

eTable 1. Characteristics of patients who did and did not undergo lumbar puncture to collect CSF

Characteristics	Data available	All (N=592)	CSF collected (N=446)	CSF not collected (N=146)	P value
Demographics					
Age, years	592	59.6 (7.5)	59.3 (7.3)	60.3 (8.1)	0.16
Female	592	319 (54%)	247 (55%)	72 (49%)	0.20
Education, years	542	13.3 (3.6)	13.4 (3.5)	12.8 (3.7)	0.09
Diagnosis	592				0.46
SCI		294 (50%)	226 (51%)	68 (49%)	
MCI		142 (24%)	103 (23%)	39 (28%)	
Dementia		149 (25%)	117 (26%)	32 (23%)	
Cognition					
MMSE	453	26.0 (4.1)	25.9 (4.2)	26.2 (3.7)	0.93
MoCA	563	22.7 (5.0)	22.5 (5.2)	23.3 (4.6)	0.19
RAVLT, z score	499	0.00 (1.00)	-0.02 (1.02)	0.05 (0.94)	0.55
RAVLT delayed recall, z score	498	0.00 (1.00)	-0.01 (1.01)	0.04 (0.97)	0.58
RCF, z score	486	0.00 (1.00)	-0.00 (1.02)	0.00 (0.93)	0.98
WAIS-IV coding, z score	482	0.00 (1.00)	0.03 (1.01)	-0.10 (0.97)	0.21
APOE					
ε4 carrier	519	197 (38%)	168 (39%)	29 (32%)	0.22
Imaging (visual rating scales)					
MTA	527	0.75 [0.25-1]	0.75 [0-1]	1 [0.5-1]	0.12
Abnormal MTA	527	218 (41%)	165 (40%)	53 (46%)	0.25
Fazekas	532	1 [0.5-1]	1 [0.5-1]	1 [0.5-1]	0.53
Fazekas ≥ 2	532	71 (13%)	57 (14%)	14 (12%)	0.68
Global cortical atrophy	526	1 [0.5-1.5]	1 [0.5-1.5]	1 [0.5-1.25]	0.81
Posterior atrophy	383	0.5 [0-1]	0.5 [0-1]	0.5 [0-1]	0.56

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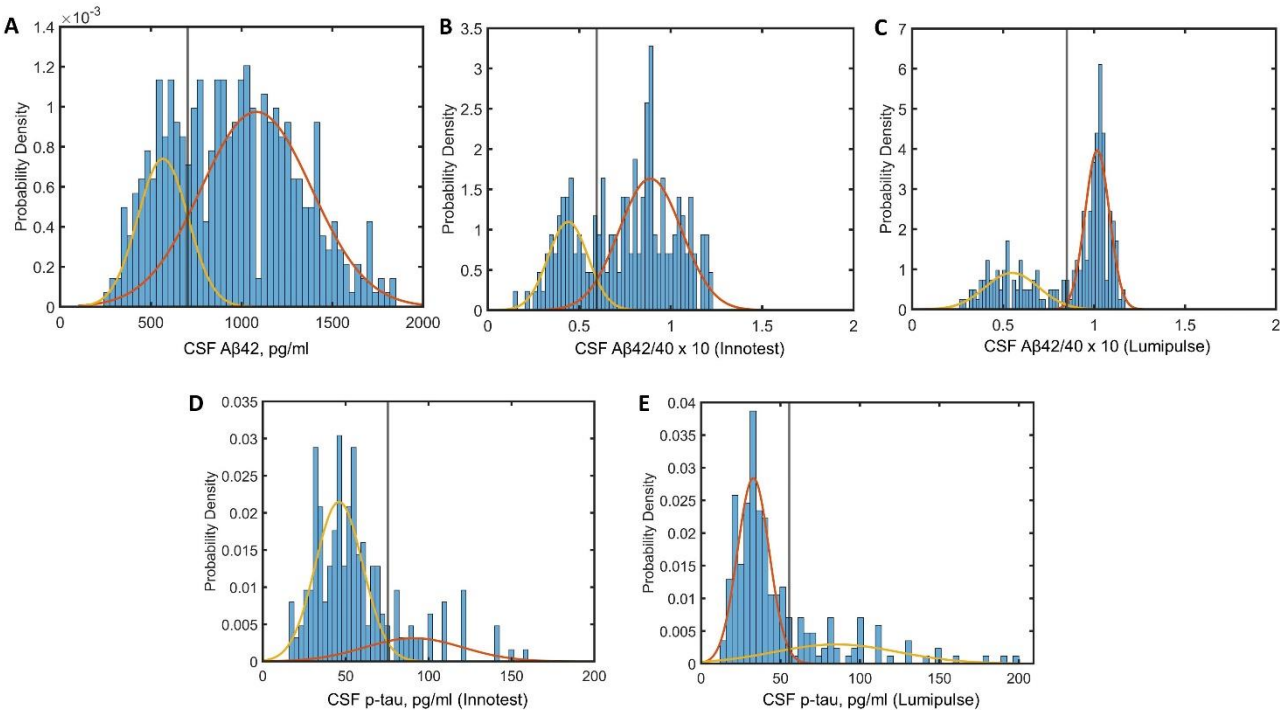
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Medical history & comorbidity					
History of stroke	584	38 (7%)	30 (7%)	8 (6%)	0.63
History of myocardial infarction	585	19 (3%)	11 (2%)	8 (6%)	0.06
Diabetes (type 1 or 2)	585	53 (9%)	39 (9%)	14 (10%)	0.70
Depression diagnosis	585	205 (35%)	149 (34%)	56 (40%)	0.18
History of malignancy	586	42 (7%)	29 (7%)	13 (9%)	0.29
Antihypertensive medication	592	217 (37%)	149 (33%)	68 (47%)	0.004
Lipid-lowering medication	592	127 (21%)	94 (21%)	33 (23%)	0.70
Antithrombotic medication	592	108 (18%)	69 (15%)	39 (27%)	0.002

Data are mean (SD), median [IQR] or N (%). P-values are shown for comparisons between participants who and did not undergo lumbar puncture to collect CSF (based on t-test, Mann-Whitney U-test, and χ^2 test as appropriate). Abnormal MTA was defined as a score of ≥ 1 (<65 years) or ≥ 1.5 (65+ years). Medication use was based on ATC code data (antihypertensives C02, 03, 07, 08, and 09; lipid-lowering medication C10; antithrombotic medication B01, including also antiplatelet therapy B01AC).

MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MTA=medial temporal lobe atrophy (mean of left and right); RAVLT=Rey Auditory Verbal Learning Test; RCF= Rey Complex Figure Test; WAIS-IV=Wechsler Adult Intelligence Scale, 4th edition.

eFigure 1. Gaussian mixture modelling density plots for CSF A β 42 (panel A), CSF A β 42/40 (panels B-C) and CSF p-tau (panels D-E). Solid lines indicate identified cut-offs.



eTable 2. Patient characteristics and comparison of the ATN profiles

	N	Normal	Non-AD pathological change				Alzheimer’s continuum				P value
		A-T-N-[a] (N=232)	A-T-N+[b] (N=43)	A-T+N-[c] (N=16)	A-T+N+[d] (N=4)	A+T-N-[e] (N=25)	A+T-N+[f] (N=24)	A+T+N-[g] (N=34)	A+T+N+[h] (N=32)		
Demographics											
Age, years	410	57.4 (7.6)	60.3 (5.9)	63.0 (7.7) ^a	62.3 (4.6)	61.7 (3.8) ^a	62.5 (6.8) ^a	61.9 (5.4) ^a	62.5 (6.1) ^a	<0.001	
Female	410	137 (59%)	19 (44%)	11 (69%)	3 (75%)	11 (44%)	12 (50%)	17 (50%)	18 (56%)	0.40	
Education, years	379	13.6 (3.6)	12.1 (4.3)	13.7 (2.8)	13.6 (3.2)	13.7 (3.1)	14.3 (3.6)	13.5 (3.0)	13.4 (3.0)	0.83	
Cognition											
MMSE	331	27.1 (3.7)	26.1 (3.2)	26.7 (4.1)	24.5 (1.9)	25.6 (4.1)	22.9 (5.2) ^{a,b}	24.1 (4.2) ^a	23.3 (5.1) ^{a,b}	<0.001	
MoCA	394	24.5 (4.0)	21.9 (4.0)	24.6 (4.2)	17.5 (6.0)	21.9 (4.6)	18.2 (6.8) ^{a,b,c,e}	20.1 (4.8) ^{a,c}	16.8 (5.7) ^{a,b,c,e}	<0.001	
RAVLT, z score	356	0.31 (0.94)	-0.18 (0.71)	0.24 (1.04)	-0.10 (1.80)	-0.46 (0.74) ^a	-0.69 (1.26) ^{a,c}	-0.73 (0.72) ^a	-1.08 (0.87) ^{a,b,c}	<0.001	
RAVLT delayed recall, z score	356	0.33 (0.86)	-0.22 (0.76)	0.12 (1.16)	-0.15 (1.49)	-0.53 (0.81) ^a	-0.66 (1.11) ^a	-0.74 (1.01) ^a	-1.17 (0.89) ^{a,b,c}	<0.001	
RCF, z score	351	0.30 (0.97)	-0.18 (0.85)	0.26 (0.95)	-0.54 (1.10)	-0.41 (0.93)	-0.80 (1.00) ^{a,c}	-0.65 (0.83) ^{a,c}	-0.96 (0.84) ^{a,c}	<0.001	
WAIS-IV coding, z score	349	0.32 (0.94)	-0.21 (1.04)	-0.10 (0.89)	-0.52 (1.10)	-0.36 (1.01)	-0.59 (0.98) ^a	-0.33 (1.03)	-0.62 (0.85) ^a	<0.001	
APOE											
ε4 carrier	399	69 (30%)	11 (26%)	9 (60%)	3 (75%)	15 (63%)	10 (43%)	20 (61%) ^a	22 (71%) ^{a,b}	<0.001	

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CSF biomarkers										
A β 42, pg/ml	410	1140 [951-1335]	957 [889-1130]	834 [774-1043]	1063 [798-1445]	598 ^{a-d} [478-613]	561 ^{a-d} [476-610]	535 ^{a-d} [476-625]	525 ^{a-d} [421-601]	< 0.001
A β 42/40 (x10)	410	0.99 [0.86-1.06]	0.98 [0.89-1.06]	0.54 ^{a,b} [0.49-0.69]	0.70 [0.62-0.92]	0.60 ^{a,b} [0.45-0.77]	0.85 [0.58-1.03]	0.41 ^{a,b,f} [0.35-0.47]	0.42 ^{a,b,f} [0.37-0.53]	< 0.001
P-tau, pg/ml	410	39 [31-50]	34 [30-41]	82 ^{a,b,e,f} [68-103]	86 ^{a,b,f} [74-88]	51 [29-62]	23 [18-52]	93 ^{a,b,e,f} [76-120]	100 ^{a,b,e,f} [84-125]	< 0.001
T-tau, pg/ml	410	248 [193-321]	241 [186-324]	569 ^{a,b,e,f} [477-646]	520 ^{a,b} [484-662]	302 [227-381]	264 [151-480]	575 ^{a,b,e,f} [486-800]	689 ^{a,b,e,f} [557-911]	< 0.001
Imaging – visual rating scales										
MTA	404	0.5 [0-1]	1 [1-2] ^{a,c,e,g}	0.5 [0-1]	1.5 [1-2]	0.5 [0-1]	2 [1.5-2.5] ^{a,c,e,g}	0.5 [0-1]	1.5 [1-2] ^{a,c,e,g}	< 0.001
Fazekas	404	1 [0.5-1]	1 [0.5-2] ^a	1 [1-1]	1.5 [1-2.5]	1 [1-1]	1 [0.5-2]	1 [0.5-1]	1 [1-1]	0.02
Fazekas $\geq$ 2	404	18 (8%)	15 (35%) ^a	0 (0%)	2 (50%)	3 (13%)	7 (30%) ^a	6 (18%)	5 (16%)	< 0.001
Global cortical atrophy	405	0.5 [0-1]	1 [0.5-1.5]	0.5 [0-1.5]	1.5 [1-2]	0.5 [0.5-1]	1.5 [1-2] ^a	1 [1-1.5] ^a	1.5 [1-2] ^{a,b,c,e}	< 0.001
Posterior atrophy	303	0 [0-1]	0.5 [0-1]	1 [0-1.5]	1 [0.5-1.5]	0.5 [0-1]	1 [0-1.5]	1 [0.5-1.5] ^a	1.5 [1-2] ^{a,b,e}	< 0.001
Imaging – automated analysis										
MTA	293	0.2 (0.3)	1.8 (0.6) ^{a,c,e,g}	0.2 (0.3)	2.3 (0.7) ^{a,c}	0.4 (0.4)	2.1 (0.7) ^{a,c,e,g}	0.5 (0.4) ^a	1.9 (0.6) ^{a,c,e,g}	< 0.001

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Medical history & comorbidity										
History of stroke	407	15 (6%)	9 (21%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (3%)	2 (6%)	0.05
History of myocardial infarction	409	6 (3%)	1 (2%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0.70
Diabetes (type 1 or 2)	408	11 (5%)	8 (19%)	0 (0%)	0 (0%)	3 (12%)	5 (21%)	3 (9%)	4 (13%)	0.02
Depression diagnosis	409	91 (39%)	15 (35%)	4 (25%)	1 (25%)	9 (36%)	4 (17%)	6 (18%)	9 (28%)	0.09
History of malignancy	409	13 (6%)	4 (9%)	1 (6%)	0 (0%)	0 (0%)	2 (8%)	2 (6%)	5 (16%)	0.56
Antihypertensive medication	410	74 (32%)	20 (47%)	5 (31%)	1 (25%)	7 (28%)	9 (38%)	11 (32%)	10 (31%)	0.76
Lipid-lowering medication	410	41 (18%)	19 (44%) ^a	6 (38%)	0 (0%)	5 (20%)	4 (17%)	7 (21%)	8 (25%)	0.02
Antithrombotic medication	410	34 (15%)	13 (30%)	3 (19%)	0 (0%)	2 (8%)	3 (13%)	3 (9%)	5 (16%)	0.18

ATN classification is based on data-driven cut-offs for CSF A β 42 (A) and CSF p-tau (T) and MTA as a marker of N. Data are mean (SD), median [IQR], or N (%). Group differences in characteristics were analyzed with Kruskal-Wallis test (continuous variables), linear regression

(cognition variables; models adjusted for age, sex, education), and logistic regression (dichotomous variables). P-values are shown for the overall comparison of ATN profiles (main effect of ATN profile); superscript letters denote statistically significant ($p < 0.05$) pairwise comparisons after Bonferroni correction if the overall model was statistically significant ($p < 0.05$). [a] A–T–N–, [b] A–T–N+, [c] A–T+N–, [d] A–T+N+, [e] A+T–N–, [f] A+T–N+, [g] A+T+N–, [h] A+T+N+. Medication use was based on ATC code data (antihypertensives C02, 03, 07, 08, and 09; lipid-lowering medication C10; antithrombotic medication B01, including also antiplatelet therapy B01AC).

A β 42= β -amyloid 1–42; A β 42/40=ratio of β -amyloid 1–42 and 1–40 ($\times 10$); AD=Alzheimer's disease; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MTA=medial temporal lobe atrophy (mean of left and right); p-tau=tau phosphorylated at threonine 181; RAVLT=Rey Auditory Verbal Learning Test; RCF= Rey Complex Figure Test; t-tau=total tau; WAIS-IV=Wechsler Adult Intelligence Scale, 4th edition.