

Maryam Abdolmaleki,^{1,2} Cara Lwin,^{1,2,3} Dandan Liu,^{1,2,3} Timothy J. Hohman,^{1,2,4} Henrik Zetterberg,⁵⁻¹⁰ Angela Jefferson,^{1,2,4,11} Corey J. Bolton^{1,2,11}

¹Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA; ²Vanderbilt Alzheimer's Disease Research Center, Vanderbilt University Medical Center, Nashville, TN, USA; ³Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA; ⁴Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA; Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Sweden; ⁶Sahlgrenska University Hospital, Mölndal, Sweden; ⁷UCL Institute of Neurology, Queen Square, London, UK; ⁸UK Dementia Research Institute at UCL, London, UK; ⁹Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China; ¹⁰Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA; ¹¹Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

VANDERBILT MEMORY & ALZHEIMER'S CENTER

Background

- Blood-based biomarkers (BBM) enable scalable detection of Alzheimer's disease (AD) pathology.
- Plasma p-tau231 and GFAP reflect distinct biological processes and change at different stages of AD.
- Prior studies show BBM performance varies across the disease continuum, but cognitive stage is often ignored.
- It is unclear how objective cognitive impairment and subjective cognitive decline affect BBM accuracy for amyloid pathology.
- Our objective was To examine the association between selective serotonin reuptake inhibitors (SSRI) use and fluid tau biomarkers in cognitively unimpaired (CU) older adults.

Methods

- Vanderbilt Memory and Aging Project participants, free of clinical dementia or stroke (n=335, 72.9±7 years, 52.5% CU, 39.4% mild cognitive impairment (MCI), 11% SSRI users (n=38), (**Table 1**), completed a comprehensive evaluation at study enrollment, including, but not limited to, a blood draw and lumbar puncture.
- Linear regression models related SSRI use to biomarker levels (plasma: p-tau231, GFAP, NfL, Aβ42, Aβ42/40; cerebrospinal fluid (CSF): total tau, p-tau181, Aβ42), adjusting for age, sex, education, race/ethnicity, cognitive status, and apolipoprotein E (*APOE*)-ε4 status.
- Follow-up models assessed interactions with sex, diagnosis, *APOE*-ε4, and amyloid status.
- Sensitivity analysis was performed for outlier exclusion, and false discovery rate correction was performed to correct for multiple comparisons.

Table 1. Participant Characteristics Stratified by SSRI Use

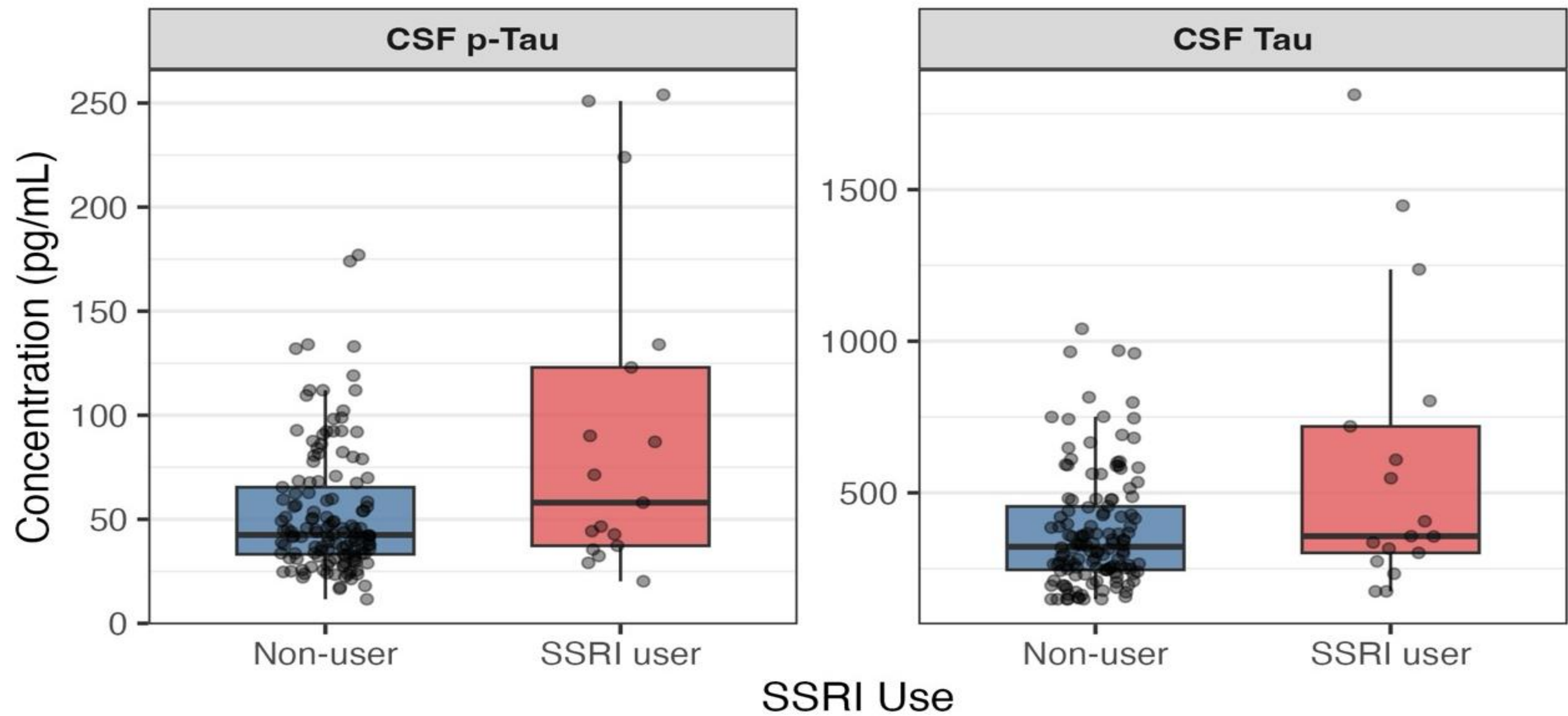
	Overall (N=335)	Non-users (N=297)	SSRI users (N=38)	p-value
Age, years	72.9±7.3	73.1±7.3	71.2±7.3	0.07
Female, n (%)	137 (40.9)	112 (37.7)	25 (65.8)	<0.001
Education, years	15.9±2.7	16.1±2.6	14.5±2.3	<0.001
Non-Hispanic White, n (%)	290 (86.6)	253 (85.2)	37 (97.4)	0.04
<i>APOE</i> -ε4 carrier, n (%)	115 (34.3)	97 (32.7)	18 (47.4)	0.07
GDS score	3.6±3.6	3.2±3.2	6.5±5.0	<0.001
Cognitively Unimpaired, n (%)	176 (52.5)	166 (55.9)	10 (26.3)	<0.001
Mild Cognitive Impairment, n (%)	132 (39.4)	106 (35.7)	26 (68.4)	

Note. Values are denoted as mean±standard deviation or frequency. Bold font indicates p-values <0.05. *APOE*=apolipoprotein E gene; GDS=Geriatric Depression Scale.

Results

- In the primary adjusted analyses, SSRI use was associated with higher CSF total tau and higher CSF p-tau181 levels.
- SSRI use was not associated with plasma p-tau231, and no clear associations were observed for the other plasma biomarkers examined.
- Although the CSF findings were significant in the primary models, they did not remain significant after FDR correction.
- In sensitivity analyses excluding outliers, the associations with CSF total tau and CSF p-tau181 were attenuated and no longer statistically significant.
- Interaction analyses showed a significant sex interaction for both CSF total tau and CSF p-tau181.
- In stratified analyses, the association between SSRI use and higher CSF tau biomarkers was observed in women, but not in men.
- Subgroup analyses also suggested stronger associations in participants with MCI, while no clear associations were observed in CU participants.
- No significant interactions were observed by *APOE*-ε4 status or amyloid status.

Figure 1. CSF p-Tau and Total Tau by SSRI Use



Conclusions

- In this sample of non-demented older adults, SSRI use was associated with higher CSF tau biomarkers in the primary analyses.
- However, these findings did not survive multiple-comparison correction and were not robust in sensitivity analyses excluding outliers.
- No association was observed between SSRI use and plasma p-tau231.
- Overall, these findings do not support a protective association between SSRI use and tau pathology in earlier stages of Alzheimer's disease.
- The observed pattern may reflect confounding by indication, and the stronger associations seen in women and participants with MCI warrant further study.