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

eFigure 1. Distribution of Time Points of Visits in Relation to Diagnosis of Confirmed Disability Worsening With (A) and Independent of Clinical Relapses (B)
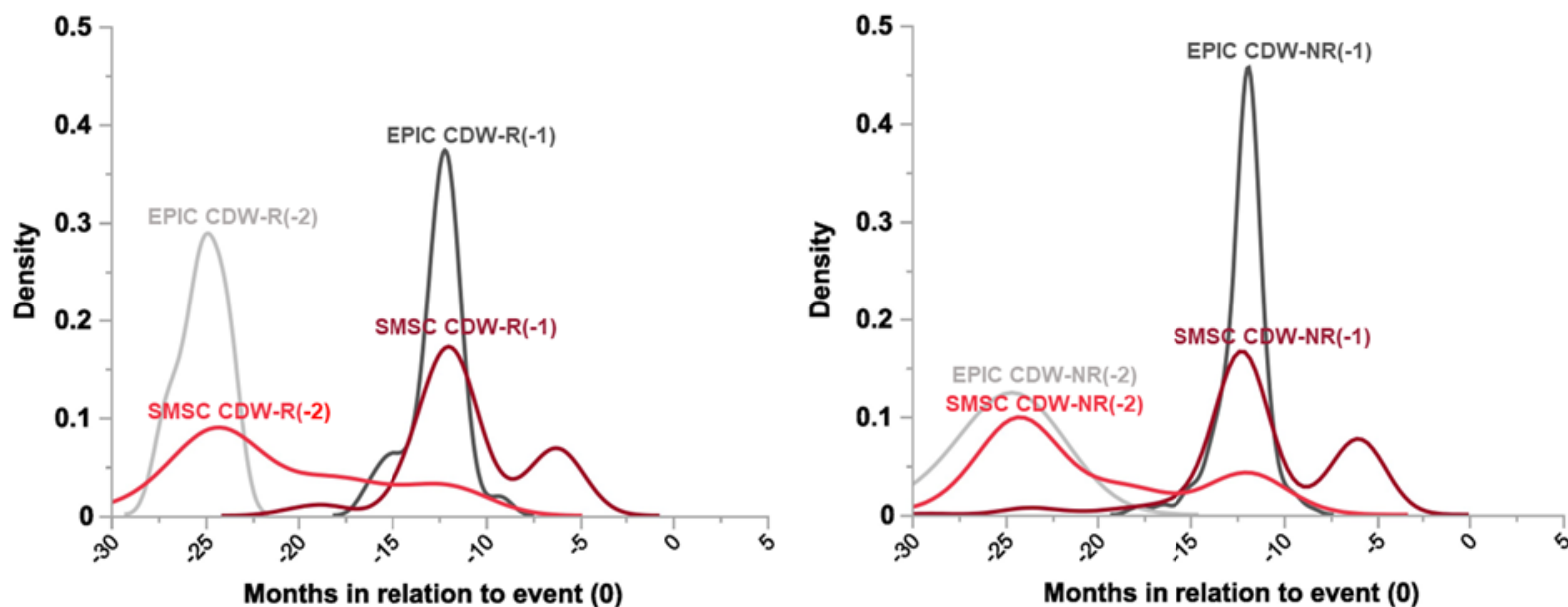
CDW-R: Disability worsening associated with clinical relapses, CDW-NR: Disability worsening independent of clinical relapses. CDW-R/CDW-NR(-2): Two visits preceding the event. CDW-R/CDW-NR(-1): Visit directly preceding the event. SMSC visits (red) showed bimodal distribution due to the high proportion of 6-monthly follow-up visits compared to EPIC (grey, almost exclusively yearly visits).

eFigure 2. NfL Dynamics in Relation to Disability Worsening Independent of Clinical Relapses in Relation to Expanded Disability Status Scale at Sampling
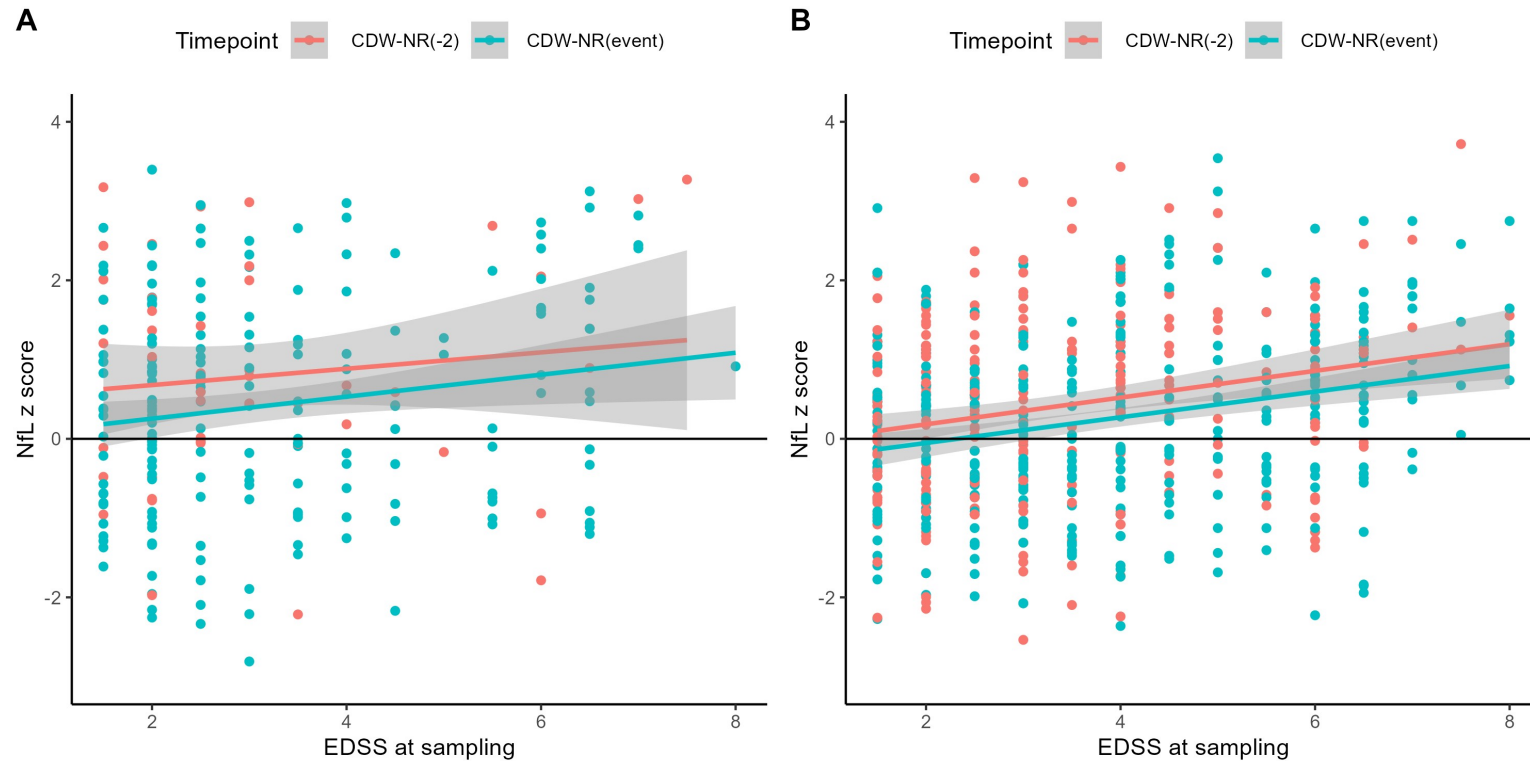

Figure showing the neurofilament light chain (NfL) z scores (y axis) at disability worsening independent of clinical relapses event visit (CDW-NR[event], turquoise) and at CDW-NR(-2) (red) in the EPIC cohort (**A**) and the SMSC (**B**) over the EDSS score at sampling (x axis). At both visits, in both studies, NfL z scores increase with EDSS at a similar magnitude /rate and are higher at CDW are on average higher at CDW-NR(-2) compared to CDW-NR(event). CDW-NR: Confirmed disability worsening independent of clinical relapses. CDW-NR(event)/(-2): CDW-NR event visit, or two visits preceding the event, EDSS: Expanded disability status scale.

eFigure 3. Subgroup Analysis in Relapsing Remitting Multiple Sclerosis: NfL Dynamics in Relation to Disability Worsening Independent of Clinical Relapses
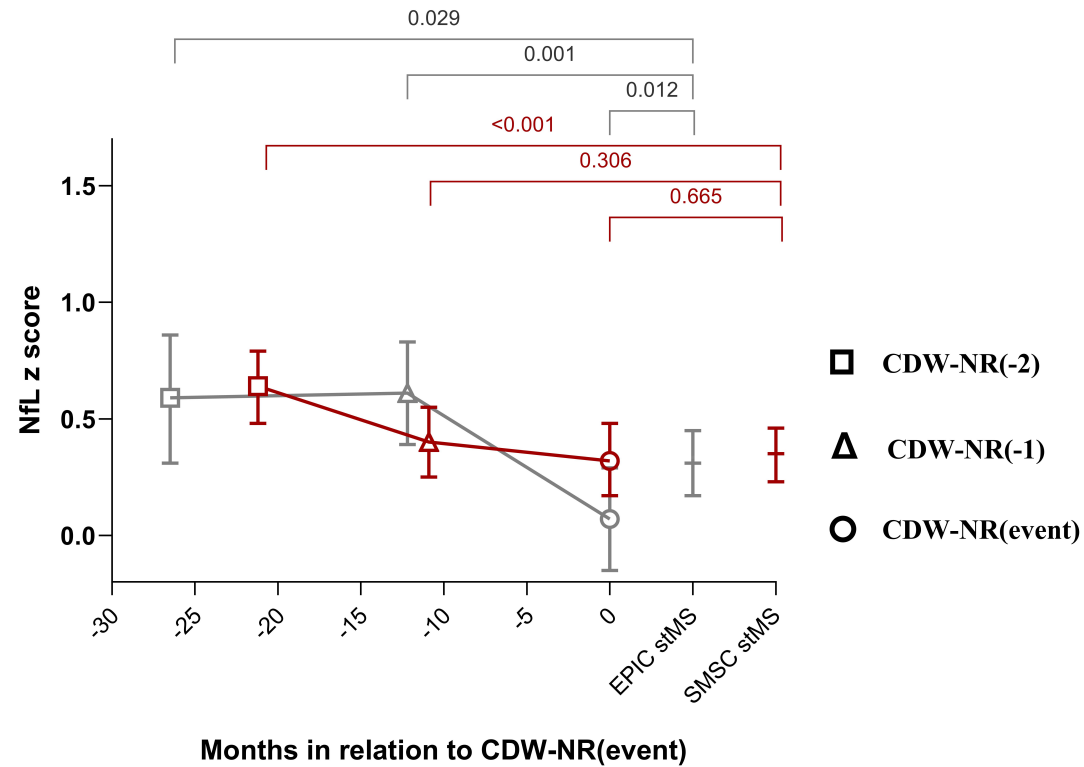
Y axis showing the marginal means of NfL z scores and p values from mixed linear models correcting for age, sex, disease course (relapsing vs. progressive MS), DMT categories (high-efficacy monoclonal antibodies, oral DMT, platform DMT, and untreated), and recent relapse (within 90 days) for CDW-NR. CDW-NR: Confirmed disability worsening independent of clinical relapses. stMS: stable MS participants without evidence of disease activity or progression.

eFigure 4. Sensitivity Analysis in Patients With Complete MRI Information at Each Visit: NfL Dynamics in Relation to Confirmed Disability Worsening Independent of Clinical Relapses Adjusted for Clinical and Radiological Disease Activity
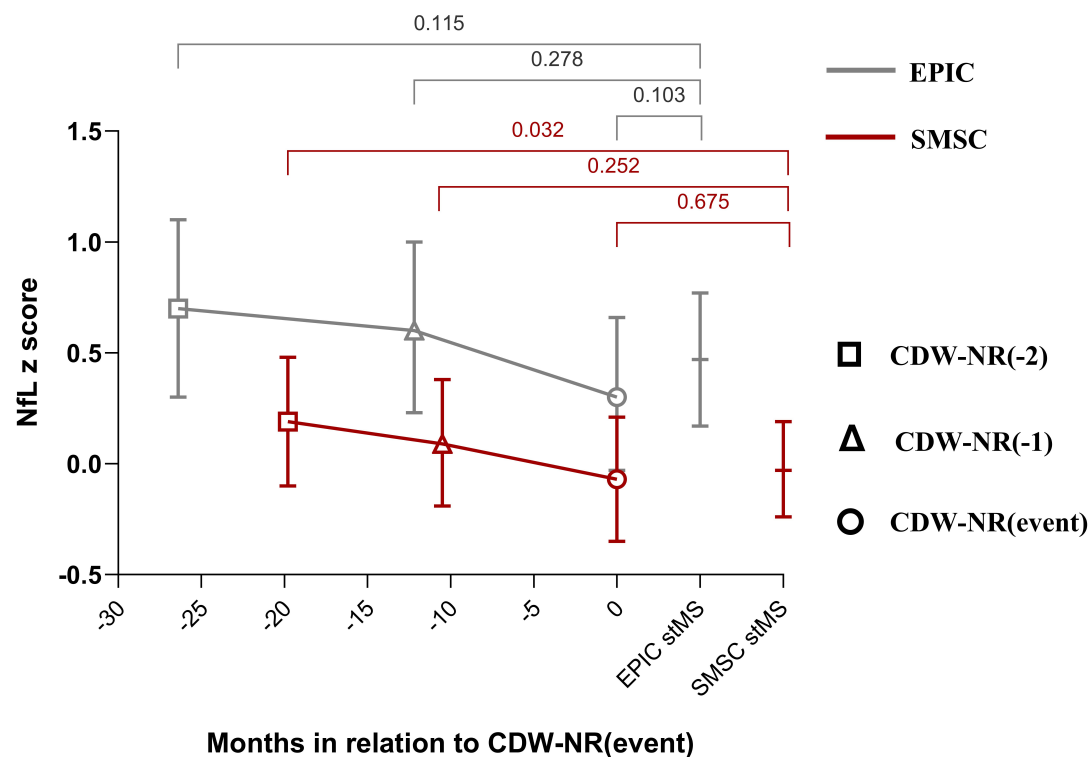
Y axis showing the marginal means of NfL z scores and *p* values from mixed linear models correcting for age, sex, disease course (relapsing vs. progressive MS), DMT categories (high-efficacy monoclonal antibodies, oral DMT, platform DMT, and untreated), and any kind of disease activity (clinical and radiological) over the year preceding the visit of interest. CDW-NR: Confirmed disability worsening independent of clinical relapses, stMS: Stable MS participants without evidence of disease activity or worsening.

eTable 1. NfL *z* Score (Marginal Means) in Relation to Confirmed Disability Worsening With and Independent of Clinical Relapses Compared to Stable Multiple Sclerosis

Visit	EPIC				SMSC			
	n	NfL z score (marginal means and 95% CI)	Difference vs stMS	*p*	*n*	NfL z score (marginal means and 95% CI)	Difference vs stMS	*p*
CDW-R								
CDW-R(-2)	10	0.52 [-0.13 – 1.16]	-0.02 [-0.65 – 0.61]	0.956	85	0.54 [0.33 – 0.75]	0.14 [-0.05 – 0.32]	0.147
CDW-R(-1)	34	1.24 [0.87 – 1.62]	0.71 [0.35 – 1.07]	<0.001	97	0.72 [0.52 – 0.93]	0.32 [0.14 – 0.49]	<0.001
CDW-R(event)	36	0.79 [0.43 – 1.12]	0.26 [-0.09 – 0.61]	0.151	93	0.94 [0.73 – 1.15]	0.53 [0.36 – 0.71]	<0.001
CDW-R(+1)	35	0.48 [0.10 – 0.85]	-0.06 [-0.41 – 0.29]	0.745	83	0.55 [0.34 – 0.77]	0.15 [-0.04 – 0.33]	0.122
stMS	2562	0.53 [0.39 – 0.68]	-	-	6019	0.41 [0.29 – 0.52]	-	-
CDW-NR								
CDW-NR(-2)	87	0.76 [0.51 – 1.01]	0.23 [0.01 – 0.45]	0.040	313	0.62 [0.48 – 0.76]	0.28 [0.18 – 0.37]	<0.001
CDW-NR(-1)	182	0.80 [0.61 – 1.00]	0.27 [0.11 – 0.44]	<0.001	357	0.43 [0.29 – 0.57]	0.09 [0.00 – 0.18]	0.056
CDW-NR(event)	191	0.29 [0.09 – 0.50]	-0.23 [-0.39 – -0.08]	0.004	342	0.36 [0.22 – 0.50]	0.01 [-0.08 – 0.11]	0.777
CDW-NR(+1)	185	0.67 [0.47 – 0.87]	0.14 [-0.02 – 0.30]	0.090	299	0.36 [0.21 – 0.50]	0.01 [-0.09 – 0.11]	0.811
stMS	2562	0.53 [0.39 – 0.66]	-	-	6019	0.34 [0.23 – 0.45]	-	-

Estimated marginal means of NfL z score together with 95% CI and *p* values, and estimated differences in NfL z score compared to stMS from mixed linear models correcting for age, sex, disease course (relapsing vs progressive MS), DMT categories (high-efficacy monoclonal antibodies, oral DMT, platform DMT, and untreated), and recent relapse (within 90 days). NfL: Neurofilament light chain, CI: Confidence interval, stMS: Stable MS samples, CDW-R: Confirmed disability progression with clinical relapses, CDW-NR: Confirmed disability progression independent of clinical relapses, CDW-R/CDW-NR(-1): One visit preceding the event, CDW-R/CDW-NR(-2): Two visits preceding the event, CDW-R/CDW-NR(event): Visit at the time of first diagnosing of EDSS worsening, CDW-R/CDW-NR(+1): Visit confirming EDSS worsening.

eTable 2. Mixed Effect Models Estimating Longitudinal NfL *z* Scores in Context of Confirmed Disability Worsening With Clinical Relapses

Fixed effect terms		*EPIC*				*SMSC*			
		Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
CDW-R status vs stMS	CDW-R(-2)	-0.02	-0.65	0.61	0.956	0.14	-0.05	0.32	0.147
	CDW-R(-1)	0.71	0.35	1.07	<0.001	0.32	0.14	0.49	<0.001
	CDW-R(event)	0.26	-0.09	0.61	0.151	0.53	0.36	0.71	<0.001
	CDW-R(+1)	-0.06	-0.41	0.29	0.745	0.15	-0.04	0.33	0.122
	Relapse samples (within a year)	0.53	0.41	0.64	<0.001	0.38	0.32	0.45	<0.001
Sex	Female vs male	0.01	-0.16	0.18	0.935	0.06	-0.05	0.17	0.282
Age (per 10 years change)		-0.13	-0.20	-0.06	<0.001	-0.13	-0.17	-0.09	<0.001
Disease course at sampling	PMS vs RMS	0.37	0.19	0.56	<0.001	0.12	-0.05	0.29	0.168
EDSS at sampling		0.05	0.02	0.09	0.007	0.13	0.10	016	<0.001
DMT vs untreated	Monoclonal	-0.52	-0.70	-0.34	<0.001	-0.46	-0.55	-0.38	<0.001
	Orals	-0.47	-0.65	-0.29	<0.001	-0.36	-0.45	-0.28	<0.001
	Platforms	-0.11	-0.22	0.00	0.054	-0.20	-0.32	-0.09	0.001
Recent activity	Relapse within 90 days yes vs no	0.12	-0.05	0.29	0.155	0.53	0.43	0.63	<0.001
BMI (EPIC only)		-0.05	-0.06	-0.03	<0.001	/	/	/	/

Estimated additive effects on NfL z score together with 95% CI and *p* values from individual multivariable mixed effects models for EPIC (left) and SMSC (right). We used an indicator variable 'CDW-R status' to assign each visit either a time point related to CDW-R or not and used time points outside CDW-R and not after a relapse (i.e. stable MS samples) as a reference. NfL: Neurofilament light chain, CI: Confidence interval, stMS: Stable MS samples, CDW-R: Confirmed disability worsening with clinical relapses, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index.

eTable 3. Mixed Effect Models Estimating Longitudinal NfL *z* Scores in Context of Confirmed Disability Worsening Independent of Clinical Relapses

Model fixed effect terms		*EPIC*				*SMSC*			
		Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
CDW-NR status vs stMS	CDW-NR(-2)	0.23	0.01	0.45	0.040	0.28	0.18	0.37	<0.001
	CDW-NR(-1)	0.27	0.11	0.44	0.001	0.09	0.00	0.18	0.056
	CDW-NR(event)	-0.23	-0.39	-0.08	0.004	0.01	-0.08	0.11	0.777
	CDW-NR(+1)	0.14	-0.02	0.30	0.090	0.01	-0.09	0.11	0.811
	Relapse samples (within a year)	0.52	0.41	0.63	<0.001	0.39	0.32	0.46	<0.001
Sex	Female vs male	0.02	-0.15	0.18	0.861	0.07	0.04	0.18	0.192
Age (per 10 years change)		-0.13	-0.20	-0.06	0.000	-0.13	-0.17	-0.09	<0.001
Disease course at sampling	PMS vs RMS	0.38	0.21	0.56	<0.001	0.27	0.11	0.42	0.001
EDSS at sampling		0.05	0.01	0.09	0.009	0.11	0.08	0.13	<0.001
DMT vs untreated	Monoclonal	-0.57	-0.74	-0.40	<0.001	-0.40	-0.49	-0.32	<0.001
	Orals	-0.50	-0.67	-0.32	<0.001	-0.31	-0.38	-0.23	<0.001
	Platforms	-0.10	-0.20	-0.004	0.041	-0.12	-0.23	-0.01	0.026
Recent activity	Relapse within 90 days yes vs no	0.13	-0.03	0.29	0.102	0.55	0.45	0.65	<0.001
BMI (EPIC only)		-0.04	-0.06	-0.03	<0.001	/	/	/	/

Estimated additive effects on NfL z score together with 95% CI and *p* values from individual multivariable mixed effects models for EPIC (left) and SMSC (right). We used an indicator variable 'CDW-NR status' to assign each visit either a time point related to CDW-NR or not and used time points outside CDW-NR and not after a relapse (i.e. stable MS samples) as a reference. NfL: Neurofilament light chain, CI: Confidence interval, stMS: Stable MS samples, CDW-NR: Confirmed disability worsening independent of clinical relapses, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index.

eTable 4. Subgroup Analysis in People With Relapsing-Remitting Multiple Sclerosis: NfL *z* Score (Marginal Means) in Relation to Confirmed Disability Worsening Independent of Clinical Relapses Compared to Stable Multiple Sclerosis

Visit	EPIC				SMSC			
	n	NfL z score (marginal means and 95% CI)	Difference vs stMS	*p*	*n*	NfL z score (marginal means and 95% CI)	Difference vs stMS	*p*
CDW-NR(-2)	73	0.59 [0.31 – 0.86]	0.28 [0.03 – 0.53]	0.029	250	0.64 [0.48 – 0.79]	0.29 [0.18 – 0.40]	<0.001
CDW-NR(-1)	152	0.61 [0.39 – 0.83]	0.30 [0.12 – 0.49]	0.001	278	0.40 [0.25 – 0.55]	0.05 [-0.05 – 0.15]	0.306
CDW-NR(event)	151	0.07 [-0.15 – 0.29]	-0.23 [-0.42 – -0.05]	0.012	255	0.32 [0.17 – 0.48]	-0.02 [-0.13 – 0.08]	0.665
CDW-NR(+1)	143	0.50 [0.28 – 0.72]	0.19 [0.01 – 0.38]	0.043	215	0.29 [0.13 – 0.45]	-0.06 [-0.17 – 0.06]	0.330
stMS	2108	0.31 [0.17 – 0.45]	-	-	5476	0.35 [0.23 – 0.46]	-	-

Estimated marginal means of NfL z score together with 95% CI and *p* values, and estimated differences in NfL z score compared to stMS from mixed linear models correcting for age, sex, disease course (relapsing vs progressive MS), DMT categories (high-efficacy monoclonal antibodies, oral DMT, platform DMT, and untreated), and recent relapse (within 90 days). NfL: Neurofilament light chain, CI: confidence interval, stMS: Stable MS samples. CDW-NR: Confirmed disability progression independent of clinical relapses. CDW-NR(-1): One visit preceding the event, CDW-NR(-2): Two visits preceding the event, CDW-NR(event): Visit at the time of first diagnosing of EDSS worsening, CDW-NR(+1): Visit confirming EDSS worsening.

eTable 5. Subgroup Analysis in People With Relapsing-Remitting Multiple Sclerosis: Mixed-Effects Models Evaluating Longitudinal NfL *z* Scores in Cases With Confirmed Disability Worsening Independent of Clinical Relapses in Participants With Relapsing-Remitting Multiple Sclerosis

Model fixed effect terms		*EPIC*				*SMSC*			
		Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
CDW-NR status vs stMS	CDW-NR(-2)	0.28	0.03	0.53	0.029	0.29	0.18	0.40	<0.001
	CDW-NR(-1)	0.30	0.12	0.49	0.001	0.05	-0.05	0.15	0.306
	CDW-NR(event)	-0.23	-0.42	-0.05	0.012	-0.02	-0.13	0.08	0.665
	CDW-NR(+1)	0.19	0.01	0.38	0.043	-0.06	-0.17	0.06	0.330
	Relapse samples (within a year)	0.56	0.44	0.67	<0.001	0.39	0.32	0.46	<0.001
Sex	Female vs male	0.02	-0.16	0.21	0.807	0.07	-0.04	0.19	0.207
Age (per 10 years change)		-0.12	-0.21	-0.06	<0.001	-0.13	-0.17	-0.08	<0.001
EDSS at sampling		0.03	-0.02	0.07	0.251	0.11	0.08	0.14	<0.001
DMT vs untreated	Monoclonal	-0.65	-0.86	-0.44	<0.001	-0.44	-0.53	-0.35	<0.001
	Orals	-0.43	-0.63	-0.22	<0.001	-0.33	-0.41	-0.25	<0.001
	Platforms	-0.12	-0.23	-0.004	0.043	-0.14	-0.25	-0.03	0.014
Activity	Any activity within a year yes vs no	0.17	-0.01	0.34	0.058	0.57	0.47	0.67	<0.001
BMI (EPIC only)		-0.04	-0.06	-0.03	<0.001	/	/	/	/

Estimated additive effects on NfL z score together with 95% CI and *p* values from individual multivariable mixed effects models for EPIC (left) and SMSC (right). We used an indicator variable 'CDW-NR status' to assign each visit either a time point related to CDW-NR or not and used time points outside CDW-NR and not after a relapse (i.e. stable MS samples) as a reference. NfL: Neurofilament light chain, CI: confidence interval, stMS: Stable MS samples, CDW-NR: Confirmed disability worsening independent of clinical relapses, EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index.

eTable 6. Sensitivity Analyses in SMSC Restricted to Yearly Visits: NfL *z* Score (Marginal Means) in Relation to Confirmed Disability Worsening

Model fixed effect terms	CDW-R					CDW-NR				
	n	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	*n*	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
CDW(-2)	52	0.44	0.20	0.69	<0.001	187	0.20	0.07	0.33	0.002
CDW(-1)	72	0.35	0.14	0.57	0.001	228	0.13	0.01	0.24	0.038
CDW(event)	71	0.38	0.17	0.60	0.001	225	00	-0.12	0.12	0.979
CDW(+1)	60	0.04	-0.19	0.27	0.709	191	-0.04	-0.17	0.09	0.545
stMS	4244	0.43	0.30	0.56	-	4244	0.38	0.25	0.50	-

Estimated marginal means of NfL z score together with 95% CI and *p* values, and estimated differences in NfL z score compared to stMS from mixed linear models correcting for age, sex, disease course (relapsing vs progressive MS), DMT categories (high-efficacy monoclonal antibodies, oral DMT, platform DMT, and untreated), and recent relapse (within 90 days). NfL: Neurofilament light chain, CI: confidence interval, stMS: Stable MS samples, CDW-R: Confirmed disability progression with clinical relapses, CDW-NR: Confirmed disability progression independent of clinical relapses. CDW-R/CDW-NR(-1): One visit preceding the event, CDW-R/CDW-NR(-2): Two visits preceding the event, CDW-R/CDW-NR(event): Visit at the time of first diagnosing of EDSS worsening, CDW-R/CDW-NR(+1): Visit confirming EDSS worsening.

eTable 7. Sensitivity Analysis in Participants With MRI Information Available at Each Visit: Mixed-Effects Models Estimating Longitudinal NfL *z* Scores in Context of Confirmed Disability Worsening Independent of Clinical Relapses, Accounting for Clinical and Magnetic Resonance Imaging Activity

Model fixed effect terms		EPIC				SMSC			
		Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	Estimate	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
CDW-NR status vs stMS	CDW-NR(-2)	0.23	-0.06	0.52	0.115	0.22	0.02	0.42	0.032
	CDW-NR(-1)	0.13	-0.11	0.38	0.278	0.12	-0.08	0.32	0.252
	CDW-NR(event)	-0.15	-0.34	0.03	0.103	-0.04	-0.24	0.15	0.675
	CDW-NR(+1)	0.25	0.05	0.45	0.013	-0.14	-0.36	0.09	0.236
	Relapse samples (within a year)	0.33	0.15	0.50	<0.001	-0.01	-0.19	0.17	0.898
Sex	Female vs male	0.004	-0.18	0.19	0.967	0.10	-0.06	0.27	0.222
Age (per 10 years change)		-0.03	-0.12	0.06	0.498	-0.10	-0.17	-0.03	0.006
Disease course at sampling	PMS vs RMS	0.45	0.20	0.70	<0.001	0.07	-0.23	0.37	0.634
EDSS at sampling		0.08	0.02	0.13	0.005	0.14	0.08	0.19	<0.001
DMT vs untreated	Monoclonal	-0.38	-0.62	-0.13	0.003	-0.05	-0.27	0.17	0.646
	Orals	-0.29	-1.37	0.79	0.595	-0.16	-0.35	0.03	0.103
	Platforms	-0.05	-0.19	0.09	0.514	0.01	-0.25	0.26	0.966
Activity	Any activity within a year yes vs no	0.06	-0.06	0.19	0.315	0.40	0.28	0.51	<0.001
BMI (EPIC only)		-0.06	-0.07	-0.04	<0.001	/	/	/	/

Estimated additive effects on NfL z score together with 95% CI and *p* values from individual multivariable mixed effects models for EPIC (left) and SMSC (right). We used an indicator variable 'CDW-NR status' to assign each visit either a time point related to CDW-NR or not and used time points outside CDW-NR and not after a relapse (i.e. stable MS samples) as a reference. NfL: Neurofilament light chain, CI: Confidence interval, stMS: Stable MS samples, CDW-NR: Confirmed disability worsening independent of clinical relapses, EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index.

eTable 8. Association Between NfL *z* Score and Future Risk of Confirmed Disability Worsening with Clinical Relapses at Visit CDW-R(-1)

Variables		EPIC				SMSC			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score (continuous scale)		1.19	0.97	1.47	0.096	1.20	0.99	1.46	0.060
Sex	Female vs male	1.28	0.61	2.66	0.514	0.98	0.64	1.49	0.920
Age (per 10 years change)		0.88	0.59	1.3	0.510	0.83	0.69	1.00	0.049
Disease course at sampling	PMS vs RMS	2.71	0.56	13.17	0.218	0.60	0.24	1.53	0.286
EDSS at baseline		0.66	0.44	1	0.050	1.07	0.90	1.26	0.456
DMT vs untreated*	Monoclonal	1.03	0.51	2.06	0.933	0.58	0.31	1.06	0.077
	Orals					0.82	0.46	1.45	0.490
	Platforms					0.44	0.16	1.21	0.112
Recent activity	Relapse within 90 days yes vs no	1.49	0.48	4.64	0.493	2.1	0.98	4.37	0.057
BMI (EPIC only)		1.05	1.00	1.11	0.071	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-R Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-R: Confirmed disability worsening with clinical relapses, CDW-R(-1): One visit preceding the event, CI: Confidence interval, PMS/ RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately

eTable 9. Association Between NfL *z* Score > 1.0 and Future Risk of Confirmed Disability Worsening with Clinical Relapses at Visit CDW-R(-1)

Variables		EPIC				SMSC			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score > 1.0		1.91	0.94	3.87	0.073	1.70	1.10	2.61	0.017
Sex	Female vs male	1.24	0.59	2.61	0.569	0.98	0.64	1.49	0.925
Age (per 10 years change)		0.88	0.59	1.29	0.503	0.83	0.69	1.001	0.051
Disease course at sampling	PMS vs RMS	2.62	0.53	12.9	0.236	0.60	0.24	1.53	0.284
EDSS at baseline		0.66	0.44	1	0.052	1.07	0.91	1.26	0.442
DMT vs untreated*	Monoclonal	1.04	0.52	2.08	0.905	0.58	0.32	1.08	0.086
	Orals					0.82	0.46	1.45	0.493
	Platforms					0.45	0.16	1.22	0.117
Recent activity	Relapse within 90 days yes vs no	1.47	0.47	4.65	0.509	2.11	1.01	4.39	0.047
BMI (EPIC only)		1.05	1	1.11	0.071	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-R Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-R: Confirmed disability worsening with clinical relapses, CDW-R(-1): One visit preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately

eTable 10. Association Between NfL *z* Score and Future Risk of Confirmed Disability Worsening with Clinical Relapses at Visit CDW-R(-2)

Variables		*EPIC*				*SMSC*			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score (continuous scale)		0.88	0.63	1.22	0.441	1.01	0.82	1.23	0.956
Sex	Female vs male	1.54	0.46	5.13	0.485	1.11	0.69	1.77	0.672
Age (per 10 years change)		0.97	0.9	1.04	0.362	0.80	0.66	0.98	0.032
Disease course at sampling	PMS vs RMS	1.89	0.07	51.92	0.706	0.36	0.11	1.22	0.102
EDSS at baseline		0.78	0.38	1.62	0.509	1.11	0.93	1.34	0.240
DMT vs untreated*	Monoclonal					0.54	0.27	1.07	0.079
	Orals	1.57	0.43	5.70	0.497	0.87	0.48	1.61	0.664
	Platforms					0.19	0.04	0.83	0.027
Recent activity	Relapse within 90 days yes vs no	1.02	0.11	9.29	0.989	1.29	0.52	3.24	0.583
BMI (EPIC only)		1.06	0.97	1.16	0.166	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-R Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-R: Confirmed disability worsening with clinical relapses, CDW-R(-2): two visits preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately

eTable 11. Association Between NfL *z* Score > 1.0 and Future Risk of Confirmed Disability Worsening with Clinical Relapses at Visit CDW-R(-2)

Variables		*EPIC*				*SMSC*			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score > 1.0		0.65	0.19	2.25	0.494	1.09	0.67	1.77	0.726
Sex	Female vs male	1.55	0.47	5.03	0.470	1.11	0.69	1.77	0.673
Age (per 10 years change)		0.97	0.89	1.04	0.363	0.81	0.66	0.99	0.039
Disease course at sampling	PMS vs RMS	1.88	0.07	51.97	0.709	0.36	0.11	1.20	0.097
EDSS at baseline		0.78	0.38	1.61	0.505	1.11	0.93	1.33	0.248
DMT vs untreated*	Monoclonal	1.56	0.43	5.72	0.500	0.54	0.28	1.08	0.082
	Orals					0.88	0.48	1.62	0.679
	Platforms					0.19	0.04	0.84	0.028
Recent activity	Relapse within 90 days yes vs no	1.00	0.11	9.07	0.997	1.27	0.50	3.19	0.614
BMI (EPIC only)		1.07	0.98	1.16	0.133	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-R Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-R: Confirmed disability worsening with clinical relapses, CDW-R(-2): two visits preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately.

eTable 12. Association Between NfL *z* Score and Future Risk of Confirmed Disability Worsening Independent of Clinical Relapses at Visit CDW-NR(-1)

Variables		EPIC				SMSC			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	p	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score (continuous scale)		1.19	1.07	1.33	0.001	1.02	0.94	1.10	0.717
Sex	Female vs male	1.29	0.94	1.76	0.115	0.88	0.73	1.06	0.169
Age (per 10 years change)		1.36	1.14	1.61	0.001	1.17	1.07	1.27	0.001
Disease course at sampling	PMS vs RMS	3.21	1.98	5.22	<0.001	2.33	1.67	3.24	<0.001
EDSS at baseline		0.59	0.51	0.69	<0.001	1.04	0.97	1.12	0.283
DMT vs untreated*	Monoclonal	1.04	0.77	1.41	0.782	1.10	0.85	1.42	0.480
	Orals					1.19	0.90	1.57	0.230
	Platforms					0.81	0.53	1.24	0.322
Recent activity	Relapse within 90 days yes vs no	0.78	0.4	1.51	0.453	1.04	0.62	1.73	0.894
BMI (EPIC only)		1.03	1.00	1.06	0.036	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-NR Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-NR: Confirmed disability worsening independent of clinical relapses, CDW-NR(-1): One visit preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately.

eTable 13. Association Between NfL *z* Score > 1.0 and Future Risk of Confirmed Disability Worsening Independent of Clinical Relapses at Visit CDW-NR(-1)

Variables		EPIC				SMSC			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score > 1.0		1.40	1.06	1.85	0.017	0.94	0.76	1.17	0.600
Sex	Female vs male	1.27	0.93	1.75	0.132	0.88	0.73	1.06	0.176
Age (per 10 years change)		1.34	1.13	1.59	0.001	1.16	1.06	1.27	0.001
Disease course at sampling	PMS vs RMS	3.28	2.02	5.34	<0.001	2.35	1.69	3.28	<0.001
EDSS at baseline		0.6	0.51	0.69	<0.001	1.04	0.97	1.12	0.244
DMT vs untreated*	Monoclonal	1.06	0.78	1.43	0.717	1.09	0.84	1.42	0.500
	Orals					1.18	0.89	1.57	0.242
	Platforms					0.81	0.53	1.23	0.317
Recent activity	Relapse within 90 days yes vs no	0.8	0.41	1.56	0.519	1.06	0.63	1.77	0.826
BMI (EPIC only)		1.03	1.00	1.06	0.062	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-NR Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-NR: Confirmed disability worsening independent of clinical relapses, CDW-NR(-1): One visit preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index.
*DMT group were merged in EPIC due to the low number of events in each group separately

eTable 14. Association Between NfL *z* Score and Future Risk of Confirmed Disability Worsening Independent of Clinical Relapses at Visit CDW-NR(-2)

Variables		EPIC				SMSC			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score continuous		1.16	1.01	1.33	0.030	1.14	1.04	1.24	0.004
Sex	Female vs male	1.38	0.9	2.11	0.138	0.88	0.73	1.07	0.190
Age (per 10 years change)		1.03	1.01	1.06	0.007	1.16	1.07	1.27	<0.001
Disease course at sampling	PMS vs RMS	2.07	1.03	4.15	0.040	1.81	1.32	2.48	<0.001
EDSS at baseline		0.71	0.58	0.88	0.001	1.06	0.99	1.14	0.100
DMT vs untreated*	Monoclonal	1.32	0.89	1.98	0.171	1.11	0.84	1.48	0.462
	Orals					1.23	0.91	1.66	0.180
	Platforms					1.00	0.65	1.55	0.996
Recent activity	Relapse within 90 days yes vs no	0.75	0.32	1.77	0.513	0.54	0.30	1.00	0.051
BMI (EPIC only)		1.01	0.97	1.05	0.714	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-NR Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-NR: Confirmed disability worsening independent of clinical relapses, CDW-NR(-2): Two visits preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately

eTable 15. Association Between NfL *z* Score > 1.0 and Future Risk of Confirmed Disability Worsening Independent of Clinical Relapses at Visit CDW-NR(-2)

Variables		*EPIC*				*SMSC*			
		HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*	HR	Lower Bound of 95% CI	Upper Bound of 95% CI	*p*
NfL z score > 1.0		1.25	0.84	1.87	0.274	1.49	1.20	1.84	<0.001
Sex	Female vs male	1.37	0.89	2.11	0.148	0.88	0.73	1.07	0.208
Age (per 10 years change)		1.03	1.01	1.06	0.010	1.17	1.07	1.27	<0.001
Disease course at sampling	PMS vs RMS	2.13	1.06	4.3	0.034	1.79	1.30	2.47	<0.001
EDSS at baseline		0.72	0.58	0.88	0.002	1.06	0.99	1.14	0.108
DMT vs untreated*	Monoclonal	1.34	0.9	2.01	0.153	1.12	0.85	1.49	0.419
	Orals					1.23	0.91	1.66	0.179
	Platforms					1.01	0.65	1.56	0.969
Recent activity	Relapse within 90 days yes vs no	0.79	0.34	1.85	0.588	0.55	0.30	1.00	0.051
BMI (EPIC only)		1.00	0.97	1.04	0.836	/	/	/	/

Estimated hazard rations (HR) from a multivariable time-to-CDW-NR Cox regression model using NfL z score as a time-varying covariate. NfL: Neurofilament light chain, CDW-NR: Confiremd disability worsening independent of clinical relapses, CDW-NR(-2): Two visit preceding the event, CI: Confidence interval, PMS/RMS: Progressive/ relapsing multiple sclerosis. EDSS: Expanded disability status scale, DMT: Disease modifying treatments, BMI: Body mass index. *DMT group were merged in EPIC due to the low number of events in each group separately