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## Elevated Blood Pressure is Associated with Advanced Brain Aging in Midlife: A 30-year Follow-up of The CARDIA Study

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### Abstract

**Background:** High blood pressure (BP) is a risk factor for late-life brain health, however, the association of elevated BP with brain health in midlife is unclear.

**Methods:** We identified 661 participants from the Coronary Artery Risk Development in Young Adults (age 18–30 at baseline) with 30 years of follow-up and brain MRI at Year 30. Cumulative exposure of BP was estimated by time-weighted averages (TWA). Ideal cardiovascular health was defined as systolic BP <120 mm Hg, diastolic BP <80 mm Hg. Brain age was calculated using previously-validated high dimensional machine learning pattern analyses.

**Results:** Every 5 mmHg increment in TWA systolic BP was associated with approximately 1-year greater brain age (95% confidence interval [CI]: 0.50 to 1.36). Participants with TWA systolic or diastolic BP over the recommended guidelines for ideal cardiovascular health, had on average 3-year greater brain age (95% CI: 1.00–4.67; 95% CI: 1.45–5.13, respectively).

**Conclusion:** Elevated BP from early to middle adulthood, even below clinical cut-offs, is associated with advanced brain aging in midlife.

### INTRODUCTION

Hypertension in midlife, especially if not treated effectively, has consistently been associated with an increased risk of dementia including Alzheimer's disease (AD) in late-life [1].

Moreover, pooled analysis has shown that high blood pressure (BP) in midlife is associated

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Conflict of Interest

The authors declare that there are no conflicts of interest.

with a 60% increased risk of dementia [2]. High BP levels can have detrimental brain effects, including stroke and increased White matter hyperintensity volume [3,4]. Evidence from observational studies and randomized clinical trials such as SPRINT-MIND, suggest that treating hypertension in mid or late-life could decrease the risk of cognitive impairment [5]. However, the neuronal and other damage associated with elevated BP exposure may begin even before midlife. Therefore, control of elevated BP earlier in the life course may be necessary to effectively reduce the public health burden of Alzheimer's disease and related dementias (ADRD). Previous work within the Coronary Artery Risk Development in Young Adults study (CARDIA) have suggested that not only hypertension but also elevated BP above recommended guidelines across young to mid-adulthood may negatively affect cognitive outcomes in midlife [6,7]

In order to design more effective population-based prevention strategies, additional work is needed to fully understand how elevated BP over the life course influences cognition and brain aging. The aging process is characterized by major variations in cognitive and neurodegenerative trajectories [8]. Recently developed machine learning methods for brain age prediction at an individual level (as opposed to chronological age), are more sensitive in capturing age-related brain atrophy than traditional neuroimaging methods such as total brain volume [9–11]. This approach is particularly relevant earlier in life when age-related changes may be subtle or harder to detect via traditional structural imaging techniques.

Our goal was to determine the association between systolic and diastolic BP levels in young/mid adulthood and brain aging patterns in midlife in a diverse cohort of Black and White adults.

## METHODS

### Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective cohort study investigating the development of and risk factors for cardiovascular disease [12]. Briefly, starting in 1985, 5115 Black and White community dwelling adults between 18 and 30 years of age were recruited from population-based samples of 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Within each center, recruitment was balanced by sex, age, and educational level. The criteria for inclusion and exclusions were the following; 1) participants had to be aged 18–30 years at the time of the initial telephone recruitment interview; 2) participants had to have a permanent address in the target area.; 3) participants could not be deaf, mute or blind; they could not be pregnant at the time of the examination; they had to be able to complete all parts of the examination (exercise test, interviews, questionnaires, etc.)

Participants completed follow-up examinations every 2 to 5 years for 30 years: 1987 to 1988 (year 2), 1990 to 1991 (year 5), 1992 to 1993 (year 7), 1995 to 1996 (year 10), 2000 to 2001 (year 15), 2005 to 2006 (year 20), 2010 to 2011 (year 25), and 2015–2016 (Year 30). A majority of the group has been examined at each of the follow-up examinations (91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively). At each examination, participants provided written informed consent, and study protocols were reviewed by institutional

review boards at each study site and the CARDIA Coordinating Center. Further details regarding the design and recruitment of CARDIA have been previously reported [12].

At the Year 30 visit, a subset of CARDIA participants completed neuroimaging as part of the CARDIA Brain Magnetic Resonance Imaging (MRI) Ancillary Study. This sub-study was conducted at three sites (Birmingham, AL; Minneapolis, MN; and Oakland, CA). The sub-study aimed for balance within four strata of ethnicity/race (Black, White) and sex (male/female). Exclusion criteria for the MRI sub-study included any contra-indication to MRI or a body size that was too large for the MRI tube bore. Further details regarding the design of CARDIA and the Brain MRI ancillary study have been previously reported [13].

Our sample consists of the 662 CARDIA participants who had brain magnetic resonance imaging (MRI) at year 30. Further inclusion criteria were BP assessments at least at 3 time points, including at Year 30, resulting in our analytic cohort of 661 adults. Compared with the main sample at baseline, the participants of our analytic cohort were more likely to be White, have more years of education, and less likely to smoke ( $p < 0.001$  for all); there was no difference in baseline systolic or diastolic BP, however, there was a significant difference in systolic and diastolic BP at year 30 ( $p < 0.001$  and  $p = 0.003$ , respectively), with those not included in the MRI sample having on average higher systolic and diastolic BP.

### Blood Pressure Measurement

Before each clinic examination, participants were asked to fast and to abstain from smoking or heavy physical activity for at least 12 hours before the visit. Certified technicians collected 3 measures of resting blood pressure at 1-minute intervals using a Hawksley random-zero sphygmomanometer (WA Baum Co, Copaugue, NY) at baseline and years 2, 5, 7, 10, and 15. At years 20 and 25, and 30 a digital blood pressure monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used. The oscillometric values were calibrated to the random-zero values after a study of both devices at Year 20. In this analysis, systolic and diastolic BP measures were calculated as the average of the second and third measurements. We used the criteria by the American Heart Association for ideal cardiovascular health to define ideal BP: SBP  $< 120$  mmHg, DBP  $< 80$  mmHg [14]. Hypertension was defined as systolic BP  $\geq 140$  mmHg, diastolic BP  $\geq 90$  mmHg, in keeping with criteria used at the time.

### Neuroimaging protocol

The MRI scans were acquired on 3T scanners located at each CARDIA study sites: Siemens 3T Tim Trio/VB15 platform in Minneapolis and in Oakland and Philips 3T Achieva/2.6.3.6 platform in Birmingham. Standard quality assurance protocols using phantoms previously developed for the Functional Bioinformatics Research Network and the Alzheimer's disease Neuroimaging Initiative were used. Structural images used for this study were acquired with 1 mm isotropic 3D T1 and T2 sequences. Scan acquisition parameters have been previously described [13], and were processed using previously described methods [15–17]. In brief, structural images were processed using an automated multispectral computer algorithm which classified all supratentorial brain tissue into gray matter, White matter, and cerebral spinal fluid and identifies anatomic regions of interest (ROI). After correction of intensity

inhomogeneities [18], a multi-atlas skull stripping algorithm was applied for the removal of extra-cerebral tissues [19]. Each T1-weighted scan was then automatically segmented into a set of anatomical gray matter ROIs using a multi-atlas label fusion method [20]. The images were visually checked for incidental findings, motion artefacts, and other quality issues.

### Calculation of Brain Age

We used a previously validated high dimensional neuroimaging pattern analysis, based on machine learning algorithms, that quantifies individual differences in age-related atrophy using MRI-derived structural brain characteristics, called Spatial Pattern of Atrophy for Recognition of Brain Aging (SPARE-BA) [9,10,21]. This method has been validated in several cohort studies including CARDIA [9,10,21,22]. Specifically, SPARE-BA was derived using 10,216 participants from the Imaging-based coordinate SysTem for AGing and NeurodeGenerative diseases (iSTAGING) consortium encompassing a wide age range (22 to 90 years), with cognitively healthy individuals ( $n = 8284$ ). The iSTAGING consortium included data from 11 cohorts including CARDIA. We calculated a brain-aging signature to estimate deviations from typical aging [10]. We developed a multivariate pattern regression model based on support vector regression to predict individualized brain age for each participant, which we defined as the SPARE-BA similar to our previous work [9,10]. The model was trained with the T1-MR scans using regional volumetric measures for structures. The brain age prediction regression made use of a radial basis function kernel. The gamma parameter was set to 0.1. Cost and epsilon parameters were kept at their defaults of 1.0 and 0.1, respectively. The training set included only cognitively normal subjects. For subjects in the training set, we performed stratified 10-fold cross-validation, stratifying on the study to preserve the relative proportion of studies in each fold. The training set for SPARE-BA is summarized consisted of ( $n=8,284$ ) subjects with the following breakdown (Penn-ABC:  $n=104$ , ADNI-1:  $n=189$ , ADNI-2:  $n=324$ , AIBL:  $n=446$ , BLSA-1.5T:  $n=92$ , BLSA-3T:  $n=964$ , CARDIA:  $n=719$ , BIOCARD:  $n=94$ , ACS:  $n=247$ , WRAP:  $n=12$ , Penn-PMC:  $n=4$ , SHIP:  $n=2739$ , UKBIOBANK:  $n=2201$ ). The mean absolute error (MAE) of age predictions was 5.3. The SPARE-BA prediction regression was run once before harmonization and once after harmonization. The mean absolute error (MAE) of age predictions was 5.255 before harmonization and 5.271 after harmonization. Although the mean absolute error of the predictions did not improve after harmonization, we observed study-by-study errors that were more-centered around zero after harmonization. Based on the median error for each study's age predictions, 11 of the 13 studies exhibited error distributions closer to zero after harmonization. Therefore, we used the SPARE-BA values after harmonization in our subsequent analyses. Lastly, we observed that age predictions were biased towards over-predicting the age of younger subjects and under-predicting the age of older subjects. [23] To correct for this bias, we adjusted SPARE-BA predicted age for age using a linear model as suggested in the literature. [23] Higher SPARE-BA values indicate greater age-related atrophy compared to normative trends of age-related changes in brain structure.

### Cognitive Function Assessment

CARDIA technicians who underwent formal training and certification administered a battery of cognitive tests at the Year 30 examination that included the Digit Symbol Substitution Test (DSST), the Stroop Test, the Rey Auditory Verbal Learning Test (RAVLT), and Verbal

Fluency [24]. Each test score was converted into z-scores, which were then added into a “global” cognitive composite score.

### Covariates

Demographic characteristics, cigarette smoking (in years), alcohol consumption and antihypertensive medication use were based on self-report. At each examination, weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus at baseline was defined as fasting plasma glucose  $\geq 126$  mg/dL, oral glucose tolerance test  $\geq 200$  mg/dL, glycosylated hemoglobin  $\geq 6.5\%$ , or use of diabetes medications. Self-reported annual family income was measured on a 9-point scale ranging from less than \$5000 (1) to \$100 000 or more (9), dichotomized as income above or below the median income category (\$16,000 through \$24,999) at Year 5 (1990–1991). Physical activity was measured with the CARDIA Physical Activity History questionnaire which queries the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months. Physical activity level was summarized as units of total activity incorporating moderate and high intensity activities. Blood was drawn by venipuncture according to a standard protocol [13]. Total cholesterol was measured enzymatically as previously described [13]. Apolipoprotein (*APOE*) phenotype was determined from plasma samples by a modification of the methods of Kamboh et al. [25] Participants were classified according to *APOE* phenotype and participants were categorized as having any epsilon 4 ( $\epsilon 4$ ) vs. no  $\epsilon 4$  allele.

### Statistical Analysis

Our primary predictor was a cumulative measure of systolic and diastolic BP over 30 years of follow-up. This was done by first estimating the mean curve for systolic and diastolic BP using linear mixed modeling of the repeated BP measurements obtained at all available visits, for each race and sex group. We used linear splines in age with knots at 30 and 40 years of age corresponding to decades of the life span, for face validity and to ensure adequate numbers of observations in each of the 3 age ranges defined by the knots. The models also included 4 random effects, one corresponding to each of the fixed effects (including the intercept), with an unstructured covariance matrix. We then calculated participant-specific blood pressure curves as best linear unbiased predictions based on the mixed models. Next, we calculated areas under the curve (AUCs) over the interval from baseline to the year 30 visit. Time-weighted averages (TWAs) of systolic and diastolic BP were calculated as the AUC divided by its total time interval (time of last observation minus time of first observation).

We then used linear regression to assess the independent associations of cumulative systolic and diastolic BP with brain age at Year 30. For each, we estimated the association adjusted for chronological age at Year 30 in Model 1 and then the association after controlling for race, sex, education, intracranial volume (ICV), and scanning site in Model 2. In Model 3, we additionally adjusted for any antihypertensive medication use across the 30-year follow-up. In additional models, we also controlled for baseline BMI, diabetes mellitus, income, smoking, physical activity, total cholesterol, as well as baseline BP level.

To distinguish whether any association with brain age was attributable to BP level above or below recommended guidelines, we dichotomized the TWAs according to the recommended guidelines defined by American Heart Association criteria for ideal cardiovascular health.

Interactions between blood pressure and sex, race, and *APOE*  $\epsilon$ 4 carrier status, respectively, on the association with brain age were assessed. If the interactions were significant, we used stratified analysis.

We used linear regression to assess the associations of TWA systolic and diastolic BP with the composite cognitive measure at Year 30, as well as the association between the cognitive measures and brain age.

All analyses were completed with STATA version 15.1, and R 4.0.4. Packages used in R were dplyr, effects, and ggplot 2. Significance testing was 2-sided with the significance level set at  $p < 0.05$ .

## RESULTS

At Year 30, the participant mean age was 55.3 ( $\pm 3.5$ ), 40.0% were Black, 52.1% were female, and mean years of education was 14.1 ( $\pm 2.2$ ) (Table 1). At Year 30, the mean SBP and DBP were 118.9 ( $\pm 15.8$ ) and 72.9 ( $\pm 11.1$ ), respectively. The median brain age was 54.26 (IQR= 59.03–49.29). By Year 30, 108 participants (16.3%) were on antihypertensive medication, while 99 participants (15.0%) met the criteria for hypertension but were not taking treatment, 70 (10.6%) participants reported being on treatment but still met the criteria for hypertension at the Year 30 visit.

TWA systolic and diastolic BP (per every 5-point mmHg) over the follow-up were associated with approximately 1-year and half a year greater brain age ( $\beta$ : 0.93, 95% CI: 0.50 to 1.36;  $\beta$ : 0.45, 0.04 to 0.86, respectively), adjusted for chronological age, sex, education, race, ICV, and scanning site. The association between systolic BP and brain age was similar after additionally adjusting for antihypertensive medication use, however for diastolic BP, the association was attenuated (Table 2). Further adjustment for baseline smoking status, total cholesterol, income, physical activity, diabetes, BMI, and BP, produced similar results ( $\beta$ : 1.11, 95% CI: 0.51 to 1.71 for systolic BP, and  $\beta$ : 0.24, 95% CI: -0.34 to 0.82 for diastolic BP). As a sensitivity analysis, we reran the regression models with BP TWAs excluding BP at Year 30 and the results were similar; TWA systolic and diastolic BP (per every 5-point mmHg) over the follow-up were associated with approximately 1-year and half a year greater brain age ( $\beta$ : 0.83, 95% CI: 0.50 to 1.36;  $\beta$ : 0.38, -0.05 to 0.81, respectively), adjusted for chronological age, sex, education, race, ICV, and scanning site.

We next investigated whether the associations between BP and brain age were attributable to exposure levels above recommended guidelines for ideal cardiovascular health, by estimating the effects of normal (below American Heart Association guidelines) and elevated (above American Heart Association guidelines) TWA BP exposures. 19.2% ( $n=127$ ) of participants had elevated TWA systolic BP, while 8.6% ( $n=57$ ) had elevated diastolic BP. Participants with elevated TWA systolic or diastolic BP had on average a brain age 3.3 years greater than those with ideal levels, adjusted for chronological age,

sex, education, race, ICV, and scanning site (Figure 1). Elevated systolic or diastolic BP explained 20% of the variance in brain age ( $r^2=0.2$ ,  $\Delta=0.25$ ). In order to detect this effect size with an alpha of 0.001, adjusting for covariates, 140 participants were needed to achieve a power of 90% in this analysis.

There was no interaction between elevated BP and antihypertensive medication use ( $p=0.963$  for systolic BP and  $p=0.080$  for diastolic BP) on the association with brain age and further adjustment for antihypertensive medication use produced similar results (Table 3). We additionally adjusted for baseline smoking status, BMI, total cholesterol, physical activity, diabetes, income, and systolic and diastolic BP, and the results remained similar ( $\beta$ : 3.88, 95% CI: 2.20 to 5.56 for systolic BP and  $\beta$ : 2.46, 95% CI: 0.31 to 4.62 for diastolic BP). In order to ascertain if participants with hypertension were driving the association between elevated BP and higher brain age, we excluded those meeting the criteria for hypertension at Year 30 ( $n=200$ , 30%); elevated BP was still associated with higher brain age ( $\beta$ : 3.90, 95% CI: 1.58 to 6.22, for systolic BP, but not for diastolic BP ( $\beta$ :  $-0.02$ , 95% CI:  $-4.33$  to 4.29).

We also investigated interactions between race, TWA blood pressure, and brain age (for interactions between systolic BP and race:  $p=0.06$ ; diastolic BP and race:  $p=0.96$ ). After stratification, the association per every 5 mmHg increment in TWA systolic BP was stronger among Black participants ( $\beta$ : 1.18, 95% CI: 0.53 to 1.83) compared to White ( $\beta$ : 0.61, 95% CI: 0.02 to 1.20). We did not find any significant interaction between sex and TWA blood pressure on brain age or for *APOE* genotype and blood pressure on brain age ( $p>0.10$  for all).

TWA systolic and diastolic BP were associated with composite Year 30 cognitive performance (per 5-point increment:  $\beta$ :  $-0.07$ , 95% CI:  $-0.10$  to  $-0.03$ ;  $\beta$ :  $-0.07$ , 95% CI:  $-0.10$  to  $-0.03$ , respectively), adjusted for age, sex, education, and race. The specific associations between cognitive tests and TWA BP are shown in Supplementary Table 1. Moreover, those with elevated systolic or diastolic BP had lower cognitive performance ( $\beta$ :  $-0.17$ , 95% CI:  $-0.29$  to  $-0.05$ ;  $\beta$ :  $-0.15$ , 95% CI:  $-0.32$  to 0.02, respectively). There was no interaction between elevated systolic or diastolic BP and antihypertensive medication use on the association with cognitive performance ( $p=0.724$ ,  $p=0.182$ , respectively). However, adjusting for medication attenuated the association ( $\beta$ :  $-0.11$ , 95% CI:  $-0.24$  to 0.01;  $\beta$ :  $-0.09$ , 95% CI:  $-0.25$  to 0.08).

Finally, higher brain age was associated with lower scores on the cognitive composite ( $\beta$ :  $-0.02$ , 95% CI:  $-0.03$  to  $-0.01$ ), adjusted for age, sex, education, race, ICV, and scanning site.

## DISCUSSION

In this biracial cohort of community-dwelling adults followed from early adulthood to midlife, we found a) elevated systolic and diastolic BP across young to mid-adulthood are associated with advanced brain aging even at midlife; systolic and diastolic BP above the recommended guidelines was associated with a 3-year greater brain age than those with ideal levels b) higher brain age was associated with worse cognitive performance in midlife.



These findings suggest that the effects of elevated BP on the brain may begin earlier, even when below the clinical cut-off of hypertension.

The relationship between systolic BP and advanced brain aging was more pronounced in Black participants in this study. This is in line with emerging evidence suggesting that racial disparities in cognitive outcomes may also reflect the unequal burden of cardiovascular disease among Blacks [27,28]. A recent study reported that cumulative blood pressure explains some of the disparities in late-life cognitive decline on global cognition and memory in Blacks compared to Whites [28]. These studies suggest that the race/ethnic differences may largely reflect racial disparities over the life course in, for example, education, access to resources including health care, exposure to discrimination, and exposures to environmental toxins [29]. Additional research is needed to determine what underlies these health disparities and to develop interventions that target those with the highest risk.

Elevated BP has consistently been associated with brain atrophy in dementia-free middle-aged and older adults. Prior reports indicate that hypertension is associated with brain atrophy [30], particularly in the frontal and temporal lobes [31]. One study reported that participants who were currently taking antihypertensive medication (as a proxy for chronic hypertension) had advanced brain aging patterns compared to those who were not taking antihypertensive medication [9]. Previous studies on the association between BP levels and brain atrophy or advanced aging have focused on clinical cut-offs for hypertension, often with only one point in time. Few studies have investigated the effect of longitudinal BP levels on brain health. One study with BP measurements in midlife found that high and increasing blood pressure was associated with increased white matter hyperintensities (WMH) volume and smaller brain volumes in late-life [32]. Recent work within CARDIA found that early-onset hypertension was associated with midlife cognitive impairment, however, not with macro-structural brain differences [33]. Our results suggest that elevated BP in young to mid-adulthood may accelerate brain aging as early as in midlife. This highlights the importance of utilizing neuroimaging markers that are more sensitive to age-related changes earlier in life, as these are subtler or harder to detect via traditional structural imaging techniques.

In the present study, BP levels, especially above the recommended guidelines, across young adulthood to midlife, were associated with advanced brain aging in midlife. The clinical implication is that long-term elevated systolic BP beginning in young adulthood may be harmful to the brain earlier in life than expected, even when below the bounds of a clinical hypertension diagnosis. The observed association between BP and pre-mature brain aging in this study is supported by findings from other studies of older adult populations, showing that vascular risk factors such as high BP, are associated with higher atrophy in old age. [28, 34,35] Previous investigations have focused primarily on the association between vascular risk factors exposures and cognitive function after 50 years of age without considering the contribution of early adult exposures. [28, 34,35] Our findings add to a small but growing number of studies suggesting that vascular risk exposure should be considered earlier in life in order to achieve maximum benefit from prevention strategies.[6,36, 37] The association between elevated BP and higher brain age was not driven by participants with hypertension,

which may also explain why adjusting for antihypertensive medication did not alter the association much between BP and brain age. There may be several possible reasons for this. For example, by Year 30, out of those who met the criteria for hypertension, 39% had good controlled hypertension, while 36% met the criteria but were not taking treatment, and 25% were on anti-hypertensive treatment but still had high BP. This may reflect that some people with high BP are undiagnosed, or not receiving or taking appropriate treatment. Studies with detailed longitudinal information on treatment and neuroimaging are warranted to gain more insight into the benefit of antihypertensive treatment on premature brain aging.

A pathologic feature of hypertension-related brain injury is small vessel injury, which may be a mechanism underlying the association between elevated BP and advanced brain age. Indeed, long-term hypertension is known to cause vascular hypertrophy and microvascular damage, which result in regional cerebral blood flow dysfunction and lead to White matter disease and neuronal loss [38]. Previous studies have suggested that elevated BP is associated with several imaging markers including atrophy and evidence of small vessel disease [39–41]. Advanced brain aging, defined as a significant deviation from typical age-related atrophy is associated with significant gray matter volume reduction in widespread frontal and parietal regions and more restricted temporal lobe areas [9]. Advanced atrophy may be the result of several vascular and neurodegenerative processes, therefore, more work is warranted to understand the mechanisms whereby elevated blood pressure contributes to such processes.

The strengths of this study include the diverse cohort of young Black and White individuals at enrolment, long duration of follow-up and assessment of BP and detailed biomedical variables over 30 years, and use of the high dimensional neuroimaging pattern analysis that increases the statistical power to detect brain aging-related changes, compared to approaches that use whole brain or regional analyses. Limitations of this study include that the CARDIA MRI sample, compared with the main CARDIA cohort, were more likely to be White, have more years of education, less likely to smoke, and lower systolic and diastolic BP on average. Therefore, the selectivity of the study sample may limit the generalizability of the findings and the underestimation of results. Furthermore, the brain age measure, while sensitive to volumetric changes of normal aging, could be affected by the presence of other, unmeasured neuropathology. In addition, brain age was assessed at one-time point and we were not able to address the changes in brain aging over time. Brain maintenance is best measured longitudinally, by demonstrating relative preservation of brain morphology. An alternate is a residual approach, where, for example, an individual's current brain status is compared with the state typically expected at that age, which is how brain age was derived for this study. Such machine learning methods for brain age prediction at an individual level (as opposed to chronological age), are more sensitive in capturing age-related brain atrophy than traditional neuroimaging methods such as total brain volume. However, longitudinal studies are essential to understanding the mechanisms underpinning the relationship between BP exposure and brain aging patterns and to assess the potential long-term benefits of more intensive BP control at younger ages, ideally through long-term, large trials or from longer-term follow-up of previously established trials and large cohorts.

In the present study, elevated BP levels across young and mid-adulthood, even when below clinical cut-offs, were associated with an advanced brain age of 3 years, as well as lower cognitive performance in midlife. Elevated but subclinical BP levels may be potential modifiable risk factors for accelerated cognitive aging. Although it is unclear whether treatment is warranted, this subgroup, may represent a critical target group for early prevention. Additional long-term investigations that examine the effects of elevated BP and antihypertensive treatment, coupled with repeated imaging data in younger populations, are required to fully determine the implications for effective population-based interventions over the life course.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## REFERENCES

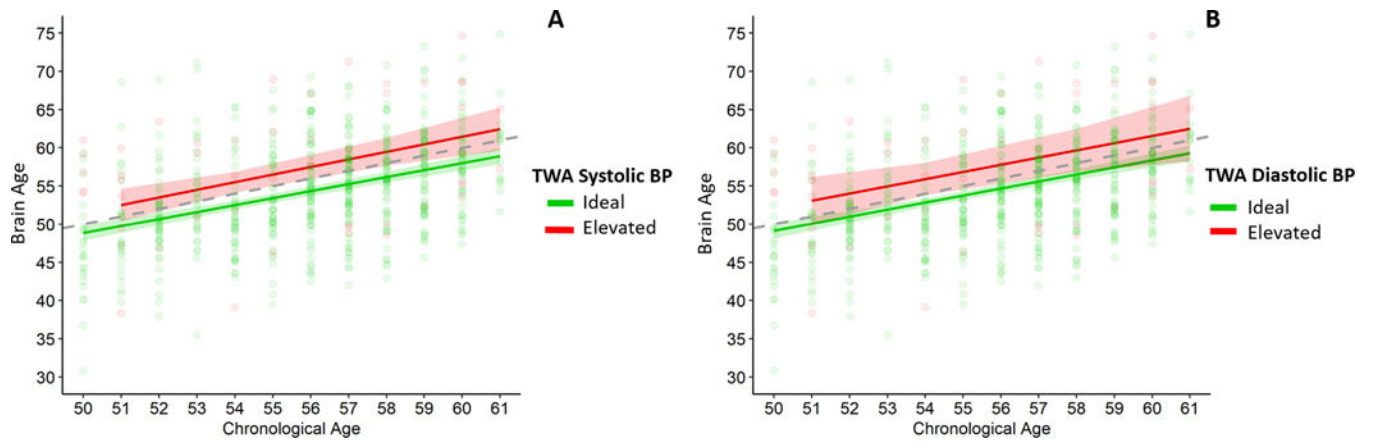
- [1]. Qiu C. Preventing Alzheimer's Disease by Targeting Vascular Risk Factors: Hope and Gap. *J Alzheimer's Dis* 2012;32:721–31. 10.3233/JAD-2012-120922. [PubMed: 22842870]
- [2]. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011;10:819–28. 10.1016/S1474-4422(11)70072-2. [PubMed: 21775213]
- [3]. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension* 2016;68. 10.1161/HYP.0000000000000053.
- [4]. Habes M, Erus G, Toledo JB, Zhang T, Bryan N, Launer LJ, et al. White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain* 2016;139:1164–79. 10.1093/brain/aww008. [PubMed: 26912649]
- [5]. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia. *JAMA* 2019;321:553. 10.1001/jama.2018.21442. [PubMed: 30688979]
- [6]. Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer RA, et al. Early Adult to Midlife Cardiovascular Risk Factors and Cognitive Function. *Circulation* 2014;129:1560–7. 10.1161/CIRCULATIONAHA.113.004798. [PubMed: 24687777]
- [7]. Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, et al. Cumulative Blood Pressure Exposure During Young Adulthood and Mobility and Cognitive Function in Midlife. *Circulation* 2020;141:712–24. 10.1161/CIRCULATIONAHA.119.042502. [PubMed: 31747780]
- [8]. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog Neurobiol* 2014;117:20–40. 10.1016/j.pneurobio.2014.02.004. [PubMed: 24548606]
- [9]. Habes M, Janowitz D, Erus G, Toledo JB, Resnick SM, Doshi J, et al. Advanced brain aging: relationship with epidemiologic and genetic risk factors, and overlap with Alzheimer disease atrophy patterns. *Transl Psychiatry* 2016;6:e775–e775. 10.1038/tp.2016.39. [PubMed: 27045845]

- [10]. Habes M, Pomponio R, Shou H, Doshi J, Mamourian E, Erus G, et al. The Brain Chart of Aging: Machine-learning analytics reveals links between brain aging, White matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. *Alzheimer's Dement* 2021;17:89–102. 10.1002/alz.12178. [PubMed: 32920988]
- [11]. Cole JH, Franke K. Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. *Trends Neurosci* 2017;40:681–90. 10.1016/j.tins.2017.10.001. [PubMed: 29074032]
- [12]. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, et al. Cardia: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–16. 10.1016/0895-4356(88)90080-7. [PubMed: 3204420]
- [13]. Launer LJ, Lewis CE, Schreiner PJ, Sidney S, Battapady H, Jacobs DR, et al. Vascular Factors and Multiple Measures of Early Brain Health: CARDIA Brain MRI Study. *PLoS One* 2015;10:e0122138. 10.1371/journal.pone.0122138.
- [14]. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010;121:586–613. 10.1161/CIRCULATIONAHA.109.192703. [PubMed: 20089546]
- [15]. Goldszal AF, Davatzikos C, Pham DL, Yan MXH, Bryan RN, Resnick SM. An Image-Processing System for Qualitative and Quantitative Volumetric Analysis of Brain Images. *J Comput Assist Tomogr* 1998;22:827–37. 10.1097/00004728-199809000-00030. [PubMed: 9754125]
- [16]. Shen Dinggang, Davatzikos C. HAMMER: hierarchical attribute matching mechanism for elastic registration. *IEEE Trans Med Imaging* 2002;21:1421–39. 10.1109/TMI.2002.803111. [PubMed: 12575879]
- [17]. Zacharaki EI, Kanterakis S, Bryan RN, Davatzikos C. Measuring Brain Lesion Progression with a Supervised Tissue Classification System, 2008, p. 620–7. 10.1007/978-3-540-85988-8\_74.
- [18]. Tustison NJ, Avants BB, Cook PA, Yuanjie Zheng, Egan A, Yushkevich PA, et al. N4ITK: Improved N3 Bias Correction. *IEEE Trans Med Imaging* 2010;29:1310–20. 10.1109/TMI.2010.2046908. [PubMed: 20378467]
- [19]. Doshi J, Erus G, Ou Y, Gaonkar B, Davatzikos C. Multi-Atlas Skull-Stripping. *Acad Radiol* 2013;20:1566–76. 10.1016/j.acra.2013.09.010. [PubMed: 24200484]
- [20]. Doshi J, Erus G, Ou Y, Resnick SM, Gur RC, Gur RE, et al. MUSE: MULti-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. *Neuroimage* 2016;127:186–95. 10.1016/j.neuroimage.2015.11.073. [PubMed: 26679328]
- [21]. Eavani H, Habes M, Satterthwaite TD, An Y, Hsieh M-K, Honnorat N, et al. Heterogeneity of structural and functional imaging patterns of advanced brain aging revealed via machine learning methods. *Neurobiol Aging* 2018;71:41–50. 10.1016/j.neurobiolaging.2018.06.013. [PubMed: 30077821]
- [22]. Habes M, Erus G, Toledo JB, Bryan N, Janowitz D, Doshi J, et al. Regional tract-specific White matter hyperintensities are associated with patterns of aging-related brain atrophy via vascular risk factors, but also independently. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2018;10:278–84. 10.1016/j.dadm.2018.02.002.
- [23]. Le TT, Kuplicki RT, McKinney BA, Yeh H-W, Thompson WK, Paulus MP. A Nonlinear Simulation Framework Supports Adjusting for Age When Analyzing BrainAGE. *Front Aging Neurosci* 2018;10. 10.3389/fnagi.2018.00317.
- [24]. Reis JP, Loria CM, Launer LJ, Sidney S, Liu K, Jacobs DR, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol* 2013;73:170–9. 10.1002/ana.23836. [PubMed: 23443990]
- [25]. Kamboh MI, Ferrell RE, Kottke B. Genetic studies of human apolipoproteins. V. A novel rapid procedure to screen apolipoprotein E polymorphism. *J Lipid Res* 1988;29:1535–43. [PubMed: 3241128]
- [26]. Cherbuin N, Walsh EI, Shaw M, Luders E, Anstey KJ, Sachdev PS, et al. Optimal Blood Pressure Keeps Our Brains Younger. *Front Aging Neurosci* 2021;13. 10.3389/fnagi.2021.694982.

- [27]. Xiong C, Luo J, Coble D, Agboola F, Kukull W, Morris JC. Complex interactions underlie racial disparity in the risk of developing Alzheimer's disease dementia. *Alzheimer's Dement* 2020;16:589–97. 10.1002/alz.12060. [PubMed: 32067357]
- [28]. Levine DA, Gross AL, Briceño EM, Tilton N, Kabeto MU, Hingtgen SM, et al. Association Between Blood Pressure and Later-Life Cognition Among Black and White Individuals. *JAMA Neurol* 2020;77:810. 10.1001/jamaneurol.2020.0568. [PubMed: 32282019]
- [29]. Caunca MR, Odden MC, Glymour MM, Elfassy T, Kershaw KN, Sidney S, et al. Association of Racial Residential Segregation Throughout Young Adulthood and Cognitive Performance in Middle-aged Participants in the CARDIA Study. *JAMA Neurol* 2020;77:1000. 10.1001/jamaneurol.2020.0860. [PubMed: 32364578]
- [30]. Korf ESC, White LR, Scheltens P, Launer LJ. Midlife Blood Pressure and the Risk of Hippocampal Atrophy. *Hypertension* 2004;44:29–34. 10.1161/01.HYP.0000132475.32317.bb. [PubMed: 15159381]
- [31]. Beauchet O, Celle S, Roche F, Bartha R, Montero-Odasso M, Allali G, et al. Blood pressure levels and brain volume reduction. *J Hypertens* 2013;31:1502–16. 10.1097/HJH.0b013e32836184b5. [PubMed: 23811995]
- [32]. Suvisa K, Lima JAC, Yano Y, Tan ZS, Cheng S, Niiranen TJ. Early-but Not Late-Onset Hypertension Is Related to Midlife Cognitive Function. *Hypertension* 2021;97:2–9. 10.1161/HYPERTENSIONAHA.120.16556. [PubMed: 33461314]
- [33]. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol* 2019;18:942–52. 10.1016/S1474-4422(19)30228-5. [PubMed: 31444142]
- [34]. Wartolowska KA, Webb AJS. Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK Biobank cohort study. *Eur Heart J* 2021;42:750–7. 10.1093/eurheartj/ehaa756. [PubMed: 33238300]
- [35]. fjhiojpfjk
- [36]. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol* 2019;18:942–52. 10.1016/S1474-4422(19)30228-5. [PubMed: 31444142]
- [37]. Yaffe K, Bahorik AL, Hoang TD, Forrester S, Jacobs DR, Lewis CE, et al. Cardiovascular risk factors and accelerated cognitive decline in midlife. *Neurology* 2020;95:e839–46. 10.1212/WNL.0000000000010078. [PubMed: 32669394]
- [38]. Sun D, Thomas EA, Launer LJ, Sidney S, Yaffe K, Fornage M. Association of blood pressure with cognitive function at midlife: A Mendelian randomization study. *BMC Med Genomics* 2020;13:1–9. 10.1186/s12920-020-00769-y. [PubMed: 31900157]
- [39]. Smith EE, Beaudin AE. New insights into cerebral small vessel disease and vascular cognitive impairment from MRI. *Curr Opin Neurol* 2018;31:36–43. 10.1097/WCO.0000000000000513. [PubMed: 29084064]
- [40]. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, et al. Effects of systolic blood pressure on White-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol* 2012;11:1039–47. 10.1016/S1474-4422(12)70241-7. [PubMed: 23122892]
- [41]. McNeil CJ, Myint PK, Sandu A-L, Potter JF, Staff R, Whalley LJ, et al. Increased diastolic blood pressure is associated with MRI biomarkers of dementia-related brain pathology in normative ageing. *Age Ageing* 2018;47:95–100. 10.1093/ageing/afx102. [PubMed: 29106439]

### RESEARCH IN CONTEXT

1. Systematic review: There have been several studies evaluating the relationship between blood pressure (BP) and brain atrophy, showing that midlife elevated blood pressure is associated with more atrophy in old age. However, there is a lack of studies investigating the association between blood pressure earlier in life and midlife brain health.
2. Interpretation: Having an elevated average BP across 30 years during young to mid-adulthood, even below clinical cutoffs for hypertension, is associated with a 3-year advanced brain age and worse cognitive function midlife. This suggests that elevated BP in young adulthood may have effects on brain health already in midlife, presenting as an “older” brain compared to age peers.
3. Future directions: CARDIA is an ongoing study, therefore longitudinal associations between BP in young to mid-adulthood and brain aging will be essential to understand the early effects of BP on the rate of brain aging. Moreover, the effects of anti-hypertensive medication will be important to investigate in future studies of such young populations.



**Figure 1.**

Association of cumulative blood pressure above (elevated) or below (normal) recommended guidelines\* and brain age at midlife among 661 CARDIA participants.

CARDIA, Coronary Artery Risk Development in Young Adults. A) Association between brain age and chronological age by normal or elevated cumulative systolic BP; B)

Association between brain age and chronological age by normal or elevated cumulative diastolic BP. Gray dashed line indicates brain age=chronological age. Models have been adjusted for sex, education, race, intracranial volume, and scanning site.

**Table 1.**

Demographic and Characteristics of the 661 CARDIA Participants with Brain MRI.

Variable mean (sd), n (%)	Value
Age at baseline, y (SD)	25.3 ( $\pm$ 3.5)
Age at year 30, y (SD)	55.3 ( $\pm$ 3.5)
Brain age at year 30, y (SD)	54.34 ( $\pm$ 7.2)
Female, n (%)	345 (52.1)
Black, n (%)	265 (40.0)
Education, y (SD)	14.1 ( $\pm$ 2.2)
Income < median (%)	231 (40.9)
Smoker/former smoker at baseline (%)	156 (23.6)
Alcohol consumer at baseline (%)	581 (87.9)
Diabetes at baseline (%)	7 (1.1)
Body mass index at baseline (SD)	23.3 ( $\pm$ 3.6)
<i>APOE</i> $\epsilon$ 4 carrier (%)	189 (30.7)
Physical exercise at baseline, exercise units (SD)	406.2 (273.5)
Total cholesterol at baseline mg/dL	176.6 (32.9)
Systolic blood pressure, mm Hg	
Baseline (SD)	110 ( $\pm$ 10.3)
Year 30 (SD)	118.9 ( $\pm$ 15.8)
Time-weighted average (SD)	111.9 ( $\pm$ 8.8)
Diastolic blood pressure, mm Hg	
Baseline (SD)	69.0 ( $\pm$ 9.0)
Year 30 (SD)	72.9 ( $\pm$ 11.1)
Time-weighted average (SD)	70.9 ( $\pm$ 6.8)



**Table 2.** Association of time-weighted average blood pressure and brain age at midlife among 661 CARDIA participants.

Blood pressure	β-coefficient (95% CI) Brain Age					
	Model 1 <sup>a</sup>	p	Model 2 <sup>b</sup>	p	Model 3 <sup>c</sup>	p
Systolic BP						
Per 5-point mmHg increment	0.84 (0.45 to 1.23)	<0.001	0.93 (0.50 to 1.36)	<0.001	0.83 (0.35 to 1.31)	0.001
Diastolic BP						
Per 5-point mmHg increment	0.47 (0.10 to 0.83)	0.014	0.44 (0.04 to 0.04)	0.032	0.25 (-0.21 to 0.71)	0.278

CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; BP, Blood Pressure;

<sup>a</sup> Adjusted for chronological age.

<sup>b</sup> Additionally adjusted for chronological age, sex, education, race, intracranial volume, and scanning site.

<sup>c</sup> Additionally adjusted for hypertensive medication.

**Table 3.**

Association of time-weighted average blood pressure above (elevated) or below (normal) recommended guidelines for ideal blood pressure levels\* and brain age at midlife among 661 CARDIA participants.

	N (%)	Chronological age, Mean (SD) <sup>a</sup>	Brain Age, Mean (SD) <sup>a</sup>	$\beta$ -coefficient (95% CI) Brain Age					
				Model 1 <sup>b</sup>	p	Model 2 <sup>c</sup>	p	Model 3 <sup>d</sup>	p
Systolic BP									
Normal	535 (80.8)	55.4 ( $\pm$ 3.5)	53.8 ( $\pm$ 7.0)	Reference		Reference		Reference	
Elevated	127 (19.2)	55.1 ( $\pm$ 3.5)	56.7 (8.0)	3.21 (1.94 to 4.48)	<0.001	3.33 (1.98 to 4.67)	<0.001	3.07 (1.63 to 4.51)	<0.001
Diastolic BP									
Normal	605 (91.4)	55.2 ( $\pm$ 3.5)	54.1 ( $\pm$ 7.2))	Reference		Reference		Reference	
Elevated	57 (8.6)	54.9 ( $\pm$ 3.8)	57 ( $\pm$ 8.4)	3.42 (1.63 to 5.21)	<0.001	3.28 (1.44 to 5.12)	0.001	2.81 (0.89 to 4.72)	0.004

CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; BP, Blood Pressure.

\* Defined by American Heart Association criteria for ideal cardiovascular health, Systolic BP<120; Diastolic BP<80.

<sup>a</sup> Unadjusted group means and standard deviations.

<sup>b</sup> Adjusted for chronological age.

<sup>c</sup> Additionally adjusted for chronological age, sex, education, race, intracranial volume, and scanning site.

<sup>d</sup> Additionally adjusted for hypertensive medication.