



Sex modulates the association between Alzheimer’s-related neuroinflammation and affective symptoms



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Aim

Investigate whether neuroinflammatory markers are associated with depressive and anxiety symptoms in a sex-dependent manner in the context of AD

Methods

- 50 cognitively unimpaired and 30 cognitively impaired individuals
- Scanned with amyloid-β-PET ([¹⁸F]AZD4694) and tau-PET ([¹⁸F]MK6240)
- Plasma glial fibrillary acidic protein (GFAP), and CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2) assessments
- Depressive and anxiety symptoms evaluated using the Geriatric Depression Scale (GDS-30) and the Generalized Anxiety Disorder-7 (GAD-7)
- Associations examined using multiple linear regression models

Conclusions

- o Microglial activation (sTREM2) was associated with greater anxiety and depressive symptoms in males
- o Astrocytic reactivity (GFAP) was linked to lower depressive symptoms in females
- o The three-way interactions suggest that these relationships are further modulated by amyloid-β burden
- o Sex-specific neuroinflammatory pathways may:
 - link AD pathology to affective symptoms
 - highlight the importance of sex in the development of targeted therapeutic strategies

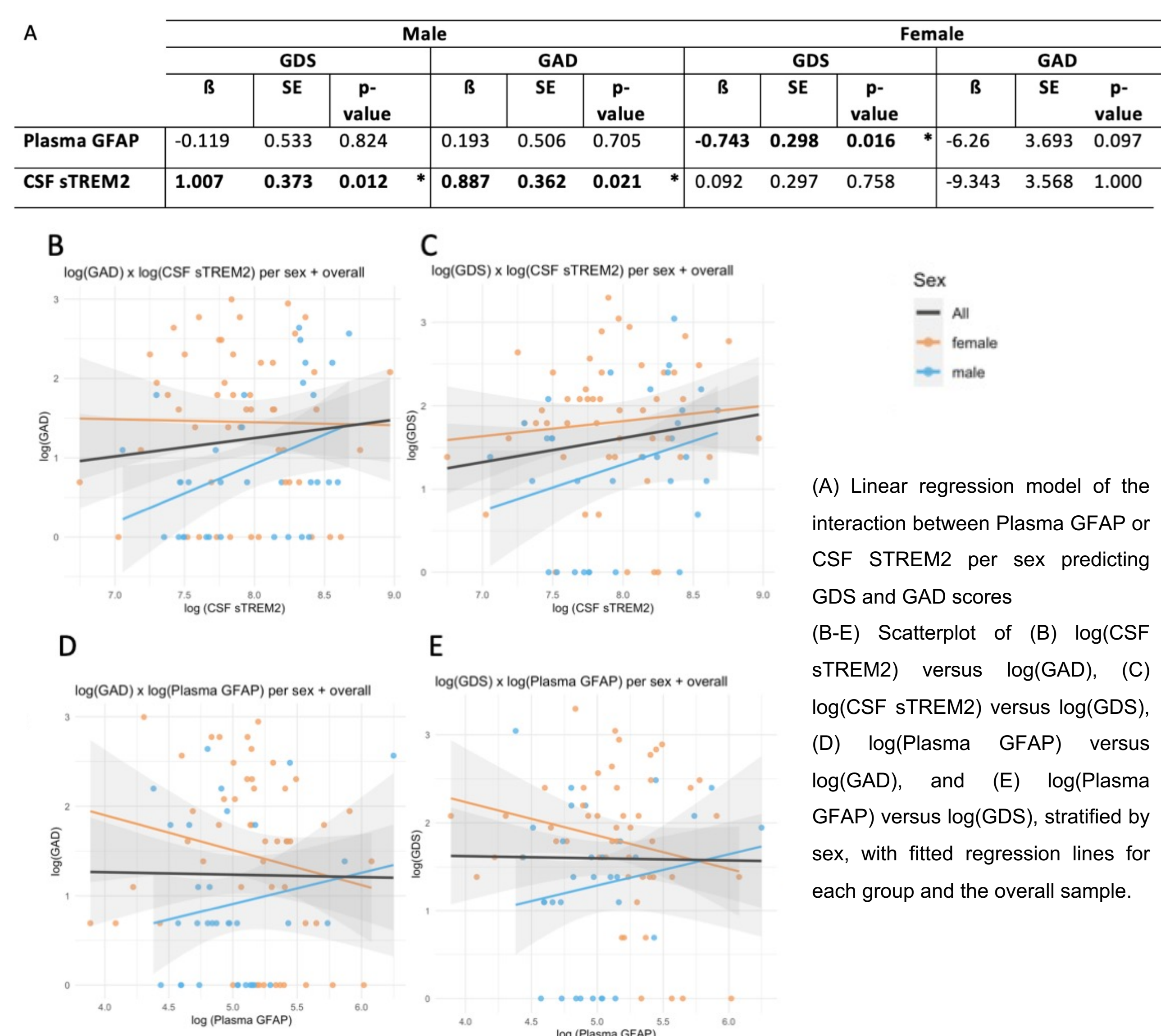
Results

Higher anxiety was positively associated with CSF sTREM2 in a sex-dependent manner, with a significant sTREM2 × male interaction.

	Variable	GDS				GAD			
		β	SE	t value	p-value	β	SE	t value	p-value
Plasma GFAP	log(plasma GFAP)	-0.771	0.300	-2.569	0.0123 *	-0.615	0.338	-1.818	0.0733 .
	Sex (male)	-4.332	2.301	-1.882	0.0638 .	-4.360	2.594	-1.681	0.0971 .
	Age	-0.006	0.019	-0.311	0.7566	-0.010	0.021	-0.480	0.6326
	Aβ-PET neocortical SUVR	0.311	0.217	1.434	0.1558	0.260	0.244	1.064	0.2909
	Tau-PET temporal SUVR	0.282	0.151	1.869	0.0657 .	-0.014	0.170	-0.081	0.9354
CSF sTREM2	Plasma GFAP × sex (male)	0.737	0.456	1.617	0.1104	0.729	0.514	1.419	0.1602
	log(CSF sTREM2)	0.134	0.300	0.446	0.657	-0.033	0.328	-0.100	0.920
	Sex (male)	-5.485	3.608	-1.520	0.133	-8.705	3.939	-2.210	0.0303 *
	Age	-0.015	0.019	-0.804	0.424	-0.015	0.021	-0.723	0.472
	Aβ-PET neocortical SUVR	0.289	0.197	1.472	0.145	0.303	0.215	1.414	0.162
	Tau-PET temporal SUVR	0.122	0.158	0.768	0.445	-0.151	0.173	-0.875	0.384
	CSF sTREM2 × sex (male)	0.614	0.452	1.361	0.178	1.006	0.493	2.041	0.0449 *

Linear regression model of the interaction between Plasma GFAP or CSF sTREM2 with sex predicting GDS and GAD scores

In sex-stratified analyses, GFAP was negatively associated with depressive symptoms in women. sTREM2 was positively associated with both depression and anxiety in men.



There were significant three-way interactions between amyloid-β:
-GFAP and male sex for depressive symptoms
-sTREM2 and male sex for anxiety
No significant interactions were found in tau-based models.

	Variable	GDS				GAD			
		β	SE	t value	p-value	β	SE	t value	p-value
Plasma GFAP	log (plasma GFAP)	-0.896	0.873	-1.026	0.308	-0.360	1.021	-0.353	0.726
	Sex (male)	13.796	8.129	1.697	0.094 .	7.941	9.509	0.835	0.407
	Aβ-PET neocortical SUVR	-0.154	3.125	-0.049	0.961	1.529	3.657	0.418	0.677
	Age	0.004	0.019	0.223	0.824	-0.004	0.022	-0.195	0.846
	Tau-PET temporal SUVR	0.349	0.149	2.341	0.022 *	0.021	0.174	0.120	0.905
	GFAP × sex (male)	-2.901	1.611	-1.801	0.076 .	-1.649	1.885	-0.875	0.385
	GFAP × Aβ-PET	0.072	0.580	0.124	0.902	-0.228	0.678	-0.336	0.738
	Male × Aβ-PET	-10.027	4.838	-2.073	0.042 *	-7.651	5.658	-1.352	0.181
	GFAP × sex (male) × Aβ-PET	1.973	0.921	2.142	0.036 *	1.448	1.077	1.344	0.183
	GFAP × sex (male) × Tau-PET	0.017	0.759	0.023	0.982	-0.607	0.836	-0.727	0.470
CSF sTREM2	Log (CSF sTREM2)	-0.839	0.904	-0.928	0.357	0.133	0.996	0.133	0.894
	Sex (male)	-3.526	6.235	-0.565	0.574	3.705	6.867	0.540	0.591
	Tau-PET temporal SUVR	0.246	4.265	0.058	0.954	3.247	4.696	0.691	0.492
	Age	-0.006	0.019	-0.333	0.740	-0.010	0.021	-0.494	0.623
	Aβ-PET neocortical SUVR	0.345	0.240	1.436	0.156	0.236	0.265	0.893	0.375
	GFAP × sex (male)	0.643	1.172	0.549	0.585	-0.917	1.291	-0.711	0.480
	GFAP × Tau-PET	0.017	0.759	0.023	0.982	-0.607	0.836	-0.727	0.470
	Male × Tau-PET	-0.976	5.019	-0.195	0.846	-5.910	5.527	-1.069	0.289
	GFAP × sex (male) × Tau-PET	0.135	0.916	0.148	0.883	1.200	1.009	1.190	0.238
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	GFAP × sex (male) × Aβ-PET	0.135	0.916	0.148	0.883	1.200	1.009	1.190	0.238
CSF sTREM2	Log (CSF sTREM2)	0.933	1.090	0.857	0.395	1.596	1.169	1.366	0.176
	Sex (male)	-7.750	11.534	-0.672	0.504	17.052	12.370	1.379	0.173
	Aβ-PET neocortical SUVR	4.232	5.403	0.783	0.436	8.441	5.794	1.457	0.150
	Age	-0.021	0.019	-1.126	0.264	-0.019	0.021	-0.899	0.372
	Tau-PET temporal SUVR	0.176	0.162	1.085	0.282	-0.174	0.174	-1.000	0.321
	sTREM2 × sex (male)	0.770	1.453	0.530	0.598	-2.318	1.558	-1.488	0.141
	sTREM2 × Aβ-PET	-0.541	0.693	-0.781	0.437	-1.065	0.743	-1.433	0.156
	Male × Aβ-PET	0.758	6.958	0.109	0.914	-16.617	7.462	-2.227	0.029 *
	sTREM2 × sex (male) × Aβ-PET	-0.013	0.882	-0.015	0.988	2.151	0.946	2.275	0.026 *
	sTREM2 × sex (male) × Tau-PET	-0.013	0.882	-0.015	0.988	2.151	0.946	2.275	0.026 *
Plasma GFAP	Log (CSF sTREM2)	0.124	0.770	0.161	0.872	0.877	0.814	1.078	0.285
	Sex (male)	-7.719	13.039	-0.592	0.556	15.472	13.785	1.122	0.266
	Tau-PET temporal SUVR	0.257	4.496	0.057	0.955	5.340	4.753	1.124	0.265
	Age	-0.015	0.020	-0.816	0.417	-0.010	0.021	-0.461	0.646
	Aβ-PET neocortical SUVR	0.319	0.224	1.426	0.158	0.099	0.236	0.420	0.676
	sTREM2 × sex (male)	0.924	1.574	0.587	0.559	-1.977	1.664	-1.188	0.239
	sTREM2 × Tau-PET	-0.010	0.528	-0.018	0.985	-0.656	0.558	-1.176	0.244
	Sex (male) × Tau-PET	1.454	10.936	0.133	0.895	-19.461	11.560	-1.683	0.097 .
	sTREM2 × sex (male) × Tau-PET	-0.205	1.308	-0.157	0.876	2.390	1.383	1.728	0.089 .
	sTREM2 × sex (male) × Aβ-PET	-0.205	1.308	-0.157	0.876	2.390	1.383	1.728	0.089 .

Linear regression model: three-way interactions between Plasma GFAP or CSF sTREM2, sex and Aβ or Tau predicting GDS and GAD scores