

# Influence of Demographic and Health Factors on Clinical Vulnerability or Resilience to Amyloid Pathology Assessed by Plasma p-tau217

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Amyloid plaques do not always lead to clinical Alzheimer’s disease (AD), and understanding the factors behind this discordance is essential for improving risk prediction and guiding personalized prevention strategies. The emergence of blood-based biomarkers has revolutionized the ability to detect AD pathology in a scalable and accessible manner. Among these, p-tau217 has distinguished itself as one of the most sensitive and specific markers for AD pathology. Identifying demographic and health characteristics that contribute to these differences in resilience and vulnerability is important for clarifying why the clinical presentation of AD varies across the population.

## Aims

- Utilize plasma p-tau217 as a surrogate indicator of underlying AD pathology to investigate the factors influencing clinical outcomes
- Examine how demographic and health characteristics influence AD risk across participants stratified by pathological status (low vs. high p-tau217), including those with discordance between plasma p-tau217–based amyloid status and clinical presentation.

## Methodology

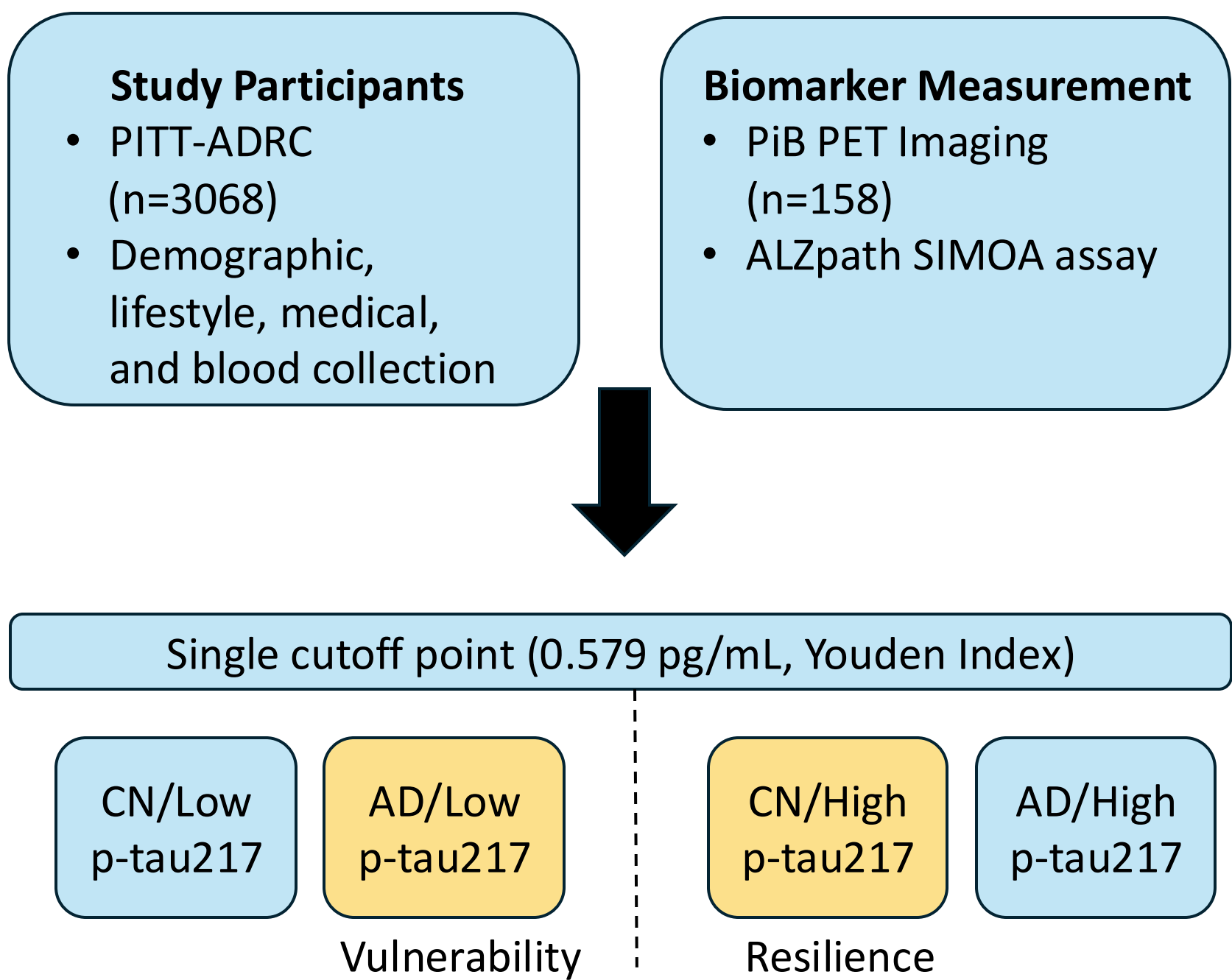


Figure 1. Flow diagram of research methods

## Conclusion

### Vulnerability Profile (AD+/Low p-tau217)

- Discordant AD+ individuals represent a high-vulnerability phenotype, where multiple risk factors compensate for or act independently of measurable tau pathology to produce clinical disease.

### Resilience Profile (CN/High p-tau217)

- These individuals may tolerate greater underlying pathology (elevated p-tau217) without manifesting clinical symptoms, reflecting protective effects of reserve and lower comorbidity burden.

## Results

Table 1. Cohort characteristics across four groupings

| Total cohort size: N = 3068       |                             |                             |         |                              |                               |         |
|-----------------------------------|-----------------------------|-----------------------------|---------|------------------------------|-------------------------------|---------|
| Characteristic                    | p-tau217 Low                |                             |         | p-tau217 High                |                               |         |
|                                   | CN / Low (Concordant) N=671 | AD / Low (Discordant) N=381 | p-value | CN / High (Discordant) N=199 | AD / High (Concordant) N=1817 | p-value |
| <b>Demographics / Genetics</b>    |                             |                             |         |                              |                               |         |
| Age                               | 67.5 [11.8] N=671           | 75.8 [11.1] N=381           | <0.001  | 72.2 [11.9] N=199            | 76 [11.5] N=1817              | <0.001  |
| Education                         | 16 [5] N=671                | 12 [4] N=381                | <0.001  | 16 [5] N=199                 | 12 [4] N=1817                 | <0.001  |
| APOE ε4 carrier                   |                             |                             | <0.001  |                              |                               | <0.001  |
| APOE ε4 positive                  | 190/666 (28.5%)             | 155/379 (40.9%)             |         | 96/195 (49.2%)               | 1120/1803 (62.1%)             |         |
| Race                              |                             |                             | 0.136   |                              |                               | 0.145   |
| NHW                               | 550/666 (82.6%)             | 325/377 (86.2%)             |         | 179/198 (90.4%)              | 1687/1810(93.2%)              |         |
| B/AA                              | 116/666 (17.4%)             | 52/377 (13.8%)              |         | 19/198 (9.6%)                | 123/1810 (6.8%)               |         |
| Sex                               |                             |                             | 0.046   |                              |                               | 0.139   |
| Female                            | 437/671 (65.1%)             | 224/381 (58.8%)             |         | 119/199 (59.8%)              | 1183/1817 (65.1%)             |         |
| Male                              | 234/671 (34.9%)             | 157/381 (41.2%)             |         | 80/199 (40.2%)               | 634/1817 (34.9%)              |         |
| <b>Lifestyle</b>                  |                             |                             |         |                              |                               |         |
| Smoke Years                       | 15 [20] N=132               | 22.5 [24] N=76              | <0.001  | 25 [17.8] N=56               | 20 [28] N=375                 | 0.825   |
| Alcohol Frequency                 | 35/107 (32.7%)              | 5/23 (21.7%)                | 0.455   | 14/46 (30.4%)                | 83/197 (42.1%)                | 0.181   |
| Alcohol Occasions                 | 107/160 (66.9%)             | 23/50 (46%)                 | 0.012   | 46/63 (73%)                  | 200/393 (50.9%)               | 0.001   |
| Packs Per Day                     | 44/132 (33.3%)              | 25/74 (33.8%)               | 1       | 23/56 (41.1%)                | 129/375 (34.4%)               | 0.369   |
| Tobacco <30 Days                  | 9/379 (2.4%)                | 9/179 (5%)                  | 0.123   | 5/135 (3.7%)                 | 48/1037 (4.6%)                | 0.826   |
| <b>Metabolics</b>                 |                             |                             |         |                              |                               |         |
| BMI                               | 27.3 [7.9] N=397            | 27.6 [7.1] N=178            | 0.467   | 27.3 [5.6] N=131             | 26.1 [6] N=1027               | 0.004   |
| Diastolic BP                      | 80 [14] N=403               | 80 [14] N=186               | 0.924   | 80 [12] N=138                | 80 [12] N=1067                | 0.438   |
| Height                            | 65 [5] N=397                | 64.5 [5.5] N=178            | 0.055   | 65 [5.2] N=132               | 64 [5] N=1029                 | 0.004   |
| Systolic BP                       | 138 [26] N=403              | 140 [22] N=186              | 0.034   | 138 [22] N=138               | 140 [23] N=1067               | 0.407   |
| Weight                            | 166 [55.5] N=403            | 164 [48.8] N=182            | 0.095   | 171 [51] N=135               | 154 [46] N=1051               | <0.001  |
| <b>Medical Conditions</b>         |                             |                             |         |                              |                               |         |
| Active depression in last 2 years | 89/386 (23.1%)              | 78/181 (43.1%)              | <0.001  | 20/135 (14.8%)               | 440/1043 (42.2%)              | <0.001  |
| Anxiety                           | 23/160 (14.4%)              | 15/50 (30%)                 | 0.019   | 13/63 (20.6%)                | 108/395 (27.3%)               | 0.286   |
| B12 deficiency                    | 22/387 (5.7%)               | 13/182 (7.1%)               | 0.575   | 12/135 (8.9%)                | 70/1039 (6.7%)                | 0.368   |
| Depression episodes >2 years ago  | 105/384 (27.3%)             | 40/180 (22.2%)              | 0.215   | 33/135 (24.4%)               | 197/1025 (19.2%)              | 0.168   |
| Diabetes                          | 28/387 (7.2%)               | 33/182 (18.1%)              | <0.001  | 18/136 (13.2%)               | 114/1045 (10.9%)              | 0.389   |
| Hypercholesterolemia              | 189/387 (48.8%)             | 96/181 (53%)                | 0.369   | 81/135 (60%)                 | 586/1042 (56.2%)              | 0.46    |
| Hypertension                      | 153/387 (39.5%)             | 92/182 (50.5%)              | 0.014   | 72/136 (52.9%)               | 511/1046 (48.9%)              | 0.412   |
| Incontinence - bowel              | 0/387 (0%)                  | 12/182 (6.6%)               | <0.001  | 2/136 (1.5%)                 | 37/1045 (3.5%)                | 0.305   |
| Incontinence - urinary            | 22/387 (5.7%)               | 31/181 (17.1%)              | <0.001  | 9/136 (6.6%)                 | 138/1045 (13.2%)              | 0.027   |
| Stroke                            | 14/386 (3.6%)               | 21/182 (11.5%)              | <0.001  | 6/136 (4.4%)                 | 50/1043 (4.8%)                | 1       |
| TBI                               | 28/158 (17.7%)              | 12/50 (24%)                 | 0.502   | 13/63 (20.6%)                | 77/390 (19.7%)                | 0.89    |
| Thyroid disease                   | 68/387 (17.6%)              | 27/181 (14.9%)              | 0.471   | 30/136 (22.1%)               | 214/1042 (20.5%)              | 0.654   |

Continuous variables are presented as median [IQR] with available sample size (N). Categorical variables are presented as n/N (%), where N excludes missing and unknown values. P values compare CN vs AD within each p-tau217 group using Wilcoxon rank-sum tests for continuous variables and Fisher’s exact tests for categorical variables.

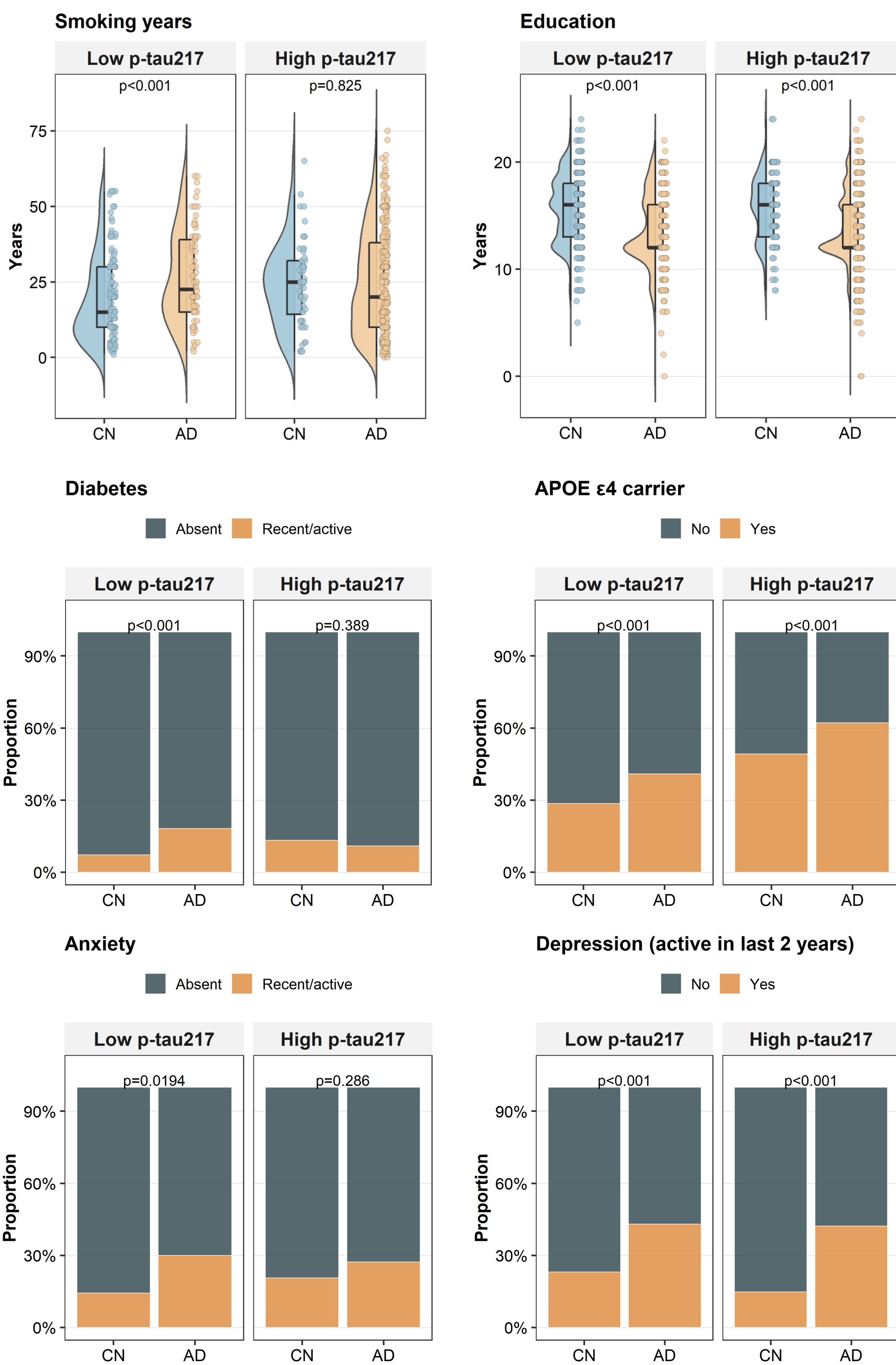
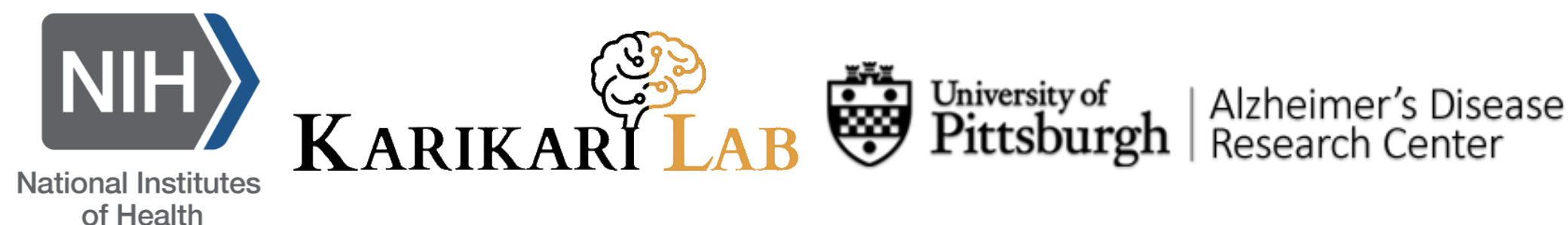


Figure 2. Factors with significant effect on vulnerability and/or resilience against Aβ pathology. Continuous features (smoking years and education) are displayed using half-violin plots with boxplots and points. Categorical features (diabetes, APOE carrier, anxiety, and active depression) are displayed using proportions. Within low and high p-tau217 groups, comparisons between CN and AD groups are preformed separately and reflected with p-values (Wilcoxon test for continuous variables; Fisher’s exact test for categorical variables).

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## References

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