Received: 20 May 2022 | Revised: 12 September 2022 | Accepted: 5 October 2022

DOI: 10.1002/alz.12866

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Associations among hypertension, dementia biomarkers, and cognition: The MEMENTO cohort

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Funding information
Fondation Plan Alzheimer, Grant/Award Number: 2008-2012; French Ministry of Research; French National Research Agency; AVID; GE Healthcare; Fujirebio

Abstract

Introduction: Approximately 40% of dementia cases could be delayed or prevented acting on modifiable risk factors including hypertension. However, the mechanisms underlying the hypertension–dementia association are still poorly understood.

Methods: We conducted a cross-sectional analysis in 2048 patients from the MEMENTO cohort, a French multicenter clinic-based study of outpatients with either isolated cognitive complaints or mild cognitive impairment. Exposure to hypertension was defined as a combination of high blood pressure (BP) status and antihypertensive treatment intake. Pathway associations were examined through structural equation modeling integrating extensive collection of neuroimaging biomarkers and clinical data.

Results: Participants treated with high BP had significantly lower cognition compared to the others. This association was mediated by higher neurodegeneration and higher white matter hyperintensities load but not by Alzheimer's disease (AD) biomarkers.

Discussion: These results highlight the importance of controlling hypertension for prevention of cognitive decline and offer new insights on mechanisms underlying the hypertension–dementia association.

KEYWORDS
amyloid beta 42, cognition, cortical thickness, fluorodeoxyglucose positron emission tomography, hippocampal volume, hypertension, mediation, positron emission tomography amyloid, structural equation model, tau, white matter hyperintensities

Highlights

- Paths of hypertension–cognition association were assessed by structural equation models.
- The hypertension–cognition association is not mediated by Alzheimer's disease biomarkers.
- The hypertension–cognition association is mediated by neurodegeneration and leukoaraiosis.
- Lower cognition was limited to participants treated with uncontrolled blood pressure.
- Blood pressure control could contribute to promote healthier brain aging.

1 | INTRODUCTION

While the global population ages, the number of persons with dementia is increasing and could rise from 57.4 million globally in 2019 to 152.8 million in 2050.[1] Dementia is not inevitable as up to 40% of cases could be prevented or delayed by modifying 12 risk factors, including hypertension.[2–4]

Hypertension is one of the most common conditions that degrade cerebral circulation, and prolonged high blood pressure (BP) is a cause of stroke and vascular dementia.[5–8] Several studies suggest that high BP manifested in midlife may also contribute to an increased risk of dementia due to Alzheimer's disease (AD) in late life.[9–11] Two meta-analyses supported this result[11,12] while two other studies concluded an inverse association between late-life hypertension and AD.[13,14]

To better understand the association between hypertension and cognition and build successful intervention strategies, integrated pathways analyses are required to elucidate the mechanistic underlying processes. Imaging and cerebrospinal fluid (CSF) biomarkers have the potential to objectively measure normal biological or pathogenic processes in vivo, and allow taking into account simultaneously multifactorial cerebral processes that can mediate the association between

hypertension and cognition including white matter lesions (WMLs), neurodegeneration, or AD biomarkers.[15–20]

We addressed this question in the MEMENTO cohort, a large clinic-based study in France, and sought to assess the mediating effect of dementia biomarkers, CSF and neuroimaging, on the association between hypertension and lower cognitive performance.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed literature using PubMed. Despite numerous studies and reviews on the link between hypertension and dementia risk, few studies have used integrative methods to study the association of hypertension simultaneously with brain imaging markers and cognition. To our knowledge, none has studied biomarkers of Alzheimer's disease (AD) pathology to investigate in a unique model the interrelationships among hypertension, biomarkers of AD pathology, biomarkers of neurodegeneration, and cognition in a large sample of patients recruited consecutively.
2. **Interpretation**: Our results suggest that the impact of hypertension on cognition is mediated by neurodegeneration and white matter hyperintensities but not through AD pathology. Only participants with uncontrolled hypertension (treated by antihypertensives, high blood pressure) had lower cognition compared to the others. Our findings highlight the importance of controlling hypertension for prevention of cognitive decline.
3. **Future Directions**: Future studies integrating longitudinal data will be necessary to confirm the causality of the associations observed and to consider the temporality of the different biomarkers.

2 | METHODS

2.1 | Study population

The MEMENTO cohort is a clinic-based study of patients presenting with a large variety of cognitive symptoms or subjective cognitive complaints, who were enrolled between April 2011 and June 2014, within the French national network of memory clinics.[21] Main inclusion criteria were a Clinical Dementia Rating (CDR) scale score ≤0.5, mild cognitive impairment (< 1 standard deviation [SD] below the age, sex, and education-level thresholds in one or more cognitive test[s]), or isolated subjective cognitive complaint (for people older than 60). Exclusion criteria included history of head trauma with persistent neurological deficits, stroke in the last 3 months or with persistent neurological deficits, brain tumor, epilepsy, schizophrenia, known mutation in familial AD genes, and illiteracy. All examinations (including neuropsychological battery administration, clinical examinations, brain magnetic resonance imaging [MRI], CSF samples, and fluorodeoxyglucose [FDG] and amyloid positron emission tomography [PET]) followed standardized procedures. Among the 2323 participants included in the MEMENTO cohort, 2048 participants from 26 study centers were included in this analysis after exclusion of participants with all blood pressure measurements missing.

2.2 | Standard protocol approvals, registrations, and patient consents

This study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. The MEMENTO cohort protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35) and was registered in ClinicalTrials.gov (Identifier: NCT01926249).

2.3 | Data collection

BP was measured three times in a seated position after 2 minutes of rest, and the mean of systolic (SBP) and diastolic (DPB) measures were calculated. Participants were classified as having high BP at baseline visit if the mean of SBP measures was ≥140 mm Hg or the mean of DBP measures was ≥90 mm Hg. Medications were recorded based on participants' reports, medical records, and prescriptions. Active substances were centrally coded using the Anatomical Therapeutic Chemical (ATC) classification system. Participants were considered treated by antihypertensive drug if at least one of the five major drug classes intake was recorded: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and thiazide diuretics.

Four groups of exposure were defined as a combination of high BP status and antihypertensive drugs intake: (1) untreated, normal BP (reference category = no hypertension), (2) untreated, high BP, (3) treated, normal BP (controlled BP), (4) treated, high BP (uncontrolled BP).

2.4 | Neuropsychological evaluation

Memory was assessed by the total score at the three free recalls of the Free and Cued Selective Reminding Test (FCSRT),[22] semantic verbal fluency via "animal" words (number cited in 120 seconds), and executive functions by Trail Making Test (TMT) Part B[23] (mean number of correct move per second).

2.5 | Dementia biomarkers assessment

Brain MRI was mandatory. Images were acquired after a standardization of the imaging processes and coordinated by the CATI (http://cati-

neuroimaging.com), a neuroimaging platform dedicated to multicenter studies.[24] MRI scanners with 1.5 and 3 Tesla were used across centers. All MRI scans acquired were centralized, quality checked, and post-processed to obtain standardized measurements for each participant. Total intracranial volume, whole-brain, gray matter, and white matter volumes were assessed with Statistical Parametric Mapping 12,[25] hippocampal volumes with the SACHA software,[26] and mean cortical thickness of each hemisphere with FreeSurfer 5.3 averaged in the regions of interest (ROIs) of the Desikan–Killiany atlas.[27] WML volumes were estimated using WHASA software.[28] Brain parenchymal fraction was computed as the sum of gray matter and white matter volumes divided by total intracranial volume. Total hippocampal volume was computed as the sum of left and right volumes.

2.6 | [18F] FDG-PET

18F-FDG-PET was optional and available for 1187 individuals of the analytical sample. PET images were acquired after a standardization of the acquisition and reconstruction imaging parameters, coordinated by the CATI.[29] After a centralized quality check and postprocessing, the following measures were obtained: Mean FDG-PET uptake for the ROIs of the Automated Anatomical Labeling atlas relative to the pons reference region,[30] including partial volume correction, and mean FDG-PET uptake for a set of AD-specific ROIs inferred from the Alzheimer's Disease Neuroimaging Initiative database,[31] expressed as standardized uptake value ratios (SUVRs).

2.7 | PET amyloid imaging

PET amyloid imaging was available for 577 participants of the analytical sample, using either 18F-florbetapir (Amyvid, Eli Lilly; $N = 396$) or 18F-flutemetamol (Vizamyl, GE Healthcare; $N = 181$) radioligands. Mean brain amyloid SUVR was standardized (z-score) by radioligand.

2.8 | CSF sampling

Lumbar puncture was proposed to all participants and available for 304 participants of the analytical sample. Centralized measurements of amyloid beta (Aβ) 42 peptide (Aβ42), Aβ 40 peptide (Aβ40), and phosphorylated tau (p-tau) levels were performed using the standardized INNOTEST sandwich enzyme-linked immunosorbent assay (Fujirebio).

2.9 | Confounding factors

Sociodemographic information recorded at baseline included age, sex, and education (baccalaureate and above vs. less). Diabetes was defined as the presence of fasting blood glucose ≥7 mmol/L (≥126 mg/dl) or non-fasting blood glucose ≥11.1 mmol/L (≥200 mg/dl) or antidiabetic drug intake or self-reported history of diabetes. Body mass index (BMI) was computed from measured height and weight. History of cardiovascular disease was defined as a self-reported history of myocardial infarction, angina pectoris, coronary artery, or peripheral artery disease. Apolipoprotein E (*APOE*) ε2, ε3, or ε4 alleles were determined by KBiosciences (www.kbioscience.co.uk; now Biosearch Techhnologies). *APOE*-ε4 status was defined as presence of at least one ε4 allele.

2.10 | Statistical analyses

Baseline characteristics were compared according to hypertension groups as previously defined using chi-square test and analysis of variance for categorical and continuous variables comparisons, respectively.

A structural equation model (SEM) was used to examine a potential mediating role of dementia CSF and neuroimaging biomarkers in the association between hypertension status and cognition (Figure 1). Four dimensions were considered: white matter hyperintensity (WMH) volume and three latent variables defined as the common factor of their manifest variables:

- AD pathology measured by CSF Aβ42/Aβ40 ratio and p-tau, and amyloid PET SUVR;
- Neurodegeneration measured by mean cortical thickness, hippocampal volume, brain parenchymal fraction, and FDG PET SUVR;
- Cognition measured by the verbal fluency, the total free reminding, and the TMT B scores;

For ease of interpretation, the four dimensions were standardized (mean 0, variance 1) so that one unit corresponds to the SD of a given dimension. The indirect effects of each hypertension category (vs. reference = "untreated, normal blood pressure") on cognition through the dimensions were estimated with their 95% confidence interval (95% CI), using a path analysis technique. All linear regressions of mediators and cognition were adjusted for the following potential confounders factors: age, sex, education, diabetes, BMI, cardiovascular history, and *APOE* ε4 status. Missing values for observed indicators of latent variables and for confounding factors (see description in Table S1 in supporting information) were handled using a full information maximum likelihood (FIML) approach, robust to missingness at random.[32] The main model, assessed by fit indices robust to non-normal data[33] showed a satisfying fit (comparative fit index [CFI] = 0.92, Tucker–Lewis index [TLI] = 0.88, root mean square error of approximation [RMSEA] = 0.042 [90% confidence interval = 0.038–0.046], and standardized root mean square residual [SRMR] = 0.039). Sensitivity analyses explored potential differences in the findings by sex, age (dichotomized according to median age), and *APOE* status by adding interaction terms with the exposure of interest.

Analyses were conducted using R version 4.0.2 and the lavaan package version 0.6.9 for SEM analysis.[34]

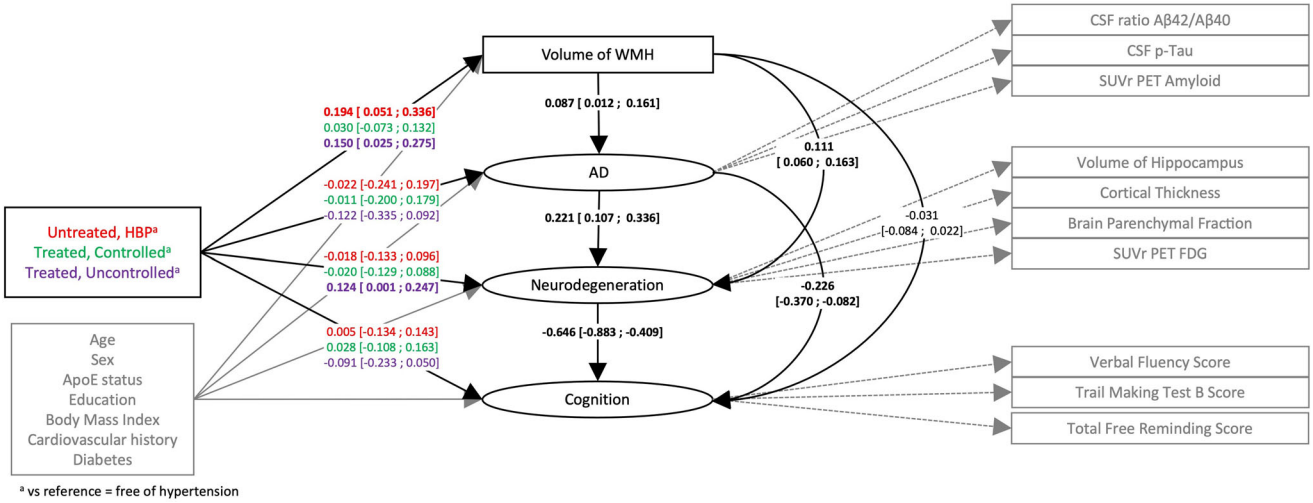

FIGURE 1 Hypothetical structural equation model and estimates of the associations described: The MEMENTO cohort, 2011–2014. Aβ42/Aβ40, ratio of amyloid beta 42 on amyloid beta 40 proteins; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; HBP, high blood pressure; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; WMH, white matter hyperintensities

2.11 | Data availability statement

Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article, and as long as data transfer is in agreement with EU legislation on the general data protection regulation.

3 | RESULTS

Mean age (SD) of participants was 71.3 (8.5) years, 60% were female, and 40% had education level of baccalaureate and above (Table 1). Sixty percent of participants had mild cognitive impairment (CDR scale score = 0.5) versus isolated cognitive complaints (CDR score = 0). The mean CDR Sum of Boxes was 0.61 (SD = 0.72). Approximately two thirds of participants (67.5%) had hypertension and 23.1% were treated for hypertension and uncontrolled. There were statistically significant differences in participant characteristics according to hypertension status (Table 1). Compared to participants untreated with normal blood pressure, those "treated, uncontrolled" tended to have the more pejorative profile: they were 6.7 years older on average, they were less educated, and had more often cardiovascular history or diabetes. They also had lower cognitive performances on average and worse brain FDG-PET and MRI markers. Compared to participants "untreated, normal BP," those "treated, uncontrolled" had worse brain structural and cognitive profile, a finding observed to a lower extent in "treated, controlled" and "untreated, high BP" groups. AD biomarkers (measured through CSF or amyloid PET) distribution did not vary by hypertension status.

The pathway analysis performed using SEM is summarized in Figure 1, and estimates of direct and total associations of hypertension status with AD pathology, WML volume, neurodegeneration, and cognition are further presented in Table 2. See Table S2 in supporting information for the direct and total estimated associations of adjustment covariates on dementia biomarkers and cognition; Table 3 for those of WMH, AD pathology, and neurodegeneration; and Table S3 in supporting information for factor loadings and percentage of residual variance of the observed variables for each latent dimension. AD pathology captured 67.7%, 49.4%, and 74.1% of the total variance of, respectively, CSF Aβ42/Aβ40 ratio, CSF p-tau, and amyloid PET SUVR. Neurodegeneration captured 25.8%, 45.7%, 55.5%, and 37.4% of the total variance of, respectively, the mean cortical thickness, hippocampal volume, brain parenchymal fraction, and FDG PET SUVR. Cognition captured 51%, 40.4%, and 37.1% of the total variance of, respectively, the free Reminding Test, Verbal Fluency, and TMT B.

Adjusted for potential confounders and hypertension, higher levels of neurodegeneration and AD pathology were independently and directly associated with lower cognition (mean difference [MD] = −0.646 SD, 95% CI = [−0.883; −0.409], MD = −0.226 SD, 95% CI = [−0.370; −0.082], respectively). In contrast, WMH was associated with cognition through its effect on AD pathology (MD = 0.087 SD, 95% CI = [0.012; 0.161]) and neurodegeneration (MD = 0.111 SD, 95% CI = [0.060; 0.163]). Adjusted on WMH volume, AD pathology was also indirectly associated with cognition through its association with neurodegeneration (MD = 0.221 SD, 95% CI = [0.107; 0.336]).

The whole pathway of association did not differ in the "treated, controlled" group compared to the reference "untreated, normal BP" group (free of hypertension). Compared to the reference group, "untreated, high BP" or "treated, uncontrolled" groups were significantly associated with higher WML load (MD = 0.194 SD, 95% CI = [0.051; 0.336] and MD = 0.150 SD, 95% CI = [0.025; 0.275], respectively). The "treated, uncontrolled" group was also significantly directly associated with higher neurodegeneration than in the refer-

TABLE 1 Study sample characteristics globally and by hypertension management status: The MEMENTO cohort, 2011–2014

	Full sample	Sample stratified by antihypertensive treatment high blood pressure status				
		Untreated, normal blood pressure	Untreated, high blood pressure	Treated, controlled	Treated, uncontrolled	
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS	*N* = 2048	*N* = 666	*N* = 379	*N* = 530	*N* = 473	*P*-value
Age, mean (SD), years	71.3 (8.5)	68.0 (9.1)	72.1 (7.7)	71.7 (7.7)	74.7 (7.4)	<0.001
Male sex, no. (%)	777 (40%)	213 (32.0%)	142 (37.5%)	224 (42.3%)	198 (41.9%)	<0.001
At least one *APOE* ε4 carried, no. (%)	571 (30%)	186 (29.4%)	113 (31.7%)	146 (29.1%)	126 (27.7%)	0.675
Baccalaureate or higher, no. (%)	803 (40%)	303 (45.6%)	154 (40.6%)	188 (35.5%)	158 (33.4%)	<0.001
BMI, mean (SD), kg/m^2	25.6 (4.3)	24.3 (4.0)	25.5 (4.0)	26.6 (4.5)	26.6 (4.3)	<0.001
Cardiovascular history, no. (%)	303 (10%)	28 (4.2%)	31 (8.2%)	125 (23.6%)	119 (25.2%)	<0.001
of which Myocardial infarction, no. (%)	68 (3.3%)	2 (0.3%)	6 (1.6%)	31 (5.8%)	29 (6.1%)	<0.001
of which Stroke, no. (%)	85 (4.2%)	11 (1.7%)	8 (2.1%)	33 (6.2%)	33 (7.0%)	<0.001
Diabetes, no. (%)	226 (10%)	38 (5.7%)	24(6.3%)	85 (16.0%)	79 (16.7%)	<0.001
Dyslipidemia, no. (%)	1090 (53.2%)	317 (47.6%)	197 (52.0%)	304 (57.4%)	272 (57,5%)	<0,001
Glomerular Filtration Rate (mL/min)	78.8 (17.9)	85.5 (16.8)	78.8 (16.4)	77.1 (19.5)	75.5 (17.8)	<0.001
Averaged SBP, mean (SD), mmHg	136.9 (18.5)	123.0 (10.8)	152.1 (11.6)	126.3 (9.7)	156.1 (10.8)	<0.001
Averaged DBP, mean (SD), mmHg	76.8 (10.2)	72.8 (7.9)	83.6 (9.7)	72.6 (8.3)	81.9 (10.1)	<0.001
NEUROPSYCHOLOGICAL TESTING RESULTS	***N* = 2032**	***N* = 665**	***N* = 374**	***N* = 525**	***N* = 468**	
Clinical Dementia Rating = 0.5, no. (%)	1209 (60%)	381 (57.5%)	209 (55.3%)	326 (61.7%)	293 (62.1%)	0.100
CDR Sum of Boxes, mean (SD), score	0.61 (0.72)	0.54 (0.60)	0.57 (0.72)	0.64 (0.70)	0.72 (0.86)	<0.001
Free Reminding Test, mean (SD), tot. score	25.9 (8.4)	27.3 (8.1)	26.2 (8.3)	25.8 (8.4)	23.8 (8.4)	<0.001
Trail Making Test B, mean (SD), good move/s	0.25 (0.12)	0.27 (0.12)	0.25 (0.12)	0.26 (0.13)	0.23 (0.11)	<0.001
Verbal Fluency, mean (SD), words	28.3 (8.7)	29.4 (8.8)	28.2 (8.3)	28.2 (8.9)	26.8 (8.4)	<0.001
Brain Imaging markers	***N* = 1938**	***N* = 628**	***N* = 354**	***N* = 505**	***N* = 451**	
Cortical thickness, mean (SD), mm	2.60 (0.15)	2.62 (0.15)	2.60 (0.15)	2.60 (0.14)	2.58 (0.15)	<0.001
Volume of hippocampus, mean (SD), cm^2	5.40 (0.77)	5.52 (0.77)	5.38 (0.71)	5.44 (0.79)	5.19(0.77)	<0.001
Brain parenchymal fraction, mean (SD), %	71.18 (6.65)	73.29 (6.40)	70.95 (5.52)	70.80(6.60)	68.86(6.98)	<0.001
WMH volume, mean (SD), log(mm^3)	1.73 (1.11)	1.47 (1.08)	1.82 (1.16)	1.74 (1.09)	2.02(1.06)	<0.001
FDG PET MARKERS	***N* = 1187**	***N* = 382**	***N* = 226**	***N* = 309**	***N* = 270**	
SUVr, mean (SD), ratio	1.73 (0.19)	1.76 (0.19)	1.73 (0.19)	1.72 (0.19)	1.68(0.19)	<0.001
CEREBROSPINAL FLUID BIOMARKERS	***N* = 304**	***N* = 105**	***N* = 58**	***N* = 74**	***N* = 67**	
CSF Aβ42/Aβ40, mean (SD), ratio	0.08 (0.04)	0.09 (0.04)	0.08 (0.04)	0.08 (0.04)	0.08(0.03)	0.145
CSF p-tau, mean (SD), pg/ml	62.79 (29.49)	61.48 (32.54)	62.75 (23.41)	62.13 (28.34)	65.63(30.86)	0.835
AMYLOID PET MARKERS	***N* = 577**	***N* = 178**	***N* = 124**	***N* = 143**	***N* = 132**	
SUVT, mean (SD), ratio	0.020 (1.020)	0.007 (1.040)	0.128 (1.080)	0.005 (0.966)	-0.046(1.000)	0.576

Note: Statistical tests used are chi-square and analysis of variance for categorical and continuous variables, respectively.

Abbreviations: SD, standard deviation; *APOE*, apolipoprotein E; BMI, body mass index; WMH, white matter hyperintensities; PET, positron emission tomography; FDG fluorodeoxyglucose; SUVR, standardized uptake value ratio; CSF, cerebrospinal fluid; Aβ, amyloid beta; p-tau, phosphorylated tau; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2 Estimates of direct and total effects of hypertension status on dementia biomarkers and cognition computed from structural equation model: The MEMENTO cohort, 2011–2014

	Direct effects[a]				Total effects[a]		
Antihypertensive treatment High blood pressure status	Pathway variable	β, SD	[95% CI]	*P*-value	β, SD	[95% CI]	*P*-value
Untreated, high blood pressure	Volume of WMH	0.194	[0.051; 0.336]	0.008			
	AD Biomarkers	−0.022	[−0.241; 0.197]	0.842	−0.005	[−0.223; 0.212]	0.961
	Neurodegeneration	−0.018	[−0.133; 0.096]	0.753	0.002	[−0.112; 0.116]	0.973
	Cognition	0.005	[−0.134; 0.143]	0.949	−0.001	[−0.137; 0.134]	0.983
Treated, controlled	Volume of WMH	0.030	[−0.073; 0.132]	0.572			
	AD biomarkers	−0.011	[−0.200; 0.179]	0.912	−0.008	[−0.198; 0.182]	0.934
	Neurodegeneration	−0.020	[−0.129; 0.088]	0.711	−0.019	[−0.124; 0.086]	0.725
	Cognition	0.028	[−0.108; 0.163]	0.689	0.041	[−0.091; 0.173]	0.545
Treated, uncontrolled	Volume of WMH	0.150	[0.025; 0.275]	0.018			
	AD biomarkers	−0.122	[−0.335; 0.092]	0.264	−0.109	[−0.322; 0.104]	0.318
	Neurodegeneration	0.124	[0.001; 0.247]	0.048	0.117	[−0.002; 0.235]	0.053
	Cognition	−0.091	[−0.233; 0.050]	0.206	−0.147	[−0.283; −0.010]	0.035

Note: Estimates (β and 95% Confidence Interval) are reported for one standard deviation increase of the pathway variable. They correspond to the mean difference compared to participants free of hypertension.
Abbreviations: AD, Alzheimer's disease; SD, standard deviation; WMH, white matter hyperintensities.

[a] Direct effect is the coefficient in the direct regression between the explanatory variable and the outcome. Total effect is the combination of the coefficients involved in all the existing paths between the explanatory variable and the outcome (Figure 1).

TABLE 3 Estimates of direct and total effects of observed and latent variables in the structural part of the model: The MEMENTO cohort, 2011–2014

From	To	Direct effects[a]			Total effects[a]		
		β, SD	95% CI	*P*-value	*β*, SD	95% CI	*P*-value
Volume of WMH	AD neuropathology	0.087	[0.012; 0.161]	0.023			
	Neurodegeneration	0.111	[0.060; 0.163]	<0.001	0.131	[0.085; 0.176]	<0.001
	Cognition	−0.031	[-0.084; 0.022]	0.251	−0.135	[−0.179; −0.091]	<0.001
AD pathology	Neurodegeneration	0.221	[0.107; 0.336]	<0.001			
	Cognition	−0.226	[−0.370; −0.082]	0.002	−0.369	[−0.492; −0.246]	<0.001
Neurodegeneration	Cognition	−0.646	[−0.883; −0.409]	<0.001			

Note: Estimates (*β* and 95% confidence interval) are reported for one standard deviation increase of the pathway variable. They correspond to the mean effect for one standard deviation increase of the explanatory variable.

Abbreviations: AD, Alzheimer's disease; SD, standard deviation; WMH, white matter hyperintensities.

[a]Direct effect is the coefficient in the direct regression between the explanatory variable and the outcome. Total effect is the combination of the coefficients involved in all the existing paths between the explanatory variable and the outcome (Figure 1).

ence group (MD = 0.124 SD, 95% CI = [0.001; 0.247]). No hypertension status was significantly associated with AD pathology.

The "treated, uncontrolled" group was the only group globally associated with lower cognition than in the reference group (MD = −0.147 SD, 95% CI = [−0.283; −0.010]). This association was mainly carried out by higher neurodegeneration: once adjusted for neurodegeneration, AD pathology and WML volumes, there was no direct effect of any hypertension exposure on cognition (MD = −0.091 SD, 95% CI = [−0.233; 0.050], $P = 0.21$ for "treated, uncontrolled" vs. reference group). Sensitivity analyses did not suggest pathway modification according to sex and *APOE* (Table S4, Table S5 in supporting information; overall likelihood ratio tests for interactions $P = 0.545$ and $P = 0.223$, respectively). Few modulations were observed though for the "treated, uncontrolled" (Table S6 in supporting information) group according to age. The greater volume of WMH for "treated, uncontrolled" group compared to the reference was carried by participants aged above 71.9 years old (MD = 0.273, 95% CI = [0.107; 0.439] vs. MD = −0.022 95% CI = [−0.143; 0.099] for participants aged 71.9 years old and less).

4 | DISCUSSION

In a cross-sectional analysis of a large clinical cohort including participants with either isolated cognitive complaints or mild cognitive impairment, we report that the deleterious effect of uncontrolled hypertension on cognitive performance is mainly mediated through markers of neurodegeneration and WML load whereas AD biomarkers (amyloid, p-tau) do not seem to have a substantial influence. Interestingly after adjusting on both confounding factors and dementia biomarkers, cognition of participants "untreated, high BP," or "treated, controlled" did not differ from cognition of the reference group (no hypertension). We adjusted our model for overweight (BMI) and diabetes, which are often comorbidities with hypertension. Further adjusted for hypercholesterolemia did not change our results (data not shown).

The "untreated, high BP" group is likely to gather heterogeneous profiles, that is, some participants with recent high BP (and therefore untreated), others with high BP due to white coat effect and this could explain that it is not associated with lower cognition and greater neurodegeneration. It has already been reported that "untreated, high BP" individuals have higher WML volume than "untreated, normal BP" individuals and it is also possible that the impact on cognition could be seen later in time.[17,35]

The observation that neither cognition, nor dementia biomarkers, differed between "treated, normal bp" and "untreated, normal BP" groups is in favor of effective treatment and control of hypertension to be protective for cognition.[36–38] These results indicate that identifying people with uncontrolled hypertension and intervening against hypertension might be a key to prevent the occurrence of dementia.

Several neuroimaging studies have consistently reported effects of hypertension on brain structure and function despite large heterogeneity. Some were restricted to small and selected samples.[39–41] Various definitions of hypertension were considered (either binary

[HBP or treated vs. no hypertension] or continuous SBP/DBP measures, or by taking into account antihypertensive treatment status and blood pressure control). Age at hypertension assessment varied from mid-life[42] to late life. In the Risk Development in Young Adults (CARDIA) Study, white matter integrity (fractional anisotropy [FA]) was investigated in relation to hypertension control in 698 community-dwelling adults (mean age 50 years). They reported no difference in mean FA for participants who were hypertensive but not taking antihypertensive medication, and participants whose hypertension was controlled at normotensive levels through antihypertensives compared to participants who were normotensive. In contrast, mean FA was lower in subjects on antihypertensive drugs but whose blood pressure remained high (i.e., uncontrolled). These results are in line with ours, pointing out that uncontrolled hypertension, even in middle-aged individuals, has an impact on brain structure. However in this report the mediating effect of FA on the hypertension/cognition association was not reported.

The Systolic Blood Pressure Intervention Trial (SPRINT) tested the effect of intensive SBP control (SBP target < 120 mm Hg) versus a standard SBP treatment goal (SBP < 140 mm Hg) total in 9361 randomized participants aged 50 years or older, with SBP 130 to 180 mm Hg at screening visit and increased cardiovascular risk.[43-45] Cognitive results from secondary analysis of the trial indicated a lower rate of mild cognitive impairment with intensive SBP control, with an inconclusive effect on probable dementia.[44] Our findings are consistent with this result as insufficient BP control may be associated with mild cognitive impairment.

Our study is the first to investigate the mediating role of multimodal biomarkers of dementia on the association between hypertension control and cognition. We did not show that AD biomarkers mediated this association. These findings indicate that uncontrolled hypertension may impact brain structure regardless of AD neuropathological changes or before facilitating its development.[46]

Another hypothesis is that high BP may induce a chronic neuroinflammation reaction of the brain, which subsequently contributes to brain structural atrophy by releasing neurotoxic immune mediators.[47] Accumulating evidence has suggested that chronic neuroinflammation is increasingly emerging as an important pathological factor in the development and progression of AD. According to this theory, it is apparent that abnormal Aβ deposition can activate microglia and astrocytes, trigger an innate immune response, and subsequently release inflammatory mediators, which contribute to disease development and progression.[48] Thus chronic inflammation could be a pathophysiological mechanism that supports our findings about association among inadequate control of blood pressure, neurodegeneration, and lower cognition.

There were also some limitations in our study. First, for some biomarkers, particularly AD biomarkers, the rate of missing data was high (85% for CSF biomarkers, 71% for amyloid PET biomarkers). We were, however, able to perform the analysis on the total sample using the full information maximum likelihood estimation (FIML) under the realistic missing at random (MAR) hypothesis, which states that the probability of missing data does not depend on unobserved data.[32] It seemed indeed plausible that systematic differences between observed and missing values for AD biomarkers can be entirely explained by other observed variables (three markers of cognition, four markers for neurodegeneration and covariates including age, sex, *APOE*, education, and cardiovascular risk factor). Also, as MEMENTO cohort recruitment is clinic based, the observed findings may not fully translate in the general older population. On the other hand, undertaking a population-based study with such clinical and subclinical investigations would be challenging, and would also lead to a selection in participation. Selection occurs in both clinical and population-based cohorts and in MEMENTO we have undertaken to minimize it. Finally, by considering a cross-sectional study, the temporal relationship among hypertension status, dementia biomarkers, and cognition were not taken into account, and causal interpretations require cautiousness. The findings thus warrant further exploration in longitudinal studies.

The study has also strengths. A wide range of biomarkers was acquired in a highly standardized setting on >2000 participants allowing a multi-dimensional assessment of brain aging and pathology biomarkers. Using SEM, all this information was simultaneously leveraged in a mediation analysis of the hypertension–cognition association, offering a unique insight on underlying mechanisms.

To conclude, we showed that uncontrolled hypertension is associated with worse brain structure and function. It is possible that these individuals (a quarter of our sample) may not be adhering to their treatment, may not be receiving adequate treatment, or may be phenotypically disposed to high blood pressure. Strategies aiming at optimizing BP control in these individuals could contribute to promoting a healthier brain and dementia prevention.

ACKNOWLEDGMENTS

The MEMENTO cohort is funded by the Fondation Plan Alzheimer (Alzheimer Plan 2008-2012), and the French Ministry of Research (MESRI, DGRI) through the Plan Maladies Neurodégénératives (2014-2019). This work was also supported by CIC 1401-EC, Bordeaux University Hospital (CHU Bordeaux, sponsor of the cohort), Inserm, and the University of Bordeaux. This work received funding from the French National Research Agency (ANR) as part of the Investment for the Future Programme ANR-18-RHUS-0002. The MEMENTO cohort has received funding support from AVID, GE Healthcare, and FUJIREBIO through private–public partnerships. The Insight-PreAD substudy was promoted by INSERM in collaboration with the Institut du Cerveau et de la Moelle Epinière, Institut Hospitalo-Universitaire, and Pfizer and has received support within the "Investissement d'Avenir" (ANR-10-AIHU-06) program. The funders had no role in study design; in data collection, analysis, and interpretation; or in writing of report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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How to cite this article: Lespinasse J, Chêne G, Mangin J-F, et al. Associations among hypertension, dementia biomarkers, and cognition: The MEMENTO cohort. *Alzheimer's Dement*. 2022;00-00. https://doi.org/10.1002/alz.12866