Supplemental Online Content

Hu YH, Halstead MR, Bryan RN, et al. Association of early adulthood 25-year blood pressure trajectories to cerebral lesions and brain structure in midlife. *JAMA Netw Open*. 2022;5(3):e221175. doi:10.1001/jamanetworkopen.2022.1175

eMethods.

eFigure. Sample Flowchart

eTable 1. CARDIA Participant Characteristics for Individuals With and Without MRI Scan Data at Year 25 and Year 30

eTable 2. Systolic and Diastolic Blood Pressure and Mean Arterial Pressure at Each Study Examination by Blood Pressure Trajectory Group in the MRI Sample

eTable 3. Systolic and Diastolic Blood Pressure and Mean Arterial Pressure at Each Study Examination by Blood Pressure Trajectory Group in the MRI Sample

eTable 4. Prevalence of Hypertension at Each Study Examination by Blood Pressure Trajectory Group in the MRI Sample

eTable 5. Brain Characteristics of the MRI Subset by SBP/DBP Trajectory Group—CARDIA Cohort: Year 25 and Year 30 Exam

eTable 6. The Association of Systolic Blood Pressure (SBP) Trajectory With Brain Outcomes (Reference SBP Trajectory: Low-Stable, Overall n = 853)

eTable 7. The Association of Diastolic Blood Pressure (DBP) Trajectory With Brain Outcomes (Reference DBP Trajectory: Low-Stable, Overall n = 853)

eTable 8. The Association of Systolic Blood Pressure (SBP) Trajectory With Cognitive Function Outcomes at Year 30 Examination (Reference SBP Trajectory: Low-Stable, Overall n = 2736)

eTable 9. The Association of Diastolic Blood Pressure (DBP) Trajectory With Cognitive Function Outcomes at Year 30 Examination (Reference DBP Trajectory: Low-Stable, Overall n = 2736)

eTable 10. The Association of Mean Arterial Pressure (MAP) Trajectory With Cognitive Function Outcomes at Year 30 Examination (Reference MAP Trajectory: Low-Stable, Overall n = 2736)

eTable 11. The Association of Systolic Blood Pressure (SBP) Trajectory With Brain Outcomes After Adjustment of Year 25 and Year 30 BP Measure (Reference SBP Trajectory: Low-Stable, Overall n = 853)
eTable 12. The Association of Diastolic Blood Pressure (DBP) Trajectory With Brain Outcomes After Adjustment of Year 25 and Year 30 BP Measure (Reference DBP Trajectory: Low-Stable, Overall n = 853)

eTable 13. The Association of Mean Arterial Pressure (MAP) Trajectory With Brain Outcomes After Adjustment of Year 25 and Year 30 BP Measure (Reference MAP Trajectory: Low-Stable, Overall n = 853)

eReferences.

This supplemental material has been provided by the authors to give readers additional information about their work.
The sample for the CARDIA Brain magnetic resonance imaging (MRI) sub-study was initially enrolled at Y25 exam from 3 of the CARDIA field centers: Birmingham, Minneapolis, and Oakland. Each of the 3 centers had a target sample size for the sub-study, with the aim of achieving a balance within 4 strata of ethnicity/race (black/white) and sex (men/women). When the target sample size was reached, enrollment was ended. Exclusion criteria included a contraindication to MRI or a body size that was too large to enable the MRI examination. At year 25, 719 individuals from the CARDIA cohort underwent brain MRI examination. This same baseline sample was re-invited for a second scan in the Y30 follow-up. As some participants did not have a second exam (n=231), we recruited new participants (n=175) giving a total of 663; 488 had repeat MRIs. We merged the sample with good quality MRI scans to increase the sample size (n=885).

Details on the MRI hardware and quality control

All brain MRI scans were performed per CARDIA protocol using 3-Tesla magnetic resonance scanners, and standardized across machines using a common machine head phantom (Oakland: Siemens [Munich, Germany] 3T Tim Trio/VB 15 platform; Minneapolis: Siemens 3T Tim Trio/VB 15 platform; and Birmingham: Philips [Best, the Netherlands] 3T Achieva/2.6.3.6 platform). Structural [3D sagittal T1, T2, and fluid-attenuated inversion recovery] and pseudo-continuous arterial spin labeling sequences were acquired. Brain MRI imaging analyses, quality control checks, and atlas registration were performed at the CARDIA Brain MRI Reading Center (Department of Radiology, University of Pennsylvania, Philadelphia, PA) according to standardized protocols as described previously. Brain microstructural tissue integrity was estimated from axial diffusion tensor images using previously described parameters.

Details on the combination of Y25 and Y30 MRI data

The brain magnetic resonance imaging (MRI) was conducted for a subset of CARDIA participants at exams of Y25 (n=719) and Y30 (n=663). Of the unique 885 subjects with MRI scans, 485 had repeated exams of good quality. To increase our sample size, we pooled the data from the 2 exams by calculating the weighted average for each brain measure. When combining the MRI measures (means), it seems appropriate to weight them according to the amount of noise (ex., due to machine error) associated with each. In addition, the MRI measures measured at Y30 exam may have larger variance than Y25 (biological portion). To get a weighted average, per sequence, we first estimated the noise and biological portions for each MRI outcomes based on the repeated data. The MRI measures at exams of Y25 and Y30 can be written as:

\[ X_{i1} = U_i + T_{i1} \]
\[ X_{i2} = A U_i + T_{i2} \]
\[ U_i \sim N(0, \sigma^2) ; T_{i1} \sim N(0, \sigma^2/w) ; T_{i2} \sim N(0, \sigma^2/w) \]

We define \( X_{ij} \) as the observed trait value of individual i at the j\(^{th} \) exam (i.e., \( X_{i1} \) is the MRI outcome at the exam Y25), \( U_i \) as the real trait value of individual i, and \( T_{ij} \) as the noise component of individual i at the j\(^{th} \) exam. \( A \) is the weight that represents the unequal variances at the different time points (biological portion). All \( T_{ij} \) are independent from \( U_i \) and independent from one another. In addition, we assume \( U_i \) is normal with mean 0 and variance \( \sigma^2 \), and \( T_{ij} \) is normal with mean 0 and variance \( \sigma^2/w \). And the weighted average was calculated as:
\[ \hat{U} = (wX_{i1} + wAX_{i2})/(1 + w + A^2w) \]

To get \( w \) and \( A \), we first estimated the slope of the regression model \( X_{i2} \sim X_{i1} \):

\[ E[X_{i2}X_{i1}]/\text{var}(X_{i1}) = (A\sigma^2)/(\sigma^2 + \sigma^2/w) = Aw/(1 + w) \]

And then, we calculated the ratio of variances (\( \delta \)):

\[ \text{var}(X_{i2})/\text{var}(X_{i1}) = (A^2\sigma^2 + \sigma^2/w)/(\sigma^2 + \sigma^2/w) = (A^2w + 1)/(1 + w) \]

In short, we solved the quadratic equation to get \( w \) and \( A \):

\[ Aw/(1 + w) = \text{Slope (}\beta\text{)} \]

\[ (A^2w + 1)/(1 + w) = \text{variance ratio (}\delta\text{)} \]

And \( w \) and \( A \) are equal to:

\[ w = \frac{\delta - 1 - 2\beta^2 - \sqrt{(\delta - 1)^2 + (4\beta)^2}}{2(\beta^2 - \delta)} \]

\[ A = \beta \frac{1 + w}{w} \]

The weighted average was calculated as the following formulas:

- Subjects with repeated MRI measures:
  \[ \text{Weighted average} = (wX_{i1} + wAX_{i2})/(1 + w + A^2w) \]

- Subjects with one-time point data at Y25:
  \[ \text{Weighted average} = (wX_{i1})/(1 + w) \]

- Subjects with one-time point data at Y30:
  \[ \text{Weighted average} = (wAX_{i2})/(1 + A^2w) \]

**Correcting volume measures for intracranial volume differences between Y25 and Y30**

There was a within person change in total intracranial volume (ICV), which should be constant over time. To account for this, the tissue volume needs to be benchmarked against the same standard. Therefore, all volume measures at the exam of Y30 were corrected by the following equation before calculating the weighted average.

\[ \text{Adjusted Y30 volume measure} = \text{Raw Y30 volume measure} \times (Y25 \text{ ICV} / Y30 \text{ ICV}) \]

**Details of group-based trajectory modeling**

Group-based trajectory modeling (GBTM, SAS Proc Traj, v9.4) was used to identify unique polynomial functions that define both intercepts and slopes for each group trajectory. We identified 5 distinct trajectories for each blood pressure trait, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), across 25 years. The CARDIA has measured blood pressure at each of exam, with up to 8 BP measures. Blood pressure measured during pregnancy was removed from GBTM analysis. Subjects with at least 3 repeated BP measures from Y0 to Y25 were included in the trajectory modeling.

As reported in Allen et al.’s JAMA study, we hypothesized 5 trajectory groups for each blood pressure trait. We then investigated models with a varying number of trajectory groups in a stepwise manner, starting with the highest polynomial (ex., cubic function) for each group trajectory. If the highest polynomial is not statistically significantly different from 0 (\( p > .05 \)), we replaced it with a lower polynomial function (ex., quadratic or linear function). The final number of trajectories were determined by the Bayesian Inclusion Criteria (BIC), with larger negative values for the BIC signifying better fit.
To ensure that Proc Traj program accurately assigned each subject to the appropriate trajectory group, four diagnostic criteria were used to evaluate the adequacy of the selected models: 1) the average posterior probability (AvePP) calculated for each trajectory group exceeded 0.7 threshold; 2) the estimated probability of group membership (π) should correspond closely to the proportion of the sample assigned to the group (number of people in that group / total number of subjects); 3) the confidence intervals around estimated group memberships (π) should be reasonably narrow; 4) the odds of correct classification (OCC) for each trajectory group exceeded the minimum threshold of 5, where OCC is defined by \([AvePP/(1-AvePP)] / [π/(1- π)]\).
eFigure. Sample Flowchart

CARDIA biracial cohort of 5,115 healthy men and women at baseline (Y0) (Aged 18-30)

Exclusion criteria:
- Fewer than 3 exams with BP measures
- BP measures while pregnant

4,677 with at least 3 repeated BP measures during a 25-year follow-up period (8 exams)

Modeled blood pressure trajectory (Y0-Y25)
- Systolic blood pressure (n=4,677)
- Diastolic blood pressure (n=4,676)
- Mean arterial pressure (n=4,676)

Main analysis
MRI subset (n=885)
Underwent brain MRI at the Y25 or Y30 exams
- Y25 MRI only (n=229)
- Y30 MRI only (n=171)
- Y25 and Y30 (n=485)

Excluded individuals with:
- Missing covariates (n=11)
  - Diabetes diagnosis (n=1)
  - Antihypertensive medication use (n=3)
  - Smoking status (n=7)
- No intracranial volume measure (n=21)

MRI subset (final model) (n=853)
Individuals with one of MRI outcomes
- Volume of total brain and total grey matter (n=853)
- Total normal-looking white matter volume and abnormal white matter volume (n=846)
- Grey matter cerebral blood flow (n=753)
- White matter fractional anisotropy (n=777)

© 2022 Hu YH et al. JAMA Network Open.
| 0. Mean number of exams (Range: 3-8)ᵇ | Overall sample (n=4,677) | No MRI subset (n=3,792) | MRI subset (n=885) | p-value |
|--------------------------------------|--------------------------|-------------------------|------------------|---------|
| Overall (n=4,677)                    | 6.87(1.51)               | 6.68(1.58)              | 7.67(0.78)       | <.0001  |

1. Blood pressure trajectory

**SBP Trajectory Group**

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Low-stable | 1,071 (22.9) | 858 (22.6) | 213 (24.1) | 0.02    |
| Moderate-gradual | 2,122 (45.4) | 1,713 (45.2) | 409 (46.2) | 0.15    |
| Moderate-increasing | 333 (7.1) | 280 (7.4) | 53 (6.0) | 0.18    |
| Elevated-stable | 991 (21.2) | 797 (21.0) | 194 (21.9) | 0.02    |
| Elevated-increasing | 160 (3.4) | 144 (3.8) | 16 (1.8) | 0.15    |

**DBP Trajectory Group**

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Low-stable | 941 (20.1) | 756 (19.9) | 185 (20.9) | 0.24    |
| Moderate-gradual | 2,062 (44.1) | 1,663 (43.9) | 399 (45.1) | 0.15    |
| Moderate-increasing | 519 (11.1) | 440 (11.6) | 79 (8.9) | 0.18    |
| Elevated-stable | 940 (20.1) | 753 (19.9) | 187 (21.1) | 0.02    |
| Elevated-increasing | 214 (4.6) | 179 (4.7) | 35 (4.0) | 0.15    |

**MAP Trajectory Group**

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Low-stable | 917 (19.6) | 730 (19.3) | 187 (21.1) | 0.15    |
| Moderate-gradual | 2,056 (44.0) | 1,671 (44.0) | 385 (43.5) | 0.18    |
| Moderate-increasing | 439 (9.4) | 368 (9.7) | 71 (8.0) | 0.02    |
| Elevated-stable | 1,018 (21.8) | 814 (21.5) | 204 (23.1) | 0.15    |
| Elevated-increasing | 246 (5.2) | 208 (5.5) | 38 (4.3) | 0.15    |

2. Sociodemographics

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Ageᵇ | 50.19(3.65) | 50.15(3.67) | 50.31(3.60) | 0.24    |
| Male | 2,108 (45.1) | 1,689 (44.5) | 419 (47.3) | 0.14    |
| Black | 2,343 (50.1) | 1,977 (52.1) | 366 (41.4) | 0.0001 |

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Education | 1,489 (39.8) | 1,140 (40.0) | 349 (39.4) | 0.0001 |
| College | 1,506 (40.3) | 1,106 (38.8) | 400 (45.2) | 0.0001 |
| Graduate school | 743 (19.9) | 607 (21.2) | 136 (15.4) | 0.0001 |

3. Clinical measures

|分期 | Overall sample | No MRI subset | MRI subset | p-value |
|------|----------------|---------------|------------|---------|
| Hypertensionᶜ | 1,997 (53.4) | 1,560 (54.7) | 437 (49.4) | 0.0001 |
| Taking antihypertensive Rx | 942 (27.1) | 731 (28.2) | 211 (23.9) | 0.02    |
| BMI | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Category       | <25 | 30 > BMI ≥ 25 | ≥ 30 | Diabetes |
|----------------|-----|---------------|------|----------|
|                | 880 (25.2) | 627 (24.1) | 253 (28.6) | 1,094 (31.4) | 784 (30.1) | 310 (35.0) | 1,515 (43.4) | 1,193 (45.8) | 322 (36.4) |
| Diabetes       | 568 (15.3) | 452 (16.0) | 116 (13.1) | 0.04 |

4. Behavior

| Category       | Current smoker | Alcohol use | Physical activity, median (IQR) |
|----------------|----------------|-------------|---------------------------------|
|                | 584 (17.0) | 2,711 (78.2) | 276.0 (131.25-488.0) |
|                | 436 (17.0) | 2,019 (78.3) | 270.0 (124.0-480.0) |
|                | 148 (16.9) | 692 (78.2) | 291.0 (144.0-507.0) |
|                | 0.97 | 1.00 | 0.07 |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP=Mean arterial pressure [(SBP*1/3)+(DBP*2/3)]; IQR=Interquartile range.

a: All covariates (i.e., sociodemographics and health condition) were collected at the Y25 exam. For participants with Y30 MRI only, missing covariates were updated using Y30 information.
b: Data was reported as mean and SD
c: SBP≥130 or DBP≥80 or taking antihypertensive medication
d: Differences in categorical variables assessed with chi-square and continuous variables with a non-parametric test for comparing means (or medians for physical activity).
Table 2. Systolic and diastolic blood pressure and mean arterial pressure at each study exam by blood pressure trajectory group in the MRI sample

| SBP Trajectory Group | Year 0 (n=873) | Year 2 (n=833) | Year 5 (n=824) | Year 7 (n=815) | Year 10 (n=816) | Year 15 (n=811) | Year 20 (n=822) | Year 25 (n=856) |
|----------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| SBP (mm Hg)          | M(SD)          | M(SD)          | M(SD)          | M(SD)          | M(SD)          | M(SD)          | M(SD)          | M(SD)          |
| Overall              | 110.35(10.51)  | 107.81(10.23)  | 107.70(11.04)  | 108.61(11.75)  | 112.31(13.35)  | 114.27(13.34)  | 117.70(14.73)  |
| Low-stable           | 101.05(7.33)   | 98.32(6.61)    | 97.19(6.40)    | 98.04(6.48)    | 97.65(6.93)    | 99.68(7.26)    | 101.13(6.47)   | 104.32(8.32)   |
| Moderate-gradual     | 109.30(7.81)   | 106.88(7.08)   | 106.40(6.75)   | 108.27(7.20)   | 111.32(8.81)   | 113.69(8.18)   | 117.71(9.95)   |
| Moderate-increasing  | 112.65(7.59)   | 111.35(7.23)   | 111.98(10.90)  | 113.11(8.66)   | 115.74(9.84)   | 127.88(11.96)  | 135.26(16.71)  | 146.72(15.89)  |
| Elevated-stable      | 120.86(7.49)   | 117.75(8.41)   | 118.42(8.48)   | 120.41(8.23)   | 122.92(11.05)  | 123.31(10.19)  | 122.62(11.02)  |
| Elevated-increasing  | 126.44(13.64)  | 124.73(13.47)  | 133.87(9.62)   | 134.43(12.21)  | 140.79(14.38)  | 139.17(16.25)  | 143.96(15.43)  |
| DBP Trajectory Group | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    | DBP (mm Hg)    |
| Overall              | 68.98(9.20)    | 67.98(9.00)    | 69.69(9.75)    | 69.47(9.65)    | 72.18(9.62)    | 73.73(11.11)   | 70.89(10.77)   | 73.13(10.84)   |
| Low-stable           | 62.24(7.32)    | 60.46(5.93)    | 60.20(6.71)    | 60.08(6.89)    | 62.38(6.37)    | 62.33(6.69)    | 59.58(5.96)    | 62.07(7.12)    |
| Moderate-gradual     | 69.01(7.38)    | 68.12(8.40)    | 71.89(8.02)    | 71.89(8.05)    | 77.97(8.43)    | 84.04(9.53)    | 84.51(11.01)   | 87.81(8.43)    |
| Moderate-increasing  | 67.29(7.24)    | 66.51(6.78)    | 68.29(6.63)    | 67.58(6.01)    | 70.33(6.12)    | 71.83(6.95)    | 69.95(6.94)    | 72.57(7.62)    |
| Elevated-stable      | 76.53(7.31)    | 75.73(7.04)    | 77.73(7.32)    | 78.05(6.44)    | 80.37(6.97)    | 81.42(7.73)    | 76.20(7.89)    | 76.46(7.92)    |
| Elevated-increasing  | 83.35(8.42)    | 81.15(10.12)   | 88.09(7.29)    | 86.88(10.56)   | 87.97(8.11)    | 95.00(9.72)    | 88.03(10.83)   | 88.84(11.52)   |
| MAP Trajectory Group | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    | MAP (mm Hg)    |
| Overall              | 82.77(8.60)    | 81.26(8.49)    | 82.36(9.47)    | 82.51(9.27)    | 84.57(9.77)    | 86.59(11.15)   | 85.34(11.17)   | 87.98(11.72)   |
| Low-stable           | 75.56(6.30)    | 73.43(5.33)    | 72.96(5.80)    | 73.36(5.75)    | 74.50(5.64)    | 75.02(6.03)    | 73.61(5.46)    | 75.50(6.53)    |
| Moderate-gradual     | 81.25(6.35)    | 79.83(5.91)    | 80.61(5.91)    | 80.30(5.34)    | 82.45(5.90)    | 84.70(6.66)    | 84.14(6.77)    | 87.48(7.79)    |
| Moderate-increasing  | 83.22(7.37)    | 82.26(7.27)    | 84.35(8.07)    | 85.03(6.93)    | 90.21(8.83)    | 96.76(10.70)   | 100.12(12.31)  | 105.84(10.60)  |
| Elevated-stable      | 89.50(6.46)    | 88.20(6.55)    | 90.11(6.72)    | 90.38(6.51)    | 92.51(7.01)    | 93.84(8.05)    | 91.05(7.97)    | 91.28(7.78)    |
| Elevated-increasing | 96.81(8.90) | 94.56(10.00) | 101.07(7.76) | 101.25(8.89) | 101.24(9.77) | 107.89(9.21) | 103.24(12.77) | 104.83(12.94) |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP=Mean arterial pressure \(\left\{\frac{\text{SBP}*1/3}{\text{DBP}*2/3}\right\}\); M=Mean; SD=Standard deviation.
| SBP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|----------------------|--------|--------|--------|--------|---------|---------|---------|--------|
| Overall              | 110.35(10.51) | 107.81(10.23) | 107.70(11.04) | 108.61(11.03) | 109.36(11.75) | 112.31(13.35) | 114.27(13.34) | 117.70(14.73) |
| Low-stable           | 101.05(7.33)  | 98.32(6.61)   | 97.19(6.40)   | 98.04(6.48)   | 97.65(6.93)   | 99.68(7.26)   | 101.13(6.47)  | 104.32(8.32)  |
| Moderate-gradual     | 109.30(7.81)  | 106.88(7.08)  | 106.40(6.75)  | 106.85(6.54)  | 108.27(7.20)  | 111.32(8.81)  | 113.69(8.18)  | 117.71(9.95)  |
| Moderate-increasing  | 112.65(7.59)  | 111.35(7.23)  | 111.98(10.90) | 113.11(8.66)  | 115.74(9.84)  | 127.88(11.96) | 135.26(16.71) | 146.72(15.89) |
| Elevated-stable      | 120.86(7.49)  | 117.75(8.41)  | 118.42(8.48)  | 120.41(8.23)  | 120.82(8.95)  | 122.92(11.05) | 123.31(10.19) | 122.62(11.02) |
| Elevated-increasing  | 126.44(13.64) | 124.73(13.47) | 133.87(9.62)  | 134.43(12.21) | 134.00(14.80) | 140.79(14.38) | 139.17(16.25) | 143.96(15.43) |

| DBP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|----------------------|--------|--------|--------|--------|---------|---------|---------|--------|
| Overall              | 68.98(9.20)  | 67.98(9.00)  | 69.69(9.75)  | 69.47(9.65)  | 72.18(9.62)  | 73.73(11.11) | 70.89(10.77) | 73.13(10.84)  |
| Low-stable           | 62.24(7.32)  | 60.46(5.93)  | 60.20(6.71)  | 60.08(6.89)  | 62.38(6.37)  | 62.33(6.69)  | 59.58(5.96)  | 62.07(7.12)   |
| Moderate-gradual     | 69.01(7.38)  | 68.12(8.40)  | 71.89(8.02)  | 71.89(8.05)  | 77.97(8.43)  | 84.04(9.53)  | 84.51(11.01) | 87.81(8.43)   |
| Moderate-increasing  | 67.29(7.24)  | 66.51(6.78)  | 68.29(6.63)  | 67.58(6.01)  | 70.33(6.12)  | 71.83(6.95)  | 69.95(6.94)  | 72.57(7.62)   |
| Elevated-stable      | 76.53(7.31)  | 75.73(7.04)  | 77.73(7.32)  | 78.05(6.44)  | 80.37(6.97)  | 81.42(7.73)  | 76.20(7.89)  | 76.46(7.92)   |
| Elevated-increasing  | 83.35(8.42)  | 81.15(10.12) | 88.09(7.29)  | 86.88(10.56) | 87.97(8.11)  | 95.00(9.72)  | 88.03(10.83) | 88.84(11.52)  |

| MAP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|----------------------|--------|--------|--------|--------|---------|---------|---------|--------|
| Overall              | 82.77(8.60)  | 81.26(8.49)  | 82.36(9.47)  | 82.51(9.27)  | 84.57(9.77)  | 86.59(11.15) | 85.34(11.17) | 87.98(11.72)  |
| Low-stable           | 75.56(6.30)  | 73.43(5.33)  | 72.96(5.80)  | 73.36(5.75)  | 74.50(5.64)  | 75.02(6.03)  | 73.61(5.46)  | 75.50(6.53)   |
| Moderate-gradual     | 81.25(6.35)  | 79.83(5.91)  | 80.61(5.91)  | 80.30(5.34)  | 82.45(5.90)  | 84.70(6.66)  | 84.14(6.77)  | 87.48(7.79)   |
| Moderate-increasing  | 83.22(7.37)  | 82.26(7.27)  | 84.35(8.07)  | 85.03(6.93)  | 90.21(8.83)  | 96.76(10.70) | 100.12(12.31) | 105.84(10.60) |
| Elevated-stable      | 89.50(6.46)  | 88.20(6.55)  | 90.11(6.72)  | 90.38(6.51)  | 92.51(7.01)  | 93.84(8.05)  | 91.05(7.97)  | 91.28(7.78)   |
| Elevated-increasing | 96.81(8.90) | 94.56(10.00) | 101.07(7.76) | 101.25(8.89) | 101.24(9.77) | 107.89(9.21) | 103.24(12.77) | 104.83(12.94) |
|---------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP=Mean arterial pressure [(SBP*1/3)+(DBP*2/3)]; M=Mean; SD=Standard deviation.
### Table 4. Prevalence of hypertension at each study exam by blood pressure trajectory group in the MRI sample

| Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|--------|--------|--------|--------|---------|---------|---------|---------|
| (n=873)| (n=833)| (n=824)| (n=815)| (n=816) | (n=811) | (n=822) | (n=856) |
| **Overall** |          |        |        |         |         |         |         |
| No.(%)  | 121 (13.9) | 91 (10.9) | 121 (14.7) | 140 (17.2) | 177 (21.7) | 263 (32.4) | 224 (27.2) | 339 (39.6) |

#### SBP Trajectory Group

| SBP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|----------------------|--------|--------|--------|--------|---------|---------|---------|---------|
| Low-stable           | 3 (1.4) | 0 (0.0) | 3 (1.5) | 1 (0.5) | 3 (1.5) | 8 (3.9) | 6 (3.0) | 11 (5.3) |
| Moderate-gradual     | 30 (7.4) | 24 (6.2) | 25 (6.6) | 26 (6.8) | 50 (13.1) | 87 (23.3) | 72 (18.6) | 143 (35.8) |
| Moderate-increasing  | 11 (21.6) | 5 (10.4) | 11 (22.4) | 9 (20.0) | 13 (31.0) | 34 (79.1) | 35 (76.1) | 48 (98.0) |
| Elevated-stable      | 67 (35.1) | 56 (30.6) | 69 (37.5) | 94 (51.9) | 100 (55.2) | 120 (67.8) | 97 (55.7) | 122 (65.9) |
| Elevated-increasing  | 10 (62.5) | 6 (40.0) | 13 (86.7) | 10 (71.4) | 11 (73.3) | 14 (100.0) | 14 (100.0) | 15 (93.8) |

#### DBP Trajectory Group

| DBP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|----------------------|--------|--------|--------|--------|---------|---------|---------|---------|
| Low-stable           | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.1) | 2 (1.1) | 14 (7.8) |
| Moderate-gradual     | 18 (4.6) | 10 (2.7) | 14 (3.7) | 11 (3.0) | 25 (6.7) | 52 (14.2) | 52 (13.9) | 104 (26.7) |
| Moderate-increasing  | 9 (12.0) | 4 (5.6) | 11 (15.5) | 14 (20.0) | 29 (42.0) | 57 (82.6) | 57 (81.4) | 71 (94.7) |
| Elevated-stable      | 69 (37.1) | 55 (30.6) | 68 (38.9) | 88 (50.0) | 95 (54.3) | 121 (70.8) | 87 (49.4) | 119 (66.1) |
| Elevated-increasing  | 25 (73.5) | 22 (66.7) | 28 (87.5) | 27 (81.8) | 28 (87.5) | 31 (100.0) | 26 (96.3) | 31 (96.9) |

#### MAP Trajectory Group

| MAP Trajectory Group | Year 0 | Year 2 | Year 5 | Year 7 | Year 10 | Year 15 | Year 20 | Year 25 |
|---------------------|--------|--------|--------|--------|---------|---------|---------|---------|
| Low-stable          | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.1) | 2 (1.1) | 8 (4.4) |
| Moderate-gradual    | 19 (5.0) | 9 (2.5) | 13 (3.6) | 9 (2.5) | 24 (6.7) | 55 (15.9) | 49 (13.5) | 105 (27.9) |
| Moderate-increasing | 8 (11.8) | 5 (7.6) | 11 (16.4) | 12 (19.4) | 25 (39.1) | 47 (75.8) | 48 (78.7) | 66 (98.5) |
| Elevated-stable     | 65 (32.2) | 55 (28.1) | 65 (34.6) | 91 (47.9) | 98 (51.3) | 125 (66.1) | 95 (50.0) | 125 (63.8) |
| Elevated-increasing | 28 (75.7) | 22 (62.9) | 32 (88.9) | 28 (77.8) | 30 (85.7) | 34 (100.0) | 30 (96.8) | 35 (97.2) |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP=Mean arterial pressure [(SBP*1/3)+(DBP*2/3)].

a: Hypertension defined as systolic blood pressure ≥130 or diastolic blood pressure ≥80 or taking antihypertensive medication.
### Table 5. Brain characteristics of the MRI subset by SBP/DBP trajectory group – CARDIA cohort: Year 25/Year 30 exam\(^a,b\)

|                          | Overall | Trajectory group |                                       |                                       |                                       |                                       | p-value \(^c\) |
|--------------------------|---------|------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------|
|                          | M(SD)   | M(SD)            | M(SD)                                 | M(SD)                                 | M(SD)                                 | M(SD)                                 |                |
| **SBP Trajectory Group** |         |                  |                                       |                                       |                                       |                                       |                |
| **1. Brain volume measures (cm\(^3\))** |         |                  |                                       |                                       |                                       |                                       |                |
| Valid n                  | 853     | 207              | 398                                   | 50                                    | 183                                   | 15                                    |                |
| Total brain\(^d\)       | 0.85(0.03) | 0.85(0.03)      | 0.86(0.03)                            | 0.85(0.03)                            | 0.85(0.03)                            | 0.84(0.04)                            | 0.03           |
| Gray matter\(^d\)       | 0.46(0.02) | 0.47(0.02)      | 0.47(0.02)                            | 0.46(0.02)                            | 0.46(0.02)                            | 0.45(0.03)                            | 0.001          |
| Valid n                  | 846     | 205              | 396                                   | 50                                    | 180                                   | 15                                    |                |
| Normal-looking white matter\(^d\) | 0.38(0.02) | 0.38(0.02)  | 0.38(0.02)                            | 0.38(0.02)                            | 0.38(0.02)                            | 0.38(0.02)                            | 0.42           |
| Abnormal white matter\(^e\) | 0.19(0.14) | 0.18(0.12)  | 0.19(0.13)                            | 0.27(0.25)                            | 0.19(0.14)                            | 0.31(0.27)                            | <0.001         |
| **2. White matter fractional anisotropy** |         |                  |                                       |                                       |                                       |                                       |                |
| Valid n                  | 777     | 187              | 367                                   | 42                                    | 168                                   | 13                                    |                |
| **3. Gray matter cerebral blood flow (mL/100g/min)** |         |                  |                                       |                                       |                                       |                                       |                |
| Valid n                  | 753     | 193              | 343                                   | 41                                    | 163                                   | 13                                    |                |
| **DBP Trajectory Group** |         |                  |                                       |                                       |                                       |                                       |                |
| **1. Brain volume measures (cm\(^3\))** |         |                  |                                       |                                       |                                       |                                       |                |
| Valid n                  | 853     | 181              | 385                                   | 73                                    | 181                                   | 33                                    |                |
| Total brain\(^d\)       | 0.85(0.03) | 0.85(0.02)      | 0.85(0.03)                            | 0.86(0.03)                            | 0.85(0.03)                            | 0.85(0.03)                            | 0.17           |
| Gray matter\(^d\)       | 0.46(0.02) | 0.47(0.02)      | 0.47(0.02)                            | 0.46(0.02)                            | 0.46(0.02)                            | 0.46(0.03)                            | 0.05           |
| Valid n                  | 846     | 180              | 382                                   | 72                                    | 179                                   | 33                                    |                |
| Normal-looking white matter\(^d\) | 0.38(0.02) | 0.38(0.01)  | 0.38(0.02)                            | 0.38(0.01)                            | 0.38(0.02)                            | 0.38(0.02)                            | 0.69           |
| Abnormal white matter\(^e\) | 0.19(0.14) | 0.19(0.12)  | 0.18(0.13)                            | 0.23(0.19)                            | 0.19(0.15)                            | 0.26(0.19)                            | <0.001         |
| **2. White matter fractional anisotropy** |         |                  |                                       |                                       |                                       |                                       |                |

© 2022 Hu YH et al. *JAMA Network Open.*
| Valid n | 777 | 166 | 356 | 62 | 163 | 30 | 753 | 169 | 344 | 64 | 147 | 29 | 0.008 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3. Gray matter cerebral blood flow (mL/100g/min)** | 29.72(7.2) 2 | 30.64(7.6) 2 | 30.11(7.36) | 29.81(6.3) 5 | 28.25(6.85) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) | 27.08(5.24) |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
SBP=systolic blood pressure; DBP=diastolic blood pressure.
a: Based on the cases with complete data on the outcome and all covariates.
b: Data is reported as mean (M) and standard deviation (SD).
c: p-value was based on one-way analysis of variance test.
d: Reported as brain volume to intracranial volume ratio.
e: Log transformation was applied due to skew distribution.
|                     | Low-stable (n=207) | Moderate-gradual (n=398) | Moderate-increasing (n=50) | Elevated-stable (n=183) | Elevated-increasing (n=15) |
|---------------------|--------------------|--------------------------|---------------------------|--------------------------|--------------------------|
| **Model 1 estimations** |
| Total brain volume  | -0.06 -0.03 (0.02, 0.08) | -0.09 (-0.18, 0.01) | 0.14 | -0.02 (-0.09, 0.05) | 0.69 | -0.18 (-0.34, 0.02) | 0.06 |
| Total gray matter volume | -0.08 -0.03 (0.13) | -0.12 (-0.25, 0.02) | 0.19 | -0.008 (-0.11, 0.09) | 0.98 | -0.31 (-0.54, 0.08) | 0.03 |
| Normal white matter volume | -0.04 0.009 (-0.05, 0.07) | -0.07 (-0.18, 0.04) | 0.25 | -0.02 (-0.10, 0.06) | 0.64 | -0.05 (-0.23, 0.14) | 0.08 |
| Abnormal white matter volume | 0.18 0.14 (-0.03, 0.31) | 0.74 (0.43, 1.04) | <0.01 | 0.24 (0.02, 0.47) | 0.00 | 0.11 (0.59, 1.64) | 0.01 |
| White matter fractional anisotropy | 0.23 -0.12 (-0.30, 0.05) | -0.38 (-0.70, 0.05) | 0.06 | -0.15 (-0.38, 0.08) | 0.23 | -0.58 (-1.12, 0.03) | 0.08 |
| Gray matter cerebral blood flow | 0.45 0.007 (-0.16, 0.18) | -0.08 (-0.39, 0.23) | 0.67 | -0.18 (-0.40, 0.04) | 0.10 | -0.32 (-0.84, 0.20) | 0.31 |
| **Model 2 estimations** |
| Total brain volume  | 0.01 0.03 (-0.02, 0.09) | 0.34 | 0.003 0.07 | 0.03 | 0.16 (-0.32, 0.00) | 0.03 |
| Total gray matter volume | -0.02 0.05 (-0.02, 0.13) | 0.32 | 0.08 (-0.22, 0.05) | 0.30 | 1.05 (0.53, 1.58) | 0.30 |
| Normal white matter volume | 0.02 0.01 (-0.05, 0.07) | 0.79 | -0.07 (-0.18, 0.04) | 0.30 | -0.03 (-0.22, 0.15) | 0.03 |
| Abnormal white matter volume | 0.19 0.14 (-0.04, 0.31) | 0.25 | 0.72 (0.40, 1.03) | <0.01 | 0.15 (0.53, 1.58) | 0.03 |
| White matter fractional anisotropy | 0.24 -0.11 (-0.28, 0.07) | 0.34 | -0.31 (-0.64, 0.02) | 0.09 | 0.34 (0.53, 1.04) | 0.03 |
| Gray matter cerebral blood flow | 0.68 0.05 (-0.12, 0.22) | 0.67 | 0.02 (-0.29, 0.34) | 0.19 | 0.32 (-0.84, 0.19) | 0.31 |
| **Model 3 estimations** |
| Total brain volume  | 0.01 0.04 (-0.01, 0.10) | 0.44 | 0.001 0.09 | 0.85 | -0.13 (-0.30, 0.03) | 0.04 |
| Total gray matter volume | -0.01 0.06 (-0.02, 0.14) | 0.44 | -0.09 (-0.21, 0.08) | 0.09 | -0.25 (-0.49, 0.01) | 0.03 |
| Normal white matter volume | 0.03 0.02 (-0.04, 0.08) | 0.65 | -0.05 (-0.16, 0.06) | 0.90 | 0.007 (-0.20, 0.18) | 0.09 |

© 2022 Hu YH et al. *JAMA Network Open.*
|                          |       |                  |       |                  |       |                  |       |                  |       |                  |
|--------------------------|-------|------------------|-------|------------------|-------|------------------|-------|------------------|-------|------------------|
| Abnormal white matter   | 0.18  | 0.12 (-0.06, 0.30) | 0.44  | 0.67 (0.35, 0.99) | 0.0   | 0.18 (-0.07, 0.42) | 0.4   | 0.99 (0.45, 1.52) | 0.0   | 0.06             |
| volume                   |       |                  |       |                  |       |                  |       |                  |       |                  |
| White matter fractional | 0.27  | -0.07 (-0.25, -0.10) | 0.60  | -0.23 (-0.56, 0.11) | 0.4   | -0.009 (-0.25, 0.24) | 0.9   | -0.38 (-0.93, 0.17) | 0.4   | 4                |
| anisotropy               |       |                  |       |                  |       |                  |       |                  |       |                  |
| Gray matter cerebral     | 0.68  | 0.06 (-0.11, 0.23) | 0.65  | 0.03 (-0.29, 0.35) | 0.9   | -0.10 (-0.33, 0.14) | 0.6   | -0.30 (-0.83, 0.23) | 0.5   | 2                |
| blood flow               |       |                  |       |                  |       |                  |       |                  |       |                  |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
CI=confidence interval.
a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. q ≤0.1 was considered statistically significant.
b: For the volume of total brain, gray matter and hippocampus, n= 853; normal-looking white matter and abnormal white matter volume, n=846; white matter fractional anisotropy and mean diffusivity, n=777; and cerebral blood flow n=753.
c: All outcomes were standardized to Z-score values.
d: All models were adjusted for age, sex, race, education, and field center. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication. Tissue volume measures models additionally adjusted for total intracranial volume; white matter fractional anisotropy and gray matter cerebral blood flow models additionally adjusted for total brain volume.
e: Abnormal white matter volume was log-transformed before standardizing to Z-score values.
f: Adjusted means based on the estimated model when intracranial volume/total brain volume was standardized, and age and physical activity level centered.
Table 7. The association of diastolic blood pressure (DBP) trajectory with brain outcomes (reference DBP trajectory: Low-stable, overall n=853)\textsuperscript{a,b,c,d}

|                      | Low-stable \((n=181)\) | Moderate-gradual \((n=385)\) | Moderate-increasing \((n=73)\) | Elevated-stable \((n=181)\) | Elevated-increasing \((n=33)\) |
|----------------------|-------------------------|-------------------------------|-------------------------------|-----------------------------|-----------------------------|
|                      | Mean\textsuperscript{f} | \(\beta\) (95% CI) | \(\beta\) (95% CI) | \(\beta\) (95% CI) | \(\beta\) (95% CI) |
| **Model 1 estimations** |                         |                               |                               |                               |                               |
| Total brain volume   | -0.04                   | -0.004 (-0.06, 0.05)          | 0.8 9                         | -0.04 (-0.13, 0.04)          | 0.4 6                       |
|                      |                         |                               |                               |                               |                               |
| Total gray matter volume | -0.07                  | 0.02 (-0.06, 0.11)           | 0.6 4                         | -0.05 (-0.18, 0.07)          | 0.5 1                       |
|                      |                         |                               |                               |                               |                               |
| Normal white matter volume | -0.02                 | -0.03 (-0.09, 0.03)          | 0.4 7                         | -0.04 (-0.14, 0.06)          | 0.4 8                       |
|                      |                         |                               |                               |                               |                               |
| Abnormal white matter volume\textsuperscript{e} | 0.30                   | -0.09 (-0.27, 0.09)          | 0.4 7                         | 0.21 (-0.08, 0.49)           | 0.2 4                       |
|                      |                         |                               |                               |                               |                               |
| White matter fractional anisotropy | 0.26                  | -0.09 (-0.27, 0.09)          | 0.4 6                         | -0.31 (-0.60, -0.02)         | 0.1 1                       |
|                      |                         |                               |                               |                               |                               |
| Gray matter cerebral blood flow | 0.53                  | -0.08 (-0.25, 0.09)          | 0.4 7                         | -0.23 (-0.50, 0.04)          | 0.2 1                       |
|                      |                         |                               |                               |                               |                               |
| **Model 2 estimations** |                         |                               |                               |                               |                               |
| Total brain volume   | 0.03                   | -0.006 (-0.06, 0.05)          | 0.8 6                         | -0.04 (-0.12, 0.05)          | 0.5 6                       |
|                      |                         |                               |                               |                               |                               |
| Total gray matter volume | -0.01                 | 0.02 (-0.06, 0.10)           | 0.6 8                         | -0.04 (-0.17, 0.09)          | 0.6 6                       |
|                      |                         |                               |                               |                               |                               |
| Normal white matter volume | 0.05                  | -0.03 (-0.10, 0.03)          | 0.5 2                         | -0.04 (-0.14, 0.06)          | 0.5 8                       |
|                      |                         |                               |                               |                               |                               |
| Abnormal white matter volume\textsuperscript{e} | 0.30                   | -0.09 (-0.27, 0.09)          | 0.5 2                         | 0.19 (-0.11, 0.48)           | 0.4 2                       |

© 2022 Hu YH et al. *JAMA Network Open*. 
|                          |        |        |        |        |        |        |
|--------------------------|--------|--------|--------|--------|--------|--------|
| White matter fractional anisotropy | 0.25   | -0.09 (-0.27, 0.09) | 0.5 3 | -0.26 (-0.56, 0.03) | 0.2 9 | -0.20 (-0.42, 0.02) | 0.2 9 | -0.25 (-0.63, 0.14) | 0.4 2 |
| Gray matter cerebral blood flow | 0.74   | -0.03 (-0.21, 0.14) | 0.7 8 | -0.13 (-0.40, 0.15) | 0.5 3 | -0.17 (-0.38, 0.05) | 0.3 8 | -0.41 (-0.78, -0.04) | 0.2 3 |

**Model 3 estimations**

|                          |        |        |        |        |        |        |
|--------------------------|--------|--------|--------|--------|--------|--------|
| Total brain volume       | 0.03   | -0.003 (-0.06, 0.05) | 0.9 5 | -0.02 (-0.11, 0.07) | 0.8 2 | -0.02 (-0.09, 0.05) | 0.8 2 | -0.08 (-0.20, 0.04) | 0.6 1 |
| Total gray matter volume | -0.001 | 0.03 (-0.06, 0.11) | 0.7 5 | -0.02 (-0.16, 0.11) | 0.8 3 | 0.005 (-0.10, 0.11) | 0.9 5 | -0.15 (-0.33, 0.03) | 0.5 8 |
| Normal white matter volume | 0.05 | -0.03 (-0.09, 0.04) | 0.6 8 | -0.02 (-0.13, 0.08) | 0.8 2 | -0.04 (-0.12, 0.04) | 0.6 8 | -0.001 (-0.14, 0.14) | 0.9 9 |
| Abnormal white matter volume | 0.27 | -0.10 (-0.29, 0.08) | 0.6 8 | 0.13 (-0.17, 0.42) | 0.6 8 | -0.09 (-0.32, 0.14) | 0.6 8 | 0.38 (-0.02, 0.78) | 0.4 7 |
| White matter fractional anisotropy | 0.27 | -0.08 (-0.26, 0.11) | 0.6 8 | -0.21 (-0.51, 0.10) | 0.6 1 | -0.14 (-0.37, 0.09) | 0.6 1 | -0.15 (-0.55, 0.25) | 0.6 8 |
| Gray matter cerebral blood flow | 0.74 | -0.03 (-0.21, 0.14) | 0.8 3 | -0.13 (-0.42, 0.15) | 0.6 8 | -0.17 (-0.39, 0.05) | 0.6 1 | -0.42 (-0.81, -0.03) | 0.3 1 |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985–2016
CI=confidence interval.

a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. q ≤0.1 was considered statistically significant.

b: For the volume of total brain, gray matter and hippocampus, n= 853; normal-looking white matter and abnormal white matter volume, n=846; white matter fractional anisotropy and mean diffusivity, n=777; and cerebral blood flow n=753.

c: All outcomes were standardized to Z-score values.

d: All models were adjusted for age, sex, race, education, and field center. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication. Tissue volume measures models additionally adjusted for total intracranial volume; white matter fractional anisotropy and gray matter cerebral blood flow models additionally adjusted for total brain volume.

e: Abnormal white matter volume was log-transformed before standardizing to Z-score values.

f: Adjusted means based on the estimated model when intracranial volume/total brain volume was standardized, and age and physical activity level centered.
### Table 8. The association of systolic blood pressure (SBP) trajectory with cognitive function outcomes at Y30 exam (reference SBP trajectory: Low-stable, overall n=2,736) a,b,c,d

|                 | Low-stable (n=705) | Moderate-gradual (n=1,225) | Moderate-increasing (n=197) | Elevated-stable (n=538) | Elevated-increasing (n=71) |
|-----------------|--------------------|----------------------------|-----------------------------|-------------------------|---------------------------|
| **Model 1 estimations** |                    |                            |                             |                         |                           |
| RAVLT           | 0.66               | -0.11 (-0.20, -0.03)       | 0.04                        | -0.23 (-0.38, -0.09)    | 0.01                      |
|                 |                    |                             |                             | -0.18 (-0.29, -0.06)    | 0.01                      |
|                 |                    |                             |                             | -0.40 (-0.63, -0.18)    | 0.00                      |
| DSST            | 0.25               | -0.04 (-0.13, 0.05)        | 0.45                        | -0.18 (-0.33, -0.04)    | 0.04                      |
|                 |                    |                             |                             | -0.19 (-0.31, -0.08)    | 0.07                      |
|                 |                    |                             |                             | -0.37 (-0.59, -0.15)    | 0.08                      |
| Stroop test     | -0.27              | 0.07 (-0.02, 0.16)         | 0.22                        | 0.24 (0.08, 0.39)       | 0.01                      |
|                 |                    |                             |                             | 0.16 (0.04, 0.28)       | 0.03                      |
|                 |                    |                             |                             | 0.28 (0.04, 0.52)       | 0.06                      |
| **Model 2 estimations** |                    |                            |                             |                         |                           |
| RAVLT           | 0.60               | -0.11 (-0.19, -0.02)       | 0.09                        | -0.20 (-0.35, -0.05)    | 0.08                      |
|                 |                    |                             |                             | -0.14 (-0.25, -0.02)    | 0.09                      |
|                 |                    |                             |                             | -0.31 (-0.54, -0.09)    | 0.08                      |
| DSST            | 0.20               | -0.02 (-0.11, 0.07)        | 0.76                        | -0.12 (-0.26, 0.03)     | 0.25                      |
|                 |                    |                             |                             | -0.12 (-0.23, -0.00)    | 0.17                      |
|                 |                    |                             |                             | -0.22 (-0.44, 0.00)     | 0.17                      |
| Stroop test     | -0.22              | 0.06 (-0.04, 0.15)         | 0.34                        | 0.19 (0.03, 0.34)       | 0.09                      |
|                 |                    |                             |                             | 0.11 (-0.01, 0.23)      | 0.19                      |
|                 |                    |                             |                             | 0.16 (-0.08, 0.40)      | 0.32                      |
| **Model 3 estimations** |                    |                            |                             |                         |                           |
| RAVLT           | 0.61               | -0.09 (-0.18, 0.00)        | 0.33                        | -0.16 (-0.31, -0.00)    | 0.31                      |
|                 |                    |                             |                             | -0.09 (-0.21, 0.03)     | 0.44                      |
|                 |                    |                             |                             | -0.24 (-0.48, -0.01)    | 0.31                      |
| DSST            | 0.21               | -0.002 (-0.09, 0.09)       | 0.99                        | -0.08 (-0.22, 0.07)     | 0.57                      |
|                 |                    |                             |                             | -0.07 (-0.19, 0.05)     | 0.48                      |
|                 |                    |                             |                             | -0.15 (-0.38, 0.08)     | 0.46                      |
| Stroop test     | -0.23              | 0.03 (-0.06, 0.13)         | 0.65                        | 0.14 (-0.02, 0.30)      | 0.44                      |
|                 |                    |                             |                             | 0.06 (-0.07, 0.19)      | 0.60                      |
|                 |                    |                             |                             | 0.08 (-0.16, 0.33)      | 0.65                      |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
Abbreviations: RAVLT=Rey Auditory Verbal Learning Test; DSST=Digital symbol substitution test; CI=confidence interval.
a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparisons. q ≤0.1 was considered statistically significant.
b: All outcomes were standardized to Z-score values.
c: All models were adjusted for age, sex, race, education, and field center. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication.
d: Adjusted means based on the estimated model when intracranial volume/total brain volume was standardized, and age and physical activity level centered.
eTable 9. The association of diastolic blood pressure (DBP) trajectory with cognitive function outcomes at Y30 exam (reference DBP trajectory: Low-stable, overall n=2736).a,b,c,d

|                          | Low-stable (n=587) | Moderate-gradual (n=1,205) | Moderate-increasing (n=309) | Elevated-stable (n=531) | Elevated-increasing (n=104) |
|--------------------------|-------------------|---------------------------|-----------------------------|-------------------------|---------------------------|
|                          | Mean^d β (95% CI) | q                         | β (95% CI)                  | q                       | β (95% CI)                  |
| Model 1 estimations      |                   |                           |                             |                         |                           |
| RAVLT                    | 0.66              | -0.07 (-0.16, 0.02)       | 0.2                         | -0.24 (-0.37, -0.11)    | 0.004                      |
| DSST                     | 0.24              | 0.02 (-0.07, 0.11)        | 0.6                         | -0.14 (-0.27, -0.01)    | 0.10                      |
| Stroop test              | -0.28             | 0.07 (-0.02, 0.17)        | 0.2                         | 0.18 (0.04, 0.32)       | 0.10                      |
| Model 2 estimations      |                   |                           |                             |                         |                           |
| RAVLT                    | 0.60              | -0.07 (-0.16, 0.02)       | 0.3                         | -0.20 (-0.33, -0.07)    | 0.004                      |
| DSST                     | 0.18              | 0.05 (-0.04, 0.14)        | 0.5                         | -0.05 (-0.18, 0.08)     | 0.56                       |
| Stroop test              | -0.23             | 0.06 (-0.04, 0.15)        | 0.4                         | 0.12 (-0.02, 0.26)      | 0.20                       |
| Model 3 estimations      |                   |                           |                             |                         |                           |
| RAVLT                    | 0.61              | -0.06 (-0.15, 0.03)       | 0.6                         | -0.16 (-0.30, -0.02)    | 0.20                       |
| DSST                     | 0.19              | 0.06 (-0.03, 0.14)        | 0.6                         | -0.01 (-0.14, 0.12)     | 0.90                       |
| Stroop test              | -0.23             | 0.05 (-0.05, 0.14)        | 0.6                         | 0.08 (-0.07, 0.22)      | 0.60                       |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
Abbreviations: RAVLT=Rey Auditory Verbal Learning Test; DSST=Digital symbol substitution test; CI=confidence interval.

a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. q ≤0.1 was considered statistically significant.
b: All outcomes were standardized to Z-score values.
c: All models were adjusted for age, sex, race, education, and field center. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication.

d: Adjusted means based on the estimated model when intracranial volume/total brain volume was standardized, and age and physical activity level centered.
| Table 10. The association of mean arterial pressure (MAP) trajectory with cognitive function outcomes at Y30 exam (reference MAP trajectory: Low-stable, overall n=2736) a,b,c,d |
|---------------------------------|------------------|-----------------|------------------|------------------|------------------|------------------|
|                                 | Low-stable       | Moderate-gradual | Moderate-increasing | Elevated-stable | Elevated-increasing |                  |
|                                 | (n=598)          | (n=1,184)        | (n=267)           | (n=567)         | (n=120)           |                  |
| Mean\[^d\] \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) | \(q\) \(\beta (95\% \text{ CI})\) |
| **Model 1 estimations**         |                  |                  |                  |                  |                  |                  |
| RAVLT                           | 0.68             | -0.12 (-0.21, -0.03) | 0.02             | -0.31 (-0.44, -0.17) | <.01             | -0.16 (-0.27, -0.05) | 0.02             | -0.33 (-0.52, -0.15) | 0.04             |
| DSST                            | 0.26             | -0.03 (-0.12, 0.06)  | 0.74             | -0.21 (-0.35, -0.08) | 0.01             | -0.17 (-0.28, -0.06) | 0.01             | -0.29 (-0.47, -0.11) | 0.01             |
| Stroop test                     | -0.27            | 0.05 (-0.05, 0.15)  | 0.53             | 0.23 (0.08, 0.37)   | 0.01             | 0.17 (0.05, 0.29)   | 0.02             | 0.30 (0.10, 0.49)   | 0.01             |
| **Model 2 estimations**         |                  |                  |                  |                  |                  |                  |
| RAVLT                           | 0.61             | -0.11 (-0.20, -0.02) | 0.11             | -0.26 (-0.40, -0.12) | 0.07             | -0.13 (-0.25, -0.02) | 0.11             | -0.28 (-0.46, -0.09) | 0.03             |
| DSST                            | 0.20             | 0.01 (-0.08, 0.10)  | 0.97             | -0.12 (-0.26, 0.01) | 0.77             | -0.1 (-0.22, 0.01)  | 0.17             | -0.16 (-0.35, 0.02) | 0.07             |
| Stroop test                     | -0.21            | 0.02 (-0.07, 0.12)  | 0.89             | 0.16 (0.02, 0.31)   | 0.14             | 0.12 (0.00, 0.24)   | 0.14             | 0.21 (0.02, 0.41)   | 0.12             |
| **Model 3 estimations**         |                  |                  |                  |                  |                  |                  |
| RAVLT                           | 0.62             | -0.10 (-0.19, -0.01) | 0.23             | -0.22 (-0.36, -0.08) | 0.04             | -0.10 (-0.22, -0.02) | 0.43             | -0.21 (-0.41, -0.02) | 0.23             |
| DSST                            | 0.20             | 0.02 (-0.07, 0.11)  | 0.88             | -0.08 (-0.22, 0.06) | 0.55             | -0.07 (-0.18, 0.05) | 0.55             | -0.10 (-0.29, 0.09) | 0.58             |
| Stroop test                     | -0.22            | 0.01 (-0.09, 0.11)  | 0.91             | 0.12 (-0.03, 0.27)  | 0.43             | 0.08 (-0.04, 0.21)  | 0.50             | 0.15 (-0.06, 0.36)  | 0.46             |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
Abbreviations: RAVLT=Rey Auditory Verbal Learning Test; DSST=Digital symbol substitution test; CI=confidence interval.

a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. \(q \leq 0.1\) was considered statistically significant.
b: All outcomes were standardized to Z-score values.
c: All models were adjusted for age, sex, race, education, and field center. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication.
d: Adjusted means based on the estimated model when intracranial volume/total brain volume was standardized, and age and physical activity level centered.
eTable 11. The association of systolic blood pressure (SBP) trajectory with brain outcomes after adjustment of Y25/Y30 BP measure (reference SBP trajectory: Low-stable, overall n=853) a,b,c,d

|                      | Low-stable (n=207) | Moderate-gradual (n=398) | Moderate-increasing (n=50) | Elevated-stable (n=183) | Elevated-increasing (n=15) |
|----------------------|---------------------|--------------------------|---------------------------|-------------------------|---------------------------|
|                      | Mean ± SE           | Mean ± SE                | Mean ± SE                 | Mean ± SE               | Mean ± SE                 |
| **Model 1 estimations** |                     |                          |                           |                         |                           |
| Total brain volume   | -0.05 ± 0.02        | -0.12 ± 0.02             | 0.22 ± 0.03               | -0.03 ± 0.01            | 0.63 ± 0.11               |
| Total gray matter volume | -0.10 ± 0.06       | -0.07 ± 0.07             | 0.63 ± 0.01               | 0.01 ± 0.01             | 0.91 ± 0.17               |
| Normal white matter volume | -0.003 ± 0.02     | -0.18 ± 0.03             | 0.09 ± 0.07               | -0.07 ± 0.04            | 0.31 ± 0.01               |
| Abnormal white matter volume | 0.24 ± 0.09       | 0.58 ± 0.09              | 0.08 ± 0.07               | 0.18 ± 0.07             | 0.33 ± 0.04               |
| White matter fractional anisotropy | 0.15 ± 0.05       | 0.14 ± 0.06              | 0.65 ± 0.03               | 0.05 ± 0.04             | 0.84 ± 0.04               |
| Gray matter cerebral blood flow | 0.31 ± 0.04      | 0.35 ± 0.06              | 0.27 ± 0.04               | 0.0 (-0.24, 0.25)       | 0.99 ± 0.16               |
|                      |                     |                          |                           |                         |                           |
| **Model 2 estimations** |                     |                          |                           |                         |                           |
| Total brain volume   | 0.02 ± 0.02         | -0.11 ± 0.02             | 0.29 ± 0.04               | -0.02 ± 0.02            | 0.81 ± 0.02               |
| Total gray matter volume | -0.03 ± 0.06       | -0.06 ± 0.04             | 0.793 ± 0.02              | 0.02 ± 0.01             | 0.87 ± 0.01               |
| Normal white matter volume | 0.07 ± 0.02       | -0.18 ± 0.03             | 0.19 ± 0.04               | -0.06 ± 0.02            | 0.38 ± 0.04               |
| Abnormal white matter volume | 0.24 ± 0.10       | 0.59 ± 0.09              | 0.08 ± 0.07               | 0.17 ± 0.02             | 0.40 ± 0.06               |
| White matter fractional anisotropy | 0.17 ± 0.05       | -0.12 ± 0.04             | 0.81 ± 0.01               | -0.01 ± 0.02            | 0.95 ± 0.04               |
| Gray matter cerebral blood flow | 0.54 ± 0.17      | 0.40 ± 0.04              | 0.28 ± 0.05               | 0.05 ± 0.02             | 0.87 ± 0.05               |
|                      |                     |                          |                           |                         |                           |
| **Model 3 estimations** |                     |                          |                           |                         |                           |
| Total brain volume   | 0.03 ± 0.03         | -0.09 ± 0.04             | 0.71 ± 0.04               | -0.001 ± 0.02           | 0.98 ± 0.02               |
| Total gray matter volume | -0.03 ± 0.08       | -0.02 ± 0.02             | 0.920 ± 0.04              | 0.05 ± 0.03             | 0.73 ± 0.01               |
| Normal white matter volume | 0.07 ± 0.02       | -0.16 ± 0.04             | 0.35 ± 0.05               | -0.05 ± 0.01            | 0.73 ± 0.12               |

© 2022 Hu YH et al. *JAMA Network Open.*
|                         | Abnormal white matter volume<sup>a</sup> | White matter fractional anisotropy | Gray matter cerebral blood flow |
|-------------------------|------------------------------------------|-----------------------------------|--------------------------------|
|                         | 0.24                                    | 0.18                              | 0.54                           |
|                         | 0.07 (-0.13, 0.27)                      | 0.004 (-0.19, 0.20)               | 0.19 (-0.00, 0.38)             |
|                         | 0.73                                    | 0.98                              | 0.37                           |
|                         | 0.51 (0.09, 0.94)                       | 0.02 (-0.42, 0.46)                | 0.44 (0.02, 0.86)              |
|                         | 0.32                                    | 0.98                              | 0.35                           |
|                         | 0.10 (-0.17, 0.38)                      | 0.10 (-0.17, 0.38)                | 0.08 (-0.18, 0.34)             |
|                         | 0.73                                    | 0.73                              | 0.75                           |
|                         | 0.82 (0.22, 1.43)                       | -0.13 (-0.75, 0.50)               | 0.1 (-0.49, 0.70)              |
|                         | 0.27                                    | 0.83                              | 0.85                           |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
CI=confidence interval.

a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. q ≤0.1 was considered statistically significant.
b: For the volume of total brain, gray matter and hippocampus, n= 853; normal-looking white matter and abnormal white matter volume, n=846; white matter fractional anisotropy and mean diffusivity, n=777; and cerebral blood flow n=753.
c: All outcomes were standardized to Z-score values.
d: All models were adjusted for age, sex, race, education, field center, and Y25/Y30 measure. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication. Tissue volume measures models additionally adjusted for total intracranial volume; white matter fractional anisotropy and gray matter cerebral blood flow models additionally adjusted for total brain volume.
e: Abnormal white matter volume was log-transformed before standardizing to Z-score values.
f: Adjusted means based on the estimated model when intracranial volume/total brain volume and Y25/Y30 BP measure were standardized, and age and physical activity level centered.
Table 12. The association of diastolic blood pressure (DBP) trajectory with brain outcomes after adjustment of Y25/Y30 BP measure (reference DBP trajectory: Low-stable, overall n=863)\textsuperscript{a,b,c,d}

| Model 1 estimations | Low-stable (n=181) | Moderate-gradual (n=385) | Moderate-increasing (n=73) | Elevated-stable (n=181) | Elevated-increasing (n=33) |
|---------------------|-------------------|--------------------------|---------------------------|--------------------------|----------------------------|
|                     | Mean\textsuperscript{f} | β (95% CI) | q | β (95% CI) | q | β (95% CI) | q | β (95% CI) | q |
| Total brain volume  | -0.05 (-0.13, 0.09) | 0.78 | -0.02 (-0.09, 0.06) | 0.75 | 0.01 (-0.06, 0.07) | 0.85 | -0.08 (-0.22, 0.05) | 0.66 |
| Total gray matter volume | -0.11 (-0.14, 0.17) | 0.85 | 0.03 (-0.08, 0.14) | 0.70 | 0.05 (-0.04, 0.14) | 0.66 | -0.11 (-0.30, 0.09) | 0.66 |
| Normal white matter volume | -0.01 (-0.18, 0.07) | 0.66 | -0.07 (-0.15, 0.02) | 0.61 | -0.04 (-0.11, 0.03) | 0.66 | -0.05 (-0.21, 0.10) | 0.70 |
| Abnormal white matter volume\textsuperscript{e} | 0.50 (-0.49, 0.22) | 0.66 | -0.22 (-0.47, 0.03) | 0.60 | -0.23 (-0.43, -0.03) | 0.29 | 0.13 (-0.31, 0.58) | 0.70 |
| White matter fractional anisotropy | 0.20 (-0.57, 0.15) | 0.66 | -0.17 (-0.42, 0.08) | 0.66 | -0.05 (-0.26, 0.15) | 0.70 | -0.2 (-0.65, 0.25) | 0.66 |
| Gray matter cerebral blood flow | 0.34 (-0.23, 0.46) | 0.70 | -0.04 (-0.28, 0.20) | 0.79 | 0.06 (-0.13, 0.25) | 0.70 | -0.12 (-0.55, 0.31) | 0.70 |

Model 2 estimations

| Total brain volume | 0.02 (-0.13, 0.08) | 0.76 | -0.02 (-0.10, 0.05) | 0.70 | -0.002 (-0.06, 0.06) | 0.95 | -0.09 (-0.23, 0.04) | 0.67 |
| Total gray matter volume | -0.04 (-0.15, 0.17) | 0.94 | 0.02 (-0.09, 0.13) | 0.83 | 0.04 (-0.05, 0.13) | 0.67 | -0.12 (-0.32, 0.08) | 0.67 |
| Normal white matter volume | 0.07 (-0.19, 0.06) | 0.67 | -0.07 (-0.16, 0.02) | 0.67 | -0.04 (-0.11, 0.03) | 0.67 | -0.05 (-0.21, 0.10) | 0.67 |
| Abnormal white matter volume\textsuperscript{e} | 0.52 (-0.49, 0.22) | 0.67 | -0.22 (-0.47, 0.03) | 0.67 | -0.22 (-0.42, -0.02) | 0.37 | 0.12 (-0.33, 0.56) | 0.76 |
| White matter fractional anisotropy | 0.22 (-0.58, 0.13) | 0.67 | -0.18 (-0.43, 0.07) | 0.67 | -0.07 (-0.27, 0.13) | 0.67 | -0.2 (-0.65, 0.24) | 0.67 |
| Gray matter cerebral blood flow | 0.57 (-0.23, 0.47) | 0.67 | -0.03 (-0.27, 0.21) | 0.85 | 0.07 (-0.13, 0.26) | 0.67 | -0.15 (-0.58, 0.28) | 0.67 |

Model 3 estimations

| Total brain volume | 0.02 (-0.12, 0.01) | 0.96 | -0.01 (-0.09, 0.07) | 0.96 | 0.004 (-0.06, 0.07) | 0.96 | -0.06 (-0.21, 0.08) | 0.96 |
| Total gray matter volume | -0.04 (-0.13, 0.20) | 0.96 | 0.04 (-0.08, 0.16) | 0.96 | 0.05 (-0.04, 0.14) | 0.96 | -0.09 (-0.29, 0.12) | 0.96 |
| Normal white matter volume | 0.07 (-0.17, 0.09) | 0.96 | -0.05 (-0.14, 0.04) | 0.96 | -0.04 (-0.11, 0.03) | 0.96 | -0.02 (-0.19, 0.14) | 0.96 |

\textsuperscript{a}Adjusted for age, sex, history of hypertension, \textsuperscript{b}adjusted for age, sex, history of hypertension, \textsuperscript{c}adjusted for age, sex, history of hypertension, \textsuperscript{d}adjusted for age, sex, history of hypertension, \textsuperscript{e}adjusted for age, sex, history of hypertension, \textsuperscript{f}adjusted for age, sex, history of hypertension.

© 2022 Hu YH et al. JAMA Network Open.
| Abnormal white matter volume | 0.51 | -0.24 (-0.61, 0.13) | 0.96 | -0.31 (-0.57, -0.04) | 0.41 | -0.25 (-0.45, -0.05) | 0.41 | -0.03 (-0.50, 0.43) | 0.96 |
| White matter fractional anisotropy | 0.23 | -0.14 (-0.51, 0.23) | 0.96 | -0.10 (-0.37, 0.16) | 0.96 | -0.05 (-0.25, 0.15) | 0.96 | -0.08 (-0.54, 0.39) | 0.96 |
| Gray matter cerebral blood flow | 0.57 | 0.13 (-0.23, 0.48) | 0.96 | -0.03 (-0.28, 0.23) | 0.96 | 0.07 (-0.13, 0.26) | 0.96 | -0.15 (-0.60, 0.30) | 0.96 |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
CI=confidence interval.

a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. q ≤0.1 was considered statistically significant.
b: For the volume of total brain, gray matter and hippocampus, n= 853; normal-looking white matter and abnormal white matter volume, n=846; white matter fractional anisotropy and mean diffusivity, n=777; and cerebral blood flow n=753.
c: All outcomes were standardized to Z-score values.
d: All models were adjusted for age, sex, race, education, field center, and Y25/Y30 measure. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication. Tissue volume measures models additionally adjusted for total intracranial volume; white matter fractional anisotropy and gray matter cerebral blood flow models additionally adjusted for total brain volume.
e: Abnormal white matter volume was log-transformed before standardizing to Z-score values.
f: Adjusted means based on the estimated model when intracranial volume/total brain volume and Y25/Y30 BP measure were standardized, and age and physical activity level centered.
|                         | Low-stable (n=181) | Moderate-gradual (n=385) | Moderate-increasing (n=73) | Elevated-stable (n=181) | Elevated-increasing (n=33) |
|-------------------------|--------------------|-------------------------|---------------------------|-------------------------|---------------------------|
| **Model 1 estimations** |                    |                         |                           |                         |                           |
| Total brain volume      | -0.06              | 0.01 (-0.05, 0.07)     | 0.87                      | 0.03 (-0.09, 0.14)     | -0.01 (-0.09, 0.07)       | -0.08 (-0.22, 0.06)       | 0.60                      |
| Total gray matter volume| -0.11              | 0.05 (-0.04, 0.14)     | 0.60                      | 0.06 (-0.11, 0.23)     | 0.05 (-0.07, 0.16)        | -0.09 (-0.29, 0.12)       | 0.67                      |
| Normal white matter volume | -0.01             | -0.029 (-0.10, 0.04)   | 0.67                      | -0.04 (-0.17, 0.10)    | -0.07 (-0.16, 0.01)       | -0.07 (-0.23, 0.09)       | 0.67                      |
| Abnormal white matter volume | 0.34             | -0.05 (-0.26, 0.15)    | 0.81                      | 0.32 (-0.06, 0.69)     | -0.02 (-0.27, 0.23)       | 0.36 (-0.09, 0.81)        | 0.35                      |
| White matter fractional anisotropy | 0.17   | -0.03 (-0.23, 0.18)    | 0.89                      | -0.19 (-0.57, 0.19)    | -0.21 (-0.47, 0.04)       | 0.35                      | -0.18 (-0.64, 0.28)       | 0.67                      |
| Gray matter cerebral blood flow | 0.29           | 0.14 (-0.05, 0.34)     | 0.37                      | 0.31 (-0.06, 0.69)     | -0.02 (-0.27, 0.23)       | 0.91                      | -0.08 (-0.51, 0.36)       | 0.87                      |
| **Model 2 estimations** |                    |                         |                           |                         |                           |                           |                           |
| Total brain volume      | 0.01               | 0.01 (-0.06, 0.07)     | 0.87                      | 0.03 (-0.08, 0.15)     | -0.01 (-0.09, 0.07)       | -0.08 (-0.22, 0.06)       | 0.64                      |
| Total gray matter volume| -0.05              | 0.04 (-0.05, 0.14)     | 0.64                      | 0.08 (-0.09, 0.25)     | 0.04 (-0.07, 0.16)        | -0.10 (-0.30, 0.11)       | 0.64                      |
| Normal white matter volume | 0.06              | -0.032 (-0.10, 0.04)   | 0.65                      | -0.03 (-0.17, 0.10)    | -0.07 (-0.17, 0.02)       | -0.07 (-0.22, 0.09)       | 0.69                      |
| Abnormal white matter volume | 0.36              | -0.05 (-0.25, 0.16)    | 0.82                      | 0.31 (-0.07, 0.69)     | -0.007 (-0.26, 0.25)      | 0.34 (-0.11, 0.80)        | 0.45                      |
| White matter fractional anisotropy | 0.17          | -0.03 (-0.23, 0.17)    | 0.84                      | -0.19 (-0.56, 0.19)    | -0.22 (-0.48, 0.04)       | 0.45                      | -0.16 (-0.62, 0.30)       | 0.76                      |
| Gray matter cerebral blood flow | 0.52            | 0.17 (-0.03, 0.37)     | 0.45                      | 0.33 (-0.04, 0.70)     | 0.02 (-0.23, 0.27)        | 0.90                      | -0.10 (-0.53, 0.33)       | 0.82                      |
| **Model 3 estimations** |                    |                         |                           |                         |                           |                           |                           |
| Total brain volume      | 0.01               | 0.02 (-0.05, 0.08)     | 0.95                      | 0.07 (-0.05, 0.19)     | 0.01 (-0.07, 0.10)        | -0.03 (-0.18, 0.12)       | 0.95                      |
| Total gray matter volume| -0.05              | 0.06 (-0.03, 0.15)     | 0.95                      | 0.12 (-0.05, 0.30)     | 0.08 (-0.05, 0.20)        | -0.04 (-0.25, 0.18)       | 0.95                      |
| Normal white matter volume | 0.06             | -0.03 (-0.10, 0.05)    | 0.95                      | -0.01 (-0.15, 0.13)    | -0.06 (-0.15, 0.04)       | 0.95                      | -0.03 (-0.20, 0.14)       | 0.95                      |

© 2022 Hu YH et al. JAMA Network Open.
| Measurement                                      | Value      | 95% CI                  | p-value  | 95% CI                  | p-value  | 95% CI                  | p-value  | 95% CI                  | p-value  |
|-------------------------------------------------|------------|-------------------------|----------|-------------------------|----------|-------------------------|----------|-------------------------|----------|
| Abnormal white matter volume*                  | 0.36       | (-0.29, 0.13)           | 0.95     | (0.19, 0.60)            | 0.95     | (-0.36, 0.19)           | 0.95     | (-0.36, 0.13)           | 0.95     |
| White matter fractional anisotropy             | 0.17       | (-0.20, 0.21)           | 0.97     | (-0.48, 0.31)           | 0.95     | (-0.41, 0.13)           | 0.95     | (-0.50, 0.48)           | 0.97     |
| Gray matter cerebral blood flow                | 0.52       | (-0.03, 0.38)           | 0.95     | (-0.05, 0.73)           | 0.95     | (-0.23, 0.30)           | 0.97     | (-0.54, 0.39)           | 0.95     |

Data source: The Coronary Artery Risk Development in Young Adults (CARDIA), 1985-2016
CI=confidence interval.
a: q-value was calculated using Benjamini-Hochberg method for the adjustment of multiple comparison. \( q \leq 0.1 \) was considered statistically significant.
b: For the volume of total brain, gray matter and hippocampus, \( n = 853 \); normal-looking white matter and abnormal white matter volume, \( n = 846 \); white matter fractional anisotropy and mean diffusivity, \( n = 777 \); and cerebral blood flow, \( n = 753 \).
c: All outcomes were standardized to Z-score values.
d: All models were adjusted for age, sex, race, education, field center, and Y25/Y30 BP measure. In Model 2, BMI, diabetes, physical activity level (log-transformed), current smoking status, and alcohol use were added. Model 3 was additionally adjusted for antihypertensive medication. Tissue volume measures models additionally adjusted for total intracranial volume; white matter fractional anisotropy and gray matter cerebral blood flow models additionally adjusted for total brain volume.
e: Abnormal white matter volume was log-transformed before standardizing to Z-score values.
f: Adjusted means based on the estimated model when intracranial volume/total brain volume and Y25/Y30 BP measure were standardized, and age and physical activity level centered.
eReferences
1. Launer LJ, Lewis CE, Schreiner PJ, et al. Vascular factors and multiple measures of early brain health: CARDIA brain MRI study. PloS one. 2015;10(3)

2. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA. 2014;311(5):490-497.

3. Nagin DS, NAGIN D. Group-based modeling of development. Harvard University Press; 2005.