Table S1: Correlation index[1] between tfGFAP in serum and sMMSE score across time and divided by degree of neuropathology.

	AD and Non-AD			**AD**		
	T1 (N=106)	T2 (N=64)	T3 (N=149)	T1 (N=100)	T2 (N=60)	T3 (N=138)
ρ [95%CI]	**-0.24 [-0.44, -0.01]**	**-0.5 [-0.68, -0.27]**	**-0.32 [-0.48, -0.14]**	-0.19 [-0.41, 0.04]	**-0.48 [-0.67, -0.24]**	**-0.27 [-0.44, -0.08]**
P-value	0.039	< 0.000	0.001	0.11	<0.000	0.005

[1]Spearman correlation. The statistically significant correlation indexes are in bold.

Table S2. Demographic characteristics of the longitudinal subsample

	Alzheimer Disease Neuropathological Change [1]		
	Low/Non-AD (n= 6)	Intermediate (n=13)	High (n=82)
Age at serum collection at Time 1	79.8 (7.6)	86.7 (3.8)	83.4 (5.6)
GFAP serum levels	492.6 (359.1)	648.4 (337.2)	684.2 (337.5)
Days from serum collection Time 3 to death	142.2 (132.2)	128.3 (85.4)	147.9 (157.1)
Women	5 (83.3%)	10 (76.9%)	69 (84.1%)
APOE-ε4 carrier	0 (0%)	4 (30.8%)	41 (50.6%)

[1]ADNC Score: High (ADNC=3), Intermediate (ADNC=2), Low (ADNC=1), Non-AD (ADNC=0)
Data are mean (SD) or frequencies (%)

Table S3. Association between the longitudinal change of serum tfGFAP and the trajectory of SMMSE score.

	All sample									
	Rate of change in cognitive performance					**Cognitive performance intercept**				
Independent variables	$\boldsymbol{\beta}$ [95%CI]	**p-value**	$\boldsymbol{R^2}$	$\mathbf{AIC_c}$	**Deviance** F; P-value	$\boldsymbol{\beta}$ [95%CI]	**p-value**	$^{1}\boldsymbol{R^2}$	$\mathbf{AIC_c}$	**Deviance** F; P-value
Rate of change of serum tfGFAP	3.26 [-0.56, 7.08]	0.09	0.03	334.663	14.063 P< 0.001	**-23.55 [-36.22, 10.87]**	**<0.001**	0.15	509.773	13.333 P<0.001
Rate of change of serum tfGFAP adjusted by covariates[1]	-1.25 [-4.71, 2.21]	0.47	0.37	306.352		-9.53 [-21.13, 2.06]	0.11	0.44	482.926	
	Only individuals with higher post-mortem pathology (ADNC>2)									
Rate of change of trGFAP	1.8 [-2.15, 5.76]	0.37	0.00	287.445	17.074 P< 0.001	**-19.07 [-32.31, -5.84]**	**0.01**	0.11	439.531	15.864 P< 0.001
Rate of change of serum trGFAP adjusted by covariates[1]	-3.3 [-6.72, 0.12]	0.06	0.44	254.662		-3.1 [-14.73, 8.53]	0.60	0.48	408.878	

[1]Covariates were estimated age at onset, number of days between extraction date and death date, and sex.
CI, confidence intervals; R^2, Adjusted R^2; AIC_C, corrected Akaike criterion.

Table S4. Association between levels of serum tfGFAP and brain atrophy.

tfGFAP ~ Atrophy	**Complete sample (AD and Non-AD)**				**Only individuals with AD**			
	$\boldsymbol{\beta}$ [95%CI]	**p-value**	$\boldsymbol{R^2}$	$\mathbf{AIC_c}$	$\boldsymbol{\beta}$ [95%CI]	**p-value**	$\boldsymbol{^1R^2}$	$\mathbf{AIC_c}$
Time point 1	-0.0004 [0, 0]	0.132	0.05	57.688	-3e-04 [0, 0]	0.274	0.07	38.051
Time point 2	-0.0006 [0, 0]	0.080	0.27	25.22	-0.0004 [0, 0]	0.297	0.30	19.124
Time point 3	**-0.019 [-0.03, -0.01]**	**0.008**	0.17	979.59	-0.0141 [-0.03, 0]	0.070	0.14	892.451

The analysis was adjusted by covariates such as serum extraction age, estimated age at onset, number of days between extraction date and death date, and sex. CI, confidence intervals; R^2, Adjusted R^2; AIC_C, corrected Akaike criterion.

Table S5. Association between serum tfGFAP and post-mortem neuropathology at time points 1 and 2.

tfGFAP ~ neuropathology		**Timepoint 1**				**Timepoint 2**			
Model	**Independent variables**	$\boldsymbol{\beta}$**[95%CI]**	**p-value**	$\boldsymbol{R^2}$	$\mathbf{AIC_c}$	$\boldsymbol{\beta}$**[95%CI]**	**p-value**	$\boldsymbol{R^2}$	$\mathbf{AIC_c}$
[1]Basic model[1]	Covariates			0.04	56.731			0.24	26.643
[2]NIA-A	Intermediate	-0.2816 [-0.79, 0.23]	0.275	0.17	43.822	a	a	0.32	22.166
	High	0.2569 [-0.17, 0.69]	0.240			-0.2077 [-0.79, 0.38]	0.479		
[3]NIA-B	Intermediate	**0.4383 [0.11, 0.77]**	**0.010**	**0.19**	**42.879**	0.1503 [-0.27, 0.57]	0.476	**0.41**	**14.615**
	High	**0.5661 [0.3, 0.83]**	**< 0.001**			**0.5341 [0.23, 0.84]**	**< 0.001**		
[4]NIA-C	Intermediate	**0.2039 [-0.02, 0.42]**	**0.069**	0.14	48.194	**0.2843 [0.01, 0.56]**	**0.043**	0.33	21.186
	High	**0.2934 [0.13, 0.45]**	**< 0.001**			**0.2923 [0.11, 0.48]**	**0.002**		
[5]NIA-A+ NIA-B+ NIA-C	Intermediate NIA-A	-0.3226 [-0.99, 0.35]	0.340	**0.20**	**46.932**	a	a	0.39	21.904
	High NIA-A	0.0073 [-0.7, 0.72]	0.984			0.1967 [-0.43, 0.82]	0.529		
	Intermediate NIA-B	0.2355 [-0.2, 0.67]	0.287			0.0151 [-0.58, 0.61]	0.959		
	High NIA-B	0.1925 [-0.3, 0.68]	0.438			0.2856 [-0.32, 0.89]	0.346		
	Intermediate NIA-C	0.1142 [-0.16, 0.39]	0.412			0.0878 [-0.29, 0.46]	0.642		
	High NIA-C	0.1908 [-0.07, 0.45]	0.148			0.1245 [-0.19, 0.44]	0.429		
[6]ADNC	Intermediate	**0.415 [0.12, 0.71]**	**0.006**	0.17	43.905	0.109 [-0.25, 0.47]	0.544	0.34	20.772
	High	**0.5081 [0.26, 0.75]**	**< 0.001**			**0.356 [0.08, 0.63]**	**0.013**		

The reference group in each model was their respective lower category (Non/Low NIA-A, Non/Low NIA-B, Non/Low NIA-C).
Significant coefficients and better goodness-of-fit indexes are in bold.
[a]There were no subjects with Non/Low NIA-A at time point 2.
CI, confidence intervals; R^2, Adjusted R^2; AIC_C, corrected Akaike criterion.
[1] Basic model equation: $tfGFAP_{t(i)} = \beta_0 + \beta_1$*Age extraction+ β_2*Age onset + β_3*T3-exitus + β_4* Sex
[2]Model equation: $tfGFAP_{t(i)} = \beta_0 + \beta_1$*NIA-A + β_2* Age extraction+ β_3*Age onset + β_4*T3-exitus + β_5* Sex
[3]Model equation: $tfGFAP_{t(i)} = \beta_0 + \beta_1$*NIA-B + β_2* Age extraction+ β_3*Age onset + β_4*T3-exitus + β_5* Sex
[4]Model equation: $tfGFAP_{t(i)} = \beta_0 + \beta_1$*NIA-C + β_2* Age extraction+ β_3*Age onset + β_4*T3-exitus + β_5* Sex
[5]Model equation: $tfGFAP_{t(i)} = \beta_0 + \beta_1$*NIA-A + β_2*NIA-B + β_3*NIA-C + β_4*Age extraction+ β_5*Age onset + β_6*T3-exitus + β_7* Sex

[6]Model equation: $tfGFAP_{t(i)}$ = β_0 + β_1*ADNC + β_2* Age extraction+ β_3*Age onset + β_4*T3-exitus + β_5* Sex

Table S6. Association between levels of serum tfGFAP and post-mortem neuropathology.

	[2]Post-mortem pathology adjusted by covariates				[3]Post-mortem pathology adjusted by covariates and ADNC			
Independent variables	**β[95%CI]**	**P-value**	***R²***	**AIC$_c$**	**β[95%CI]**	**P-value**	**R²**	**AICc**
Basic model[1]	-	-	0.13	1011.15	-	-	0.20	1001.04
Braak a-syn	3.14 [-0.81, 7.09]	0.12	0.14	1010.81	2.53 [-1.29, 6.35]	0.19	0.20	1001.50
LPC	2.43 [-1.66, 6.52]	0.24	0.11	932.61	2.1 [-1.79, 6]	0.30	0.19	921.66
VST	-1.35 [-4.73, 2.03]	0.43	0.14	849.73	0.46 [-2.81, 3.73]	0.78	0.25	835.02
VCING	1.3 [-2.18, 4.77]	0.46	0.13	986.06	0.66 [-2.69, 4.01]	0.70	0.20	976.05
CAA intensity	0.73 [-2.61, 4.08]	0.67	0.13	954.88	-0.67 [-3.98, 2.65]	0.70	0.20	945.77
CAA stage	2.5 [-2.2, 7.2]	0.29	0.04	567.46	1.47 [-3, 5.95]	0.51	0.15	559.70
AGD	**-6.93 [-12.26, -1.59]**	**0.01**	0.17	1006.64	**-6.11 [-11.28, -0.94]**	**0.02**	0.23	997.65
ARTAG	1.2 [-2, 4.4]	0.46	0.13	1012.80	1.01 [-2.06, 4.09]	0.52	0.20	1002.86
ARTAG LTM	0.25 [-3, 3.49]	0.88	0.13	1006.74	-0.04 [-3.16, 3.07]	0.98	0.19	996.65
ARTAG CORTEX	1.82 [-1.61, 5.26]	0.30	0.13	1005.61	1.24 [-2.08, 4.56]	0.46	0.20	996.08
HS AHC	3.04 [-0.61, 6.69]	0.10	0.13	938.47	2.74 [-0.74, 6.23]	0.12	0.21	927.88
HS PHC	**4.03 [0.59, 7.47]**	**0.02**	0.17	965.63	**3.64 [0.34, 6.94]**	**0.03**	0.24	955.50
LATE stage	**3.64 [0.12, 7.17]**	**0.04**	0.15	995.05	2.99 [-0.42, 6.4]	0.09	0.22	985.94

The reference group in each case was their respective lower category (Non/Low pathology, coded as 0). Significant coefficients and better goodness-of-fit indexes are in bold. CI, confidence intervals; R^2, Adjusted R^2; AIC_C, corrected Akaike criterion.

Braak a-syn, Braak stage for alpha synuclein; LPC, Lewy pathology consensus criteria; VST, Deramecourt's vascular score; VCING, Vascular cognitive impairment neuropathology guidelines; CAA, amyloid angiopathy; AGD, argyrophilous grains; ARTAG, aging-related tau astrogliopathy; LMT, medial temporal lobe; HS AHC, hippocampal sclerosis in anterior hippocampus; HS PHC, hippocampal sclerosis in posterior hippocampus.

Covariates included in the models are age at serum extraction, estimated age at onset, number of days between last serum collection and death date, and sex.

[1]Basic model equation: $tfGFAP_{t3} = \beta_0 + \beta_1$*Age extraction+ β_2*Age onset + β_3*T3-exitus + β_4* Sex

[2]Model equation: $tfGFAP_{t3} = \beta_0 + \beta_1$*Neuropathology + β_2*Age extraction+ β_3*Age onset + β_4*T3-exitus + β_5* Sex

[3]Model equation: $tfGFAP_{t3} = \beta_0 + \beta_1$* Neuropathology + β_2*ADNC + β_3* Age extraction+ β_4*Age onset + β_5*T3-exitus + β_6* Sex

Table S7. Unstandardized and standardized estimated coefficients of the path analysis of the partial mediation model with serum tfGFAP as mediator.

1. Partial mediation model with NIA-C as independent variable and tfGFAP as mediator

Parameters	$B[95\%CI]$	**p-value**	β	R^2
tfGFAP on NIA-C (a)	3.26 [0.99 - 5.54]	P<0.001	0.24	0.57
NIA-B on tfGFAP (b)	0.02 [6.2-E3 - 0.02]	P<0.001	0.27	
NIA-B on NIA-C (c')	0.5 [0.37 - 0.64]	P<0.001	0.65	
Indirect effect (Mediation = a*b)	0.05 [0.01 - 0.09]	0.02	0.07	
Total effect (Total = a*b + c')	0.55 [0.41 - 0.7]	P<0.001	0.71	
Proportion of mediation (Med/Tot*100)	9.18 [2.26 - 16.1]	0.01	9.2	

2. Partial mediation model with NIA-A as independent variable and tfGFAP as mediator

Parameters	$B[95\%CI]$	**p-value**	β	R^2
tfGFAP on NIA-A (a)	8.69 [3.82 - 13.57]	P<0.001	0.32	0.49
NIA-B on tfGFAP (b)	0.01 [3.6-E3 - 0.02]	0.01	0.25	
NIA-B on NIA-A (c')	0.93 [0.52 - 1.34]	P<0.001	0.58	
Indirect effect (Mediation: a*b)	0.12 [0.05 - 0.2]	P<0.001	0.08	
Total effect (a*b + c')	1.05 [0.65 - 1.45]	P<0.001	0.66	
Proportion of mediation (Med/Tot*100)	11.74 [2.99 - 20.49]	0.01	11.7	

Table S8. Area of GFAP quantified on post-mortem tissue, and its relationship with levels of serum GFAP (T3).

	Basic model		Model 1	
	ρ	P-value	ρ	P-value
Area GFAP in SEC[1]				
Complete sample	**0.2073**	**0.0175***	**0.2127**	**0.0163***
Only subjects with Braak stages 5 and 6	0.1601	0.1011	**0.2063**	**0.0375***
Subjects with Braak stages below 5	0.2046	0.3265	0.1500	0.4946
Area GFAP in Amygdala				
Complete sample	0.0299	0.7367	0.0674	0.4554
Only subjects with Braak stages 5 and 6	0.1208	0.2198	0.1697	0.0898 (+)
Subjects with Braak stages below 5	-0.0252	0.9069	-0.0273	0.9041
Sum SEC and Amygdala[2]				
Complete sample	0.1569	0.0781(+)	**0.1804**	**0.0459***
Only subjects with Braak stages 5 and 6	0.1752	0.0767(+)	**0.2253**	**0.0249***
Subjects with Braak stages below 5	0.0357	0.8686	0.0141	0.9503

'+' P<.10; '*' p<.05

Statistically significant partial correlation indexes (Spearman) in bold.

Model 1: Basic model controlling for the effect of age at collection and sex.

[1]Superior entorhinal cortex

[2]Sum of pixels of GFAP in superior entorhinal cortex and amygdala

Table S9. Area of GFAP quantified on post-mortem tissue, and its relationship with brain weight.

	Basic model		Model 1	
	ρ	P-value	ρ	P-value
Area GFAP in SEC[1]				
Complete sample	**-0.1832**	**0.0393***	-0.1697	0.0606(+)
Only subjects with Braak stages 5 and 6	-0.1482	0.1372	-0.1192	0.2423
Subjects with Braak stages below 5	-0.3248	0.1132	-0.2912	0.1777
Area GFAP in Amygdala				
Complete sample	0.0395	0.6618	0.0171	0.8519
Only subjects with Braak stages 5 and 6	0.0285	0.7771	0.0153	0.8814
Subjects with Braak stages below 5	-0.2057	0.3349	-0.1935	0.3884
Sum SEC and Amygdala[2]				
Complete sample	-0.1046	0.2497	-0.1087	0.2391
Only subjects with Braak stages 5 and 6	-0.0582	0.5669	-0.0730	0.4820
Subjects with Braak stages below 5	-0.2427	0.2532	-0.2136	0.3398

'+' P<.10; '*' p<.05

Statistically significant partial correlation indexes (Spearman) in bold.

Model 1: Basic model controlling for the effect of age at collection and sex.

[1]Superior entorhinal cortex

[2]Sum of pixels of GFAP in superior entorhinal cortex and amygdala

Table S10. Area of CD68 quantified in superior entorhinal cortex (SEC) and its correlation with levels of serum GFAP (T3), area of GFAP on post-mortem tissue, and brain weight.

	Basic model		Model 1	
	ρ	P-value	ρ	P-value
Serum GFAP	-0.2808	0.0834	**-0.4063**	**0.0139***
Area GFAP in SEC	-0.1979	0.2335	-0.1263	0.4698
Area GFAP in Amygdala	-0.2703	0.1109	-0.2517	0.1577
Sum SEC and Amygdala[1]	-0.1825	0.2867	-0.1411	0.4334
Brain weight	-0.1351	0.5814	-0.0002	0.9993

'+' P<.10; '*' p<.05

Statistically significant partial correlation indexes (Spearman) in bold.

Model 1: Basic model controlling for the effect of age at collection and sex.

[1]Sum of pixels of GFAP in superior entorhinal cortex and amygdala