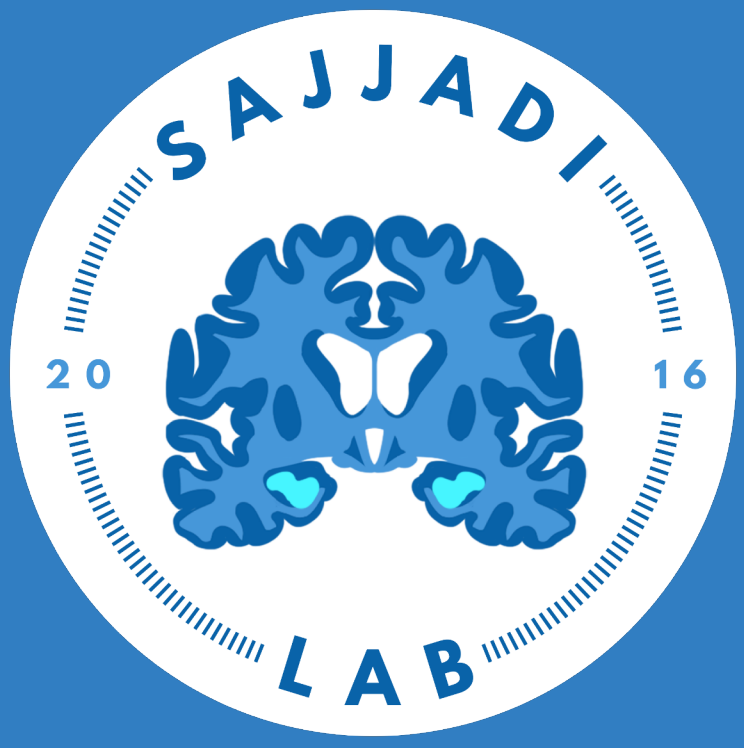


# Association of Aging-Related Tau Astrogliopathy to Neuropathologies and Demographics in the Oldest-Old

Katherine M. O'Donnell<sup>1</sup>, Davis C. Woodworth<sup>1</sup>, Brittany N. Dugger<sup>2</sup>, La Rissa Vasquez<sup>2</sup>, Syed A. Bukhari<sup>3</sup>, Claudia H. Kawas<sup>1</sup>, Maria M. Corrada<sup>1</sup>, Thomas J. Montine<sup>3</sup>, and S. Ahmad Sajjadi<sup>1</sup>

<sup>1</sup>University of California, Irvine. <sup>2</sup>University of California, Davis. <sup>3</sup>Stanford University



## Background

- **Aging-related Tau Astrogliopathy (ARTAG)** is a 4R tauopathy associated with greater age
- How ARTAG fits in with other neuropathologic changes (NC) is still not well understood
- **Study Aims:** In an oldest-odl cohort:
  - **Characterize the frequency of ARTAG**
  - **Examine how ARTAG features are associated with common aging-related NCs.**

## Methods

- Neuropathology data from *The 90+ Study* (N = 454)
- ARTAG Classification (predictors):
  - Severity: None, Occasional, Numerous
  - Region: MTL, Lobar, Subcortical
  - Tissue Subtype: White Matter (WM), Gray Matter (GM), Subpial, Subependymal
- Other NCs (outcomes):
  - Ordinal: ADNC, LATE-NC, CAA, arteriolosclerosis, atherosclerosis
  - Binary: Hippocamoal sclerosis of aging (HS-A), infafcts, Lewy bodies, microvascular lesions (MVLs)
- Statistical Analyses:
  - Ordinal or binary logistic regressions
  - Ajusted for age at death, sex, and education

| Characteristic                  | Overall<br>N = 454 <sup>1</sup> | ARTAG Severity    |                         |                       | P-<br>value <sup>2</sup> |
|---------------------------------|---------------------------------|-------------------|-------------------------|-----------------------|--------------------------|
|                                 |                                 | None <sup>1</sup> | Occasional <sup>1</sup> | Numerous <sup>1</sup> |                          |
| Age at Death                    | 97.5 (95.1, 100.0)              | 96.7 (94.1, 99.0) | 98.0 (95.7, 100.4)      | 98.2 (95.9, 100.4)    | 0.002                    |
| Gender (Female)                 | 306 (67%)                       | 129 (72%)         | 156 (68%)               | 21 (48%)              | 0.010                    |
| Education Level (College+)      | 230 (51%)                       | 85 (47%)          | 119 (52%)               | 26 (59%)              | 0.3                      |
| APOE Genotype 4                 | 84 (20%)                        | 37 (23%)          | 42 (19%)                | 5 (12%)               | 0.3                      |
| ADNC (Intermediate/High)        | 324 (71%)                       | 126 (70%)         | 166 (72%)               | 32 (73%)              | 0.9                      |
| LATE-NC (Hipp/Cortex)           | 139 (31%)                       | 37 (21%)          | 83 (36%)                | 19 (43%)              | <0.001                   |
| HS-A                            | 59 (13%)                        | 16 (8.9%)         | 32 (14%)                | 11 (25%)              | 0.015                    |
| CAA (Mod/Severe)                | 190 (42%)                       | 81 (45%)          | 93 (40%)                | 16 (36%)              | 0.5                      |
| Arteriolosclerosis (Mod/Severe) | 253 (56%)                       | 103 (57%)         | 130 (57%)               | 20 (45%)              | 0.3                      |
| Atherosclerosis (Mod/Severe)    | 177 (39%)                       | 77 (43%)          | 84 (37%)                | 16 (36%)              | 0.4                      |
| MVL (2/3)                       | 111 (24%)                       | 39 (22%)          | 58 (25%)                | 14 (32%)              | 0.3                      |
| Infarct (2/3)                   | 71 (16%)                        | 23 (13%)          | 40 (17%)                | 8 (18%)               | 0.4                      |
| LB Braak Stage (IV/V/VI)        | 65 (14%)                        | 27 (15%)          | 29 (13%)                | 9 (20%)               | 0.4                      |
| Lewy Body (Amygdala)            | 93 (20%)                        | 33 (18%)          | 46 (20%)                | 14 (32%)              | 0.13                     |
| All Potential PART              | 111 (24%)                       | 42 (23%)          | 58 (25%)                | 11 (25%)              | >0.9                     |
| Definite PART                   | 42 (9.3%)                       | 14 (7.8%)         | 22 (9.6%)               | 6 (14%)               | 0.4                      |
| Potential PART                  | 69 (15%)                        | 28 (16%)          | 36 (16%)                | 5 (11%)               | 0.8                      |

<sup>1</sup> Median (Q1, Q3); n (%)

<sup>2</sup> Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

**Table-1. Participant characteristics by ARTAG severity.**

- **Participant characteristics (Table-1)**
  - Average age at death of 97.5 years
  - Around half of participants (57%) had ARTAG
  - ARTAG strongly related to age
  - ARTAG more common in men
- **ARTAG regional co-occurrence (Fig-1)**
  - Within participants with ARTAG, MTL was the most common (87%), followed by Lobar (51%)
  - Within participants with ARTAG, subpial was the most common (44%), followed by WM (35%), GM (28%), and subependymal (14%)
  - Varying degrees of overlap in ARTAG subtypes
- **Regression results (Fig-2)**
  - LATE-NC was strongly associated with ARTAG:
    - Severity in a dose-dependent fashion
    - Both MTL and lobar
    - WM subtype specifically
  - Lobar ARTAG associated with ADNC
  - MTL ARTAG associated with HS-A and Amyg LB

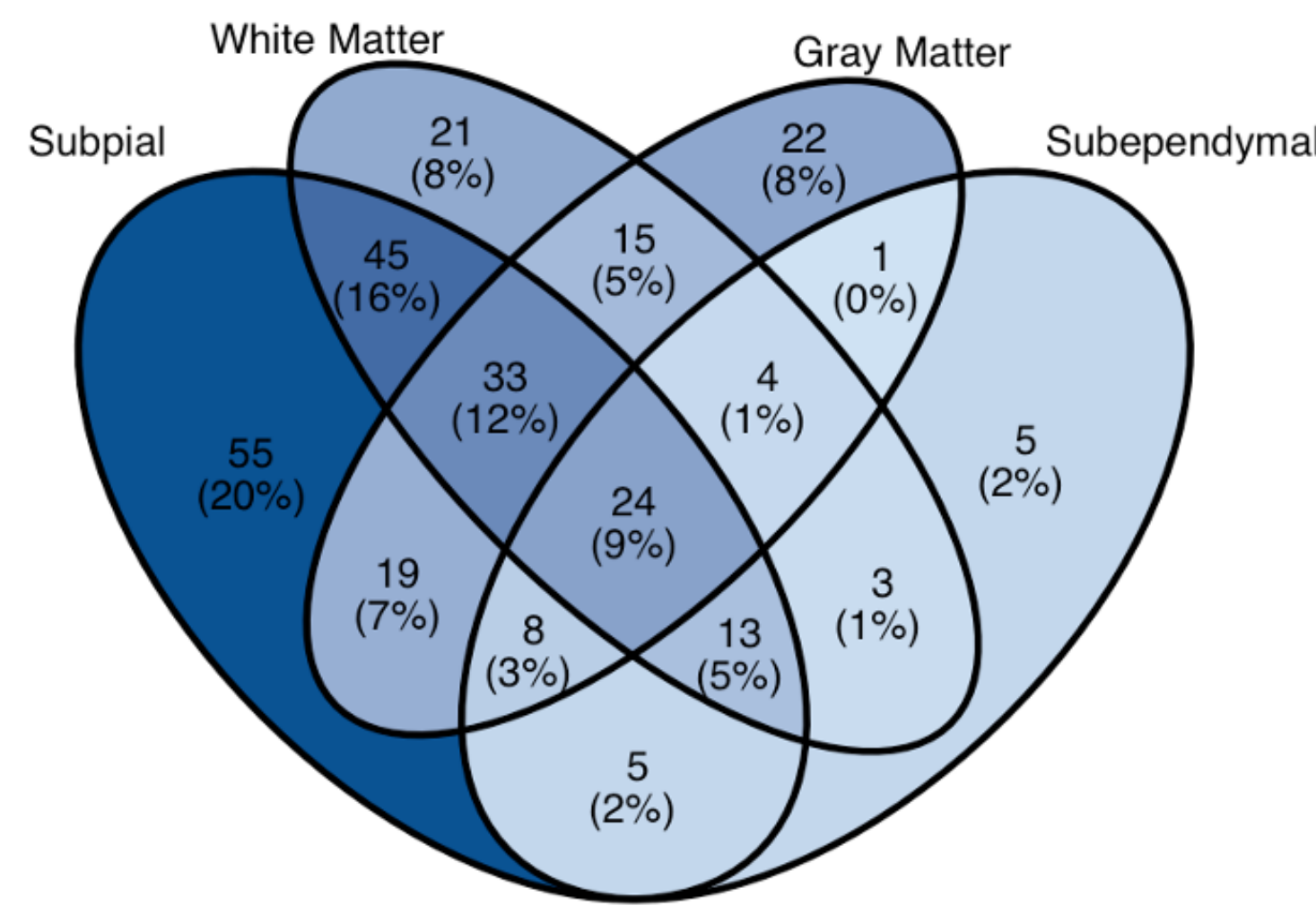


**Fig-1. ARTAG subtypes frequency, across all regions (within participants with ARTAG, n=274)**

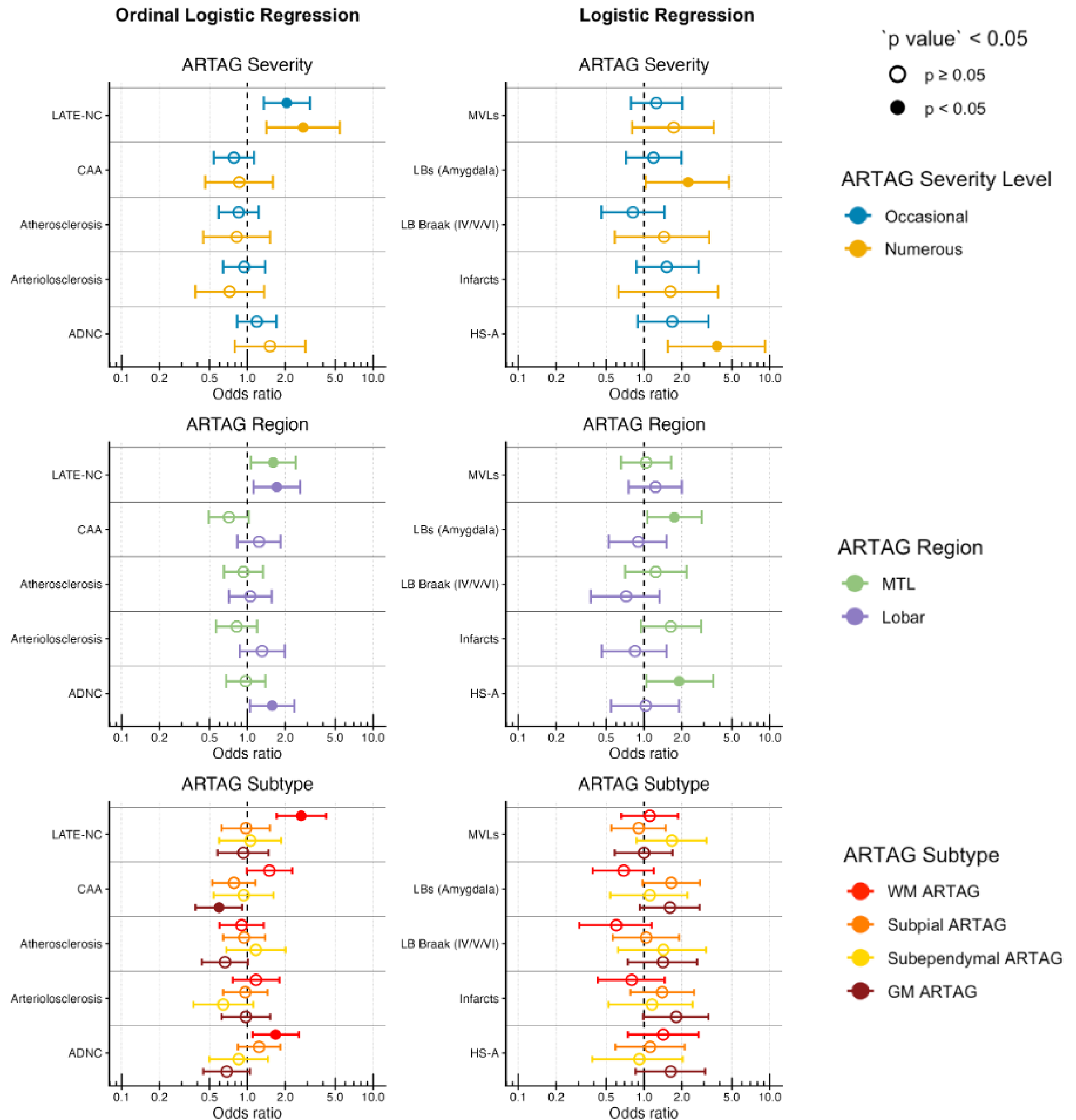


**Fig-2. Results from regression models**

## Discussion

- Even in this Oldest-Old cohort, ARTAG is highly prevalent with increasing age and the male sex, both in presence and in severity
- The strong association of LATE-NC to multiple ARTAG features (severity, region, and WM subtype) may suggest shared upstream factors
- Diverging, region-specific links (MTL vs Lobar association differences) could implicate that ARTAG may interact distinctively with localized co-pathologies like ADNC, HS-A, and Amygdala LBs

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