**SUPPLAMENTAL MATERIALS**

# Elevated aortic pulse wave velocity relates to longitudinal grey and white matter changes

Corey W. Bown, BS,[a] Omair A. Khan, MAS,[a,c] Elizabeth E. Moore, BS,[a] Dandan Liu, PhD,[a,c] Kimberly R. Pechman, PhD,[a,b] Francis E. Cambronero, BA,[a] James G. Terry, MS,[d] Sangeeta Nair, DVM, MS,[d] L. Taylor Davis, MD,[a,b,d] Katherine A. Gifford, PsyD,[a,b] Bennett A. Landman, PhD[a,d,e,f], Timothy J. Hohman, PhD,[a,b,g] John Jeffrey Carr, MD, MSc,[h] Angela L. Jefferson, PhD,[a,b,e]

[a]*Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA*

[b]*Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA*

[c]*Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA*

[d]*Department of Radiology & Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, USA*

[e]*Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA*

[f]*Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, USA*

[g]*Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA*

[h]*Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA*

DOI [to be added]

**Table I. Aortic PWV and Brain Health Sensitivity Analyses**

| | β | 95 % CI | *p-value* |
|---|---|---|---|
| **Excluding Outliers ((mm$^3$/year)/(m/s))** | | | |
| Total grey matter | -236.3 | -608.2, 135.7 | 0.21 |
| Frontal grey matter | -48.69 | -239.7, 142.3 | 0.62 |
| Temporal grey matter | -61.55 | -123.4, 0.28 | **0.05** |
| Parietal grey matter | -69.15 | -158.4, 20.08 | 0.13 |
| Occipital grey matter | -34.93 | -73.71, 3.84 | 0.08 |
| Hippocampus | -3.18 | -7.38, 1.03 | 0.14 |
| Inferior lateral ventricle | 4.88 | -4.73, 14.49 | 0.32 |
| Total WMH | -35.52 | -141.9, 70.86 | 0.51 |
| Frontal WMH | -19.69 | -78.47, 39.10 | 0.51 |
| Temporal WMH | 3.74 | -4.89, 12.38 | 0.40 |
| Parietal WMH | -16.04 | -52.65, 20.58 | 0.39 |
| Occipital WMH | -9.51 | -27.35, 8.33 | 0.30 |
| **Excluding CVD and Atrial Fibrillation ((mm$^3$/year)/(m/s))** | | | |
| Total grey matter | -255.7 | -635.9, 124.5 | 0.19 |
| Frontal grey matter | -65.34 | -259.8, 129.1 | 0.51 |
| Temporal grey matter | -64.78 | -127.9, -1.69 | **0.04** |
| Parietal grey matter | -69.97 | -160.9, 20.92 | 0.13 |
| Occipital grey matter | -30.26 | -69.61, 9.08 | 0.13 |
| Hippocampus | -4.20 | -8.29, -0.11 | **0.04** |
| Inferior lateral ventricle | 7.17 | -2.08, 16.41 | 0.13 |
| Total WMH | 22.51 | -88.05, 133.1 | 0.69 |
| Frontal WMH | -10.13 | -69.91, 49.65 | 0.74 |
| Temporal WMH | 21.25 | 9.43, 33.06 | **<0.001** |
| Parietal WMH | 3.45 | -32.58, 39.48 | 0.85 |
| Occipital WMH | 0.53 | -19.14, 20.20 | 0.96 |

**Note.** Analyses performed on n=278 participants. Models were adjusted for age, sex, race/ethnicity, education, *APOE*-ε4 status, cognitive diagnosis, and Framingham Stroke Risk Profile (excluding points assigned for age). Models excluding outliers excluded dependent variables >4 standard deviations. Models excluding for CVD and atrial fibrillation excluded participants with positive diagnoses of CVD or atrial fibrillation. CI, confidence interval; CVD, cardiovascular disease. The parameter estimates (β) are for the *PWV x time* interaction term and is interpreted as the annual changes of outcomes associated with one unit change in PWV (per 1 m/s).

DOI [to be added]

**Table II. PWV Associations with Longitudinal Grey Matter Volume and WMH Volume with Systolic Blood Pressure Included as a Continuous Covariate**

| | β | 95% CI | *p-value* |
|---|---|---|---|
| **Grey Matter Neuroimaging Markers ((mm$^3$/year)/(m/s))** | | | |
| Total grey matter | -180.5 | (-513.6, 152.7) | 0.29 |
| Frontal grey matter | -23.57 | (-194.4, 147.3) | 0.79 |
| Temporal grey matter | -42.78 | (-97.39, -11.83) | 0.12 |
| Parietal grey matter | -51.51 | (--131.4, 28.39) | 0.21 |
| Occipital grey matter | -32.95 | (-66.69, 0.80) | 0.06 |
| Hippocampus | -3.60 | (-7.17, -0.03) | **0.05** |
| Inferior lateral ventricle | 5.90 | (-2.13, 13.93) | 0.15 |
| **WMH Neuroimaging Markers ((mm$^3$/year)/(m/s))** | | | |
| Total WMH | 31.50 | (-61.47, 124.5) | 0.51 |
| Frontal WMH | -2.33 | (-52.73, 48.08) | 0.93 |
| Temporal WMH | 17.09 | (7.18, 27.0) | **<0.001** |
| Parietal WMH | 8.89 | (-21.49, 39.28) | 0.57 |
| Occipital WMH | 0.67 | (-16.01, 17.35) | 0.94 |

**Note.** Analyses performed on n=278 participants. Models were adjusted for age, sex, race/ethnicity, education, *APOE*-ε4 status, cognitive diagnosis, systolic blood pressure, and Framingham Stroke Risk Profile (excluding points assigned for age and systolic blood pressure). CI, confidence interval; FDR p-value, false discovery rate corrected p-value. The parameter estimates (β) are for the PWV x time interaction term and is interpreted as the annual changes of outcomes associated with one unit change in PWV (m/s).

DOI [to be added]

**Table III. Aortic PWV x Diagnosis x Time Interactions and Stratifications by Diagnosis with Longitudinal MRI Outcomes**

| | β | 95 % CI | *p-value* | *FDR p-value* |
|---|---|---|---|---|
| **Diagnosis Interaction ((mm³/year)/(m/s))** | | | | |
| Total grey matter | 245.1 | -367.2, 857.4 | 0.43 | 0.97 |
| Frontal grey matter | 155.5 | -150.9, 461.9 | 0.32 | 0.97 |
| Temporal grey matter | 40.37 | -68.96, 149.7 | 0.47 | 0.97 |
| Parietal grey matter | 53.77 | -87.33, 194.9 | 0.45 | 0.97 |
| Occipital grey matter | -0.96 | -67.73, 65.82 | 0.98 | 0.98 |
| Hippocampus | 0.98 | -6.13, 8.08 | 0.79 | 0.97 |
| Inferior lateral ventricle | 0.20 | -12.10, 12.49 | 0.98 | 0.98 |
| Total WMH | -40.94 | -215.1, 133.2 | 0.64 | 0.97 |
| Frontal WMH | -11.02 | -105.0, 82.94 | 0.82 | 0.97 |
| Temporal WMH | -5.37 | -24.49, 13.74 | 0.58 | 0.97 |
| Parietal WMH | -27.64 | -84.64, 29.37 | 0.34 | 0.97 |
| Occipital WMH | 6.72 | -27.81, 41.24 | 0.70 | 0.97 |
| **Normal Cognition ((mm³/year)/(m/s))** | | | | |
| Total grey matter | -249.7 | -670.4, 171.0 | 0.24 | 0.35 |
| Frontal grey matter | -107.3 | -328.9, 114.3 | 0.34 | 0.44 |
| Temporal grey matter | -51.69 | -114.5, 11.13 | 0.11 | 0.35 |
| Parietal grey matter | -64.00 | -169.0, 40.98 | 0.23 | 0.35 |
| Occipital grey matter | -24.56 | -64.37, 15.25 | 0.23 | 0.35 |
| Hippocampus | -3.56 | -7.06, -0.06 | **0.05** | 0.30 |
| Inferior lateral ventricle | 2.10 | -3.56, 7.76 | 0.47 | 0.55 |
| Total WMH | 64.46 | -29.76, 158.7 | 0.18 | 0.35 |
| Frontal WMH | 11.53 | -39.70, 62.76 | 0.66 | 0.66 |
| Temporal WMH | 20.33 | 8.98, 31.69 | **<0.001** | **0.007** |
| Parietal WMH | 26.25 | -4.89, 57.39 | 0.10 | 0.35 |
| Occipital WMH | -4.58 | -23.01, 13.84 | 0.63 | 0.66 |
| **Mild Cognitive Impairment ((mm³/year)/(m/s))** | | | | |
| Total grey matter | -8.09 | -532.2, 516.1 | 0.98 | 0.98 |
| Frontal grey matter | 140.2 | -119.2, 399.5 | 0.29 | 0.94 |
| Temporal grey matter | -17.90 | -114.0, 78.16 | 0.71 | 0.94 |
| Parietal grey matter | -11.56 | -132.5, 109.4 | 0.85 | 0.94 |
| Occipital grey matter | -45.75 | -107.2, 15.68 | 0.14 | 0.94 |
| Hippocampus | -2.98 | -9.98, 4.02 | 0.40 | 0.94 |
| Inferior lateral ventricle | 7.81 | -8.48, 24.10 | 0.35 | 0.94 |
| Total WMH | -16.26 | -206.5, 173.9 | 0.87 | 0.94 |
| Frontal WMH | -19.46 | -120.2, 81.32 | 0.70 | 0.94 |
| Temporal WMH | 12.60 | -6.52, 31.73 | 0.20 | 0.94 |
| Parietal WMH | -15.05 | -76.28, 46.18 | 0.63 | 0.94 |
| Occipital WMH | 3.83 | -29.48, 37.14 | 0.82 | 0.94 |

**Note.** Analyses performed on n=278 participants and subsequently stratified by diagnosis for n=159 NC participants and n=119 MCI participants. The interaction term was aortic PWV x time x diagnosis. Models were adjusted for age, sex, race/ethnicity, education, *APOE*-ε4 status, and Framingham Stroke Risk Profile (excluding points assigned for age). CI, confidence interval; FDR p-value, false discovery rate corrected p-value. For the diagnosis interaction model, the parameter estimates (β) are for the PWV x Diagnosis x time interaction term and is interpreted as the difference in annual changes of outcomes between MCI and NC participants associated with one unit change in PWV. For stratified models by diagnosis, the parameter estimates (β) are for the diagnosis x time interaction term and is interpreted as the annual changes of outcomes associated with one unit change in PWV.

DOI [to be added]

**Table IV. Systolic Blood Pressure Associations with Longitudinal Grey Matter Volume and WMH Volume**

| | β | 95% CI | *p-value* |
|---|---|---|---|
| **Grey Matter Neuroimaging Markers ((mm$^3$/year)/(m/s))** | | | |
| Total grey matter | -12.01 | (-66.64, 42.62) | 0.67 |
| Frontal grey matter | -9.75 | (-37.68, 18.17) | 0.49 |
| Temporal grey matter | -4.01 | (-13.00, 4.99) | 0.38 |
| Parietal grey matter | 0.04 | (-13.08, 13.15) | >0.99 |
| Occipital grey matter | 0.93 | (-4.71, 6.57) | 0.75 |
| Hippocampus | -0.07 | (-0.68, 0.54) | 0.82 |
| Inferior lateral ventricle | 1.00 | (-0.40, 2.39) | 0.16 |
| **WMH Neuroimaging Markers ((mm$^3$/year)/(m/s))** | | | |
| Total WMH | 8.37 | (-7.35, 24.08) | 0.30 |
| Frontal WMH | 3.33 | (-5.27, 11.93) | 0.45 |
| Temporal WMH | 1.78 | (0.12, 3.43) | **0.04** |
| Parietal WMH | 1.49 | (-3.68, 6.66) | 0.57 |
| Occipital WMH | 1.22 | (-1.49, 3.93) | 0.38 |

**Note.** Analyses performed on n=278 participants. Models were adjusted for age, sex, race/ethnicity, education, *APOE*-ε4 status, cognitive diagnosis, and Framingham Stroke Risk Profile (excluding points assigned for age and systolic blood pressure). CI, confidence interval; FDR p-value, false discovery rate corrected p-value. The parameter estimates (β) are for the systolic blood pressure x time interaction term and is interpreted as the annual changes of outcomes associated with one unit change in systolic blood pressure (mmHg).

DOI [to be added]

# Major Resources Table

In order to allow validation and replication of experiments, all essential research materials listed in the Methods should be included in the Major Resources Table below. Authors are encouraged to use public repositories for protocols, data, code, and other materials and provide persistent identifiers and/or links to repositories when available. Authors may add or delete rows as needed.

## Data & Code Availability

| Description | Source / Repository | Persistent ID / URL |
|---|---|---|
| Longitudinal cohort study of older adults, enriched for mild cognitive impairment | Vanderbilt Memory & Aging Project | Due to participant consent restrictions in data sharing, a subset of data is available for purposes of reproducing results or replicating procedures. Data, analytic methods, and study materials can be obtained by contacting the corresponding author. |