Online Resource 1

Supplementary methods and complete numerical results

CSF α-synuclein seed amplification assay positivity identifies a distinct soluble amyloid-β profile linked to fibrillar amyloid burden and structural neurodegeneration

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Journal of Neural Transmission - Research

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This Online Resource reports prespecified estimates and sensitivity analyses that are summarized selectively in the main manuscript. Null and nominally positive estimates are retained. No participant-level ADNI identifiers or raw participant-level measurements are included.

Supplementary analytical notes

The primary same-day proximal analysis used the original N=380 analytical backbone and exact same-day α-synuclein seed amplification assay (SAA) status. T denotes the common shorter-Aβ concentration coordinate and is unrelated to the T (tau) category of AT(N). D42 denotes Aβ42-relative depletion based on repeated participant-level out-of-fold prediction from Aβ38 and Aβ40.

The participant-disjoint replication excluded every participant present in the original N=380 backbone. T_R, D42_R, G38:40_R and D38_R were reconstructed de novo in the replication assay cohort using the same mathematical definitions and a new repeated out-of-fold sequence. Replication therefore refers to participant-independent replication of the analytical structure, not application of coefficients estimated in N=380.

Natural-history models prespecified two temporal follow-up intervals: 0-2.5 years and 2.5-5 years after the biomarker landmark. These are follow-up-time intervals only and are not diagnostic or biological disease-stage categories. Complete coefficients for both intervals and their formal contrasts are given below. Nonlinear spline tests were prespecified secondary analyses; isolated nominal findings were not used to select alternative functional forms.

The direct SAA-to-outcome bridge was specified only after SAA-coordinate and coordinate-outcome results were known and is therefore exploratory. Attenuation after conditioning on T_R and D42_R is descriptive and is not interpreted as mediation.

Supplementary Table S1. Same-day Stage-1 SAA associations and prespecified sensitivities.

Outcome / analysis	N (SAA+)	SAA+ β (95% CI)	P	R^2
T (primary)	72 (13)	-0.549 (-1.005, -0.093)	0.018	0.646
BACE1	72 (13)	-0.243 (-0.940, 0.454)	0.494	0.096
sAPPβ | BACE1	72 (13)	-0.537 (-1.129, 0.055)	0.075	0.320
D42	72 (13)	-0.223 (-0.782, 0.337)	0.436	0.294
G38:40	72 (13)	-0.250 (-1.028, 0.528)	0.528	0.114
Aβ38	72 (13)	-0.580 (-1.069, -0.092)	0.020	0.637
Aβ40	72 (13)	-0.504 (-0.946, -0.062)	0.025	0.637
Aβ42	72 (13)	-0.057 (-0.652, 0.538)	0.851	0.313
T, diagnosis-free sensitivity	72 (13)	-0.531 (-0.940, -0.122)	0.011	0.641
D42, diagnosis-free sensitivity	72 (13)	-0.271 (-0.863, 0.322)	0.370	0.262
T, SAA within 0-365 d	155 (34)	-0.352 (-0.673, -0.032)	0.031	0.572
D42, SAA within 0-365 d	155 (34)	-0.053 (-0.339, 0.233)	0.717	0.346

Continuous outcomes are standardized as specified in the frozen Stage-1 protocol. OLS models use HC3 covariance. The 0-365-day timing analysis is supportive and does not treat later SAA measurement as a baseline causal exposure.

Supplementary Table S2. Stage-1 participant bootstrap and leave-one-SAA-positive-out robustness.

Statistic	Bootstrap median	2.5th-97.5th percentile
T coefficient	-0.547	(-1.003, -0.092)
D42 coefficient	-0.200	(-0.760, 0.310)
T-D42 coefficient contrast	-0.350	(-1.159, 0.517)

Bootstrap: 2,000 participant resamples with frozen coordinates. Leave-one-SAA-positive-out T coefficient range: -0.618 to -0.417; no family of leave-one-out P values was used.

Supplementary Table S3. Participant-disjoint replication and diagnosis sensitivity.

Outcome / analysis	N (SAA+)	SAA+ β (95% CI)	P	R^2
T_R	560 (131)	-0.267 (-0.477, -0.057)	0.013	0.047
D42_R	560 (131)	0.206 (0.048, 0.365)	0.011	0.368
T_R-D42_R direct contrast	560 (131)	-0.473 (-0.743, -0.204)	0.0006	0.216
G38:40_R	560 (131)	-0.084 (-0.295, 0.127)	0.434	0.005
Aβ38	560 (131)	-0.276 (-0.491, -0.061)	0.012	0.048
Aβ40	560 (131)	-0.252 (-0.458, -0.047)	0.016	0.044
Aβ42	560 (131)	-0.313 (-0.493, -0.133)	0.0007	0.267
D38_R	560 (131)	0.121 (-0.094, 0.336)	0.269	0.008
T_R, +clinical diagnosis sensitivity	559 (131)	-0.250 (-0.463, -0.037)	0.022	0.053
T_R-D42_R, +clinical diagnosis sensitivity	559 (131)	-0.371 (-0.640, -0.102)	0.007	0.270

Primary replication models adjusted for age, sex, APOE ε4 dosage and education. The diagnosis sensitivity additionally included MCI and AD syndrome indicators.

Supplementary Table S4. Participant-disjoint complete-pipeline bootstrap.

Statistic	Bootstrap median	2.5th-97.5th percentile
T_R coefficient	-0.253	(-0.470, -0.050)
T_R-D42_R coefficient contrast	-0.457	(-0.724, -0.221)

Supplementary Table S5. Meso Scale same-day assay robustness.

Outcome / contrast	N (SAA+)	SAA+ β (95% CI)	P
T_R	82 (16)	-0.281 (-0.867, 0.305)	0.348
D42_R	82 (16)	0.141 (-0.481, 0.763)	0.657
T_R-D42_R direct contrast	82 (16)	-0.422 (-1.194, 0.350)	0.284

This sample is an assay-robustness analysis, not a second independent replication: 77 of 82 participants overlap the UPENN replication cohort.

Supplementary Table S6. First subsequent amyloid-PET mapping in the participant-disjoint cohort.

Term / test	N (SAA+)	Estimate	95% CI	P
SAA+	304 (70)	-0.408	(-10.276, 9.460)	0.935
T_R	304 (70)	-2.189	(-6.449, 2.071)	0.314
D42_R	304 (70)	34.901	(30.572, 39.229)	2.92e-56
SAA×T_R + SAA×D42_R global 2-df Wald	304 (70)	χ^2=0.405	—	0.817
SAA_POS:T_R	304 (70)	-0.114	(-10.850, 10.622)	0.983
SAA_POS:D42_R	304 (70)	-3.016	(-12.306, 6.275)	0.525

Centiloid model jointly includes SAA status, T_R, D42_R, time to PET, age, sex, APOE ε4 dosage and education. Interaction terms were assessed with the prespecified joint 2-df test.

Supplementary Table S7. Post-landmark longitudinal amyloid-PET slopes and IPW sensitivity.

Analysis	Term	N / observations	β (95% CI), CL/year	P
Unweighted	SAA_POS×TIME	123 / 244	-1.151 (-5.656, 3.354)	0.617
Unweighted	T_R×TIME	123 / 244	-1.700 (-2.498, -0.901)	3.03e-05
Unweighted	D42_R×TIME	123 / 244	2.217 (0.023, 4.411)	0.048
IPW	SAA_POS×TIME	123 / 244	-2.170 (-6.516, 2.176)	0.328
IPW	T_R×TIME	123 / 244	-1.656 (-2.526, -0.787)	0.0002
IPW	D42_R×TIME	123 / 244	2.189 (-0.079, 4.457)	0.059

The first post-SAA PET is the landmark and is excluded from later outcome observations. IPW denotes inverse-probability weighting for repeated-PET availability.

Supplementary Table S8. IPW balance diagnostics for the repeated amyloid-PET analysis.

Variable	SMD before weighting	SMD after weighting
SAA_POS	-0.149	-0.005
T_R	0.033	-0.005
D42_R	-0.420	0.045
CL1_z	-0.410	0.036
CL1_z2	-0.238	0.025
ZAGE_R	-0.088	0.089
FEMALE	0.025	-0.024
APOE4	-0.229	0.013
ZEDUC_R	-0.008	-0.059
FBB	0.064	0.019
TIME_TO_PET	0.019	-0.058

Maximum absolute SMD improved from 0.420 to 0.089. Effective sample size was 86.8 in the frozen Stage-2 run.

Supplementary Table S9a. Complete prespecified clinical joint estimates by follow-up interval (N380).

Outcome	Predictor	Follow-up interval	N	β/year (95% CI)	P
ADAS-Cog13	D42	0-2.5 y	367	0.452 (0.025, 0.880)	0.038
ADAS-Cog13	D42	2.5-5 y	367	0.676 (0.039, 1.313)	0.038
ADAS-Cog13	T	0-2.5 y	367	-0.111 (-0.678, 0.456)	0.701
ADAS-Cog13	T	2.5-5 y	367	-0.298 (-1.295, 0.699)	0.558
ADAS-Cog13	BACE1	0-2.5 y	367	-0.378 (-0.953, 0.196)	0.197
ADAS-Cog13	BACE1	2.5-5 y	367	0.135 (-0.979, 1.249)	0.812

ADAS-Cog13	sAPPβ	0-2.5 y	367	-0.023 (-0.495, 0.449)	0.923
ADAS-Cog13	sAPPβ	2.5-5 y	367	0.132 (-0.973, 1.236)	0.815
CDR-SB	D42	0-2.5 y	368	0.226 (0.085, 0.367)	0.002
CDR-SB	D42	2.5-5 y	368	0.144 (-0.073, 0.360)	0.194
CDR-SB	T	0-2.5 y	368	0.032 (-0.133, 0.197)	0.705
CDR-SB	T	2.5-5 y	368	-0.101 (-0.451, 0.249)	0.572
CDR-SB	BACE1	0-2.5 y	368	-0.170 (-0.318, -0.022)	0.024
CDR-SB	BACE1	2.5-5 y	368	0.049 (-0.296, 0.395)	0.779
CDR-SB	sAPPβ	0-2.5 y	368	-0.024 (-0.154, 0.106)	0.715
CDR-SB	sAPPβ	2.5-5 y	368	-0.049 (-0.316, 0.219)	0.721
FAQ	D42	0-2.5 y	370	1.058 (0.656, 1.460)	2.51e-07
FAQ	D42	2.5-5 y	370	0.160 (-0.399, 0.718)	0.575
FAQ	T	0-2.5 y	370	-0.237 (-0.722, 0.247)	0.336
FAQ	T	2.5-5 y	370	-0.921 (-1.756, -0.086)	0.031
FAQ	BACE1	0-2.5 y	370	-0.186 (-0.623, 0.251)	0.405
FAQ	BACE1	2.5-5 y	370	1.030 (0.244, 1.815)	0.010
FAQ	sAPPβ	0-2.5 y	370	-0.039 (-0.420, 0.342)	0.840
FAQ	sAPPβ	2.5-5 y	370	-0.191 (-0.914, 0.531)	0.604
MMSE worsening	D42	0-2.5 y	369	0.284 (-0.007, 0.574)	0.056
MMSE worsening	D42	2.5-5 y	369	0.275 (-0.187, 0.738)	0.243
MMSE worsening	T	0-2.5 y	369	-0.077 (-0.405, 0.251)	0.645
MMSE worsening	T	2.5-5 y	369	-0.259 (-1.225, 0.707)	0.599
MMSE worsening	BACE1	0-2.5 y	369	-0.096 (-0.416, 0.224)	0.557
MMSE worsening	BACE1	2.5-5 y	369	0.298 (-0.510, 1.106)	0.470
MMSE worsening	sAPPβ	0-2.5 y	369	-0.114 (-0.381, 0.153)	0.403
MMSE worsening	sAPPβ	2.5-5 y	369	-0.024 (-0.511, 0.463)	0.924

Positive clinical coefficients denote faster worsening. N380 joint models include BACE1, sAPPβ, T and D42; N560 joint models include T_R and D42_R. Covariate structure follows the frozen Stage-3 protocol.

Supplementary Table S9b. Complete prespecified clinical joint estimates by follow-up interval (N560).

Outcome	Predictor	Follow-up interval	N	β/year (95% CI)	P
ADAS-Cog13	D42_R	0-2.5 y	470	1.215 (0.621, 1.809)	6.14e-05
ADAS-Cog13	D42_R	2.5-5 y	470	0.102 (-0.606, 0.810)	0.778
ADAS-Cog13	T_R	0-2.5 y	470	0.111 (-0.222, 0.445)	0.514
ADAS-Cog13	T_R	2.5-5 y	470	-0.015 (-0.431, 0.401)	0.944
CDR-SB	D42_R	0-2.5 y	480	0.241 (0.082, 0.401)	0.003
CDR-SB	D42_R	2.5-5 y	480	0.126 (-0.096, 0.348)	0.265
CDR-SB	T_R	0-2.5 y	480	-0.018 (-0.140, 0.104)	0.773
CDR-SB	T_R	2.5-5 y	480	-0.006 (-0.180, 0.167)	0.944
FAQ	D42_R	0-2.5 y	481	0.604 (0.172, 1.035)	0.006
FAQ	D42_R	2.5-5 y	481	0.294 (-0.218, 0.806)	0.260
FAQ	T_R	0-2.5 y	481	0.172 (-0.109, 0.454)	0.231
FAQ	T_R	2.5-5 y	481	-0.230 (-0.599, 0.139)	0.222
MMSE worsening	D42_R	0-2.5 y	471	0.568 (0.258, 0.878)	0.0003
MMSE worsening	D42_R	2.5-5 y	471	0.259 (-0.113, 0.631)	0.172
MMSE worsening	T_R	0-2.5 y	471	-0.081 (-0.244, 0.081)	0.328
MMSE worsening	T_R	2.5-5 y	471	0.066 (-0.222, 0.354)	0.652

Positive clinical coefficients denote faster worsening. N380 joint models include BACE1, sAPPβ, T and D42; N560 joint models include T_R and D42_R. Covariate structure follows the frozen Stage-3 protocol.

Supplementary Table S10a. Complete prespecified whole-brain-loss joint estimates by follow-up interval (N380).

Predictor	Follow-up interval	N	β percentage-points/year (95% CI)	P
D42	0-2.5 y	343	0.180 (0.109, 0.250)	5.21e-07
D42	2.5-5 y	343	0.150 (-0.125, 0.425)	0.286
T	0-2.5 y	343	-0.144 (-0.237, -0.051)	0.003
T	2.5-5 y	343	-0.329 (-0.650, -0.007)	0.045
BACE1	0-2.5 y	343	-0.045 (-0.138, 0.048)	0.346
BACE1	2.5-5 y	343	0.328 (0.028, 0.628)	0.032
sAPPβ	0-2.5 y	343	-0.042 (-0.114, 0.029)	0.247

sAPPβ	2.5-5 y	343	0.269 (0.045, 0.494)	0.019

Higher whole-brain KN-BSI loss indicates greater atrophy. N380 and N560 use the corresponding joint predictor sets defined above.

Supplementary Table S10b. Complete prespecified whole-brain-loss joint estimates by follow-up interval (N560).

Predictor	Follow-up interval	N	β percentage-points/year (95% CI)	P
D42_R	0-2.5 y	360	0.214 (0.107, 0.322)	9.29e-05
D42_R	2.5-5 y	360	-0.091 (-0.239, 0.057)	0.226
T_R	0-2.5 y	360	-0.077 (-0.142, -0.011)	0.021
T_R	2.5-5 y	360	0.104 (-0.024, 0.233)	0.111

Higher whole-brain KN-BSI loss indicates greater atrophy. N380 and N560 use the corresponding joint predictor sets defined above.

Supplementary Table S11a. Formal contrasts between follow-up intervals (clinical).

Cohort	Outcome	Predictor	0-2.5 minus 2.5-5 y β difference (95% CI)	P
N380	CDR-SB	BACE1	-0.219 (-0.637, 0.198)	0.303
N380	CDR-SB	sAPPβ	0.024 (-0.302, 0.351)	0.883
N380	CDR-SB	T	0.133 (-0.303, 0.569)	0.551
N380	CDR-SB	D42	0.082 (-0.216, 0.381)	0.588
N380	ADAS-Cog13	BACE1	-0.513 (-1.930, 0.903)	0.478
N380	ADAS-Cog13	sAPPβ	-0.155 (-1.477, 1.167)	0.818
N380	ADAS-Cog13	T	0.187 (-1.150, 1.523)	0.784
N380	ADAS-Cog13	D42	-0.224 (-1.088, 0.640)	0.612
N380	FAQ	BACE1	-1.215 (-2.271, -0.160)	0.024
N380	FAQ	sAPPβ	0.152 (-0.777, 1.082)	0.748
N380	FAQ	T	0.683 (-0.442, 1.809)	0.234
N380	FAQ	D42	0.898 (0.105, 1.692)	0.026
N380	MMSE worsening	BACE1	-0.394 (-1.372, 0.585)	0.430
N380	MMSE worsening	sAPPβ	-0.090 (-0.737, 0.556)	0.784
N380	MMSE worsening	T	0.182 (-0.966, 1.330)	0.756
N380	MMSE worsening	D42	0.008 (-0.651, 0.668)	0.980
N560	CDR-SB	T_R	-0.012 (-0.255, 0.232)	0.925
N560	CDR-SB	D42_R	0.115 (-0.186, 0.416)	0.453
N560	ADAS-Cog13	T_R	0.126 (-0.516, 0.768)	0.700
N560	ADAS-Cog13	D42_R	1.113 (-0.002, 2.229)	0.050
N560	FAQ	T_R	0.402 (-0.148, 0.953)	0.152
N560	FAQ	D42_R	0.310 (-0.495, 1.114)	0.450
N560	MMSE worsening	T_R	-0.147 (-0.529, 0.235)	0.449
N560	MMSE worsening	D42_R	0.309 (-0.259, 0.876)	0.287

A nonzero contrast tests whether the prespecified coefficient during 0-2.5 years differs from the coefficient during 2.5-5 years. These temporal contrasts were not used to define diagnostic or biological stages or to select a post-result time-varying model.

Supplementary Table S11b. Formal contrasts between follow-up intervals (MRI).

Cohort	Outcome	Predictor	0-2.5 minus 2.5-5 y β difference (95% CI)	P
N380	Whole-brain loss	BACE1	-0.373 (-0.716, -0.030)	0.033
N380	Whole-brain loss	sAPPβ	-0.311 (-0.565, -0.057)	0.016
N380	Whole-brain loss	T	0.185 (-0.170, 0.540)	0.307
N380	Whole-brain loss	D42	0.030 (-0.262, 0.322)	0.841
N560	Whole-brain loss	T_R	-0.181 (-0.350, -0.012)	0.036
N560	Whole-brain loss	D42_R	0.306 (0.077, 0.535)	0.009

A nonzero contrast tests whether the prespecified coefficient during 0-2.5 years differs from the coefficient during 2.5-5 years. These temporal contrasts were not used to define diagnostic or biological stages or to select a post-result time-varying model.

Supplementary Table S12. Complete tau-PET burden and progression estimates.

Cohort	Tau	Model	Predictor / term	N	β (95% CI)	P
N380	nonPVC	componentwise	BACE1	28	0.135 (-0.307, 0.578)	0.550
N380	nonPVC	componentwise	sAPPβ	28	-0.008 (-0.554, 0.537)	0.976
N380	nonPVC	componentwise	T	28	0.068 (-0.422, 0.557)	0.786
N380	nonPVC	componentwise	D42	28	0.847 (0.094, 1.600)	0.027
N380	nonPVC	joint_exploratory	BACE1	28	0.232 (-0.403, 0.868)	0.474

N380	nonPVC	joint_exploratory	sAPPβ	28	-0.205 (-0.829, 0.418)	0.519
N380	nonPVC	joint_exploratory	T	28	-0.043 (-0.685, 0.599)	0.895
N380	nonPVC	joint_exploratory	D42	28	0.904 (0.054, 1.754)	0.037
N380	PVC	componentwise	BACE1	25	0.059 (-0.454, 0.573)	0.821
N380	PVC	componentwise	sAPPβ	25	-0.018 (-0.581, 0.545)	0.949
N380	PVC	componentwise	T	25	0.052 (-0.485, 0.588)	0.850
N380	PVC	componentwise	D42	25	0.917 (0.260, 1.575)	0.006
N380	PVC	joint_exploratory	BACE1	25	0.091 (-0.697, 0.879)	0.820
N380	PVC	joint_exploratory	sAPPβ	25	-0.255 (-0.935, 0.424)	0.462
N380	PVC	joint_exploratory	T	25	0.104 (-0.535, 0.743)	0.750
N380	PVC	joint_exploratory	D42	25	0.990 (0.264, 1.717)	0.008
N560	nonPVC	joint	T_R	96	0.086 (-0.107, 0.279)	0.380
N560	nonPVC	joint	D42_R	96	0.525 (0.125, 0.924)	0.010
N560	PVC	joint	T_R	89	0.056 (-0.150, 0.262)	0.592
N560	PVC	joint	D42_R	89	0.574 (0.165, 0.983)	0.006
N560	nonPVC	tau_progression_gee	T_R	47	-0.009 (-0.056, 0.039)	0.724
N560	nonPVC	tau_progression_gee	D42_R	47	0.033 (-0.030, 0.096)	0.299

Tau-burden coefficients are standardized outcome effects. Progression terms are post-landmark GEE interactions with time. The non-PVC first-subsequent-tau analysis was primary; PVC was a sensitivity analysis.

Supplementary Table S13. Formal T-versus-D42 contrasts for subsequent tau burden.

Cohort	Tau variant	Contrast	N	β difference (95% CI)	P
N380	nonPVC	T-D42	28	-0.947 (-1.894, -0.001)	0.050
N560	nonPVC	T_R-D42_R	96	-0.438 (-0.875, -0.001)	0.049
N380	PVC	T-D42	25	-0.887 (-1.800, 0.027)	0.057
N560	PVC	T_R-D42_R	89	-0.518 (-0.976, -0.060)	0.027

Supplementary Table S14. Prespecified restricted-cubic-spline nonlinearity tests.

Cohort	Outcome	Predictor	Domain / tau variant	Joint P	0-2.5 y P	2.5-5 y P	Tau P
N380	CDR-SB	BACE1	Clinical	0.251	0.483	0.271	—
N380	CDR-SB	sAPPβ	Clinical	0.169	0.172	0.144	—
N380	CDR-SB	T	Clinical	0.100	0.041	0.198	—
N380	CDR-SB	D42	Clinical	0.903	0.942	0.654	—
N380	ADAS-Cog13	BACE1	Clinical	0.430	0.287	0.659	—
N380	ADAS-Cog13	sAPPβ	Clinical	0.386	0.587	0.171	—
N380	ADAS-Cog13	T	Clinical	0.285	0.343	0.484	—
N380	ADAS-Cog13	D42	Clinical	0.589	0.304	0.871	—
N380	FAQ	BACE1	Clinical	0.118	0.915	0.073	—
N380	FAQ	sAPPβ	Clinical	0.946	0.850	0.750	—
N380	FAQ	T	Clinical	0.427	0.544	0.460	—
N380	FAQ	D42	Clinical	0.630	0.829	0.338	—
N380	MMSE worsening	BACE1	Clinical	0.220	0.211	0.621	—
N380	MMSE worsening	sAPPβ	Clinical	0.403	0.189	0.387	—
N380	MMSE worsening	T	Clinical	0.920	0.768	0.704	—
N380	MMSE worsening	D42	Clinical	0.534	0.546	0.575	—
N560	CDR-SB	T_R	Clinical	0.562	0.287	0.590	—
N560	CDR-SB	D42_R	Clinical	0.179	0.116	0.747	—
N560	ADAS-Cog13	T_R	Clinical	0.085	0.030	0.120	—
N560	ADAS-Cog13	D42_R	Clinical	0.556	0.317	0.969	—
N560	FAQ	T_R	Clinical	0.010	0.005	0.063	—
N560	FAQ	D42_R	Clinical	0.287	0.255	0.711	—
N560	MMSE worsening	T_R	Clinical	0.439	0.257	0.350	—
N560	MMSE worsening	D42_R	Clinical	0.140	0.520	0.082	—
N380	Whole-brain loss	BACE1	MRI	0.345	0.618	0.222	—
N380	Whole-brain loss	sAPPβ	MRI	0.763	0.625	0.657	—
N380	Whole-brain loss	T	MRI	0.910	0.672	0.867	—
N380	Whole-brain loss	D42	MRI	1.07e-05	0.0002	0.0001	—
N560	Whole-brain loss	T_R	MRI	0.768	0.769	0.705	—

N560	Whole-brain loss	D42_R	MRI	0.769	0.612	0.483	—
N560	meta-temporal tau	T_R	nonPVC	—	—	—	0.039
N560	meta-temporal tau	D42_R	nonPVC	—	—	—	0.711
N560	meta-temporal tau	T_R	PVC	—	—	—	0.603
N560	meta-temporal tau	D42_R	PVC	—	—	—	0.588

Spline knots were fixed at the 10th, 50th and 90th percentiles of the corresponding predictor. No post-result shape selection was performed. Isolated nominal nonlinear tests that did not reproduce across cohorts/outcomes were not interpreted as stable evidence of nonlinearity.

Supplementary Table S15. Exploratory direct SAA-to-natural-history outcome bridge.

Outcome	Model	Follow-up interval / landmark	N	SAA+ β (95% CI)	P
CDR-SB	A: SAA total	0-2.5 y	480	0.178 (-0.162, 0.519)	0.305
CDR-SB	A: SAA total	2.5-5 y	480	-0.014 (-0.497, 0.470)	0.955
CDR-SB	B: +T_R/D42_R	0-2.5 y	480	0.135 (-0.186, 0.456)	0.410
CDR-SB	B: +T_R/D42_R	2.5-5 y	480	0.054 (-0.414, 0.521)	0.822
ADAS-Cog13	A: SAA total	0-2.5 y	470	-0.075 (-1.179, 1.030)	0.894
ADAS-Cog13	A: SAA total	2.5-5 y	470	-0.087 (-1.511, 1.338)	0.905
ADAS-Cog13	B: +T_R/D42_R	0-2.5 y	470	-0.102 (-1.133, 0.929)	0.846
ADAS-Cog13	B: +T_R/D42_R	2.5-5 y	470	0.090 (-1.271, 1.450)	0.897
FAQ	A: SAA total	0-2.5 y	481	0.710 (-0.159, 1.580)	0.109
FAQ	A: SAA total	2.5-5 y	481	-0.400 (-1.634, 0.833)	0.525
FAQ	B: +T_R/D42_R	0-2.5 y	481	0.662 (-0.195, 1.519)	0.130
FAQ	B: +T_R/D42_R	2.5-5 y	481	-0.255 (-1.501, 0.991)	0.688
MMSE worsening	A: SAA total	0-2.5 y	471	0.281 (-0.279, 0.841)	0.325
MMSE worsening	A: SAA total	2.5-5 y	471	-0.572 (-1.185, 0.041)	0.067
MMSE worsening	B: +T_R/D42_R	0-2.5 y	471	0.226 (-0.301, 0.752)	0.401
MMSE worsening	B: +T_R/D42_R	2.5-5 y	471	-0.416 (-1.011, 0.180)	0.171
Whole-brain loss	A: SAA total	0-2.5 y	360	0.233 (0.041, 0.424)	0.017
Whole-brain loss	A: SAA total	2.5-5 y	360	-0.190 (-0.649, 0.269)	0.417
Whole-brain loss	B: +T_R/D42_R	0-2.5 y	360	0.140 (-0.047, 0.327)	0.142
Whole-brain loss	B: +T_R/D42_R	2.5-5 y	360	-0.012 (-0.487, 0.463)	0.960
Subsequent tau, non-PVC	A: SAA total	first subsequent tau	96	-0.101 (-0.691, 0.489)	0.738
Subsequent tau, non-PVC	B: +T_R/D42_R	first subsequent tau	96	-0.089 (-0.684, 0.507)	0.771
Subsequent tau, PVC	A: SAA total	first subsequent tau	89	-0.013 (-0.680, 0.654)	0.970
Subsequent tau, PVC	B: +T_R/D42_R	first subsequent tau	89	0.018 (-0.657, 0.694)	0.957
Tau progression	A: SAA total	post-tau landmark	47	-0.002 (-0.196, 0.192)	0.984
Tau progression	B: +T_R/D42_R	post-tau landmark	47	0.000 (-0.081, 0.081)	0.996

These models were specified after the SAA-coordinate and coordinate-outcome findings were known. Model B conditions additionally on T_R and D42_R. Differences between Models A and B are descriptive and are not mediation estimates.

Supplementary Table S16. Descriptive A/S biological cross-classification in the participant-disjoint cohort (±365-day amyloid-PET window).

Category	N	Operational description
A+S+	81	Amyloid-PET positive and SAA positive
A-S+	31	Amyloid-PET negative and SAA positive
A?S+	19	No eligible amyloid-PET classification and SAA positive
A+S-	199	Amyloid-PET positive and SAA negative
A-S-	159	Amyloid-PET negative and SAA negative
A?S-	71	No eligible amyloid-PET classification and SAA negative

A denotes the contemporaneous amyloid-PET category and S denotes αSyn-SAA status. This classification is descriptive only: PET availability was not used to restrict or adjust the primary SAA-soluble analyses, A? was never recoded as A−, and clinical syndrome labels were not treated as etiological diagnoses.