

Supplementary Table 1. Time to neuroinflammatory event (years) following tumour necrosis factor- α inhibitor (TNFi) treatment start stratified by country and arthritic disease.

Population (N _{ARTIS} /N _{DANBIO})	Time to neurological event Median, years (IQR)	
	Sweden	Denmark
All neuroinflammatory diagnoses		
RA patients (54/21)	3.6 (1.1-6.8)	3.2 (1.4-5.1)
PsA and AS patients (49/26)	3.8 (1.7-5.9)	3.1 (1.4-8.6)
Demyelinating diseases of the central nervous system and optic neuritis		
RA patients (40/15)	3.8 (1.1-7.7)	3.7 (1.4-5.5)
PsA and AS patients (40/19)	4.2 (1.8-6.1)	3.3 (1.4-8.0)
Multiple sclerosis		
RA patients (6/4)	2.4 (1.0-3.6)	8.9 (4.4-9.8)
PsA and AS patients (14/6)	4.0 (2.1-5.2)	2.5 (1.0-3.8)
Inflammatory polyneuropathies		
RA patients (14/6)	3.0 (1.2-5.1)	2.8 (0.7-4.3)
PsA and AS patients (9/7)	2.4 (1.0-3.8)	2.8 (1.3-11.4)

Numbers and medians (IQR; interquartile range) among TNFi exposed patients experiencing a neuroinflammatory event during follow-up (N=150). AS, ankylosing spondylitis; IQR, interquartile range; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, tumour necrosis factor- α inhibitor.

Supplementary Table 2. Sensitivity and sub-analyses for risk of neuro-inflammatory events for TNFi exposed patients compared to non-exposed patients stratified for country and arthritic disease.

	Sweden							Denmark						
	Pyrs TNFi exp	Pyrs TNFi unexp	N events among TNFi exp	N events among TNFi unexp	IR/1,000 pyrs among TNFi exp	IR/1,000 pyrs among TNFi unexp	TNFi exposed versus unexposed HR (95% CI)	Pyrs TNFi exp	Pyrs TNFi unexp	N events among TNFi exp	N events among TNFi unexp	IR/1,000 pyrs among TNFi exp	IR/1,000 pyrs among TNFi unexp	TNFi exposed versus unexposed HR (95% CI)
Rheumatoid arthritis														
"On drug" analysis														
Crude	84,711	560,320	28	216	0.33	0.39	0.85 (0.57-1.27)	31,242	108,685	10	30	0.32	0.28	1.09 (0.53-2.25)
Adjusted for sex and calendar time							0.87 (0.58-1.3)							0.75 (0.35-1.63)
Sex (adjusted for calendar year)														
Female	111,020	404,929	42	133	0.38	0.33	1.04 (0.73-1.49)	39,718	78,236	15	18	0.38	0.23	1.49 (0.69-3.22)
Male	34,481	155,391	12	83	0.35	0.53	0.80 (0.43-1.49)	13,531	30,449	6	12	0.44	0.39	1.14 (0.37-3.58)
Follow-up time (years) (adjusted for sex and calendar year)														
<1	18,043	74,923	10	41	0.55	0.55	0.97 (0.48-1.99)	7,064	24,167	5	9	0.71	0.37	2.05 (0.63-6.63)
1-4	59,479	230,670	25	91	0.42	0.39	1.16 (0.73-1.85)	23,722	60,867	10	19	0.42	0.31	1.14 (0.48-2.75)
≥5	67,979	254,726	19	84	0.28	0.33	0.88 (0.53-1.47)	22,463	23,304	6	2	0.27	0.086	1.97 (0.31-12.54)
Age at treatment start (years) (adjusted for sex and calendar year)														
<50	46,890	106,382	16	46	0.34	0.43	0.78 (0.44-1.38)	17,051	23,197	7	10	0.41	0.43	0.60 (0.17-2.08)
50-64	67,813	210,721	22	70	0.32	0.33	1.03 (0.63-1.67)	24,148	39,323	10	10	0.41	0.25	1.97 (0.75-5.19)
≥65	30,798	243,217	16	100	0.52	0.41	1.24 (0.72-2.13)	12,050	46,166	4	10	0.33	0.22	3.06 (0.89-10.51)
Patients with full information on smoking and DAS28-CRP ³														
Crude								38,179	64,963	15	16	0.39	0.25	1.61 (0.79-3.29)
Adjusted for sex and calendar year														1.45 (0.61-3.44)
Additionally, adjusted for smoking														1.48 (0.62-3.50)
Additionally, adjusted for DAS28-CRP														1.54 (0.62-3.83)
Unexposed patients retrieved from ARTIS														
Crude	145,501	194,143	54	65	0.37	0.33	1.12 (0.78-1.63)							

Adjusted for sex and calendar year							1.06 (0.73-1.56)							
Unexposed patients who switch or escalate csDMARD treatment (2006-2017) ^b														
Crude	75,771	63,125	26	33	0.34	0.52	0.69 (0.41-1.16)							
Adjusted for sex and calendar year							0.69 (0.41-1.17)							
Additionally, adjusted for disease duration							0.76 (0.44-1.33)							
Prevalent unexposed patients from NPR and ARTIS exposed patients, 2006 and onwards ^b														
Crude	75,771	424,072	26	153	0.34	0.36	0.96 (0.63-1.47)							
Adjusted for sex and calendar year							0.92 (0.59-1.42)							
Prevalent unexposed patients from NPR and ARTIS exposed patients, 2011 and onwards ^b														
Crude	26,768	261,076	13	98	0.49	0.38	1.21 (0.67-2.19)							
Adjusted for sex and calendar year							1.19 (0.63-2.22)							
Ankylosing spondylitis and psoriatic arthritis														
"On drug" analysis														
Crude	56,221	364,715	30	147	0.53	0.40	1.24 (0.83-1.86)	20,500	30,933	12	6	0.59	0.19	2.53 (0.95-6.77)
Adjusted for sex and calendar time							1.41 (0.93-2.14)							2.02 (0.71-5.73)
Sex (adjusted for calendar year)														
Female	36,731	180,510	28	82	0.76	0.45	1.67 (1.06-2.62)	11,910	15858	12	4	1.0	0.25	2.50 (0.74-8.48)
Male	46,146	184,204	21	65	0.46	0.35	1.37 (0.81-2.3)	17,959	15075	14	2	0.78	0.13	5.81 (1.23-27.39)
Follow-up time (years) (adjusted for sex and calendar year)														
<1	12,967	45,907	7	37	0.54	0.81	0.71 (0.31-1.64)	4,420	8,281	3	2	0.68	0.24	1.85 (0.22-15.31)
1-4	38,896	146,427	24	62	0.62	0.42	1.79 (1.09-2.97)	14,368	18,307	14	2	0.97	0.11	7.93 (1.74-36.13)
≥5	31,015	172,381	18	48	0.58	0.28	2.1 (1.19-3.7)	11,081	4,302	9	2	0.81	0.46	1.31 (0.26-6.65)
Age at treatment start (years) (adjusted for sex and calendar year)														
<50	53,542	173,259	40	67	0.75	0.39	2.16 (1.43-3.26)	19,615	14,919	16	4	0.82	0.27	2.93 (0.90-9.56)
50-64	24,792	136,254	7	57	0.28	0.42	0.66 (0.30-1.48)	8,830	10,970	10	2	1.1	0.18	4.26 (0.81-22.26)
≥65	4,544	55,202	2	23	0.44	0.42	1.08 (0.24-4.77)	1,423	5,044	0	0	0	0	-
Patients with full information on smoking ^a														
Crude								27,498	23,247	23	6	0.84	0.26	2.94 (1.19-7.24)

Additionally, adjusted for sex and calendar year																				2.56 (0.98-6.70)
Additionally, adjusted for smoking																				2.45 (0.93-6.41)
Unexposed patients retrieved from ARTIS																				
Crude	82,878	45,518	49	11	0.59	0.24	2.07 (1.07-4.01)													
Additionally, adjusted for sex and calendar year							1.93 (0.97-3.83)													
Unexposed patients who switch or escalate csDMARD treatment (2006-2017) ^b																				
Crude	61,051	23,190	35	5	0.57	0.22	2.31 (0.89-5.96)													
Additionally, adjusted for sex and calendar year							2.54 (0.98-6.58)													
Additionally, adjusted for disease duration							2.57 (0.95-6.95)													
Prevalent unexposed patients from NPR and ARTIS exposed patients, 2006 and onwards ^b																				
Crude	61051	309337	35	105	0.57	0.34	1.60 (1.08-2.36)													
Adjusted for sex and calendar year							1.62 (1.07-2.46)													
Prevalent unexposed patients from NPR and ARTIS exposed patients, 2011 and onwards ^b																				
Crude	27274	208114	14	65	0.51	0.31	1.55 (0.85-2.80)													
Adjusted for sex and calendar year							1.38 (0.72-2.63)													

Cox proportional hazard regression with age as underlying time scale. The hazard ratios measure the relative risk of developing a neurological event for patients who are treated with TNFi compared to patients who are not treated with TNFi.

csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs; exp, exposed; unexp, unexposed; HR, Hazard Ratio; IR, Incidence rate; Pyrs: Person-years; TNFi, tumour necrosis factor- α inhibitor.

^a Only examined in DANBIO

^b Only examined in the Swedish cohort.

Supplementary Table 3. Number of neuro-inflammatory events and crude incidence rates stratified to sub-diagnoses and country.

	Sweden				Denmark			
	N events/Pyrs among TNFi exp	N events/Pyrs among TNFi unexp	IR/1,000 pyrs among TNFi exp	IR/1,000 pyrs among TNFi unexp	N events/Pyrs among TNFi exp	N events/Pyrs among TNFi unexp	IR/1,000 pyrs among TNFi exp	IR/1,000 pyrs among TNFi unexp
Ankylosing spondylitis	35/44,840	86/170,357	0.78	0.50	13/14,697	1/7,475	0.88	0.13
Psoriatic arthritis	14/38,038	61/194,358	0.37	0.31	13/15,172	5/23,458	0.86	0.21

Exp, exposed; unexp, unexposed; IR, Incidence rate; Pyrs: Person-years; TNFi, tumour necrosis factor- α inhibitor.