Supplementary Table 1. Baseline characteristics of each clinical category

	Whole	CU	MCI	ADD
Number (%)	194 (100)	53 (27.3)	86 (44.3)	55 (28.4)
Age, years (IQR)	71 (5)	67 (3)	73 (7)	74 (6)
Female, n (%)	99 (51.0)	28 (52.8)	41 (47.7)	30 (54.5)
Education, years (IQR)	13 (1)	14 (2)	13 (1)	12 (2)
APOE ε4 allele (%)				
0	101 (52.1)	41 (77.4)	44 (51.2)	16 (29.1)
1	74 (38.1)	12 (22.6)	35 (40.7)	27 (49.1)
2	19 (9.8)	0 (0)	7 (8.1)	12 (21.8)
MMSE (IQR)	27 (3)	30 (1)	27 (2)	23 (2)
ADAS-Cog (IQR)	18.8 (8.8)	6.7 (2)	20.0 (5.2)	26.7 (3.6)
CDR-SB (IQR)	2 (1)	0 (0)	2 (1)	4 (1)
FAQ (IQR)	3 (3)	0 (0)	3 (2)	9 (3)
Aβ PET, n (%)				
Negative	47 (47.0)	31 (88.6)	15 (35.7)	1 (4.3)
Positive	53 (53.0)	4 (11.4)	27 (64.3)	22 (95.7)

Numbers are median (interquartile range, IQR) for continuous variables and raw number (percentage) for categorical variables.

Abbreviations: Aβ, β-amyloid; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADD, Alzheimer's disease dementia; CDR-SB, sum of boxes of the Clinical Dementia Rating; CU, cognitively unimpaired subjects; FAQ, Functional Assessment Questionnaire; MMSE, Mini–Mental State Examination; MCI, mild cognitive impairment

Supplementary Table 2. Baseline characteristics of 3 groups

$AT(N)_{tau}$	Normal biomarkers	Non-AD pathologic changes	AD continuum	*p*-value	$AT(N)_{NfL}$	Normal biomarkers	Non-AD pathologic changes	AD continuum	*p*-value
Number (%)	52 (29.4)	10 (5.6)	115 (65.0)		**Number (%)**	39 (20.1)	23 (5.6)	115 (65.0)	
Age, years (IQR)	67 (9)	75 (4)	73 (10)	0.005	**Age, years (IQR)**	66 (8)	75 (9)	73 (10)	<.001
Female, n (%)	23 (44.2)	5 (50.0)	59 (51.3)	0.698	**Female, n (%)**	18 (46.2)	10 (43.5)	59 (51.3)	0.723
Education, years (IQR)	14 (4)	16 (0)	13 (4)	0.015	**Education, years (IQR)**	14 (4)	16 (4)	13 (4)	0.072
***APOE* ε4 allele (%)**				<.001	***APOE* ε4 allele (%)**				<.001
0	49 (94.2)	7 (70.0)	39 (33.9)		**0**	37 (94.9)	19 (82.6)	39 (33.9)	
1	3 (5.8)	3 (30.0)	57 (49.6)		**1**	2 (5.1)	4 (17.4)	57 (49.6)	
2	0 (0)	0 (0)	19 (16.5)		**2**	0 (0)	0 (10.0)	19 (16.5)	
Clinical status, n (%)				<.001	**Clinical status, n (%)**				<.001
CU	31 (59.6)	4 (40.0)	11 (9.6)		**CU**	27 (69.2)	8 (34.8)	11 (9.6)	
MCI	21 (40.4)	5 (50.0)	56 (48.7)		**MCI**	12 (30.8)	14 (60.9)	56 (48.7)	
ADD	0 (0)	1 (10.0)	48 (41.7)		**ADD**	0 (0)	1 (4.3)	48 (41.7)	
MMSE (IQR)	29 (2)	27 (5)	25 (4)	<.001	**MMSE (IQR)**	29 (2)	27 (5)	25 (4)	<.001
ADAS-Cog (IQR)	9.4 (9.1)	18.7 (15.9)	23.0 (10.0)	<.001	**ADAS-Cog (IQR)**	8.3 (7.5)	14.3 (14.7)	23.0 (10.0)	<.001
CDR-SB (IQR)	0 (0.5)	0.8 (2.8)	2.0 (2.5)	<.001	**CDR-SB (IQR)**	0 (0.5)	1.0 (1.0)	2.0 (2.5)	<.001
FAQ (IQR)	0 (0)	3 (9)	5 (8)	<.001	**FAQ (IQR)**	0 (0)	1 (3)	5 (8)	<.001
Aβ PET, n (%)				<.001	**Aβ PET, n (%)**				<.001
Negative	34 (100)	3 (50.0)	5 (10.4)		**Negative**	25 (100)	12 (0)	5 (10.4)	
Positive	0 (0)	3 (50.0)	43 (89.6)		**Positive**	0 (0)	3 (100)	43 (89.6)	
BL Aβ42, pg/mL (IQR)	485.2 (101.7)	486.3 (185.4)	240.1 (70.1)	<.001	**BL Aβ42, pg/mL (IQR)**	479.7 (84.3)	504.8 (152.3)	240.1 (70.1)	<.001
BL p-tau, pg/mL (IQR)	19.2 (4.5)	33.8 (7.9)	36.0 (23.5)	<.001	**BL p-tau, pg/mL (IQR)**	19.2 (4.1)	24.2 (13.5)	36.0 (23.5)	<.001
BL t-tau, pg/mL (IQR)	58.4 (29.6)	122.8 (57.5)	119.3 (66.3)	<.001	**BL t-tau, pg/mL (IQR)**	54.6 (24.4)	87.6 (37.5)	119.3 (66.3)	<.001
BL NfL, pg/mL (IQR)	2421.6 (1344.70)	3603.7 (2454.6)	3259.0 (1238.7)	<.001	**BL NfL, pg/mL (IQR)**	2106.9 (1118.0)	4028.7 (1598.2)	3259.0 (1238.7)	<.001

Numbers are median (interquartile range, IQR) for continuous variables and raw number (percentage) for categorical variables.

Differences in baseline characteristics of participants across 8 AT(N) profiles were first assessed using Kruskal-Wallis rank sum test for continuous variables, or a Chi-squared test for

categorical variables.

Abbreviations: Aβ, β-amyloid; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADD, Alzheimer's disease dementia; BL, baseline; CDR-SB, sum of boxes of the Clinical Dementia Rating; CU, cognitively unimpaired subjects; FAQ, Functional Assessment Questionnaire; MMSE, Mini–Mental State Examination; MCI, mild cognitive impairment; NfL, neurofilament light chain; p-tau181, tau phosphorylated at threonine 181; t-tau, total tau

Supplementary Table 3. Longitudinal changes of biomarkers

$AT(N)_{tau}$	Aβ42		p-tau181		t-tau		NfL	
	slope (β)	*p*-value	slope (β)	*p*-value	slope (β)	*p*-value	slope (β)	*p*-value
A-T-(N)-	0.005	0.601	**0.014**	0.039	0.001	0.801	0.003	0.435
A-T-(N)+	NA	NA	NA	NA	NA	NA	NA	NA
A-T+(N)-	-0.015	0.692	-0.040	0.279	-0.005	0.467	0.001	0.660
A-T+(N)+	NA	NA	NA	NA	NA	NA	NA	NA
A+T-(N)-	0.005	0.712	**0.034**	0.006	0.006	0.520	0.004	0.467
A+T-(N)+	0.013	0.473	0.106	0.117	0.013	0.216	0.216	0.455
A+T+(N)-	0.002	0.941	-0.024	0.420	0.020	0.393	0.103	0.304
A+T+(N)+	0.002	0.785	0.009	0.639	0.006	0.728	0.009	0.068

$AT(N)_{NfL}$	Aβ42		p-tau181		t-tau		NfL	
	slope (β)	*p*-value	slope (β)	*p*-value	slope (β)	*p*-value	slope (β)	*p*-value
A-T-(N)-	0.005	0.621	**0.015**	0.041	0.001	0.825	0.001	0.620
A-T-(N)+	0.006	0.810	0.008	0.595	0.001	0.953	0.013	0.336
A-T+(N)-	-0.001	0.956	-0.025	0.437	0.007	0.400	0.005	0.234
A-T+(N)+	NA	NA	NA	NA	NA	NA	NA	NA
A+T-(N)-	0.014	0.496	0.028	0.088	0.002	0.869	0.000	0.898
A+T-(N)+	-0.002	0.848	**0.057**	0.015	0.011	0.645	0.062	0.504
A+T+(N)-	0.003	0.742	0.001	0.945	0.007	0.603	0.033	0.244
A+T+(N)+	0.001	0.959	0.007	0.802	0.010	0.738	0.012	0.124

Each statistic was calculated by liner regression model, adjusting age, sex, and education years. **Bold** indicated that the results were statistically significant. The slopes and *p*-values represent differences between each AT(N) profile slope relative to zero. The statistics of AT(N) profiles with a small sample size (< 3 samples who were measured the CSF biomarkers at baseline and 12 months) were not calculated and were represented as “NA".

Supplementary Table 4. Prevalence of AT(N) profiles and biological AD according to CSF biomarkers across cohorts

Report	Cohort	N marker	Clinical Status (number)	Mean Age	A-T-(N)-	A-T-(N)+	A-T+(N)-	A-T+(N)+	A+T-(N)-	A+T-(N)+	A+T+(N)-	A+T+(N)+	Biological AD (A+T+)
Kern S, et al. ***Neurology*** 2018 [1]	H70 Gothenburg	t-tau	CU (259)	70.6	54	19	0	5	13	7	0	2	2
Ekman U, et al. ***Sci Rep*** 2018 [2]	ADNI	t-tau	CU (101)	75.5	42	2	10	7	18	0	9	12	21
			stable MCI (80)	74.5	30	0	6	5	11	0	19	29	48
			progressive MCI (74)	74.5	8	0	2	0	5	2	30	54	84
			AD (102)	75.0	4	0	2	2	10	0	19	63	82
Soldan A, et al. ***Neurology*** 2019 [3]	ACS, AIBL, BIOCARD, IMPACT, WRAP	t-tau	CU (814)	59.6	39	6	6	17	19	2	2	9	11
Carandini T, et al. ***Alzheimers Res Ther*** 2019 [4]	Univ. of Milan	t-tau	CU (9)	69	78	0	0	0	22	0	0	0	0
			MCI (132)	73	20	0	8	9	27	3	14	19	33
			AD (229)	72	0	0	2	3	25	3	15	52	67
Mattsson-Carlgren N, et al. ***Neurology*** 2020 [5]	BioFINDER-1	NfL	CU (53)	74.5	40	4	4	2	25	8	17	0	17
			MCI (14), AD (34)	71.9	2	0	2	0	10	0	59	27	86
	BioFINDER-2		CU (245)	63.6	49	1	13	2	17	0	14	3	17
			MCI (138), AD (6)	70.9	25	8	8	1	17	3	25	14	39
Lee J, et al. ***J Korean Med Sci*** 2020 [6]	Samsung Medical Center	t-tau	CU (51)	64.1	73	0	14	2	8	2	2	0	2
			Amnestic MCI (23)	67.5	4	4	9	0	30	22	4	26	30
			AD (65)	63.3	2	0	0	2	26	14	0	57	57
Grontvedt GR, et al.	Univ. Hospital of	t-tau	CU (61)	68	69	0	10	13	2	0	0	7	7

J Alzheimers Dis 2020 [7]	Trondheim		Amnestic MCI (64)	64	23	3	2	9	17	3	3	39	42
			AD (38)	63.5	3	3	0	5	18	3	0	68	68
Cousins KAQ, et al. ***Brain*** 2021 [8]	U-Penn (Autopsy)	t-tau	Amnestic AD (98)	73.5	2	0	2	3	13	11	16	52	68
			Non-amnestic AD (20)	63.5	15	0	0	0	30	10	25	20	45
			Amnestic FTLD (5)	71.0	40	0	0	0	40	20	0	0	0
			Non-amnestic FTLD (59)	65.0	64	12	3	5	12	3	0	0	0
Eckerstrom C, et al. ***Alzheimers Dement (Amst)*** 2021 [9]	Gothenburg MCI study	t-tau	SCI (194), MCI (226)	NA	33	6	8	20	8	1	1	23	24
This study	J-ADNI	t-tau	CU (46)	71.8	67	2	4	2	15	0	2	7	9
			MCI (82)	71.8	26	2	1	2	17	2	6	43	49
			AD (49)	72.2	0	0	2	0	33	4	8	53	61
		NfL	CU (46)	71.8	59	11	7	0	15	0	9	0	9
			MCI (82)	71.8	15	13	2	1	10	10	22	27	49
			AD (49)	72.2	0	0	0	2	10	27	20	41	61

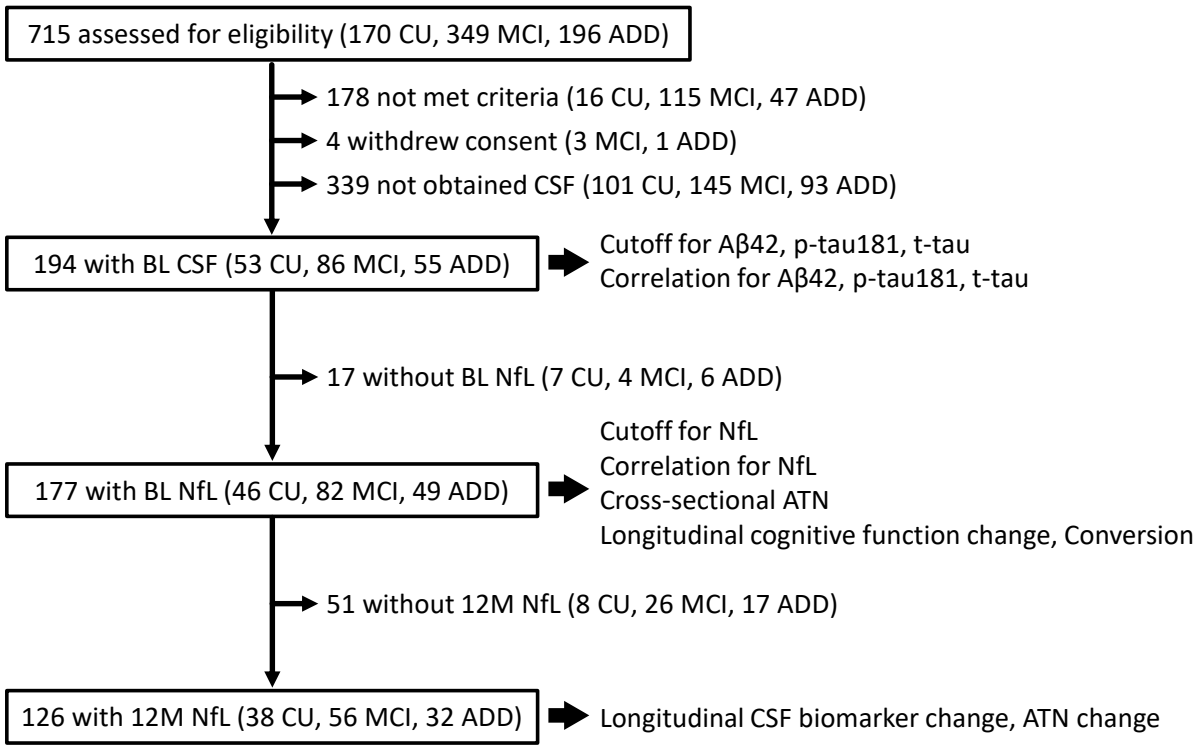
All cohorts use CSF Aβ42 as A maker and CSF p-tau181 as T marker. The number for each AT(N) profile and biological AD indicates percentage.

Abbreviations: AD, Alzheimer's disease dementia; CU, cognitively unimpaired subjects; FTLD, frontotemporal lobar degeneration; MCI, mild cognitive impairment; NA, not applicable; SCI, subjective cognitive impairment

References for supplementary Table 4

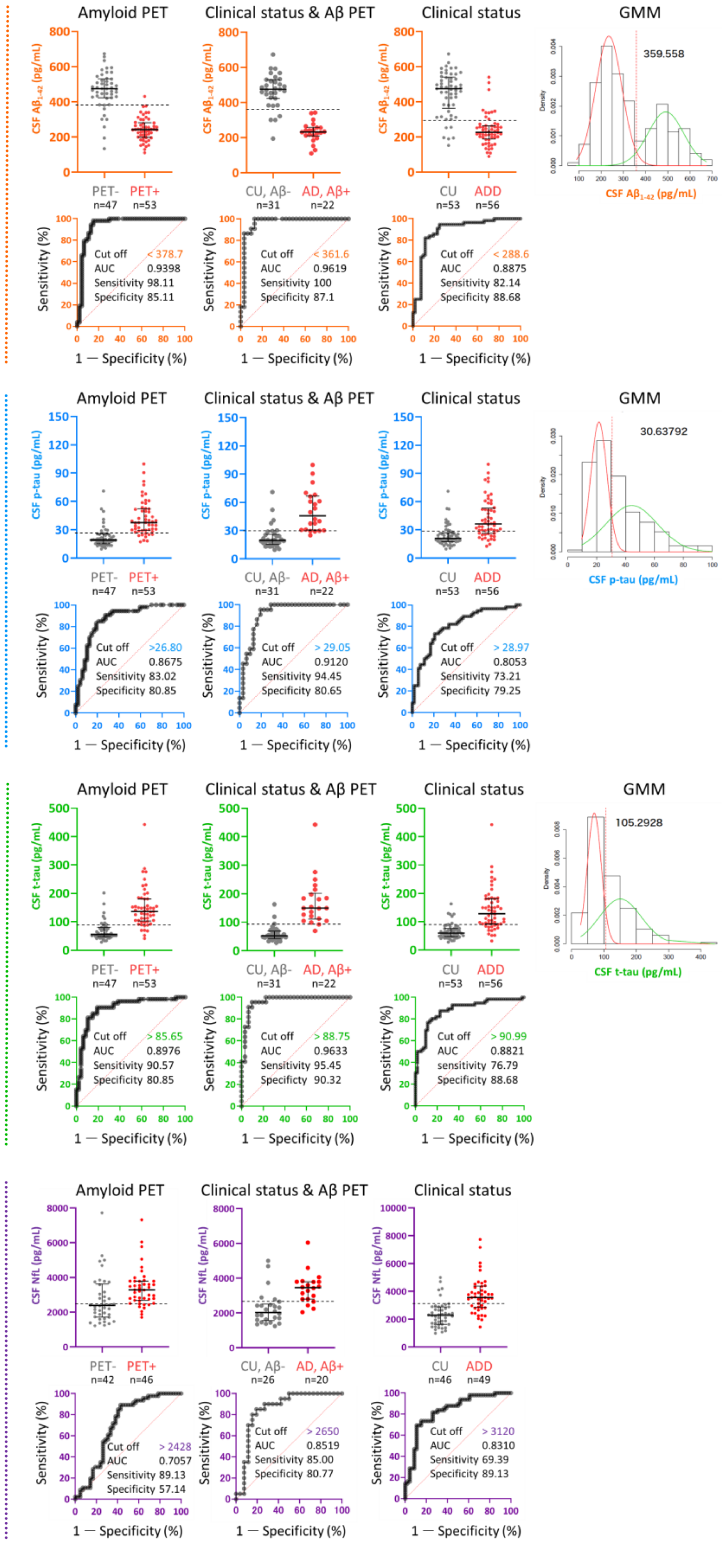
1. Kern S, Zetterberg H, Kern J, et al. Prevalence of preclinical Alzheimer disease: Comparison of current classification systems. *Neurology* 2018;90(19):e1682-e91.
2. Ekman U, Ferreira D, Westman E. The A/T/N biomarker scheme and patterns of brain atrophy assessed in mild cognitive impairment. *Sci Rep* 2018;8(1):8431.
3. Soldan A, Pettigrew C, Fagan AM, et al. ATN profiles among cognitively normal individuals and longitudinal cognitive outcomes. *Neurology* 2019;92(14):e1567-e79.
4. Carandini T, Arighi A, Sacchi L, et al. Testing the 2018 NIA-AA research framework in a retrospective large cohort of patients with cognitive impairment: from biological biomarkers to clinical syndromes. *Alzheimers Res Ther* 2019;11(1):84.
5. Mattsson-Carlgren N, Leuzy A, Janelidze S, et al. The implications of different approaches to define AT(N) in Alzheimer disease. *Neurology* 2020;94(21):e2233-e44.
6. Lee J, Jang H, Kang SH, et al. Cerebrospinal Fluid Biomarkers for the Diagnosis and Classification of Alzheimer's Disease Spectrum. *J Korean Med Sci* 2020;35(44):e361.
7. Grontvedt GR, Lauridsen C, Berge G, et al. The Amyloid, Tau, and Neurodegeneration (A/T/N) Classification Applied to a Clinical Research Cohort with Long-Term Follow-Up. *J Alzheimers Dis* 2020;74(3):829-37.
8. Cousins KAQ, Phillips JS, Irwin DJ, et al. ATN incorporating cerebrospinal fluid neurofilament light chain detects frontotemporal lobar degeneration. *Alzheimers Dement* 2021;17(5):822-30.
9. Eckerstrom C, Svensson J, Kettunen P, et al. Evaluation of the ATN model in a longitudinal memory clinic sample with different underlying disorders. *Alzheimers Dement (Amst)* 2021;13(1):e12031.

Supplementary figure 1



Supplementary Figure 1. Flowchart showing the number of participants used for each analysis

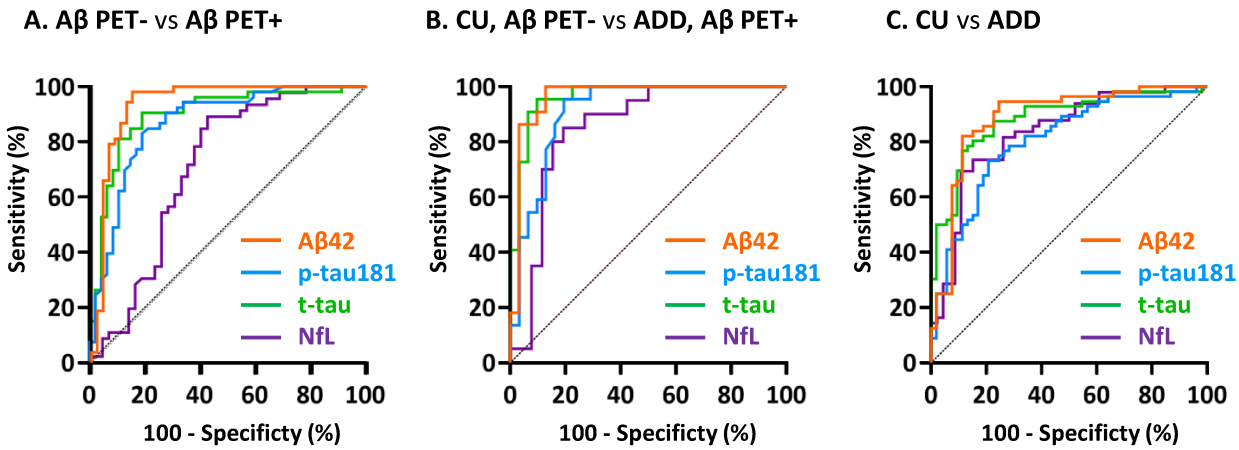
Supplementary figure 2



Supplementary figure 2. Determination of cutoff values for each of the biomarkers by different methods

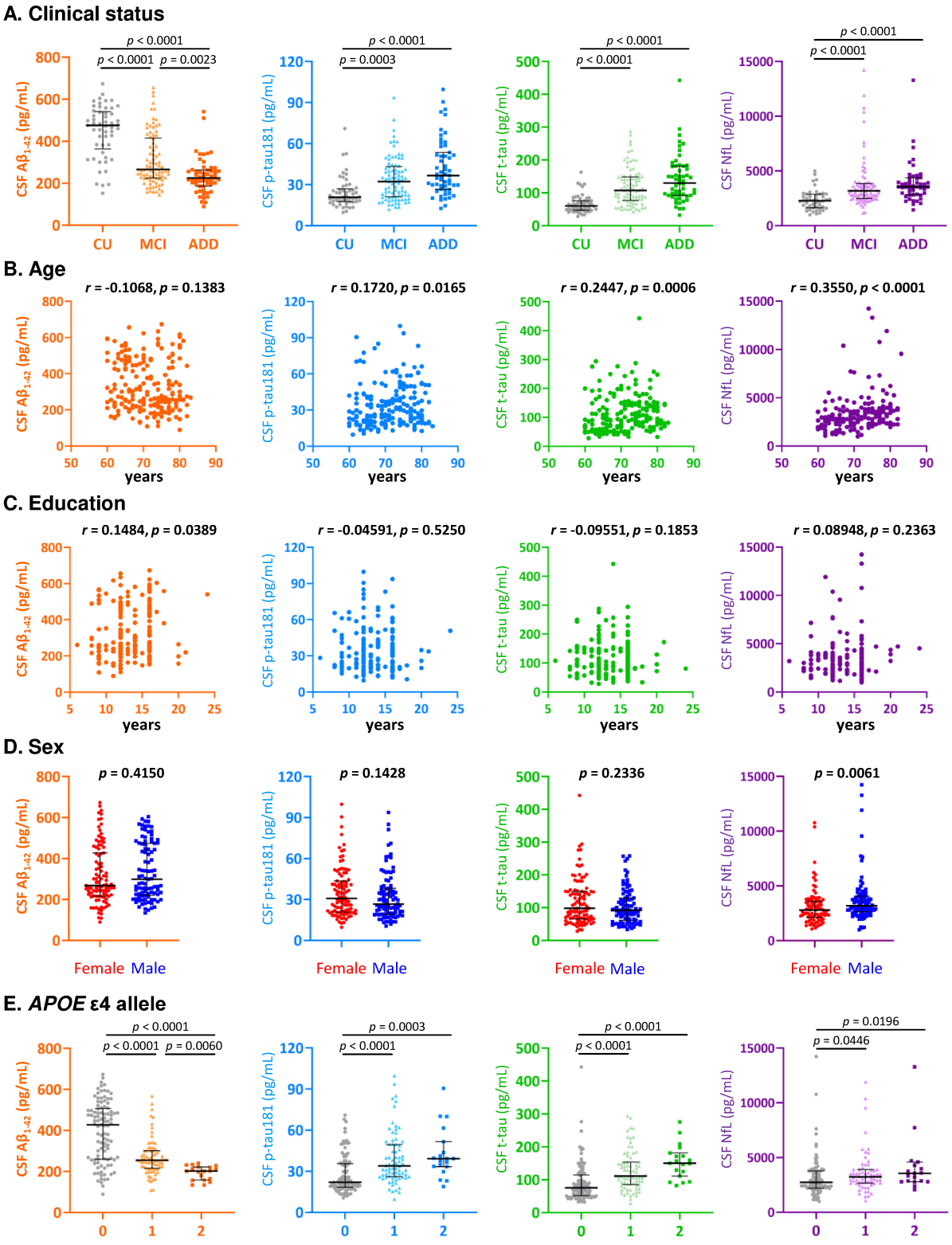
In the first column, the cutoff value was determined between Aβ PET negative (Aβ PET−) and positive (Aβ PET+) participants. In the second column, the cutoff value was determined between CU participants with Aβ PET− (CU, Aβ−) and ADD patients with Aβ PET+ (AD, Aβ+). In the third column, the cutoff value was determined between CU subjects and ADD participants. The fourth column shows the cutoff value by GMM (except NfL, which is not suitable because of the unimodal distribution). The dotted lines in upper panels in each biomarker represent the cutoff values calculated according to Youden's index. The lower panels in each biomarker show the ROC curves to determine the cutoff values. In GMM, the cutoff values are estimated as the crossing point (vertical lines) of the prevalence-weighted densities.

Supplementary figure 3



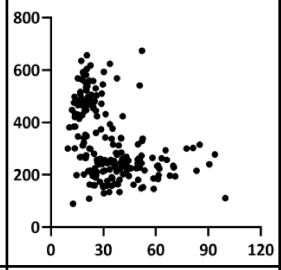
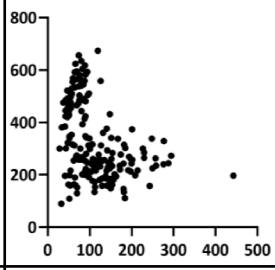
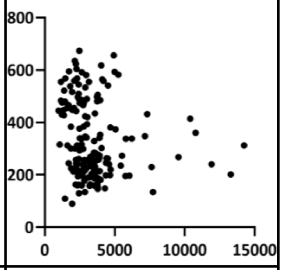
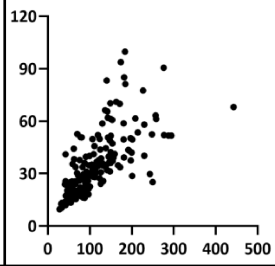
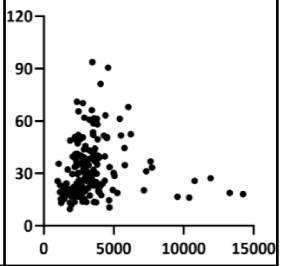
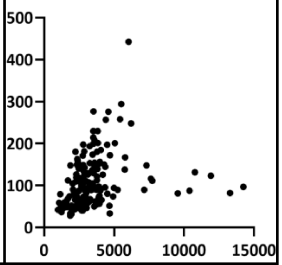
Supplementary Figure 3. ROC curves of different CSF biomarkers
(A) ROC curves that distinguish Aβ PET negative (Aβ PET−) from PET-positive (Aβ PET+) participants are shown. **(B)** ROC curves that distinguish CU participants with Aβ PET− (CU, Aβ PET−) from ADD patients with Aβ PET+ (ADD, Aβ+) are shown. **(C)** ROC curves that distinguish CU participants from ADD patients.

Supplementary figure 4



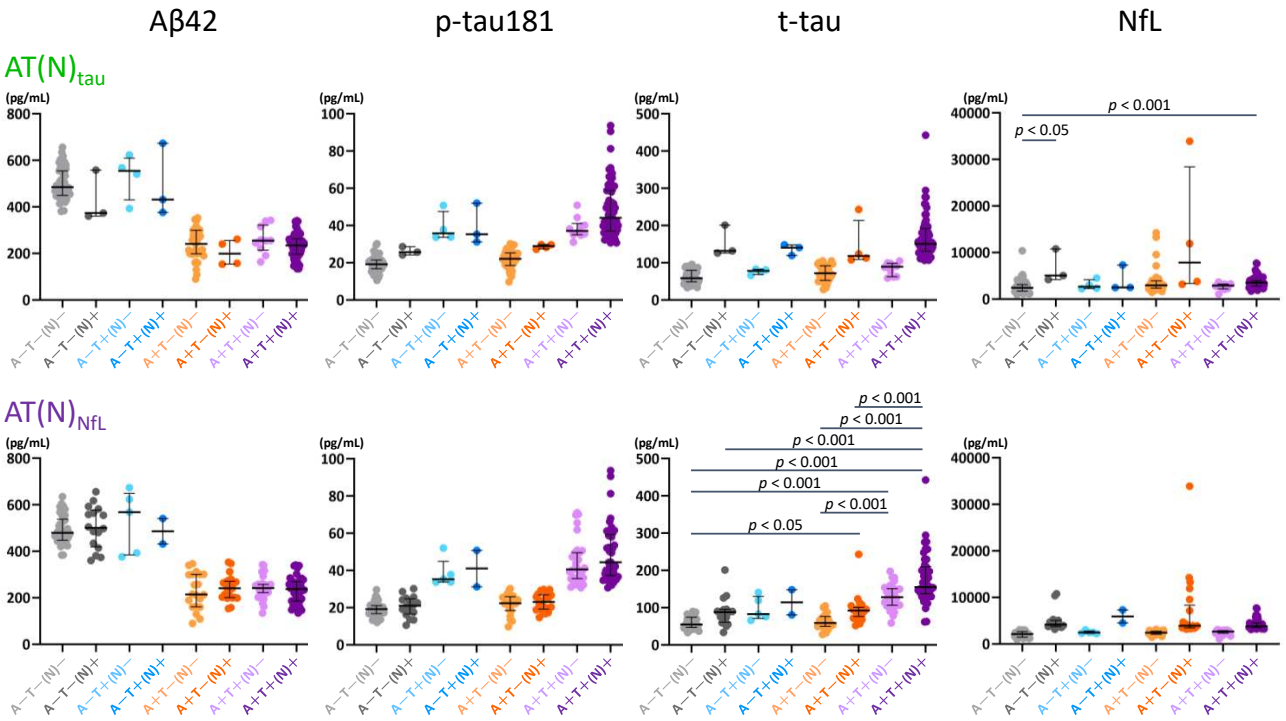
Supplementary Figure 4. Analysis of various parameters by CSF biomarkers
Parameters including clinical status **(A)**, age **(B)**, years of education **(C)**, sex **(D)**, and numbers of *APOE* ε4 allele **(E)** at baseline were analyzed by CSF biomarkers. Orange: Aβ42, blue: p-tau, green: t-tau, violet: NfL

Supplementary figure 5

	Aβ42	p-tau	t-tau	NfL
Aβ42				
p-tau	*r* = -0.4690 *p* < 0.0001			
t-tau	*r* = -0.4266 *p* < 0.0001	*r* = 0.7923 *p* < 0.0001		
NfL	*r* = -0.2165 *p* = 0.0038	*r* = 0.2487 *p* = 0.0008	*r* = 0.4907 *p* < 0.0001	

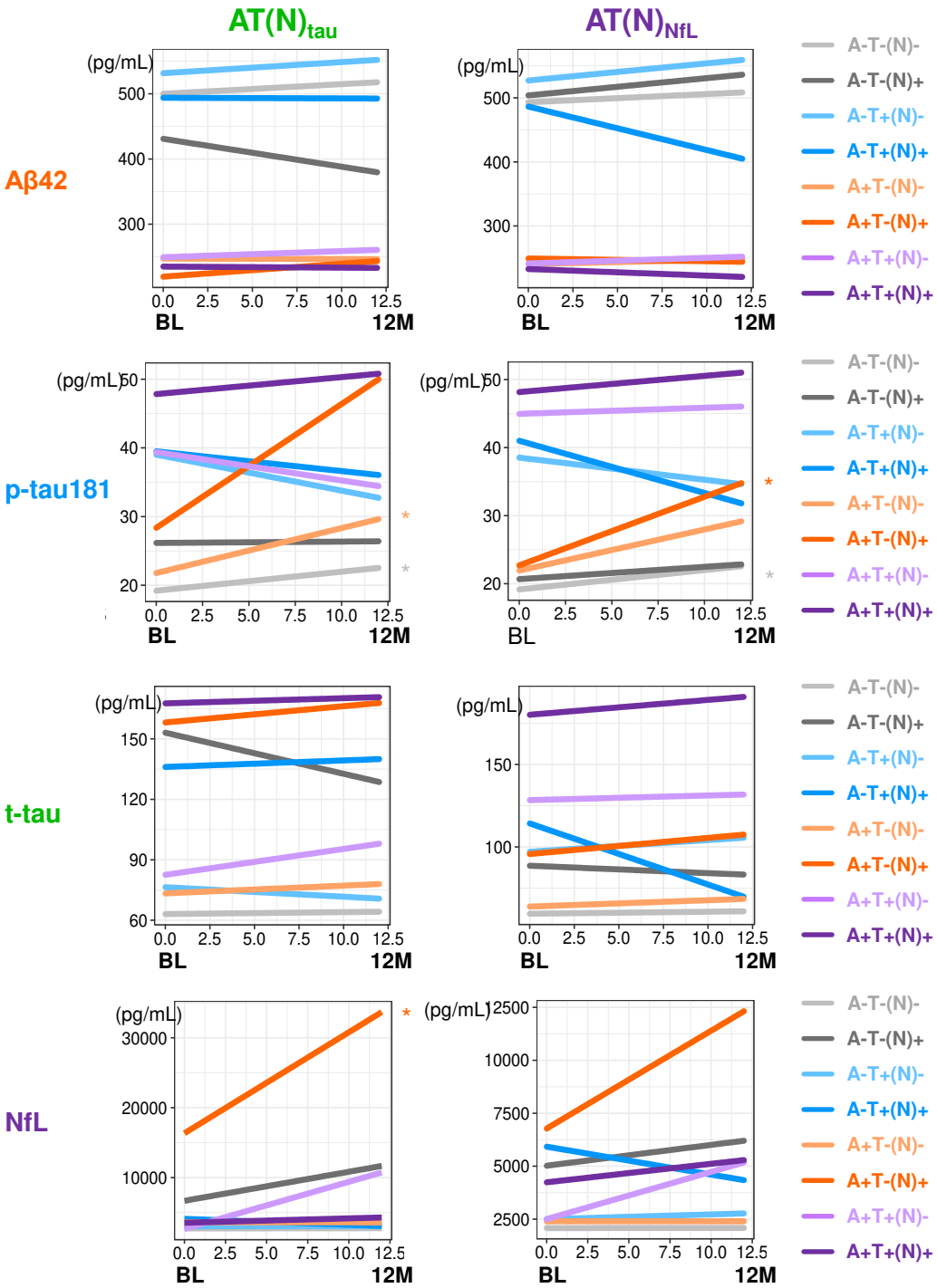
Supplementary Figure 5. Correlations between different CSF biomarkers
Scatterplots (shown in upper diagonal) and correlation coefficients (shown in lower diagonal) are presented among CSF biomarkers including Aβ42, p-tau, total tau and NfL.

Supplementary figure 6



Supplementary Figure 6. CSF biomarker levels at baseline among 8 AT(N) profiles
Upper panels show CSF biomarker levels of each of AT(N) groups stratified by $AT(N)_{tau}$ classification. Lower panels show CSF biomarker levels of each of AT(N) groups stratified by $AT(N)_{NfL}$ classification.

Supplementary figure 7



Supplementary Figure 7. Longitudinal changes of CSF biomarkers in 8 AT(N) profiles
Linear regression model adjusted for age, sex, and education years predicts the changes of each CSF biomarker over time among participants classified into eight AT(N) categories classified into $AT(N)_{tau}$ (upper panel) and $AT(N)_{NfL}$ (lower panel). Asterisk shows a significant change of slope relative to zero.