ORIGINAL ARTICLE

Hypertension is associated with worse cognitive function and hippocampal hypometabolism in Alzheimer's disease

I. Moonga*, F. Niccolini*, H. Wilson, G. Pagano, and M. Politis for the Alzheimer's Disease Neuroimaging Initiative†

Neurodegeneration Imaging Group, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology & Neuroscience (IOPPN), King's College London, London, UK

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Background and purpose: A growing body of evidence suggests that cardiovascular disease risk factors including hypertension may be linked to sporadic Alzheimer's disease (AD). It is well known that hypertension is associated with cerebrovascular disease and vascular dementia on the basis of vascular remodeling. However, the mechanisms linking hypertension and AD remain unclear.
Methods: We studied 197 patients with AD (86 male; mean age ± SD: 75.8 ± 7.4 years) from the Alzheimer's Disease Neuroimaging Initiative database with (n = 97) and without (n = 100) hypertension. We explored associations between hypertension and clinical, plasma, cerebrospinal fluid and imaging markers of AD pathology in order to elucidate the underlying mechanisms that may link AD and hypertension.
Results: We found that patients with AD with hypertension had worse cognitive function (Alzheimer's disease Assessment Scale-cognitive subscale, P = 0.038) and higher neuropsychiatric symptom burden (Neuropsychiatric Inventory Questionnaire, P = 0.016) compared with those without hypertension. Patients with AD with hypertension showed reduced glucose hypometabolism in the right (P < 0.001) and left (P = 0.007) hippocampus. No differences were found in magnetic resonance imaging volumetric measurements, [^{18}F]florbetapir uptakes, plasma and cerebrospinal fluid between patients with AD with and without hypertension.
Conclusions: Although hypertension is associated with worse cognitive function, behavioural symptoms and hippocampal glucose hypometabolism, it is not associated with evidence of increased amyloid or tau pathology. Effective management of hypertension may potentially have a therapeutic role in the alleviation of symptoms in AD.

Correspondence: M. Politis, Neurodegeneration Imaging Group, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), 125 Coldharbour Lane, Camberwell, London SE5 9NU, UK (tel.: +44 0 207 848 5682; fax: +44 0 207 848 5914; e-mail: marios.politis@kcl.ac.uk).
*These authors contributed equally.
†Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at:http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 33.9 million people worldwide [1]. The cardinal pathology in AD includes accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau, as well as synaptic loss [2]. Over the last few years, several large phase III clinical trials of putative disease-modifying treatments using antiamyloid approaches have failed [3–8]. Therefore, identifying potential modifiable risk factors of AD is crucial for primary prevention and might lead to a reduction in AD incidence.

Several studies suggest that cardiovascular disease risk factors, such as type two diabetes, dyslipidaemia, metabolic syndrome and hypertension, could be linked to sporadic AD [9–11]. Among these risk factors, hypertension may be the most detrimental [12]. It is well known that hypertension is the most significant contributing factor in cerebrovascular disease, as it can cause microvascular dysfunction and narrowing, which can lead to cerebral hypoperfusion, microhaemorrhages and encourage cerebral small vessel disease [12]. Small vessel disease can consequently lead to lacunar infarcts and leukoaraiosis, changes that are closely associated with cognitive decline and vascular dementia [12].

In contrast to the mechanisms that link hypertension and cerebrovascular disease, the pathophysiological links between hypertension and AD are more complex and may involve inflammatory processes, blood–brain barrier dysfunction, as well as cerebral hypoperfusion [13–15]. Although the exact mechanisms are not fully understood, there is strong evidence to support the hypothesis that hypertension in mid-life leads to cognitive impairment and contributes to the development of AD in later life [16]. It is also possible that hypertension may exacerbate AD symptoms and pathology.

Here, we investigated whether hypertension is associated with clinical, plasma, cerebrospinal fluid (CSF) and magnetic resonance and positron emission tomography (PET) imaging biomarkers of AD pathology in order to elucidate the underlying mechanisms that may link AD and hypertension.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. Each ADNI site received approval from an ethical committee on human experimentation before the study's initiation. Written informed consent for research was obtained from all individuals participating in the study.

Study population

From the ADNI I and II databases, a total of 197 patients with AD (86 male; mean age ± SD: 75.8 ± 7.4 years) were included in the analysis (Table 1). Inclusion criteria

Table 1 Demographic characteristics, ApoE genotype and vital signs of patients with Alzheimer's disease (AD) with and without hypertension (HTN)

	AD	AD without HTN	AD with HTN
No.	197	97 (49.2%)	100 (50.8%)
Gender (M)	86 (43.7%)	45 (46.4%)	41 (41.0%)
Age (years)	75.8 (±7.4)	76.7 (±7.2)	75.8 (±7.4)
Handedness (R)	185 (98.9%)	92 (94.8%)	93 (93.0%)
Parent history of AD	23 (11.7%)	10 (10.0%)	13 (13.0%)
ANART	13.78 (±8.9)	12.52 (±8.6)	15.04 (±9.3)
Education (years)	15.0 (±3.2)	14.7 (±3.3)	15.2 (±3.2)
Age at onset (years)	69.6 (±6.9)	69.7 (±7.6)	69.5 (±6.2)
Disease duration (years)	14.7 (±3.2)	7.0 (±8.1)	5.5 (±7.1)
ApoE genotypes (no.)	ApoE ε2-2 = 1	ApoE ε2-2 = 0	ApoE ε2-2 = 1
	ApoE ε2-3 = 6	ApoE ε2-3 = 3	ApoE ε2-3 = 3
	ApoE ε2-4 = 2	ApoE ε2-4 = 1	ApoE ε2-4 = 1
	ApoE ε3-3 = 115	ApoE ε3-3 = 49	ApoE ε3-3 = 66
	ApoE ε3-4 = 50	ApoE ε3-4 = 28	ApoE ε3-4 = 22
	ApoE ε4-4 = 23	ApoE ε4-4 = 16	ApoE ε4-4 = 7
BMI	27.0 (±5.8)	25.0 (±4.0)	29.0 (±6.7)**
SBP (mmHg)	136.7 (±17.3)	131.6 (±16.5)	141.6 (±16.7)***
DBP (mmHg)	73.5 (±9.2)	72.4 (±8.5)	74.6 (±9.8)
PP (mmHg)	63.2 (±16.0)	59.2 (±15.2)	67.0 (±15.9)**
Body temperature (°C)	36.4 (±0.4)	36.3 (±0.5)	36.5 (±0.4)
HR (bpm)	64.8 (±10.4)	64.6 (±10.2)	65.1 (±10.4)
HMIS	0.64 (±0.7)	0.65 (±0.8)	0.63 (±0.6)

ANART, American National Adult Reading Test; BMI, body mass index; bpm, beats/min; DBP, diastolic blood pressure; HMIS, Modified Hachinski Ischemic Scale; HR, heart rate; M, male; PP, pulse pressure; R, right; SBP, systolic blood pressure. $^{**}P < 0.01$; $^{***}P < 0.001$. Data are given as *n* (%) and mean ± SD.

for all participants were: age between 55 and 90 years, a minimum of 6 years' education and visual/auditory acuity adequate for neuropsychological testing. Additionally, the Modified Hachinski Ischemic Scale was completed for all subjects using information from medical records to determine the degree of vascular involvement and only subjects with a score ≤4 were included in the study. Patients with AD fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD [17], had a Clinical Dementia Rating (CDR) score of 0.5 or 1 and a Mini-Mental State Examination (MMSE) score between 20 and 26. Participants had to have an MMSE score in this range so that they could complete clinical assessments effectively.

The presence of hypertension was documented by medical history and/or confirmed by two consecutive blood-pressure (BP) measurements. Hypertension was categorized according to the classification outlined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [18]. Participants with a systolic BP reading of ≥140 mmHg and/or a diastolic BP reading of ≥90 mmHg were classed as hypertensive, whereas subjects with a systolic BP value of ≤139 mmHg as well as a diastolic BP value of ≤89 mmHg were deemed to be normotensive. Medical history was examined thoroughly in the database for evidence of hypertension for each participant using 'hypertension' as a key word and its synonyms, such as 'HTN', 'high blood pressure', 'high BP', 'elevated blood pressure', 'elevated BP' and 'increased blood pressure'. Additionally, obvious spelling mistakes such as 'hpertension' and 'hyoertension' were included. Patients with AD were subdivided into two groups according to the presence/absence of hypertension: AD with hypertension (n = 97, 49.2%; 45 male) and AD without hypertension (n = 100, 50.8%; 41 male; Table 1). Fifty-one patients with AD (55.3%) had both a history of hypertension and BP readings suggestive of hypertension, 38 patients with AD (36.9%) had only a history of hypertension with normal BP readings, and the remaining eight patients with AD (7.8%) were classified as hypertensive based only on BP readings.

Clinical assessments

Cognitive function was assessed with the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog 11) and MMSE. The ADAS-Cog 11 was not timed and the subject's score was not dependent on how rapidly the test was completed. The CDR served as a tool for quantifying the severity of symptoms of dementia and the Modified Hachinski Ischemic Scale was used to identify a likely vascular component once the dementia diagnosis has been established. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire. Depressive features and functional ability were assessed with the Geriatric Depression Scale-Short Form and Functional Assessment Questionnaire, respectively. The American National Adult Reading Test was used to assess intellectual functioning.

Plasma and cerebrospinal fluid samples

Baseline samples of plasma tau, plasma Aβ40 and 42, total plasma homocysteine, CSF total tau, CSF tau phosphorylated at threonine 181, CSF Aβ42 and CSF alpha-synuclein were collected from participants. ApoE genotyping was carried out on subjects using EDTA blood samples collected during the first visit. Full details concerning the collection, processing and storage procedures for plasma and CSF samples can be found in the ADNI procedures manual (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html). CSF samples that were thawed or contaminated with blood were excluded from our analysis in order to avoid false-positive results [19]. For subjects with two CSF samples for a single biomarker, the highest reading was used. With respect to plasma homocysteine analysis, samples were excluded if they were not frozen, packed in dry ice or received within 24 h of blood draw.

Imaging procedures and analysis

Magnetic resonance imaging analysis

All participants had 1.5- or 3.0-Tesla MRI scans completed at regular intervals during the ADNI study. Baseline T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images were acquired from all participants with AD. Scans were carried out and analysed in accordance with the ADNI MRI technical procedures manual (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html). In this study, total brain volume, brain and ventricular boundary shift integral, and hippocampal and temporal lobe volumes were evaluated. The boundary shift integral was used to assess brain and ventricular volume changes over time by determining changes in the boundaries of the respective structure in follow-up scans compared with the baseline scans [20]. Hippocampal volumes were analysed using a brain-mapping tool (Medtronic Surgical Navigation Technologies, Minneapolis, MN, USA). Temporal lobe

volume was assessed using tensor-based morphometry. In addition to volumetric analyses, the number of visible infarcts was recorded for subjects to check for underlying cerebrovascular disease. All images were reviewed by a physician specially trained in the detection of MRI infarcts. Full details of the MRI procedures can be found in the ADNI manual (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html).

Positron emission tomography analysis

[^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]florbetapir PET imaging was carried out to measure regional rates of glucose metabolism and Aβ load, respectively. A mean dose of 5 ± 0.5 mCi [^{18}F]FDG (185 MBq) was injected intravenously and data were reconstructed using a framing rate of 5 × 300 s. Regions of interest included the left and right temporal gyrus, left and right angular gyrus, posterior cingulum, and left and right hippocampus. Hippocampal metabolic activity was measured using the HipMask technique [21]. For [^{18}F]florbetapir PET imaging, a mean dose of 10.0 ± 1.5 mCi [^{18}F]florbetapir (370 MBq) was injected intravenously and data were reconstructed using a framing rate of 4 × 300 s. Structural magnetic resonance images were skull-stripped, segmented, parcellated using Freesurfer and subsequently coregistered to the participants' first florbetapir image. [^{18}F] Florbetapir standardized uptake value ratios were calculated using the whole cerebellum as a reference region. Regions of interest included frontal, anterior/posterior cingulate, lateral parietal and lateral temporal cortices. The [^{18}F]florbetapir mean of each region of interest was weighted by its volume to account for the difference in sizes of the subregions. Full details of the PET procedures can be found in the ADNI manual (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html).

Statistical analysis

Statistical analyses and graphical illustrations were performed using the Statistical Package for the Social Sciences, version 22 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA), respectively. For all variables, variance homogeneity and Gaussianity were tested with Bartlett and Kolmogorov–Smirnov tests. Multivariate analysis of variance was used to assess the main differences in clinical, CSF, plasma and imaging measurements between patients with AD with and without hypertension. If the overall multivariate test was significant, P values for each variable were calculated following Benjamini–Hochberg multiple-comparisons test in order to reduce the false discovery rate. We set the false discovery rate cut-off at 0.05. All data are presented as mean ± SD, and the level α was set for all comparisons at $P < 0.05$, corrected.

Results

Patients with AD with hypertension had significantly higher body mass index scores ($P < 0.01$), systolic BP ($P < 0.001$) and pulse pressure ($P < 0.01$) compared with those without hypertension. No differences were found for age, gender, age at onset, disease duration, years of education, American National Adult Reading Test, family history of AD, Modified Hachinski Ischemic Scale and ApoE genotype between patients with AD with and without hypertension (all $P > 0.10$; Table 1).

We found significant differences in clinical measurements between the patients with AD with and without hypertension ($P = 0.013$). Patients with AD with hypertension had significantly worse cognitive function as measured by the ADAS-Cog 11 ($P = 0.038$) and increased neuropsychiatric symptom burden ($P = 0.016$) compared with those without hypertension (Table 2; Fig. 1). Within the ADAS-Cog 11, patients with AD with hypertension scored worse on the Command item 2 ($P = 0.027$) and Word Recognition item 8 ($P = 0.034$) compared with patients with AD without hypertension. No differences were found in the total CDR scores ($P > 0.10$), MMSE scores ($P > 0.10$), Functional Assessment Questionnaire ($P = 0.088$) and Geriatric Depression Scale-Short Form ($P > 0.10$) between patients with AD with and without hypertension (Table 2).

Table 2 Clinical assessments in the group of patients with Alzheimer's disease (AD) with and without hypertension (HTN)

	AD without HTN	AD with HTN	P value*	% change
CDR	0.68 (±0.3)	0.73 (±0.3)	NS	+6.4%
MMSE	24.09 (±1.8)	23.94 (±1.8)	NS	−0.6%
ADAS-Cog 11	16.58 (±5.6)	18.00 (±5.3)	**0.038**	**+7.9%**
GDS-SF	1.79 (±1.3)	1.52 (±1.4)	NS	−17.7%
NPI-Q	2.55 (±2.5)	4.42 (±3.5)	**0.016**	**+42.3%**
FAQ	10.71 (±6.3)	12.69 (±6.6)	NS	+15.6%

ADAS-Cog 11, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR, Clinical Dementia Rating; FAQ, Functional Assessment Questionnaire; GDS-SF, Geriatric Depression Scale-Short Form; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; NS, non-significant. *All P values are Benjamini–Hochberg corrected. Data are given as mean ± SD. Bold indicates significant value ($P < 0.05$).

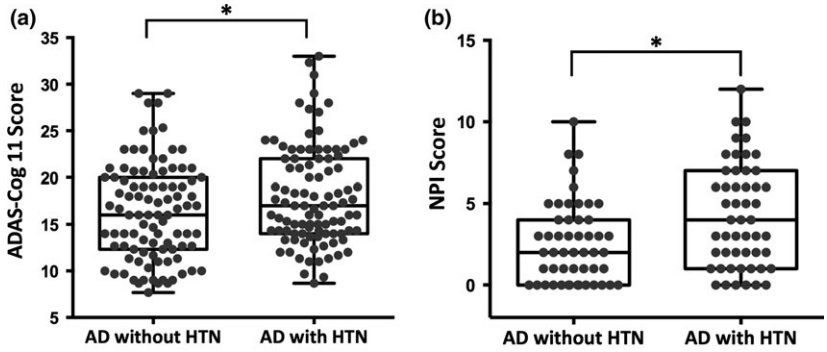

Figure 1 Cognitive and neuropsychiatric measurements in the groups of patients with Alzheimer's disease (AD) with and without hypertension (HTN). (a) Significantly higher Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog 11) scores ($P = 0.038$) and (b) Neuropsychiatric Inventory (NPI) scores ($P = 0.016$) in patients with AD with HTN compared with those without HTN. *$P < 0.05$.

Table 3 Plasma and cerebrospinal fluid (CSF) biomarkers in the group of patients with Alzheimer's disease (AD) with and without hypertension (HTN)

	AD without HTN	AD with HTN	*P* value*	% change
CSF				
α-SYN (ng/mL)	0.66 (±0.3)	0.94 (±1.1)	NS	+29.8%
Total tau (pg/mL)	111.61 (±50.8)	116.00 (±67.9)	NS	+3.8%
P-tau$_{181}$P (pg/mL)	39.11 (±20.6)	39.64 (±18.1)	NS	+1.3%
Aβ$_{142}$ (pg/mL)	142.26 (±45.3)	155.33 (±46.3)	NS	+8.4%
Plasma				
Homocysteine (μM)	9.70 (±2.7)	11.29 (±4.6)	NS	+14.1%
Tau (pg/mL)	3.1 (±1.5)	3.1 (±1.5)	NS	0.0%
Aβ$_{40}$ (pg/mL)	153.3 (±49.1)	147.9 (±40.6)	NS	−3.6%
Aβ$_{42}$ (pg/mL)	36.5 (±11.4)	35.6 (±7.9)	NS	−2.5%

Aβ, amyloid-β; NS, non-significant; P-tau$_{181}$P, tau phosphorylated at threonine 181; α-SYN, alpha-synuclein. *All *P* values are Benjamini–Hochberg corrected. Data are given as mean ± SD.

Plasma and cerebrospinal fluid biomarkers

We found no differences in plasma tau, plasma Aβ40 and 42, total plasma homocysteine, CSF total tau, CSF tau phosphorylated at threonine 181, CSF Aβ42 and CSF alpha-synuclein levels between patients with AD with and without hypertension (all $P > 0.10$; Table 3).

Imaging measurements

Magnetic resonance imaging volumetric analysis showed no differences in total brain volume, brain and ventricular boundary shift integral measurements, hippocampal and temporal lobe volumes, and the number of infarcts between patients with AD with and without hypertension (all $P > 0.10$; Table 4).

Twenty-one patients with AD without hypertension and 24 patients with AD with hypertension underwent both [^{18}F]FDG and [^{18}F]florbetapir PET scans. We found significant decreases in [^{18}F]FDG uptake in patients with AD with hypertension compared with those without hypertension ($P = 0.021$). Patients with AD with hypertension had decreased [^{18}F]FDG uptakes in the right ($P < 0.001$) and left ($P = 0.007$) hippocampus compared with patients with AD without hypertension (Table 4; Fig. 2). No differences were found in [^{18}F]florbetapir standardized uptake value ratios in any of the brain regions examined between patients with AD with and without hypertension (all $P > 0.10$; Table 4).

No differences were found in cognitive assessments, plasma and CSF biomarkers or MRI and PET measurements between patients with AD with only a history of hypertension and those with both a history of hypertension and BP readings suggestive of hypertension (all $P > 0.10$).

Discussion

Our study is the first to investigate the association between hypertension and clinical, plasma, CSF and magnetic resonance and PET imaging biomarkers of AD pathology. We found that hypertension in patients with AD is associated with worse cognitive function, increased neuropsychiatric burden and lower hippocampal glucose metabolism.

Patients with AD with hypertension scored higher on the ADAS-Cog 11 compared with normotensive patients with AD. Cognitive differences between

Table 4 Magnetic resonance imaging (MRI) and positron emission tomography (PET) measurements in the group of patients with Alzheimer's disease (AD) with and without hypertension (HTN)

	AD without HTN	AD with HTN	*P* value*	% change
MRI volumetric measurements				
Brain volume (mm^3)	1 014 743.58 (±1 173 39.0)	995 823.25 (±101 268.2)	NS	−1.9%
BSI ventricles volume (mm^3)	46.78 (±21.4)	53.40 (±26.3)	NS	+12.4%
BSI brain volume (mm^3)	995.0 (±108.7)	1019.9 (±98.8)	NS	+2.4%
Hippocampus volume (mm^3)	1608.65 (±295.3)	1638.24 (±332.5)	NS	+1.8%
Temporal lobe mean Jacobian (mm^3)	996.43 (±64.9)	988.55 (±69.1)	NS	−0.8%
No. of infarcts	0 (±0.07)	1 (±0.5)	NS	–
[^{18}F]FDG PET uptakes				
Left hippocampus	1.00 (±0.1)	0.88 (±0.1)	**0.007**	**−13.6%**
Right hippocampus	1.01 (±0.1)	0.87 (±0.1)	**< 0.001**	**−16.1%**
Left temporal gyrus	1.10 (0.1)	1.09 (±0.1)	NS	−0.9%
Right temporal gyrus	1.10 (±0.1)	1.11 (±0.1)	NS	−0.9%
Left angular gyrus	1.14 (±0.1)	1.09 (±0.2)	NS	−4.6%
Right angular gyrus	1.11 (±0.1)	1.11 (±0.1)	NS	0.0%
Posterior cingulum	1.16 (±0.1)	1.16 (±0.1)	NS	0.0%
[^{18}F]Florbetapir SUVRs				
Posterior cingulum	1.73 (±0.5)	1.84 (±0.4)	NS	+6.0%
Frontal lobe	1.56 (±0.5)	1.53 (±0.5)	NS	−2.0%
Temporal lobe	1.45 (±0.5)	1.32 (±0.5)	NS	−9.8%
Parietal lobe	1.61 (±0.5)	1.58 (±0.5)	NS	−1.9%
Insula right	1.5 (±0.5)	1.30 (±0.5)	NS	−15.4%
Insula left	1.5 (±0.5)	1.33 (±0.5)	NS	−12.8%
Temporal pole right	1.18 (±0.4)	1.09 (±0.3)	NS	−8.3%
Temporal pole left	1.20 (±0.4)	1.07 (±0.3)	NS	−12.1%
Superior temporal gyrus left	1.41 (±0.5)	1.23 (±0.4)	NS	−14.6%
Superior temporal gyrus right	1.43 (±0.5)	1.30 (±0.5)	NS	−10.0%
Parahippocampal gyrus left	1.16 (±0.4)	1.07 (±0.3)	NS	−8.4%
Parahippocampal gyrus right	1.16 (±0.4)	1.07 (±0.3)	NS	−8.4%
Hippocampus left	1.07 (±0.2)	1.05 (±0.2)	NS	−1.9%
Hippocampus right	1.05 (±0.2)	1.05 (±0.2)	NS	0.0%
Lingual gyrus right	1.36 (±0.5)	1.23 (±0.4)	NS	−10.6%
Lingual gyrus left	1.43 (±0.5)	1.30 (±0.5)	NS	−10.0%
Precuneus right	1.77 (±0.4)	1.65 (±0.5)	NS	−7.3%
Precuneus	1.77 (±0.4)	1.67 (±0.5)	NS	−6.0%
Cuneus left	1.39 (±0.5)	1.40 (±0.5)	NS	+0.7%
Cuneus right	1.43 (±0.5)	1.28 (±0.4)	NS	−11.7%
Postcentral gyrus left	1.34 (±0.5)	1.30 (±0.5)	NS	−3.1%
Postcentral gyrus right	1.36 (±0.5)	1.21 (±0.4)	NS	−12.4%
Precentral gyrus left	1.45 (±0.5)	1.35 (±0.5)	NS	−7.4%
Precentral gyrus right	1.45 (±0.5)	1.30 (±0.5)	NS	−11.5%

BSI, boundary shift integral; FDG, fluorodeoxyglucose; NS, non-significant; SUVR, standardized uptake values ratio. *All *P* values are Benjamini–Hochberg corrected. Data are given as mean ± SD. Bold indicates significant value ($P < 0.05$).

patients with AD with and without hypertension were also observed in specific items of the ADAS-Cog 11. Hypertensive patients had worse results on items testing word recognition and the ability to follow commands. Impaired verbal learning and difficulties in performing simple tasks are considered early signs of AD [22,23], thus it is possible that hypertension might be one of the earlier factors leading to the development of AD. Investigating these findings in hypertensive individuals without AD and in patients with mild cognitive impairment may shed light on this intriguing hypothesis. Previous studies have shown that hypertension in healthy elderly individuals is associated with cognitive decline and white matter lesions [24,25]. By contrast, studies examining the impact of hypertension on cognitive decline in patients with AD are limited. However, one case-control study has found that cognitive decline is accelerated by hypertension in patients with AD under the age of 65 years over a 6-month period [26]. Other studies have found that both mid-life and late-life hypertension increase the risk of AD [9,27–29]. In both cerebrovascular disease and AD, hypertension may irreversibly affect the functions of the 'neurovascular unit', a complex multicellular functional unit involved in accomplishing the processes of cerebral autoregulation and functional

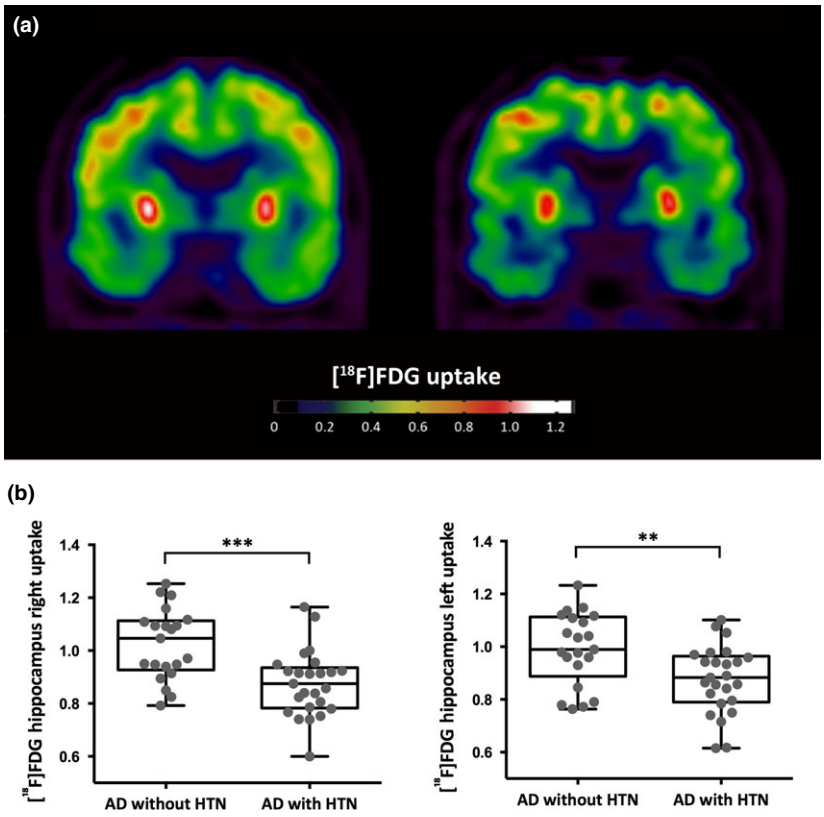

Figure 2 Glucose metabolisms in the group of patients with Alzheimer's disease (AD) with and without hypertension (HTN). (a) Coronal summed [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography images for: (left) an 82.4-year-old female with a 7-year history of AD {Mini-Mental State Examination (MMSE), 26; Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog 11), 16.7; Neuropsychiatric Inventory (NPI), 0; Functional Assessment Questionnaire (FAQ), 5; [^{18}F]FDG uptakes hippocampus, left 1.09, right 1.21} and (right) a 75.8-year-old female with an 8-year history of AD (MMSE, 26; ADAS-Cog 11, 18.7; NPI, 8; FAQ, 21; [^{18}F]FDG uptakes hippocampus, left 0.91, right 0.88). Colour bar reflects range of [^{18}F]FDG uptake intensity. (b) Significantly lower [^{18}F] FDG uptakes in the right and left hippocampus of patients with AD with HTN compared with those without HTN. $^{**}P < 0.01$, $^{***}P < 0.001$. [Colour figure can be viewed at wileyonlinelibrary.com].

hyperaemia [30]. Loss of autoregulation and reduced cerebral blood flow in response to regional brain activity may cause cerebral hypoperfusion and hypoxia. Research has suggested that, whereas mild reductions in cerebral blood flow can affect protein synthesis [13], which is essential for the synaptic plasticity involved in learning and memory, chronic hypoperfusion can increase hyperphosphorylated tau levels in the hippocampus and cortex [14], as well as cause progressive accumulation of Aβ peptides [15]. In addition to regulating cerebral blood flow, the neurovascular unit forms the basis of the blood–brain barrier. Hypertension has been found to disrupt the blood–brain barrier, an alteration that can lead to the accumulation of neurotoxic molecules in the brain such as Aβ and thrombin [13].

We found that hypertensive patients with AD had an increased neuropsychiatric symptom burden compared with normotensive patients with AD. One study has found that a history of hypertension increases the risk of neuropsychiatric symptoms such as agitation/aggression, anxiety and delusions in patients with AD [31]. A more recent study in a large cohort of 457 patients with AD also showed that a history of hypertension was associated with worse behavioural symptoms as measured by the Neuropsychiatric Inventory Questionnaire at the time of AD diagnosis [32]. One possible explanation for the link seen between hypertension and neuropsychiatric symptoms such as delusions is that there may be a reduction in cerebral blood flow in the prefrontal and temporal cortices [33].

Imaging analyses revealed decreased glucose metabolism in the hippocampus of patients with AD with hypertension. The hippocampus plays a crucial role in memory. Reduced glucose metabolism in this region of the brain may reflect underlying neuronal and synaptic dysfunction, and could explain the greater cognitive impairment observed in patients with AD with hypertension compared with those without hypertension. Glucose hypometabolism in the hippocampus and temporo-parietal areas has been extensively described in patients with AD [34] and mild cognitive impairment [35,36]. Hypertension compromises the integrity of blood vessel walls in the brain leading to hypoperfusion and decreased glucose metabolism, which can promote AD neuropathogenesis [37]. Functional failure in brain microvasculature may affect the drainage of pathological misfolded proteins [38]. It should be noted that no other regions of the brain showed changes in glucose metabolism, perhaps suggesting that the hippocampus is particularly vulnerable to changes in cerebral blood flow.

Although previous studies propose that the cerebrovascular damage could contribute to AD

pathology, we found no significant differences in [^{18}F] florbetapir standardized uptake value ratios or plasma and CSF amyloid and tau levels between patients with AD with and without hypertension. It is possible that the mechanisms of action of hypertension in lowering cognitive and neuropsychiatric performance are different from those promoting AD pathology. We also found no differences in brain and hippocampal MRI volumetric measurements between patients with AD with and without hypertension. Although research on volumetric imaging changes in patients with AD with hypertension is limited, it has been found that healthy hypertensive individuals have significantly larger ventricular volumes and brain atrophy [39]. The fact that we did not find these changes in our AD population perhaps suggests that, whereas hypertension may lead to functional brain changes such as reduced hippocampal glucose metabolism, it may have a small effect on structural volumetric brain changes for the stage of AD studied here. We also found no differences in ApoE genotype between patients with AD with and without hypertension. It is known that ApoE4 is associated with reduced lipid metabolism and vascular function, and that high cholesterol and plaque build-up lead to hypertension [40]. However, the allele is associated with younger onset AD and increases AD risk in a dose-dependent manner [30]. This may explain why no differences were detected in our sample of patients. Furthermore, ApoE4 is thought to have varying modulating influence on BP [30].

There are several important limitations of this study that need to be mentioned. In terms of methodology, there was insufficient control of antihypertensive therapy and vascular comorbidities such as diabetes and obesity. With several patients in our sample potentially on BP-lowering medication, the full negative impact of hypertension on AD symptoms and hippocampal glucose metabolism is likely to be masked and may actually be greater. Furthermore, other cardiovascular disease risk factors may independently influence AD pathology. Another point to note is that the ADNI study cohort represents a clinical trial population. As a result, our findings may have limited generalizability. Additionally, the ADNI study only recruits patients with AD with a CDR score of 0.5 or 1 and an MMSE score between 20 and 26. This means that the results obtained here are solely based on a population of patients with early to moderate AD. It is possible that hypertension may not have such an impact on AD biomarkers in later stages of the disease. The ADNI cohort also only includes subjects aged 55–90 years and AD may start developing before the age of 55 years.

In conclusion, hypertension appears to negatively affect cognitive and neuropsychiatric function and regional brain metabolism. Our findings highlight the urgent need to treat hypertension in a vulnerable age group. Effective management of hypertension may potentially have a therapeutic role in the alleviation of symptoms in AD.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011; **10:** 819–828.
2. Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discovery* 2011; **10:** 698–712.
3. Coric V, van Dyck CH, Salloway S, *et al*. Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol* 2012; **69:** 1430–1440.
4. Doody RS, Raman R, Farlow M, *et al*. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med* 2013; **369:** 341–350.
5. Doody RS, Thomas RG, Farlow M, *et al*. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014; **370:** 311–321.
6. Salloway S, Sperling R, Keren R, *et al*. A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease. *Neurology* 2011; **77:** 1253–1262.
7. Salloway S, Sperling R, Fox NC, *et al*. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014; **370:** 322–333.
8. Galasko D, Bell J, Mancuso JY, *et al*. Clinical trial of an inhibitor of RAGE-Aβ interactions in Alzheimer disease. *Neurology* 2014; **82:** 1536–1542.
9. Kivipelto M, Helkala EL, Laakso MP, *et al*. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001; **322:** 1447–1451.
10. Luchsinger JA, Gustafson DR. Adiposity, type 2 diabetes, and Alzheimer's disease. *J Alzheimer's Dis* 2009; **16:** 693–704.
11. Ahtiluoto S, Polvikoski T, Peltonen M, *et al*. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. *Neurology* 2010; **75:** 1195–1202.
12. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. *Hypertension* 2013; **62:** 810–817.
13. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* 2011; **12:** 723–738.
14. Qiu L, Ng G, Tan EK, Liao P, Kandiah N, Zeng L. Chronic cerebral hypoperfusion enhances Tau hyperphosphorylation and reduces autophagy in Alzheimer's disease mice. *Sci Rep* 2016; **6:** 23964.
15. Bennett SA, Pappas BA, Stevens WD, Davidson CM, Fortin T, Chen J. Cleavage of amyloid precursor protein elicited by chronic cerebral hypoperfusion. *Neurobiol Aging* 2000; **21:** 207–214.
16. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005; **4:** 487–499.
17. DeKosky ST, Carrillo MC, Phelps C, *et al*. Revision of the criteria for Alzheimer's disease: a symposium. *Alzheimer's Dement* 2011; **7:** e1–e12.
18. Chobanian AV, Bakris GL, Black HR, *et al*. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; **42:** 1206–1252.
19. Teunissen CE, Petzold A, Bennett JL, *et al*. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. *Neurology* 2009; **73:** 1914–1922.
20. Freeborough PA, Fox NC. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans Med Imaging* 1997; **16:** 623–629.
21. Mosconi L, Tsui WH, De Santi S, *et al*. Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. *Neurology* 2005; **64:** 1860–1867.
22. Lowndes GJ, Saling MM, Ames D, Chiu E, Gonzalez LM, Savage GR. Recall and recognition of verbal paired associates in early Alzheimer's disease. *J Int Neuropsychol Soc* 2008; **14:** 591–600.
23. Rousseaux M, Rénier J, Anicet L, Pasquier F, Mackowiak-Cordoliani MA. Gesture comprehension, knowledge and production in Alzheimer's disease. *Eur J Neurol* 2012; **19:** 1037–1044.
24. van Swieten JC, Geyskes GG, Derix MM, *et al*. Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann Neurol* 1991; **30:** 825–830.
25. Obisesan TO, Obisesan OA, Martins S, *et al*. High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. *J Am Geriatr Soc* 2008; **56:** 501–509.
26. Bellew KM, Pigeon JG, Stang PE, Fleischman W, Gardner RM, Baker WW. Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord* 2004; **18:** 208–213.
27. Launer LJ, Ross GW, Petrovitch H, *et al*. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging* 2000; **21:** 49–55.
28. Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. *Life Sci* 2003; **72:** 1125–1133.
29. Skoog I, Lernfelt B, Landahl S, *et al*. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; **347:** 1141–1145.
30. Kalaria RN, Akinyemi R, Ihara M. Does vascular pathology contribute to Alzheimer changes? *J Neurol Sci* 2012; **322:** 141–147.
31. Treiber KA, Lyketsos CG, Corcoran C, *et al*. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int Psychogeriatr* 2008; **20:** 538–553.
32. Jutkowitz E, MacLehose RF, Gaugler JE, Dowd B, Kuntz KM, Kane RL. Risk factors associated with cognitive, functional, and behavioral trajectories of newly diagnosed dementia patients. *J Gerontol A Biol Sci Med Sci* 2017; **72:** 251–258.
33. Lopez OL, Smith G, Becker JT, Meltzer CC, DeKosky ST. The psychotic phenomenon in probable Alzheimer's disease: a positron emission tomography study. *J Neuropsychiatry Clin Neurosci* 2001; **13:** 50–55.
34. Kato T, Inui Y, Nakamura A, Ito K. Brain fluorodeoxyglucose (FDG) PET in dementia. *Ageing Res Rev* 2016; **30:** 73–84.

35. Hanseeuw BJ, Schultz AP, Betensky RA, Sperling RA, Johnson KA. Decreased hippocampal metabolism in high-amyloid mild cognitive impairment. *Alzheimer's Dement* 2016; **12:** 1288–1296.
36. Sánchez-Catasús CA, Stormezand GN, van Laar PJ, De Deyn PP, Sánchez MA, Dierckx RA. FDG-PET for prediction of AD dementia in mild cognitive impairment. A review of the state of the art with particular emphasis on the comparison with other neuroimaging modalities (MRI and Perfusion SPECT). *Curr Alzheimer Res* 2017; **14:** 127–142.
37. Hughes TM, Craft S, Lopez OL. Review of the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease. *Neurodegener Dis Manag* 2015; **5:** 121–135.
38. Weller RO, Boche D, Nicoll JA. Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. *Acta Neuropathol* 2009; **118:** 87–102.
39. Salerno JA, Murphy DG, Horwitz B, *et al*. Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension* 1992; **20:** 340–348.
40. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 2013; **9:** 106–118.