

Supplementary Online Content

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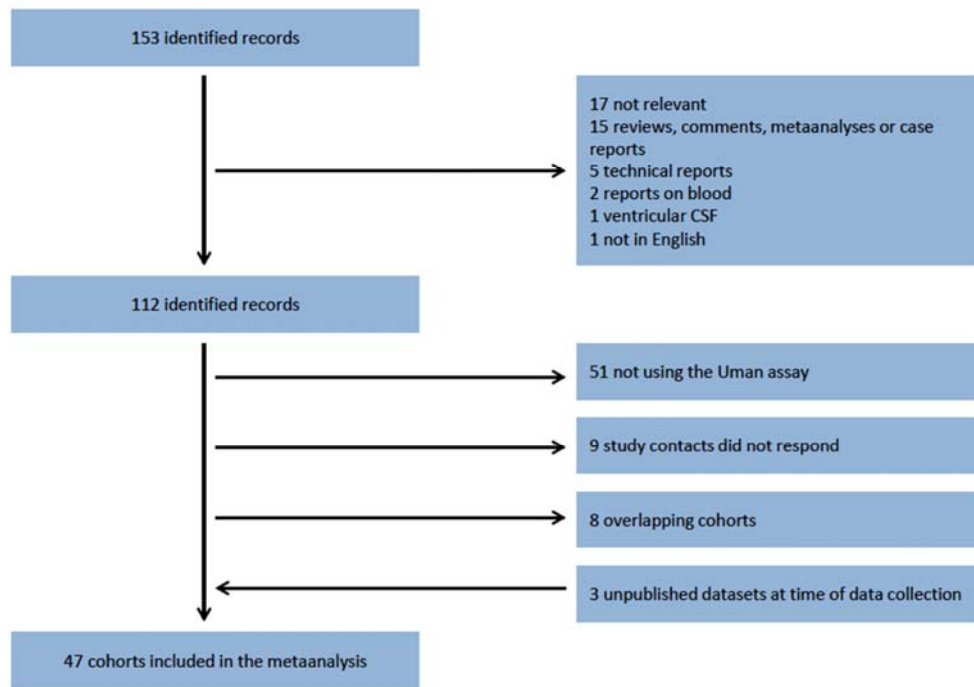
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram of Literature Search and Study Selection

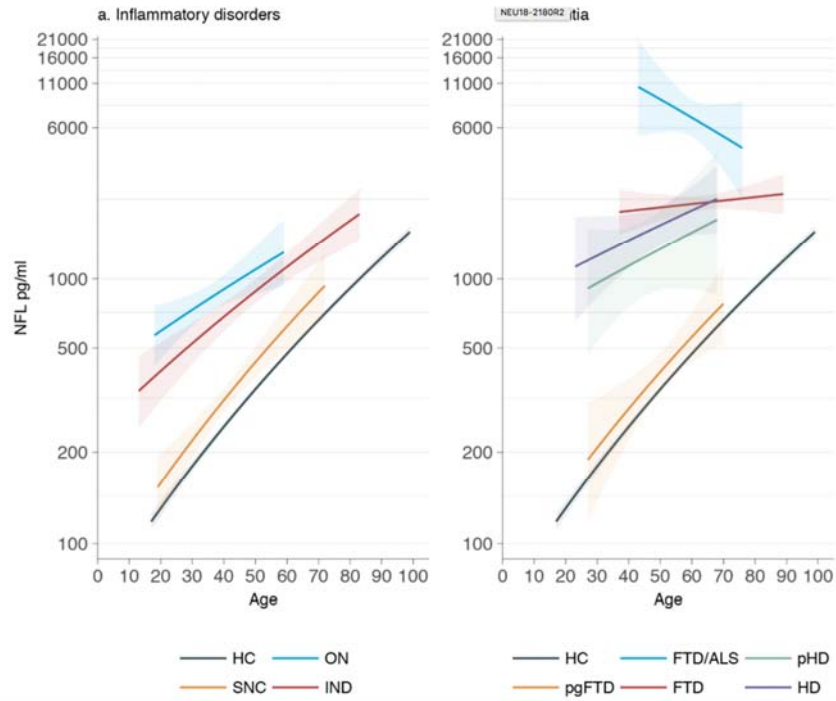
Figure 1



eFigure 2. cNfL in Neurological Conditions According to Age

Legend

Log cNfL values in picogrammes per milliliters (pg/mL) according to age in healthy controls (HC, **A and B**), Subjective neurological complaints (SNC, **A**), optic neuritis (ON, **A**), inflammatory diseases of the CNS other than MS (IND, **A**), premanifest Huntington's disease (pHD, **B**), Huntington's disease (HD, **B**), presymptomatic genetic frontotemporal dementia (pgFTD, **B**), frontotemporal dementia (FTD, **B**), combination of FTD and amyotrophic lateral sclerosis (FTD/ALS, **B**). Shades around regression lines represent standard errors.



eTable 1. Diagnostic Categories and Their Demographics

	Number of participants	% of total participants	Mean age in years (SD)	Gender (%female)	Number of contributing cohorts
Total	10,059	100.0	59.7(18.8)	54.1	47
HC	1,332	13.3	55.7 (18.8)	53.9	30
SNC	45	0.4	40.8(10.4)	86.7	2
CIS	581	5.8	34.2(10.0)	72.5	9
ON	142	1.4	35.4(9.8)	75.4	3
tRRMS	277	2.1	39.4(8.8)	87.4	6
uRRMS	1,139	11.4	37.7(9.1)	57.1	11
SPMS	162	1.6	50.8(9.4)	56.2	7
PPMS	90	0.9	49.7(11.1)	42.2	7
IND	404	4.0	49.2(15.2)	70.4	3
SCD	24	0.2	62.2(4.4)	37.5	1
MCI	227	2.3	74.2(7.3)	35.7	3
AD	1,827	18.2	72.1(8.6)	61.8	10
pgFTD	42	0.4	50.8(9.7)	66.7	1
FTD	339	3.4	64.3(9.4)	46.9	5
VaD	491	4.9	76.1(7.9)	44.2	2
DLB	183	1.8	73.5(7.1)	27.3	2
iNPH	56	0.6	72.4(6.9)	50.0	2
DNS	558	5.6	72.9(9.0)	49.8	2
MD	520	5.2	78.3(6.8)	53.1	2
pHD	13	0.1	44.4 (14.2)	53.8	1
HD	30	0.3	50.4 (12.2)	53.3	1
iHIV	27	0.3	45.1(9.5)	22.2	2
PD	375	3.7	64.7(10.8)	35.2	5
PDD	101	1.0	72.7(7.3)	27.7	2
MSA	158	1.6	63.6(8.5)	46.2	5
PSP	118	1.2	69.9(7.2)	50.0	4
CBS	49	0.5	69.2(7.2)	59.2	4
ALS	75	0.7	59.1(10.5)	33.3	2
FTD/ALS	26	0.3	60.2(7.1)	42.3	1
CIDP/GBS	26	0.3	61.3(13.6)	23.1	2
NID	418	4.2	40.5(14.4)	60.3	6
Stroke	24	0.2	72.2(11.9)	33.3	2
BD	133	1.3	40.0(13.6)	60.9	1
HIV*	14	0.1	43.4(9.5)	7.1	1
Cushing's disease*	12	0.1	45.8(13.9)	100	1
Cardiac arrest*	21	0.2	61.3(14.1)	14.3	1

Legend

HC: healthy controls; SNC: subjective neurological complaints; CIS: clinically isolated syndrome; ON: optic neuritis; uRRMS: untreated relapsing-remitting multiple sclerosis; tRRMS: treated relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; IND: inflammatory diseases of the central nervous system (CNS) other than multiple sclerosis; ALS: amyotrophic lateral sclerosis; CIDP/GBS: chronic inflammatory radiculoneuropathy and Guillain Barré syndrome; FTD: fronto temporal dementia; MCI: mild cognitive impairment; AD: Alzheimer's disease; VaD: vascular dementia; iNPH: idiopathic normal pressure hydrocephaly; MD: mixed dementia; DNS: dementia of unspecified origin; HD: Huntington's disease; pHD: premanifest HD; iHIV: HIV positive individuals with cognitive impairment; PD: Parkinson's disease; PDD: Parkinson's disease dementia; DLB: dementia with Lewy Bodies; MSA: multiple system atrophy; PSP: progressive supranuclear palsy; CBS: corticobasal syndrome; NID: non inflammatory diseases of the CNS; pgFTD: presymptomatic genetic FTD; FTD/ALS: combined FTD and ALS; HIV: HIV positive individuals; BD: bipolar disorder; SCD: subjective cognitive decline; SD: standard deviation. *Cohorts with <5 observations per gender were not included in the statistical models.

eTable 2. Cerebrospinal Fluid Neurofilament Light Percent Fold-Change Compared to Healthy Controls and Percent Yearly Decrease

Diagnosis	Fold change (95% CI) compared to HC	yearly increase in CSF NFL in % (95%CI), p-value
HC	1.00	3.30 (2.98-3.62), ****
pgFTD	1.00 (0.60-1.68)	3.34 (0.92-5.81), ***
PD	1.08 (0.87-1.33)	3.50 (2.76-4.24), ****
SCD	1.16 (0.53-2.55)	7.85 (0.70-15.51), *
SNC	1.25 (0.73-2.15)	3.48 (1.34-5.67), ****
BD	1.28 (0.85-1.94)	3.44 (2.48-4.40), ****
MCI	1.39 (1.05-1.82)	2.23 (0.88-3.60), ****
PDD	1.40 (1.03-1.92)	3.10 (1.08-5.17), ****
NID	1.53 (1.17-1.90)	3.18 (2.67- 3.69), ****
DLB	1.57 (1.22-2.01)	2.51 (0.98-4.06), ****
CIDP/GBS	1.57 (0.77-3.22)	2.49 (0.33-4.68), *
AD	1.86 (1.60-2.17)	2.01 (1.60-2.43), ****
iNPH	1.98 (1.06-3.71)	4.98 (1.71-8.35), ***
DNS	2.07 (1.71-2.51)	1.50 (0.82-2.20), ****
SPMS	2.21 (1.59-3.07)	0.70 (-0.55- 1.96), ns
PPMS	2.23 (1.51-3.31)	-0.02 (-1.45-1.42), ns
MD	2.30 (1.89-2.80)	2.42 (1.48-3.38), ****
VaD	2.49 (2.04-3.03)	1.78 (0.94-2.63), ****

PSP	2.77 (2.06-3.72)	1.13 (-0.73-3.01), ns
CIS	2.96 (2.31-3.78)	0.72 (0.12-1.33), *
tRRMS	3.25 (2.45-4.32)	-0.03 (-0.82-0.77), ns
IND	3.47 (2.66-4.52)	2.62 (2.13-3.11), ****
MSA	3.63 (2.77-4.75)	-0.68 (-2.03-0.69), ns
ON	3.73 (2.02-6.89)	2.12 (0.85-3.40), ****
uRRMS	3.84 (3.04-4.86)	-1.08 (-1.47- -0.69), ****
FTD	3.91 (3.17-4.83)	0.41 (-0.45-1.28), ns
pHD	3.94 (1.36-11.44)	1.87 (-1.12-4.94), ns
CBS	4.03 (2.61-6.21)	1.21 (-1.69-4.19), ns
Stroke	4.63 (2.12-10.09)	4.59 (1.70-7.57), ***
HD	5.88 (2.43-14.27)	1.73 (-0.47 -3.98), ns
ALS	7.58 (4.49-12.81)	0.78 (-0.86-2.45), ns
FTD/ALS	10.48 (4.85-22.67)	-2.46 (-6.42-1.67), ns
iHIV	21.36 (9.86-46.30)	1.93 (-1.07-5.02), ns

Legend: P-values: **** is $p < \text{or} = 0.0001$; *** is $p < \text{or} = 0.001$; ** is $p < \text{or} = 0.01$; * is $p < \text{or} = 0.05$; non significant (ns) is $p > 0.5$. pgFTD, presymptomatic genetic FTD; PD, Parkinson's disease; SCD, Subjective cognitive decline; SNC, subjective neurological complaints; BD, bipolar disorder; MCI, mild cognitive impairment; PDD, PD dementia; NID, non-inflammatory neurological disorders; DLB, Dementia with Lewy bodies; CIDP/GBS, chronic inflammatory demyelinating polyradiculopathy and Guillain-Barré syndrome; AD, Alzheimer's disease; iNPH, idiopathic normal pressure hydrocephalus; DNS, dementia not specified; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; MD, mixed dementia; VaD, vascular dementia; PSP, progressive supranuclear palsy; CIS, clinically isolated syndrome; uRRMS, relapsing remitting multiple sclerosis without treatment; IND, inflammatory neurological disorders other than multiple sclerosis; MSA, multiple systems atrophy; ON, optic neuritis; tRRMS, relapsing remitting multiple sclerosis with disease modifying treatment; FTD, frontotemporal dementia; CBS, corticobasal syndrome; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; FTD/ALS, combined FTD and ALS; iHIV, HIV with cognitive impairment.

eTable 3. Ratio Between Male and Female Mean Cerebrospinal Fluid Neurofilament Light Values

Diagnosis	M/F ratio	95% CI	p-value
HC	1.26	1.16-1.37	****
CIS	1.11	0.97-1.27	ns
ON	1.15	0.86-1.53	ns
Treated RRMS	1.21	1.00-1.46	*
Untreated RRMS	1.16	1.06-1.27	**
SPMS	1.38	1.09-1.74	**
PPMS	1.76	1.28-2.41	***
IND	1.76	1.50-2.07	****
SNC	0.88	0.46-1.68	ns
ALS	1.12	0.78-1.61	ns
CIDP/GBS	1.49	0.75-2.96	ns
FTD	1.01	0.86-1.18	ns
pgFTD	1.44	0.89-2.32	ns
FTD/ALS	0.90	0.50-1.61	ns
SCD	1.26	0.68-2.34	ns
MCI	1.10	0.90-1.35	ns
AD	1.21	1.13-1.30	****
iNPH	1.02	0.69-1.51	ns
VaD	1.22	1.07-1.40	**
MD	1.18	1.04-1.35	**
DNS	1.26	1.11-1.42	***
PD	1.15	0.98-1.35	ns
PDD	1.07	0.77-1.48	ns
MSA	0.91	0.72-1.15	ns
PSP	1.02	0.78-1.34	ns
CBS	1.27	0.83-1.94	ns
DLB	1.00	0.79-1.28	ns
iHIV	1.13	0.52-2.46	ns
pHD	0.98	0.43-2.22	ns
HD	1.30	0.76-2.23	ns
BD	1.39	1.07-1.80	**
Stroke	0.75	0.40-1.42	ns
NID	1.60	1.38-1.85	****

Legend M. male; F. female; HC. healthy controls; SNC. subjective neurological complaints; CIS. clinically isolated syndrome; ON. optic neuritis; RRMS. relapsing remitting multiple sclerosis; PPMS. primary progressive multiple sclerosis; SPMS. secondary progressive multiple sclerosis; IND. inflammatory neurological disorders

other than multiple sclerosis; SNC. subjective neurological complaint; ALS. amyotrophic lateral sclerosis; CIDP/GBS. chronic inflammatory demyelinating polyradiculopathy and Guillain-Barré syndrome; FTD. frontotemporal dementia; pgFTD. presymptomatic genetic FTD; ; FTD/ALS. combined FTD and ALS; SCD. Subjective cognitive decline; MCI. mild cognitive impairment; AD. Alzheimer's disease; iNPH. idiopathic normal pressure hydrocephalus; VaD. vascular dementia; MD. mixed dementia; DNS. dementia not specified; ; PD. Parkinson's disease; PDD. PD dementia; PSP. progressive supranuclear palsy; MSA. multiple systems atrophy; CBS. corticobasal syndrome; DLB. Dementia with Lewy bodies; iHIV. HIV with cognitive impairment; pHD. premanifest Huntington's disease; HD. Huntington's disease; BD. bipolar disorder; NID. non-inflammatory neurological disorders. 95% CI, 95% confidence intervals. P-values: **** is $p \leq 0.0001$; *** is $p \leq 0.001$; ** is $p \leq 0.01$; * is $p \leq 0.05$; non significant (ns) is $p > 0.5$.

eTable 4. Mean Cerebrospinal Fluid Neurofilament Light Ratios Across Clinically Similar Disorders

A

	SNC	CIS	ON	uRRMS	tRRMS	SPMS	PPMS
SNC	1	-	-	-	-	-	-
CIS	2.38 (1.41-4.00), ****	1	-	-	-	-	-
ON	3.03 (1.32-6.67), ****	1.26 (0.66-2.43), ns	1	-	-	-	-
uRRMS	3.03 (1.85-5.00), ****	1.30 (1.11-1.52), ****	1.03 (0.54-1.97), ns	1	-	-	-
tRRMS	2.63 (1.54-4.35), ****	1.10 (0.88-1.38), ns	0.87 (0.45-1.70), ns	0.85 (0.69-1.03), ns	1	-	-
SPMS	1.75 (1.02-3.03), *	0.75 (0.99-1.81), ns	0.59 (0.30-1.18), ns	0.57 (0.43-0.77), ****	0.68 (0.49-0.94), **	1	-
PPMS	1.79 (0.97-3.23), ns	0.76 (0.52-1.09), ns	0.60 (0.29-1.23), ns	0.58 (0.41-0.83), ****	0.69 (0.47-1.02), ns	1.01 (0.68-1.50), ns	1
IND	2.78 (1.64-4.76), ****	1.17 (0.95-1.44), ns	0.93 (0.48-1.80), ns	0.90 (0.75-1.08), ns	1.07 (0.75-1.08), ns	1.57 (1.14-2.16), ****	1.55 (1.05-2.28), **

B

	SCD	MCI	AD	pgFTD	FTD	FTD/ALS	VaD	DLB	iNPH	DNS	MD	pHD	HD
SCD	1	-	-	-	-	-	-	-	-	-	-	-	-
MCI	1.20 (0.53-2.73), ns	1	-	-	-	-	-	-	-	-	-	-	-
AD	1.61 (0.74-3.49), ns	1.34 (1.01-1.78), *	1	-	-	-	-	-	-	-	-	-	-
pgFTD	0.86 (0.34-2.17), ns	0.72 (0.40-1.28), ns	1.86 (1.10-3.14), **	1	-	-	-	-	-	-	-	-	-
FTD	3.33 (1.54-7.69), ****	2.86 (2.04-3.85), ****	2.08 (1.72-2.56), ****	3.85 (2.38-6.67), ****	1	-	-	-	-	-	-	-	-
FTD/ALS	9.05 (1.92-10.38), ****	7.69 (3.33-16.67), ****	5.55 (2.63-12.50), ****	10.48 (4.19-26.23), ****	2.68 (1.23-5.82), ***	1	-	-	-	-	-	-	-
VaD	2.15 (0.97-4.72), ns	1.79 (1.31-2.45), ****	1.33 (1.15-1.55), ****	2.49 (1.45-4.25), ****	0.64 (0.51-0.80), ****	0.24 (0.11-0.51), ****	1	-	-	-	-	-	-
DLB	1.35 (0.60-3.03), ns	1.13 (0.80-1.61), ns	0.84 (0.67-1.06), ns	1.57 (0.89-2.75), ns	0.40 (0.30-0.53), ****	0.15 (0.07-0.33), ****	0.63 (0.49-0.81), ****	1	-	-	-	-	-
iNPH	1.71 (0.63-4.65), ns	1.43 (0.73-2.82), ns	1.07 (0.57-2.00), ns	1.98 (0.88-4.45), ns	0.51 (0.26-0.97), *	0.19 (0.07-0.51), ****	0.80 (0.42-1.51), ns	1.27 (0.65-2.44), ns	1	-	-	-	-
DNS	1.79 (0.81-3.93), ns	1.50 (1.10-2.04), ***	1.11 (0.97-1.28), ns	2.07 (1.21-3.54), ***	0.53 (0.42-0.66), ****	0.20 (0.09-0.43), ****	0.83 (0.70-1.00), *	1.32 (1.03-1.69), **	1.04 (0.55-1.98), ns	1	-	-	-
MD	1.99 (0.90-4.38), ns	1.66 (1.22-2.77), ****	1.24 (1.07-1.43), ****	2.30 (1.35-3.94), ****	0.59 (0.47-0.74), ****	0.22 (0.10-0.48), ****	0.93 (0.77-1.11), ns	1.47 (1.14-1.89), ****	0.86 (0.45-1.64), ns	1.11 (0.93-1.32), ns	1	-	-
pHD	3.40 (0.90-12.79), ns	2.84 (0.94-8.54), ns	2.11 (0.72-6.20), ns	3.94 (1.20-12.88), **	1.01 (0.34-2.98), ns	0.38 (0.10-1.40), ns	1.58 (0.54-4.68), ns	2.51 (0.84-7.50), ns	1.98 (0.58-6.82), ns	1.90 (0.64-5.61), ns	1.71 (0.58-5.05), ns	1	-
HD	5.08 (1.55-16.60), ****	4.24 (1.68-10.72), ****	3.16 (1.29-7.75), ***	5.88 (2.11-16.42), ****	1.50 (0.61-3.73), ns	0.56 (0.17-1.81), ns	2.37 (0.96-5.86), ns	3.76 (1.50-9.41), ****	2.96 (1.00-8.76), *	2.84 (1.15-7.02), *	2.55 (1.03-6.32), *	1.49 (0.58-3.85), ns	1
iHIV	18.44 (6.12-55.55), ****	15.41 (6.79-34.99), ****	11.47 (5.22-25.20), ****	21.36 (8.42-54.19), ****	5.46 (2.45-12.16), ****	2.04 (0.68-6.06), ns	8.60 (3.87-19.08), ****	13.63 (6.06-30.68), ****	10.76 (3.99-29.06), ****	10.31 (4.65-22.84), ****	9.27 (4.18-20.57), ****	5.56 (1.45-20.00), ***	3.57 (1.12-11.11), *

C

	HC	PD	PDD	MSA	PSP	CBS
PD	1.08 (0.87-1.33), ns	1	-	-	-	-
PDD	1.40 (1.03-1.92), **	1.30 (0.93-1.82), ns	1	-	-	-
MSA	3.63 (2.77-4.75), ****	3.36 (2.55-4.45), ****	2.58 (1.77-3.77), ****	1	-	-
PSP	2.77 (2.06-3.72), ****	2.57 (1.87-3.52), ****	1.97 (1.33-2.93), ****	0.76 (0.53-1.09), ns	1	-
CBS	4.03 (2.61-6.21), ****	3.74 (2.37-5.88), ****	2.87 (1.72-4.78), ****	1.11 (0.69-1.79), ns	1.46 (0.89-2.37), ns	1
DLB	1.57 (1.22-2.01), ****	1.45 (1.09-1.93), ***	1.12 (0.78-1.59), ns	0.43 (0.31-0.60), ****	0.57 (0.40-0.81), ****	0.39 (0.24-0.63), ****

D

	HC	ALS
ALS	7.58 (4.49-12.81), ****	1
FTD/ALS	10.48 (4.85-22.67), ****	1.38 (0.55-3.48), ns
CIDP/GBS	1.57 (0.77-3.22), ns	0.21 (0.10-0.42), ****
Stroke	4.63 (2.12-10.09), ****	-
BD	1.28 (0.85-1.94), ns	-

Legend Mean CSF NfL ratios (95% confidence intervals) correspond to the ratios of the diagnosis in the entry column (y) over the diagnosis in the entry line (x) in each table. **A** SNC, subjective neurological complaints; CIS, clinically isolated syndrome; ON, optic neuritis; uRRMS, untreated relapsing remitting multiple sclerosis; tRRMS, treated relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis. **B** SCD, Subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease; pgFTD, presymptomatic genetic FTD; FTD, frontotemporal dementia; FTD/ALS, combined FTD and ALS; VaD, vascular dementia; DLB, Dementia with Lewy bodies; iNPH, idiopathic normal pressure hydrocephalus; DNS, dementia not specified; MD, mixed dementia; pHD, premanifest Huntington's disease; HD, Huntington's disease; iHIV, HIV with cognitive impairment. **C** PD, Parkinson's disease; PDD, PD dementia; MSA, multiple systems atrophy; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome, DLB, dementia with Lewy Bodies. **D** ALS, amyotrophic lateral sclerosis; FTD/ALS, combined FTD and ALS; CIDP/GBS, chronic inflammatory demyelinating polyradiculopathy and Guillain-Barré syndrome; BD, bipolar disorder. P-values: **** is $p < \text{or} = 0.0001$; *** is $p < \text{or} = 0.001$; ** is $p < \text{or} = 0.01$; * is $p < \text{or} = 0.05$; non significant (ns) is $p > 0.5$.

eTable 5. Mean Cerebrospinal Fluid Neurofilament Light Ratios per 10-Years Age Ranges

A

	uRRMS/HC	tRRMS/HC	PPMS/HC	uRRMS/tRRMS	PPMS/uRRMS
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
20 y	8.3 (6.2-11.1), ****	5.8 (3.8-8.8), ****	5.1 (2-13.1), ****	1.4 (1-2.1), <i>ns</i>	0.6 (0.2-1.6), <i>ns</i>
30 y	5.4 (4.2-6.8), ****	4.1 (3-5.7), ****	3.7 (1.8-7.4), ****	1.3 (1-1.7), <i>ns</i>	0.7 (0.4-1.4), <i>ns</i>
40 y	3.5 (2.8-4.4), ****	3 (2.2-4), ****	2.7 (1.6-4.3), ****	1.2 (0.9-1.4), <i>ns</i>	0.8 (0.5-1.2), <i>ns</i>
50 y	2.2 (1.7-2.9), ****	2.2 (1.5-3), ****	1.9 (1.3-2.8), ****	1 (0.8-1.4), <i>ns</i>	0.9 (0.6-1.2), <i>ns</i>
60 y	1.5 (1.1-2.0), **	1.6 (1.0-2.4), **	1.4 (0.9-2.2), <i>ns</i>	0.9 (0.6-1.4), <i>ns</i>	0.9 (0.6-1.5), <i>ns</i>
70 y	0.9 (0.6-1.4), <i>ns</i>	1.1 (0.6-2), <i>ns</i>	1 (0.5-2), <i>ns</i>	0.8 (0.5-1.5), <i>ns</i>	1.1 (0.5-2.1), <i>ns</i>

B

	uRRMS/HC	SPMS/HC	SPMS/uRRMS
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
20 y	8.3 (6.2-11.1), ****	4.2 (1.8-9.6), ****	0.5 (0.2-1.1), <i>ns</i>
30 y	5.4 (4.2-6.8), ****	3.3 (1.8-6), ****	0.6 (0.3-1.1), <i>ns</i>
40 y	3.5 (2.8-4.4), ****	2.5 (1.7-3.8), ****	0.7 (0.5-1.1), <i>ns</i>
50 y	2.2 (1.7-2.9), ****	2.0(1.4-2.7), ****	0.9 (0.6-1.2), <i>ns</i>
60 y	1.5 (1.1-2), **	1.5 (1-2.3), *	1.0 (0.7-1.5), <i>ns</i>
70 y	0.9 (0.6-1.4), <i>ns</i>	1.2 (0.7-2.1), <i>ns</i>	1.2 (0.7-2.2), <i>ns</i>

C

	CIS/HC	ON/HC	uRRMS/HC	CIS/IND	ON/IND	uRRMS/IND	uRRMS/CIS	uRRMS vs ON	ON/CIS
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
20 y	4.4 (3.2-6), ****	4.4 (2.1-9.2), ****	8.3 (6.2-11.1), ****	1.3 (0.8-1.7), <i>ns</i>	1.3 (0.5-2.5), <i>ns</i>	2.5 (1.7-3.3), ****	1.9 (1.4-2.5), ****	1.9 (0.9-4.1), <i>ns</i>	1.0 (0.5-2.2), <i>ns</i>
30 y	3.4 (2.6-4.4), ****	3.9 (2.1-7.4), ****	5.4 (4.2-6.8), ****	1.0(0.7-1.3), <i>ns</i>	1.1 (0.6-2.5), <i>ns</i>	1.7 (1.1-2.0), ****	1.6 (1.3-1.9), ****	1.4 (0.7-2.7), <i>ns</i>	1.2 (0.6-2.3), <i>ns</i>
40 y	2.6 (2-3.4), ****	3.5 (1.9-6.4), ****	3.5 (2.8-4.4), ****	0.8 (0.6-1.0), <i>ns</i>	1.1 (0.6-2.00), <i>ns</i>	1.1 (0.8-1.3), <i>ns</i>	1.3 (1.1-1.6), ****	1.0 (0.5-1.9), <i>ns</i>	1.3 (0.7-2.6), <i>ns</i>
50 y	2.1 (1.5-2.8), ****	3.1 (1.6-6.2), ****	2.2 (1.7-2.9), ****	0.7 (0.5-0.9), ****	1.0 (0.5-2), <i>ns</i>	0.7 (0.6-0.9), ****	1.1 (0.8-1.4), <i>ns</i>	0.7 (0.4-1.5), <i>ns</i>	1.5 (0.7-3.2), <i>ns</i>
60 y	1.6 (1.1-2.4), **	2.8 (1.2-6.4), **	1.5 (1.1-2), **	0.6 (0.4-0.8), ****	1.0 (0.4-2.4), <i>ns</i>	0.5 (0.4-0.7), ****	0.9 (0.6-1.3), <i>ns</i>	0.5 (0.2-1.2), <i>ns</i>	1.7 (0.7-4.3), <i>ns</i>
70 y	1.2 (0.7-2.1), <i>ns</i>	2.5 (0.9-6.9), <i>ns</i>	0.9 (0.6-1.4), <i>ns</i>	0.5 (0.3-0.8), ****	0.9 (0.3-2.5), <i>ns</i>	0.4 (0.3-0.5), ****	0.8 (0.5-1.3), <i>ns</i>	0.4 (0.1-1.1), <i>ns</i>	2.0 (0.7-6.1), <i>ns</i>

D

	AD/HC	FTD/HC	VaD/HC	DLB/HC	AD/FTD	DLB/AD	VaD/AD
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
50 y	2.2 (1.7-2.8), ****	5.9 (4.3-8.3), ****	3.1 (1.9-5), ****	1.7 (0.8-3.7), ns	0.4 (0.3-0.5), ****	0.8 (0.4-1.7), ns	1.4 (0.9-2.3), ns
60 y	2 (1.6-2.3), ****	4.5 (3.6-5.6), ****	2.7 (1.9-3.7), ****	1.6 (1.0-2.6),* ****	0.4 (0.3-0.6), ****	0.8 (0.5-1.3), ns	1.4 (1-1.9), *
70 y	1.7 (1.5-2), ****	3.4 (2.7-4.2), ****	2.3 (1.9-2.9), ****	1.5 (1.1-2), ****	0.5 (0.4-0.6), ****	0.9 (0.7-1.1), ns	1.3 (1.1-1.6), ****
80 y	1.5 (1.3-1.8), ****	2.5 (1.8-3.5), ****	2 (1.6-2.5), ****	1.4 (1-1.9), ns	0.6 (0.4-0.8), ****	0.9 (0.7-1.2), ns	1.3 (1.1-1.6), ****
90 y	1.3 (1-1.7), ***	1.9 (1.2-3.1), ***	1.7 (1.2-2.4), ****	1.3 (0.7-2.3), ns	0.7 (0.4-1.1), ns	1 (0.5-1.7), ns	1.3 (1-1.7), ns

E

	SCD/HC	MCI/HC	AD/HC	AD/MCI
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
50 y	0.7 (0.1-4.3), ns	1.7 (0.9-3.4), ns	2.2 (1.7-2.8), ****	1.3 (0.6-2.6), ns
60 y	1.1 (0.5-2.5), ns	1.6 (1.0-2.4), ns	2 (1.6-2.3), ****	1.3 (0.8-2), ns
70 y	1.7 (0.5-6.4), ns	1.4 (1-1.9), **	1.7 (1.5-2), ****	1.2 (0.9-1.7), ns
80 y	2.6 (0.2-32.5), ns	1.3 (0.9-1.7), ns	1.5 (1.3-1.8), ****	1.2 (0.9-1.7), ns
90 y	4.0 (0.1-180.8), ns	1.1 (0.7-1.9), ns	1.3 (1-1.7), ***	1.2 (0.7-2), ns
	SCD/HC	MCI/HC	AD/HC	AD/MCI
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
50 y	0.7 (0.1-4.3), ns	1.7 (0.9-3.4), ns	2.2 (1.7-2.8), ****	1.3 (0.6-2.6), ns
60 y	1.1 (0.5-2.5), ns	1.6 (1.0-2.4), ns	2 (1.6-2.3), ****	1.3 (0.8-2), ns

70 y	1.7 (0.5-6.4), ns	1.4 (1-1.9), **	1.7 (1.5-2), ****	1.2 (0.9-1.7), ns
80 y	2.6 (0.2-32.5), ns	1.3 (0.9-1.7), ns	1.5 (1.3-1.8), ****	1.2 (0.9-1.7), ns
90 y	4.0 (0.1-180.8), ns	1.1 (0.7-1.9), ns	1.3 (1-1.7), ***	1.2 (0.7-2), ns

F

		FTD vs HC	FTD/ALS vs HC	pgFTD vs FTD	FTD/ALS vs FTD
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
50 y	1.2 (0.7-2.1), ns	5.9 (4.3-8.3), ****	20.9 (6.7-64.6), ****	0.2 (0.1-0.4), ****	3.5 (1.1-11.2), **
60 y	1.2 (0.6-2.4), ns	4.5 (3.6-5.6), ****	11.8 (5.5-25.1), ****	0.3 (0.1-0.5), ****	2.6 (1.2-5.7), ***
70 y	1.2 (0.5-3.4), ns	3.4 (2.7-4.2), ****	6.6 (2.2-19.6), ****	0.4 (0.1-1), *	2.0 (0.7-5.9), ns
80 y	1.2 (0.3-5.1), ns	2.5 (1.8-3.5), ****	3.7 (0.6-21.5), ns	0.5 (0.1-2.1), ns	1.5 (0.3-8.7), ns
90 y	1.2 (0.2-7.9), ns	1.9 (1.2-3.1), ***	2.1 (0.2-25.6), ns	0.7 (0.1-4.3), ns	1.1 (0.1-13.9), ns

G

	PD vs HC	PDD vs HC	MSA vs HC	PSP vs HC	CBS vs HC	DLB vs HC	PSP vs PD	MS A vs PD	CBS vs PD
Age	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p	ratio (95% CI), p
50 y	1.1 (0.8-1.4), ns	1.4 (0.5-3.5), ns	6.3 (4-9.9), ****	4 (1.8-8.6), ****	5.6 (1.8-17.8), ****	1.7 (0.8-3.7), ns	3.7 (1.7-8.3), ****	5.9 (3.6-9.7), ****	5.3 (1.6-17.1), ****
60 y	1.1 (0.9-1.4), ns	1.3 (0.7-2.4), ns	4.3 (3.2-5.6), ****	3.2 (2-5.1), ****	4.6 (2.4-8.9), ****	1.6 (1.0-2.6), *	2.9 (1.8-4.8), ****	3.9 (2.9-5.3), ****	4.2 (2.1-8.3), ****
70 y	1.1 (0.9-1.4), ns	1.3 (0.9-1.9), ns	2.9 (2.1-3.9), ****	2.6 (1.9-3.5), ****	3.7 (2.4-5.7), ****	1.5 (1.1-2), ****	2.3 (1.7-3.2), ****	2.6 (1.9-3.6), ****	3.4 (2.1-5.3), ****
80 y	1.1 (0.8-1.5), ns	1.3 (0.8-2), ns	1.9 (1.2-3.2), ***	2.1 (1.3-3.4), ****	3 (1.4-6.5), ****	1.4 (1-1.9), ns	1.9 (1.1-3.1), **	1.7 (1-3), ns	2.7 (1.2-6), **
90 y	1.1 (0.7-1.8), ns	1.3 (0.6-2.7), ns	1.3 (0.6-2.8), ns	1.7 (0.8-3.7), ns	2.5 (0.7-8.8), ns	1.3 (0.7-2.3), ns	1.5 (0.6-3.4), ns	1.1 (0.5-2.6), ns	2.1 (0.6-8), ns

Legend HC, healthy controls; A CIS, clinically isolated syndrome; ON, optic neuritis; uRRMS, untreated relapsing remitting multiple sclerosis; IND, inflammatory neurological diseases. B tRRMS, treated relapsing remitting multiple sclerosis; uRRMS, untreated relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis. C uRRMS, untreated relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. D AD, Alzheimer's disease; FTD, frontotemporal dementia; VaD, vascular dementia; DLB, Dementia with Lewy bodies. E pgFTD, presymptomatic genetic FTD; FTD, frontotemporal dementia; FTD/ALS, combined FTD and ALS. F SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease. G PD, Parkinson's disease; PDD, PD dementia; MSA, multiple systems atrophy; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome, DLB, dementia with Lewy Bodies. P-values: **** is $p < \text{or} = 0.0001$; *** is $p < \text{or} = 0.001$; ** is $p < \text{or} = 0.01$; * is $p < \text{or} = 0.05$; non significant (ns) is $p > 0.5$. 95% CI, 95% confidence intervals.

eTable 6. Intercohort Heterogeneity Coefficient for Diagnostic Categories With More Than One Contributing Cohort

diagnosis	I2	Number of cohorts
HC	0.35	30
CIS	0.01	9
ON	0	3
Treated RRMS	0	6
Untreated RRMS	0.01	12
SPMS	0.02	8
PPMS	0.02	6
IND	0	3
SNC	0	2
ALS	0.04	2
CIDP/GBS	0	2
FTD	0.13	5
MCI	0	3
AD	0.21	11
iNPH	0	2
VaD	0.36	2
MD	0.58	2
DNS	0.83	2
PD	0.09	5
PDD	0.84	2
MSA	0.43	5
PSP	0.30	4
CBS	0	4
DLB	0.83	2
iHIV	0.96	2
Stroke	0.93	2
NID	0.53	6

Legend Inter-cohort heterogeneity coefficient (I2). Low I2 < 0.2; intermediate I2 0.2-0.6; high I2 >0.6. HC, healthy controls; SNC, subjective neurological complaints; CIS, clinically isolated syndrome; ON, optic neuritis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; IND, inflammatory neurological disorders other than multiple sclerosis; SNC, subjective neurological complaint; ALS, amyotrophic lateral sclerosis; CIDP/GBS, chronic inflammatory demyelinating polyradiculopathy and Guillain-Barré syndrome; FTD, frontotemporal dementia; MCI, mild cognitive impairment; AD, Alzheimer’s disease; iNPH, idiopathic normal pressure hydrocephalus; VaD, vascular dementia; MD, mixed dementia; DNS, dementia not specified; PD, Parkinson’s disease; PDD, PD dementia; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy; CBS, corticobasal syndrome; DLB, Dementia with Lewy bodies; iHIV, HIV with cognitive impairment; pHD, premanifest Huntington’s disease; HD, Huntington’s disease; BD, bipolar disorder; NID, non-inflammatory neurological disorders.

Glossary

AD: Alzheimer's disease
ALS: amyotrophic lateral sclerosis
BD: bipolar disorder
CBS: corticobasal syndrome
CIDP/GBS: chronic inflammatory polyradiculopathy/Guillain Barré syndrome
CIS: clinically isolated syndrome
DLB: dementia with Lewy bodies
DNS: dementia not specified
FTD: frontotemporal dementia
FTD/ALS: frontotemporal dementia/amyotrophic lateral sclerosis
HC: healthy controls
HD: Huntington's disease
HIV: human immunodeficiency virus
iHIV: human immunodeficiency virus with cognitive impairment
IND: inflammatory neurological conditions of the central nervous system
iNPH: idiopathic normal pressure hydrocephalus
MCI: mild cognitive impairment
MD: mixed dementia
MSA: multiple system atrophy
NID: non-inflammatory neurological conditions of the central nervous system
ON: optic neuritis
PD: Parkinson's disease
PDD: Parkinson's disease dementia
pgFTD: presymptomatic genetic frontotemporal dementia
pHD: premanifest Huntington's disease
PPMS: primary progressive multiple sclerosis
PSP: progressive supranuclear palsy
SCD: subjective cognitive decline
SNC: subjective neurological complaint
SPMS: secondary progressive multiple sclerosis
tRRMS: treated relapsing-remitting multiple sclerosis
uRRMS: untreated relapsing-remitting multiple sclerosis
VaD: vascular dementia