have been associated with increased neuritic plaque density (Petrovitch *et al.*, 2000), NFT density (Petrovitch *et al.*, 2000; Arvanitakis *et al.*, 2018), *in vivo* brain markers of  $A\beta$  deposition (Langbaum *et al.*, 2012; Toledo *et al.*, 2012) and reduced glucose metabolism in Alzheimer's dementia-vulnerable brain regions (Langbaum *et al.*, 2012).

Several candidate mechanisms linking hypertension to Alzheimer's dementia have been proposed. Chronic hypertension promotes inward vascular remodelling (Heagerty *et al.*, 1993) and alters autoregulation mechanisms of the cerebrovasculature (Matsushita *et al.*, 1994;

Jennings *et al.*, 2005), rendering the brain susceptible to cerebral hypoperfusion and reduced blood-brain barrier integrity. This cerebrovascular dysfunction may in turn lead to  $A\beta$  oligomerization (Wang *et al.*, 2010), altered processing of the  $A\beta$  protein precursor (Tesco *et al.*, 2007; Zhang *et al.*, 2007; Li *et al.*, 2009; Koike *et al.*, 2010) and increased tau phosphorylation (Koike *et al.*, 2010). Cerebral deposition of  $A\beta$  may be further exacerbated by hypertension-induced upregulation of the receptor for advanced glycation end products, which mediates  $A\beta$  influx from blood circulation into the brain (Carnevale *et al.*, 2012). In addition to its effects on  $A\beta$  production and deposition, hypertension may also diminish  $A\beta$  clearance. Clearance of  $A\beta$  through the perivascular spaces is driven by recoil and reflection waves generated by the vessel wall (Schley *et al.*, 2006), which are dampened when arteries stiffen due to chronic hypertension (Mitchell, 2014). Furthermore, concentrations of the  $A\beta$ -degrading enzymes angiotensin-converting enzyme and insulin degrading enzyme are reduced among hypertensive individuals, leading to diminished  $A\beta$  catabolism (Miners *et al.*, 2011; Ashby *et al.*, 2016).

Hypertension is also a known contributor to atherosclerosis, especially of the circle of Willis (Ingall *et al.*, 1991). The circle of Willis is a ring of vessels surrounding the optic chiasm and pituitary stalk that connects the anterior and posterior circulations of the brain. According to the predominant response-to-injury model of atherosclerosis, elevated blood pressure causes swelling and stretching of blood vessel walls and consequent blood vessel endothelium injury, which in turn initiates a cascade of inflammatory events leading to atherosclerotic plaque formation (Ross, 1993). The circle of Willis may be especially vulnerable to atherosclerosis due to its curved shape and branching arteries, which tend to induce turbulent flow and increase endothelial injury (Chiu

and Chien, 2011). Circle of Willis atherosclerosis has itself been proposed as a risk factor for Alzheimer's dementia (Kalback *et al.*, 2004) and has been linked to increased neuritic plaque burden (Roher *et al.*, 2003; Honig *et al.*, 2005; Beach *et al.*, 2007; Yarchoan *et al.*, 2012), density of NFTs (Roher *et al.*, 2003; Beach *et al.*, 2007; Yarchoan *et al.*, 2012) and *in vivo* neuroimaging markers of amyloid deposition (Hughes *et al.*, 2014). Notably, some of the mechanisms linking hypertension to Alzheimer's dementia are believed to be at least partly mediated through intracranial atherosclerosis, including those involving reduced cerebral blood flow and impaired perivascular A $\beta$  clearance (Gupta and Iadecola, 2015). Taken together, this research suggests that the impact of hypertension on Alzheimer's dementia pathogenesis may indirectly involve intracranial atherosclerosis.

To our knowledge, no research has attempted to disentangle whether hypertension contributes to Alzheimer's dementia neuropathology directly or indirectly through intracranial atherosclerosis. Therefore, we used simultaneous joint statistical (i.e. mediation) modelling to investigate the direct effect of hypertension on Alzheimer's dementia neuropathology as well as the indirect effect of hypertension through circle of Willis atherosclerosis. We hypothesized that hypertension would be associated with increased neuritic plaque and NFT pathology indirectly through its association with circle of Willis atherosclerosis.

## Materials and methods

### Participants

Observational data from the National Alzheimer's Coordinating Center (NACC) database were used in this study. The NACC is a publicly available longitudinal dataset, with data collected from past and present National Institute on Aging-funded Alzheimer's Disease Centers (ADCs) across the USA. Recruitment procedures vary across ADCs and as such, the NACC database is best characterized as a referral-based or volunteer case series. For this study, clinical data were gathered from the Uniform Data Set (UDS) and neuropathological data from the Neuropathological Data Set. Research using the NACC database was approved by the University of Washington Institutional Review Board. Informed consent was obtained at participating ADCs.

This analysis used data from 32 ADCs. Decedents from the NACC database included in the current study were required to have both UDS and Neuropathological Data Set data available as of the June 2018 data freeze. Decedents were additionally excluded for the following reasons: (i) missing data on Alzheimer's dementia neuropathology variables, vascular neuropathology variables, vascular risk factor variables and demographic and clinical covariates; (ii) history of clinical stroke; and (iii)

clinical diagnosis other than normal cognition, mild cognitive impairment (MCI) or Alzheimer's dementia. After implementation of exclusion criteria, the final sample consisted of 2198 decedents [mean (standard deviation) age at last visit 80.51 (1.95) and 47.1% female] (see [Supplementary Table 1](#) for descriptive statistics of the total sample).

### Vascular risk factors

#### Hypertension

A combination of two measures from the NACC-UDS was used to determine hypertension diagnosis. The first of these measures was self-reported hypertension, for which the NACC-UDS provides three categories: absent, remote/inactive and recent/active. Decedents were deemed recent/active if they self-reported being currently hypertensive or if they still required active management and/or medication for hypertension, remote/inactive if they had a history of hypertension but were no longer hypertensive and not currently managing or taking anti-hypertensive medications and absent if they did not have a history of hypertension. The second was self-reported current use of anti-hypertensive medications. Decedents were classified as hypertensive if they (i) self-reported remote/inactive or recent/active hypertension or (ii) were currently using an anti-hypertensive medication. Continuous measures of systolic and diastolic blood pressure were available in a subset of the sample ( $n=1647$ ) and were evaluated in secondary analyses.

#### Other vascular risk factors

Several additional vascular risk factors are collected as part of the NACC-UDS, including history of hypercholesterolaemia, diabetes, heart attack, atrial fibrillation, congestive heart failure and transient ischaemic attack, as well as tobacco use within the past 30 days. All of these variables, with the exception of tobacco use within the past 30 days, are coded as absent, remote/inactive and recent/active. These variables were considered negative if absent and positive if remote/inactive or recent/active. All data on vascular risk factors, including hypertension-related variables, were obtained from each participant's last visit prior to death.

### Neuropathology

#### Alzheimer's disease neuropathology

Neuropathological evaluations were conducted by individual ADCs according to their own protocols. As such, these protocols may differ between ADCs but relied on consensus guidelines and were collected following a standardized Neuropathology Form and Coding Guidebook. Alzheimer's dementia neuropathology was graded according to Consortium to Establish a Registry for Alzheimer's Disease criteria for neuritic plaques (Mirra *et al.*, 1991) and Braak staging for NFTs (Braak

and Braak, 1991). Staining techniques differed across individual ADCs and included modified Bielschowsky, Gallyas stains, tau immunostains and other silver stains or thioflavin-S. Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque scores were graded as zero, mild, moderate or frequent. Neuritic plaques were evaluated in the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule and possibly hippocampus/entorhinal cortex and occipital cortex. Braak staging was re-coded from the original seven stages to a four-category classification to improve inter-rater reliability and to facilitate interpretation (Nagy et al., 1998; Hyman et al., 2012). These categories were Braak Stage 0, Braak Stages I and II, Braak Stages III and IV, and Braak Stages V and VI. NFTs for Braak staging were evaluated in the transentorhinal/entorhinal region for Braak Stage I/II, limbic regions for Braak Stage III/IV, and neocortical regions including primary cortices for Braak Stage V/VI (Braak and Braak, 1991; Nagy et al., 1998).

### Vascular neuropathology

The NACC-Neuropathological Data Set provides separate variables for circle of Willis atherosclerosis, cerebral amyloid angiopathy (CAA), infarcts/lacunae and microinfarcts. Circle of Willis atherosclerosis and CAA were rated as none, sparse (mild), moderate and frequent (severe). For atherosclerotic vascular pathology, ratings were based on the severity of intimal and medial fibrofatty atheromatous plaques in the circle of Willis. The assessment was qualitative and subjective and reflected an estimate of overall severity rather than with respect to an individual vessel. CAA was detected using amyloid stains (e.g. Congo red, thioflavin-S or A $\beta$  immunostaining) in accordance with individual ADC protocols. For neuropathological evaluations prior to 2014, the assessment was qualitative and subjective and indicated an estimate of overall severity rather than an individual vessel. Further guidelines on grading severity were incorporated into the NACC Neuropathology Form and Coding Guidebook in January 2014. For post-2014 CAA semi-quantitative grading, none was defined as absent CAA, mild was defined as scattered positivity in parenchymal and/or leptomeningeal vessels, possibly in only one brain area, moderate was defined as intense positivity in many parenchymal and/or leptomeningeal vessels and severe was defined as widespread (more than one brain area) intense positivity in parenchymal and leptomeningeal vessels. Grossly observed infarcts/lacunae and microinfarcts were classified as absent or present. Prior to January 2014, acute and old infarcts/lacunae and microinfarcts were not distinguished and regions assessed were not formally recorded. After January 2014, only old infarcts/lacunae and microinfarcts were used for grading, which were evaluated in cerebral cortex, subcortical cerebral white matter and periventricular white matter, deep

cerebral grey matter or internal capsule and brainstem or cerebellum.

### Clinical diagnosis

All decedents received a clinical diagnosis at their last visit prior to death. Clinical diagnosis in the NACC database is based on multi-disciplinary consensus or clinical judgement using information from the comprehensive UDS evaluation. Clinical Dementia Rating Scale Sum of Boxes scores were available to further characterize disease severity across clinical groups.

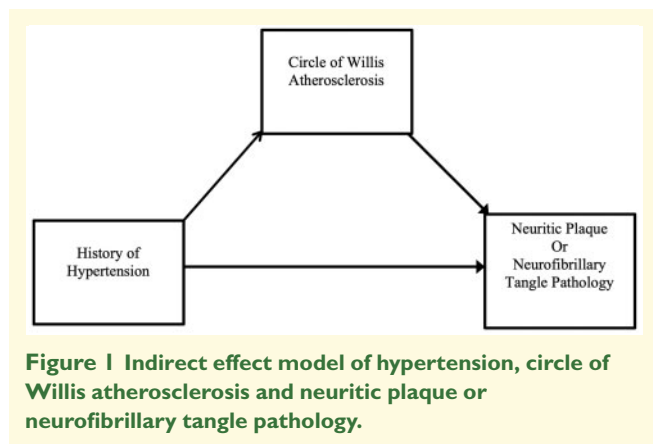
### Other covariates

Demographic characteristics of age at last visit, sex and race/ethnicity, as well as use of anti-hypertensive medications were collected as part of approximately annual UDS clinical evaluations. Owing to the small number of non-White decedents, race/ethnicity was classified as White versus non-White. Decedents with no apolipoprotein epsilon 4 allele (APOE  $\epsilon$ 4) were considered APOE  $\epsilon$ 4-negative and decedents with one or more  $\epsilon$ 4 alleles were considered APOE  $\epsilon$ 4-positive.

### Statistical analysis

Initial analyses compared clinical groups on demographic, disease severity, vascular risk factor and neuropathological characteristics using one-way ANOVA and chi-square tests.

Main analyses consisted of joint simultaneous (i.e. mediation) modelling of associations between hypertension, circle of Willis atherosclerosis and Alzheimer's dementia neuropathology. Alzheimer's dementia neuropathology was operationalized as either neuritic plaque or NFT pathology and models were specified separately for these two types of Alzheimer's dementia neuropathology. Mediation analysis involves simultaneous estimation of a set of regression coefficients in order to evaluate pathways of influence between several variables. This is achieved by partitioning the total effect of an exposure variable (e.g. hypertension) on an outcome (e.g. Alzheimer's dementia neuropathology) into an indirect effect through a mediator (e.g. circle of Willis atherosclerosis) and a direct effect of the exposure on the outcome. In the current study, the indirect effect of hypertension on Alzheimer's dementia neuropathology was mediated through circle of Willis atherosclerosis and the direct effect reflected the association of hypertension on Alzheimer's dementia neuropathology after adjusting for circle of Willis atherosclerosis. In the first regression equation, hypertension was entered to predict degree of circle of Willis atherosclerosis and in the second regression, hypertension and circle of Willis atherosclerosis were both included as predictors of neuritic plaque frequency or NFT density. Figure 1 presents a path diagram of modelled relationships between primary variables of interest. The indirect effect was calculated as the product



of the association of hypertension with circle of Willis atherosclerosis and of circle of Willis atherosclerosis with Alzheimer's dementia neuropathology. Given the well-known non-normality of product term distributions (MacKinnon *et al.*, 2007), a 95% bias-corrected bootstrapped confidence interval (CI) with 5000 bootstrap samples was used to evaluate indirect effect significance (Mackinnon *et al.*, 2004). Models were conducted in the overall sample as well as separately on cases stratified by clinical group (normal cognition, MCI and Alzheimer's dementia dementia). Both circle of Willis atherosclerosis and neuritic plaque/NFT neuropathology variables were treated as ordinal and a logit link function with maximum likelihood estimation was used for parameter estimation. Parameter estimates were exponentiated and expressed as odds ratios (ORs). All paths in all models were adjusted for age at last visit, sex, non-White race, APOE  $\epsilon 4$  positivity and presence of other vascular risk factors (hypercholesterolaemia, diabetes, current smoking, heart attack, atrial fibrillation, congestive heart failure and transient ischaemic attack). Owing to concerns about the consistency of neuropathological classifications across different ADCs, we also ran additional sensitivity analyses using alternative dichotomous classifications of circle of Willis atherosclerosis and Alzheimer's dementia neuropathology following procedures previously used within the NACC database (Graff-Radford *et al.*, 2016; Alosco *et al.*, 2017). All findings remained the same (see Supplementary Tables 2 and 3). Original four-category ordinal classifications were therefore retained due to their superior precision.

In follow-up models, we adjusted for the presence of infarcts, lacunes and microinfarcts and for CAA along all paths. In addition, in the subset of the sample with available blood pressure data, we explored the direct and indirect effects of continuous measures of systolic and diastolic blood pressure on Alzheimer's dementia neuropathology through circle of Willis atherosclerosis. Some research has suggested a quadratic relationship between late-life blood pressure and cognitive impairment, with

both lower and higher blood pressure associated with worse cognition (Glynn *et al.*, 1999; Morris *et al.*, 2002). Therefore, we tested for both linear and quadratic effects in these models. Blood pressure measurements were standardized to facilitate parameter interpretation and anti-hypertensive medication use was included as an additional covariate in these blood pressure models. Finally, to explore other neuropathologies commonly observed in Alzheimer's dementia, we also evaluated indirect effects of hypertension through circle of Willis atherosclerosis on diffuse amyloid-beta plaques and CAA.

Alpha level was set at  $P < 0.05$ , two-tailed for all tests. To address concerns about alpha rate inflation in the context of multiple statistical tests, Benjamini and Hochberg's procedure was used to control for the false discovery rate (Benjamini and Hochberg, 1995). False discovery rate was controlled at 0.05 and 0.10 and was applied separately to the overall sample and after stratification of the overall sample by clinical diagnosis. MPlus version 8.1 was used for joint simultaneous modelling.

## Data availability

The data used in this study are openly available upon request from the NACC at <https://www.alz.washington.edu>.

## Results

### Demographic, vascular risk factor and neuropathological characteristics

As expected, the Alzheimer's dementia group exhibited greater neuritic plaque and NFT pathology and was at a more advanced clinical stage on the Clinical Dementia Rating Scale Sum of Boxes than the normal cognition group, while the MCI group exhibited levels of Alzheimer's dementia neuropathology and clinical stage intermediate to the other two groups (see Table 1). In addition, individuals in the Alzheimer's dementia group were more likely to have at least one APOE  $\epsilon 4$  allele than the MCI and normal cognition groups. The Alzheimer's dementia group was less likely to have hypertension, diabetes, congestive heart failure and atrial fibrillation compared to MCI and normal cognition groups. Regarding vascular neuropathology, the Alzheimer's dementia group was less likely to have microinfarcts than the MCI group but had a greater degree of CAA than MCI and normal cognition groups. On demographic characteristics, the Alzheimer's dementia group was younger and less likely to be female than both MCI and normal cognition groups and slightly less educated than the normal cognition group.

**Table 1 Comparisons across clinical diagnostic groups**

	Normal cognition (n = 372)	MCI (n = 239)	Alzheimer's dementia (n = 1587)	Omnibus test	P-value
<b>Demographics</b>					
Age at last visit (years)	84.25 (9.49) <sup>3</sup>	86.64 (11.02) <sup>3</sup>	79.01 (10.89) <sup>1,2</sup>	$F(2,2195) = 56.29$	<0.001
Education (years)	15.59 (2.89) <sup>3</sup>	15.33 (3.04)	15.10 (3.25) <sup>1</sup>	$F(2,2182) = 3.66$	0.026
Interval between last visit and death (months)	11.80 (8.02)	12.11 (8.76)	12.02 (9.08)	$F(2,2195) = 0.11$	0.894
Sex (% female)	217 (58.3) <sup>3</sup>	122 (51.0) <sup>3</sup>	697 (43.9) <sup>1,2</sup>	$\chi^2 = (2,2198) = 26.77$	<0.001
Race/ethnicity (% non-Hispanic White)	14 (3.8)	6 (2.5)	89 (5.6)	$\chi^2 = (2,2198) = 5.59$	0.061
APOE $\epsilon 4+$ (% positive)	83 (22.3) <sup>3</sup>	63 (26.4) <sup>3</sup>	896 (56.5) <sup>1,2</sup>	$\chi^2 = (2,2198) = 188.58$	<0.001
Clinical Dementia Rating Scale sum of boxes	0.15 (0.51) <sup>2,3</sup>	1.83 (1.65) <sup>1,3</sup>	12.48 (5.08) <sup>1,2</sup>	$F(2,1644) = 1595.01$	<0.001
<b>Vascular risk factors</b>					
Hypertension (% positive)	307 (82.5) <sup>3</sup>	184 (77.0) <sup>3</sup>	1001 (63.1) <sup>1,2</sup>	$\chi^2 = (2,2198) = 53.96$	<0.001
Systolic blood pressure <sup>a</sup>	131.62 (19.09)	129.39 (17.91)	128.78 (19.82)	$F(2,1644) = 2.75$	0.064
Diastolic blood pressure <sup>a</sup>	70.75 (11.08)	71.34 (10.19)	72.01 (10.85)	$F(2,1644) = 1.84$	0.160
Diabetes (% positive)	57 (15.3) <sup>3</sup>	28 (11.7)	162 (10.2) <sup>1</sup>	$\chi^2 = (2,2198) = 7.97$	0.019
Hypercholesterolaemia (% positive)	195 (52.4)	121 (50.6)	840 (52.9)	$\chi^2 = (2,2198) = 0.45$	0.800
Congestive heart failure (% positive)	56 (15.1) <sup>3</sup>	35 (14.6) <sup>3</sup>	100 (6.3) <sup>1,2</sup>	$\chi^2 = (2,2198) = 41.08$	<0.001
Atrial fibrillation (% positive)	80 (21.5) <sup>3</sup>	46 (19.2) <sup>3</sup>	198 (12.5) <sup>1,2</sup>	$\chi^2 = (2,2198) = 23.88$	<0.001
Heart attack (% positive)	50 (13.4)	28 (11.7)	159 (10.0)	$\chi^2 = (2,2198) = 3.91$	0.141
Current smoking (% positive)	14 (3.8)	7 (2.9)	34 (2.1)	$\chi^2 = (2,2198) = 3.45$	0.179
Transient ischaemic attack (% positive)	35 (9.4)	29 (12.1)	128 (8.1)	$\chi^2 = (2,2198) = 4.57$	0.102
<b>Vascular neuropathology</b>					
Atherosclerosis				$\chi^2 = (6,2198) = 7.23$	0.300
None	73 (19.6)	43 (18.0)	344 (21.7)		
Mild	134 (36.0)	86 (36.0)	620 (39.1)		
Moderate	119 (32.0)	83 (34.7)	446 (28.1)		
Severe	46 (12.4)	27 (11.3)	177 (11.2)		
Cerebral amyloid angiopathy				$\chi^2 = (6,2198) = 166.61$	<0.001
None	209 (57.9)	130 (55.8)	445 (28.7)		
Mild	98 (27.1)	55 (23.6)	497 (32.1)		
Moderate	40 (11.1)	31 (13.3)	384 (24.8)		
Severe	14 (3.9)	17 (7.3)	224 (14.5)		
Infarcts/lacunae (% positive)	69 (18.5)	53 (22.2)	274 (17.3)	$\chi^2 = (2,2198) = 3.48$	0.176
Microinfarcts (% positive)	75 (20.2)	65 (27.2) <sup>3</sup>	278 (17.5) <sup>2</sup>	$\chi^2 = (2,2198) = 13.02$	0.001
<b>Alzheimer's disease neuropathology</b>					
Consortium to Establish a Registry for Alzheimer's Disease plaque score				$\chi^2 = (6,2198) = 551.08$	<0.001
None	170 (45.7)	70 (29.3)	127 (8.0)		
Sparse	85 (22.8)	62 (25.9)	152 (9.6)		
Moderate	70 (18.8)	56 (23.4)	305 (19.2)		
Frequent	47 (12.6)	51 (21.3)	1003 (63.2)		
Braak tangle stage				$\chi^2 = (2,2198) = 695.03$	<0.001
Stage 0	28 (7.5)	12 (5.0)	40 (2.5)		
Stages I–II	175 (47.0)	65 (27.2)	128 (8.1)		
Stages III–IV	140 (37.6)	109 (45.6)	276 (17.4)		
Stages V–VI	29 (7.8)	53 (22.2)	1143 (55.7)		

APOE  $\epsilon 4$  = apolipoprotein epsilon 4 allele; MCI = mild cognitive impairment.

Superscripts denote significant post-hoc differences between each diagnostic group and the class number indicated (1 = Normal Cognition, 2 = Mild Cognitive Impairment, 3 = Alzheimer's Dementia). <sup>a</sup>Based on sample of 1647 cases.

## Direct and indirect effects of hypertension on Alzheimer's disease neuropathology

In the overall sample, there were significant associations of hypertension with circle of Willis atherosclerosis ( $t = 2.707$ ,  $P = 0.007$ , OR = 1.29) and circle of Willis atherosclerosis with neuritic plaques ( $t = 3.643$ ,  $P < 0.001$ , OR = 1.20) and NFTs ( $t = 2.393$ ,  $P = 0.017$ , OR = 1.13), leading to significant indirect effects of hypertension on neuritic plaques (OR = 1.01, 95% CI = 1.004–

1.03) and NFTs (OR = 1.01, 95% CI = 1.001–1.02) (see Table 2). In addition, there was a significant negative association of hypertension with neuritic plaques ( $t = -3.074$ ,  $P = 0.002$ , OR = 0.73) and NFTs ( $t = -2.292$ ,  $P = 0.022$ , OR = 0.82) along the direct path. Thus, hypertension was associated with greater Alzheimer's dementia neuropathology through its effect on circle of Willis atherosclerosis, but after adjusting for this effect, was associated with less Alzheimer's dementia neuropathology

**Table 2** Direct and indirect effects of hypertension on circle of Willis atherosclerosis and Alzheimer's disease neuropathology

	HTN → atherosclerosis	Atherosclerosis → ADNP	HTN → ADNP	HTN → atherosclerosis → ADNP
Overall sample (N = 2198)				
Neuritic plaques	1.29 (1.07–1.54)**	1.20 (1.09–1.32)***	0.73 (0.59–0.89)**	1.01 (1.004–1.03)**
Neurofibrillary tangles	1.29 (1.07–1.54)**	1.13 (1.02–1.24)*	0.82 (0.62–0.97)*	1.01 (1.001–1.02)*
Alzheimer's dementia sample (N = 1587)				
Neuritic plaques	1.29 (1.05–1.58)*	1.31 (1.15–1.47)***	0.85 (0.67–1.04)	1.01 (1.003–1.03)*
Neurofibrillary tangles	1.29 (1.05–1.58)*	1.18 (1.03–1.35)*	0.94 (0.71–1.22)	1.01 (1.001–1.02)*
MCI sample (N = 239)				
Neuritic plaques	1.15 (0.54–2.50)	0.97 (0.69–1.36)	0.98 (0.45–2.18)	1.00 (0.95–1.03)
Neurofibrillary tangles	1.15 (0.54–2.50)	1.13 (0.76–1.58)	1.53 (0.66–3.27)	1.00 (0.98–1.05)
Normal cognition sample (N = 372)				
Neuritic plaques	1.63 (0.95–2.75)	1.00 (0.80–1.26)	0.70 (0.40–1.25)	1.00 (0.94–1.04)
Neurofibrillary tangles	1.63 (0.95–2.75)	0.85 (0.67–1.08)	0.98 (0.54–1.73)	0.99 (0.94–1.003)

All analyses adjusted for age, sex, APOE ε4, non-White race and other vascular risk factors; parenthetical values for the HTN → atherosclerosis → ADNP path reflect a 95% bias-corrected bootstrapped confidence interval; ADNP = Alzheimer's disease neuropathology; HTN = hypertension; MCI = mild cognitive impairment.

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

through its direct effect. Statistical significance of all of the results described above was retained using a 0.05 false discovery rate.

After stratification by clinical group, there were again significant associations of hypertension with circle of Willis atherosclerosis ( $t=2.471$ ,  $P = 0.013$ , OR = 1.29) and of circle of Willis atherosclerosis with neuritic plaques ( $t=4.290$ ,  $P < 0.001$ , OR = 1.31) and NFTs ( $t=2.382$ ,  $P = 0.017$ , OR = 1.18), leading to significant indirect effects of hypertension on neuritic plaques (OR = 1.01, 95% CI = 1.003–1.03) and NFTs (OR = 1.01, 95% CI = 1.001–1.02). However, hypertension was not associated with neuritic plaques or NFTs along the direct path. In addition, there were no significant direct or indirect effects within MCI or normal cognition groups. After correction for false discovery rate at 0.05, only the association between circle of Willis atherosclerosis and neuritic plaques remained significant. No additional associations were significant when false discovery rate was controlled at 0.10.

Adjustment for the presence of infarcts, lacunes or microinfarcts (see [Supplementary Table 4](#)) and for CAA (see [Supplementary Table 5](#)) had minimal impact on modelled associations.

## Direct and indirect effects of blood pressure on Alzheimer's disease neuropathology

In the overall sample, there were no significant linear or quadratic effects of systolic blood pressure on neuritic plaques or NFTs along the direct pathway, nor was there a significant quadratic effect of hypertension on circle of Willis atherosclerosis (see [Table 3](#)). In contrast, there were significant linear associations of systolic blood pressure with circle of Willis atherosclerosis ( $t=2.643$ ,  $P = 0.008$ , OR = 1.13) and of circle of Willis atherosclerosis

with neuritic plaques ( $t=2.989$ ,  $P = 0.003$ , OR = 1.19) and NFTs ( $t=2.243$ ,  $P = 0.025$ , OR = 1.14), resulting in significant indirect effects of hypertension on neuritic plaques (OR = 1.01, 95% CI = 1.001–1.01) and NFTs (OR = 1.003, 95% CI = 1.001–1.01) through circle of Willis atherosclerosis. All significant associations described above remained significant when false discovery rate was set at 0.10. In contrast, only associations between systolic blood pressure and circle of Willis atherosclerosis and of circle of Willis atherosclerosis with neuritic plaques remained significant when false discovery rate was limited to 0.05.

Similarly, within the Alzheimer's dementia group, there was a significant positive linear association of systolic blood pressure with circle of Willis atherosclerosis ( $t=2.211$ ,  $P = 0.027$ , OR = 1.13) and a significant positive association of circle of Willis atherosclerosis with neuritic plaques ( $t=3.788$ ,  $P < 0.001$ , OR = 1.34) and NFTs ( $t=2.393$ ,  $P = 0.017$ , OR = 1.22), leading to significant indirect effects of systolic blood pressure through circle of Willis atherosclerosis on both neuritic plaques (OR = 1.01, 95% CI = 1.001–1.02) and NFTs (OR = 1.003, 95% CI = 1.001–1.01). However, there were no significant quadratic effects of systolic blood pressure on circle of Willis atherosclerosis and neither quadratic nor linear associations of systolic blood pressure with neuritic plaques or NFTs were significant along the direct path. Only the association of circle of Willis atherosclerosis with neuritic plaque pathology remained significant after false discovery rate correction at 0.05 and 0.10.

For diastolic blood pressure in the overall sample, there was a significant quadratic association between hypertension and neuritic plaque pathology ( $t = -2.053$ ,  $P = 0.040$ , OR = 0.95) along the direct pathway, in which high (82.49 mm Hg) ( $t = -2.092$ ,  $P = 0.036$ ) but not average (71.67 mm Hg) ( $t=0.000$ ,  $P = 1.000$ ) or low (60.85 mm Hg) ( $t=0.240$ ,  $P = 0.810$ ) diastolic blood pressure was associated with less neuritic plaque

**Table 3** Direct and indirect effects of systolic blood pressure on circle of Willis atherosclerosis and Alzheimer's disease neuropathology

	HTN → atherosclerosis	Atherosclerosis → ADNP	HTN → ADNP	HTN → atherosclerosis → ADNP
Overall sample (N = 1647)				
Neuritic plaques	1.13 (1.03–1.23)**	1.19 (1.03–1.23)**	0.99 (0.90–1.10)	1.01 (1.001–1.01)*
Neurofibrillary tangles	1.13 (1.03–1.23)**	1.14 (1.01–1.29)*	0.94 (0.85–1.29)	1.003 (1.001–1.01)*
Alzheimer's dementia sample (N = 1114)				
Neuritic plaques	1.13 (1.02–1.26)*	1.34 (1.15–1.57)***	0.95 (0.83–1.08)	1.01 (1.001–1.02)*
Neurofibrillary tangles	1.13 (1.02–1.26)*	1.22 (1.03–1.42)*	0.92 (0.81–1.06)	1.003 (1.001–1.01)*
MCI sample (N = 198)				
Neuritic plaques	1.15 (0.82–1.58)	0.85 (0.58–1.26)	1.34 (0.94–1.77)	0.99 (0.95–1.01)
Neurofibrillary tangles	1.15 (0.82–1.58)	1.10 (0.72–1.61)	1.24 (0.87–1.70)	1.00 (0.99–1.03)
Normal cognition sample (N = 335)				
Neuritic plaques	1.21 (0.96–1.52)	0.97 (0.76–1.23)	1.18 (0.94–1.49)	1.00 (0.97–1.01)
Neurofibrillary tangles	1.21 (0.96–1.52)	0.85 (0.66–1.10)	1.09 (0.86–1.38)	0.99 (0.98–1.001)

All analyses adjusted for age, sex, presence of APOE ε4 allele, non-White race, other vascular risk factors and use of any anti-hypertensive medication; parenthetical values for the HTN → atherosclerosis → ADNP path reflect a 95% bias-corrected bootstrapped confidence interval; ADNP = Alzheimer's disease neuropathology; HTN = hypertension; MCI = mild cognitive impairment.

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

**Table 4** Direct and indirect linear effects of diastolic blood pressure on circle of Willis atherosclerosis and Alzheimer's disease neuropathology

	HTN → atherosclerosis	Atherosclerosis → ADNP	HTN → ADNP	HTN → atherosclerosis → ADNP
Overall sample (N = 1647)				
Neuritic plaques	1.11 (1.00–1.23)	1.20 (1.07–1.35)**	0.94 (0.84–1.03) <sup>a</sup>	1.01 (1.00–1.01)
Neurofibrillary tangles	1.11 (1.00–1.23)	1.14 (1.01–1.28)*	0.92 (0.83–1.03)	1.01 (1.00–1.01)
Alzheimer's dementia sample (N = 1114)				
Neuritic plaques	1.14 (1.001–1.28)*	1.35 (1.16–1.57)***	0.89 (0.76–1.003) <sup>b</sup>	1.01 (1.001–1.02)*
Neurofibrillary tangles	1.14 (1.001–1.28)*	1.22 (1.04–1.43)*	0.89 (0.77–1.02)	1.004 (1.001–1.01)*
MCI sample (N = 198)				
Neuritic plaques	1.06 (0.72–1.51)	0.86 (0.59–1.27)	1.25 (0.87–1.74)	1.00 (0.96–1.01)
Neurofibrillary tangles	1.06 (0.72–1.51)	1.11 (0.73–1.62)	1.15 (0.80–1.66)	1.00 (0.99–1.02)
Normal cognition sample (N = 335)				
Neuritic plaques	1.06 (0.83–1.31)	0.98 (0.77–1.25)	0.95 (0.75–1.20)	1.00 (0.99–1.01)
Neurofibrillary tangles	1.06 (0.83–1.31)	0.86 (0.67–1.11)	0.90 (0.73–1.14)	1.00 (0.99–1.003)

All analyses adjusted for age, sex, presence of APOE ε4 allele, non-White race, other vascular risk factors and use of any anti-hypertensive medication; parenthetical values for the HTN → atherosclerosis → ADNP path reflect a 95% bias-corrected bootstrapped confidence interval; ADNP = Alzheimer's disease neuropathology; HTN = hypertension; MCI = mild cognitive impairment.

<sup>a</sup>A significant non-linear direct effect of diastolic blood pressure on neuritic plaques was included in this model ( $t = -2.053$ ,  $P = 0.029$ ,  $OR = 0.94$ ).

<sup>b</sup>A significant non-linear direct effect of diastolic blood pressure on neuritic plaques was included in this model ( $t = -2.186$ ,  $P = 0.04$ ,  $OR = 0.95$ ).

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

pathology (see Table 4). In contrast, neither quadratic associations between diastolic blood pressure and NFTs nor linear associations between diastolic blood pressure and neuritic plaques and NFTs were significant. Along the indirect pathway, there were significant associations of circle of Willis atherosclerosis with neuritic plaques ( $t = 3.140$ ,  $P = 0.002$ ,  $OR = 1.20$ ) and NFTs ( $t = 2.350$ ,  $P = 0.019$ ,  $OR = 1.14$ ); however, associations of hypertension with circle of Willis atherosclerosis failed to achieve significance ( $t = 1.952$ ,  $P = 0.051$ ,  $OR = 1.11$ ), leading to non-significant indirect effects of diastolic blood pressure on neuritic plaques ( $OR = 1.01$ , 95%  $CI = 1.00–1.01$ ) and NFTs ( $OR = 1.01$ , 95%  $CI = 1.00–1.01$ ). Significant associations of circle of Willis atherosclerosis with neuritic plaques and NFTs were maintained

at a false discovery rate of 0.10. In contrast, only the association between circle of Willis atherosclerosis and neuritic plaques was maintained at false discovery rate of 0.05.

After stratification by clinical diagnosis, linear direct effects on neuritic plaques and NFTs were again non-significant within the Alzheimer's dementia group (see Table 4). There was, however, a significant negative quadratic association of diastolic blood pressure with neuritic plaques ( $t = -2.186$ ,  $P = 0.029$ ,  $OR = 0.94$ ), in which diastolic blood pressure was associated with less neuritic plaque pathology at high diastolic blood pressure levels ( $>82.86$  mm Hg) ( $t = -2.730$ ,  $P = 0.006$ ,  $OR = 0.83$ ), but not at average (72.01 mm Hg) ( $t = -1.730$ ,  $P = 0.084$ ,  $OR = 1.00$ ) or low levels (61.16 mm Hg)



**Table 5** Direct and indirect effects of hypertension on circle of Willis atherosclerosis and diffuse amyloid plaques and cerebral amyloid angiopathy

	HTN → atherosclerosis	Atherosclerosis → ADNP	HTN → ADNP	HTN → atherosclerosis → ADNP
Overall sample (N = 2007 for diffuse plaques, N = 2198 for CAA)				
Diffuse plaques	1.29 (1.07–1.54)**	1.16 (1.05–1.29)**	0.83 (0.67–1.03)	1.01 (1.002–1.02)*
CAA	1.29 (1.07–1.54)**	1.11 (1.001–1.21)*	0.78 (0.65–0.95)*	1.01 (1.001–1.02)*
Alzheimer's dementia sample (N = 1458 for diffuse plaques, N = 1587 for CAA)				
Diffuse plaques	1.29 (1.05–1.58)*	1.18 (1.03–1.35)*	0.91 (0.70–1.18)	1.01 (1.001–1.02)*
CAA	1.29 (1.05–1.58)*	1.13 (1.01–1.26)*	0.83 (0.67–1.03)	1.01 (1.001–1.02)*
MCI sample (N = 212 for diffuse plaques, N = 239 for CAA)				
Diffuse plaques	1.15 (0.54–2.47)	1.12 (0.77–1.62)	0.85 (0.40–1.79)	1.00 (0.98–1.09)
CAA	1.15 (0.54–2.50)	0.91 (0.62–1.34)	0.98 (0.44–2.24)	1.00 (0.94–1.01)
Normal cognition sample (N = 337 for diffuse plaques, N = 372 for CAA)				
Diffuse plaques	1.63 (0.96–2.79)	1.08 (0.85–1.38)	1.04 (0.59–1.83)	1.01 (0.98–1.08)
CAA	1.63 (0.95–2.75)	1.11 (0.85–1.47)	0.88 (0.47–1.67)	1.01 (0.99–1.06)

All analyses adjusted for age, sex, APOE ε4, non-White race and other vascular risk factors; parenthetical values for the HTN → atherosclerosis → ADNP path reflect a 95% bias-corrected bootstrapped confidence interval; ADNP = Alzheimer's disease neuropathology; CAA = cerebral amyloid angiopathy; HTN = hypertension; MCI = mild cognitive impairment.

\* $P < 0.05$ ; \*\* $P < 0.01$ .

( $t = 0.605$ ,  $P = 0.545$ , OR = 1.05). Regarding indirect effects, there was a significant positive linear association of diastolic blood pressure with circle of Willis atherosclerosis ( $t = 1.988$ ,  $P = 0.047$ , OR = 1.14) and of circle of Willis atherosclerosis with neuritic plaques ( $t = 3.950$ ,  $P < 0.001$ , OR = 1.36) and NFTs ( $t = 2.425$ ,  $P = 0.015$ , OR = 1.22), leading to significant indirect effects of diastolic blood pressure on neuritic plaques (OR = 1.01, 95% CI = 1.001–1.02) and NFTs (OR = 1.004, 95% CI = 1.001–1.01). Following false discovery rate correction at 0.05 and 0.10, only the association of circle of Willis atherosclerosis with neuritic plaques remained significant.

In contrast, there were no significant direct or indirect effects of systolic or diastolic blood pressure on neuritic plaques or NFTs within MCI and normal cognition groups.

### Direct and indirect effects of hypertension on diffuse plaques and cerebral amyloid angiopathy

Similar to findings for core Alzheimer's dementia neuropathologies (i.e. neuritic plaques and NFT), there was evidence of indirect effects of hypertension through circle of Willis atherosclerosis on both diffuse plaques (OR = 1.01, 95% CI = 1.002–1.01) and CAA (OR = 1.01, 95% CI = 1.001–1.01) in the overall sample and within the Alzheimer's dementia group (see Table 5). There were also significant negative direct effects of hypertension on CAA in the overall sample ( $t = -2.557$ ,  $P = 0.011$ , OR = 0.78), but not for diffuse plaques. After correction for multiple comparisons, all associations within the overall sample remained significant at 0.05 and 0.10 levels, while associations of within the Alzheimer's dementia group were no longer significant.

## Discussion

This study evaluated direct and indirect effects of hypertension through circle of Willis atherosclerosis on Alzheimer's dementia neuropathology in a large autopsy-based sample of 2198 decedents. In the overall sample, hypertension was associated with increased circle of Willis atherosclerosis, which was in turn associated with greater neuritic plaque and NFT pathology, leading to significant indirect effects of hypertension on Alzheimer's dementia neuropathology through circle of Willis atherosclerosis. In contrast, after adjustment for these indirect effects, hypertension was associated with less neuritic plaque and NFT pathology along the direct pathway. Following stratification of the sample by clinical diagnosis, similar indirect effects were observed among individuals with Alzheimer's dementia. These effects remained significant after adjusting for cerebral infarction and CAA and similar indirect effects were observed for continuous measures of both systolic and diastolic blood pressure. Similarly, we also observed significant indirect effects of hypertension on diffuse plaques and CAA through circle of Willis atherosclerosis in the overall sample and within the Alzheimer's dementia sample. In contrast, neither direct nor indirect effects of hypertension, systolic blood pressure or diastolic blood pressure on Alzheimer's dementia neuropathology were found within normal cognition or MCI groups.

These results are consistent with several previous findings. For one, prior research has also shown that hypertension contributes to atherosclerosis, presumably by injuring the vascular endothelium and triggering an atherogenic inflammatory response (Ross, 1993). For another, several previous studies have found that circle of Willis atherosclerosis is associated with increased neuritic plaque and NFT pathology (Roher *et al.*, 2003; Honig

*et al.*, 2005; Beach *et al.*, 2007; Yarchoan *et al.*, 2012; Hughes *et al.*, 2014).

In contrast, a few studies have failed to find associations between circle of Willis atherosclerosis and neuritic plaque and NFT pathology (Kosunen *et al.*, 1995; Itoh *et al.*, 1999; Dolan *et al.*, 2010; Zheng *et al.*, 2013). This may be due to sample differences across studies, as significant effects of atherosclerosis on Alzheimer's dementia neuropathology were found only among Alzheimer's dementia cases in this study while previous studies have evaluated decedents across the clinical spectrum. Another possible reason may be different recruitment procedures, as most of these prior negative studies were drawn from general community samples or non-Alzheimer's dementia-specific prospective studies whereas the current study relied on an Alzheimer's dementia-focused post-mortem convenience sample, which may have introduced an ascertainment bias and inflated effect sizes (Chui *et al.*, 2012). Lastly, the sample size of the current study was over 10-fold larger than any of these past studies and thus had greater power to detect significant effects. Consistent with this explanation, ORs from previous studies that reported sufficient data to calculate effect sizes have ranged from 1.1 to 1.5, which is in line with the statistically significant ORs documented in the current study (1.13–1.33) (Dolan *et al.*, 2010; Zheng *et al.*, 2013). This concordance suggests that the current study may in fact be consistent with these previous negative studies.

Notably, we did not find evidence of a positive quadratic association between systolic or diastolic blood pressure and Alzheimer's dementia neuropathology along either direct or indirect pathways. Prior research demonstrating positive quadratic effects of blood pressure has only evaluated these associations in relation to cognitive functioning (Glynn *et al.*, 1999; Morris *et al.*, 2002; Gorelick *et al.*, 2012) while studies exploring associations of blood pressure with Alzheimer's dementia neuropathology have consistently found positive linear, but not quadratic, associations between these variables (Petrovitch *et al.*, 2000; Arvanitakis *et al.*, 2018). This suggests that previously documented curvilinear associations may be indexing non-Alzheimer's dementia pathology (Morris *et al.*, 2002).

Contrary to our hypotheses, however, we did find a negative quadratic direct effect of diastolic blood pressure on Alzheimer's dementia neuropathology, in which high levels of diastolic blood pressure were associated with less Alzheimer's dementia neuropathology as well as a negative direct effect of hypertension diagnosis on Alzheimer's dementia neuropathology in the overall sample. One explanation of this finding is that high diastolic blood pressure may be protective against Alzheimer's dementia neuropathology by limiting blood flow reductions in the context of increased cerebrovascular resistance (Paulson *et al.*, 1990; Nation *et al.*, 2013). Alternatively, given that elevated blood pressure is associated with

premature mortality (Danaei *et al.*, 2009), these negative direct associations may be a statistical artefact of a survivor bias, in which only the healthiest individuals with hypertension and high diastolic blood pressure lived long enough to be included in the NACC-Neuropathological Data Set. Replication of this finding is needed to disentangle these competing explanations.

Overall, the current study suggests that hypertension and higher late-life blood pressure levels may promote Alzheimer's dementia pathology indirectly through their effects on circle of Willis atherosclerosis. Previous research has shown that hypertension may contribute to Alzheimer's dementia pathogenesis through atherosclerosis-dependent pathways involving cerebral hypoperfusion and diminished perivascular clearance (Gupta and Iadecola, 2015) and atherosclerosis-independent pathways involving increased influx of A $\beta$  from the blood into the brain (Carnevale *et al.*, 2012) and diminished A $\beta$  catabolism (Miners *et al.*, 2011; Ashby *et al.*, 2016). In the current study, the impact of hypertension on Alzheimer's dementia pathology along the atherosclerosis-independent pathway (i.e. the direct effect) was not associated with greater Alzheimer's dementia neuropathology. This finding suggests that these latter two mechanisms may be less impactful than those involving cerebral hypoperfusion and A $\beta$  clearance.

Similar mechanisms may also underlie the relationship between hypertension and CAA. CAA is present in up to 80% of Alzheimer's dementia cases (Jellinger, 2002). Previous research has suggested that hypertension may promote CAA through its disruption of vessel wall integrity and consequent role in reducing cerebral blood flow and impairing A $\beta$  clearance (Weller *et al.*, 2008; Okamoto *et al.*, 2012; Shah *et al.*, 2012; Hawkes *et al.*, 2014; Jandke *et al.*, 2018). Given the involvement of circle of Willis atherosclerosis in both of these mechanisms and the observation of an indirect effect of hypertension on CAA through circle of Willis atherosclerosis in this study, circle of Willis atherosclerosis may also represent an important area of convergence for hypertension and CAA.

The current study is subject to a few limitations. Data used in this study were cross-sectional. As such, the direction of influence between hypertension, circle of Willis atherosclerosis and Alzheimer's dementia pathology cannot be definitively demonstrated. In addition, this study may be subject to an ascertainment bias. Decedents in this sample were also relatively healthy, especially in the Alzheimer's dementia group, which may reflect recruitment procedures that excluded individuals with elevated cerebrovascular risk. In addition, as discussed earlier, the current sample may be subject to a survivor bias given that hypertension is associated with premature mortality (Danaei *et al.*, 2009). These latter two limitations may have attenuated effect sizes in the current study and as such, these effects sizes may represent lower-end estimates. Some significant effects failed to survive correction

for false discovery rate, although, importantly, all significant effects observed in the overall sample remained significant after correction. Main analyses in this study also relied on self-reported hypertension, which may be subject to error. Notably, however, findings were replicated using objective measures of systolic and diastolic blood pressure, suggesting that self-report error did not account for observed effects. Also, neuropathological assessment protocols varied across individual ADCs, which may have reduced reliability of classifications. However, neuropathological data were collected using consensus guidelines and entered into a standardized Neuropathology Form and Coding Guidebook. Further, main analyses remained significant when using alternative dichotomous classifications of circle of Willis atherosclerosis, neuritic plaques and NFTs that were intended to improve reliability (Graff-Radford *et al.*, 2016; Alosco *et al.*, 2017). Finally, there were large differences in sample sizes across clinical groups, which may have limited power to detect effects in the MCI and normal cognition groups.

Future research should explore indirect effects of other vascular risk factors on Alzheimer's dementia neuropathology through circle of Willis atherosclerosis. Prospective longitudinal studies incorporating *in vivo* measures of intracranial atherosclerosis and Alzheimer's dementia pathology would help clarify the time course and direction of influence between vascular risk factors, atherosclerosis and Alzheimer's dementia pathology. Additional studies exploring these processes in samples enriched for mixed Alzheimer's dementia/vascular neuropathology may elucidate additional effects. Ultimately, further clarification of intermediate pathways linking vascular risk factors to Alzheimer's dementia may facilitate identification of important intervention targets.

In conclusion, this is the largest study to date to explore the impact of hypertension on post-mortem Alzheimer's dementia neuropathology. Hypertension was found to increase Alzheimer's dementia neuropathology indirectly through its effect on circle of Willis atherosclerosis. This effect could be due to persistent cerebral hypoperfusion leading to  $A\beta$  production and tau phosphorylation or diminished clearance of  $A\beta$ . Circle of Willis atherosclerosis may be an important point of convergence between vascular risk factors, cerebrovascular changes and Alzheimer's dementia neuropathology.

## Supplementary material

Supplementary material is available at *Brain Communications* online.

## Acknowledgements

The authors are grateful to the NACC study investigators and participants for providing the data used in this article.

## Funding

This manuscript was supported by grants from VA Clinical Science Research & Development (Merit Award 1I01CX001842 to K.J.B.), the Alzheimer's Association (AARG-18-566254 to K.J.B.), the Dana Foundation (to K.J.B.), and the National Institute on Aging of the National Institutes of Health (R01 AG063782 to K.J.B. and K24 AG026431 and R01 AG049810 to M.W.B.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The NACC database is funded by National Institute on Aging of the National Institutes of Health Grant U01 AG016976. NACC data are contributed by the National Institute on Aging funded Alzheimer's Disease Centers: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI Marie-Francoise Chesselet, MD, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine, MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

## Competing interests

G.M.L.E., A.J.W., D.A.N., and K.J.B. report no competing interests. M.W.B. is a paid consultant for Eisai, Novartis and Roche Pharmaceuticals and receives royalties from Oxford University Press.

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