The Journal of Prevention of Alzheimer's Disease 13 (2026) 100579

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Hypertension acts together with Aβ pathology in late-life to promote memory loss

Lucas U Da Ros[a,j,1], João Pedro Ferrari-Souza[b,j,1], Marco Antônio de Bastiani[a], Lucas A. Hauschild[c], Bruna Bellaver[d], Pamela C.L. Ferreira[d], Douglas Teixeira Leffa[d], Guilherme Povala[d], Firoza Z. Lussier[d], Mira Chamoun[e,f], Gleb Bezgin[e,f], Andrea L. Benedet[g], Nesrine Rahmouni[e,f], Arthur C. Macedo[e,f], Kaj Blennow[g,h,o,p], Nicholas Ashton[g,m,n], Henrik Zetterberg[g,h,q,r,s,t], Wyllians Vendramini Borelli[a,b,i], Diogo O. Souza[b], Tharick A. Pascoal[d,l], Pedro Rosa-Neto[e,f,u,v], Eduardo R. Zimmer[a,b,j,k,*], for the Alzheimer's Disease Neuroimaging Initiative[2]

[a] *Graduate Program in Biological Sciences: Pharmacology and Therapeuctis, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[b] *Graduate Program in Biological Sciences: Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[c] *Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[d] *Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA*
[e] *Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, QC, Canada*
[f] *Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada*
[g] *Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
[h] *Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden*
[i] *Memory Center, Hospital Moinhos de Vento, Porto Alegre, RS, Brazil*
[j] *Neuroscience Unit, Hospital Moinhos de Vento, Porto Alegre, RS, Brazil*
[k] *Department of Pharmacology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[l] *Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA*
[m] *Banner Alzheimer's Institute and University of Arizona, Phoenix, AZ, USA*
[n] *Banner Sun Health Research Institute, Sun City, AZ, USA*
[o] *Paris Brain Institute, ICM, Pitié-Salpètrière Hospital, Sorbonne University, Paris, France*
[p] *Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC, Hefei, PR China*
[q] *Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK*
[r] *UK Dementia Research Institute at UCL, London, UK*
[s] *Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China*
[t] *Wisconsin Alzheimer's Disease Research Center, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA*
[u] *McConnel Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada*
[v] *Peter O'donnell Jr Brain Institute, The University of Texas Southwestern Medical center, Dallas, TX, USA*

ARTICLE INFO

Keywords:
Hypertension
Alzheimer's disease
Modifiable risk factor

ABSTRACT

Midlife hypertension (HTN) contributes to cognitive decline in Alzheimer's disease (AD). However, the exact effect of late-life HTN on the AD pathology and on cognitive decline is still controversial. Here, we aimed to assess the impact of HTN and AD pathology in cognitively unimpaired (CU) individuals over 65 years of age on longitudinal cognitive decline. We evaluated 637 CU individuals from two independent cohorts (475 CU individuals from the ADNI cohort; and 162 CU individuals from the TRIAD cohort), with a follow-up of up to 6 years. Linear mixed-effects models showed that HTN and Aβ acted together to promote longitudinal cognitive decline, especially memory loss, in a synergistic way, with a dose-dependent association of blood pressure and Aβ

---

[*] Corresponding author to Neuroscience Unit, Hospital Moinhos de Vento, Porto Alegre, RS, Brazil.
E-mail address: eduardo.zimmer@hmv.org.br (E.R. Zimmer).

[1] Contributed equally as the first author.

[2] 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.

https://doi.org/10.1016/j.tjpad.2026.100579
Received 5 December 2025; Received in revised form 28 March 2026; Accepted 21 April 2026

pathology. Hence, HTN in late-life confers additional risk for cognitive decline, particularly for memory loss, in CU individuals at risk of developing dementia due to AD and is a potential modifiable risk factor even at older age.

1. Introduction

Vascular risk factors (VRFs) are well-established contributors for developing dementia, and, more specifically, Alzheimer's disease (AD) [1–7]. We recently showed that multiple VRFs, including hypertension (HTN), act together with amyloid β (Aβ) and tau pathologies to promote cognitive decline [8]. HTN is considered especially relevant among the VRFs due to its prevalence and strong contribution to AD dementia onset [9]. However, available evidence suggests that this relationship might differ across the lifespan, with different results observed for the effect of midlife and late-life HTN on AD risk [10–16].

HTN in midlife is established as a contributor for future cognitive decline [17] and proposed by the Lancet Standing Commission as a modifiable risk factor for dementia [9]. By contrast, in late-life (aged > 65 years), the impact of HTN on cognitive decline remains controversial. While some studies support that elevated blood pressure (BP) in late-life is associated with increased AD risk [17,18], others indicate a protective relationship [19–22]. Notably, HTN and Aβ pathology commonly co-occur in the older population. Therefore, elucidating the interplay between HTN and Aβ on cognitive decline is imperative to better delineate the complex role of HTN - at different life stages - on dementia onset [8,23]. Moreover, given that cognitive domains are differentially affected across the stages of AD progression, it is also important to determine whether the effects are restricted to specific domains or reflect a global pattern of cognitive deterioration [8].

In a set of 637 cognitively unimpaired (CU) individuals over 65 years from two independent research cohorts, we longitudinally evaluated the association of HTN and AD pathology with longitudinal cognitive decline. We were particularly interested in evaluating the effects across different cognitive domains. Also, we tested the direct relationship between HTN and longitudinal AD biomarker changes. We hypothesized that elevated BP acts together with Aβ pathology to promote higher rates of cognitive decline in older individuals.

2. Methods

2.1. Cohorts

Data were downloaded from Alzheimer's Disease Neuroimaging Initiative (ADNI) database, (https://ida.loni.usc.edu), which was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD, designed to assess different biomarkers associated with the progression of mild cognitive impairment (MCI) and early AD. Complete information about ADNI recruitment and eligibility criteria can be found elsewhere [8]. Institutional Review Boards of all involved sites approved the ADNI study and all research participants or their authorized representatives provided written informed consent.

We also studied participants from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort at McGill University, Canada (https://triad.tnl-mcgill.com), created in 2017 to assess biomarker trajectories and interactions as drivers of dementia. Detailed information about TRIAD recruitment and eligibility criteria can be found elsewhere [24]. This study was approved by the Douglas Mental Health University Institute Research Ethics Board and the Montreal Neurological Institute PET working committee, and all participants provided written informed consent.

2.2. Participants and clinical assessment:

We evaluated 637 CU individuals from two cohorts. We used age > 65 years as a cutoff for defining late-life [9]. Sensitivity analyzes showed similar findings using a different age cutoff (**Supplemental Table 1**). All participants presented Mini-Mental State Examination (MMSE) scores ≥ 24 and Clinical Dementia Rating (CDR) of 0. To investigate the longitudinal cognitive trajectory and risk of progression to cognitive impairment, we assessed individuals with available baseline medical data and baseline AD biomarkers (CSF Aβ_{1-42} and p-tau$_{181}$ or Aβ-PET), as well as longitudinal clinical assessments (up to 6 years). A subset of 357 ADNI participants with longitudinal CSF biomarker data was also analyzed. Information about medical history and use of medications was manually assessed in study records by three independent investigators (JPFS, LAH, and LUDR); the findings were cross-checked, and any discordance was discussed until an agreement was reached [8]. Individuals were considered to have HTN if they had a previous diagnosis registered in the cohort records or were currently using an antihypertensive drug (**Supplementary Material**), regardless of time of onset or exposure duration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the average from the screening and baseline measurements and were used as continuous variables. This methodology aligns with clinical guidelines recommending multiple measurements over several weeks for accurate blood pressure assessment [25]. The time interval between these two measurements had a median (IQR) of 41 (33) days.

2.3. Cognitive assessment:

In the ADNI cohort, we used the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium composite scores for memory, executive function, language, and visuospatial function. Briefly, they assessed all available tests from the cognitive battery and assigned them to one of the domains. Then, all these results were modeled together to calculate a single value for each domain, which is available in the ADNI dataset. This method was designed to allow for inter-cohort comparability [26]. As an outcome for global cognitive performance, we used the Preclinical Alzheimer's Cognitive Composite (mPACC; for further details, see **Supplementary Material**). Clinical progression was defined as an increase equal to or greater than 1 point in the CDR-SB score over the follow-up period [27,28]. In the TRIAD cohort, we assessed memory, executive, language, and visuospatial cognitive domains using composite scores in a similar manner. Memory was assessed using immediate and delayed logical memory tasks, as well as immediate and delayed recall from the Rey Auditory Verbal Learning Test. Language abilities were measured by category fluency and Boston Naming Test. The Birmingham Object Recognition Battery assessed visuospatial function, while executive function was evaluated via Trail-Making Test–B time, digit span backward, and letter fluency (D words). All raw test scores were subsequently Z-transformed based on the mean and standard deviation of CU older adults. Composite scores were calculated by averaging the z-scores of the tests assessed in each cognitive domain [29,30].

2.4. Biomarkers assessment:

CSF Aβ_{1-42} and p-tau$_{181}$ were measured using fully automated Elecsys immunoassays (Roche Diagnostics) as previously reported [31,32]. Measurements outside the analytical range for Aβ_{1-42} (*i.e.*, below 200 pg/mL or above 1700 pg/mL) and p-tau$_{181}$ (i..e, below 8 pg/mL or above 120 pg/mL) were set to their respective technical limits. Individuals were classified as Aβ+ or Aβ- based on CSF p-tau$_{181}$/Aβ$_{1–42}$ ratio > 0.025 [33,34] in the ADNI cohort. Aβ-PET images were acquired 40–70 min after intravenous bolus injection of the radiotracer ([^{18}F] NAV4694). A global SUVR was estimated for each participant by averaging the SUVRs from the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices using the cerebellar gray matter as a reference region. Individuals were classified as Aβ+ or Aβ- based on the global neocortical Aβ-PET SUVR, with the cutoff defined as 1.55 in the TRIAD cohort [35]. Further information regarding the procedures relating to image acquisition and processing can be found elsewhere [30,35].

2.5. Statistical analysis:

At baseline, Student's t-test (continuous variables) and contingency $\chi 2$ test (categorical variables) were used for comparison between HTN groups. For all analyses, HTN (HTN- and HTN+) and Aβ pathology (Aβ- and Aβ+) were considered dichotomous variables. Linear mixed-effects (LME) models were utilized to investigate the associations between HTN, Aβ pathology, and longitudinal cognitive scores, incorporating random intercepts and slopes. Baseline was defined as the first neuropsychological assessment for the participant. For inclusion in longitudinal models, individuals were required to have clinical assessments (HTN status) established at or prior to this baseline cognitive assessment, with biomarker collection occurring within 1.2 years. The median (IQR) time difference between neuropsychological assessment and biomarker collection was 6 (16) days. Sensitivity analyzes showed similar findings using different time intervals cutoffs (**Supplemental Table 2**). The mean and median observation time was 3.7 and 3.9 years, respectively (maximum follow-up of 6 years). Importantly, neither baseline HTN nor Aβ status was associated with the length of follow-up or the number of longitudinal assessments (**Supplemental Figure 1**), indicating a low likelihood of differential attrition bias in our sample. Follow-up assessments are reported in **Supplemental Table 3**.

Primary analyses testing individual and combined effects of HTN and Aβ pathology on longitudinal cognitive trajectories were replicated across the ADNI and TRIAD cohorts. Secondary analyses were conducted using continuous BP values. Also, LME models were employed to assess the impact of HTN on the longitudinal trajectory of CSF AD biomarkers (CSF Aβ$_{1–42}$ and p-tau$_{181}$), which were treated as continuous variables. Time was operationalized as years from baseline and models were corrected for age, sex, apolipoprotein E ε4 (*APOEε4*) status, years of education, and additional VRFs, including cardiovascular disease, left ventricular hypertrophy, heart failure, diabetes mellitus, hyperlipidemia, smoking and atrial fibrillation (see **Supplementary Material**). LME-based analyses were implemented using the R package "lme4". Fitness of models were evaluated using Quantile-Quantile (QQ) Plots (for more details, see **Supplementary Material).** Time-to-event analysis was conducted to assess the risk of clinical progression *(i.e.,*1-point increase in the CDR-SB score) according to HTN and Aβ pathology status using Cox proportional hazard, which accounted for the following predictors: group, age, sex, years of education and *APOEε4* status. Kaplan-Meier curves illustrate observed survival probabilities across groups, which were statistically compared using the generalized log-rank test. Statistical significance level was set as $p < 0.05$, two-tailed. The R Statistical Software was used to perform all statistical analyses (R version 4.3.1, http://www.r-project.org/).

3. Results

A total of 475 CU individuals from ADNI were included in our main analysis, of whom 56 % were women and 93 % were white (Table 1). The mean (SD) age of our population was 73 (5.6) years, 51 % had a diagnosis of HTN, and 26 % were Aβ+. At baseline, HTN+ individuals were significantly older than HTN- individuals and, as expected, exhibited significantly higher SBP and DBP values. All other demographic characteristics were well-balanced between groups. Although HTN+ individuals exhibited a trend towards worse cognitive performance at baseline, this difference did not achieve statistical significance. All antihypertensive drugs considered are listed in **Supplementary Table 4.**

Table 1
Demographics and clinical information of ADNI participants.

	Overall (n = 475)	HTN- (n = 235)	HTN+ (n = 240)	p-value
Age, years	73.6 (5.6)	72.9 (5.5)	74.3 (5.7)	0.0089
Female, No. (%)	264 (55.6)	135 (57.4)	129 (53.8)	0.470
Years of education, years	16.5 (2.5)	16.6 (2.5)	16.4 (2.6)	0.321
APOEε4 carriers, No. (%)	137 (28.8)	68 (28.9)	69 (28.8)	0.999
MMSE score	29.1 (1.1)	29.2 (1.1)	29.0 (1.2)	0.063
Aβ+ status, No. (%)	130 (27.4)	61 (26.0)	69 (28.8)	0.526
SBP, mmHg	134 (14.5)	131 (14.2)	137 (14.1)	0.0000018
DBP, mmHg	74.5 (8.2)	73.4 (8.2)	75.5 (8.1)	0.0071
Follow-up, years	3.72 (1.8)	3.66 (1.8)	3.79 (1.8)	0.4278

Continuous variables are presented as mean (SD). Student's t-test (continuous variables) and contingency $\chi 2$ test (categorical variables) were used for comparison between HTN groups. Abbreviations: Aβ = amyloid-β; ADNI = Alzheimer's Disease Neuroimaging Initiative; APOEε4 = Apolipoprotein E ε4; DBP = diastolic blood pressure; HTN = hypertension; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure, SD = standard deviation.

3.1. HTN in late-life and aβ pathology acted jointly to promote memory loss

HTN in late-life exacerbated the effect of Aβ pathology on memory function, and their interaction was associated with longitudinal memory loss (Fig. 1a; HTN x Aβ x time: $\beta = -0.05$, $p = 0.012$). HTN alone had no significant effect on any cognitive domain. When analyzing the interaction between continuous SBP and Aβ status, we could see a dose-dependent effect on memory function (SBP x Aβ x time, $\beta = -0.01$, $p = 0.046$; Fig. 1b). The model analyzing DBP had a similar trend, but did not reach statistical significance (DBP x Aβ x Time, $\beta = -0.01$, $p = 0.129$). Language ability deterioration was driven by Aβ pathology (Aβ x Time, $\beta = -0.03$, $p = 0.014$), and HTN did not play a role in this association (all $p \geq 0.856$; Fig. 1d). No significant effects for HTN, Aβ, or their interaction were observed on executive function (all $p \geq 0.108$; Fig. 1c) and visuospatial function (all $p \geq 0.349$; Fig. 1e). All LME model coefficients are shown in Table 2. Sensitivity analysis assessing global cognitive decline (**Supplemental Figure 2**) and models assessing Aβ positivity with Aβ-PET showed similar findings (**Supplemental Figure 3**).

3.2. Greater risk of conversion into cognitive impairment in hypertensive aβ+ individuals

In time-to-event analysis, Kaplan-Meier curves demonstrated that the Aβ+HTN+ group presented a separated survival probability curve over 6 years in comparison to Aβ-HTN-, Aβ-HTN+, Aβ+HTN- (log-rank $p < 0.001$). Cox-proportional hazard models supported that the Aβ+HTN+ had the highest risk of clinical progression (Fig. 1f; adjusted HR = 7.79, $p < 0.001$). Adjusted HRs from the Cox proportional hazard regression model are reported in **Supplemental Table 5.**

3.3. HTN in late-life had no impact on AD pathology

HTN in late-life had no impact in predicting the baseline levels nor the longitudinal trajectory of CSF p-tau$_{181}$/Aβ$_{1-42}$ ratio (HTN x time: $\beta = -0.006$, $p = 0.215$; Fig. 2). Similar results were observed for analysis assessing CSF p-tau$_{181}$ and Aβ$_{1-42}$ individually (**Supplemental Figure 4**), further supporting that HTN did not affect AD CSF biomarkers**.**

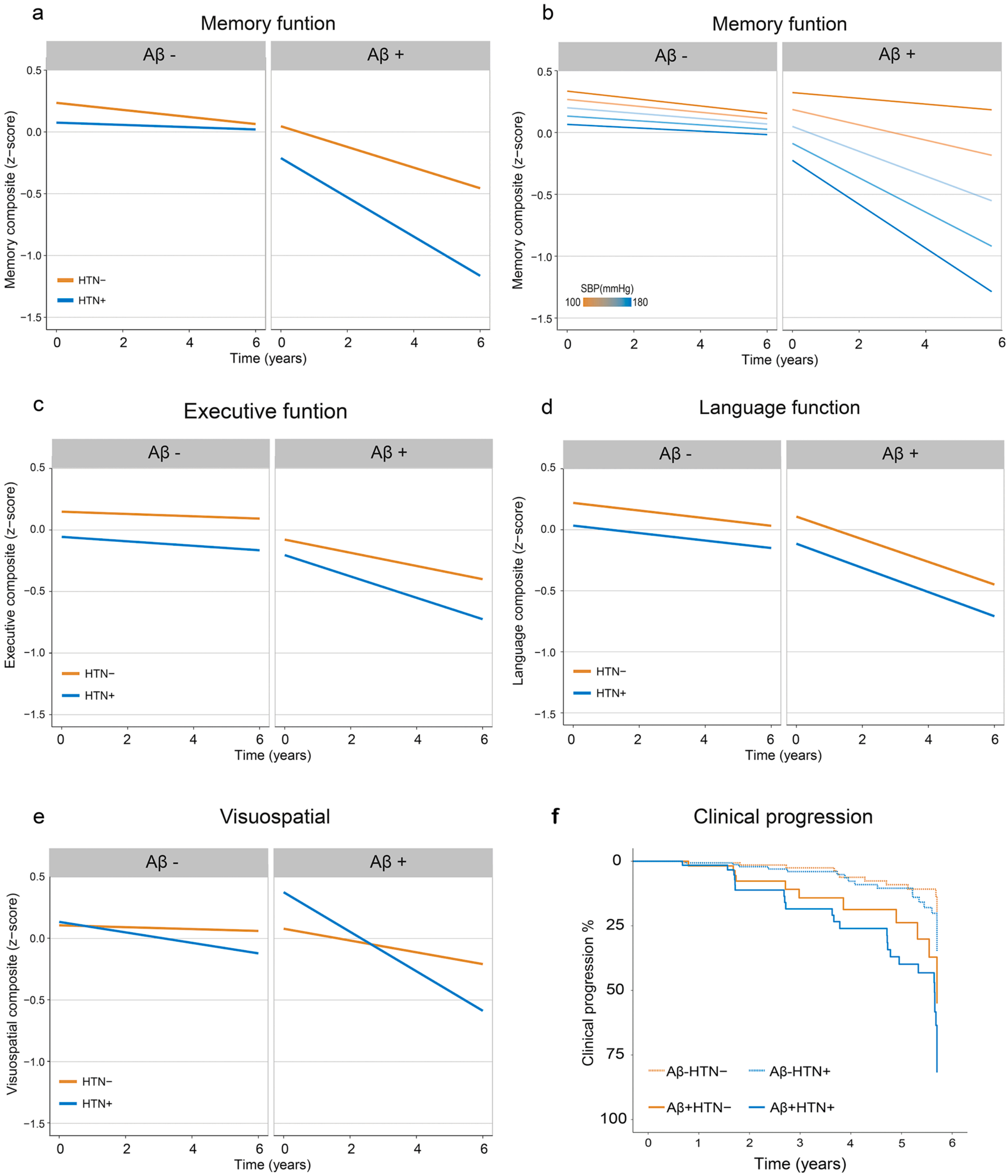

Fig. 1. HTN together with Aβ pathology in late-life is associated with longitudinal memory deterioration. Predicted longitudinal trajectories for memory function estimated from LME models according to baseline (**a**) Aβ pathology and HTN, as well as (**b**) Aβ pathology and SBP. Longitudinal trajectories for (**c**) executive function, (**d**) language function, and (**e**) visuospatial function estimated from LME models according to baseline HTN and Aβ pathology. (**f**) Kaplan-Meyer curves for clinical progression according to baseline HTN and Aβ pathology. All models were adjusted for age, gender, apolipoprotein E ε4 (*APOEε4*) status, other VRFs, and years of education.

Table 2
LME model coefficients.

	ADNI		TRIAD	
	β (95 % CI)	*P*-value	β (95 % CI)	*P*-value
Model[a]: Memory composite ~ Aβ x HTN x Time + Covariates[*] x time				
Aβ	-0.07 (-0.19 to 0.05)	0.255	-0.19 -0.56 to 0.19)	0.333
HTN	-0.06 (-0.15 to 0.03)	0.173	-0.20 (-0.48 to 0.09)	0.174
Aβ x Time	-0.02 (-0.05 to 0.01)	0.140	0.16 (-0.03 to 0.35)	0.106
HTN x Time	0.01 (-0.01 to 0.03)	0.366	0.10 (-0.05 to 0.24)	0.182
Aβ x HTN x Time	-0.05 (-0.09 to -0.01)	**0.012**	-0.64 (-0.94 to -0.34)	**< 0.001**
Model[b]: Language composite ~ Aβ x HTN x Time + Covariates[*] x time				
Aβ	-0.08 (- 0.17 to 0.01)	0.084	0.18 (-0.21 to 0.56)	0.366
HTN	- 0.05 (-0.18 to 0.08)	0.468	0.06 (-0.23 to 0.35)	0.689
Aβ x Time	-0.03 (-0.06 to -0.01)	**0.014**	-0.20 (-0.36 to -0.04)	**0.015**
HTN x Time	-0.001 (-0.02 to 0.02)	0.856	0.02 (-0.10 to 0.14)	0.796
Aβ x HTN x Time	0.00 1(-0.03 to 0.04)	0.896	0.12 (-0.12 to 0.37)	0.327
Model[c]: Executive composite ~ Aβ x HTN x Time + Covariates[*] x time				
Aβ	0.11 (-0.17 to 0.01)	0.086	0.10 (-0.25 to 0.46)	0.565
HTN	-0.08 (-0.17 to 0.00)	0.057	-0.07 (-0.19 to 0.34)	0.592
Aβ x Time	-0.03 (-0.06 to 0.01)	0.108	-0.04 (-0.23 to 0.14)	0.647
HTN x Time	-0.001 (-0.03 to 0.02)	0.763	-0.11 (-0.25 to 0.02)	0.102
Aβ x HTN x Time	-0.01 (-0.05 to 0.03)	0.676	-0.04 (-0.32 to 0.25)	0.797
Model[d]: Visual spatial composite ~ Aβ x HTN x Time + Covariates[*] x time				
Aβ	-0.01 (-0.10 to 0.09)	0.857	-0.01 (-0.56 to 0.54)	0.976
HTN	-0.05 (-0.12 to 0.09)	0.134	0.07 (-0.34 to 0.49)	0.728
Aβ x Time	-0.01 (-0.05 to 0.02)	0.470	0.20 (-0.12 to 0.54)	0.222
HTN x Time	-0.03 (-0.02 to 0.02)	0.822	-0.06 (-0.32 to 0.18)	0.587
Aβ x HTN x Time	-0.02 (-0.07 to 0.02)	0.349	-0.40 (-0.92 to 0.11)	0.125

Table 2. HTN refers to a dichotomous variable (HTN- *vs.* HTN+), Aβ pathology refers to a dichotomous variable (Aβ- *vs.* Aβ+). All coefficients derive from the model including the interaction of Aβ x HTN x Time adjusted for the interaction of Covariates*Time.

[*] Covariates: age, gender, *APOE*ε4 status, other VRFs, years of education, and their interaction with time.

[a] Marginal R^2: ADNI = 0.23; TRIAD = 0.17.

[b] Marginal R^2: ADNI = 0.15; TRIAD = 0.23.

[c] Marginal R^2: ADNI = 0.19; TRIAD = 0.19.

[d] Marginal R^2: ADNI = 0.06; TRIAD = 0.55.

3.4. Validation of findings in an independent cohort

Next, we aimed to validate our main findings in an independent cohort. We assessed 162 TRIAD CU individuals, with a mean (SD) age of 72.6 years (5.1), 68 % were women, 43 % had HTN, and 26 % were Aβ+ (**Supplemental Table 6**). Group distributions based on HTN and Aβ were similar between ADNI and TRIAD cohorts (Supplemental Table 7). Like the results observed in the ADNI cohort , longitudinal memory loss was impacted by the synergistic effect of HTN and Aβ pathology (HTN x Aβ x time: $\beta = -0.64$, $p < 0.001$; Fig. 3). Again, similarly to the ADNI, longitudinal language function deterioration was only associated with Aβ pathology (Aβ x time: $\beta = -0.2$, $p = 0.015$) and no significant association with longitudinal executive function (all $p \geq 0.102$) and visuospatial trajectories (all $p \geq 0.125$) were found. QQ-plots corroborated the adequacy of LME models as no deviation from normality was identified in our models (data not shown). Model coefficients for analyses in TRIAD and ADNI cohorts are shown in Table 2.

4. Discussion

In the present study, we found that HTN together with Aβ pathology in late-life was associated with longitudinal cognitive decline in CU elderly individuals - particularly affecting the memory domain - across two independent cohorts. Of note, the joint effects of HTN and Aβ occurred as a function of continuous BP levels and were further corroborated by time-to-event analyses demonstrating that Aβ+ individuals with HTN are at higher risk of clinical progression. Lasty, we observed that HTN was not directly related to the baseline levels and longitudinal trajectories of CSF AD biomarkers.

Our results are supported by previous animal model studies showing that HTN accelerates AD-related changes in mice [36]. Yet, a greater number of studies have reported an association between midlife - rather than late-life - HTN and cognitive decline [13]. Some evidence supported the concept that HTN has a U-shaped association with dementia risk, with elevated BP in late-life exerting protective effects on cognitive outcomes [19,20,22]. By contrast, two cohort studies assessing a combined pool of more than 6000 individuals have shown that the effect of HTN on cognitive decline and incident dementia persists from mid to late-life [37,38].

One could hypothesize that this heterogeneity occurs due to the differences in the age composition of the investigated populations, because, even within late-life cohorts, there are conflicting results when assessing individuals in their 60s or 70s with those in their 80s or 90s [39,40]. Building on prior evidence, our results align more closely with studies involving the younger segment of this age spectrum, and show that prevalent HTN in late-life individuals, regardless of the time of diagnosis, also has a role in cognitive deterioration later in life by acting together with Aβ pathology.

Interestingly, we found that the combined effect of HTN and Aβ pathology specifically affects the memory-related cognitive domain. This finding may be attributed to the early contribution of HTN to AD development, given that memory loss is typically one of the earliest clinical manifestations of typical AD [29]. Previous studies support this interpretation by highlighting the early involvement of vascular dysfunction in the pathophysiological progression of AD [41]. Taking together with the fact that HTN and Aβ pathology commonly co-occur in the elderly, and that HTN is a modifiable risk factor, these observations suggest that proper BP control might be a potential target for slowing memory decline in individuals at high risk of AD.

Our findings indicate that HTN is not associated with baseline levels or longitudinal changes in CSF $A\beta_{1\text{–}42}$ or p-tau$_{181}$. The existing literature presents conflicting evidence concerning the impact of HTN on AD pathophysiology. While some studies show a direct effect of HTN in the longitudinal trajectories of AD biomarkers [42], others found no

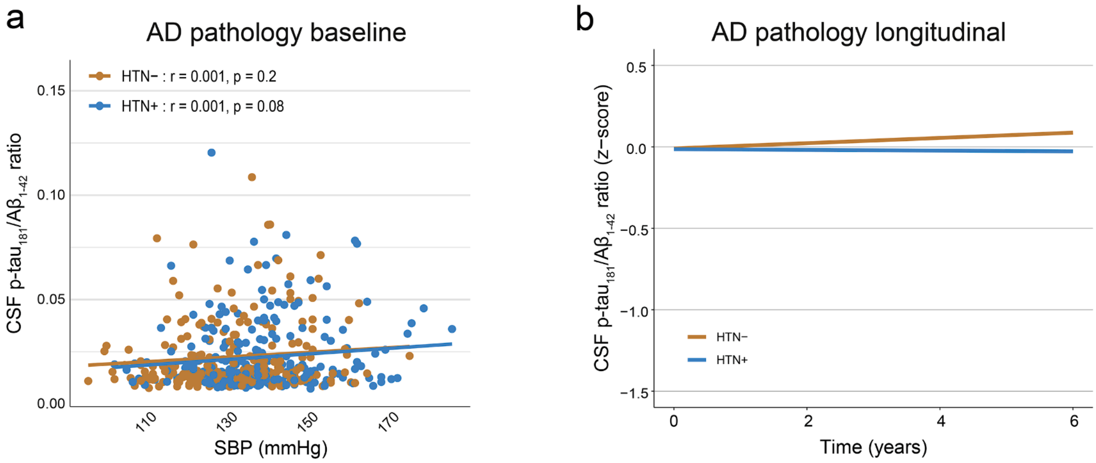

Fig. 2. HTN had no effect on Aβ pathology. (**a**)Scatterplot showing the association between SBP levels and CSF p-tau$_{181}$/Aβ$_{1–42}$ ratio.(**b**) Predicted longitudinal trajectory of CSF p-tau$_{181}$/Aβ$_{1–42}$ ratio estimated from LME models according to HTN.

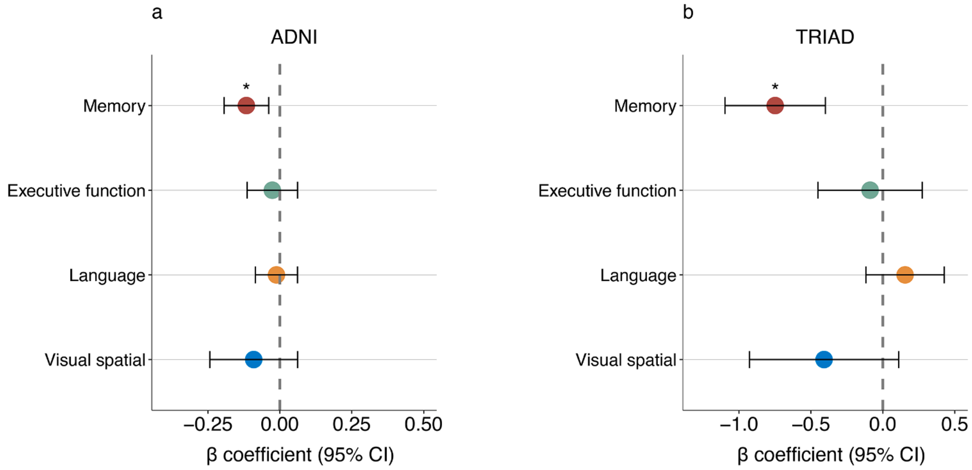

Fig. 3. TRIAD and ADNI cohorts showed similar patterns. Adjusted β coefficients and 95 % confidence intervals extracted from the LME models assessing the interactive effect of HTN and Aβ pathology on memory, executive, language and visuospatial functions from (a) ADNI and (b) TRIAD.

association [43]. Similarly, post-mortem studies have also yielded inconsistent results: some identified a direct relationship between HTN and AD-related pathology, whereas others observed an association with cerebrovascular changes but not with AD hallmarks (*i.e.*, neuritic plaques and neurofibrillary tangles) [44–46]. A recent report from the population-based FRAMINGHAM study supported the absence of a direct relationship between BP and Aβ PET accumulation [47], which is in line with our data showing that HTN is not associated with CSF Aβ$_{1–42}$ decrease. Our results are in favor of the notion that HTN and AD pathology act jointly but through different mechanisms to promote cognitive decline.

In recent years, anti-Aβ immunotherapy was shown to have an effect on slowing AD progression by up to 35% in early stages of the disease [48,49]. Based on the concept that pathophysiological progression starts decades before symptoms onset, it has also been proposed that better outcomes could potentially be observed by treating individuals in asymptomatic preclinical stages. Yet, a recent study found no benefit of anti-Aβ immunotherapy in preclinical AD after 4.5 years [50]. One possible explanation is that targeting Aβ alone may be insufficient to slow pathology and cognitive decline in at-risk CU individuals, suggesting the need for complementary therapies [51].

In the context of finding alternatives to enhance the efficacy of current therapies, recent investigations have demonstrated a small, but statistically significant, effect of treating HTN in the prevention of incident mild cognitive impairment and dementia [52,53]. Furthermore, a Mendelian randomization study showed a benefit in treating HTN in older patients for preventing incident dementia [54]. This, coupled with evidence that anti-hypertensive drugs moderate the interaction between BP and AD [55], supports the idea that proper HTN control can improve anti-Aβ therapy outcomes within multi-target AD strategies.

Methodological strengths of the present work include the use of two independent clinically characterized cohorts for studying aging and dementia, the use of detailed neuropsychological testing to evaluate longitudinal cognitive trajectories across different domains, and the availability of AD fluid and imaging biomarkers in a population of CU individuals.

Some limitations should be acknowledged. Participants were volunteers interested in dementia research, potentially introducing self-selection bias. Individuals with HTN may also have higher dropout rates which could cause attrition bias, although follow-up analyses suggest minimal impact on our findings [56]. HTN was self-reported, preventing assessment of age at onset; thus, results reflect prevalent late-life HTN, and effects across the lifespan cannot be determined [20, 22]. Both cohorts excluded individuals at high cerebrovascular risk, limiting generalizability to broader populations. Variability in the definition of late-life may also influence interpretation, it has been defined as age greater than 60 years [19], greater than 65 years[9,37] and has been further stratified into more groups even within late-life spectrum [22], although our findings were consistent across definitions. Finally, the predominantly white samples may limit applicability to other ethnic groups [57].

In conclusion, our work suggests that HTN and Aβ pathology act together in late-life to promote memory loss in CU individuals. Proper HTN treatment is a potential strategy to enhance the efficacy of currently available treatments for AD in a multi-target approach.

Funding

This work was supported by CNPq 306815/2025–7 (ERZ) and CAPES 88887.176367/2025–00 (LUDR). ERZ is supported by CAPES (#88881.996985/2024–01), CNPq (#12410/2018–2, #435642/2018–9, #312306/2021–0, #409066/2022–2, #447074/2023–7, #409595/2023–3, and #444880/2024–0), Instituto Nacional de Ciência e Tecnologia em Excitotoxicidade Neuroproteção (#465671/2014–4), Instituto Nacional de Ciência e Tecnologia em Saúde Cerebral (#406020/2022–1), Instituto Serrapilheira (#Serra-1912–31365; and #R-2401–47242), FAPERGS (#21/2551–0000673-0 and #85053.824.30451.24062024), Alzheimer's Association (#21–850670; #22–928689; #23–1148735; and #BFECAA2024), National Academy of Neuropsychology and Alzheimer's Association (#22–92838), Michael J. Fox Foundation (#MJFF-023158), and the Ministério da Saúde (#00030420240118–003490). The contents of this publication are solely the author's responsibility and do not represent the official views of these institutions.

Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Data from the ADNI cohort can be accessed from https://ida.loni.usc.edu. Anonymized data from the TRIAD cohort can be obtained by request from a qualified academic researcher, solely for the purpose of reproducing the procedures and findings reported in this article.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used GPT-4o in order to improve readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of interest

LUDR reports no disclosures relevant to the manuscript. JPF-S reports no disclosures relevant to the manuscript. MADB is a co-founder and a minority shareholder at masima. LAH reports no disclosures relevant to the manuscript. BB reports no disclosures relevant to the manuscript. WVB is a co-founder and a minority shareholder at masima. TAP reports no disclosures relevant to the manuscript. PRN has served in the scientific advisory board of Novo Nordisk, Eisai, Ely Lilly. PRN also served as a consultant to Eisai, and Cerveau radiopharmaceuticals. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; KB has served as a consultant at advisory boards or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. ERZ has served on scientific advisory boards and/or as a consultant or speaker for Nintx, Novo Nordisk, Biogen, Eli Lilly, Magdalena Biosciences, and Masima. He is also a co-founder and minority shareholder of Masima.

CRediT authorship contribution statement

Lucas U Da Ros: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **João Pedro Ferrari-Souza:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Marco Antônio de Bastiani:** Software, Methodology, Formal analysis. **Lucas A. Hauschild:** Data curation. **Bruna Bellaver:** Writing – review & editing, Validation. **Pamela C.L. Ferreira:** Writing – review & editing, Validation. **Douglas Teixeira Leffa:** Writing – review & editing, Supervision. **Guilherme Povala:** Writing – review & editing, Software. **Firoza Z. Lussier:** Writing – review & editing. **Mira Chamoun:** Writing – review & editing. **Gleb Bezgin:** Writing – review & editing. **Andrea L. Benedet:** Writing – review & editing. **Nesrine Rahmouni:** Writing – review & editing. **Arthur C. Macedo:** Writing – review & editing. **Kaj Blennow:** Writing – review & editing, Funding acquisition. **Nicholas Ashton:** Writing – review & editing, Data curation. **Henrik Zetterberg:** Writing – review & editing, Funding acquisition. **Wyllians Vendramini Borelli:** Writing – review & editing, Supervision, Conceptualization. **Diogo O. Souza:** Writing – review & editing, Supervision. **Tharick A. Pascoal:** Writing – review & editing, Funding acquisition. **Pedro Rosa-Neto:** Writing – review & editing, Funding acquisition. **Eduardo R. Zimmer:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eduardo Rigon Zimmer reports a relationship with Novo Nordisk Inc that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California.

We acknowledge all study participants and the staff of the McGill University Research Center for Studies in Aging. We thank D. Jolly, A. Kostikov, M. Samoila-Lactatus, K. Ross, M. Boudjemeline, and S. Li for assisting in the radiochemistry production, as well as R. Strauss, E. Strauss, G. Gagné, C. Mayhew, T. Vinet-Celluci, K. Wan, S. Sbeiti, M. Jin Joung, M. Olmand, R. Nazar, H.-H. Hsiao, R. Bouhachi, and A. Aliaga for helping with the acquisition of the data. We thank the Colin J. Adair Charitable Foundation. We also acknowledge S. Jones and L. Chouliaras at the University of Cambridge for discussing the findings. The views expressed are those of the authors and not necessarily those of the National Institute for Health Research (NIHR) or the Department of Health and Social Care.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100579.

References

[1] Masters CL, et al. Alzheimer's disease. Nat Rev Dis Primers 2015;1:15056.
[2] Luchsinger JA, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 2005;65:545–51.
[3] Kivipelto M, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322:1447–51.
[4] Ott A, et al. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;53:1937–42.
[5] Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2010;67:505–12.
[6] Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 2007;166:367–78.
[7] Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J Alzheimers Dis 2017;56:215–28.
[8] Ferrari-Souza JP, et al. Vascular risk burden is a key player in the early progression of Alzheimer's disease. Neurobiol Aging 2024;136:88–98.
[9] Livingston G, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet 2024;404:572–628.
[10] Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's Disease: a systematic review and meta-analysis. J Alzheimers Dis 2019;71:307–16.
[11] Levine DA, et al. Blood pressure and cognitive decline over 8 years in middle-aged and older black and white Americans. Hypertension 2019;73:310–8.
[12] Yu J-T, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. J Neurol Neurosurg Psychiatry 2020;91:1201–9.
[13] Ou Y-N, et al. Blood pressure and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 209 prospective studies. Hypertension 2020;76:217–25.
[14] Iadecola C, et al. Impact of hypertension on cognitive function: a scientific statement from the American heart association. Hypertension 2016;68:e67–94.
[15] Launer LJ, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21:49–55.
[16] Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277–81.
[17] Blood pressure from mid- to late life and risk of incident dementia. Neurology https://www.neurology.org/doi/10.1212/WNL.0000000000004741.
[18] Amier RP, et al. Hypertensive exposure markers by MRI in relation to cerebral small vessel disease and cognitive impairment. JACC Cardiovasc Imaging 2021;14:176–85.
[19] Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. Ageing Res Rev 2009;8:61–70.
[20] Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 2005;4:487–99.
[21] Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–46.
[22] van Dalen JW, et al. Association of systolic blood pressure with dementia risk and the role of age, U-shaped associations, and mortality. JAMA Intern Med 2022;182:142–52.
[23] Lespinasse J, et al. Associations among hypertension, dementia biomarkers, and cognition: the MEMENTO cohort. Alzheimers Dement 2023;19:2332–42.
[24] Therriault J, et al. Association of apolipoprotein E ε4 with medial temporal tau independent of amyloid-β. JAMA Neurol 2020;77:470–9.
[25] Muntner P, et al. Measurement of blood pressure in humans: a scientific statement from the American heart association. Hypertension 2019;73:e35–66.
[26] Mukherjee S, et al. Cognitive domain harmonization and cocalibration in studies of older adults. Neuropsychology 2023;37:409–23.
[27] Donohue MC, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol 2014;71:961–70.
[28] Donohue MC, et al. Cross-validation of optimized composites for preclinical Alzheimer's disease. Alzheimers Dement 2017;3:123–9.
[29] Therriault J, et al. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. Nat Aging 2022;2:526–35.
[30] Ferrari-Souza JP, et al. Astrocyte biomarker signatures of amyloid-β and tau pathologies in Alzheimer's disease. Mol Psychiatry 2022;27:4781–9.
[31] Bittner T, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement 2016;12:517–26.
[32] Lifke V, et al. Elecsys® Total-tau and Phospho-tau (181P) CSF assays: analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. Clin Biochem 2019;72:30–8.
[33] Brum WS, et al. Clinical relevance of three-range cutpoints in Alzheimer's disease CSF biomarkers. Alzheimers Dement 2021;17.
[34] Hansson O, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement 2018;14:1470–81.
[35] Therriault J, et al. Determining amyloid-β positivity using 18F-AZD4694 PET imaging. J Nucl Med 2021;62:247–52.
[36] Cifuentes D, et al. Hypertension accelerates the progression of Alzheimer-like pathology in a mouse model of the disease. Hypertension 2015;65:218–24.
[37] McGrath ER, et al. Blood pressure from mid- to late life and risk of incident dementia. Neurology 2017;89:2447–54.
[38] Walker KA, et al. Association of midlife to late-life blood pressure patterns with incident dementia. JAMA 2019;322:535–45.
[39] Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. Curr Hypertens Rep 2017;19.
[40] Li G, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. J Am Geriatr Soc 2007;55:1161–7.
[41] Iturria-Medina Y, et al. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 2016;7:11934.
[42] Bos I, et al. Vascular risk factors are associated with longitudinal changes in cerebrospinal fluid tau markers and cognition in preclinical Alzheimer's disease. Alzheimers Dement 2019;15:1149–59.
[43] Vemuri P, et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. Ann Neurol 2017;82:706–18.
[44] Arvanitakis Z, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology 2018;91:e517–25.
[45] Wang LY, et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study. J Am Geriatr Soc 2009;57:1975–81.
[46] Petrovitch H, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. Neurobiol Aging 2000;21:57–62.
[47] Mulligan M, et al. Blood pressure trajectories and amyloid- and tau-PET burden in cognitively healthy adults: the Framingham heart study (P1-9.009). Neurology 2024;102.
[48] van Dyck CH, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9–21.
[49] Mintun MA, et al. Donanemab in early Alzheimer's disease. N Engl J Med 2021;384:1691–704.
[50] Sperling RA, et al. Trial of solanezumab in preclinical Alzheimer's disease. N Engl J Med 2023;389:1096–107.
[51] Rafii MS, et al. The AHEAD 3-45 study: design of a prevention trial for Alzheimer's disease. Alzheimers Dement 2023;19:1227–33.
[52] Gupta A, et al. Treatment of hypertension reduces cognitive decline in older adults: a systematic review and meta-analysis. BMJ Open 2020;10:e038971.
[53] He J, et al. Blood pressure reduction and all-cause dementia in people with uncontrolled hypertension: an open-label, blinded-endpoint, cluster-randomized trial. Nat Med 2025:1–8.
[54] Hughes D, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. JAMA 2020;323:1934–44.
[55] Guo Y, et al. Anti-hypertensive drugs moderate the relationship of blood pressure with Alzheimer's pathologies and neurodegenerative markers in non-demented hypertensive older adults. J Prev Alzheimer 19s Dis 2024. https://doi.org/10.14283/jpad.2024.40.
[56] Lacey RJ, Jordan KP, Croft PR. Does attrition during follow-up of a population cohort study inevitably lead to biased estimates of health status? PLoS One 2013;8:e83948.
[57] Race, R. & Health, C. *Racism, and cardiovascular health: applying a social determinants of health framework to racial/ethnic disparities in cardiovascular disease.*