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Early but Not Late Onset Hypertension is Related to Midlife Cognitive Function

Karri Suvila, MD¹, Joao A.C. Lima², Yuichiro Yano, MD, PhD³, Zaldy S. Tan, MD, MPH⁴, Susan Cheng, MD, MPH^{5,6,7}, Teemu J. Niiranen, MD^{1,8}

¹Division of Medicine, Turku University Hospital and University of Turku, Turku, Finland ²Division of Cardiology, Johns Hopkins University, Baltimore, Maryland, USA ³Department of Family Medicine and Community Health, Duke University, Durham, USA ⁴Department of Neurology, Jona Goldrich Center for Alzheimer's and Memory Disorders, Cedars-Sinai Medical Center, Los Angeles, USA ⁵Division of Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, USA ⁶Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, USA ⁷Framingham Heart Study, Framingham, USA ⁸Department of Public Health Solutions, Finnish Institute for Health and Welfare, Turku, Finland

Abstract

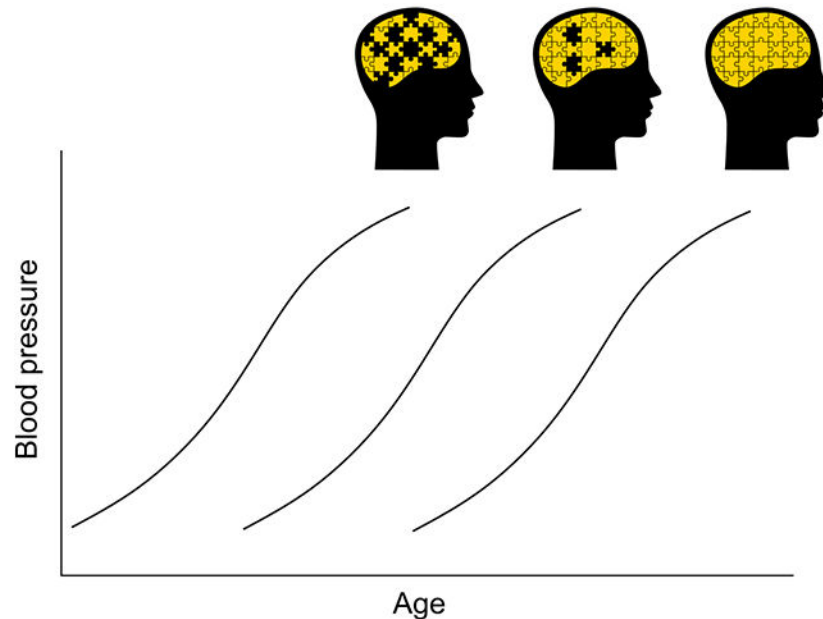
Hypertension is related to increased risk of cognitive decline in a highly age-dependent manner. However, conflicting evidence exists on the relation between age of hypertension onset and cognition. Our goal was to investigate the association between early- vs. late-onset hypertension and mid-life cognitive performance in 2946 Coronary Artery Risk Development in Young Adults study participants (mean age 55±4, 57% women). The participants underwent 9 repeat examinations, including blood pressure measurements, between 1985–1986 and 2015–2016. The participants underwent brain MRI imaging and completed Digit Symbol Substitution test (DSST), Rey Auditory Verbal Learning test (RAVLT), Stroop Interference test and the Montreal Cognitive Assessment (MoCA) to evaluate cognitive function at the Year 30 exam. We assessed the relation between age of hypertension onset and cognitive function using linear regression models adjusted for cognitive decline risk factors, including systolic blood pressure. We observed that individuals with early-onset hypertension (onset at <35 years) had 0.24±0.09, 0.22±0.10, 0.27±0.09, and 0.19±0.07 lower standardized z-scores in DSST, Stroop test, MoCA, and a composite cognitive score than participants without hypertension ($p<0.05$ for all). In contrast, hypertension onset at 35 years was not associated with cognitive function ($p>0.05$ for all). In a subgroup of 559 participants neither early- nor late-onset hypertension was related to macrostructural brain alterations ($p>0.05$ for all). Our results indicate that early-onset hypertension is a potent risk factor for midlife cognitive impairment. Thus, age of hypertension onset assessment in clinical practice could improve risk stratification of cognitive decline in hypertensive patients.

Corresponding Author: Karri Suvila; address: Department of Internal Medicine, University of Turku, Kiinamyllynkatu 4–8, 20014, Turku, Finland; kahesuv@utu.fi; telephone: +358 23130000.

Conflicts of Interest(s)/Disclosure(s)

None.

Graphical Abstract



Keywords

Hypertension; age of onset; cognition; brain; risk factors; follow-up studies

Introduction

Numerous studies have suggested strong correlations between hypertension and risk for cognitive impairment, morphologic brain changes, and dementia.¹⁻³ However, lack of clear consensus remains on the impact of age on the relationship between hypertension and cognition-related outcomes. The persistent equipoise concerning this relationship may be related to important yet previously under-studied heterogeneity of effects.

Accumulating evidence indicates that the relation between blood pressure (BP) and cognitive function is age-dependent.⁴⁻⁷ Prior findings indicate that high midlife BP is associated with cognitive decline and altered brain structure later in life.⁸⁻¹¹ Some evidence suggests that elevated BP in young adulthood could impair the cognitive capacity already in middle-aged individuals.¹²⁻¹⁵ On the other hand, high BP in elderly individuals does not seem to predict cognitive impairment, and even a protective effect has been observed.¹⁶⁻¹⁹ Considering the global challenge of aging populations and increasing burden of dementia,^{20,21} it is crucial to understand in more detail the BP-related mechanisms leading to cognitive decline.

Although the impact of elevated BP on cognition seems age-dependent, the relation between age of hypertension onset and cognitive function remains unclear. In prior studies, we have demonstrated that early-onset hypertension is an important risk factor for subclinical cardiovascular disease and cardiovascular mortality.^{22,23} Hypertension onset by midlife has

been reported to be associated with an increased risk for dementia in women, but not in men.²⁴ However, in another study, hypertension onset in late-life surprisingly protected against dementia.²⁵ Therefore, more evidence on the impact of hypertension onset age besides chronological age and improved individualized approaches for estimating risk of cognitive decline are called for. In this study, we therefore aimed to further elucidate whether early-versus late-onset hypertension is related to cognitive impairment and structural brain changes already by midlife in 2946 CARDIA (Coronary Artery Risk Development in Young Adults) study participants. We hypothesized that early-onset hypertension would associate more robustly with worse cognitive function and smaller brain volumes than late-onset hypertension.

Methods

Study sample

Our study sample includes participants from the prospective CARDIA cohort study.²⁶ All data and materials of the CARDIA study have been made publicly available at the National Institutes of Health's Biologic Specimen and Data Repository Information Coordinating Center and can be accessed at <https://biolincc.nhlbi.nih.gov/studies/cardia/>. The CARDIA cohort was recruited in 1985–1986 and involved 5115 participants (mean age 25±4 years, range 18–30 years). The cohort included individuals of different ethnic backgrounds, sex, and educational levels across four study centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). We studied participants who attended the Year 30 exam of the CARDIA study in 2015–2016 (n=3358). The flow of this study is visualized in Figure S1 in the online-only Data Supplement. We included 2946 of these individuals in our study sample after excluding subjects with missing covariate or outcome data (n=412). Additionally, 599 of these participants also attended a brain MRI substudy. All study participants provided informed consent and the study protocol was approved by each centers' institutional committee.

Exposures and covariates

The participants underwent up to nine regularly conducted follow-up examinations between 1985–1986 (Year 0 exam) and 2015–2016 (Year 30 exam). At each exam, BP was measured three times after 5 minutes of quiet rest from the right arm of all participants in sitting position by centrally trained technicians.^{22,26} A random zero mercury sphygmomanometer was used through the six first follow-up exams, and we calibrated the oscillometric recordings obtained with Omron model HEM907XL from the last three exams to corresponding sphygmomanometer values to attain comparable values.²⁷ In accordance with previous studies,²³ we defined hypertension onset as BP ≥140/90 mmHg or self-reported use of any antihypertensive medication on two successive exams and formed subgroups according to the participants' age of hypertension onset (<35 years, 35–44 years, ≥45 years, and no hypertension).

Demographic characteristics, years of completed education, smoking status, amount of alcohol intake (expressed as total ethanol consumption), and use of antihypertensive agents were assessed by self-report at all exams. Sedentary behavior time was evaluated with the

CARDIA Sedentary Behavior Questionnaire.²⁸ Weight and height were measured at each exam. Body mass index (BMI) was calculated as weight (kg)/(height (cm))². Total serum cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and glucose levels were measured from fasting samples as previously described.^{26,29} We defined diabetes as serum fasting glucose of ≥ 7 mmol/l or use of antihyperglycemics.

Cognitive function tests

Four cognitive function tests were administered by trained and certified CARDIA technicians at the Year 30 exam (between 2015 and 2016) as previously reported.³⁰ The Digit Symbol Substitution test (DSST) measures psychomotor speed, scored as number of correctly substituted symbols, therefore a higher score indicating better performance.³¹ The long-delay free recall scores from the Rey Auditory Verbal Learning test (RAVLT), counted as number of words, were used to assess verbal memory with higher score indicating better performance.³² The Stroop test measures executive function, scored as the sum of time in seconds and number of errors required to complete each subtest.³³ An interference score was calculated by subtracting the subtest two scores from the subtest three score, thus higher interference score represented worse test performance. The Montreal Cognitive Assessment (MoCA) has been demonstrated as a screening tool for mild cognitive impairment, while covering for several cognitive function components, such as orientation, calculations, memory and executive function.³⁴ Higher MoCA score indicates better global cognitive function. All test scores were also standardized into z-scores. We used inversed z-scores for Stroop test to make interpretation similar with the other tests, thus all negative z-scores indicating worse and positive z-scores indicating better performance. A composite cognitive function score was computed as the average of z-scores from DSST, RAVLT and Stroop test to assess overall cognitive function as previously described.³⁰

Brain MRI acquisition and measures

The brain MRI substudy was performed at three study sites using 3-T MR scanners at the CARDIA Year 30 exam concurrently with the cognitive tests. Further technical and methodological details have been reported previously.³⁵ The brain MRI images were quantitatively analyzed for total brain volume (TBV), white matter volume (WMV), grey matter volume (GMV), abnormal white matter volume (AWMV) and white matter fractional anisotropy (WMFA). TBV was computed from the sagittal 3-D T1 sequence as the sum of WMV and GMV. Total intracranial volume was estimated as the sum of TBV and cerebral spinal fluid volume. AWMV was computed from the sagittal 3-D FLAIR T1 and T2 sequences. AWMV depicts the amount of brain tissue damaged by ischemia, penumbra tissue, inflammation, or demyelination. WMFA was estimated using diffusion tensor imaging and represents the micro-structural integrity of the white matter tracts. WMFA is expressed as a scalar value, ranging from 0 (isotropy) and 1 (anisotropy). Higher fractional anisotropy is often present in highly myelinated white matter tracts, whereas lower fractional anisotropy is related to aging and neurodegenerative disorders.³⁶ All brain-related values were also transformed into z-scores.

Statistical analyses

We studied the Year 30 examination characteristics in all participants and separately in subgroups by hypertension onset age. To compare the between-group differences in characteristics and cognitive function measures, we used chi-squared test for categorical variables and one-way analysis of variance for continuous variables. Alcohol intake was standardized into a z-score due to skewed distribution. Additionally, we compared the baseline characteristics between the study sample and the excluded participants using two-sample t-tests for the continuous variables and the X^2 tests for categorical variables. We assessed the relation of hypertension onset age with cognitive function and MRI measures using linear regression models, with participants without hypertension as the reference group. We also analyzed the association with cognitive function using an alternative definition for age of hypertension onset based on only elevated BP without considering antihypertensive medication use. The minimally adjusted linear regression model was adjusted for age, sex, race, and education. The fully adjusted linear regression model was adjusted for age, sex, race, education, diabetes, BMI, smoking, alcohol intake, sedentary time, use of any antihypertensive medication and present systolic BP. All models with MRI measures as the outcome variable were also adjusted for intracranial volume. All covariates were drawn from the Year 30 exam. We also examined the associations between cognitive function and hypertension onset age in subgroups by sex and race by including an onset age x subgroup interaction term in the model. We performed all analyses using SAS, version 9.4 (SAS Institute, Cary, NC, USA). The null hypothesis was rejected for two-tailed $P < 0.05$.

Results

Table 1 shows the characteristics of the whole study sample and by subgroups according to hypertension onset age. Participants with hypertension onset at <35 years of age (early-onset hypertension) were more likely to be male and African American than any of the other race-ethnic and sex categories. Individuals with early-onset hypertension were also more likely to be diabetic, smoke and use antihypertensive medication. Participants who were lost to follow-up or excluded were more likely to be men, black, and smokers compared to participants included in the study sample (Table S1 in the online-only Data Supplement). No other major differences were observed in the baseline characteristics between the included and excluded participants, although other statistically significant differences were also observed. Cognitive function test scores at the Year 30 exam are shown in Table 2 according to hypertension onset age. Individuals with hypertension onset <35 years of age had the lowest scores in all cognitive function tests, except for the Stroop test where the mean score was the highest. Participants with early-onset hypertension also had the smallest TBV, WMV and GMV (Table S2 in the online-only Data Supplement). There were statistically significant differences between the four groups in brain volumes ($p < 0.01$ for all) but not in AWMV or WMFA ($p > 0.05$ for both).

The associations between hypertension onset age subgroups and cognitive function measures are presented in Table 3. Compared to participants without hypertension, individuals with hypertension onset at <35 years of age had 0.57 ± 0.09 , 0.71 ± 0.09 , 0.50 ± 0.09 , 0.81 ± 0.09 and 0.60 ± 0.07 lower unadjusted z-scores ($\beta \pm$ standard error) for the RAVLT, DSST, Stroop test,

MoCA, and composite cognitive score in unadjusted models ($p < 0.001$ for all), respectively. The associations between early-onset hypertension group and lower z-scores for cognitive function tests remained statistically significant in the fully adjusted model ($p < 0.05$ for all), except for the RAVLT ($p = 0.22$). Hypertension onset between 35 to 44 years and 45 years or over was not related to cognitive test performance ($p > 0.05$ for all). We observed no significant sex-specific differences in the associations between hypertension onset age and cognitive function (Table S3 in the online-only Data Supplement). Similarly, even though the associations were slightly more prominent among white individuals, the trends were similar in subgroups by race (Table S4 in the online-only Data Supplement). The results were attenuated when age of hypertension onset was defined only based on elevated BP (Table S5 in the online-only Data Supplement). Moreover, hypertension onset at < 35 years of age was associated with lower TBV, WMV and GMV in the unadjusted model ($p < 0.01$ for all, Table S6 in the online-only Data Supplement). However, in the adjusted models hypertension onset age was not related to any of the brain MRI measures ($p > 0.05$ for all).

Figure 1 illustrates the relation between hypertension onset age and global cognitive function scores. Both the composite cognitive and MoCA scores were lowest in the < 35 years of hypertension onset subgroup compared to the other subgroups. In fully adjusted models, early-onset hypertension was associated with 0.19 (95% CI, 0.06–0.32) and 0.27 (95% CI, 0.10–0.44) lower z-scores for composite cognitive and MoCA scores, respectively. A linear relationship with decreasing age of hypertension onset was observed for both the composite cognitive and MoCA scores ($p < 0.01$ for trend in both). Subgroups with hypertension onset ≥ 35 years of age were not associated with cognitive dysfunction as measured by global cognitive function scores after adjusting for several potential contributing factors ($p > 0.05$ for all).

Discussion

In this study we observed that, after adjusting for several covariates (age, sex, race, education, diabetes, BMI, smoking, alcohol intake, sedentary time, antihypertensive medication use, and present systolic BP), early-onset hypertension was associated with worse cognitive test performance than late-onset hypertension. However, age of hypertension onset was not associated with any quantified brain MRI measures. Our findings suggest that early age of hypertension onset is associated with worse cognitive function in midlife, but not with commonly assessed structural brain alterations, irrespective of the present systolic BP at the time of cognitive function assessment.

Several previous studies, including data from the CARDIA study, have demonstrated that the relation between BP and cognition is highly dependent on the individual's age at exposure and outcome assessment.^{8,11,18,37,38} However, most of these former studies have not considered impact of hypertension onset age in their analyses. Results from The 90+ Study indicated that self-reported hypertension onset after 80 years is associated with lower dementia risk.²⁵ In that study, compared to individuals without self-reported hypertension, hypertension onset between 80 to 89 years and ≥ 90 years was related to hazard ratios (HR) of 0.58 (95% CI 0.34–0.98) and 0.37 (95% CI 0.19–0.73) for developing all-cause dementia, respectively. In another report from the Multiphasic Health Checkups study, however,

hypertension onset during mid-adulthood was associated with HR of 1.68 (95% CI 1.20–2.34) for late-life dementia in women, compared to those with stable normotension.²⁴ The study sample included individuals with a wide age-spectrum (from 30 to 56 years), with no further analyses according to their hypertension onset age. In addition, the analyses were not adjusted for alcohol intake, sedentary time, or physical activity. The results from our study support the findings from these two studies, indicating that particularly early-onset hypertension is a risk factor for impaired midlife cognitive function, whereas late-onset hypertension is not. Considering that hypertension is a symptomless condition, distinguishing between the actual age of hypertension onset from the age at hypertension diagnosis is virtually impossible. In this study, the maximum delay between hypertension onset and hypertension diagnosis was 5 years (the time between follow-up visits) and this delay may be even longer in everyday clinical practice. The impact of early-onset hypertension on cognitive function was less prominent when an alternative definition of hypertension onset age which did not consider antihypertensive medication use was used (Table S5 in the online-only Data Supplement). However, omitting initiation of antihypertensive medication use from the definition of hypertension onset age will most likely lead to misclassification as even well-controlled hypertensive individuals have considerable residual cardiovascular disease risk. Nevertheless, given that worse cognitive performance relates to increased dementia risk,^{15,31} early-onset hypertension may predispose to overt dementia later in life.

Cumulative BP burden is an important contributing factor for cognitive impairment.^{13,14,39–43} Given the chronic nature of hypertension, it is presumable that long-term exposure is a major determinant for the adverse effects of hypertension on cognitive function. Most previous studies in this domain have used complex formulas to estimate BP exposure from repeated BP measurements during follow-up. A recent study on 191 CARDIA study participants demonstrated that higher cumulative BP was associated with worse cognitive performance and gait.¹⁵ However, the study sample was considerably smaller compared to this study and the clinical applicability of the exposure variable may be limited. Compared to other indices of cumulative BP burden, age of hypertension onset is likely to similarly represent the overall hypertension chronicity level. Yet, hypertension onset age could act as a feasible surrogate measure to assess an individual's overall lifetime exposure to BP and risk of hypertension in offspring.²³ Additionally, as onset or presence of hypertension at much older age do not seem to confer increased risk for cognitive decline,^{16,18,25} assessment of hypertension onset age could aid clinicians to differentiate high-risk individuals from those who are unlikely to experience cognitive impairment. This may also have important implications for hypertensive patients as adequate hypertension treatment has been suggested to slow, or even prevent, cognitive decline and development of dementia.^{44,45}

Unlike cognitive function, the relation between long-term BP burden and structural brain changes in midlife remains unclear.^{5,6} In our study, we did not observe an association between hypertension onset age and TBV, WMV, GMV, AWMV or WMFA. However, most previous studies have reported morphologic brain alterations only after midlife.^{5,11} This is further supported by observations from the Framingham Heart Study, which demonstrated that relevant age-related differences in MRI-quantified brain volumes begin and gradually

increase after the age of 50 years.⁴⁶ Structural brain changes are commonly present in hypertensive individuals with dementia, although the optimal age and protocols for imaging remain disputed.⁴⁷ Therefore cognitive function tests are used to detect altered cognitive function at an early age prior to manifestation of structural brain changes or overt dementia. Our results suggest that the potential harms of early-onset hypertension are detectable already in midlife prior to quantifiable structural brain changes.

The strengths of our study include a large, diverse study population with up to 30 years of regular follow-up visits. 65.7 % of individuals who participated in the baseline examination took part in examination 9. The study sample included less men, African Americans and smokers compared to individuals excluded or lost to follow-up. (Table S1 in the online-only Data Supplement) No other clinically significant differences were observed between these two groups. However, MRI was performed in a subsample, resulting in loss of statistical power for the MRI-related outcomes. Additionally, our findings may not be generalizable to the entire age spectrum as our study sample did not include elderly individuals. Another strength of our study is that we were able to reliably determine the actual age of hypertension onset in virtually all participants as the participants were young at study baseline. However, an even longer follow-up time and availability of data for incident dementia could perhaps have enabled us to provide more comprehensive answers on the relation of hypertension with cognitive function. Considering our observational study design, future studies with prospective and experimental study designs and varying study populations are needed to draw even more robust conclusions on the impact of hypertension onset age on cognition. Additionally, we had no information on history of acute stroke, which could have impacted the results. As another limitation, baseline data on cognitive function or brain MRI measurements were not available. Yet, we adjusted our analyses for several other factors that correlate with cognitive function, such as education. Moreover, we were unable to adjust the analyses for antihypertensive treatment intensity during follow-up. However, we aimed to minimize this effect by adjusting for prevalent antihypertensive medication use.

Perspectives

Overall, our findings expand the current knowledge of adverse events related to early-onset hypertension beyond cardiovascular disease related outcomes.^{22,23} In effect, the timing of hypertension onset appears to impact cognitive function rather than structural brain alterations, which may reflect features specific to hypertension-related brain pathophysiology that warrant further investigation. Previous literature suggests that impaired neurophysiological function in younger individuals may precede the detected neuroanatomical changes in elderly hypertensive persons.^{7,48} The potential underlying mechanisms of early-onset hypertension on cognition might result from long-term exposure to high BP, or via induced early vascular aging, leading to microvascular brain changes. Thus, these initial cognitive changes related to early-onset hypertension could potentially be detected through functional brain imaging techniques such as PET imaging.⁴⁹ However, extended follow-up of these individuals to later life may also reveal an association between the age of hypertension onset and macrostructural brain changes, such as decreased brain volumes. Nevertheless, assessing age of hypertension onset could offer advantages in

dementia risk stratification of hypertensive individuals in clinical practice, as previous data suggests that hypertension onset age could also be defined reliably by self-report.^{22,25} Given the current evidence on the risks of early-onset hypertension, physicians treating high BP should be aware of the age at which their patients initially developed hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

- Early-onset hypertension is a strong and highly heritable risk factor for cardiovascular disease.
- The association between age of hypertension onset and midlife cognition is unclear.

What Is Relevant?

- Early-onset and not late-onset hypertension is associated with functional cognitive impairment in midlife.
- Early- and late-onset hypertension are not related to structural brain changes in midlife.

Summary

Our results expand previous evidence on early-onset hypertension being an important independent risk factor for adverse events. Assessing age of hypertension onset could improve the dementia risk stratification of individuals with hypertension.

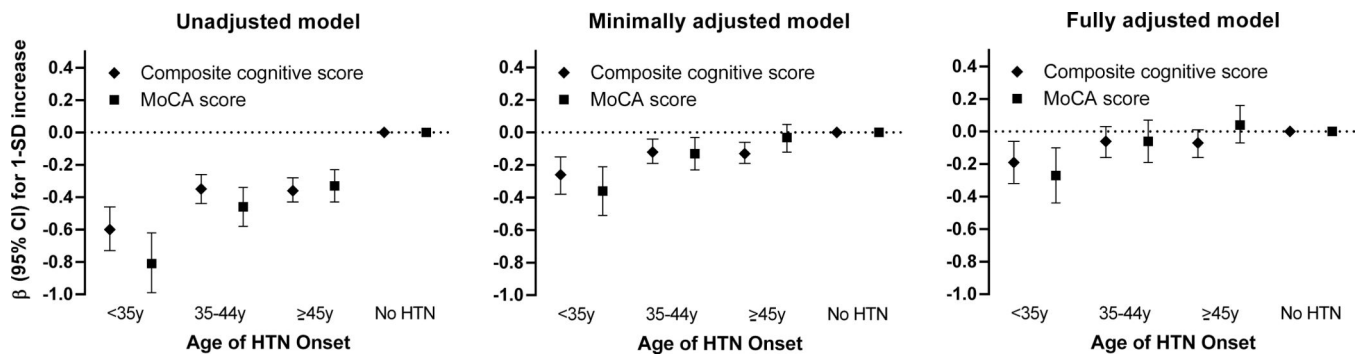


Figure 1. Association between hypertension onset age and 1-SD increase in mean global cognitive function scores at Year 30.

Minimally adjusted model is adjusted for age, sex, race, and education. Fully adjusted model is adjusted for age, sex, race, education, diabetes, body mass index, smoking, alcohol intake, sedentary time, use of antihypertensive medication and systolic blood pressure. Composite cognitive score was computed as the average of the Digit Symbol Substitution test, the Rey Auditory Verbal Learning test, and the inversed Stroop interference test score. HTN, hypertension; y, year; MoCA, Montreal Cognitive Assessment.

Table 1.

Characteristics of the study sample and in subgroups by hypertension onset age.

Characteristic	All	HTN Onset Age				p-value
		< 35 y	35–44 y	45 y	No HTN	
N	2946	112	277	426	2131	
Age, years	55.1 (3.6)	55.1 (3.5)	54.2 (3.7)	56.6 (3.0)	54.9 (3.6)	<0.001
Age, range	48–60	48–60	48–60	49–60	48–60	-
Women, n (%)	1689 (57.3)	59 (52.7)	162 (58.5)	240 (56.3)	1228 (57.6)	0.71
Black race, n (%)	1373 (46.6)	87 (77.7)	203 (73.3)	261 (61.3)	822 (38.6)	<0.001
Body mass index, kg/m ²	30.4 (6.8)	33.7 (7.3)	34.6 (7.1)	32.7 (6.9)	29.2 (6.3)	<0.001
Current smoker, n (%)	425 (14.4)	23 (20.5)	43 (15.5)	80 (18.8)	279 (13.1)	0.004
Total cholesterol, mmol/l	5.0 (1.0)	4.7 (1.0)	4.7 (1.0)	4.8 (1.0)	5.1 (0.9)	<0.001
HDL-cholesterol, mmol/l	1.6 (0.5)	1.5 (0.6)	1.5 (0.5)	1.5 (0.5)	1.6 (0.5)	<0.001
Systolic blood pressure, mmHg	118 (15.1)	125 (17.6)	126 (17.7)	125 (16.6)	116 (13.2)	<0.001
Diastolic blood pressure, mmHg	72.2 (10.5)	75.8 (11.5)	77.4 (11.2)	76.0 (11.1)	70.6 (9.7)	<0.001
Use of antihypertensive medication, n (%)	943 (32.0)	104 (92.9)	253 (91.3)	374 (87.8)	212 (10.0)	<0.001
Diabetes, n (%)	385 (13.1)	39 (34.8)	82 (29.6)	109 (25.6)	155 (7.3)	<0.001
Alcohol intake, ml/day (median, IQR)	2.4 (0–14.6)	0 (0–7.7)	2.4 (0–12.2)	0 (0–14.3)	4.8 (0–15.3)	0.07
Education, years	14.9 (1.9)	14.1 (1.9)	14.4 (1.9)	14.5 (1.9)	15.0 (1.9)	<0.001
Sedentary time, h/day	7.5 (4.2)	9.1 (4.3)	8.6 (4.5)	8.0 (4.3)	7.2 (4.0)	<0.001

Values are obtained from the Year 30 exam. Values are reported as mean (SD) unless stated otherwise. HTN, hypertension; y, years; IQR, interquartile range.

Table 2.

Mean unadjusted cognitive function scores at Year 30 exam according to hypertension onset age.

	All	HTN Onset Age				p-value
		<35 y	35–44 y	45 y	No HTN	
N	2946	112	277	426	2131	-
RAVLT, words	8.5 (3.4)	6.9 (3.2)	7.5 (3.4)	7.7 (3.4)	8.9 (3.4)	<0.001
DSST, symbols	68.0 (17)	58.0 (18)	64.0 (17)	62.9 (16)	70.1 (16)	<0.001
Stroop test, score	22.5 (12)	27.5 (14)	24.9 (13)	25.1 (14)	21.4 (11)	<0.001
Composite cognitive score, z	0.0 (0.7)	-0.5 (0.8)	-0.2 (0.8)	-0.2 (0.8)	0.1 (0.7)	<0.001
MoCA, score	23.9 (3.9)	21.2 (3.9)	22.5 (3.9)	23.1 (4.1)	24.4 (3.7)	<0.001

Values are reported as mean (SD). Stroop interference test score equals seconds and number of errors, with higher score indicating worse performance. Composite cognitive score is calculated as the average z-scores from RAVLT, DSST and inverted Stroop test. HTN, hypertension; y, years; DSST, Digit Symbol Substitution test; RAVLT, Rey Auditory Verbal Learning test; MoCA, Montreal Cognitive Assessment.

Table 3.

Association ($\beta \pm SE$) of hypertension onset age with cognitive performance at Year 30.

Age of hypertension onset	RAVLT	DSST	Stroop test	Composite cognitive score	MoCA
N	2946	2946	2946	2946	2946
Unadjusted model					
<35 years	-0.57±0.09*	-0.71±0.09*	-0.50±0.09*	-0.60±0.07*	-0.81±0.09*
35–44 years	-0.40±0.06*	-0.36±0.06*	-0.29±0.06*	-0.35±0.05*	-0.46±0.06*
45 years	-0.34±0.05*	-0.42±0.05*	-0.30±0.05*	-0.36±0.04*	-0.33±0.05*
No hypertension	Ref.	Ref.	Ref.	Ref.	Ref.
Minimally adjusted model					
<35 years	-0.21±0.08 [‡]	-0.34±0.08*	-0.24±0.09 [‡]	-0.26±0.06*	-0.36±0.08*
35–44 years	-0.14±0.06 [‡]	-0.12±0.05 [‡]	-0.09±0.06	-0.12±0.04 [‡]	-0.13±0.05 [‡]
45 years	-0.10±0.05 [‡]	-0.16±0.05*	-0.12±0.05 [‡]	-0.13±0.03*	-0.03±0.04
No hypertension	Ref.	Ref.	Ref.	Ref.	Ref.
Fully adjusted model					
<35 years	-0.12±0.09	-0.24±0.09 [‡]	-0.22±0.10 [‡]	-0.19±0.07 [‡]	-0.27±0.09 [‡]
35–44 years	-0.07±0.07	-0.03±0.07	-0.08±0.07	-0.06±0.05	-0.06±0.07
45 years	-0.03±0.06	-0.07±0.06	-0.11±0.07	-0.07±0.04	0.04±0.06
No hypertension	Ref.	Ref.	Ref.	Ref.	Ref.

Values are for 1-SD difference estimate (beta) with standard error. Minimally adjusted model is adjusted for age, sex, race, and education. Fully adjusted model is adjusted for age, sex, race, education, diabetes, body mass index, smoking, alcohol intake, sedentary time, use of antihypertensive medication, and systolic blood pressure.

* P<0.001

[‡] P<0.01

[‡] P<0.05. DSST, Digit Symbol Substitution test; RAVLT, Rey Auditory Verbal Learning test; MoCA, Montreal Cognitive Assessment.