Supplementary Material

High Soluble Amyloid-β_{42} Predicts Normal Cognition in Amyloid-Positive Individuals with Alzheimer's Disease-Causing Mutations

Statistical Analysis

Data were described with mean and standard deviation to summarize continuous data and frequency and percentage for categorical data. All statistical analyses were performed using STATA 17.

Model development

The primary outcome was analyzed using modified Poisson regression analysis to estimate the relative risk (RR) as appropriate for cohort data analysis. The primary model (model 1) included CDR progression as a dependent variable and z-standardized forms of CSF $A\beta_{42}$, CSF t-tau and p-tau, and SUVR levels as primary independent variables after adjusting for age at onset, sex, education, *APOE4*, and duration of follow-up. The results of the primary model were validated by performing multiple sensitivity analyses: (a) model 2 (additional adjustment) after additionally adjusting for CDR baseline distribution using modified Poisson regression analysis; (b) model 3 (different modeling approach) after additionally adjusting for CDR baseline distribution but analyzing the time to first CDR progression using Cox proportional hazards model. Time to CDR progression was computed from the baseline visit to the year when the first CDR progression was observed. CDR non-progression was considered a censored event. The Cox regression analysis was performed after assessing the proportionality assumption using Schoenfeld residual-based test; (c) model 4 (under different assumptions) analyzing the time to first CDR progression using stratified Cox proportional hazards model by assuming different baseline survival functions according to CDR baseline; (d) model 5 (different adjustment) analyzing CDR progression using modified Poisson regression analysis after adjusting for age (instead of age at onset), CDR baseline, sex, education, *APOE4*, and duration of follow-up; (e) model 6 (addressing multicollinearity) analyzing CDR progression using modified Poisson regression analysis after adjusting for age, sex, education, *APOE4*, and duration of follow-up but excluding t-tau or p-tau from the model due to strong positive correlation between t-tau and p-tau levels; (f) model 7 (addressing missing data) analyzing CDR progression using modified Poisson

regression analysis after multiple missing imputations on missing data. The missing imputations were carried out 10 times by using chained equations with truncated regression for continuous variables with a restricted range. On each dataset, modified Poisson regression analysis was performed by considering CDR progression as a dependent variable and z-standardized forms of CSF $A\beta_{42}$, CSF t-tau and p-tau, and SUVR levels as primary independent variables after adjusting for age at onset (or age), sex, education, *APOE4*, and duration of follow-up. The aggregated results from 10 iterations of modified Poisson regression analysis on imputed datasets were obtained to estimate the RR for the associations. All these models were developed separately for PiB-PET positive samples and the overall cohort. All the binary secondary outcomes were analyzed using modified Poisson regression analysis. The analysis included progression to CDR $\geq$ 0.5, progression to CDR $\geq$1, MMSE $\leq$ 24, or CDR-SB $\geq$ 4.5 as a dependent variable whereas z-standardized forms of CSF $A\beta_{42}$, CSF t-tau and p-tau, and SUVR levels as primary independent variables after adjusting for age at onset, sex, education, *APOE4*, and duration of follow-up. The quantitative secondary outcomes were analyzed using linear regression models by considering FDG-PET or normalized hippocampi volume as a dependent variable whereas z-standardized forms of CSF $A\beta_{42}$, CSF t-tau and p-tau, and SUVR levels as primary independent variables after adjusting for age at onset, sex, education, *APOE4*, and duration of follow-up. The analyses of secondary outcomes were confirmed by performing multiple sensitivity analyses: (a) model with a different adjustment including age (instead of age at onset), sex, education, *APOE4*, and duration of follow-up; (b) model after adjusting for age, sex, education, *APOE4*, and duration of follow-up but excluding t-tau or p-tau from the model due to strong positive correlation between t-tau and p-tau levels. Since the subjects close to the SUVR level of 1.42 (borderline positive) may be classified as PiB-PET negative using different assays, we further confirmed results from all models for PiB-PET positive samples after excluding subjects within 5% of the SUVR threshold. Since our primary objective was to develop an explanatory model, all the critical covariates were adjusted regardless of their significance level.

Results interpretation

Since our intention was to facilitate a descriptive comparison of the effect sizes associated with CSF $A\beta_{42}$ with SUVR, CSF t-tau and p-tau levels in the same direction, the RR obtained

from the modified Poisson regression analysis or hazard ratio (HR) obtained from the Cox models associated with SUVR, CSF t-tau and p-tau levels was inverted (1/RR or 1/HR). Therefore, RR or HR provides the risk of outcome associated with one standard deviation higher in CSF $A\beta_{42}$ levels whereas one standard deviation lower in CSF t-tau, CSF p-tau and SUVR levels. Regression coefficient (RC) estimated from linear models provides the increase or decrease in outcome associated with one standard deviation increase in CSF $A\beta_{42}$ levels, CSF t-tau, CSF p-tau and SUVR levels. We did not use any automated selection criteria to adjust covariates in multivariable analyses as per the recommendation for the association study. All the critical covariates were adjusted in the primary analyses [1]. We did not conduct sensitivity analyses to select the best predictors or best models. We performed multiple sensitivity analyses as recommended to assess the robustness of the findings only [1]. The primary findings reported in this study were also confirmed using multiple logistic regression analyses, unadjusted and limited adjusted covariates in relative risk regression analyses (results are not shown). Our findings also indicate that there was no significant impact of collinearity between p-tau and t-tau on the relationship between CSF $A\beta_{42}$ and CDR progression.

Cut-off determination of CSF $A\beta_{42}$ levels

The cut-off of CSF $A\beta_{42}$ levels for predicting CDR progression was determined using a simple receiver operating characteristic curve (ROC) analysis. The cut-off yielding similar and maximum sensitivity and specificity was considered the final threshold. We also validated the cut-off of CSF $A\beta_{42}$ levels for predicting CDR progression after adjusting for age, sex, education, *APOE4,* and duration of follow-up. Using the estimated cutoff of CSF $A\beta_{42}$, we also compared progression-free survival using a Kaplan-Meier analysis, tested with a log-rank test.

Predictive probabilities for CDR progression

Since logistic regression generally overestimates the effect size for the common binary outcomes and may not be appropriate for cohort studies, we used a modified Poisson regression as the primary method of data analysis. Although modified Poisson regression is suitable for estimating RR, it may not be appropriate for obtaining predicted probabilities. Therefore, we used multiple logistic regression for obtaining predictive probabilities of CDR progression by CSF $A\beta_{42}$ and SUVR levels after adjusting for CSF t-tau, CSF p-tau, age at onset, sex, education,

APOE4, and duration of follow-up. A contour probability plot was constructed to estimate the probability of CDR progression according to CSF $A\beta_{42}$ and PiB-PET SUVR levels using adjusted logistic regression with differences in baseline CSF $A\beta_{42}$ levels determined using an unpaired t-test.

REFERENCE

[1] Dwivedi AK (2022) How to write statistical analysis section in medical research. *J Investig Med*, doi: 10.1136/jim-2022-002479.

Supplementary Table 1. Distribution of baseline characteristics between cohorts with missing data and without missing data

	PiB-PET-positive cohort			**Overall mutation carrier cohort**		
	Without missing	With missing	p	Without missing	With missing	p
N	93	15		162	70	
Age (y)	40.9 (10.4)	41.7 (10.9)	0.78	37.6 (10.5)	39.8 (11.9)	0.17
Age at onset	44.8 (7.4)	47.0 (5.9)	0.29	47.1 (7.4)	47.1 (5.8)	0.98
Sex (female)	48 (52%)	7 (47%)	0.72	91 (56.2%)	39 (55.7%)	0.95
Education (y)	13.8 (3.1)	14.1 (2.3)	0.71	14.3 (3.0)	14.4 (3.2)	0.79
APOE4 carriers	35 (38%)	5 (33%)	0.75	53 (32.7%)	19 (27.1%)	0.40
CSF $A\beta_{42}$ (pg/ml), mean (SD)	264.6 (107.9)	NA		361.5 (182.8)	289.6 (200.3)	0.056
SUVR (amyloid-PiB-PET)	2.6 (1.0)	2.4 (0.9)	0.69	1.9 (1.1)	1.8 (0.9)	0.54
t-tau, (pg/ml)	146.5 (89.3)	51.5 (2.0)	0.14	112.0 (84.4)	107.2 (66.8)	0.76
p-tau, (pg/ml)	82.7 (37.8)	34.7 (5.2)	0.078	62.1 (38.7)	60.9 (32.0)	0.87
CDR at baseline			0.11			<0.001
0	49 (53%)	6 (40%)		114 (70.4%)	33 (47.1%)	
0.5	27 (29%)	6 (40%)		30 (18.5%)	30 (42.9%)	
1	15 (16%)	2 (13%)		15 (9.3%)	5 (7.1%)	
2	2 (2%)	0 (0%)		3 (1.9%)	0 (0.0%)	
3	0 (0%)	1 (7%)		0 (0.0%)	2 (2.9%)	
CDR-SB at baseline	1.7 (2.5)	2.2 (4.5)	0.53	1.1 (2.2)	1.5 (3.0)	0.23
MMSE at baseline	26.4 (4.6)	26.0 (6.8)	0.76	27.4 (3.9)	26.5 (5.3)	0.14
FDG-PET at baseline (SUVR)	1.8 (0.3)	1.8 (0.2)	0.38	1.8 (0.2)	1.9 (0.2)	0.36
Average hippocampi baseline (mm3)	4032.8 (685.6)	3957.5 (863.0)	0.70	4199.2 (612.3)	4099.3 (666.5)	0.31
Normalized hippocampi baseline (mm^3)	4032.5 (686.4)	3958.5 (864.4)	0.71	4198.9 (613.3)	4099.1 (667.6)	0.32

N, number of subjects; *APOE4*, Apolipoprotein ε4; CDR, clinical dementia rating; CDR-SB, CDR sum of boxes; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phosphorylated-tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; MMSE, Mini-Mental State Examination; FDG, fluorodeoxyglucose; pg, picogram; ml, milliliter; mm, millimeter. Data are expressed in mean ± standard deviation (SD) or frequency (%).

Supplementary Table 2. Adjusted associations of baseline CSF $A\beta_{42}$, SUVR, p-tau and t-tau levels with CDR progression and time to CDR progression outcome in individuals with Alzheimer's disease-causing mutations

	CDR progression				Time to first CDR progression				Time to first CDR progression stratified by baseline CDR			
	RR*	**95% CI**		**p**	**HR#**	**95% CI**		**p**	**HR#**	**95% CI**		**p**
PiB-PET-positive cohort												
CSF $A\beta_{42}$	0.35	0.19	0.67	0.001	0.37	0.18	0.77	0.008	0.45	0.22	0.90	0.023
SUVR (PiB-PET)	0.80	0.67	0.96	0.016	0.79	0.62	1.02	0.075	0.77	0.59	1.00	0.049
CSF t-tau	0.99	0.70	1.41	0.946	0.88	0.61	1.30	0.528	0.99	0.65	1.52	0.956
CSF p-tau	0.73	0.50	1.06	0.100	0.63	0.40	0.98	0.041	0.56	0.34	0.92	0.020
PiB-PET-positive (SUVR ≥ 1.49)												
CSF Aβ42	0.38	0.19	0.75	0.006	0.40	0.18	0.87	0.020	0.48	0.23	1.00	0.051
SUVR (PiB-PET)	0.80	0.67	0.96	0.016	0.80	0.61	1.04	0.096	0.77	0.59	1.00	0.053
CSF t-tau	0.99	0.69	1.41	0.960	0.88	0.60	1.30	0.513	0.99	0.64	1.52	0.954
CSF p-tau	0.73	0.50	1.06	0.107	0.64	0.41	1.01	0.056	0.56	0.34	0.93	0.027
Overall cohort												
CSF $A\beta_{42}$	0.47	0.30	0.76	0.002	0.51	0.31	0.86	0.011	0.56	0.35	0.92	0.022
SUVR (PiB-PET)	0.81	0.67	0.97	0.022	0.79	0.62	1.01	0.062	0.76	0.58	1.00	0.048
CSF t-tau	0.92	0.63	1.35	0.667	0.83	0.56	1.25	0.374	0.92	0.58	1.45	0.720
CSF p-tau	0.76	0.50	1.15	0.195	0.62	0.40	0.97	0.037	0.53	0.33	0.86	0.011

*Relative risk (RR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; #Hazard ratio (HR) of progression is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phospho-tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; CDR, clinical dementia rating. All CSF and SUVR values are standardized. *Analysis adjusted for CDR at baseline, age at onset, sex, education, *APOE4* status and duration of follow-up; #Analysis adjusted for CDR at baseline, age at onset, sex, education, and *APOE4* status; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 3. Adjusted associations of baseline CSF $A\beta_{42}$, SUVR, p-tau and t-tau levels with CDR progression and time to first CDR progression after excluding t-tau or p-tau from the analysis

	CDR progression				**Time to first CDR progression**			
	RR*	**95%CI**		**p**	**HR#**	**95%CI**		**p**
PiB-PET-positive cohort								
CSF $A\beta_{42}$	0.37	0.19	0.72	0.003	0.43	0.20	0.95	0.036
SUVR (PiB-PET)	0.76	0.64	0.91	0.003	0.74	0.57	0.94	0.016
CSF t-tau	1.03	0.75	1.43	0.840	0.93	0.66	1.33	0.722
CSF p-tau	0.67	0.47	0.95	0.028	0.56	0.37	0.84	0.006
PiB-PET-positive (SUVR ≥ 1.49)								
CSF $A\beta_{42}$	0.38	0.19	0.76	0.007	0.45	0.20	1.03	0.058
SUVR (PiB-PET)	0.76	0.64	0.92	0.003	0.74	0.57	0.96	0.023
CSF t-tau	1.06	0.76	1.47	0.718	0.95	0.66	1.35	0.773
CSF p-tau	0.67	0.47	0.95	0.025	0.56	0.37	0.86	0.008
PiB-PET-positive cohort without p-tau								
CSF $A\beta_{42}$	0.36	0.19	0.68	0.002	0.42	0.20	0.88	0.022
SUVR (PiB-PET)	0.79	0.67	0.93	0.005	0.78	0.62	0.98	0.032
CSF t-tau	0.81	0.64	1.04	0.099	0.68	0.52	0.90	0.007
PiB-PET-positive cohort without t-tau								
CSF $A\beta_{42}$	0.37	0.19	0.72	0.003	0.43	0.20	0.95	0.036
SUVR (PiB-PET)	0.76	0.65	0.91	0.002	0.73	0.57	0.93	0.010
CSF p-tau	0.69	0.53	0.89	0.004	0.53	0.39	0.70	<0.001
Overall cohort								
CSF $A\beta_{42}$	0.52	0.31	0.86	0.012	0.60	0.34	1.07	0.082
SUVR (PiB-PET)	0.76	0.63	0.91	0.003	0.73	0.58	0.93	0.009
CSF t-tau	0.93	0.65	1.35	0.727	0.87	0.60	1.25	0.451
CSF p-tau	0.71	0.48	1.06	0.100	0.57	0.38	0.86	0.007
Overall cohort without p-tau								
CSF $A\beta_{42}$	0.49	0.30	0.81	0.005	0.55	0.32	0.95	0.033
SUVR (PiB-PET)	0.75	0.64	0.89	0.001	0.72	0.58	0.90	0.004
CSF t-tau	0.77	0.60	0.98	0.032	0.64	0.49	0.85	0.002

Overall cohort without t-tau								
CSF $A\beta_{42}$	0.52	0.31	0.87	0.013	0.61	0.34	1.09	0.092
SUVR (PiB-PET)	0.76	0.63	0.91	0.003	0.73	0.57	0.93	0.010
CSF p-tau	0.68	0.53	0.86	0.002	0.51	0.38	0.67	<0.001

*Relative risk (RR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; #Hazard ratio (HR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; CI: confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; CDR, clinical dementia rating. *Adjusted for CDR at baseline, age, education, sex, and *APOE4*, and duration of follow-up; #Adjusted for CDR at baseline, age, education, sex, and *APOE4*; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 4. Adjusted associations of baseline CSF $A\beta_{42}$, SUVR, p-tau and t-tau levels with CDR progression after missing imputations

	RR*	95% CI		p	RR#	95% CI		p
PiB-PET-positive cohort								
CSF $A\beta_{42}$	0.62	0.88	0.44	0.008	0.49	0.74	0.32	0.001
SUVR (PiB-PET)	0.77	0.65	0.92	0.004	0.76	0.64	0.91	0.002
CSF t-tau	0.99	0.69	1.43	0.960	0.93	0.68	1.28	0.652
CSF p-tau	0.78	0.53	1.14	0.195	0.77	0.55	1.07	0.118
Overall mutation carrier cohort								
CSF $A\beta_{42}$	0.65	0.93	0.45	0.017	0.52	0.81	0.34	0.004
SUVR (PiB-PET)	0.76	0.65	0.90	0.002	0.76	0.64	0.90	0.002
CSF t-tau	1.06	0.75	1.49	0.752	0.98	0.74	1.31	0.897
CSF p-tau	0.72	0.50	1.03	0.069	0.73	0.54	0.99	0.043

Relative risk (RR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; CDR, clinical dementia rating. *Adjusted for age at onset, education, sex, *APOE4*, and duration of follow-up; #Adjusted for age, education, sex, *APOE4*, and duration of follow-up; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 5. Adjusted associations of baseline CSF and SUVR levels with key secondary outcomes after adjusting for age instead of age at onset along with other covariates

	PiB-PET-positive cohort				PiB-PET-positive cohort, SUVR ≥ 1.49				Overall mutation carrier cohort			
	RR*	**95% CI**		**p**	**RR***	**95% CI**		**p**	**RR***	**95%CI**		**p**
Progression to CDR ≥ 0.5												
CSF $A\beta_{42}$	0.58	0.39	0.85	0.005	0.64	0.43	0.96	0.029	0.55	0.37	0.81	0.002
SUVR (PiB-PET)	0.75	0.64	0.88	0.001	0.77	0.65	0.91	0.002	0.71	0.61	0.84	<0.001
CSF t-tau	1.01	0.85	1.19	0.941	0.99	0.83	1.16	0.865	1.03	0.87	1.22	0.700
CSF p-tau	0.68	0.53	0.86	0.001	0.69	0.55	0.88	0.003	0.62	0.50	0.78	<0.001
Progression to CDR ≥ 1												
CSF $A\beta_{42}$	0.30	0.14	0.64	0.002	0.33	0.15	0.73	0.006	0.32	0.16	0.61	0.001
SUVR (PiB-PET)	0.69	0.54	0.88	0.003	0.69	0.53	0.90	0.006	0.65	0.52	0.83	<0.001
CSF t-tau	1.03	0.79	1.33	0.823	1.01	0.78	1.30	0.955	1.02	0.79	1.32	0.901
CSF p-tau	0.55	0.35	0.86	0.009	0.55	0.34	0.88	0.013	0.50	0.32	0.77	0.002
CDR-SB ≥ 4.5 at last visit[#]												
CSF $A\beta_{42}$	0.35	0.17	0.70	0.003	0.38	0.19	0.77	0.007	0.32	0.18	0.58	<0.001
SUVR (PiB-PET)	0.78	0.63	0.96	0.021	0.77	0.61	0.96	0.020	0.73	0.60	0.88	0.002
CSF t-tau	1.16	0.85	1.59	0.342	1.14	0.85	1.52	0.397	1.20	0.88	1.64	0.237
CSF p-tau	0.48	0.30	0.76	0.002	0.47	0.29	0.75	0.002	0.41	0.27	0.65	<0.001
MMSE≤24 at last visit[#]												
CSF $A\beta_{42}$	0.37	0.20	0.66	0.001	0.38	0.21	0.68	0.001	0.34	0.19	0.60	<0.001
SUVR (PiB-PET)	0.79	0.61	1.01	0.057	0.81	0.64	1.04	0.102	0.73	0.57	0.93	0.011
CSF t-tau	1.04	0.65	1.67	0.860	1.04	0.66	1.64	0.864	1.06	0.68	1.67	0.783
CSF p-tau	0.61	0.38	0.97	0.035	0.64	0.40	1.01	0.053	0.52	0.33	0.83	0.006

*Relative risk (RR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; CDR-SB, CDR sum of boxes; MMSE, Mini-Mental State Examination; FDG, fluorodeoxyglucose; All CSF and SUVR values are standardized. Analysis adjusted for age, sex, education, *APOE4*, and duration of follow-up; [#]Analysis also adjusted for CDR-SB at baseline or MMSE at baseline; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 6. Adjusted associations of baseline CSF and SUVR levels with key secondary outcomes after excluding t-tau or p-tau from the analysis due to collinearity

	PiB-PET-positive cohort				Overall mutation carrier cohort			
	RR*	**95%CI**		**p**	**RR***	**95%CI**		**p**
Progression to CDR ≥ 0.5 without p-tau								
CSF $A\beta_{42}$	0.55	0.37	0.80	0.002	0.49	0.34	0.71	<0.001
SUVR (PiB-PET)	0.78	0.67	0.91	0.001	0.72	0.62	0.84	<0.001
CSF t-tau	0.80	0.70	0.92	0.001	0.78	0.68	0.89	0.001
Progression to CDR ≥ 1 without p-tau								
CSF $A\beta_{42}$	0.29	0.14	0.59	0.001	0.29	0.16	0.52	<0.001
SUVR (PiB-PET)	0.76	0.63	0.93	0.008	0.70	0.58	0.86	0.001
CSF t-tau	0.76	0.64	0.89	0.001	0.71	0.60	0.84	<0.001
CDR-SB ≥ 4.5 at last visit without p-tau[#]								
CSF $A\beta_{42}$	0.35	0.19	0.65	0.001	0.29	0.17	0.48	<0.001
SUVR (PiB-PET)	0.86	0.72	1.02	0.087	0.78	0.66	0.91	0.002
CSF t-tau	0.83	0.70	0.98	0.026	0.80	0.68	0.94	0.009
MMSE≤24 at last visit without p-tau[#]								
CSF $A\beta_{42}$	0.37	0.22	0.64	<0.001	0.33	0.19	0.55	<0.001
SUVR (PiB-PET)	0.83	0.65	1.05	0.121	0.75	0.59	0.95	0.019
CSF t-tau	0.79	0.63	1.00	0.050	0.74	0.61	0.91	0.005
Progression to CDR ≥ 0.5 without t-tau								
CSF $A\beta_{42}$	0.58	0.39	0.85	0.005	0.55	0.37	0.80	0.002
SUVR (PiB-PET)	0.75	0.64	0.88	0.001	0.71	0.61	0.84	<0.001
CSF p-tau	0.68	0.58	0.80	<0.001	0.64	0.54	0.76	<0.001
Progression to CDR ≥ 1 without t-tau								
CSF $A\beta_{42}$	0.30	0.14	0.64	0.002	0.32	0.16	0.61	0.001
SUVR (PiB-PET)	0.69	0.55	0.88	0.002	0.65	0.52	0.83	<0.001
CSF p-tau	0.56	0.40	0.79	0.001	0.51	0.37	0.70	<0.001
CDR-SB ≥ 4.5 at last visit without t-tau[#]								
CSF $A\beta_{42}$	0.35	0.18	0.69	0.002	0.31	0.17	0.54	<0.001
SUVR (PiB-PET)	0.79	0.65	0.97	0.026	0.74	0.61	0.88	0.001
CSF p-tau	0.56	0.39	0.81	0.002	0.50	0.34	0.74	<0.001

MMSE≤24 at last visit without t-tau[#]								
CSF $A\beta_{42}$	0.37	0.20	0.66	0.001	0.33	0.19	0.59	<0.001
SUVR (PiB-PET)	0.79	0.62	1.01	0.059	0.73	0.57	0.93	0.012
CSF p-tau	0.63	0.44	0.89	0.009	0.55	0.39	0.79	0.001

*Relative risk (RR) is with one standard deviation higher in CSF $A\beta_{42}$ levels and lower in CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid b-amyloid peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; CDR-SB, CDR sum of boxes; MMSE, Mini-Mental State Examination; FDG, fluorodeoxyglucose. All CSF and SUVR values are standardized. Analysis adjusted for age, sex, education, *APOE4*, and duration follow-up; [#]Analysis also adjusted for CDR-SB at baseline or MMSE at baseline; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 7. Adjusted associations between baseline CSF and SUVR levels with secondary outcomes of normalized hippocampi volume and FDG-PET at last visit

	PiB-PET-positive cohort				PiB-PET-positive cohort with SUVR ≥ 1.49				Overall mutation carrier cohort			
	RC*	**95% CI**		**p**	**RC***	**95% CI**		**p**	**RC***	**95% CI**		**p**
Hippocampi volume (normalized) at last visit[#]												
CSF $A\beta_{42}$	319.91	73.97	565.86	0.012	377.01	148.05	605.97	0.002	58.88	-47.49	165.25	0.276
SUVR (PiB-PET)	-220.40	-380.39	-60.41	0.008	-196.45	-362.24	-30.67	0.021	-204.70	-341.07	-68.33	0.004
CSF t-tau	-32.73	-214.81	149.36	0.721	-61.98	-248.18	124.22	0.509	-13.76	-163.81	136.29	0.856
CSF p-tau	-179.21	-412.15	53.73	0.129	-146.62	-385.66	92.41	0.225	-219.06	-405.74	-32.37	0.022
FDG-PET at last visit[#]												
CSF $A\beta_{42}$	0.14	0.03	0.24	0.011	0.16	0.04	0.28	0.008	0.05	-0.01	0.11	0.116
SUVR (PiB-PET)	-0.07	-0.13	0.00	0.055	-0.07	-0.14	0.01	0.075	-0.07	-0.13	-0.01	0.022
CSF t-tau	-0.05	-0.11	0.02	0.185	-0.05	-0.12	0.02	0.18	-0.05	-0.12	0.02	0.17
CSF p-tau	-0.01	-0.10	0.07	0.783	-0.01	-0.10	0.08	0.813	-0.01	-0.09	0.07	0.799
Hippocampi volume (normalized) at last visit[##]												
CSF $A\beta_{42}$	305.51	33.89	577.12	0.028	314.50	50.05	578.96	0.02	35.02	-76.49	146.54	0.536
SUVR (PiB-PET)	-188.09	-347.79	-28.39	0.022	-165.05	-328.55	-1.56	0.048	-176.15	-310.23	-42.08	0.01
CSF t-tau	4.11	-151.78	159.99	0.958	-38.87	-188.15	110.41	0.605	15.06	-120.09	150.21	0.826
CSF p-tau	-189.87	-398.14	18.41	0.073	-143.70	-352.05	64.65	0.173	-228.39	-401.91	-54.86	0.01
FDG-PET at last visit[##]												
CSF $A\beta_{42}$	0.15	0.04	0.27	0.011	0.17	0.04	0.31	0.012	0.05	-0.02	0.11	0.144
SUVR (PiB-PET)	-0.07	-0.13	0.00	0.064	-0.07	-0.15	0.00	0.064	-0.07	-0.13	-0.01	0.018
CSF t-tau	-0.03	-0.09	0.03	0.354	-0.04	-0.10	0.03	0.252	-0.04	-0.10	0.03	0.241
CSF p-tau	-0.03	-0.11	0.05	0.457	-0.03	-0.11	0.06	0.5	-0.03	-0.10	0.04	0.439

*Regression coefficient (RC) is with one standard deviation higher in CSF $A\beta_{42}$ levels, CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid amyloid-beta peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose. [#]Adjusted for age at onset, education, sex, *APOE4*, and duration of follow-up*;* [##]Adjusted for age, education, sex, *APOE4*, and duration of follow-up; All CSF and SUVR values are standardized; Overall cohort includes PiB-PET-positive and negative samples.

Supplementary Table 8. Adjusted associations of baseline CSF and SUVR levels with secondary outcomes of normalized hippocampi volume and FDG-PET at last visit after excluding t-tau or p-tau from the analysis due to collinearity

	PiB-PET-positive cohort				Overall mutation carrier cohort			
	RC*	**95%CI**		**p**	**RC***	**95%CI**		**p**
Hippocampi volume (normalized) at last visit, without p-tau								
CSF $A\beta_{42}$	349.62	79.19	620.04	0.012	77.01	-33.02	187.03	0.169
SUVR (PiB-PET)	-189.82	-350.28	-29.36	0.021	-202.88	-333.63	-72.14	0.003
CSF t-tau	-126.99	-253.67	-0.31	0.049	-150.20	-262.95	-37.45	0.009
FDG-PET at last visit, without p-tau								
CSF $A\beta_{42}$	0.16	0.05	0.27	0.004	0.05	-0.01	0.11	0.086
SUVR (PiB-PET)	-0.07	-0.13	0.004	0.064	-0.07	-0.13	-0.02	0.013
CSF t-tau	-0.05	-0.11	0.003	0.065	-0.06	-0.11	-0.01	0.022
Hippocampi volume (normalized) at last visit, without t-tau								
CSF $A\beta_{42}$	305.77	35.72	575.82	0.027	36.09	-75.78	147.96	0.525
SUVR (PiB-PET)	-187.76	-344.54	-30.99	0.02	-175.39	-307.77	-43.01	0.01
CSF p-tau	-186.54	-346.97	-26.11	0.023	-216.57	-353.46	-79.68	0.002
FDG-PET at last visit, without t-tau								
CSF $A\beta_{42}$	0.15	0.04	0.27	0.01	0.05	-0.02	0.11	0.164
SUVR (PiB-PET)	-0.07	-0.14	0.001	0.052	-0.07	-0.13	-0.01	0.016
CSF p-tau	-0.05	-0.12	0.01	0.104	-0.06	-0.12	-0.003	0.039

*Regression coefficient (RC) is with one standard deviation higher in CSF $A\beta_{42}$ levels, CSF t-tau, CSF p-tau and SUVR levels; CI, confidence interval; CSF, cerebrospinal fluid; $A\beta_{42}$, 42-amino acid b-amyloid peptide; t-tau, total tau; p-tau, phospho-Tau; PiB-PET, Pittsburgh compound B positron emission tomography; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose. #Analysis adjusted for age, education, sex, *APOE4*, and duration of follow-up; All CSF and SUVR values are standardized; Overall cohort includes PiB-PET-positive and negative samples.

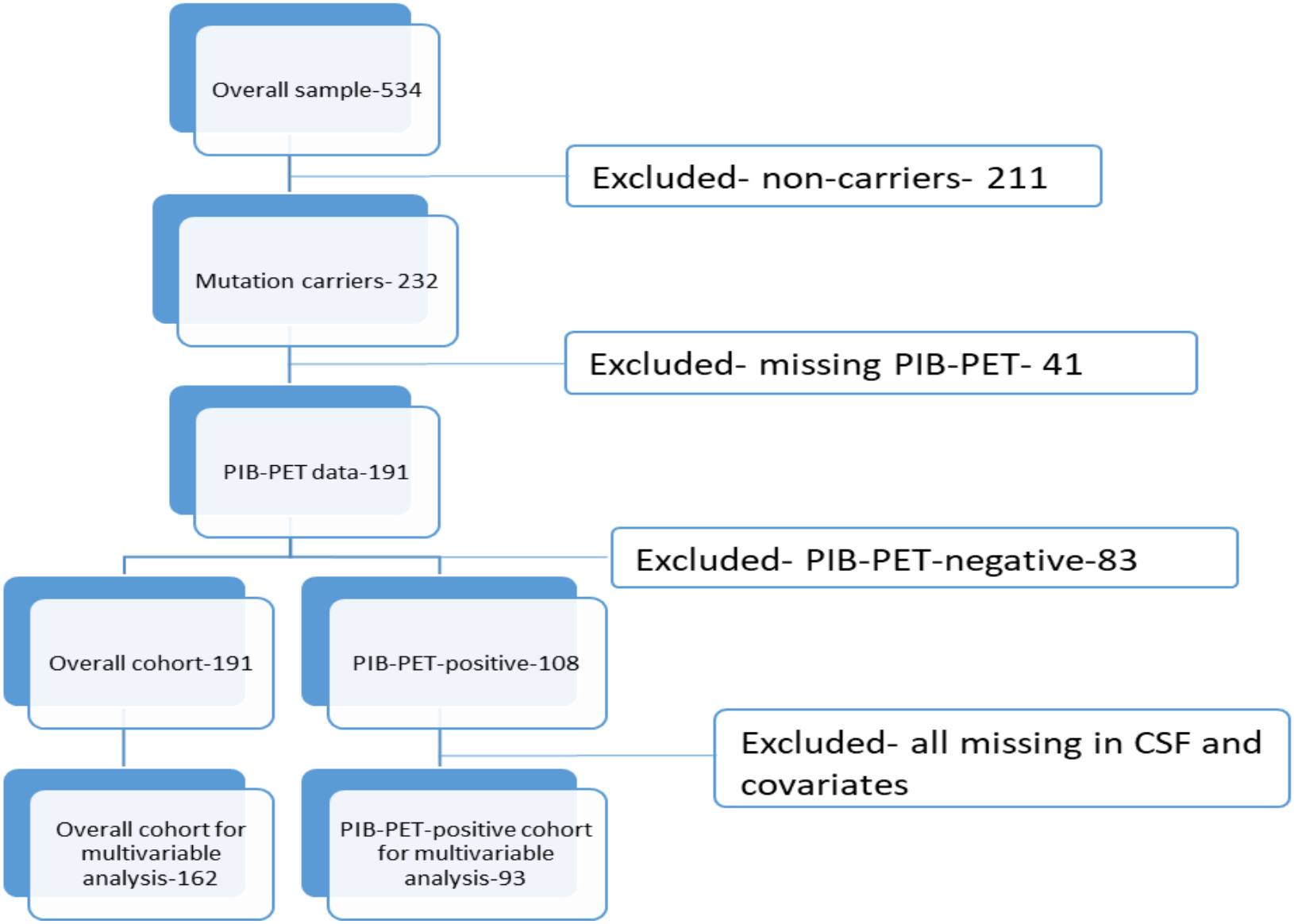
Supplementary Table 9. A compilation of the literature demonstrating a role of Aβ peptides in memory and synaptic plasticity via the alpha-7 nicotinic acetylcholine receptor signaling. The table is arranged alphabetically based on the name of the last author.

Lab	*Institution*	Paper
Alberini	*Mount Sinai School of Medicine, USA*	1. Garcia-Osta A, Alberini CM. Amyloid beta mediates memory formation. *Learning and Memory* 2009; **16**: 267–72.
Bouzat	*CONICET, Bahía Blanca, Argentina*	2. Lasala M, Fabiani C, Corradi J, Antollini S, Bouzat C. Molecular modulation of human α7 nicotinic receptor by amyloid-β peptides. *Frontiers in Cellular Neuroscience* 2019; **13**: 1–11.
Cao	*School of Life Sciences, East China Normal University, China*	3. Duan Y, Lv J, Zhang Z, *et al.* Exogenous Aβ1-42 monomers improve synaptic and cognitive function in Alzheimer's disease model mice. *Neuropharmacology* 2022; **209**: 109002.
Dineley	*University of Texas Medical Branch, USA*	4. Dineley KT, Westerman M, Bui D, Bell K, Ashe KH, Sweatt JD. Amyloid Activates the Mitogen-Activated Protein Kinase Cascade via Hippocampal α7 Nicotinic Acetylcholine Receptors: In Vitro and In Vivo Mechanisms Related to Alzheimer's Disease. 2001; **21**: 4125–33. 5. Dineley KT, Bell KA, Bui D, Sweatt JD. β-amyloid peptide activates α7 nicotinic acetylcholine receptors expressed in Xenopus oocytes. *Journal of Biological Chemistry* 2002; **277**: 25056–61. 6. Bell KA, O'Riordan KJ, Sweatt JD, Dineley KT. MAPK recruitment by β-amyloid in organotypic hippocampal slice cultures depends on physical state and exposure time. *Journal of Neurochemistry* 2004; **91**: 349–61. 7. Hernandez CM, Kayed R, Zheng H, Sweatt JD, Dineley KT. Loss of α7 nicotinic receptors enhances β-amyloid oligomer accumulation, exacerbating early-stage cognitive decline and septohippocampal pathology in a mouse model of Alzheimer's disease. *Journal of Neuroscience* 2010; **30**: 2442–53.
Eusebi	*Università La Sapienza, Italy*	8. Grassi F, Palma E, Tonini R, Amici M, Ballivet M, Eusebi F. Amyloid β1-42 peptide alters the gating of human and mouse α-bungarotoxin-sensitive nicotinic receptors. *Journal of Physiology* 2003; **547**: 147–57.
Fejtova	*Leibniz Institute for Neurobiology, Germany*	9. Lazarevic V, Fieńko S, Andres-Alonso M, *et al.* Physiological concentrations of amyloid beta regulate recycling of synaptic vesicles via alpha7 acetylcholine receptor and CDK5/calcineurin signaling. *Frontiers in Molecular Neuroscience* 2017; **10**: 1–14.
Hascup	*Southern Illinois University School of Medicine, USA*	10. Hascup KN, Hascup ER. Soluble Amyloid-β42 Stimulates Glutamate Release through Activation of the α7 Nicotinic Acetylcholine Receptor. *Journal of Alzheimer's Disease* 2016; **53**: 337–47. 11. Hascup ER, Sime LN, Peck MR, Hascup KN. Amyloid-β42 stimulated hippocampal lactate release is coupled to glutamate uptake. *Scientific Reports* 2022; **12**: 1–11.
Marchi	*University of Genoa, Italy*	12. Zappettini S, Grilli M, Olivero G, *et al.* Beta amyloid differently modulate nicotinic and muscarinic receptor subtypes which stimulate in vitro and in vivo the release of glycine in the rat hippocampus. *Frontiers in Pharmacology* 2012; **3 JUL**: 1–9.

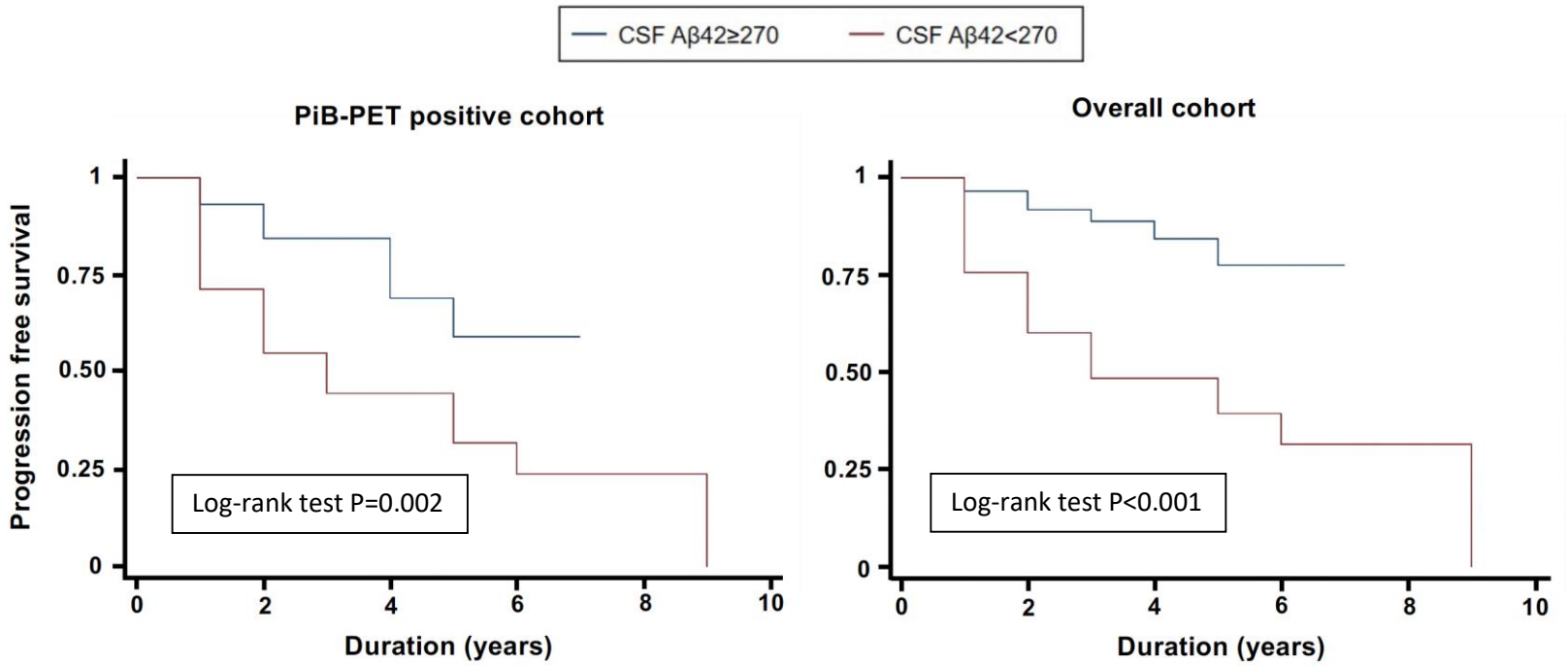
		13. Mura E, Zappettini S, Preda S, *et al.* Dual effect of beta-amyloid on α7 and α4β2 nicotinic receptors controlling the release of glutamate, aspartate and GABA in rat hippocampus. *PLoS ONE* 2012; **7**. DOI:10.1371/journal.pone.0029661.
Nichols	*University of Hawaii, USA*	14. Dougherty JJ, Wu J, Nichols RA. B-Amyloid Regulation of Presynaptic Nicotinic Receptors in Rat Hippocampus and Neocortex. *Journal of Neuroscience* 2003; **23**: 6740–7. 15. Wu J, Khan GM, Nichols RA. Dopamine release in prefrontal cortex in response to β-amyloid activation of α7* nicotinic receptors. *Brain Research* 2007; **1182**: 82–9. 16. Mehta TK, Dougherty JJ, Wu J, Choi CH, Khan GM, Nichols RA. Defining pre-synaptic nicotinic receptors regulated by beta amyloid in mouse cortex and hippocampus with receptor null mutants. *Journal of Neurochemistry* 2009; **109**: 1452–8. 17. Khan GM, Tong M, Jhun M, Arora K, Nichols RA. β-Amyloid activates presynaptic α7 nicotinic acetylcholine receptors reconstituted into a model nerve cell system: Involvement of lipid rafts. *European Journal of Neuroscience* 2010; **31**: 788–96. 18. Lawrence JLM, Tong M, Alfulaij N, *et al.* Regulation of Presynaptic Ca2+, Synaptic Plasticity and Contextual Fear Conditioning by a N-Terminal β-Amyloid Fragment. *Journal of Neuroscience* 2014; **34**: 14210–8. 19. Tong M, Arora K, White MM, Nichols RA. Role of key aromatic residues in the ligand-binding domain of α7 nicotinic receptors in the agonist action of β-amyloid. *Journal of Biological Chemistry* 2011; **286**: 34373–81.
Nishizaki	*Hyogo College of Medicine, Japan*	20. Tozaki H, Matsumoto A, Kanno T, *et al.* The inhibitory and facilitatory actions of amyloid-β peptides on nicotinic ACh receptors and AMPA receptors. *Biochemical and Biophysical Research Communications* 2002; **294**: 42–5.
Puzzo	*University of Catania, Italy*	21. Puzzo D, Privitera L, Leznik E, *et al.* Picomolar amyloid-β positively modulates synaptic plasticity and memory in hippocampus. *Journal of Neuroscience* 2008; **28**: 14537–45. 22. Puzzo D, Privitera L, Fa' M, *et al.* Endogenous amyloid-β is necessary for hippocampal synaptic plasticity and memory. *Annals of Neurology* 2011; **69**: 819–30. 23. Ricciarelli R, Puzzo D, Bruno O, *et al.* A novel mechanism for cyclic adenosine monophosphate-mediated memory formation: Role of amyloid beta. *Annals of Neurology* 2014; **75**: 602–7. 24. Palmeri A, Ricciarelli R, Gulisano W, *et al.* Amyloid-β peptide is needed for cgmp-induced long-term potentiation and memory. *Journal of Neuroscience* 2017; **37**: 6926–37. 25. Gulisano W, Melone M, Ripoli C, *et al.* Neuromodulatory Action of Picomolar Extracellular Aβ42 Oligomers on Presynaptic and Postsynaptic Mechanisms Underlying Synaptic Function and Memory. *The Journal of Neuroscience* 2019; **39**: 5986–6000. 26. Tropea MR, Li Puma DD, Melone M, *et al.* Genetic deletion of α7 nicotinic acetylcholine receptors induces an age-dependent Alzheimer's disease-like pathology. *Progress in Neurobiology* 2021; 102154.

Rylett	*University of Western Ontario, Canada*	27. Young KF, Pasternak SH, Rylett RJ. Oligomeric aggregates of amyloid β peptide 1-42 activate ERK/MAPK in SH-SY5Y cells via the α7 nicotinic receptor. *Neurochemistry International* 2009; **55**: 796–801.
Wang	*City College of New York, USA*	28. Wang HY, Lee DHS, Davis CB, Shank RP. Amyloid peptide Aβ1-42 binds selectively and with picomolar affinity to α7 nicotinic acetylcholine receptors. *Journal of Neurochemistry* 2000; **75**: 1155–61. 29. Wang HY, Lee DHS, D'Andrea MR, Peterson PA, Shank RP, Reitz AB. β-Amyloid1-42 binds to α7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. *Journal of Biological Chemistry* 2000; **275**: 5626–32.
Whiteaker	*St. Joseph's Hospital and Medical Center, Phoenix, USA*	30. George AA, Vieira JM, Xavier-Jackson C, *et al.* Implications of oligomeric amyloid-beta (oAβ42) signaling through α7β2-nicotinic acetylcholine receptors (nAChRs) on basal forebrain cholinergic neuronal intrinsic excitability and cognitive decline. *Journal of Neuroscience* 2021; **41**: 555–75.
Williams	*King's College London, UK*	31. Abbott JJ, Howlett DR, Francis PT, Williams RJ. Aβ1-42 modulation of Akt phosphorylation via α7 nAChR and NMDA receptors. *Neurobiology of Aging* 2008; **29**: 992–1001.
Xu	*Saint Louis University School of Medicine, USA*	32. Morley J, Farr S, Banks W, Johnson S, Yamada K, Xu L. A Physiological Role for Amyloid Beta Protein: Enhancement of Learning and Memory. *Nature Precedings* 2008. DOI:10.1038/npre.2008.2119.1.
Yakel	*NIH, Lab. of Signal Transduction, North Carolina, USA*	33. Pettit DL, Shao Z, Yakel JL. beta-Amyloid(1-42) peptide directly modulates nicotinic receptors in the rat hippocampal slice. *J Neurosci* 2001; **21**: 1–5.

Supplementary Figure 1. Flowchart of sample size at each stage of analysis



Supplementary Figure 2. Progression-free survival between subjects with CSF $A\beta_{42} \geq 270$ pg/ml and CSF $A\beta_{42} < 270$ pg/ml.



Appendix A

```
clear
use finalanalysis
**********Variables description**********
/*cohorts:
newmutationpet==1 /* PiB-PET positive*/
nepet1==1 /* PiB-PET positive after excluding 5%*/
Outcomes:
progresscdrf; CDR progression (0 vs. 1)
consecutive; progression to CDR≥0.5 consecutive (0 vs. 1)
cdrgreater1f; progression to CDR≥1 (0 vs. 1)
lastcdrsum4; CDR-SB ≥ 4.5 at last visit (0 vs. 1)
lastmmse24; MMSE≤24 at last visit (0 vs. 1)
lastnorvolume ; Hippocampi volume (normalized) at last visit (continuous)
lastfdg; FDG-PET at last visit (continuous)
follow5new: time to first CDR progression
Primary variables of interest:
stdab42: standadrized CSFAB42 (csf_xmap_ab420)
stdsuvr: standadrized SUVR (pib_fsuvr_rsf_tot_cortmean0)
stdtau: standadrized t-tau (csf_xmap_tau0)
stdptau: standadrized p-tau (csf_xmap_ptau0)

Covariates for adjustment and sensitvity analyses:
meyo_onset_mean0: age at onset (continuous)
visitage0: age at baseline (continuous)
sex1male2female0: sex (male:2 female:1)
educyears0: education (years) (continuous)
apoecarrier0: APOE4 (0 vs. 1)
cdrglob0: CDR at baseline (ordinal)
cdrsum0: CDR-SB at baseline (continuous)
mmse0: MMSE at baseline (continuous)
follow: duration of follow up (continuous)

Additional covariates:
fdg_fsuvr0: FDG-PET at baseline (continuous)
nortotalvolume0: Hippocampi volume (normalized) at baseline(continuous)
totalvolume0: Average hippocampi at baseline (continuous)
missing: data with or without missing (0 vs. 1)
revab42: reverse of CSFAB42
newid14: id*/
**********Table 1 and supplementary Table 1**********
table1, vars(visitage0 contn\sex1male2female0 cat\ educyears0 contn\apoecarrier0 cat\cdrcatb
cat\ ///
csf_xmap_ab420 contn\ pib_fsuvr_rsf_tot_cortmean0 contn\csf_xmap_tau0
contn\csf_xmap_ptau0 contn\cdrglob0 cat\ ///
```

```
cdrsum0 contn\mmse0 contn\fdg_fsuvr0 contn\totalvolume0 contn\lastvolume
contn\nortotalvolume0 contn\ lastnorvolume contn\ ) ///
onecol cmiss saving(summary.xls, sheet((`i'), replace)) format(%2.1f)
table1 if newmutationpet==1, vars(visitage0 contn\sex1male2female0 cat\ educyears0
contn\apoecarrier0 cat\cdrcatb cat\ ///
csf_xmap_ab420 contn\ pib_fsuvr_rsf_tot_cortmean0 contn\csf_xmap_tau0
contn\csf_xmap_ptau0 contn\cdrglob0 cat\ ///
cdrsum0 contn\mmse0 contn\fdg_fsuvr0 contn\totalvolume0 contn\lastvolume
contn\nortotalvolume0 contn\ lastnorvolume contn\ ) ///
onecol cmiss saving(summary.xls, sheet((`i'), replace)) format(%2.1f)
table1 if newmutationpet==1 , by(missing) vars(visitage0 contn\meyo_onset_mean0
contn\sex1male2female0 cat\ educyears0 contn\apoecarrier0 cat\ ///
csf_xmap_ab420 contn\ pib_fsuvr_rsf_tot_cortmean0 contn\csf_xmap_tau0
contn\csf_xmap_ptau0 contn\cdrglob0 cat\ ///
cdrsum0 contn\mmse0 contn\fdg_fsuvr0 contn\totalvolume0 contn\nortotalvolume0 contn\) ///
onecol saving(missing.xls, sheet(PET, replace)) format(%2.1f)
table1 , by(missing) vars(visitage0 contn\meyo_onset_mean0 contn\sex1male2female0 cat\
educyears0 contn\apoecarrier0 cat\ ///
csf_xmap_ab420 contn\ pib_fsuvr_rsf_tot_cortmean0 contn\csf_xmap_tau0
contn\csf_xmap_ptau0 contn\cdrglob0 cat\ ///
cdrsum0 contn\mmse0 contn\fdg_fsuvr0 contn\totalvolume0 contn\nortotalvolume0 contn\) ///
onecol saving(missing.xls, replace) format(%2.1f)
**********Figure 1 analysis**********
poisson progresscdrf stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow if newmutationpet==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow if nepet1==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow, vce(robust) irr
**********Supplementary table 2 analysis**********
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow if newmutationpet==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow if nepet1==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow, vce(robust) irr
stset follow5new, failure(progresscdrf)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0 if newmutationpet==1, vce(robust)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0 if nepet1==1, vce(robust)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0, vce(robust)

stcox stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0 if newmutationpet==1, vce(robust) strata(cdrglob0)
```

```
stcox stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0 if nepet1==1, vce(robust) strata(cdrglob0)
stcox stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0 sex1male2female0
apoecarrier0, vce(robust) strata(cdrglob0)
********** Supplementary table 3 analysis**********
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0
sex1male2female0 apoecarrier0 follow if newmutationpet==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0
sex1male2female0 apoecarrier0 follow if nepet1==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 follow if newmutationpet==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdptau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 follow if newmutationpet==1, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0
sex1male2female0 apoecarrier0 follow, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdtau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 follow, vce(robust) irr
poisson progresscdrf stdab42 stdsuvr stdptau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 follow, vce(robust) irr

stset follow5new , failure(progresscdrf)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 if newmutationpet==1, vce(robust)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0 if nepet1==1, vce(robust)
stcox stdab42 stdsuvr stdtau cdrglob0 visitage0 educyears0 sex1male2female0 apoecarrier0 if
newmutationpet==1, vce(robust)
stcox stdab42 stdsuvr stdptau cdrglob0 visitage0 educyears0 sex1male2female0 apoecarrier0 if
newmutationpet==1, vce(robust)
stcox stdab42 stdsuvr stdtau stdptau cdrglob0 visitage0 educyears0 sex1male2female0
apoecarrier0, vce(robust)
stcox stdab42 stdsuvr stdtau cdrglob0 visitage0 educyears0 sex1male2female0 apoecarrier0,
vce(robust)
stcox stdab42 stdsuvr stdptau cdrglob0 visitage0 educyears0 sex1male2female0 apoecarrier0,
vce(robust)
********** Supplementary table 4 analysis**********
clear
use finalanalysis
drop if newmutationpet!=1
keep newid14 csf_xmap_ab420 pib_fsuvr_rsf_tot_cortmean0 csf_xmap_tau0 csf_xmap_ptau0
meyo_onset_mean0 visitage0 cdrglob0 educyears0 sex1male2female0 apoecarrier0 progresscdrf
follow
mi set wide
mi misstable summarize csf_xmap_ab420 pib_fsuvr_rsf_tot_cortmean0 csf_xmap_tau0
csf_xmap_ptau0 visitage0 educyears0 meyo_onset_mean0
```

```
mi register imputed pib_fsuvr_rsf_tot_cortmean0 csf_xmap_ab420 csf_xmap_tau0
csf_xmap_ptau0 meyo_onset_mean0 visitage0 educyears0
mi impute chained (truncreg, ll(75) ul(1050)) csf_xmap_ab420 (truncreg, ll(0.8) ul(5.8))
pib_fsuvr_rsf_tot_cortmean0 (truncreg, ll(7.0) ul(564)) csf_xmap_tau0 (truncreg, ll(10.0)
ul(200)) csf_xmap_ptau0 (truncreg, ll(18) ul(70)) meyo_onset_mean0 (truncreg, ll(25) ul(66))
educyears0= visitage0 sex1male2female0 apoecarrier0, add(10) rseed (091107) force
mi passive: egen stdab42= std(csf_xmap_ab420)
mi passive: egen stdtau= std(csf_xmap_tau0)
mi passive: egen stdptau= std(csf_xmap_ptau0)
mi passive: egen stdsuvr=std(pib_fsuvr_rsf_tot_cortmean0)
mi estimate: poisson progresscdrf stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow, irr vce(robust)
mi estimate: poisson progresscdrf stdab42 stdsuvr stdtau stdptau visitage0 educyears0
sex1male2female0 apoecarrier0 follow, irr vce(robust)
clear
use finalanalysis
keep newid14 csf_xmap_ab420 pib_fsuvr_rsf_tot_cortmean0 csf_xmap_tau0 csf_xmap_ptau0
meyo_onset_mean0 visitage0 cdrglob0 educyears0 sex1male2female0 apoecarrier0 progresscdrf
mutationcarrier1yes0no0 follow
mi set wide
mi misstable summarize csf_xmap_ab420 pib_fsuvr_rsf_tot_cortmean0 csf_xmap_tau0
csf_xmap_ptau0 visitage0 educyears0 meyo_onset_mean0
mi register imputed pib_fsuvr_rsf_tot_cortmean0 csf_xmap_ab420 csf_xmap_tau0
csf_xmap_ptau0 meyo_onset_mean0 visitage0 educyears0
mi impute chained (truncreg, ll(75) ul(1050)) csf_xmap_ab420 (truncreg, ll(0.8) ul(5.8))
pib_fsuvr_rsf_tot_cortmean0 (truncreg, ll(7.0) ul(564)) csf_xmap_tau0 (truncreg, ll(10.0)
ul(200)) csf_xmap_ptau0 (truncreg, ll(18) ul(70)) meyo_onset_mean0 (truncreg, ll(25) ul(66))
educyears0= visitage0 sex1male2female0 apoecarrier0, add(10) rseed (091107) force
mi passive: egen stdab42= std(csf_xmap_ab420)
mi passive: egen stdtau= std(csf_xmap_tau0)
mi passive: egen stdptau= std(csf_xmap_ptau0)
mi passive: egen stdsuvr=std(pib_fsuvr_rsf_tot_cortmean0)
mi passive: gen pet0=1 if pib_fsuvr_rsf_tot_cortmean0 >=1.42
mi passive: replace pet0=0 if pib_fsuvr_rsf_tot_cortmean0 <1.42
mi passive : gen newmutationpet=1 if mutationcarrier1yes0no0==1 & pet0==1
mi passive : replace newmutationpet=0 if mutationcarrier1yes0no0==1 & pet0==0
mi estimate: poisson progresscdrf stdab42 stdsuvr stdtau stdptau meyo_onset_mean0 educyears0
sex1male2female0 apoecarrier0 follow, irr vce(robust)
mi estimate: poisson progresscdrf stdab42 stdsuvr stdtau stdptau visitage0 educyears0
sex1male2female0 apoecarrier0 follow, irr vce(robust)


********** Table 2 and Supplementary tables 5 and 6 analysis**********
clear
use finalanalysis
foreach var in consecutive cdrgreater1f {
```

```
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0
follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0
follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0
follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau educyears0 sex1male2female0 apoecarrier0 visitage0 follow
if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau educyears0 sex1male2female0 apoecarrier0 visitage0 follow,
vce(robust) irr
poisson `var' stdab42 stdsuvr stdptau educyears0 sex1male2female0 apoecarrier0 visitage0
follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdptau educyears0 sex1male2female0 apoecarrier0 visitage0
follow, vce(robust) irr
}
********** Table 2 and Supplementary tables 5 and 6 analysis**********
foreach var in lastcdrsum4 {
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
meyo_onset_mean0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdptau cdrsum0 educyears0 sex1male2female0 apoecarrier0
visitage0 follow, vce(robust) irr
}
foreach var in lastmmse24 {
```

```
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow if nepet1==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdtau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow, vce(robust) irr

poisson `var' stdab42 stdsuvr stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1, vce(robust) irr
poisson `var' stdab42 stdsuvr stdptau mmse0 educyears0 sex1male2female0 apoecarrier0 visitage0 follow, vce(robust) irr
}
********** Supplementary tables 7 and 8 analysis**********
foreach var in lastnorvolume lastfdg {
reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow if newmutationpet==1 , vce(robust)
reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow if nepet1==1 , vce(robust)
reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 meyo_onset_mean0 follow , vce(robust)
 reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1 , vce(robust)
reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0 follow if nepet1==1 , vce(robust)
reg `var' stdab42 stdsuvr stdtau stdptau educyears0 sex1male2female0 apoecarrier0 visitage0 follow , vce(robust)
 }
foreach var in lastnorvolume lastfdg {
reg `var' stdab42 stdsuvr stdtau educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1 , vce(robust)
reg `var' stdab42 stdsuvr stdtau educyears0 sex1male2female0 apoecarrier0 visitage0 follow , vce(robust)
reg `var' stdab42 stdsuvr stdptau educyears0 sex1male2female0 apoecarrier0 visitage0 follow if newmutationpet==1 , vce(robust)
reg `var' stdab42 stdsuvr stdptau educyears0 sex1male2female0 apoecarrier0 visitage0 follow , vce(robust)
```

```
 }
************************** ROC analysis***********************************
senspec progresscdrf revab42, sensitivity(sensitivity) specificity(specificity)
generate difference = abs(sensitivity-specificity)
egen min = min(difference)
list csf_xmap_ab420 revab42 if difference == min /*chosen nearest value*/

xi: pscore progresscdrf visitage0 cdrglob0 educyears0 sex1male2female0 apoecarrier0 follow,
logit pscore(myscore)
gen iptweight= progresscdrf/myscore + (1-progresscdrf)/(1-myscore)
senspec progresscdrf revab42 [pw=iptweight], sensitivity(sens0) specificity(spec0)
generate addifference = abs(sens0-spec0)
egen admin = min(difference)
list csf_xmap_ab420 revab42 if difference == admin /*chosen nearest value*/
**************************************************************************
```