

Correlation of Plasma Biomarkers With Amyloid and Tau PET in Normal, Subjective Cognitive Decline, and Mild-Cognitive Impairment Subjects

Allal Boutajangout¹, Arjun V. Masurkar², Ricardo S. Osorio², Ludovic Debure¹, MobeenaGhuman¹, Wajiha Ahmed¹, Alok Vedvyas¹, Elizabeth Pirraglia^{3,4}, Jon Links², Louisa Bokacheva², Brianna Vega², Mark A. Bernard², Karyn Marsh¹, Omonigho M Bubus⁵, Joshua Chodosh⁶, Yongzhao Shao³, Henry Rusinek⁷, Thomas Wisniewski¹

(1)NYU Alzheimer's Disease Research Center, New York, NY, USA, (2)NYU Grossman School of Medicine, New York, NY, USA, (3)Center for Cognitive Neurology, New York, NY, USA, (4)Center for Cognitive Neurology, New York University Langone Health, New York, NY, USA, (5)Center for Sleep and Brain Health, Department of Psychiatry, NYU Langone Health, New York, NY, USA, (6)Department of Psychiatry, New York, NY, USA, (7)Department of Population Health, New York, NY, USA, (8)NYU Grossman School of Medicine, New York, NY, USA, (9)New York University Grossman School of Medicine, New York, NY, USA, (10)Alzheimer's Disease Research Center, New York University Langone Health, New York, NY, USA

Background

- Plasma biomarkers may allow efficient, less invasive methods to assess early-stage AD/ABRD. Moreover, they can canvas multiple processes, including inflammation, vascular disease, and blood-brain barrier (BBB) dysfunction. How they reflect cerebral amyloid and tau deposition remains an area of active exploration.
- The goal of this study is the identification of novel plasma biomarkers in Normal, SCD, and MCI subjects and assessing the correlation between plasma biomarkers and neuroimaging findings.

Methods

	Normal Cognition	Subjective Cognitive Decline	Mild Cognitive Impairment
Amyloid PET (N=186)	N=66 (female=59%)	N=100 (females=73%)	N=25 (female=68%)
Mean age on amyloid PET	71.6	75.5	73.6
Tau PET (N=144)	N=49 (female=59%)	N=78 (female=68%)	N=17 (female=65%)
Mean age on tau PET	71.6	75.4	75.1

Emerging AD Plasma Biomarkers using Single Molecule Analysis (SIMOA) Technology

Detection and dosage of biomarkers in bio-fluid samples (pg/ml sensitivity)

Neurology 4 Plex E Kit: - Aβ40 (4.3 Kda) - Aβ42 (4.5 Kda) - NfL (~70kDa) - GFAP (~50kDa)	Cytokine 10-Plex Kit IFN-γ, IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, TNFα
Angiogenesis 6-Plex Kit (hFGF (basic), hPIGF, hAng-2, hHB-EGF, hVEGF, and hHGF)	pTau181 V2 Kit pTau 181 V2

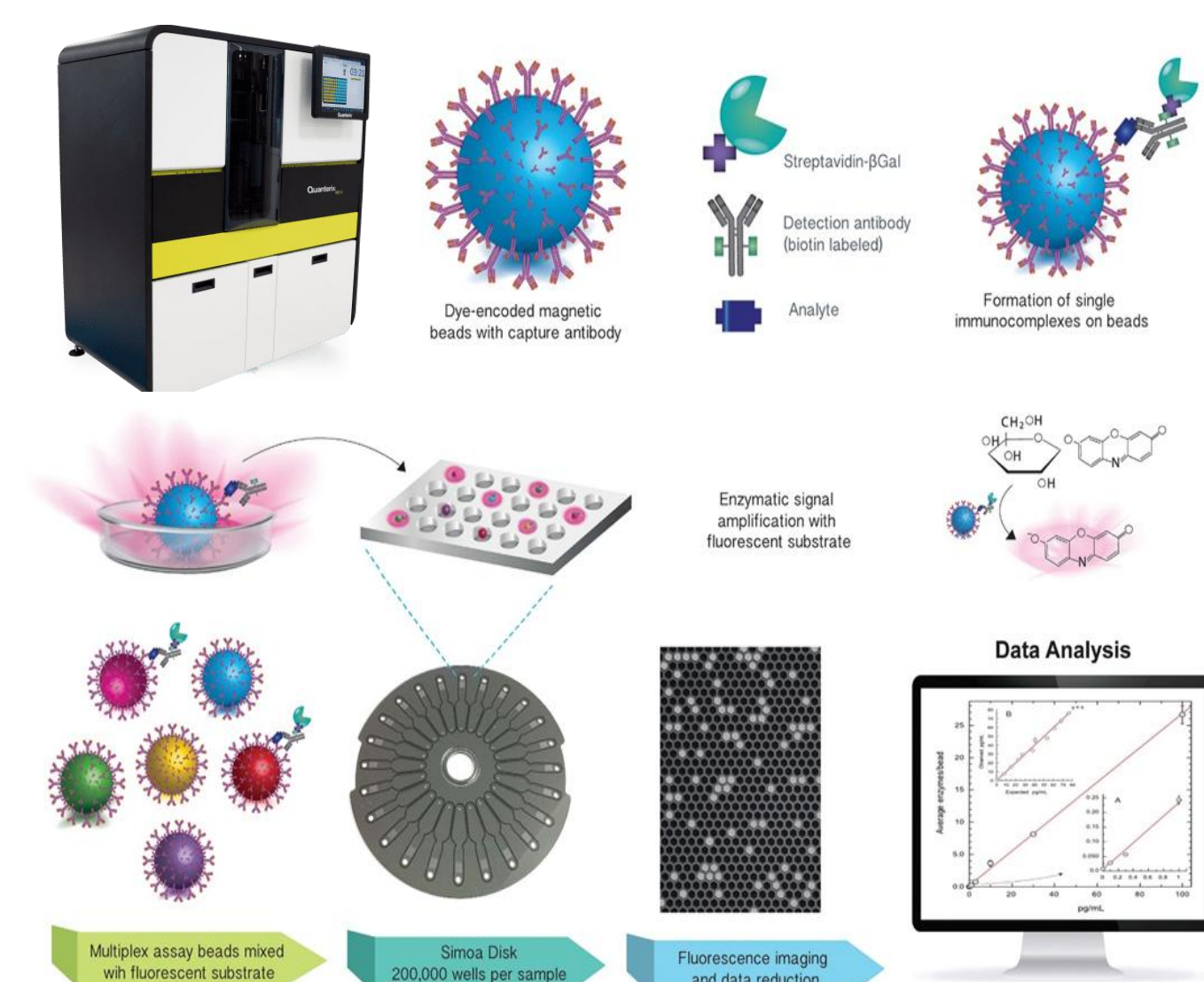


Figure 1: Aβ40, Aβ42, Neurofilament light (NFL), and Glial fibrillary acidic protein (GFAP) were measured using Neurology 4-Plex E kits. Neuroinflammation levels were measured using cytokine 10-Plex kits (IFN-γ, IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, TNFα), and BBB dysfunction was measured using angiogenesis 6-Plex kits (hFGF (basic), hPIGF, hAng-2, hHB-EGF, hVEGF, and hHGF). Phospho-tau181 was measured using the pTau181 V2 Kit.

Results

Plasma Aβ levels show trends between NL and MCI

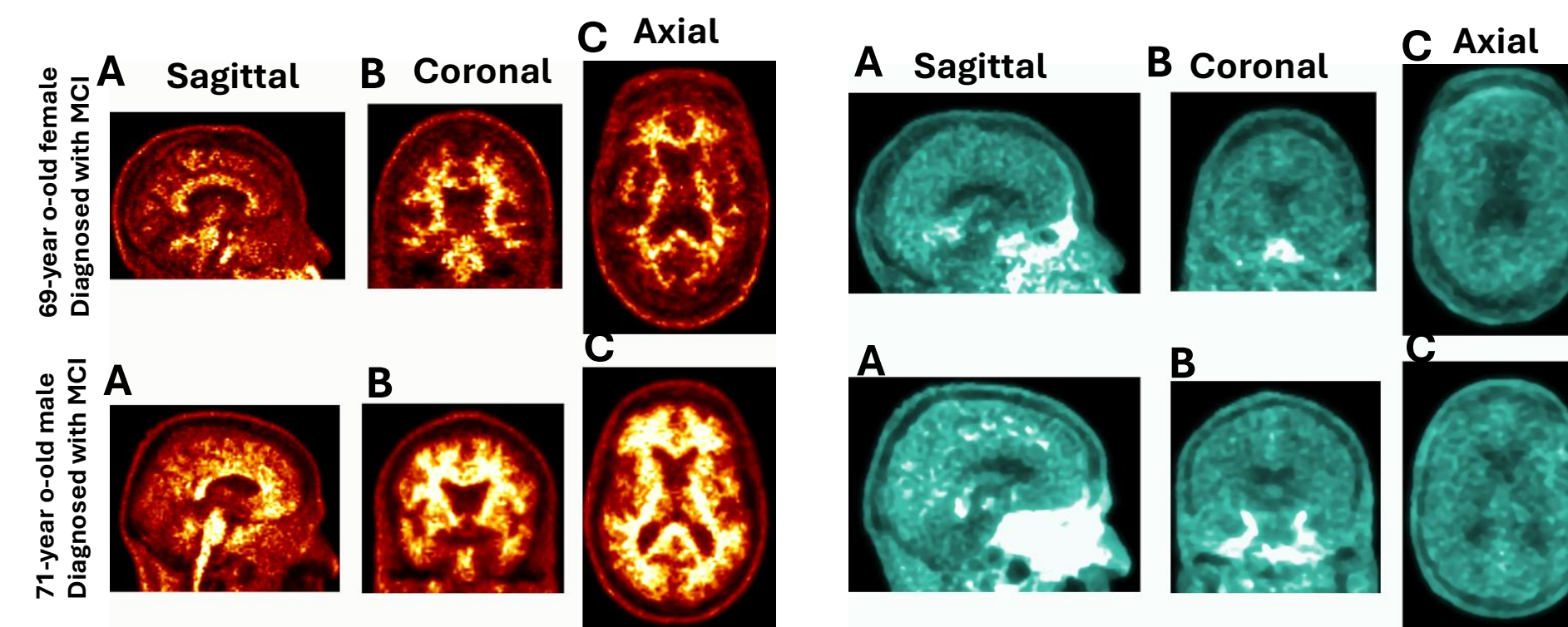


Figure 2: PET exams from two patients depicting the uptake of 18F-Florbetaben (FBB) tracer. Upper row: Figures 1 A, B, & C show sagittal, coronal, and axial sections from a 69-year-old female patient diagnosed with mild cognitive impairment, with an FBB global SUVR of 0.93. Lower row: Figures 1D, E, & F show scans from a 71-year-old male patient, with a global SUVR of 1.22. Note the generalized increase of tracer uptake in both patients, as is evident by the hotter colors seen throughout the cortical brain matter. White matter has some affinity to the tracer in normal brains, and that amount of tracer uptake was adjusted for in our calculations. Note the nonspecific tracer uptake in the mucosa, salivary glands, oral/nasal cavities, and nasopharynx of this lipophilic tracer.

Figure 3: 18F-MK6240 tau PET images from two patients. Upper row: Figures 2 A, B, & C show sagittal, coronal, and axial sections from a 69-year-old female patient (same patient as in Figure 1) diagnosed with mild cognitive impairment, with a global tau SUVR of 0.94. Lower row: Figures 2D, E, & F show scans from a 71-year-old male patient, with a global tau SUVR of 1.25. Note nonspecific tracer uptake in the mucosa, salivary glands, oral/nasal cavities, and nasopharynx of this lipophilic tracer

Significant results with pTau181 and pTau181/Aβ42 ratio

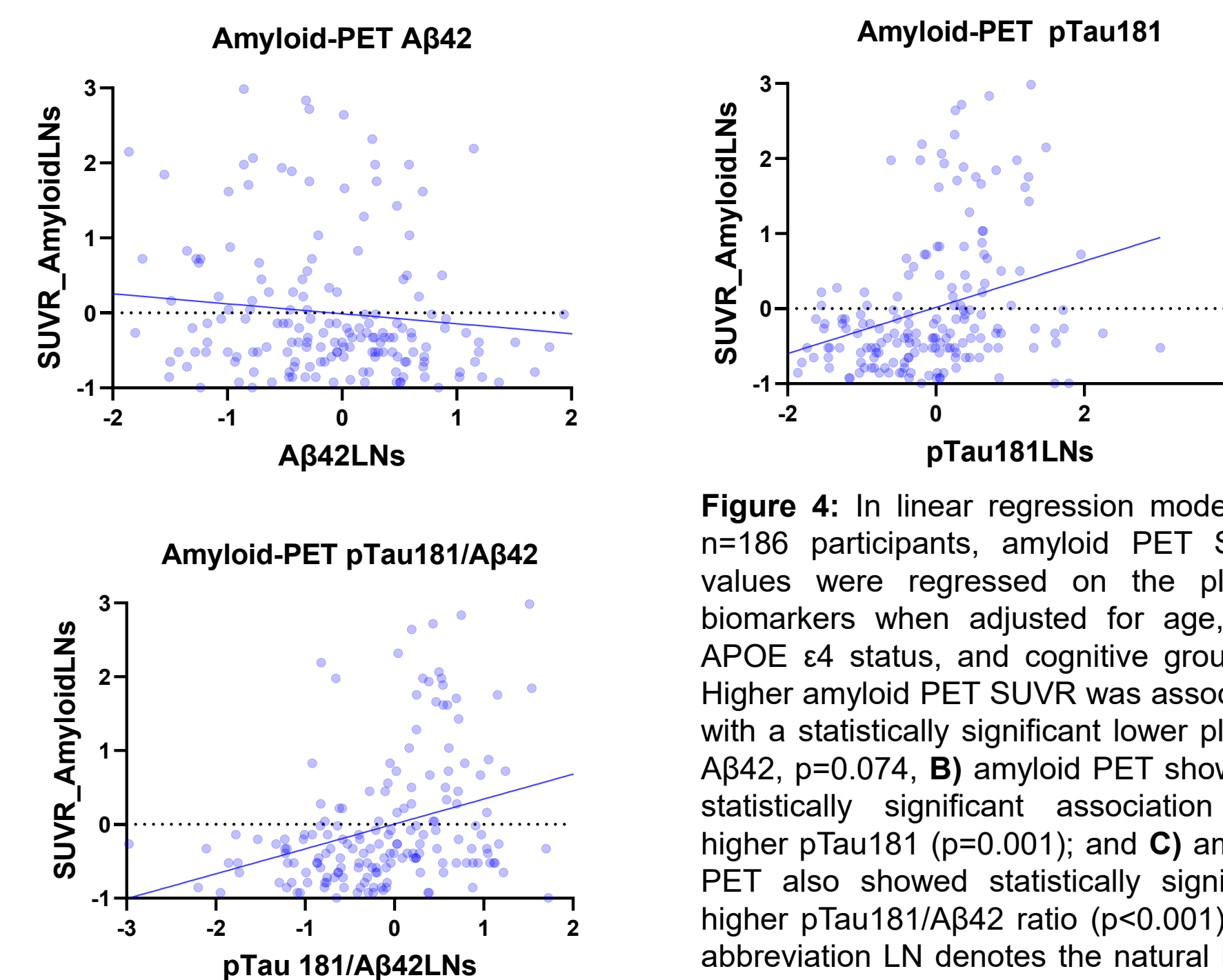


Figure 4: In linear regression models on n=186 participants, amyloid PET SUVR values were regressed on the plasma biomarkers when adjusted for age, sex, APOE ε4 status, and cognitive group. **A)** Higher amyloid PET SUVR was associated with a statistically significant lower plasma Aβ42, p=0.074, **B)** amyloid PET showed a statistically significant association with higher pTau181 (p=0.001); and **C)** amyloid PET also showed statistically significant higher pTau181/Aβ42 ratio (p<0.001). The abbreviation LNs denotes the natural log of Aβ42, and the natural log of pTau 181/Aβ42 ratios.

Significant association between tau PET and plasma Aβ42

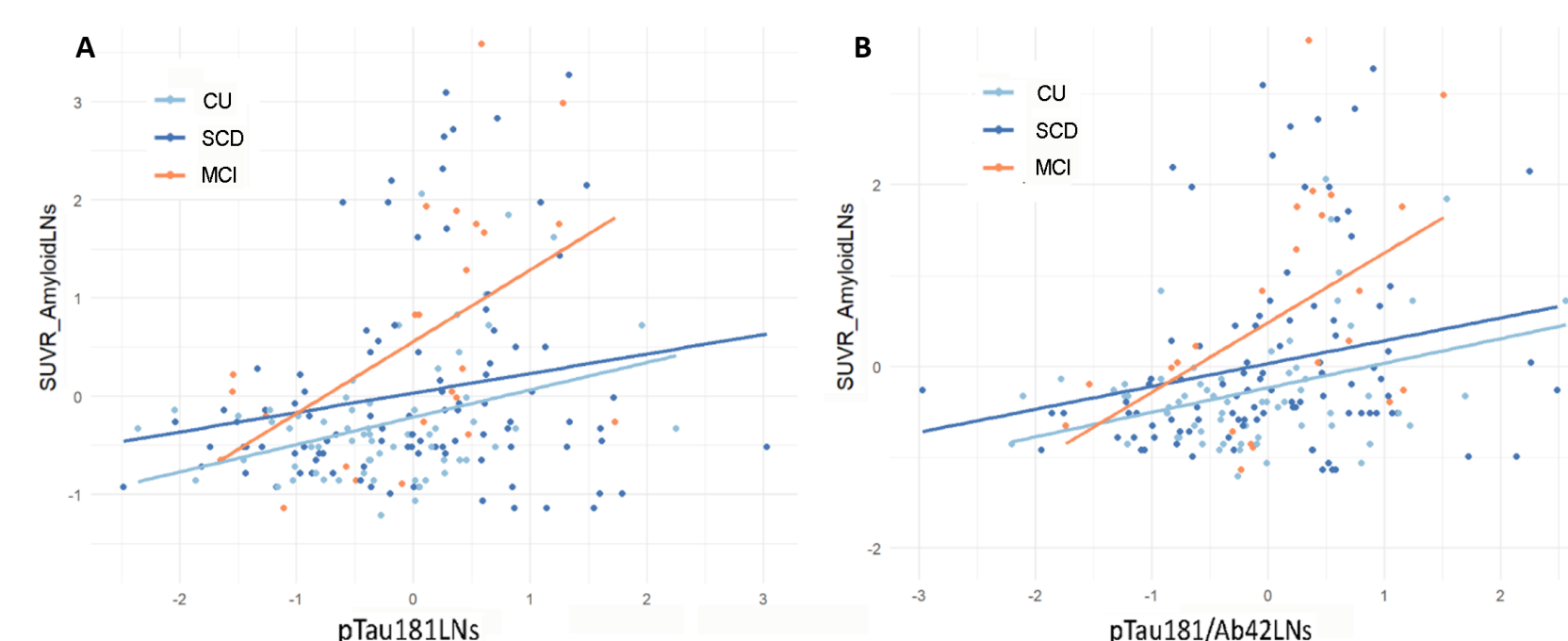


Figure 5: pTau181 amyloid PET SUVR (A) and pTau181/Aβ42 amyloid PET SUVR (B) interaction terms reveal trends (p=0.09 and p=0.06) for differential relationship across clinical groups. This is evidenced by the steepness of the slopes (orange trend lines) detailing the association between amyloid PET and plasma biomarkers in the MCI group. Note: the steeper the slope of the trend line, the stronger the association between plasma marker and PET imaging. The abbreviation LNs denotes the natural log of pTau 181 amyloid SUVR values and the natural log of pTau 181/Aβ42 ratios.

Significant difference with multiple cytokines

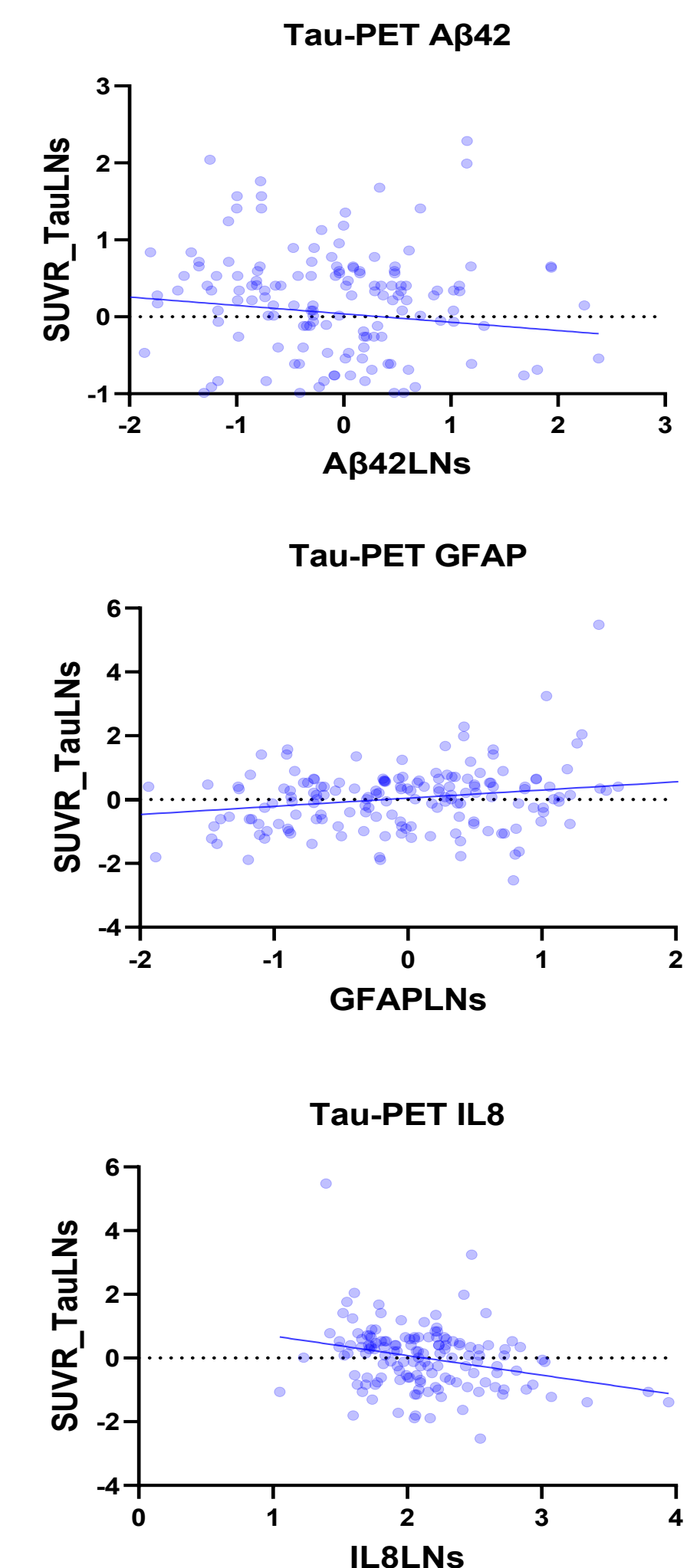


Figure 6: Tau PET Aβ42 showed a regression with plasma biomarkers when adjusted for age, sex, APOE ε4 status, and cognitive groups. **A)** Higher Tau PET SUVR showed trends with lower plasma Aβ42 (p=0.072). **B)** Higher tau PET uptake was associated with higher GFAP levels, p=0.020. **C)** Statistically significant low IL8 levels were observed, p<0.001. The abbreviation LNs denotes the natural log of Tau PET Aβ42 SUVR values, the natural log of GFAP, and the natural log of IL-8 levels

Conclusion

- Linear regression with adjustment for age, sex, and cognitive group showed trends of higher amyloid PET SUVR with lower plasma Aβ42 levels.
- Linear regression with adjustment for age, sex, and cognitive group showed a higher amyloid PET SUVR associated with higher pTau 181, and higher pTau 181/Aβ42 ratio.
- Higher tau PET SUVR was associated with lower Aβ42, higher GFAP, and lower IL-8 levels.

References

- Xue Wu, Zhenxu Xiao, Jingwei Yi, Saineng Ding, Hongchen Gu, Wanqing Wu, Jianfeng Luo, Xiaoni Liang, Li Zheng, Hong Xu, Qianhua Zhao and Ding Ding. Development of a Plasma Biomarker Diagnostic Model Incorporating Ultrasensitive Digital Immunoassay as a Screening Strategy for Alzheimer Disease in a Chinese Population. Clinical Chemistry. 1–12 (2021)
- Filippo Baldacci, Simone Lista, Maria Laura Manca, Patrizia A. Chiesa, Enrica Cavedo, Pablo Lemerrier, Henrik Zetterberg, Kaj Blennow, Marie-Odile Habert, Marie Claude Potier, Bruno Dubois, Andrea Vergallo, Harald Hampel. Age and sex impact plasma NFL and t-Tau trajectories in individuals with subjective memory complaints: a 3-year follow-up study. Alzheimer's Research & Therapy (2020) 12:147. doi.org/10.1186/s13195-020-00704-4
- Frontera JA, Boutajangout A, Masurkar AV, Betensky R, Ge Y, Vedvyas A, Debure L, Moreira A, Lewis A, Huang J, Thawani S, Balcer L, Galetta S, Wisniewski T. Comparison of Serum Neurodegenerative Biomarkers among Hospitalized COVID-19 Patients versus Non-COVID Subjects with Normal Cognition, Mild Cognitive Impairment or Alzheimer's Dementia. Alzheimer's and Dementia, 18(5):899-910, 2022. PMID: PMC9011610
- Masurkar AV, Bansal N, Prince DK, Winkelmayer WC, Ortiz DF, Ramos G, Soomro Q, Vedvyas A, Osorio RS, Bernard MA, Debure L, Ahmed W, Boutajangout A, Wisniewski T, Charytan DM. Alzheimer Disease-Related Biomarkers in Patients on Maintenance Hemodialysis. Kidney Med. 2024 Aug 28;6(11):100897. PMID: PMC11440795