Appendix

Table of Contents

Table S5 Five years before the first demyelinating claim or MS symptom onset: rate ratios for physician and hospital encounters by ICD chapter, comparing MS cases and controls

Table S6 Five years before the first demyelinating claim or MS symptom onset: rate ratios of physician encounters by physician specialty, comparing MS cases and controls

Table S7 Five years before the first demyelinating claim or MS symptom onset: proportion with a least one prescription by ATC level 1

Table S8 Prevalence of morbidities during the five years before the first demyelinating claim or MS symptom onset

Figure S1a Rate ratios of physician visits by ICD chapter between cases and controls in the 5 years before the first demyelinating claim

The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date. The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls.

Figure S1b Rate ratios of physician visits by ICD chapter between cases and controls in the 5 years before MS symptom onset
The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date.
The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls.
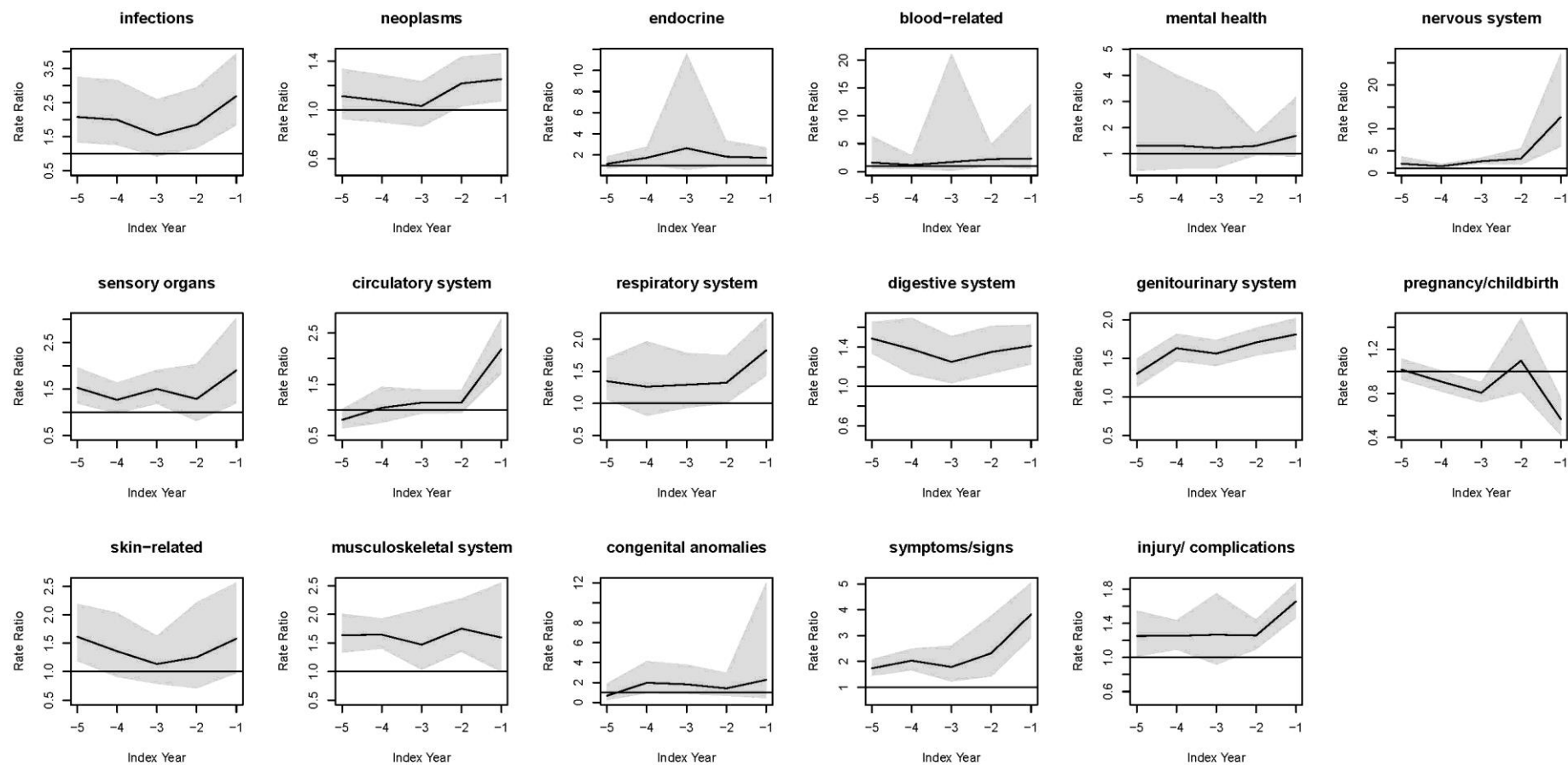
Figure S1c Rate ratios of hospitalizations by ICD chapter between cases and controls in the 5 years before the first demyelinating claim

The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date. The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls.
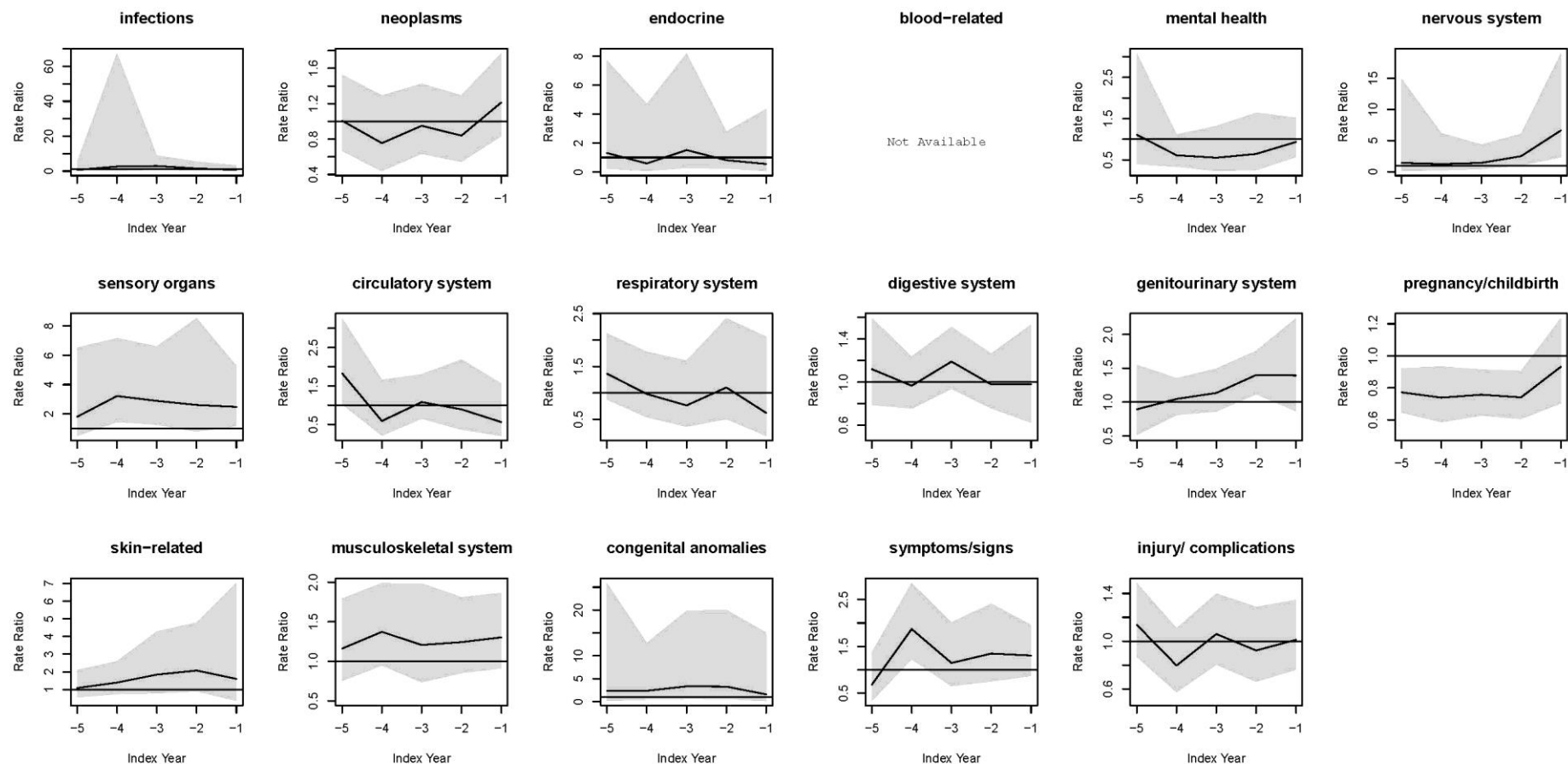
Figure S1d Rate ratios of hospitalizations by ICD chapter between cases and controls in the 5 years before MS symptom onset

The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date. The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls. Due to privacy regulations, and as required by the data custodians, graphs were too few individuals were represented were not shown (e.g. the ICD chapter for 'blood-related' conditions could not be shown)
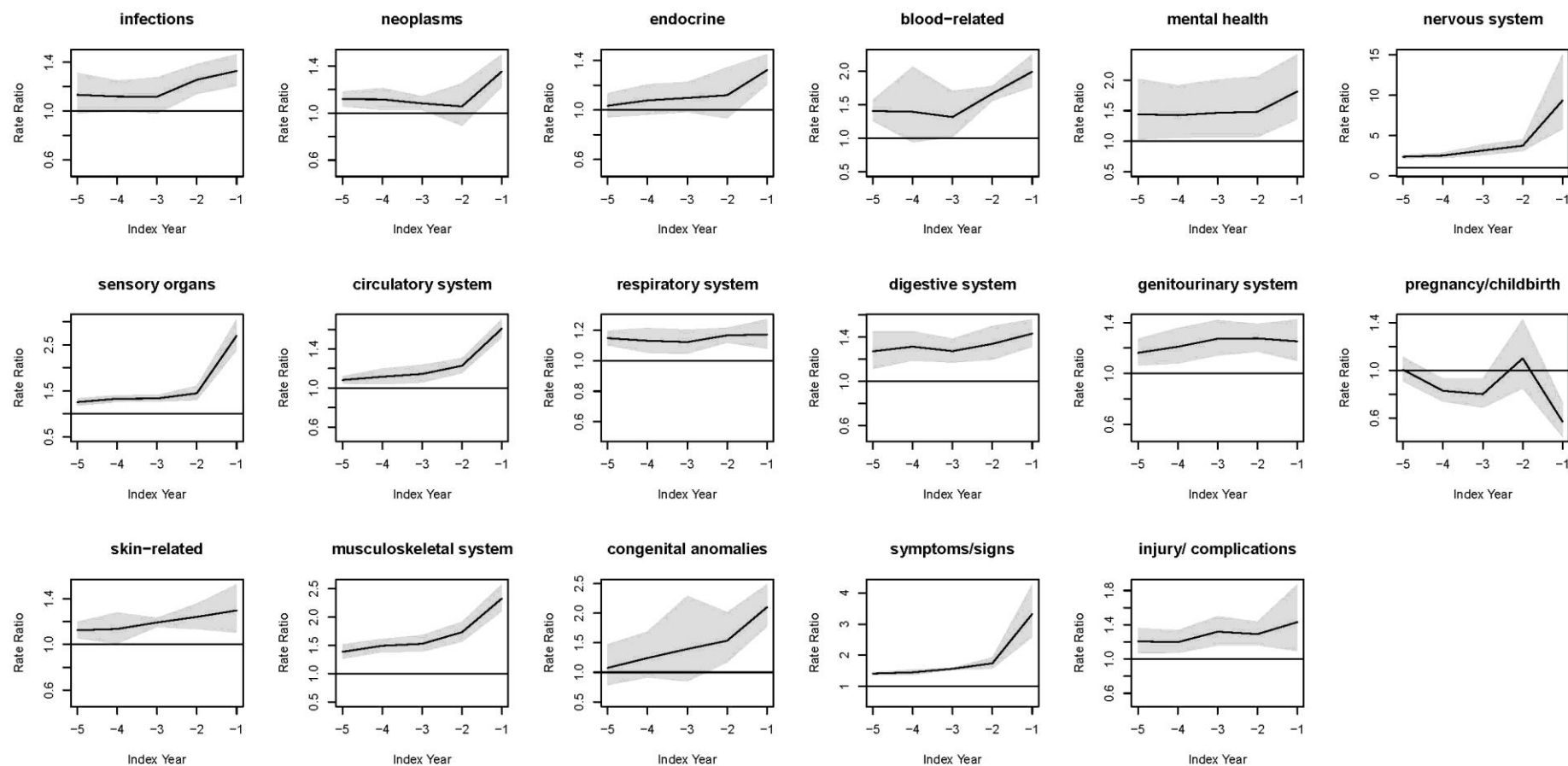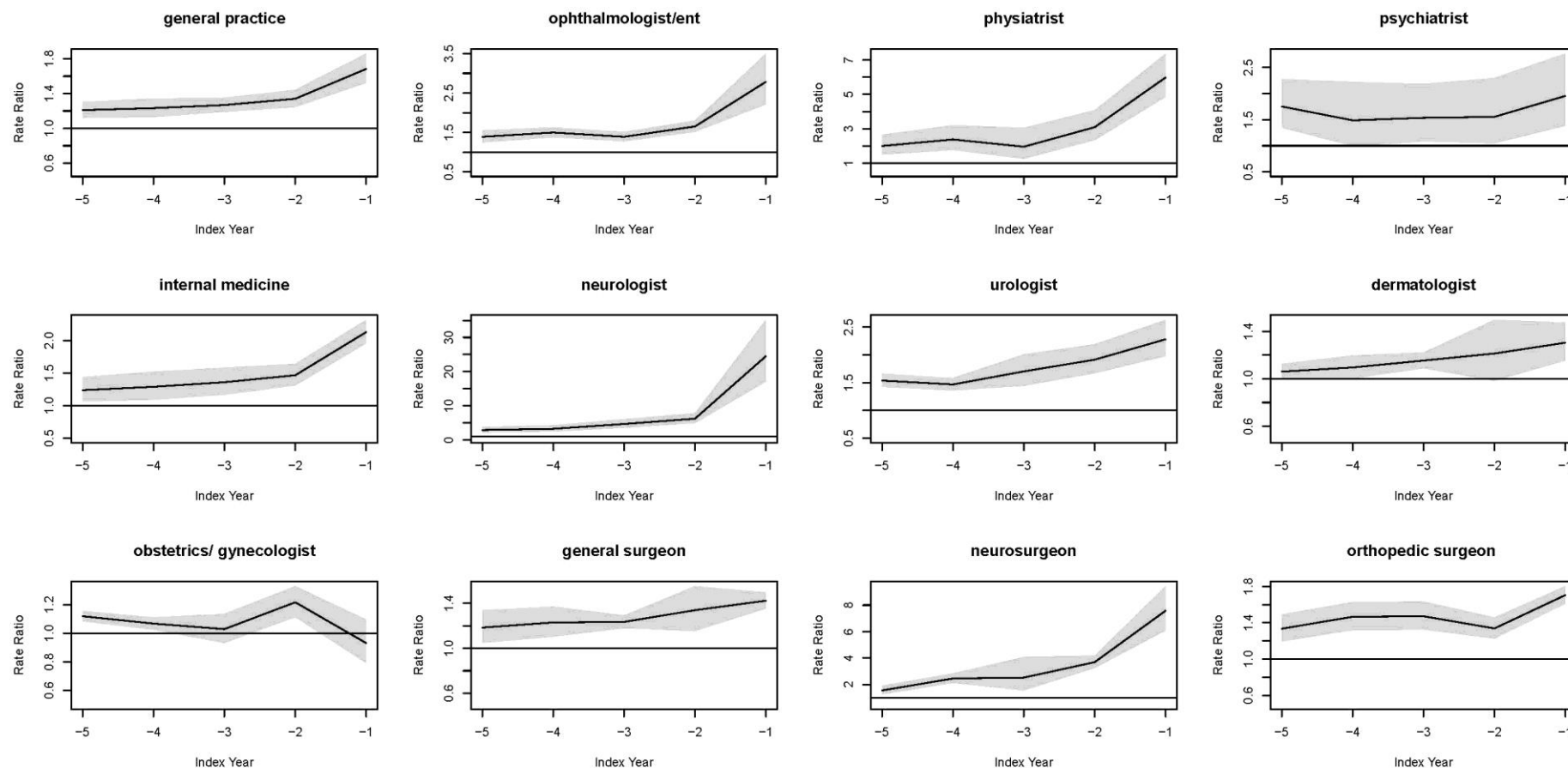
Figure S1e Rate ratios of physician visits by physician specialty between cases and controls in the 5 years before the first demyelinating claim
The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date.
The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls.
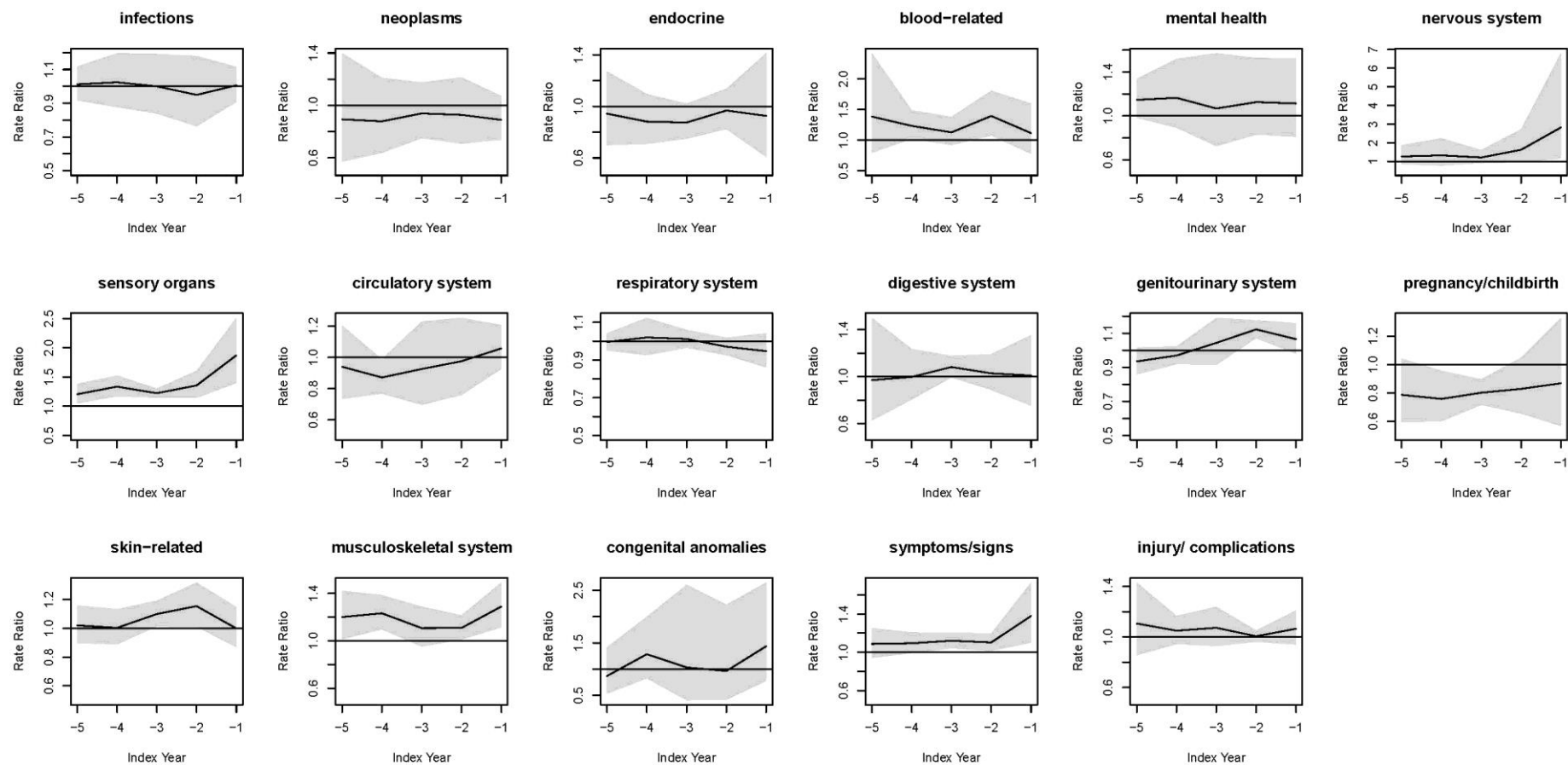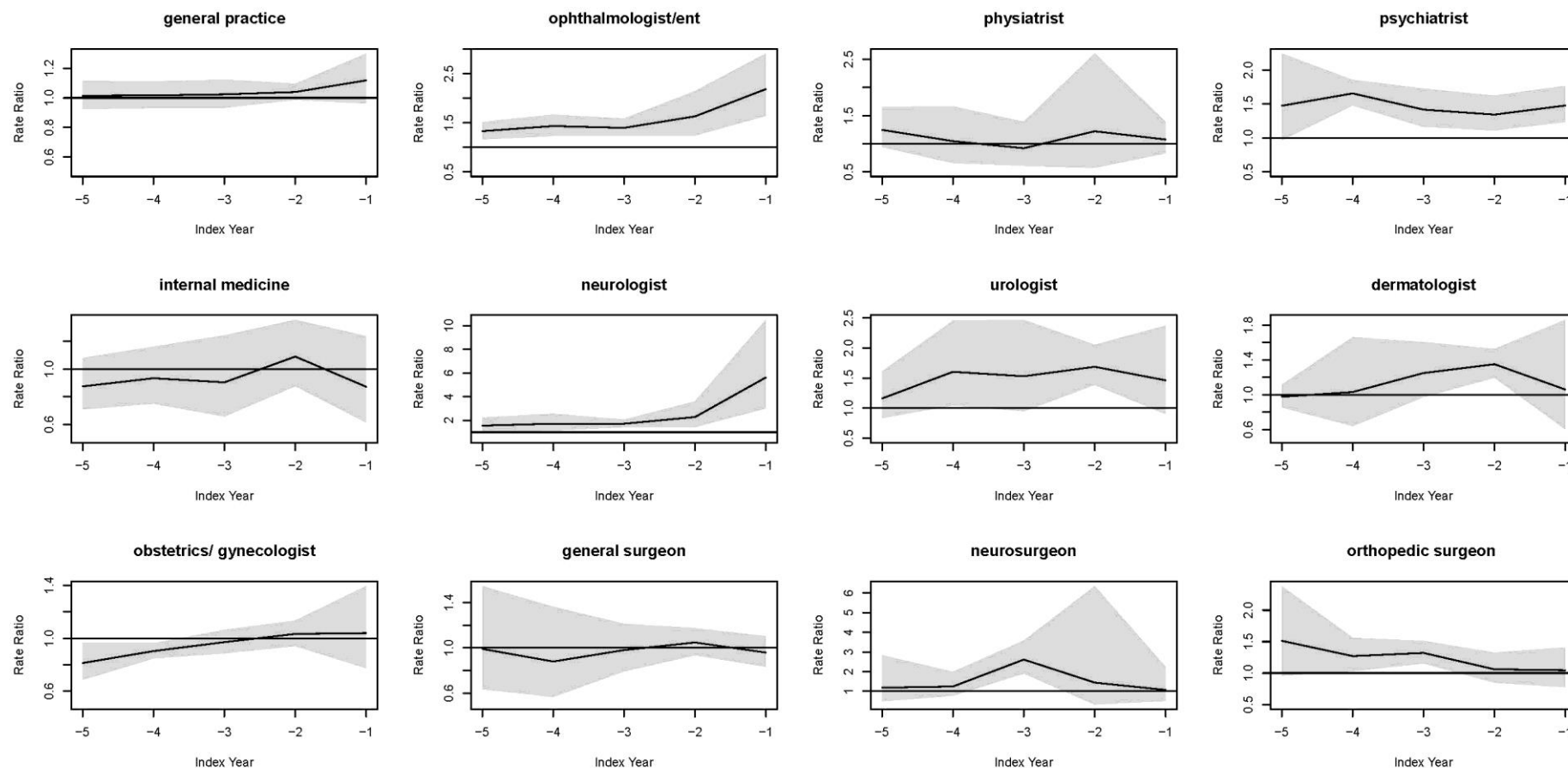
Figure S1f Rate ratios of physician visits by physician specialty between cases and controls in the 5 years before MS symptom onset
The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date.
The y-axis shows the rate ratios (RR) and the shaded area indicates the corresponding 95% confidence intervals; an RR>1 indicates increased health service utilization in the cases relative to the matched controls.
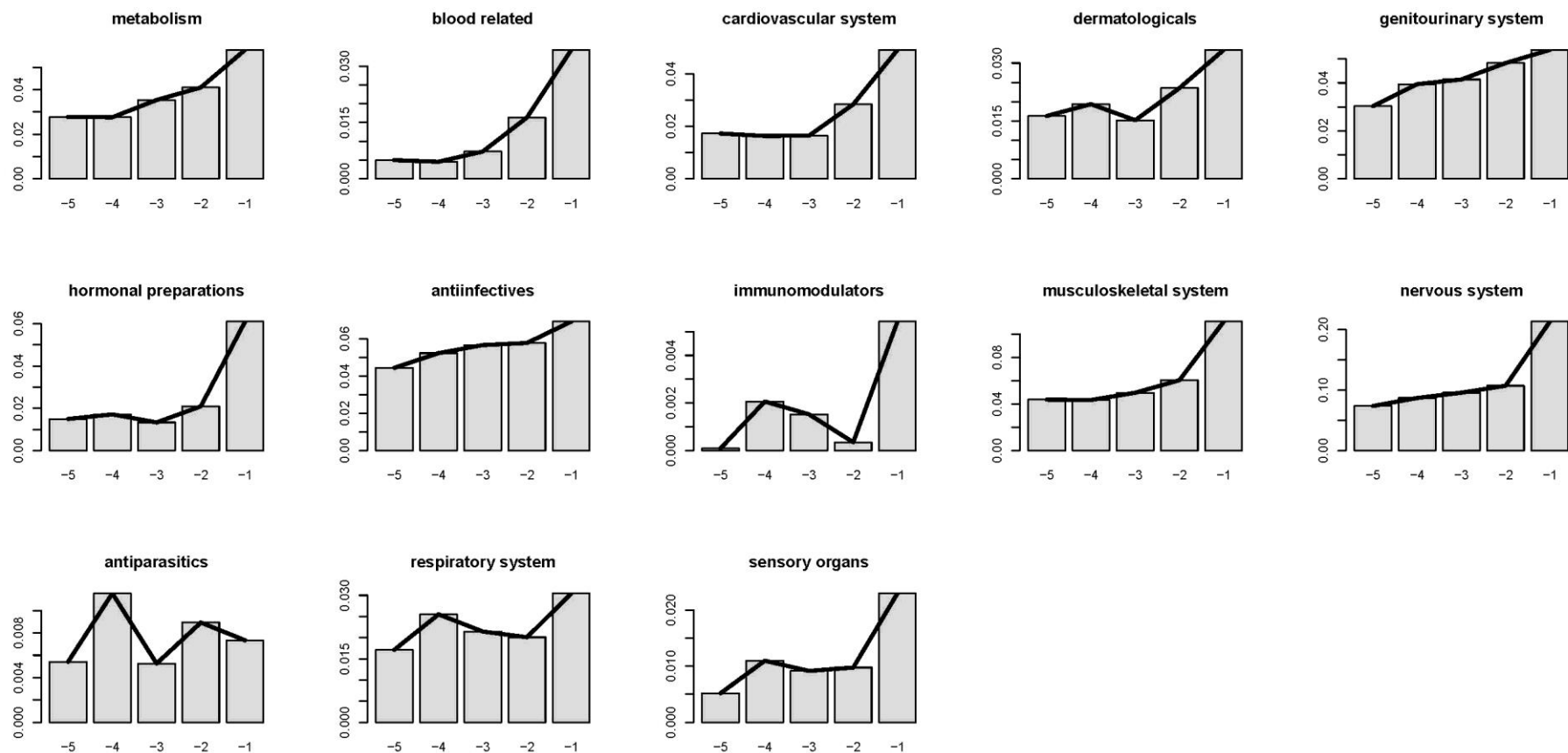
Figure S1g Proportional differences between cases and controls by drug class (ATC level 1) in the 5 years before the first demyelinating claim

ATC=Anatomical Therapeutic Chemical. The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date. The y-axis shows the difference in the proportion of cases and the proportion of controls who filled at least 1 prescription. Positive numbers represent a larger proportion of cases filling at least 1prescription. Negative numbers represent a larger proportion of controls filling at least 1 prescription
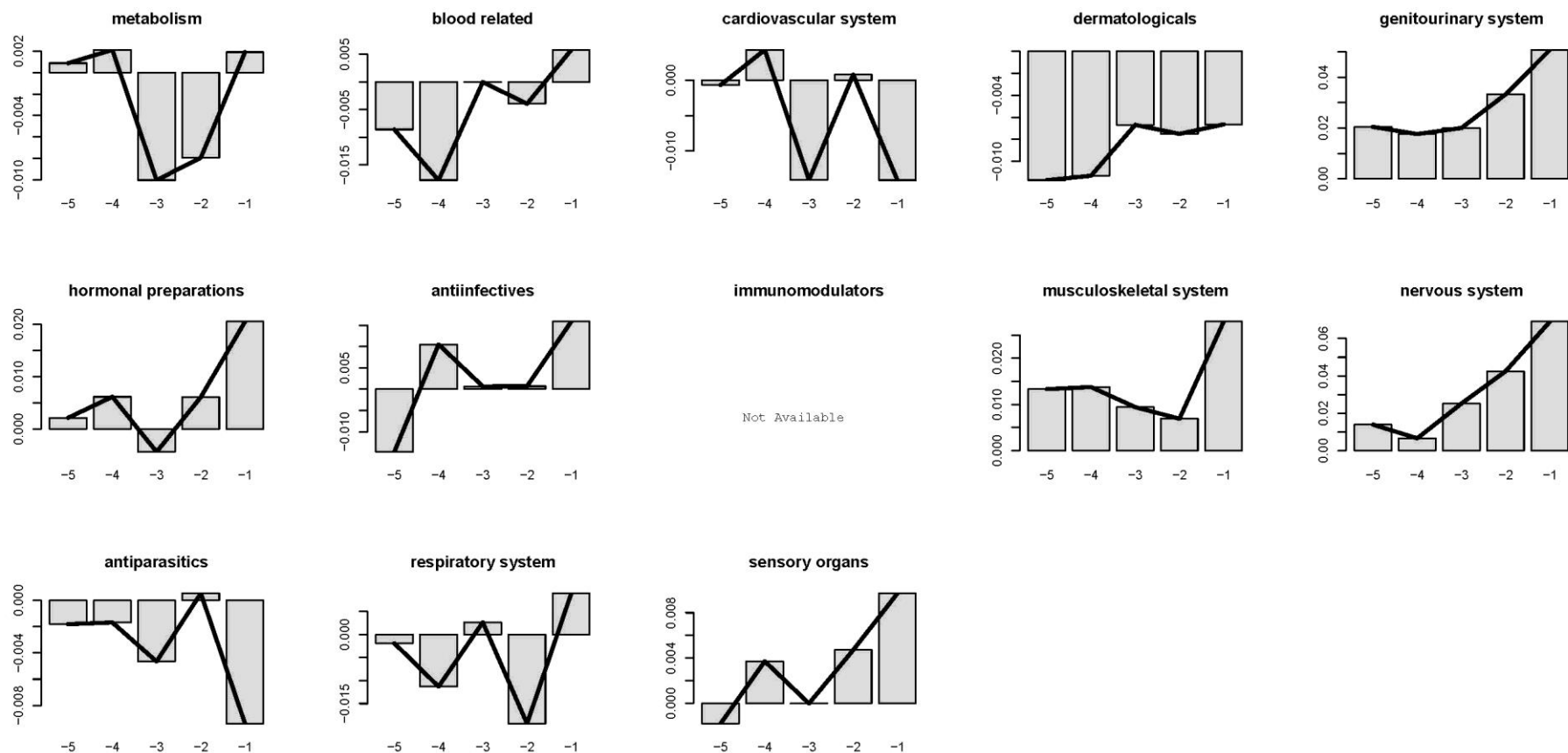
Figure S1h Proportional differences between cases and controls by drug class (ATC level 1) in the 5 years before MS symptom onset

ATC=Anatomical Therapeutic Chemical. The x-axis represents the five-year prodromal period in years before the index date, e.g., '-5' indicates the fifth year and '-1' indicates the one year prior to the index date. The y-axis shows the difference in the proportion of cases and the proportion of controls who filled at least 1 prescription. Positive numbers represent a larger proportion of cases filling at least 1prescription. Negative numbers represent a larger proportion of controls filling at least 1 prescription. Due to privacy regulations, and as required by the data custodians, graphs were too few individuals were represented were not shown (e.g. the drug class 'immunomodulators' could not be shown)

Table S1 Data availability within each of the four Canadian provinces

	British Columbia	Saskatchewan	Manitoba	Nova Scotia
Physician data[1]	April 1991-December 2013	January 1996-April 2014	April 1984-December 2013	January 1990-December 2013
Hospital data[1]	January 1986-December 2013	January 1996-April 2014	April 1984-December 2013	January 1990-December 2013
Prescription data[1]	January 1996-December 2013	January 1996-April 2014	April 1996-December 2013	N/A
MS-specific clinical data	August1980-December 2008	N/A	January 1989-December 2013	January 1980- December 2013

Key: 1 health administrative datasets; N/A = not available

Table S2 Multiple sclerosis specific and demyelinating disease related codes used for identifying people with MS and the respective index date (i.e., first recorded demyelinating event)

	ICD-9	ICD-10	Drug identification number
MS specific diagnosis			
Multiple sclerosis	340	G35	N/A
Demyelinating disease			
Optic neuritis	377.3	H46	N/A
Acute transverse myelitis	323.82 341.2	G37.3	N/A
Acute disseminated encephalomyelitis	323	G36.9	N/A
Demyelinating disease of CNS unspecified	341.9	G37.8	N/A
Other acute disseminated demyelination		G36	N/A
Neuromyelitis optica	341.0	G36.0	N/A
MS specific prescription, brand name (generic)			
Betaseron (IFNB-1b)	N/A	N/A	02169649
Extavia (IFNB-1b)			02337819
Avonex (IFNB-1a)	N/A	N/A	02237770 02269201
Rebif (IFNB-1a)	N/A	N/A	02281708 02277492 02237317 02237319 02237320 02318253 02318261
Copaxone (glatiramer acetate)	N/A	N/A	02233014 02245619
Tysabri (natalizumab)	N/A	N/A	02286386
Gilenya (fingolimod)	N/A	N/A	02365480
Tecfidera (dimethyl fumarate)	N/A	N/A	02404508
Aubagio (teriflunomide)	N/A	N/A	02416328
Lemtrada (alemtuzumab)	N/A	N/A	02418320

Table S3a Study outcomes: diagnostic codes for the ICD chapters

ICD Chapters	Diagnostic Codes	Brief overview and study-specific comments‡
Certain infectious and parasitic diseases	ICD-9: 001 – 139 ICD-10: A00 – B99	These include bacterial, viral, parasitic, and fungal infections. Some organ-specific infections, such as cystitis and pneumonia, are included in separate chapters.
Neoplasms	ICD-9: 140 – 239 ICD-10: C00 – D49	These include malignant and benign neoplasms.
Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders	ICD-9: 240 – 279 ICD-10: E00 – E89	These include: disorders of the endocrine glands, such as thyroiditis and diabetes mellitus; nutritional deficiencies; and other metabolic/immunity disorders.
Diseases Of The Blood And Blood-Forming Organs	ICD-9: 280– 289 ICD-10: D50 – D89	These include: anemias, such as iron or B12 deficiency; hemolytic and aplastic anemias; and diseases of the white blood cells
Mental, Behavioral and Neurodevelopmental disorders	ICD-9: 290 – 319 ICD-10: F00 – F99	These include: mood disorders, such as depression and bipolar disorder; non-mood psychotic disorders; anxiety; intellectual disabilities; developmental disorders; and emotional disorders
Diseases of the nervous system	ICD-9: 320 – 359 ICD-10: G00 – G99	These include: inflammatory disease of the central nervous system, such as meningitis; extrapyramidal and movement disorders, such as Parkinson's disease and dystonia; neurodegenerative disease; polyneuropathies; and paroxysmal disorders, such as epilepsy and migraine. **Demyelinating diseases were excluded (Table S2).**
Diseases of the sense organs	ICD-9: 360 – 389 ICD-10: H00-H95	These include: disorders of the eye, such as visual disturbances, disorders of the lens, retina, or eyelid; and disorders of the ear, such as hearing loss, vertiginous syndromes, and otitis media/externa. **Disorders of the optic nerve were excluded (Table S2).**
Diseases of the circulatory system	ICD-9: 390 – 459 ICD-10: I00 – I99	These include: hypertensive diseases; heart diseases, such as ischemic or pulmonary heart disease; cerebrovascular disease, such as the occlusion of cerebral arteries; and disease of the veins and arteries, such as atherosclerosis and varicose veins.
Diseases of the respiratory system	ICD-9: 460 – 519 ICD-10: J00 – J99	These include: respiratory infections, such as influenza and pneumonia; chronic respiratory

		disease, such as asthma and bronchitis; and diseases of the pleura.
Diseases of the digestive system	ICD-9: 520 – 579 ICD-10: K00 – K95	These include: disease of the intestines, such as irritable bowel syndrome; diseases of the liver, such as hepatitis and inflammatory liver disease; disorders of the gallbladder, such as acute pancreatitis; ulcers; and hernia.
Diseases of the genitourinary system	ICD-9: 580 – 629 ICD-10:N00 – N99	These include: disorders of the urinary tract, such as chronic kidney disease, nephritis, and cystitis; and disease of the genital organs, such as sexual dysfunction, disorders of the prostate, pelvic inflammatory disorders, absent or excessive menstruation; and disorders of the breast, such as unspecified lump in breast.
Pregnancy, childbirth and the puerperium	ICD-9: 630-679 ICD-10: O00–O99, and O9A	These include: encounters for delivery; maternal care related to the fetus, such as multiple gestation and fetal problems; pregnancy with abortive outcomes; maternal disorders, such as diabetes mellitus, excessive vomiting, and venous complications.
Diseases of the skin and subcutaneous tissues	ICD-9: 680 – 709 ICD-10: L00 – L99	These include: infections of the skin; dermatitis and eczema; erythema; and papulosquamous disorders, such as psoriasis.
Diseases of the musculoskeletal system and connective tissues	ICD-9: 710 – 739 ICD-10: M00 – M99	These include: arthropathies; dorsopathies; osteopathies; spondylopathies; osteoarthritis; and disorders of the muscles.
Congenital anomalies	ICD-9: 740-759 ICD-10: Q00–Q99	These include congenital malformations of the nervous system, circulatory system, respiratory system, genital organs, urinary system, eyes, and ears.
Symptoms, Signs, And Ill-Defined Conditions	ICD-9: 780 – 799 ICD-10: R00 – R99	These include symptoms and signs involving the circulatory, respiratory, nervous, musculosckeletal, genitourinary system. As well as, symptoms involving cognition, emotional state, behaviour, speech. Abnormal findings on examination of blood, urine or other body fluids.
Injury and poisoning External causes of morbidity Complication of surgical and medical care	ICD-9: 800-999 ICD-9: E800 – E999 ICD-10: S00 – T98 ICD-10: V00-Y99	These include: injuries and burns; poisoning; accidents; slipping and falls; and misadventures during surgical and medical care.

Conditions originating in the perinatal period (ICD-9: 760-779/ ICD-10: P00–P96) were not assessed

‡Specified conditions were excluded, as per the study design (outlined in the Methods)

Table S3b Study outcomes: drug classes based on the Anatomical Therapeutic Chemical Classification System, Level

Table S3c Study outcomes: physician specialty

Anatomical group (ATC level 1)	ATC Code	Brief overview and study-specific comments‡
Alimentary tract and metabolism	A	These include: drugs for gastrointestinal disorders; anti-nauseants; bile and liver therapy; antidiarrheals; vitamins; and drugs used in diabetes.
Blood and blood forming organs	B	These include: antithrombotic agents; anti-hemorrhagics; anti-anemic preparations; and blood substitutes.
Cardiovascular system	C	These include: anti-hypertensives; diuretics; vasodilators; and lipid modifying agents.
Dermatologicals	D	These include: antifungals; anti-psoriatics; antibiotics and corticosteroids for dermatological use; preparations for treatment of wounds and ulcers; and anti-acne preparations.
Genito-urinary system and sex hormones	G	These include: gynecological anti-infectives; sex hormones, modulators of the genital system; and urologicals
Systemic hormonal preparations, excluding sex hormones and insulins	H	These include: pituitary and hypothalamic hormones; corticosteroids; thyroid therapy; pancreatic hormones; and calcium homeostasis
Antiinfectives for systemic use	J	These include: anti-bacterials, anti-mycotics, anti-mycobacterials and antivirals for systemic use; immunoglobulins; and vaccines
Antineoplastic and immunomodulating agents	L	These include: anti-neoplastic agents; endocrine therapy; immunostimulants; and immunosuppressants **MS specific drugs were excluded (Table S2)**
Musculo-skeletal system	M	These include: anti-inflammatory and anti-rheumatic products; topical products for joint/muscular pain; muscle relaxants; anti-gout preparations; and drugs for treatment of bone disease.
Nervous system	N	These include: anesthetics; analgesics; anti-epileptics; anti-parkinsons drugs; and psycholeptics; psychoanaleptics. **MS specific drugs were excluded (Table S2)**
Anti-parasitic products, insecticides and repellents	P	These include: anti-protozoals; anti-helmintics; and ectoparasticides
Respiratory system	R	These include: nasal and throat preparations; drugs for obstructive airway diseases; cough and cold preparations; and antihistamines for systemic use.
Sensory organs	S	These include ophthalmologicals and otologicals.
Various	V	These include: allergens; diagnostics agents; nutrients; contrast media; radiopharmaceuticals; and surgical dressings

Physician speciality
Primary care provider / general practice
Ophthalmologist and otolaryngologist
Physiatrist (i.e. physical medicine & rehabilitation specialist)
Psychiatrist (also includes neuropsychiatrist)
Internal medicine physician (also includes rheumatologist, cardiologist, and gastroenterology)
Neurologist
Urologist
Dermatologist
Obstetrics and gynecologist
General surgeon
Neurosurgeon
Orthopedic surgeon

Table S3d Study outcomes: algorithms used to identify morbidities

Morbidity	Years of data	Algorithm: number and type of encounters	ICD9 codes	ICD10 codes
Mental health				
Any mood or anxiety disorder	5	≥1 H or ≥5P	300.0, 300.2, 296.0, 296.1, 296.04, 296.14, 296.4, 296.44, 296.5, 296.54, 296.6, 296.7, 296.8, 296.2, 296.3, 298.0, 300.4, 311	F40, F41, F31, F32, F33, F34
Schizophrenia	2	≥1H or ≥2P	295	F20, F25
Vascular				
Hypertension	2	≥1H or ≥2P	401-405	I10-I13, I15
Hyperlipidemia	5	≥1H or ≥2P	272	E780, E782, E784, E785
Diabetes	5	≥1H or ≥2P	250	E10 -E14
Ischemic heart disease	5	≥1 H or ≥2P	410–414	I20–I25
Other neurologic				
Epilepsy	3	≥1 H OR ≥2P	345	G40, G41
Other				
Fibromyalgia	3	≥5 (H or P)	729.1	M79.7
Irritable bowel syndrome	2	≥1 H or ≥2P	564.1	K58
Chronic lung disease	5	≥1H or ≥2P	493, 491, 492, 496	J45, J46, J40, J42, J43, J44
Autoimmune				
Inflammatory bowel disease	All available data	≥5 (H or P)	555, 556	K50, K51

Key: ICD: International Classification of Diseases; ATC: Anatomical Therapeutic Chemical; H: hospital; P: physician visits; Rx: prescription

Table S3d Study outcomes: algorithms used to identify morbidities (continued)

Morbidity	Years of data	Algorithm: number and type of encounters	ICD9 codes	ICD10 codes	ATC codes
Neurological					
Migraine	2	≥2 (H or P or Rx)	345, 625.4	G43	N02CA N02CC N02CX
Autoimmune					
Thyroid disorder (Autoimmune)[1]	1	≥1H or ≥1P or ≥1Rx	242, 376.21, 376.22, 245,	E05.0 E06.3	H03AA01 H03AA05 H03BA02 H03BA03 H03BB02 H03CA
Psoriasis	3	≥2 (H or P or Rx)	696.0, 696.1	L40, M07.0-M07.3	D05AC01 D05AC51 D05AX D05AX02 D05AX03 D05AX05 D05AX52 D05BA03 D05BB02

Key: ICD: International Classification of Diseases; ATC: Anatomical Therapeutic Chemical; H: hospital; P: physician visits; Rx: prescription

[1] People who were either diagnosed with thyroid neoplasm, underwent thyroid surgery, or filled a prescription for lithium (ATC= N05AN01) pre-'onset' of a thyroid condition were not included here

Table S4a Characteristics of the health administrative cohorts by province at the index date

Characteristics at the index date[1]	British Columbia		Saskatchewan		Manitoba		Nova Scotia	
	MS population N=6,863	Controls N=31,865	MS population N=1,806	Controls N=9,002	MS population N=2,992	Controls N=14,960	MS population N=2,290	Controls N=11,113
Sex, N (%)								
Men	1.824 (25·2)	8,554 (23·6)	562 (31·1)	2,795 (31·0)	823 (27·5)	4,115 (27·5)	586 (25·6)	2,854 (25·7)
Women	5.039 (69·5)	23,311 (64·4)	1,244 (68·9)	6,207 (69·0)	2,169 (72·5)	10,845 (72·5)	1,704 (74·4)	8,259 (74·3)
Age (yrs):								
Mean (SD)	44·9 (13·5)	44·7 (13·4)	43·3 (14·1)	43·3 (14·3)	40·9 (13·1)	40.9 (13·1)	42.9 (12·7)	42.9 (12·7)
<30	859 (11·8)	4,081 (11·3)	322 (17·8)	1,605 (17·8)	597 (20·0)	2,989 (20·0)	333 (14·5)	1,619 (14·6)
30 to <50	3,827 (52·8)	17,898 (49·4)	945 (52·3)	4,683 (52·0)	1,704 (57·0)	8,503 (56·8)	1,375 (60·0)	6,647 (59·8)
≥50	2,177 (30·0)	9,886 (27·3)	539 (29·8)	2,714 (30·1)	691 (23·1)	3,468 (23·2)	582 (25·4)	2,847 (25·6)
SES, N (%)								
1 (lowest income quintile)	1,173 (16·2)	5,537 (15·3)	361 (20·0)	1,792 (19·9)	455 (15·2)	2,527 (16·9)	422 (18·4)	2,273 (20·5)
2	1,297 (17·9)	5,964 (16·5)	360 (19·9)	1,824 (20·3)	579 (19·4)	2,850 (19·1)	460 (20·1)	2,313 (20·8)
3	1,431 (19·7)	6,357 (17·6)	363 (20·1)	1,783 (19·8)	672 (22·5)	3,127 (20·9)	468 (20·4)	2,196 (19·8)
4	1,433 (19·8)	6,782 (18·7)	361 (20·0)	1,795 (19·9)	582 (19·5)	3,158 (21·1)	494 (21·6)	2,224 (20·0)
5 (highest income quintile)	1,376 (19·0)	6,532 (18·0)	361 (20·0)	1,798 (20·0)	663 (22·2)	3,211 (21·5)	440 (19·2)	2,062 (18·6)
Missing	153 (2·1)	693 (1·9)	0	10 (0·1)	41 (1·4)	87 (0·6)	6 (0·3)	45 (0·4)
Index year, N (%)								
1990-1997	693 (9·6)	3,171 (8·8)	0	0	1,084 (36·2)	5,420 (36·2)	491 (21·4)	2,370 (21·3)
1998-2005	3,457 (47·7)	15,959 (44·1)	859 (47·6)	4,281 (47·6)	1,113 (37·2)	5,565 (37·2)	1,026 (44·8)	4,974 (44·8)
2006-2013	2,713 (37·4)	12,735 (35·2)	947 (52·4)	4,721 (52·4)	795 (26·6)	3,975 (26·6)	773 (33·8)	3,769 (33·9)
Time (yrs) between index date and diagnosis date, Mean (SD)[2]	1.1 (1.9)	NA	1.0 (1.7)	NA	1.5 (2.7)	NA	1.2 (2.0)	NA

MS: multiple sclerosis; N/A: not applicable; yrs: years; SD: standard deviation; SES: socioeconomic status. [1] The index date represents the first demyelinating disease related code, as recorded by a physician. [2] The diagnosis date represents the third MS code

Table S4b Characteristics of the MS Clinic-derived cohorts by province at the index date

Characteristics at the index date[1]	British Columbia		Manitoba		Nova Scotia	
	MS population N=966	Controls N=4,826	MS population N=1,117	Controls N=5,585	MS population N=1,119	Controls N=5,595
Sex, N (%)						
Men	238 (24·6)	1190 (24·7)	313 (28·0)	1565 (28·0)	283 (25·3)	1,415 (25·3)
Women	728 (75·4)	3,636 (75·3)	804 (72·0)	4,020 (72·0)	836 (74·7)	4,180 (74·7)
Age (yrs):						
Mean (SD)	37·5 (10·2)	37·5 (10·2)	35·1 (10·4)	35·1 (10·4)	36·9 (10·3)	36·9 (10·3)
<30	233 (24·1)	1,149 (23·8)	365 (32·7)	1,801 (32·2)	299 (26·7)	1,485 (26·5)
30 to <50	638 (66·0)	3,182 (65·9)	647 (57·9)	3,269 (58·5)	706 (63·1)	3,544 (63·3)
≥50	95 (9·8)	495 (10·3)	105 (9·4)	515 (9·2)	114 (10·2)	566 (10·1)
SES, N (%)						
1 (lowest income quintile)	153 (15·8)	829 (17·2)	191 (17·1)	868 (15·5)	208 (18·6)	1,143 (20·4)
2	180 (18·6)	853 (17·7)	203 (18·2)	1,021 (18·3)	233 (20·8)	1,203 (21·5)
3	189 (19·6)	932 (19·3)	252 (22·6)	1,166 (20·9)	249 (22·3)	1,146 (20·5)
4	204 (21·1)	1,028 (21·3)	212 (19·0)	1,201 (21·5)	218 (19·5)	1,083 (19·4)
5 (highest income quintile)	215 (22·3)	1,024 (21·2)	256 (22·9)	1,303 (23·3)	209 (18·7)	1,005 (18·0)
Missing	25 (2·6)	160 (3·3)	<6 (<0.5)[3]	26 (0·5)	<6 (<0.5)[3]	15 (0·3)
Index year, N (%)						
1989-1997	207 (21·4)	1,035 (21·4)	320 (28·6)	1,600 (28·6)	182 (16·3)	910 (16·3)
1998-2005	726 (75·2)	3,626 (75·1)	421 (37·7)	2,105 (37·7)	537 (48·0)	2,685 (48·0)
2006-2013	33 (3·4)	165 (3·4)	376 (33·7)	1,880 (33·7)	400 (35·7)	2,000 (35·7)
Time (yrs) between index date and diagnosis date, Mean (SD)	2.1 (1.9)	NA	2.5 (3.5)	NA	2.7 (2.4)	NA

MS: multiple sclerosis; N/A: not applicable; yrs: years; SD: standard deviation; SES: socioeconomic status. Due to privacy regulations, and as required by the data custodians, cells with less than 6 cases cannot be reported

[1] The index date represents the date of MS symptom onset, as recorded by an MS neurologist.

Table S5 Five years before the first demyelinating claim or MS symptom onset: rate ratios for physician and hospital encounters by ICD chapter, comparing MS cases and controls

ICD Chapter	Administrative cohort[1]		MS Clinic-derived cohort[2]	
	Physician visits	Hospital admissions	Physician visits	Hospital admissions
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Certain infectious and parasitic diseases	**1.19 (1.09-1.29)**	**1.94 (1.60-2.36)**	1.00 (0.92-1.07)	1.20 (0.58-2.45)
Neoplasms	**1.15 (1.12-1.18)**	**1.13 (1.05-1.22)**	0.91 (0.74-1.12)	0.94 (0.79-1.14)
Endocrine Nutritional and Metabolic Diseases and Immunity Disorders	**1.14 (1.03-1.27)**	1.41 (0.82-2.43)	0.93 (0.81-1.07)	0.74 (0.47-1.17)
Diseases of the Blood and Blood−Forming Organs	**1.58 (1.32-1.88)**	1.33 (0.65-2.72)	**1.24 (1.00-1.54)**	0.81 (0.28-2.35)
Mental Behavioral and Neurodevelopmental disorders	**1.53 (1.12-2.09)**	1.38 (0.60-3.21)	1.12 (0.85-1.48)	0.69 (0.34-1.41)
Diseases of the nervous system	**4.38 (3.25-5.90)**	**4.75 (3.11-7.25)**	1.70 (0.96-3.00)	**2.31 (1.05-5.10)**
Diseases of the sense organs	**1.62 (1.55-1.68)**	**1.47 (1.31-1.65)**	**1.40 (1.34-1.46)**	**2.28 (1.72-3.02)**
Diseases of the circulatory system	**1.26 (1.23-1.29)**	**1.29 (1.17-1.42)**	0.96 (0.86-1.08)	0.85 (0.63-1.14)
Diseases of the respiratory systems	**1.15 (1.09-1.21)**	**1.37 (1.08-1.74)**	0.99 (0.96-1.01)	0.88 (0.66-1.18)
Diseases of the digestive system	**1.33 (1.22-1.44)**	**1.35 (1.18-1.54)**	1.03 (0.83-1.28)	1.05 (0.81-1.35)
Diseases of the genitourinary system	**1.24 (1.11-1.37)**	**1.59 (1.48-1.70)**	1.03 (0.98-1.08)	**1.17 (1.05-1.30)**
Pregnancy childbirth and the puerperium	**0.86 (0.82-0.91)**	**0.88 (0.84-0.92)**	**0.81 (0.73-0.90)**	**0.78 (0.71-0.86)**
Diseases of the skin and subcutaneous tissues	**1.20 (1.11-1.29)**	**1.39 (1.11-1.74)**	1.05 (0.94-1.18)	**1.37 (1.04-1.82)**
Diseases of the musculoskeletal system and connective tissues	**1.70 (1.57-1.85)**	**1.61 (1.22-2.12)**	**1.19 (1.07-1.33)**	**1.25 (1.02-1.53)**
Congenital anomalies	**1.48 (1.14-1.92)**	**1.74 (1.20-2.52)**	0.97 (0.80-1.18)	1.86 (0.54-6.36)
Symptoms, Signs, and Ill-Defined Conditions	**1.92 (1.71-2.16)**	**2.34 (2.04-2.70)**	**1.16 (1.07-1.27)**	1.21 (0.96-1.52)
Injury, poisoning, and complication of surgical/medical care	**1.29 (1.12-1.47)**	**1.31 (1.10-1.55)**	1.06 (0.95-1.18)	0.98 (0.86-1.12)

Key: RR: rate ratio; CI: confidence interval. Findings are also depicted in Figures 1 and 2
ICD chapter "Certain conditions originating in the perinatal period" was not assessed due to limited number of cases
The index dates were defined as: [1]the first demyelinating disease code or [2] the date of MS symptom onset, as recorded by an MS neurologist

Table S6 Five years before the first demyelinating claim or MS symptom onset: rate ratios of physician encounters by physician specialty, comparing MS cases and controls

Physician specialty	Administrative cohort[1] RR (95%CI)	MS Clinic-derived cohort[2] RR (95%CI)
Primary care provider/general practice	**1.35 (1.25-1.45)**	1.04 (0.96-1.13)
Ophthalmologist and Otolaryngologist	**1.76 (1.64-1.90)**	**1.61 (1.44-1.80)**
Physiatrist	**3.20 (2.86-3.57)**	1.07 (0.95-1.21)
Psychiatrist	**1.66 (1.20-2.30)**	**1.48 (1.36-1.62)**
Internal medicine physicians	**1.53 (1.39-1.67)**	0.93 (0.76-1.14)
Neurologist	**9.02 (7.53-10.80)**	**2.66 (1.64-4.30)**
Urologist	**1.80 (1.61-2.01)**	**1.49 (1.15-1.91)**
Dermatologist	**1.16 (1.10-1.23)**	1.14 (0.91-1.42)
Obstetrics and gynecologist	**1.07 (1.04-1.11)**	0.95 (0.90-1.00)
General surgeon	**1.29 (1.21-1.36)**	0.97 (0.79-1.20)
Neurosurgeon	**3.63 (2.81-4.69)**	1.54 (0.90-2.65)
Orthopedic surgeon	**1.47 (1.43-1.52)**	**1.24 (1.17-1.32)**
All internal medicine physicians	**2.10 (2.03-2.17)**	1.14 (0.98-1.33)
All surgeons	**1.43 (1.35-1.51)**	1.09 (0.94-1.25)

Key: RR: rate ratio; CI: confidence interval. Findings are also depicted in Figures 1 and 2
The index dates were defined as: [1] the first demyelinating disease related code or [2] the date of MS symptom onset, as recorded by an MS neurologist

Table S7 Five years before the first demyelinating claim or MS symptom onset: proportion with a least one prescription by ATC level 1

| Drug class | Administrative cohort[1] | | | | MS Clinic-derived cohort[2] | | | |
| | | MS | Controls | | | MS | Controls | |
	N	No. (%)	No. (%)	p-value	N	No. (%)	No. (%)	p-value
Alimentary tract and metabolism	8122	3200 (39.4)	2500 (30.8)	**<0.001**	1005	291 (29.0)	296 (29.5)	0.808
Blood and blood forming organs	8122	951 (11.7)	596 (7.3)	**<0.001**	1005	56 (5.6)	64 (6.4)	0.453
Cardiovascular system	8122	2580 (31.8)	2005 (24.7)	**<0.001**	1005	200 (19.9)	183 (18.2)	0.325
Dermatologicals	8122	3642 (44.8)	3202 (39.4)	**<0.001**	1005	445 (44.2)	427 (42.5)	0.430
Genito-urinary system and sex hormones	8122	3382 (41.6)	2796 (34.4)	**<0.001**	1005	438 (43.6)	383 (38.1)	**0.012**
Systemic hormonal preparations	8122	2123 (26.1)	1446 (17.8)	**<0.001**	1005	203 (20.2)	158 (15.7)	**0.009**
Anti-infectives of systemic use	8122	6724 (82.8)	6169 (75.9)	**<0.001**	1005	823 (81.9)	809 (80.5)	0.414
Anti-neoplastic and immunomodulating agents	8122	247 (3.0)	173 (2.1)	**<0.001**	628	25 (4.0)	9 (1.5)	**0.007**
Musculoskeletal system	8122	4520 (55.7)	3485 (42.9)	**<0.001**	1005	480 (47.8)	419 (41.7)	**0.006**
Nervous system	8122	5853 (72.1)	4472 (55.1)	**<0.001**	1005	646 (64.3)	598 (59.5)	**0.027**
Anti-parasitic products insecticides and repellents	8122	1144 (14.1)	909 (11.2)	**<0.001**	1005	101 (10.0)	104 (10.4)	0.784
Respiratory system	8122	3131 (38.6)	2657 (32.7)	**<0.001**	1005	340 (33.8)	341 (33.9)	0.963
Sensory organs	8122	2046 (25.2)	1749 (21.5)	**<0.001**	1005	229 (22.8)	207 (20.6)	0.229

Key: ATC: Anatomical Therapeutic Chemical. Findings are also depicted in Figure 3. The drug class 'various' was not assessed due to limited number of cases.
The index dates were defined as: [1]the first demyelinating disease related code or [2] the date of MS symptom onset, as recorded by an MS neurologist

Table S8 Prevalence of morbidities during the five years before the first demyelinating claim or MS symptom onset

Morbidity	Administrative cohort[1]				MS Clinic-derived cohort[2]			
		MS	Controls			MS	Controls	
	N	No. (%)	No. (%)	p-value	N	No. (%)	No. (%)	p-value
Mental health								
Any mood or anxiety disorder[3]	13,951	3,221 (23.8)	2,152 (15.4)	**<0.001**	3,202	591 (18.5)	482 (15.1)	**<0.001**
Schizophrenia	13,951	75 (0.5)	86 (0.6)	0.385	-	-	-	-
Vascular								
Hypertension	13,951	2,001 (14.3)	1,798 (12.9)	**<0.001**	3,202	195 (6.1)	201 (6.3)	0.741
Hyperlipidemia	13,951	813 (5.8)	792 (5.7)	0.590	3,202	85 (2.6)	97 (3.0)	0.346
Diabetes	13,951	672 (4.8)	685 (4.9)	0.719	3,202	63 (2.0)	77 (2.4)	0.257
Ischemic heart disease	13,951	508 (3.6)	423 (3.0)	**0.005**	2,085[5]	29 (1.4)	32 (1.5)	0.711
Neurological								
Epilepsy	13,951	192 (1.4)	88 (0.6)	**<0.001**	2,085[5]	14 (0.7)	11 (0.5)	0.507
Migraine[4]	8,122	635 (7.8)	353 (4.3)	**<0.001**	1,005	78 (7.8)	50 (5.0)	**0.011**
Autoimmune								
Inflammatory bowel disease	13,951	97 (0.7)	74 (0.5)	0.078	1,119[5,6]	12 (1.1)	10 (0.9)	0.668
Thyroid disorder[4]	8,122	627 (7.7)	542 (6.7)	**0.009**	1,005	45 (4.5)	37 (3.7)	0.360
Psoriasis[4]	8,122	92 (1.1)	76 (0.9)	0.209	-	-	-	-
Other								
Fibromyalgia	13,951	631 (4.5)	200 (1.4)	**<0.001**	2,236[6]	47 (2.1)	36 (1.6)	0.205
Irritable bowel syndrome	13,951	523 (3.7)	269 (1.9)	**<0.001**	3202	68 (2.1)	53 (1.7)	0.168
Chronic lung disease	13,951	1,196 (8.6)	1,050 (7.5)	**0.001**	3,202	191 (6.0)	222 (6.9)	0.111

The index dates were defined as: [1] the first demyelinating disease related code or [2] the date of MS symptom onset, as recorded by the MS neurologist. [3] Includes depression, anxiety and bipolar disorder. [4] Not calculated in Nova Scotia because comprehensive prescription data are unavailable. [5] Not calculated in Manitoba because <6 cases were identified. [6] Not calculated in British Columbia because <6 cases were identified. Due to privacy regulations, and as required by the data custodians, cells with less than 6 cases cannot be reported