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# Blood Pressure and Neuropsychological Outcomes in Very Old Adults: Cross-Sectional Findings from the IlSIRENTE Cohort

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## Abstract

Investigations into the connections between hypertension-related factors and cognitive abilities, emotional state, and behavioral issues in older adults have generated inconsistent outcomes. One likely reason for these varying conclusions is that previous work has often failed to properly account for the role of angiotensin-converting enzyme inhibitors (ACEIs) when performing statistical adjustments. With this in mind, the current study explored the cross-sectional links among hypertension-related indicators, ACEI treatment, and cognitive performance, mood, and behavioral symptoms in very elderly individuals. Data for this analysis came from the IlSIRENTE database, a prospective cohort study that included every person aged 80 years and older living in the Sirente geographic area (n = 364). Blood pressure (BP) readings were obtained after participants had rested for 20 to 40 minutes while sitting upright. All medications were classified according to the Anatomical Therapeutic and Chemical coding system. Cognitive function, mood, and behavioral symptoms were evaluated using the Minimum Data Set Home Care tool. Levels of inflammatory markers in the blood were also determined.
Hypertension-related measures demonstrated significant associations with several cognitive, mood, and behavioral outcomes after adjusting for relevant covariates. Nevertheless, only the inverse relationship between hypertension and reduced difficulties with short-term memory stayed statistically significant. Compared with normotensive individuals, those with hypertension showed lower blood concentrations of inflammatory markers. The findings suggest that higher blood pressure values are linked to fewer self-reported memory complaints among very old adults. In addition, hypertensive participants had reduced levels of inflammatory markers in their blood. The use of ACEIs may influence this overall picture.

**Keywords:** Blood pressure, Neuropsychological outcomes, Older adults, IlSIRENTE cohort

## Introduction

Hypertension is a persistent medical condition defined by ongoing increases in blood pressure (BP) [1]. It is very common in older populations, affecting more than 70% of people aged 65 years and older [2]. These statistics are concerning because poorly controlled hypertension raises the risk of multiple serious health problems, such as stroke, heart attack, and heart failure [1].

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In addition to its established role in cardiovascular disease, there has been substantial interest in how hypertension might affect brain function. A number of studies have associated the worsening of hypertension with declining cognitive performance and the onset of mild cognitive impairment (MCI) as well as dementia, including Alzheimer's disease (AD) [3–5]. However, the evidence is mixed, since other research suggests that elevated blood pressure could actually offer protection, especially in very old adults, by helping to counter the damaging effects of aging on the brain's blood vessels [6–9].
One of the main underlying causes of hypertension is dysfunction within the renin-angiotensin system [10]. Overproduction and poor regulation of angiotensin II (ANGII) are known to cause harmful changes in multiple

organs, including the heart, blood vessels, and kidneys [10, 11]. In the brain, ANG II leads to significant structural and functional alterations [12–14] that become more severe with advancing age [13]. Preclinical studies have shown that treatment with angiotensin-converting enzyme inhibitors (ACEIs) can lessen the damaging impact of ANGII on brain tissue [15–17], possibly by decreasing inflammation in the surrounding environment [15–17].

To further explore this topic, the present study set out to investigate the relationships between hypertension-related parameters and various aspects of cognitive function, mood, and behavior in a carefully characterized group of very old adults. The potential modifying effect of ACEIs on these relationships was also examined.

## Materials and Methods

The present analysis relied on data extracted from the IlSIRENTE study database [18]. IlSIRENTE constituted a prospective cohort investigation carried out within the mountainous Sirente territory located in L'Aquila province, Abruzzo region, Central Italy. All procedures conformed to the ethical standards of the Declaration of Helsinki, and the study protocol obtained formal approval from the Ethics Committee at Università Cattolica del Sacro Cuore, Rome, Italy. Prior to participation, every individual gave written informed consent.

### *Study population*

During October 2003, registry offices from the 13 municipalities participating in the project supplied a full roster of residents living in the Sirente area. Study candidates were then pinpointed by identifying every person born prior to 1 January 1924 who remained resident in the region. In total, the IlSIRENTE cohort comprised 364 elderly participants.

### *Data collection*

Initial evaluations commenced in December 2003 and concluded by September 2004. Subsequent follow-up examinations occurred exactly 24 months following the baseline visit. Medical history, prescribed medications, and various lifestyle factors—including smoking status, alcohol use, and level of physical activity—were documented through established and validated survey instruments [18]. Standing height was recorded using a stadiometer, while body weight was determined on a calibrated analog scale. Body mass index (BMI) was derived by dividing the participant's weight (expressed in kilograms) by the square of their height (expressed in meters, $m^2$).

### *Hypertension parameters*

After allowing participants to rest quietly for 20 to 40 minutes, blood pressure (BP) was assessed with an aneroid sphygmomanometer and stethoscope while they sat upright. Three separate readings were obtained from the left arm and a single reading from the right arm. The final BP figure represented the average of the last two left-arm readings combined with the right-arm value. Four separate hypertension classifications were formed on the basis of: (a) participant self-report of a physician-provided diagnosis (CLI-HTN), (b) systolic BP at or above 130 mmHg (SBP-HTN), (c) diastolic BP at or above 80 mmHg (DBP-HTN), and (d) concurrent elevation of both systolic and diastolic BP (BP-HTN). These categories facilitated exploratory comparisons between hypertension indicators and measures of cognition, mood, and behavior. The decision to adopt multiple definitions stemmed from concerns that hypertension status can be overestimated due to white-coat reactions, characteristics of the measurement device, day-to-day BP fluctuations, variations in clinical practice and guideline compliance, and the influence of participants' emotional condition [19–22]. Moreover, adherence to prescribed antihypertensive therapy is frequently suboptimal among affected individuals [23]. To capture a more accurate picture of current BP status and reduce reliance on self-reported information, participants were additionally grouped into "high-normal" BP categories in line with recommendations issued by the European Society of Cardiology [24].

All medications were coded according to the Anatomical Therapeutic Chemical classification system, which uniquely identifies drugs by their primary site of action and pharmacological properties. The specific agents evaluated encompassed benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. Dedicated variables were constructed to track exposure to ACE inhibitors (ACEIs) as well as other classes of antihypertensive medication.

### *Cognitive, mood, and behavioral aspects*

Evaluation of cognitive, mood, and behavioral domains drew upon specific items drawn from sections B and E of the Minimum Data Set Home Care (MDS-HC) assessment instrument [25]. Section B contained six items spanning three cognitive domains—memory recall, decision-making capacity, and indicators suggestive of delirium—focused on the participant's own view of their cognitive abilities in recent weeks. Responses were typically dichotomous (yes/no), with the exception of item 2, which inquired about independence in organizing daily routines (for example, timing of rising, meals, choice of clothing, or planned activities) and provided five graded response options. For analysis, a binary indicator was generated distinguishing fully independent individuals (coded 0) from those showing any dependence (coded 1). Section E consisted of 16 items grouped into four broader domains addressing depressive features, anxiety, together with low mood, deterioration in mood state, presence of behavioral disturbances, and any recent shifts in such behaviors. All items except item 2 offered three response levels: (a) absent or not observed, (b) present on 1–2 of the preceding 3 days and readily modifiable, or (c) present daily across the preceding 3 days and resistant to change. These were recoded into binary form, with option (a) assigned 0 and options (b) or (c) assigned 1. Data were gathered directly from participants via structured interviews administered by qualified healthcare staff.

*Inflammatory markers*

Venous blood specimens were successfully obtained from roughly 97% of all enrolled individuals. Collection occurred following an overnight fast by an experienced phlebotomist adhering to a uniform protocol. Immediately after withdrawal, samples were centrifuged at 4 °C and subsequently frozen at −80 °C pending laboratory processing. Concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNFα) in plasma were quantified via high-sensitivity enzyme-linked immunosorbent assay kits (ELISA; Quantikine, R&D Systems, Minneapolis, MN). Every assay was conducted in duplicate, and the mean of the paired results served as the value for statistical analyses.

*Statistical analysis*

Continuous measures were presented in the form of mean ± standard deviation (SD). Categorical measures were expressed as raw counts accompanied by their percentages. Differences between hypertensive and non-hypertensive groups (for instance, CLI-HTN compared with NON-CLI-HTN) were evaluated through independent t-tests. The connections between blood pressure indicators and cognitive, mood, or behavioral outcomes were assessed via chi-square ($X^2$) tests together with binary logistic regression. For each hypertension definition (such as SBP-HTN), chi-square analyses examined how common each outcome was among those with versus without hypertension. In the regression models, BP-related factors served as the predictors, while every binary response from the MDS-HC served as the outcome. All contrasts involved the affected group (e.g., CLI-HTN) against the unaffected group (e.g., NON-CLI-HTN), using the unaffected group as the reference. Direct comparisons across the separate hypertension definitions (e.g., CLI-HTN against SBP-HTN) were not carried out. Final adjusted models accounted for age, sex, BMI, physical activity levels, number of co-existing diseases, smoking status, unintentional weight loss, years of education, intake of antipsychotic or antidepressant medicines, and use of ACEIs. A P-value < 0.05 was considered statistically significant for every test, and all tests were conducted as two-sided. The entire set of analyses was executed with SPSS software (version 23.0, SPSS Inc., Chicago, IL, United States).

## Results and Discussion

Participant features from this investigation appear in **Table 1** under the CLI-HTN grouping. Those identified as hypertensive according to blood pressure measurements were generally younger, weighed less, and showed greater physical activity than the normotensive individuals. The hypertensive categories displayed raised systolic blood pressure levels overall. Raised diastolic blood pressure appeared specifically in the SBP-HTN, DBP-HTN, and BP-HTN categories. Among participants in the BP-HTN category, normotensive individuals received antipsychotic prescriptions more often than the hypertensive ones. A large share of participants in the hypertensive portion of the CLI-HTN category were using ACEIs, which aligned with expectations.

**Table 1.** Participant features from this investigation.

| Variable | Overall sample (n = 364) | Normotensive group (n = 179) | Hypertensive group (n = 185) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Age (years, mean ± SD) | 85.8 ± 4.8 | 86.1 ± 4.9 | 85.5 ± 4.7 |
| Female participants (n, %) | 244 (67.0%) | 116 (64.8%) | 128 (69.2%) |
| Body mass index (kg/m²) | 25.6 ± 4.5 | 25.4 ± 4.5 | 25.7 ± 4.5 |
| Body weight (kg) | 62.7 ± 12.8 | 62.3 ± 13.2 | 63.0 ± 12.4 |
| Height (m) | 1.56 ± 0.08 | 1.56 ± 0.09 | 1.56 ± 0.09 |
| Current smokers (n, %) | 84 (23.0%) | 44 (24.6%) | 40 (21.6%) |
| Reported weight loss (n, %) | 69 (19.0%) | 33 (18.4%) | 36 (19.5%) |
| Physically active individuals (n, %) | 65 (17.8%) | 32 (17.9%) | 33 (17.8%) |
| Systolic blood pressure (mmHg) | 145.4 ± 24.8 | 141.8 ± 23.1* | 148.4 ± 26.0 |
| Diastolic blood pressure (mmHg) | 81.0 ± 13.1 | 80.0 ± 11.6 | 81.6 ± 14.5 |
| Multimorbidity (yes, n, %) | 11 (3.0%) | 9 (4.9%)* | 2 (1.1%) |
| Use of antipsychotic medication (yes, n, %) | 22 (6.0%) | 14 (3.8%) | 8 (2.2%) |
| Use of antidepressant medication (yes, n, %) | 8 (2.1%) | 4 (1.1%) | 4 (1.1%) |
| Use of ACE inhibitors (yes, n, %) | 103 (28.2%) | 0 (0.0%)* | 103 (55.7%) |
| School attendance (n, %) | 10 (2.7%) | 6 (1.6%) | 4 (1.1%) |
| No formal education (n, %) | 2 (0.5%) | 1 (0.3%) | 1 (0.3%) |
| ≤ 8th grade education (n, %) | 331 (90.9%) | 163 (44.8%) | 168 (46.2%) |
| 9–11 years of schooling (n, %) | 9 (2.4%) | 3 (0.8%) | 6 (1.6%) |
| High school education (n, %) | 7 (1.9%) | 3 (0.8%) | 4 (1.1%) |
| Technical or vocational training (n, %) | 4 (1.0%) | 2 (0.5%) | 2 (0.5%) |
| Some college education (n, %) | 1 (0.2%) | 1 (0.3%) | 0 (0.0%) |

Main characteristics of study participants (n = 364).
Data are shown as mean ± SD and n (%). *P < 0.05 vs Hypertensive.

**Table 2** displays the unadjusted links between hypertension indicators and aspects of cognitive performance, mood state, and behavior. Across nearly all classification approaches, hypertensive individuals described fewer issues with short-term memory, procedural memory, and deterioration in decision-making ability than normotensive individuals. The single exception involved procedural memory within the CLI-HTN category. Inside the SBP-HTN category, hypertensive participants also showed a lower rate of shifts in mental function. On mood and behavior measures, those in the BP-HTN category noted reduced feelings of sadness, unrealistic fears, repeated health worries, and anxious statements. They also showed more visible facial signs of sadness, had more frequent crying spells, withdrew more often from activities they once enjoyed, and engaged less socially. Ongoing anger appeared mainly among those classified as hypertensive through combined high systolic and diastolic readings. In both the CLI-HTN and DBP-HTN categories, hypertensive individuals mentioned more repeated crying episodes. In addition, the CLI-HTN hypertensive group reported lower levels of social contact. Beyond these findings, no other meaningful links were detected.

**Table 2.** The unadjusted links between hypertension indicators and aspects of cognitive performance, mood state, and behavior.

| Variable | BP-HTN | DBP-HTN | SBP-HTN | Hypertensive |
|---|---|---|---|---|
| **Cognitive Domain** | | | | |
| Difficulties with short-term memory (yes) | 3 (0.8)* | 67 (18.4)* | 47 (12.9)* | 46 (12.6)* |
| Impairment in procedural memory (yes) | 1 (0.3)* | 35 (9.6)* | 36 (9.9)* | 29 (8.0) |
| Decline in decision-making ability (yes) | 0 (0.0)* | 54 (14.8)* | 52 (14.3)* | 43 (11.8)* |
| Alterations in mental functioning (yes) | 0 (0.0) | 2 (0.5) | 1 (0.3)* | 2 (0.5) |
| Agitation and confusion (yes) | 0 (0.0) | 4 (1.1) | 3 (0.8) | 4 (1.1) |
| **Mood and Behavioral Domain** | | | | |
| Feelings of sadness or depression (yes) | 7 (1.9)* | 75 (20.6) | 72 (19.8) | 60 (16.5) |
| Persistent irritability/anger (yes) | 0 (0.0) | 13 (3.6)* | 13 (3.6)* | 5 (1.4) |
| Presence of unrealistic fears (yes) | 1 (0.3)* | 24 (6.6) | 27 (7.4) | 19 (5.2) |

| | | | | |
|---|---|---|---|---|
| Recurrent somatic health complaints (yes) | 2 (0.5)* | 48 (13.2) | 51 (14.0) | 39 (10.7) |
| Recurrent anxiety-related complaints (yes) | 2 (0.5)* | 34 (9.3) | 37 (10.2) | 28 (7.7) |
| Observable expressions of sadness, worry, or pain (yes) | 2 (0.5)* | 48 (13.2) | 48 (13.2) | 38 (10.4) |
| Frequent crying episodes (yes) | 2 (0.5)* | 28 (7.7)* | 27 (7.4) | 23 (6.3)* |
| Withdrawal from previously enjoyed activities (yes) | 2 (0.5)* | 45 (12.4) | 48 (13.2) | 41 (11.3) |
| Reduced social engagement (yes) | 1 (0.3)* | 41 (11.3) | 45 (12.4) | 41 (11.3)* |
| Mood deterioration (yes) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Wandering behavior (yes) | 1 (0.3) | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| Verbal aggression symptoms (yes) | 0 (0.0) | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| Physical aggression symptoms (yes) | 0 (0.0) | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| Inappropriate or disruptive social behavior (yes) | 2 (0.5) | 4 (1.1) | 2 (0.5) | 0 (0.0) |
| Resistance to care (yes) | 0 (0.0) | 2 (0.5) | 2 (0.5) | 0 (0.0) |
| Changes in behavioral symptoms (yes) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.3) |

Non-adjusted associations between hypertension-related parameters and cognitive function, mood, and behavioral aspects.

Data are shown as n (%). *P < 0.05 for the chi-square test within the group. The term — yes — refers to the presence of the condition. Comparisons were performed between condition (e.g., CLI-HTN) versus non-condition (e.g., NON-CLI-HTN), with the last used as the reference group (omitted).

Adjusted binary logistic regression outcomes for the relationships between hypertension indicators and cognitive, mood, and behavioral measures—after controlling for other relevant factors—are provided in **Table 3**. Hypertensive status in both the CLI-HTN and BP-HTN categories was tied to a smaller chance of reporting short-term memory difficulties. In the BP-HTN group, hypertensive individuals also experienced less reduction in social contacts, while the CLI-HTN hypertensive group showed greater reduction in social contacts. Higher systolic blood pressure, when examined continuously, correlated with fewer complaints about declining decision-making skills. Those with high systolic plus high diastolic blood pressure (BP-HTN) described fewer instances of sadness or depressive feelings, unrealistic fears, and anxious complaints. They further displayed fewer facial signs linked to sadness, pain, or worry and withdrew less from enjoyable activities. On the other hand, participants classified as hypertensive solely on the basis of high systolic blood pressure mentioned more repeated crying episodes.

**Table 3.** Adjusted binary logistic regression outcomes for the relationships between hypertension indicators and cognitive, mood, and behavioral measures.

| Outcome variable | P-value | Adjusted OR (95% CI) | Hypertension measure |
|---|---|---|---|
| **Short-term memory difficulties** | 0.003 | 0.52 (0.29, 0.93) | CLI-HTN |
| | 0.679 | 0.87 (0.46, 1.65) | SBP-HTN |
| | 1.017 | 1.01 (0.53, 1.92) | DBP-HTN |
| | 0.003 | 0.09 (0.01, 0.44) | BP-HTN |
| **Procedural memory impairment** | 0.964 | 0.98 (0.42, 2.26) | SBP-HTN |
| | 0.660 | 1.21 (0.51, 2.83) | DBP-HTN |
| | 0.104 | 0.10 (0.01, 1.59) | BP-HTN |
| **Decline in decision-making ability** | 0.995 | 0.000 | BP-HTN |
| | 0.862 | 0.94 (0.47, 1.86) | DBP-HTN |
| | 0.034 | 0.98 (0.97, 0.99) | SBP |
| **Changes in mental functioning** | 0.234 | 6.63 (0.29, 149.7) | SBP-HTN |
| **Feelings of sadness and depressive symptoms** | 0.003 | 0.24 (0.10, 0.62) | BP-HTN |
| **Persistent anger** | 0.999 | 0.000 | SBP-HTN |
| | 0.999 | 0.000 | DBP-HTN |
| **Presence of unrealistic fears** | 0.040 | 0.11 (0.01, 0.90) | BP-HTN |
| **Anxiety-related complaints** | 0.040 | 0.19 (0.04, 0.92) | BP-HTN |
| **Facial expressions indicating sadness, pain, or worry** | 0.003 | 0.09 (0.02, 0.45) | BP-HTN |

| | | | |
|---|---|---|---|
| **Recurrent crying or tearfulness** | 0.054 | 2.30 (0.98, 5.40) | CLI-HTN |
| | 0.013 | 5.43 (1.43, 20.6) | SBP-HTN |
| **Withdrawal from previously enjoyed activities** | 0.003 | 0.09 (0.02, 0.44) | BP-HTN |
| **Reduced social interaction** | 0.042 | 1.94 (1.02, 3.67) | CLI-HTN |
| | 0.005 | 0.05 (0.01, 0.41) | BP-HTN |

Associations between hypertension-related parameters and cognitive aspects.
*Models adjusted for age, sex, body mass index, multimorbidity, unintentional loss of weight, smoking habits, schooling years, physical activity, and antipsychotic and antidepressant drugs. Bold indicates significance according to p-values and confidence intervals. Comparisons were performed between condition (e.g., CLI-HTN) versus non-condition (e.g., NON-CLI-HTN), with the last used as the reference group.

**Table 4** presents the binary regression findings for hypertension indicators and cognitive, mood, and behavioral outcomes when further stratified according to ACEI treatment. After additional adjustment for ACEI use, the only links that stayed statistically meaningful were the lower rates of short-term memory problems observed in hypertensive individuals from the CLI-HTN and BP-HTN categories.

**Table 4.** The binary regression findings for hypertension indicators and cognitive, mood, and behavioral outcomes were further stratified according to ACEI treatment.

| Outcome variable | P-value | Adjusted OR (95% CI) | Hypertension indicator |
|---|---|---|---|
| **Short-term memory difficulties** | 0.019 | 0.47 (0.25, 0.88) | CLI-HTN |
| | 0.003 | 0.08 (0.01, 0.43) | BP-HTN |
| **Decline in decision-making ability** | 0.157 | 1.056 (0.979, 1.140) | SBP |
| **Feelings of sadness and depressive symptoms** | 0.999 | 0 | BP-HTN |
| **Presence of unrealistic fears** | 0.999 | 0 | BP-HTN |
| **Anxiety-related complaints** | 0.597 | 1.45 (0.36, 5.81) | BP-HTN |
| **Facial expressions of sadness, pain, or worry** | 0.736 | 1.23 (0.37, 4.09) | BP-HTN |
| **Recurrent crying or tearfulness** | 0.103 | 3.54 (0.77, 16.1) | SBP-HTN |
| **Withdrawal from activities of interest** | 0.752 | 0.75 (0.23, 2.40) | BP-HTN |
| **Reduced social interaction** | 0.104 | 1.80 (0.88, 3.65) | CLI-HTN |
| | 0.953 | 1.03 (0.30, 3.47) | BP-HTN |

Associations between hypertension-related parameters and cognitive aspects according to ACEI use.

Models controlled for age, sex, body mass index, presence of multiple chronic conditions, unintentional weight loss, smoking habits, physical activity, years of schooling, and intake of antipsychotic as well as antidepressant medications. Bold font marks results reaching statistical significance on the basis of p-values, together with confidence intervals. All group contrasts compared the condition-positive category (for example, CLI-HTN) with the condition-negative category (for example, NON-CLI-HTN), treating the negative category as the reference.

Plasma levels of markers of inflammation by HTN category appear in **Figure 1**. Individuals classified as hypertensive within the BP-HTN category displayed reduced circulating amounts of IL-6 and CRP when compared with normotensive counterparts. No further noteworthy differences surfaced for the remaining markers.

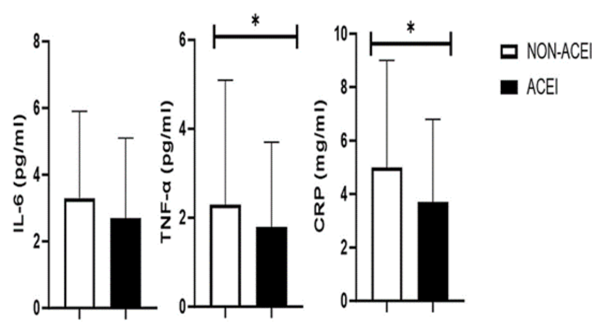


**Figure 1**. Blood concentration of interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein according to the use of ACE inhibitors. * $P < 0.05$.

Outcomes of this investigation point to connections between various HTN-linked indicators and a broad array of cognitive, emotional, and behavioral characteristics in adults of advanced age. Even so, the only robust relationships that held up after statistical adjustment for ACEI exposure concerned difficulties with short-term memory. Exploration of possible underlying biological signals revealed that those identified as hypertensive on the basis of direct blood pressure recordings showed noticeably lower plasma concentrations of IL-6 and CRP. These patterns align at least partly with previous reports describing reverse links between blood pressure readings and cognitive abilities among the oldest age groups. Nakamura *et al*. [6] observed that higher blood pressure forecasted improved overall cognitive scores three years later among very elderly Japanese participants. Parallel patterns surfaced in investigations by Corrada *et al*. [7] and Chen *et al*. [26] involving North American and Japanese adults aged 90 and beyond. Ruitenberg *et al*. [8] documented that reduced baseline systolic and diastolic blood pressure readings predicted elevated dementia likelihood in older Dutch adults. A further striking detail was that continued declines in blood pressure over the observation period coincided with new dementia cases [8]. Verghese *et al*. [9] monitored older adults across a median span of 6.7 years and determined that each 10-mmHg drop in blood pressure raised dementia risk in a meaningful way. In addition, subjects exhibiting mild or moderate systolic hypertension faced a smaller chance of Alzheimer's disease onset than peers with typical blood pressure values [9]. Li *et al*. [27] later extended this line of evidence by showing that the nature of the blood pressure–cognitive decline relationship shifts with advancing age: elevated blood pressure strongly forecasted dementia among relatively younger older adults (around 60–70 years), yet the association turned inverse among those aged 85 years or more.

A reasonable account for these observations holds that raised blood pressure could function as an adaptive response intended to uphold sufficient blood delivery to brain tissue despite progressive vascular wear associated with aging [6–9]. Vessels in later life routinely suffer erosion of structural soundness and operational efficiency, notably through diminished capacity of the inner lining to expand. Consequently, blood supply to vital organs, including the brain, diminishes [28–30]. Laboratory investigations using animal models indicate that restricted cerebral blood flow can compromise the protective blood–brain barrier, stimulate immune cells in the brain, boost production of inflammatory substances, heighten output of β-amyloid precursor protein, and impair abilities related to spatial navigation and memory retention [31–33].

Diminished cerebral blood flow, irrespective of the particular brain zones involved, correlates with heightened vulnerability to cognitive worsening both among hypertensive individuals and in combined study samples [34, 35]. Especially, inadequate perfusion reaching the medial temporal areas and posterior cingulate cortex frequently accompanies memory-related complaints [35]. Conversely, stronger cerebral blood flow associates with larger volumes in the hippocampus and amygdala structures, along with lowered overall dementia susceptibility [35]. Such evidence has encouraged the formulation of the vascular hypothesis for Alzheimer's disease. This framework supplies an alternative lens—potentially complementary or even primary—to the conventional view centered on neurodegenerative processes alone. It posits that sustained shortfalls in brain blood supply represent a core driver of the metabolic disruptions and disease mechanisms characteristic of Alzheimer's [36].

Another key observation from this investigation was that links between hypertension-related indicators and most cognitive, mood, and behavioral outcomes lost statistical significance once the models incorporated additional adjustment for ACEI exposure. ANGII could play a role in worsening cognitive abilities and altering emotional states by interfering with brain structure and physiological processes. ANGII diminishes cerebral blood flow when vessels are challenged by vasodilators such as bradykinin, compromises the blood–brain barrier, leads to the disappearance of pericytes and capillaries, and promotes the breakdown of amyloid precursor protein along with greater amyloid buildup [12–14]. These processes trigger activation of microglia [13] and elevate levels of inflammatory and oxidative stress indicators within brain tissue [12, 13, 37]. While similar alterations occur in both younger and older animals, the impact of ANGII-driven hypertension on brain impairment becomes more severe with advancing age [13].

Conversely, ACEIs enhance cerebral blood flow, help preserve the structure of both white and gray matter, lower the amount and activity of inflammatory and oxidative markers in the brain, and raise concentrations of neurotrophic factors [15–17]. In addition, an expanding body of research indicates that ACEI administration can ameliorate features of cognitive impairment and psychiatric conditions in animal models, such as reduced immobility duration, fewer social withdrawal behaviors, and improved spatial learning performance [17, 38]. In human populations, individuals receiving ACEI therapy face a decreased likelihood of cognitive deterioration, mild cognitive impairment, and

Alzheimer's disease [3–5]. These observations have been reinforced through systematic reviews and meta-analyses [33, 34]. With respect to mental health outcomes, people prescribed ACEIs showed a reduced probability of hospital admission for mood-related disorders relative to those using alternative antihypertensive agents [35].

## Conclusion

Collectively, these results imply that hypertensive individuals receiving ACEI therapy may experience fewer difficulties related to cognitive performance, mood regulation, and behavioral patterns than hypertensive individuals on other types of blood pressure medication. This pattern may stem from the influence of ACEIs on inflammatory pathways [12, 13, 37] and could account for the reduced circulating levels of IL-6 and CRP detected among hypertensive older adults in the BP-HTN category. Nonetheless, direct comparison between hypertensive participants who used ACEIs and those who did not revealed a notable difference only in the item concerning agitation and disorientation. These observations raise the possibility that additional unmeasured factors contributed to the lower inflammation levels and relatively better cognitive profile observed in the hypertensive group [35]. However, the limited number of participants (fewer than 200) and the absence of comprehensive covariate adjustment mean these findings must be interpreted cautiously, and further research addressing this topic remains essential.

The current investigation has several limitations. First, cognitive, mood, and behavioral features were evaluated exclusively through self-reported questionnaires, without employing dedicated diagnostic or screening tools. Second, the analyses did not account for the duration or timing of HTN onset [7]. Third, participants were not evaluated for the presence of the apolipoprotein E4 allele, a factor that could have affected the outcomes [36]. Fourth, plasma concentrations of other potential biological mediators, such as reactive oxygen species, were not assessed. Fifth, important details of ACEI therapy—including dosage, length of treatment, and patient adherence—were not documented [37, 38]. Sixth, the beneficial influence of ACEIs on cognitive function may depend on their ability to penetrate the blood–brain barrier; unfortunately, this information was recorded for only a subset of participants, precluding additional subgroup analyses. Seventh, because the study followed a cross-sectional design, it is impossible to determine the temporal sequence of changes or establish causal relationships among the variables examined. Eighth, information on patient adherence to prescribed antihypertensive medication was unavailable. Ninth, no standardized cognitive screening tools (for example, the mini-mental state examination) were applied to evaluate participants' mental status. Tenth, the absence of comprehensive details about the specific antihypertensive regimens used (such as concurrent diuretic therapy) restricted the possibility of more in-depth examinations. Eleventh, reliance on an oscillometric blood pressure device could have yielded results that differ from those obtained with other measurement techniques [39]. Finally, the study focused on a group of very elderly adults residing in a mountainous area; therefore, generalization of the findings to other populations should be approached with appropriate caution.

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