Hypertension

COGNITIVE DECLINE AND BLOOD PRESSURE

Hypertension, Prehypertension, and Hypertension Control

Association With Decline in Cognitive Performance in the ELSA-Brasil Cohort

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ABSTRACT: Hypertension, particularly in middle age, has been associated with worse cognitive function, but evidence is inconclusive. This study investigated whether hypertension, prehypertension, age, and duration of diagnosis, as well as blood pressure control, are associated with a decline in cognitive performance in ELSA-Brasil participants. This longitudinal study included 7063 participants, mean age 58.9 years at baseline (2008–2010), who attended visit 2 (2012–2014). Cognitive performance was measured in both visits and evaluated by the standardized scores of the memory, verbal fluency, trail B tests, and global cognitive score. The associations were investigated using linear mixed models. Hypertension and prehypertension at baseline were associated with decline in global cognitive score; being hypertension associated with reduction in memory test; and prehypertension with reduction in fluency test. Hypertension diagnose ≥55 years was associated with lower global cognitive and memory test scores, and hypertension diagnose <55 years with lower memory test scores. Duration of hypertension diagnoses was not associated with any marker of cognitive function decline. Among treated individuals, blood pressure control at baseline was inversely associated with the decline in both global cognitive and memory test scores. In this relatively young cohort, hypertension, prehypertension, and blood pressure control were independent predictors of cognitive decline in distinct abilities. Our findings suggest that both lower and older age of hypertension, but not duration of diagnosis, were associated with cognitive decline in different abilities. In addition to hypertension, prehypertension and pressure control might be critical for the preservation of cognitive function. **(*Hypertension*. 2021;77:672–681. DOI: 10.1161/HYPERTENSIONAHA.120.16080.)** • **Data Supplement**

Key Words: association ■ blood pressure ■ cognition ■ diagnosis ■ memory

Hypertension is a highly prevalent risk factor for cognitive decline and dementia,[1] potentially preventable and treatable.[2–4] Although it is not known exactly when hypertension begins to affect cognition, middle age seems to be a sensitive period in which exposure to hypertension has a subtle and lasting negative impact on the brain,[5,6] more than hypertension started at older ages.[7–9] However, variability in middle age definition among studies, as well as differences in the methods used to classify cognitive end points hinder comparability between studies.[10–12]

Conversely, earlier onset of hypertension implies longer exposure to hypertension, and longer duration has also been associated with greater cognitive decline and dementia regardless of the age of onset of hypertension.[10,13] Thus, it is possible that shorter duration of hypertension explains part of the inconsistencies among studies that investigated the effect of later-life hypertension on cognitive decline or dementia.[13] Consequently, the 2 components—age of diagnosis and duration of hypertension—must be addressed.

The use of antihypertensive medications[8,14,15] and the control of pressure levels[14] seem to moderate the association of hypertension with cognitive decline and dementia, but such effects have not yet been sufficiently explored.[16]

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Novelty and Significance

What Is New?

- Hypertension at middle and older ages were associated with faster cognitive decline.
- Duration of hypertension diagnosis was not associated with the speed of cognitive decline.

What Is Relevant?

- Noncontrolled hypertension predicted significantly faster declines in memory and global cognitive function performance than controlled hypertension.
- Both hypertension and prehypertension accelerated the decline in standardized global cognitive performance.

Summary

Our study shows that hypertension and prehypertension relate to faster cognitive decline in middle-aged and older adults and that the speed of cognitive decline was irrespective of hypertension duration. Moreover, controlled hypertension appeared to have reduced the pace of cognitive decline. Taken together, our findings emphasize the importance of diagnosing and controlling hypertension strictly and at any age spectrum to reduce loss of cognition.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
DBP	diastolic blood pressure
HDL	high-density lipoprotein
SBP	systolic blood pressure

Although prehypertension (systolic blood pressure [SBP] between 121 and 139 and diastolic blood pressure [DBP] between 81 and 89 mm Hg) has been associated with significant damage in several target organs,[17] its association with cognitive decline and dementia has been less investigated.[7,10,18] Such investigation is important because of the greater potential for prevention and reversibility of prehypertension.

This study investigated whether hypertension and prehypertension predict greater decline in cognitive tests performance in ELSA-Brasil participants after 4-year follow-up. Additionally, we assessed whether the age of diagnosis, duration, treatment status, and control of hypertension also predict greater decline in cognitive tests performance. We hypothesize that all these variables predict acceleration in cognitive decline.

METHODS

The data that support the findings of this study are available from the corresponding author on request.

Study Population

This study used data from visits 1 (2008–2010) and 2 (2012–2014) of ELSA-Brasil, a multicenter cohort with 15 105 civil servants (35–74 years old), in 6 Brazilian capitals. Detailed information on study was previously published.[19,20] ELSA-Brasil was approved by the Research Ethics Committees of the participating institutions and the National Research Ethics Committee (CONEP 976/2006). All participants signed an informed consent.

Of the 15 105 participants, 223 died and 868 did not attend visit 2, resulting in 94.2% retention rate. Cognitive function tests were applied to all baseline participants, but only to those ≥55 years old on visit 2. Therefore, 7248 participants were eligible for this analysis. Of these, those using anticholinesterase drugs (n=1) and with missing BP data (n=8) at baseline were excluded.

In addition, we excluded individuals because of (1) age at hypertension diagnoses ≤9 years (n=2); (2) normotensive individuals who reported using antihypertensives for another reason (n=44); and (3) individuals who reported stroke at baseline (n=130). Because information was missing for specific cognitive tests, our final analytical sample varied for each test (memory, N=6646; fluency, N=6805, trail B, N=6619; and global cognitive score, N=6480). The sample selection is described in Figure S1 in the Data Supplement.

Cognitive Evaluation

The response variables were the total scores of 3 cognitive tests (memory, fluency, and trail B) and the global cognitive score. Tests were applied on study visits 1 and 2, in a quiet room by highly trained interviewers using standardized protocols, recorded, and reviewed for quality control.[21,22]

The memory test score represents the sum of the number of correct words in the learning, recall, and word recognition tests. They evaluate the declarative memory and were obtained through the battery of neuropsychological tests consortium to establish record of Alzheimer disease.[23,24]

The verbal fluency test evaluates executive function, explicit memory, semantics, and language and is also part of the consortium to establish record of Alzheimer disease battery.[23,24] The categories used were the letter F and animals in visit 1 and letter A and flora (vegetables, flowers, trees, etc) in visit 2. The final score is the sum of all correct words spoken for 60 seconds. The categories of the verbal fluency test varied between visits to reduce the learning effects. Because the 2 versions of the verbal fluency test can be parallel, but not necessarily equivalent[25,26] the test scores on visit 2 were converted

into equivalent scores, comparable to the scores of the verbal fluency tests on visit 1.[27]

The trail B test evaluates attention, concentration, psychomotor speed, visuomotor scanning, and mental flexibility (executive function).[28] Only individuals who completed the trail A test performed the trail B test. The score consists of the time (in seconds) spent to complete the trail B test since the trail A test time was not recorded. For individuals who did not complete the trail B test (n=493), the time of accomplishment was estimated as being the maximum time (+ one second) taken for individuals of the same sex, age group (5 years), and schooling.[29] The trail B test score were log-transformed because its distribution was highly skewed.

The global cognitive score, measured by the global cognitive factor (factor g), was obtained from factor analysis with standardized scores (Z score) of memory, fluency, and trail B tests of participants who performed all the tests (n=6480). Factor g was the first factor and explained 64% of the total variance of cognitive tests. This proportion is a typical value of variance explained by Factor g.[30]

Previous results from ELSA-Brasil showed that the memory tests had moderate reliability, the verbal fluency tests had good reliability, and the trail B test had almost perfect reliability.[31]

For performance comparability between visits, the final scores of all tests were standardized to Z scores (based on the mean and SD of visit 1 test). Thus, the standardized scores for each test at visits 1 and 2 have mean equal to zero and SD equal to one. Therefore, a reduction in participant's Z score in any test at visit 2, except for trail B tests, signals a relative decline in participant's performance. For the trail B test, an increase in Z score in visit 2 (longer execution time) represents a performance decline in this activity.

Blood Pressure

BP was measured using a validated oscillometric device (Omron HEM 705CPINT) on the right arm after a 5-minute rest in a sitting position in a quiet, temperature-controlled room (20–24 °C). Three measurements were taken at 1-minute intervals, and the means of the last 2 measurements of SBP and DBP[32] were used.

The explanatory variables were hypertension status, age of hypertension diagnosis, duration of hypertension diagnosis, hypertension treatment, and control statuses, all obtained at visit 1.

Individuals with SBP≤120 mm Hg and DBP≤80 mm Hg and who did not use antihypertensive were classified as normal; prehypertension as SBP between 121 and 139 mm Hg or DBP between 81 and 89 mm Hg and no antihypertensive use; and hypertension as SBP≥140 mm Hg or DBP≥90 mm Hg and use of antihypertensive.

The age of hypertension diagnosis was self-reported for participants diagnosed with hypertension before study entry. For individuals found hypertensive at visit 1, the age of diagnosis was the same age at study entry plus 0.1 to differentiate from normotense participants. The age of diagnosis was then categorized as (1) middle-age hypertension (<55 years) and (2) late hypertension (≥55 years), being normotense the reference category. Duration of hypertension (visit 1 age−age of hypertension diagnosis) and analyzed as a continuous variable.

The effect of antihypertensive use per se on cognitive performance was evaluated on participants with hypertension diagnosis before study entry (N=2717) and grouped into treated and untreated. The role of BP control was evaluated only in hypertensive individuals under treatment at visit 1 (N=2650) and categorized into: controlled hypertension (SBP<140 mm Hg and DBP<90 mm Hg) and uncontrolled hypertension (SBP≥140 mm Hg or DBP≥90 mm Hg).

Covariables

Sociodemographic characteristics included sex, education, and race/skin color (White, Brown *(pardo)*, Black, yellow, and indigenous). Age was used in the analysis to index time. Thus, visit 1 age was the starting point, and visit 2 age corresponded to the initial age plus the interval (in years) between the 2 visit dates.

The health behaviors included smoking (nonsmoker, ex-smoker, and smoker), leisure physical activity, and alcohol consumption. Physical activity was evaluated by the long version of the International Physical Activity Questionnaire and grouped according to the number of MET (metabolic equivalent of task) into: light (<600 MET min/week), moderate (600±3000 MET min/week), and strong (≥3000 MET min/week).[33] Alcohol consumption (moderate, nondrinking, and excessive) according to reported weekly consumption in grams, being moderate if <210 g/week for men and <140 g/week for women, and excessive if ≥210 g/week for men and ≥140 g/week for women.[21]

Other potential confounders were body mass index (kg/m^2; continuous); total cholesterol/HDL (high-density lipoprotein) ratio (continuous), determined by the enzymatic colorimetric method (ADVIA Chemistry; Siemens)[32]; use of lipid-lowering drugs (no/yes); self-reported CVD (cardiovascular disease) (no/yes, including acute myocardial infarction, unstable angina, congestive heart failure, and coronary artery bypass grafting); atrial fibrillation (no/yes); and diabetes (no/yes). Diabetes was defined by self-reported diagnosis or any of the following criteria: use of antidiabetic drugs, or fasting glucose ≥126 mg/dL, or glucose tolerance test ≥200 mg/dL, or glycated hemoglobin ≥6.5%. Biochemical tests, weight, and height were obtained on fasting.

Statistical Analysis

Categorical variables were described as proportions and continuous variables, as medians and interquartile range, or as means and SD.

Mixed linear regression models with random intercept and slope were used to evaluate longitudinal changes in tests performance between study visits 1 and 2.[34–36] The fixed effects (β) and variance components (α) of the mixed linear models were estimated using maximum restricted likelihood methods.

The explanatory variables of interest (hypertension status, age of hypertension diagnosis, duration of hypertension, hypertension treatment, and control statuses) and covariates were ascertained at visit 1, while cognitive tests performance (response variables) at visits 1 and 2. Separate regression models were run for each cognitive test and for the global cognitive score, as well as for each explanatory variable. All explanatory and covariates were included in the models as fixed effects, and age was modeled as random effect to index time.

First, we modeled each explanatory variable of interest and age. Then, the covariates were included in the models. Next, the longitudinal change in standardized cognitive scores was

evaluated by including interaction terms between the explanatory variable and age (hypertension status × age, hypertension diagnosis age × age, duration of hypertension × age, hypertension treatment status × age, and hypertension control status × age), and the results of the fully adjusted models presented. The suitability tests confirmed the adequacy of the models presented.

Statistical significance was defined as $P<0.05$ and 95% CI. The analyses were performed using Stata software version 14 (Stata Corporation, College Station, United States).

RESULTS

The average interval between visits was 3.8 years (1.7–6.0 years). Of 7063 participants included, 55.2% were female, mean age 58.9 (SD=5.9) years at visit 1, 15.3% Black participants, and 53.4% had ≥14 years of study (Table 1). In total, 22.0% had prehypertension and 46.8% hypertension. Among hypertensive individuals, 29.8% were diagnosed at middle age, and the median duration of hypertension was 7.0 (interquartile range=1–15) years. Among those who reported hypertension at visit 1, 7.3% did not use antihypertensive medication, and among the treated hypertensive participants, 31.2% presented uncontrolled BP levels (Table 1).

After considering all covariates in the analysis, the interaction term status of hypertension × age was statistically significant for the memory, verbal fluency tests, and global cognitive score (Factor g), indicating that hypertension is associated with the greatest decline in the memory, fluency, and global cognitive score between visits, that is, as individuals age. Prehypertension, when compared with normal BP, was an independent predictor of greater decline in the verbal fluency test and global cognitive score (Table 2).

Compared with participants without hypertension, middle-age hypertension was associated with a sharper decline in memory test, and late hypertension with sharper decline in memory test and global cognitive score (Table 3).

The interaction term duration of hypertension × age was not statistically significant in any analysis ($P<0.109$ memory; 0.885 fluency; 0.266 trail B; 0.457 factor–Table S1), indicating that hypertension duration was not an independent predictor of longitudinal changes in cognitive performance in this study.

Finally, among treated hypertensive individuals, those with uncontrolled BP showed a more accelerated decline in the memory test and global cognitive score compared with controlled hypertensive individuals (Table 4). Among individuals who reported hypertension in visit 1, treatment status (no versus yes) was not associated with longitudinal changes in cognitive performance (data not shown).

Secondary analysis including individuals with prevalent stroke and persons with hypertension medications for other reasons did not change the results.

Table 1. Characteristics of the Study Population at the Baseline (2008–2010)

Characteristics	Baseline
Age, y	58.9 (5.9)
Sex, women	55.2
Schooling–time of study–y	
≥14	53.4
11–13	30.0
8–10	8.6
<8	8.0
Race or skin color	
White	54.2
Brown *(pardo)*	26.3
Black	15.3
Yellow or Indigenous	4.2
Smoking	
Never smoker	50.6
Former smoker	36.8
Current smoker	12.6
Alcohol consumption	
Moderate	60.6
Do not use	31.5
Excessive	7.9
Leisure-time physical activity	
Mild	75.3
Moderate	18.6
Vigorous	6.1
BMI, kg/m^2	27.2 (4.6)
Cardiovascular disease	8.1
Atrial fibrillation	0.3
Diabetes	22.9
Total cholesterol/HDL cholesterol ratio	3.9 (1.0)
Use of lipid-lowering drugs	19.8
Status BP	
Normal BP	31.3
Prehypertension	22.0
Hypertension	46.7
Age at diagnosis of hypertension	
Normal BP	53.3
Middle age hypertension (<55 y)	29.8
Late hypertension (≥55 y)	16.9
Exposure time to hypertension, y	7.0 (1.0–15.0)
Treated hypertension	92.7
Controlled hypertension	68.7
Memory test score (number of correct words)*	36.8 (6.1)
Verbal fluency test score (number of correct words)†	29.8 (8.4)
Trail B test score (seconds)‡	114.0 (83.0–178.0)

ELSA-Brasil (N=7063). Data are given as percentage, mean (SD), or median (range). BMI indicates body mass index; ELSA-Brasil, Brazilian Longitudinal Study of Adult Health; and HDL, high-density lipoprotein.

*Score ranging from 0 to 50 correct words.

†Score ranging from 0 to ∞ correct words remembered in a time interval of 1 min.

‡Score ranging from 1 to ∞ seconds.

Table 2. Association Between Prehypertension and Hypertension at Baseline and Cognitive Performance Over 4 Years of Follow-Up, Estimated by Linear Mixed Effects Regression

Cognitive function test	Memory tests (Z score), N=6646	Verbal fluency tests (Z score), N=6805	Trail B test (Z score), N=6619	Factor g, N=6480
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Intercept	0.7303 (0.3661 to 1.0944)*	0.6908 (0.3503 to 1.0313)*	−1.0370 (−1.3475 to −0.7266)*	0.6904 (0.4527 to 0.9281)*
Status ×hypertension				
Normal BP	Ref.	Ref.	Ref.	Ref.
Prehypertension	0.3854 (−0.1129 to 0.8838)	0.5596 (0.0948 to 1.0243)†	0.3059 (−0.1180 to 0.7298)	0.2504 (−0.0660 to 0.5668)
Hypertension	0.9158 (0.4990 to 1.3325)*	0.3374 (−0.0514 to 0.7262)	0.0694 (−0.2855 to 0.4244)	0.3823 (0.1174 to 0.6472)†
Age,‡ y	−0.0057 (−0.0114 to −0.0001)§	−0.0049 (−0.0102 to 0.0002)	0.0093 (0.0045 to 0.0140)*	−0.0080 (−0.0115 to −0.0044)*
Status hypertension × age‡				
Normal BP	Ref.	Ref.	Ref.	Ref.
Prehypertension	−0.0073 (−0.0156 to 0.0010)	−0.0095 (−0.0172 to −0.0018)†	−0.0035 (−0.0105 to 0.0034)	−0.0049 (−0.0102 to −0.0003)§
Hypertension	−0.0153 (−0.0222 to −0.0083)*	−0.0065 (−0.0129 to −0.0001)§	0.0003 (−0.0055 to 0.0061)	−0.0072 (−0.0115 to −0.0028)†

ELSA-Brasil (N=7063). Final model adjusted for age, sex, education level, race or skin color, smoking, alcohol consumption, leisure-time physical activity, body mass index, diabetes, cardiovascular disease, atrial fibrillation, total cholesterol/high-density lipoprotein ratio, use of lipid-lowering drugs, and interaction: Status hypertension × age. β indicates β coefficient.

Indicate (β); *P* value *<0.001; †<0.01; and §<0.05.

‡Age (age at baseline + follow-up time) was modeled as a random effect to index time.

Graphic representations of the mean cognitive scores' predictions for the explanatory variables were plotted to illustrate the main findings (Figures 1 and 2). As age was modeled as a random effect in the analysis, the inclinations in the figures indicate changes in performance in standardized cognitive tests and global cognitive score as individuals age during the study period.

DISCUSSION

In this large cohort of middle-aged and older adults, hypertension and prehypertension were associated with a reduction in standardized cognitive performance, assessed by a global composite score between visits 1 and 2 of the ELSA-Brasil cohort. Besides, hypertension was associated with a decrease in memory test, and prehypertension with a decrease in verbal fluency test. Regarding the age of diagnosis, hypertension in middle age predicted a reduction in memory test, while hypertension in older age predicted a decline in memory test and global cognitive score. Neither duration of hypertension nor hypertension treatment per se predicted age-related decreases in cognitive performance in the examined period. However, individuals with uncontrolled hypertension presented a sharper decline in memory test and global cognitive score when compared with those controlled. None of the hypertension variables evaluated was associated with changes in the standardized scores of the trail B test.

Hypertension has been associated with virtually all domains of cognitive function, but existing evidences suggest that hypertension does not equally affect distinct cognitive abilities over time.[5,6,37] Our results are in line with longitudinal evidences as hypertension predicted faster declines in memory tests and global cognitive score.[8,14,38,39] However, unlike other studies,[5,8,14,40,41] we found no association between hypertension and trail B test, a test that evaluates executive function, one of the most vulnerable domains to hypertension effects.[6,37]

The inverse association of prehypertension with verbal fluency observed here is consistent with most of the previous studies that evaluated executive function using this or other tests.[8,18,42,43] Few cohort studies have examined and shown that BP at prehypertensive levels predicts a reduction in cognitive performance in a large sample of middle-aged and older adults of both sexes. Most previous studies on this topic were across-sectional with very small samples[42,43] or were restricted to women[18] or evaluated only dementia.[7] Thus, this study contributes to the current literature on prehypertension and cognitive function decline, an important finding because of the greater potential for prevention as well as reversibility of prehypertension.

We found that hypertension at older ages predicted a more rapid decline in memory tests and global cognitive score, in accordance with 3 other longitudinal studies.[39,40,44] The Rotterdam and Leiden 85-plus studies observed an inverse association between high BP at older ages (65–74 years), but not at middle ages (55–64 years), and worse cognitive performance after 11 years of follow-up.[44]

The associations between hypertension or high BP at older ages and decline in cognitive performance at later stages of life are not consistent in the literature, varying from positive associations,[13,45,46] null,[47] and even protective associations.[44,48,49] In spite of the observed disagreements, on the whole, it appears that the age of hypertension onset can modify the effect of hypertension in cognitive performance decline and dementia.[12]

Table 3. Association Between Age at Diagnosis of Hypertension at Baseline and Cognitive Performance Over 4 Years of Follow-Up, Estimated by Linear Mixed Effects Regression

Cognitive function test	Memory tests (Z score), N=6646 β (95% CI)	Verbal fluency tests (Z score), N=6805 β (95% CI)	Trail B test (Z score), N=2354 β (95% CI)	Factor g, N=6480 β (95% CI)
Intercept	0.9430 (0.6536 to 1.2323)*	0.9541 (0.6847 to 1.2236)*	−0.9789 (−1.2250 to −0.7329)*	0.8375 (0.6450 to 1.0299)*
Age at diagnosis of hypertension				
Normal BP	Ref.	Ref.	Ref.	Ref.
Hypertension in middle age (<55 y)	0.4801 (0.0691 to 0.8911)†	−0.1015 (−0.4845 to 0.2813)	0.1622 (−0.1874 to 0.5119)	−0.0344 (−0.2271 to 0.2960)
Late hypertension (≥55 y)	0.9140 (0.3573 to 1.4707)*	0.2924 (−0.2213 to 0.8062)	0.2086 (−0.2613 to 0.6786)	0.4395 (0.0860 to 0.7930)†
Age,‡ y	−0.0094 (−0.0135 to −0.0052)*	−0.0094 (−0.0132 to −0.0055)*	0.0083 (0.0047 to 0.0118)*	−0.0105 (−0.0131 to −0.0078)*
Age at diagnosis of hypertension × age‡				
Normal BP	Ref.	Ref.	Ref.	Ref.
Hypertension in middle age (<55 y)	−0.0072 (−0.0141 to −0.0003)†	0.0010 (−0.0053 to 0.0074)	−0.0025 (−0.0084 to 0.0032)	−0.0006 (−0.0050 to 0.0037)
Late hypertension (≥55 y)	−0.0151 (−0.0237 to −0.0064)*	−0.0056 (−0.0135 to 0.0023)	−0.0013 (−0.0085 to 0.0059)	−0.0080 (−0.0134 to −0.0025)§

ELSA-Brasil (N=7063). Final model adjusted for age, sex, education level, race or skin color, smoking, alcohol consumption, leisure-time physical activity, body mass index, diabetes, cardiovascular disease, atrial fibrillation, total cholesterol/high-density lipoprotein ratio, use of lipid-lowering drugs, and interaction: Age at diagnosis of hypertension × age. β indicates β coefficient.

Indicate (β); *P* value *<0.001; †<0.05; and §<0.01.

‡Age (age at baseline + follow-up time) was modeled as a random effect to index time.

Our initial hypothesis anticipated based on the literature[5–9,50] that the negative effects of hypertension on cognitive function would be more critical when hypertension started at younger ages. However, the regression parameters indicate only modest effects of hypertension at middle age on the decline in memory test.

Direct comparisons between studies on middle-age hypertension and decline in cognitive function[10–12] are difficult. First, middle age comprises wide age ranges, from 35 to 68 years.[10,12] Also, the instruments that evaluate cognitive function diverge widely, are not standardized, and this might explain part of the inconsistencies found between the domains evaluated or even the tests used to evaluate a single domain.[51]

Furthermore, survival bias and censorship in older cohorts may explain part of the inconsistencies observed between the studies that addressed age of hypertension onset and cognitive performance. Finally, a potential cognitive benefit of higher BP levels in the elderly due to better brain perfusion, often present

Table 4. Association Between Hypertension Control Status in Hypertensive Individuals Under Treatment at the Baseline and Cognitive Performance Over 4 Years of Follow-Up, Estimated by Linear Mixed Effects Regression

Cognitive function test	Memory tests (Z score), N=2361 β (95% CI)	Verbal fluency tests (Z score), N=2392 β (95% CI)	Trail B test (Z score), N=6619 β (95% CI)	Factor g, N=2295 β (95% CI)
Intercept	1.2958 (0.8607 to 1.7310)*	0.8285 (0.4348 to 1.2222)*	−0.8487 (−1.2238 to −0.4737)*	0.9151 (0.6261 to 1.2041)*
Hypertension control status				
Controlled hypertension	Ref.	Ref.	Ref.	Ref.
Uncontrolled hypertension	0.7657 (0.1648 to 1.3667)†	0.1264 (−0.4161 to 0.6689)	−0.2607 (−0.7780 to 0.2564)	0.3846 (0.0029 to 0.7664)‡
Age,§ y	−0.0163 (−0.0219 to −0.0108)*	−0.0095 (−0.0145 to −0.0045)*	0.0072 (0.0025 to 0.0120)†	−0.0125 (−0.0160 to −0.0090)*
Hypertension control status × age§				
Controlled hypertension	Ref.	Ref.	Ref.	Ref.
Uncontrolled hypertension	−0.0126 (−0.0222 to −0.0030)†	−0.0038 (−0.0124 to 0.0047)	0.0059 (−0.0022 to 0.0141)	−0.0074 (−0.0134 to −0.0013)†

ELSA-Brasil (N=2650). Final model adjusted for age, sex, education level, race or skin color, smoking, alcohol consumption, leisure-time physical activity, body mass index, diabetes, cardiovascular disease, atrial fibrillation, total cholesterol/high-density lipoprotein ratio, use of lipid-lowering drugs, and interaction: control status of hypertension × age. β indicates β coefficient.

Indicate (β); *P* value ‡<0.05; †<0.01; * <0.001.

§Age (age at baseline + follow-up time) was modeled as a random effect to index time.

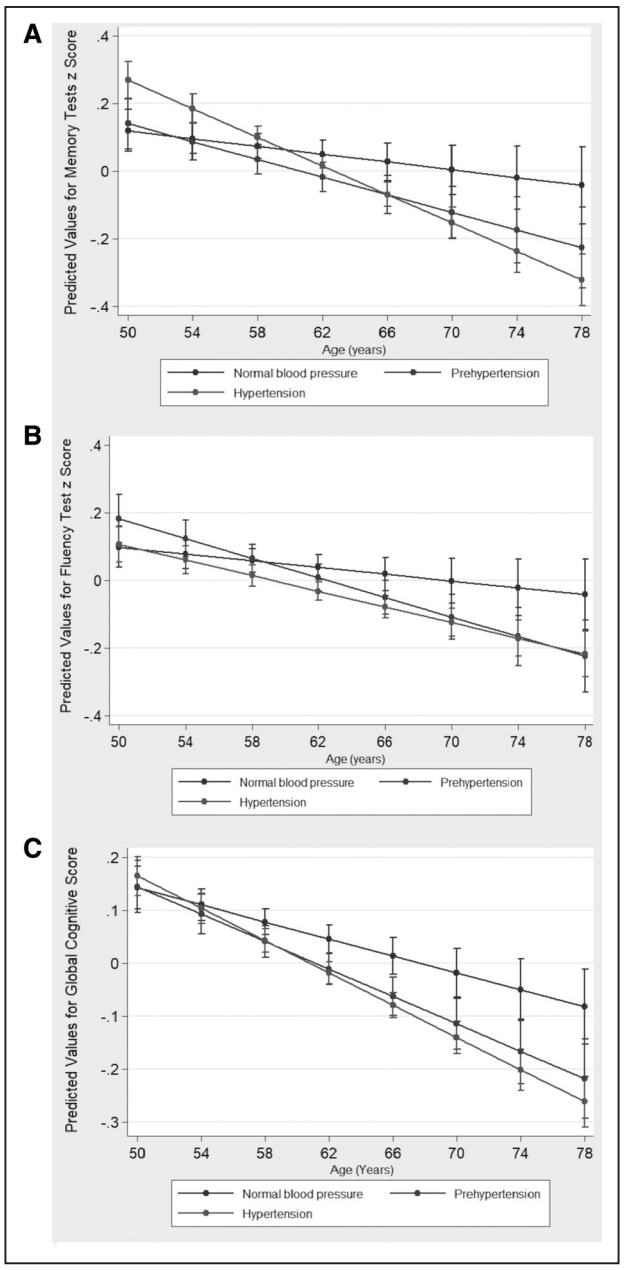

Figure 1. Longitudinal trajectories* in the predicted Z scores† (95% CI) of the cognitive tests according to hypertension status at visit 1. ELSA-Brasil (2008–2010 and 2012–2014). The memory test (**A**), verbal fluency (**B**) and the global cognitive score (**C**). *As age was modeled as a random effect in data analysis, this figure shows changes in cognitive performance over time (ie, as individuals age). †Predicted figures are dependent variable values based on estimated regression coefficients and a prediction on the values of independent variables after adjustments (age, sex, education level, race or skin color, smoking, alcohol consumption, leisure-time physical activity, body mass index, diabetes, cardiovascular disease, atrial fibrillation, total cholesterol/high-density lipoprotein ratio, use of lipid-lowering drugs and interaction: Status hypertension × age).

as a result of decompensated autoregulatory brain mechanisms, may hinder the analysis of the effect of hypertension onset at different ages on cognitive performance.[12,13]

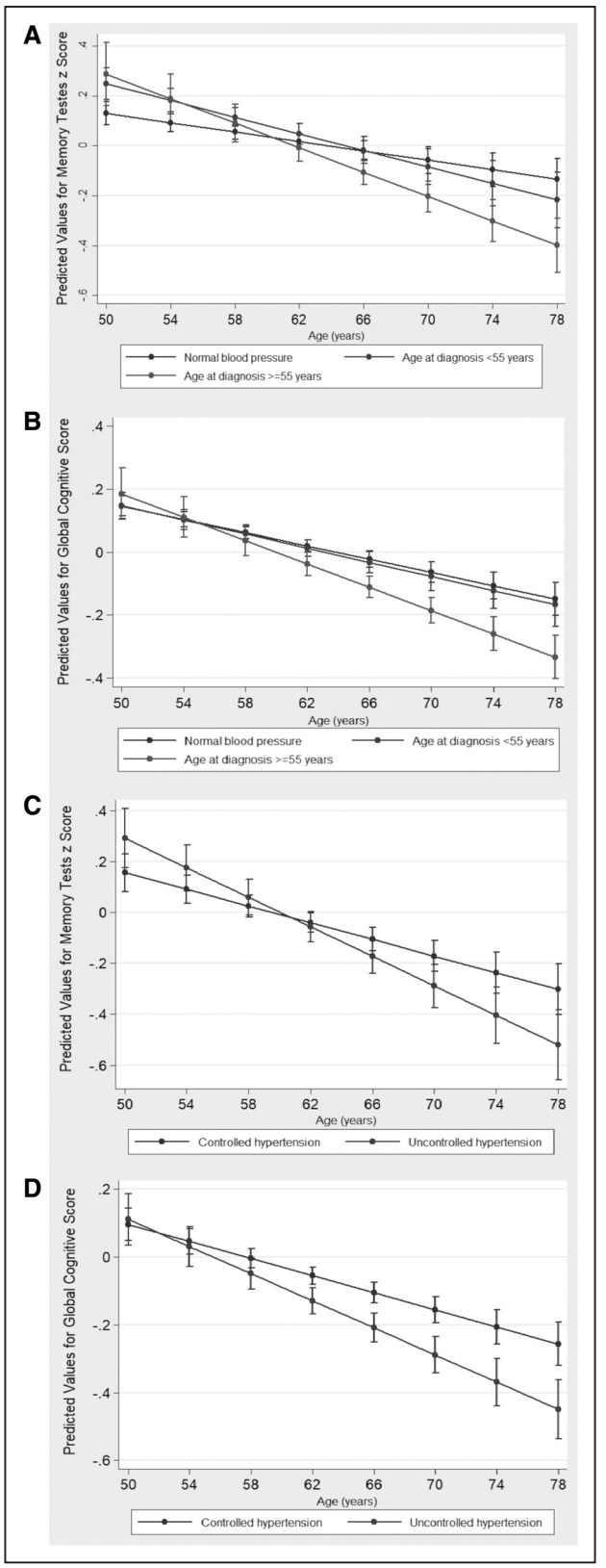

Figure 2. Longitudinal trajectories* in the predicted z score† (95% CI) of the cognitive tests according to the age of diagnosis of hypertension and the hypertension control status at visit 1. ELSA-Brasil (2008–2010 and 2012–2014). The memory test (**A** and **C**) and the global cognitive score (**B** and **D**). *As age was modeled as a random effect in data analysis, (*Continued*)

Figure 2 Continued. this figure shows changes in cognitive performance over time (ie, as individuals age). †Predicted figures are dependent variable values based on estimated regression coefficients (mean ratios observed in regression) and a prediction on the values of independent variables after adjustments (age, sex, education level, race or skin color, smoking, alcohol consumption, leisure-time physical activity, body mass index, diabetes, cardiovascular disease, atrial fibrillation, total cholesterol/high-density lipoprotein ratio, use of lipid-lowering drugs and interaction: age of diagnosis of hypertension × age).

Because earlier age of hypertension onset generally implies longer duration of exposure to hypertension, we analyzed these 2 components separately, but our results do not support an adverse effect of increased duration of hypertension on cognitive performance in the follow-up period, as reported by some studies.[13,14]

The analytical strategies used to disentangle age at onset and duration effects differ among studies, hindering comparisons.[37] The Normative Aging Study also addressed these 2 effects, but their results differ from ours, that is, longer exposure to hypertension predicted lower cognitive function.[13] The lack of association between duration of hypertension and cognitive performance in our study is consistent with our findings about age of hypertension diagnosis: greater effect of hypertension at older age than hypertension at middle age in cognitive performance over 4-year follow-up. Conversely, greater duration of exposure could be related to longer awareness of hypertension, and consequently, better control along time. In fact, in our cohort, the median duration of hypertension was 11 years among those with controlled hypertension and 9 years among those with uncontrolled hypertension ($p<001$; data not shown).

Our results contribute to further elucidate the potential benefits of BP control on cognitive function, as noncontrolled hypertensive individuals had significantly faster declines in memory and global cognitive function performance than controlled individuals. Contrariwise, we found no effect of hypertension treatment per se on cognitive function, in line with recently published finding.[52] Few studies have evaluated the control status of hypertension.[14] We do not know the causes of inadequate control of hypertension in ELSA-Brasil: low adherence to treatment, more severe form of hypertension, or more advanced stage of the disease. Although important, such analysis is beyond the scope of this study.

Several pathophysiological mechanisms have linked hypertension to anatomic and functional alterations of the brain.[53,54] Hypertension, by producing pulsatile stress, can lead to remodeling of cerebral blood vessels, favoring lipohyalinosis, atherosclerosis in the large intracranial arteries, and arteriosclerosis in the smaller arterioles resulting in reduced cerebral blood flow.[6] Cerebral hypoxia can lead to oxidative stress, which, in turn, can affect vascular tonus, endothelial function and induce chronic inflammation.[53,55] Hypertension can also alter neurochemical transmission, basic cellular functions of neurons, and brain autoregulation,[51] and together, the impairment of these functions can modify the permeability of the blood-brain barrier, allowing the entry of toxic substances into the brain.[6] These alterations in brain structure and function can lead to microvascular brain damage that manifests as chronic ischemia, silent lacunar infarctions,[56] hyperintensity of the white substance, resulting from the disease of small vessels,[5] and brain atrophy.[57] These alterations, in turn, are associated with an increased risk of dementia and other neurological dysfunctions.[51,58]

The strengths of this study include large sample from a middle-income country, high compliance rate, and evaluation of different cognitive abilities. Among the limitations, we cannot rule out misclassifications of age of hypertension onset since it was self-reported by hypertensive individuals at baseline. Furthermore, we compared cognitive performances in 2 visits. Our study population is relatively young, has a high level of education, and has been followed-up for a relatively short time. The high schooling of our cohort, due to mechanisms involving greater cognitive reserve, may contribute to better initial cognitive performance or delayed cognitive decline in the follow-up period,[59] hindering our ability to detect a more pronounced modifying effect of age of hypertension onset on cognitive decline in distinct abilities. ELSA-Brasil did not perform a comprehensive screening to rule out cognitive impairment at entry, and stroke information was self-reported. In addition, our results cannot be extrapolated to unevaluated domains and abilities.

Finally, participants who refused to attend visit 2 were younger, had less education, and higher prevalences of smokers and obesity than those who attended wave 2 (data not shown). Although the losses are small, because these factors are associated with hypertension and decline in cognitive function, these losses may have contributed to underestimate the observed associations.

PERSPECTIVES

This study, based on a large and a relatively young cohort from a middle-income country, corroborates and advance previous findings showing that both hypertension and prehypertension are associated with worse longitudinal trajectories in overall cognitive performance and different cognitive abilities after about 4-year follow-up. Our results contradict a possible age-dependent effect of hypertension on cognitive function performance since we found that both older ages and middle age onsets of hypertension were associated with faster declines in standardized cognitive performance tests, hence no effect of duration of hypertension on cognitive performance was detected. Of importance,

our findings suggest that control of BP levels may be critical to preserving cognitive function at all ages.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental materials

Online Figure I
Online Table I

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