

# Association of allostatic load with cerebral free water in Hispanic/Latino adults: Findings from the SOL-INCA-MRI Study (HCHS/SOL)

César Anthony Moreno<sup>1</sup>, Addison Berg<sup>1</sup>, Mayra L. Estrella<sup>2</sup>, Pauline Maillard<sup>1</sup>, Ariana M. Stickel<sup>3</sup>, Carmen Isasi<sup>4</sup>, Fernando D. Testai<sup>5</sup>, Martha L. Daviglus<sup>5</sup>, Frank J. Penedo<sup>6</sup>, Tatjana Rundek<sup>6</sup>, Linda C. Gallo<sup>3</sup>, Hector M. González<sup>7</sup>, Charles DeCarli<sup>1</sup>, Shraddha Sapkota<sup>1</sup>

<sup>1</sup>University of California, Davis, <sup>2</sup>Rush Alzheimer's Disease Center, Rush University Medical Center, <sup>3</sup>San Diego State University, <sup>4</sup>Albert Einstein College of Medicine, <sup>5</sup>University of Illinois, Chicago, <sup>6</sup>University of Miami, <sup>7</sup>University of California, San Diego



## Introduction

- Allostatic load (AL) reflects cumulative multisystem physiological dysregulation that may reflect exposure to chronic stress. AL has been linked to cognitive decline and is disproportionately elevated in Hispanic/Latino adults relative to other racial/ethnic groups<sup>1,2</sup>.
- Cerebral free water (FW), derived from magnetic resonance (MRI) diffusion tensor imaging (DTI), is a sensitive biomarker of neuroinflammation and cerebrovascular white matter damage<sup>3</sup>.
- Goal:** To investigate whether AL is associated with FW and cognitive performance in Hispanic/Latino older adults. We had two research aims:
  - Aim I:** Examine the association between AL and FW (-10 years later) in the overall group and by Hispanic/Latino heritage. We expect that higher AL will be associated with greater FW and this association will differ by heritage groups.
  - Aim II:** Test cross-sectional associations between AL and cognitive performance at visit 1 (baseline) and visit 2 (-7 years later). We expect that higher AL will be associated with poorer cognitive performance at both visits.

## Methods

- Participants:**
  - We used Hispanic/Latino adults from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)- Investigation of Neurocognitive Aging-MRI (INCA-MRI) (N = 2,442, baseline age = 52.0 ± 8.9 years, 67% female; *Table 1*). Participants were from four HCHS/SOL field centers: Bronx, Chicago, Miami, and San Diego.
- Allostatic Load (AL):**
  - We used a count-based index of 16 biological markers summed across five physiological domains (cardiometabolic/lipid metabolism, glucose metabolism, cardiopulmonary, parasympathetic, inflammation) (*Table 2*).
  - Following prior AL calculation, each of the 16 biological markers across the five domains received 1 point if it fell in the top quartile or the participant was on related medication, and the points were summed (range 0-16).
- Cerebral free water (FW):**
  - DTI was used to measure extracellular water content.
  - FW is the average white matter voxels of water diffusing freely.
- Cognition:**
  - We used two neuropsychological tests to examine cognition at both visits<sup>4,5</sup>.
    - Brief Spanish-English Verbal Learning Test (B-SEVLT; trials 1-3 [immediate recall] and delayed recall): Assesses episodic memory (EM). Immediate recall captures initial encoding and learning capacity and delayed recall evaluates memory consolidation and retention.
    - Word Fluency Test (WF; Letter A and Letter F): Assesses working memory (WM) through phonemic verbal fluency by asking participants to name as many words as they can in 60 seconds starting with A or F.
- Statistical Analysis:**
  - Aim I:** Multivariable regression analyses
    - Model: AL → FW in the overall group and by heritage<sup>6</sup>.
  - Aim II:** Confirmatory factor analysis to test for latent cognitive domain at visits 1 (V1) and 2 (V2).
  - Path analysis of AL and latent cognitive domain at visits 1 and 2.
  - All analyses were performed in R version 4.5 and Mplus version 8.6<sup>7</sup>.
  - Covariates: Models were adjusted for age, sex, education, income, heritage, field center, language, years in the US, cigarette use, alcohol use, physical activity, diet quality, depressive symptoms, and doctor visit frequency as a measure of fluctuating health and access to healthcare. Models with FW were also adjusted for DTI b-values.

## Results

Table 1. Participant characteristics by heritage groups.

| Characteristic                       | Mexican (n=956) | Dominican (n=210) | Central/South American (n=488) | Cuban (n=357)  | Puerto Rican (n=377) | Other (n=54)   | Total (N=2442) |
|--------------------------------------|-----------------|-------------------|--------------------------------|----------------|----------------------|----------------|----------------|
| Age at baseline (years)              | 51.5 (8.74)     | 51.0 (9.07)       | 52.6 (8.58)                    | 52.3 (8.95)    | 52.6 (9.56)          | 51.1 (8.30)    | 52.0 (8.90)    |
| Sex (Female)                         | 654 (68.4%)     | 162 (77.1%)       | 341 (69.9%)                    | 209 (58.5%)    | 242 (64.2%)          | 32 (59.3%)     | 1640 (67.2%)   |
| Annual household Income (< \$30,000) | 576 (60.3%)     | 149 (71.0%)       | 341 (69.9%)                    | 251 (70.3%)    | 252 (66.8%)          | 29 (53.7%)     | 1598 (65.4%)   |
| Education (> HS)                     | 198 (20.7%)     | 44 (21.0%)        | 103 (21.1%)                    | 93 (26.1%)     | 102 (27.1%)          | 7 (13.0%)      | 547 (22.4%)    |
| Language preference (Spanish)        | 868 (90.8%)     | 191 (91.0%)       | 471 (96.5%)                    | 345 (96.6%)    | 198 (52.5%)          | 43 (79.6%)     | 2116 (86.7%)   |
| Years in the US                      | 24.4 (14.4)     | 20.1 (12.8)       | 18.7 (10.6)                    | 13.6 (12.8)    | 40.7 (13.4)          | 26.8 (15.4)    | 23.9 (15.5)    |
| B-SEVLT Trials 1-3 (V1)              | 24.1 (5.38)     | 23.5 (5.28)       | 24.0 (5.59)                    | 22.8 (5.24)    | 22.2 (5.77)          | 25.4 (6.86)    | 23.6 (5.54)    |
| B-SEVLT Delayed Recall (V1)          | 9.27 (2.64)     | 7.88 (2.77)       | 9.17 (2.69)                    | 8.31 (2.41)    | 8.06 (2.97)          | 9.13 (3.11)    | 8.81 (2.74)    |
| Word Fluency A (V1)                  | 9.77 (4.07)     | 8.49 (3.48)       | 9.71 (3.88)                    | 9.53 (3.67)    | 8.75 (3.80)          | 9.71 (4.62)    | 9.46 (3.92)    |
| Word Fluency F (V1)                  | 10.2 (4.23)     | 8.06 (3.60)       | 9.56 (3.66)                    | 9.03 (3.65)    | 9.26 (3.83)          | 10.0 (4.19)    | 9.59 (3.98)    |
| B-SEVLT Trials 1-3 (V2)              | 24.1 (5.39)     | 22.2 (5.53)       | 24.8 (5.65)                    | 24.6 (5.72)    | 21.4 (5.62)          | 24.4 (6.18)    | 23.7 (5.68)    |
| B-SEVLT Delayed Recall (V2)          | 9.01 (2.94)     | 7.95 (2.29)       | 9.25 (2.89)                    | 8.65 (3.03)    | 7.53 (2.87)          | 8.76 (3.23)    | 8.68 (2.96)    |
| Word Fluency A (V2)                  | 9.67 (3.96)     | 8.32 (4.70)       | 9.28 (3.88)                    | 9.33 (3.60)    | 9.43 (4.48)          | 9.49 (3.94)    | 9.39 (4.05)    |
| Word Fluency F (V2)                  | 9.04 (3.99)     | 8.12 (4.00)       | 9.18 (3.76)                    | 9.26 (3.82)    | 8.76 (4.03)          | 9.82 (3.71)    | 9.00 (3.93)    |
| Allostatic Load Score                | 4.18 (2.82)     | 4.08 (2.72)       | 3.97 (2.78)                    | 4.61 (2.90)    | 4.87 (3.03)          | 5.17 (3.05)    | 4.32 (2.87)    |
| Free Water                           | 0.199 (0.0339)  | 0.204 (0.0399)    | 0.208 (0.0335)                 | 0.216 (0.0379) | 0.217 (0.0415)       | 0.208 (0.0368) | 0.207 (0.0370) |

Note. Values for AL, FW, cognitive battery, age and years in the US represent the mean (SD). All other variables are presented as n (%).

Table 2. Allostatic load index composed of 16 biological markers.

| Physiological Domains             | Biological Markers                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cardiometabolic/ lipid metabolism | <ul style="list-style-type: none"><li>Body mass index</li><li>Waist-to-hip ratio</li><li>Serum triglycerides</li><li>Fasting level of high-density lipoprotein cholesterol</li><li>Fasting level of low-density lipoprotein cholesterol</li><li>Fasting plasma glucose</li><li>Blood glycosylated hemoglobin</li></ul> |
| Glucose metabolism                | <ul style="list-style-type: none"><li>Homeostatic model assessment of insulin resistance</li></ul>                                                                                                                                                                                                                     |
| Cardiopulmonary                   | <ul style="list-style-type: none"><li>Systolic blood pressure</li><li>Resting pulse pressure</li><li>Resting heart rate</li><li>Lung function</li></ul>                                                                                                                                                                |
| Parasympathetic                   | <ul style="list-style-type: none"><li>Square root of the mean squared difference of successive ECG NN intervals</li><li>Standard deviation of NN intervals</li></ul>                                                                                                                                                   |
| Inflammation                      | <ul style="list-style-type: none"><li>High-sensitivity C-reactive protein</li><li>Total white blood cell count</li></ul>                                                                                                                                                                                               |

Note. ECG: electrocardiogram; NN: normal-to-normal interval.

- Aim I:**
  - Overall group:** Higher AL was associated with greater FW -10 years later ( $\beta=0.0014$ , SE = 0.00022,  $p < .001$ ; *Figure 1*).
  - By heritage group:** Higher AL was associated with greater FW -10 years later in Mexican, Dominican, Central/South American, and Cuban adults, but not in Puerto Rican adults (see *Table 3*).
  - Post-hoc analyses:** Mean AL differed across heritage groups ( $p < .001$ ) and was highest among Puerto Rican adults of the defined heritage groups (*Figure 2*); Tukey-HSD confirmed significantly elevated AL in Puerto Rican relative to Mexican, Dominican, and Central/South American adults. Notably, Puerto Rican adults showed the weakest AL-FW coupling despite carrying the greatest allostatic burden.

Table 3. Effect of allostatic load on free water by heritage.

| Heritage               | Estimate | Std. Error | P-value               |
|------------------------|----------|------------|-----------------------|
| Mexican                | 0.0015   | 0.0003     | $1.67 \times 10^{-5}$ |
| Dominican              | 0.0024   | 0.0009     | $8.88 \times 10^{-3}$ |
| Central/South American | 0.0013   | 0.0005     | $8.92 \times 10^{-3}$ |
| Cuban                  | 0.0022   | 0.0006     | $6.20 \times 10^{-4}$ |
| Puerto Rican           | 0.0008   | 0.0006     | $1.75 \times 10^{-1}$ |

## Results

- Aim II:**
  - The two-factor model (*Figure 3*) provided the best fit at V1 ( $\chi^2(31) = 119.32$ ,  $p < .001$ ; RMSEA = .037 (90% CI .030-.045); CFI = .975; TLI = .948; SRMR = .017) and V2 ( $\chi^2(31) = 99.05$ ,  $p < .001$ ; RMSEA = .033 (90% CI .026-.040); CFI = .982; TLI = .962; SRMR = .015).
  - Higher baseline AL was associated with poorer WM at V1 ( $\beta = -0.026$ , SE = 0.010,  $p = .008$ ) and V2 ( $\beta = -0.040$ , SE = 0.010,  $p < .008$ ).
  - We did not observe significant associations of AL with EM V1 ( $\beta = -0.002$ , SE = 0.009,  $p = .835$ ) and V2 ( $\beta = -0.011$ , SE = 0.009,  $p = .207$ ).

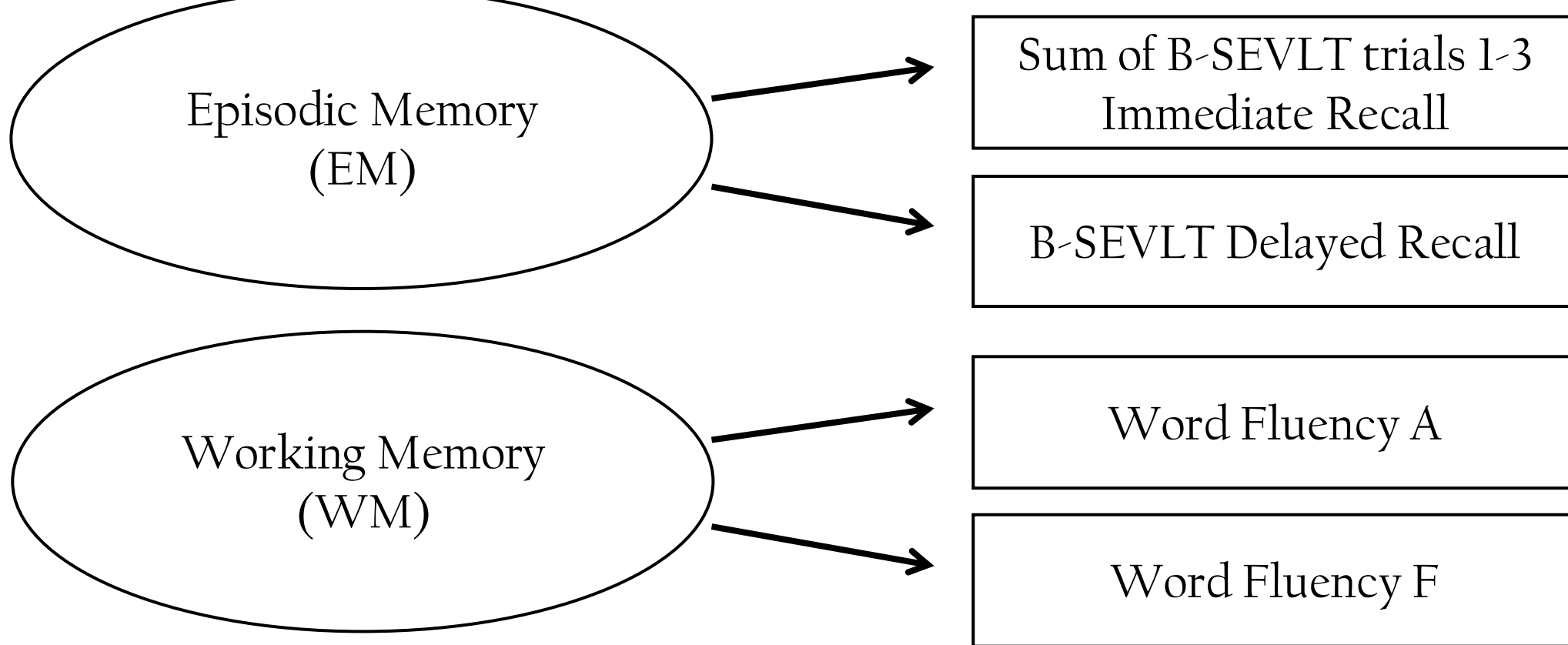


Figure 3. CFA of Cognitive Domains

## Discussion

- Higher AL was significantly associated with greater FW (-10 years later), suggesting that AL is a sensitive early marker that may capture upstream, stress-related mechanisms and potentially predict early vascular changes.
- AL was significantly associated with poorer WM but not EM, consistent with previous work<sup>2</sup>. AL may act through vascular and inflammatory pathways affecting frontal-subcortical white matter<sup>2</sup> supporting our WM findings, whereas EM depends more on medial-temporal regions vulnerable to AD-specific pathology, such as amyloid and tau, that AL may not capture.
- Future work will leverage longitudinal data to model AL trajectories and test FW as a mediator of future WM and EM.

## References

- Kaestner et al., Social Science Quarterly, 90(5), 2009.
- Estrella et al., Journal of Alzheimer's Disease, 99(3), 2024.
- Maillard et al., Neurology, 92(19), 2019.
- González et al., Archives of Clinical Neuropsychology, 30, 2015.
- Sapkota et al., Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 16, 2024.
- Salazar et al., SSM-Population Health, 2, 2016.
- Muthén & Muthén, Mplus User's Guide (8th ed.), 2017.

## Acknowledgements and Funding

We acknowledge all participants in this study and staff who support this effort. This study was supported by grants RF1 AG054548,R56 AG048642,R01 AG075758,R01 AG083894.

## Contact

camoreno@health.ucdavis.edu

