

# Associations Between Vascular-based Risk Composites and Neuroimaging and Fluid Biomarkers In Aging And Alzheimer's Disease

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## Background:

- This update to our previous work captures the larger amyloid, tau, neurodegeneration, and vascular measure framework (ATN-V), investigating composites that account for race/ethnicity, biological sex, and APOE- ε4 status.
- With advances in the treatment of early detected Alzheimer's Disease (AD) and dementias, investigating risk composites' ability to map onto the ATN-V pathology is vital.

**Learning Objective:** Determine the relationships Cardiovascular risk factors, Aging, and Incidence of Dementia Risk Score (CAIDE), Cardiometabolic Index (CMI), Framingham Risk Score (FRS), and Washington Heights-Inwood Columbia Aging Project (WHICAP) composites have with the ATN-V biomarkers in a heterogeneous community-based cohort.

## Methods:

2016-2024: Adults 55 plus were recruited into the Clinical Core of the Wake Forest Alzheimer's Disease Research Center (WFADRC) and underwent evaluation in accordance with the National Alzheimer's Coordinating Center (NACC) protocols.

Baseline neuroimaging measures acquired: amyloid and tau PET, and MRI

Baseline blood-based biomarkers acquired: pNFL, plasma glial fibrillary pGFAP, ptau217, and pTau181

## Statistical Analyses:

General linear models examined if all scores (1) differed by sex, self-reported race/ethnicity, or APOE- ε4 status, and (2) were associated with baseline neuroimaging and fluid-based biomarker metrics. Models were adjusted for age, sex, education, cognitive status, and APOE- ε4 carrier status when not already captured.

## Demographics:

| Table 1a. Demographics of sample analyzed |              |              |              |              |        |
|-------------------------------------------|--------------|--------------|--------------|--------------|--------|
|                                           | Overall      | CU           | MCI          | DEM          | p      |
|                                           | N = 784      | N = 392      | N = 290      | N = 102      |        |
| Age <sup>1</sup>                          | 70.03 (8.04) | 68.36 (7.77) | 71.47 (7.61) | 72.50 (8.66) | <0.001 |
| Race                                      |              |              |              |              | 0.016  |
| Black <sup>2</sup>                        | 194 (24.74%) | 94 (23.98%)  | 85 (29.31%)  | 15 (14.71%)  |        |
| Other <sup>2</sup>                        | 12(1.5%)     | 6(1.53%)     | 4(1.37%)     | 2(1.96%)     |        |
| White <sup>2</sup>                        | 578 (73.72%) | 292 (74.49%) | 201 (69.31%) | 85 (83.33%)  |        |
| Sex: Female                               | 522 (66.58%) | 293 (74.74%) | 177 (61.03%) | 52 (50.98%)  | <.001  |
| Education <sup>1</sup>                    | 15.78 (2.52) | 16.08 (2.34) | 15.45 (2.63) | 15.63 (2.72) | 0.012  |
| APOE- ε4 Carrier <sup>2</sup>             | 279 (35.58%) | 112 (28.57%) | 111 (38.28%) | 56 (54.90%)  | <0.001 |
| Amyloid Positive/ Total N                 | 164/397      | 46/205       | 76/144       | 42/48        |        |
| Tau Positive/Total N                      | 71/260       | 17/140       | 40/97        | 14/24        |        |
| CAIDE <sup>1</sup>                        | 6.83 (1.52)  | 6.59 (1.56)  | 7.01 (1.46)  | 7.35 (1.28)  | <0.001 |
| CMI <sup>1</sup>                          | -0.99 (0.49) | -1.05 (0.50) | -0.92 (0.48) | -0.96 (0.47) | 0.002  |
| FRS <sup>1</sup>                          | 17.84 (8.42) | 16.05 (8.39) | 19.72 (7.96) | 19.98 (8.21) | <0.001 |
| WHICAP <sup>1</sup>                       | 7.34 (5.46)  | 6.04 (4.95)  | 8.36 (5.43)  | 9.65 (6.10)  | <0.001 |

| Table 1b. Composite scores stratified by sex |              |              |  |        |
|----------------------------------------------|--------------|--------------|--|--------|
|                                              | Male         | Female       |  |        |
| CAIDE <sup>1</sup>                           | 7.36 (1.49)  | 6.56 (1.46)  |  | <0.001 |
| CMI <sup>1</sup>                             | -0.97 (0.51) | -1.01 (0.49) |  | <0.001 |
| FRS <sup>1</sup>                             | 25.76 (5.58) | 13.95 (6.67) |  | <0.001 |
| WHICAP <sup>1</sup>                          | 8.65 (5.62)  | 8.24 (5.47)  |  | <0.001 |

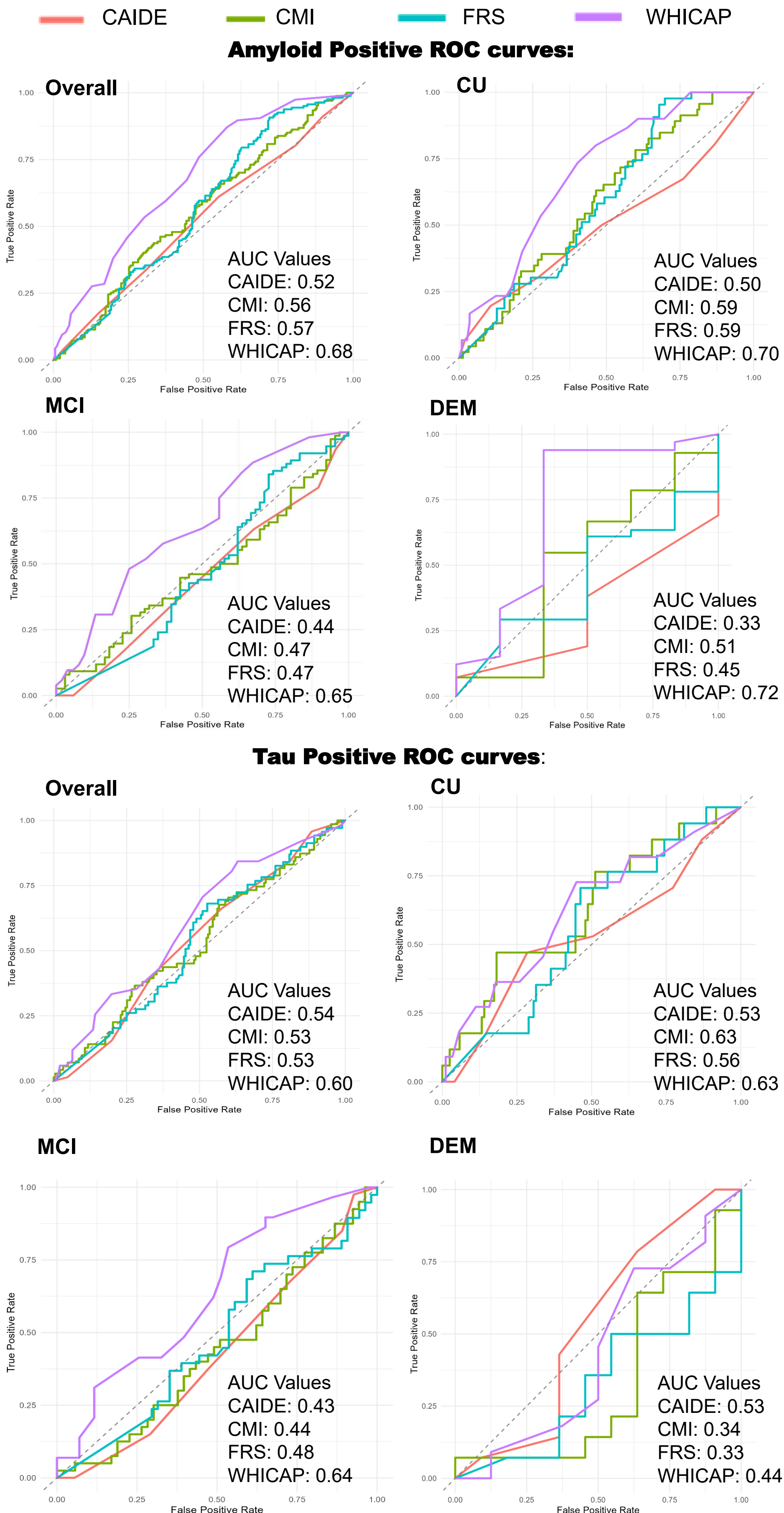
## Results:

| Table 2: Linear regressions examining associations between risk composites, neuroimaging, and fluid biomarkers |                       |                     |                     |                     |
|----------------------------------------------------------------------------------------------------------------|-----------------------|---------------------|---------------------|---------------------|
|                                                                                                                | RISK COMPOSITE SCORES |                     |                     |                     |
|                                                                                                                | CAIDE                 | CMI                 | FRS                 | WHICAP              |
| Total Brain Volume                                                                                             | β = -0.01 P = 0.007   | β = 0.0 P = 0.032   | β = -0.02 P < 0.001 | β = -0.02 P < 0.001 |
| Hippocampal Volume                                                                                             | β = -0.01 P = 0.014   | β = 0.0 P = 0.403   | β = -0.03 P < 0.001 | β = -0.03 P < 0.001 |
| Cortical Thickness                                                                                             | β = 0.0 P = 0.843     | β = 0.0 P = 0.907   | β = 0.31 P < 0.001  | β = -0.04 P < 0.001 |
| GM-CBF                                                                                                         | β = -1.11 P < 0.001   | β = -0.29 P = 0.447 | β = -2.83 P < 0.001 | β = -1.49 P < 0.001 |
| WM-CBF                                                                                                         | β = -0.2 P = 0.158    | β = 0.31 P = 0.041  | β = -0.52 P < 0.001 | β = -0.31 P = 0.049 |
| In(WMH Volume)                                                                                                 | β = 0.1 P = 0.033     | β = 0.06 P = 0.226  | β = 0.31 P < 0.001  | β = 0.48 P < 0.001  |
| NODDI FW                                                                                                       | β = 0.00 P = 0.014    | β = 0.0 P < 0.001   | β = 0.01 P < 0.001  | β = 0.01 P < 0.001  |
| DTI FA                                                                                                         | β = 0.0 P < 0.001     | β = 0.0 P = 0.227   | β = -0.01 P < 0.001 | β = -0.01 P < 0.001 |
| NFL                                                                                                            | β = 1.67 P = 0.009    | β = 0.5 P = 0.524   | β = 2.47 P < 0.001  | β = 3.95 P < 0.001  |
| GFAP                                                                                                           | β = -0.81 P = 0.858   | β = -4.05 P = 0.277 | β = 3.63 P = 0.234  | β = 24.63 P < 0.001 |
| P-tau217                                                                                                       | β = 0.01 P = 0.681    | β = -0.01 P = 0.524 | β = 0.02 P = 0.161  | β = 0.07 P < 0.001  |
| P-tau181                                                                                                       | β = 0.1 P = 0.28      | β = -0.16 P = 0.112 | β = 0.24 P = 0.003  | β = 0.35 P < 0.001  |

| Amyloid and Tau PET |                     |                     |                     |                     |
|---------------------|---------------------|---------------------|---------------------|---------------------|
| Amyloid Positivity  | OR = 0.9 P = 0.345  | OR = 1.08 P = 0.556 | OR = 1.1 P = 0.43   | OR = 1.86 P < 0.001 |
| Tau Positivity      | OR = 0.94 P = 0.696 | OR = 1.04 P = 0.8   | OR = 0.93 P = 0.656 | OR = 1.51 P = 0.035 |

Bolded values signify significant correlations at p<.05  
P-values are FDR corrected. All 95% CI <1.0. All models adjusted for age, gender, race, education, and APOE4 carrier status unless already accounted for in the composite score being analyzed. Total Brain Volume was adjusted for Intracranial Volume. Cortical Thickness in an AD-sensitive meta-temporal region of interest. Abbreviations: CAIDE = Cardiovascular risk factors, Aging, and Incidence of Dementia Risk Score; CMI = Cardiometabolic Index; FRS = Framingham Risk Score; GM = Gray Matter; WM = White Matter; CBF = Cerebral Blood Flow; WMH = White Matter Hyperintensities (Log-transformed and Adjusted for Intracranial Volume); NODDI = Neurite Orientation Density and Dispersion Imaging; FW = Freewater; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; NFL = plasma Neurofilament Light chain; GFAP = plasma Glial Fibrillary Acidic Protein; P-tau217 = phosphorylated Tau 217; P-tau181 = phosphorylated Tau at Threonine 181

## Results Continued:



## Conclusions

- CAIDE and FRS scores were higher among males (p<0.05).
- All composites were associated with total brain volume and NODDI-FW (p<.05; Table2).
- WHICAP was strongly associated with all fluid biomarkers(P<0.001) and significantly associated with increased odds of amyloid and tau positivity (p<0.05).