

eTable 1. MS-specific diagnostic and drug codes used to identify people with multiple sclerosis in the administrative cohort and to assign their first demyelinating event (index date) using the hospital, physician and pharmacy data.¹³

	ICD-9	ICD-10	Drug identification number
MS-specific diagnostic codes			
Multiple sclerosis	340	G35	-
Demyelinating disease-related codes			
Optic neuritis	377.3	H46	-
Acute transverse myelitis	323.82	G37.3	-
Acute disseminated encephalomyelitis	341.2	G36.9	-
Demyelinating disease of CNS unspecified	323	G37.8	-
Other acute disseminated demyelination	341.9	G36	-
Neuromyelitis optica	341.0	G36.0	-
MS-specific disease modifying drugs			
Interferon beta-1b	-	-	02169649, 02337819
Interferon beta-1a	-	-	02237770, 02269201, 02281708, 02277492, 02237317, 02237319, 02237320, 02318253, 02318261
Glatiramer acetate	-	-	02233014, 02245619

Natalizumab	-	-	02286386
Fingolimod	-	-	02365480
Dimethyl fumarate	-	-	02404508
Teriflunomide	-	-	02416328
Alemtuzumab	-	-	02418320

ICD: International Classification of Diseases; CNS: central nervous system. An individual's first demyelinating disease-related claim was used to determine the administrative index date (i.e., the first demyelinating event). The MS-specific prescription drugs shown were the only ones available/approved in Canada during the study period.

eTable 2. Diagnostic codes and algorithm used to identify psychiatric morbidity using administrative health data.²⁷

Comorbidity	Algorithm	ICD-9 codes	ICD-10-CA codes	BC diagnostic codes*
Psychiatric morbidity	≥1H or ≥5P within a 5-year period (with ≥1 falling within the 5 years prior to the index dates)	295.x, 296.0, 296.04, 296.1, 296.14, 296.2, 296.3, 296.4, 296.44, 296.5, 296.54, 296.6, 296.7, 296.8, 298.0, 300.0, 300.2, 300.4, 311	F20.x, F25, F31, F32, F33, F34, F40, F41	50B

ICD: International Classification of Disease; H: Hospital claim; P: Physician claims. *BC diagnostic codes: additional physician codes specific to British Columbia, Canada. Code 50B is used for both depression and anxiety.

eTable 3. Psychotropic prescriptions counted according to their Anatomical Therapeutic Chemical (ATC) code 5th level and categorized by their pharmacological class (ATC 3rd level).

Pharmacological class description (ATC 3rd level)	ATC codes and comments
Antidepressants	N06A (all drugs)
Anxiolytics	N05B (all drugs)
Mood stabilizers*	N03A (antiepileptics only: lamotrigine, carbamazepine, and valproate).
	N05A (lithium only)
Antipsychotics	N05A (all drugs except lithium).

ATC: Anatomic Therapeutic Chemical. *Based on prior literature,²⁷ ATC classification system was modified to include a “Mood stabilizers” category grouping certain antiepileptics commonly used as mood stabilizers (lamotrigine, carbamazepine and valproate) and lithium.

eTable 4. Rate ratios of physician visits for psychiatric morbidity, visits to psychiatrists, psychiatric-related hospital admissions and ‘psychotropic’ prescriptions in the five years before multiple sclerosis (MS) onset for MS cases versus matched controls in the clinical cohort

	Physician visits for psychiatric morbidity (aRR [95%CI])	Visits to psychiatrists (aRR [95%CI])	Psychiatric-related hospital admissions (aRR [95%CI])	Psychotropic prescriptions (aRR [95%CI])
Year -5 × MS	1.08 (0.80-1.45)	1.03 (0.53-1.99)	1.84 (0.59-5.72)	1.55 (0.98-2.46)
Year -4 × MS	1.33 (0.97-1.82)	1.29 (0.70-2.37)	1.05 (0.37-2.95)	1.22 (0.85-1.74)
Year -3 × MS	1.31 (0.98-1.74)	1.50 (0.80-2.80)	1.18 (0.36-3.90)	1.00 (0.71-1.40)
Year -2 × MS	1.41 (1.10-1.82)	1.36 (0.78-2.36)	0.73 (0.23-2.37)	0.94 (0.70-1.27)
Year -1 × MS	1.12 (0.86-1.47)	1.21 (0.69-2.13)	1.93 (0.67-5.54)	1.13 (0.83-1.55)

aRR: adjusted Rate Ratio; CI: confidence interval. The time period represents the 5-year period before the index dates. Year -5 reflects the fifth year before the index date and Year -1 the year before the index date. An adjusted rate ratio greater than 1 indicates a higher rate of visits, admissions or prescriptions filled in people with MS relative to matched controls. Models were adjusted for age at index date, sex, socioeconomic status, and index year.

eTable 5. Covariates associated with physician visits for psychiatric morbidity, visits to psychiatrists, psychiatric-related hospital admissions and ‘psychotropic’ in the five years before multiple sclerosis (MS) onset for MS cases versus matched controls in the administrative cohort

Characteristics (at the index date)	Physician visits for psychiatric morbidity (aRR [95%CI])	Visits to psychiatrists (aRR [95%CI])	Psychiatric-related hospital admissions (aRR [95%CI])	Psychotropic prescriptions (aRR [95%CI])
Sex (Reference: Women)				
Men	0.55 (0.50-0.61)	0.70 (0.58-0.85)	0.67 (0.50-0.88)	0.70 (0.61-0.79)
Age in years (continuous)	1.00 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (1.00-1.01)	1.02 (1.02-1.02)
Socioeconomic status (Reference: 1 – Most deprived)				
2	0.94 (0.83-1.07)	0.81 (0.62-1.07)	0.66 (0.46-0.94)	0.74 (0.60-0.90)
3	0.86 (0.77-0.97)	0.82 (0.64-1.05)	0.66 (0.48-0.90)	0.56 (0.46-0.68)
4	0.76 (0.67-0.86)	0.58 (0.44-0.78)	0.38 (0.26-0.54)	0.56 (0.46-0.68)
5 (most affluent)	0.76 (0.67-0.86)	0.72 (0.54-0.95)	0.38 (0.26-0.55)	0.53 (0.44-0.65)
Index year (continuous)	1.00 (0.99-1.01)	1.00 (0.99-1.02)	0.96 (0.94-0.99)	1.10 (1.09-1.12)

aRR: adjusted Rate Ratio; CI: confidence interval.

eTable 6. Covariates associated with physician visits for psychiatric morbidity, visits to psychiatrists, psychiatric-related hospital admissions and ‘psychotropic’ in the five years before multiple sclerosis (MS) onset for MS cases versus matched controls in the clinical cohort

Characteristics (at the index date)	Physician visits for psychiatric morbidity (aRR [95%CI])	Visits to psychiatrists (aRR [95%CI])	Psychiatric-related hospital admissions (aRR [95%CI])	Psychotropic prescriptions (aRR [95%CI])
Sex (Reference: Women)				
Men	0.44 (0.33-0.58)	0.43 (0.24-0.76)	0.41 (0.17-0.97)	0.59 (0.43-0.82)
Age in years (continuous)	1.02 (1.02-1.03)	1.03 (1.01-1.05)	1.00 (0.97-1.02)	1.05 (1.04-1.06)
Socioeconomic status (Reference: 1 – Most deprived)				
2	0.64 (0.45-0.92)	0.39 (0.17-0.91)	0.50 (0.20-1.23)	0.50 (0.29-0.85)
3	0.59 (0.41-0.85)	0.31 (0.14-0.70)	0.51 (0.14-1.85)	0.54 (0.32-0.93)
4	0.57 (0.40-0.82)	0.50 (0.24-1.05)	0.82 (0.31-2.15)	0.52 (0.30-0.87)
5 (most affluent)	0.64 (0.42-0.97)	0.39 (0.17-0.87)	0.24 (0.11-0.55)	0.42 (0.25-0.69)
Index year (continuous)	1.01 (0.98-1.05)	0.98 (0.89-1.07)	0.96 (0.86-1.08)	1.35 (1.31-1.39)

aRR: adjusted Rate Ratio; CI: confidence interval.