Sex and Age Differences in the Association of Serum GFAP Levels with Cognitive Decline in Cognitively Unimpaired Individuals: Results from the A4 Study

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OBJECTIVE

To investigate sex and age differences in the association between plasma GFAP levels and cognitive decline in cognitively unimpaired individuals.

CONCLUSIONS

Higher baseline plasma GFAP levels are associated with faster cognitive decline over time in cognitively unimpaired participants.

Higher baseline plasma GFAP levels are more strongly associated with cognitive decline in cognitively unimpaired females.

The association between higher baseline plasma GFAP and cognitive decline is evident across the entire age range.

ACKNOWLEDGMEN

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INTRODCUTION

Inflammation plays a central role in the pathology of Alzheimer's Disease (AD), and immune response is stronger in women. This stronger inflammatory response may contribute to higher prevalence of AD in women. Also, inflammatory response may differ by age. **Our goal** is to investigate the association of GFAP, a marker of astrocytic activity, with cognitive decline across different sex and age groups.

METHODS

- **Participants:** Cognitively unimpaired participants in the A4 and LEARN studies were included. For cross-sectional analysis we included both arms of A4 (placebo and Solanezumab) and LEARN (N=949). For longitudinal analysis we included only the placebo arm of A4 study and LEARN (N=695). The follow-up period was 240 weeks (~5 years).
- **Statistical approach:** we used linear mixed effect models and Cox regression models adjusted for age, sex and education. We also performed the analysis stratified by sex and age: 65-75 years old vs age >75.
- **Outcome variables:** Preclinical Alzheimer's Cognitive Composite (PACC) scores and change in global Clinical Dementia Rating (CDR) from 0 to > 0 in 2 consecutive visits. **Predictor variable:** Baseline plasma GFAP.

RESULTS

Cross-sectional

- Higher GFAP levels were associated with worse performance in PACC in the entire sample (Table 2).
- When stratified by sex, higher GFAP levels were associated with worse performance in PACC only in female participants (Tabel 2).
- When stratified by age, higher GFAP was associated with worse performance in PACC in both age groups (Table 2).

Longitudinal

- Elevated GFAP predicted a faster decline in PACC over time (~5 years) in the entire sample (Table 2).
- When stratified by sex, higher GFAP predicted a faster decline in PACC over time in female and male participants, but the association was stronger in female (Table 2).
- When stratified by age, higher GFAP was associated with faster decline in PACC across the entire age range (Table 2).
- In the entire sample, higher GFAP was associated with an increased risk of progression to CDR > 0 (Table 3).
- When stratified by sex, higher GFAP was associated with an increased risk of progression to CDR > 0 only in female participants (Table 3, Figure 1).
- When stratified by age, this association was significant across the entire age range (Table 3).

Table 1. Participants' characteristics in the whole sample and stratified by sex

Variable	Total (n=949)	Female (n=578)	Male (n=371)	p value
Age, mean (SD), y	70.94 (4.69)	70.76 (4.38)	71.71 (4.94)	.003
Education, mean (SD), y	16.67 (2.59)	16.28 (2.46)	17.27 (2.67)	<.001
Plasma GFAP, mean (SD), ng/mL	0.11 (0.05)	0.12 (0.06)	0.10 (0.05)	<.001
PACC score, mean (SD)	0.43 (2.5)	0.78 (2.43)	-0.09 (2.52)	<.001

Table 2. Association of serum GFAP with baseline performance and rate of change in PACC in the entire cohort and stratified by sex and age

	Baseline PACC			Rate of change in PACC		
	β	SE	p value*	β	SE	p value*
Entire cohort	-4.34	1.52	0.008	-0.17	0.03	<0.001
Female	-5.31	1.93	0.008	-0.21	0.04	<0.001
Male	-2.67	2.48	0.283	-0.14	0.06	0.018
Age 65-75	-5.80	1.89	0.008	-0.10	0.04	0.018
Age> 75	-7.49	2.68	0.008	-0.21	0.08	0.017

Total n=695; Female n=418, Male n=277, Age 65-75 n= 573, Age>75 n= 122
* P values are FDR adjusted for multiple comparison.

Table 3: Associations of baseline plasma GFAP with risk of progression to CDR>0 in the entire sample and stratified by sex and age

	Hazard Ratio	95% CI	P value	Adjusted p value
Entire cohort	1.24	1.08-1.41	0.002	0.010
Female	1.34	1.07-1.62	0.003	0.007
Male	1.16	0.96-1.40	0.119	0.119
Age 65-75	1.31	1.08-1.59	0.006	0.010
Age> 75	1.26	1.05-1.51	0.015	0.019

Total n=659; Female n=392, Male n=267, Age 65-75 n= 545, Age>75 n= 114

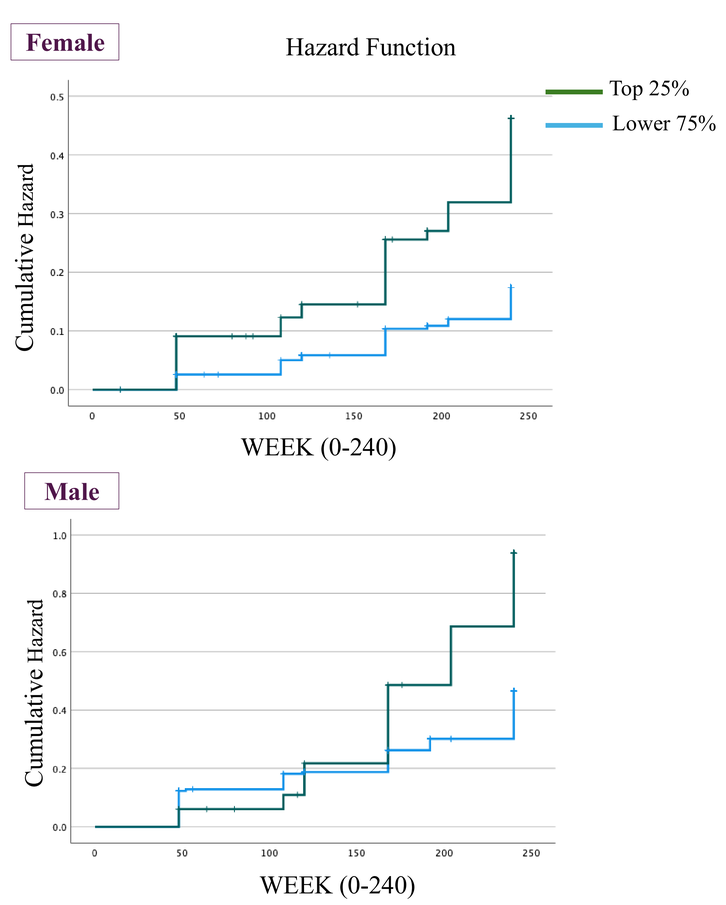

Figure 1. Estimated hazard function for progression to CDR > 0 stratified by z-scored baseline plasma GFAP levels.