Supplementary Table 1. Diagnostic codes included in determining the multiple sclerosis incident date.

|  |  |  |
| --- | --- | --- |
| Disease or condition | ICD-9-CM | ICD-10-CA |
| Multiple sclerosis | 340 | G35 |
| Neuromyelitis optica | 341 | G36.0 |
| Demyelinating disease of unspecified origin | 341.9 | G37.8 |
| Acute disseminated encephalomyelitis | 323 | G36.9 |
| Acute transverse myelitis | 323.82 | G37 |
| Optic neuritis | 377.3 | H46 |

Among those who met a validated case definition for multiple sclerosis (had ≥1 hospitalization or ≥5 ambulatory care visits and/or physician visits with a recorded code for multiple sclerosis [ICD-9 340 or ICD-10 G35 located in any diagnostic field] within a 2 year period between 1993 and 2021), the multiple sclerosis incident date was defined as the first healthcare encounter with an MS or related code with none occurring ≥5 years beforehand. Abbreviations: International Classification of Disease – Version 9 – Clinical Modification: ICD-9-CM; International Classification of Disease – Version 10 – Canadian Enhancement: ICD-10-CA.

Supplementary Table 2. Diseases and their associated codes and weights included in the Charlson Comorbidity Index.

| Disease | ICD-9-CM codes | ICD-10-CA codes |
| --- | --- | --- |
| *Disease weight one* |  |  |
| Myocardial infarction | 410, 412 | I21, I22, I25.2 |
| Congestive heart failure | 398, 402, 425, 428 | I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0 |
| Peripheral vascular disease | 440, 441, 443, 447, 557 | I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9 |
| Cerebrovascular disease | 430, 431, 432, 433, 434, 435, 436, 437, 438 | G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H34.0 |
| Dementia | 290, 294, 331 | F00, F01, F02, F03, G30, F05.1, G31.1 |
| Chronic pulmonary disease | 416, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505 | J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, I27.8, I27.9, J68.4, J70.1, J70.3 |
| Connective tissue disease | 446, 710, 714, 725 | M05, M32, M33, M34, M06, M31.5, M35.1, M35.3, M36.0 |
| Peptic ulcer disease | 531, 532, 533, 534 | K25, K26, K27, K28 |
| Mild liver disease | 070, 570, 571, 573 | B18, K73, K74, K70.0, K70.1, K70.2, K70.3, K70.9, K71.7, K71.3, K71.4, K71.5, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4 |
| Diabetes  (without complication) | 250 | E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 |
| *Disease weight two* |  |  |
| Diabetes  (with complication) | 250 | E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7, E14.2, E14.3, E14.4, E14.5, E14.7 |
| Hemiplegia and paraplegia | 334, 342, 343, 344 | G81, G82, G04.1, G11.4, G80.1, G80.2, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9 |
| Moderate or severe renal disease | 403, 582, 583, 585, 586, 588, V56 | N18, N19, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N25.0, I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2 |
| Cancer | 140-165, 170-172, 174-176, 179-195, 200- 208, 238 | C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90- C97 |
| *Disease weight three* |  |  |
| Moderate/severe  liver disease | 456, 572 | K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2 |
| *Disease weight six* |  |  |
| Metastatic Carcinoma | 196, 197, 198, 199 | C77, C78, C79, C80 |
| HIV/AIDS | 042, 043, 044 | B20, B21, B22, B24 |

To be considered as having one of the listed diseases, an individual must have had ≥1 hospitalization (associated ICD-10-CA code listed in any diagnostic field) or ≥2 physician claims (associated ICD-9-CM codes listed in any diagnostic field) of the corresponding ICD within ≤2-years. Abbreviations: HIV/AIDS = Human immunodeficiency virus / acquired immunodeficiency syndrome; ICD-9-CM = International classification of diseases, ninth revision, clinical modification; ICD-10-CA = International classification of diseases, tenth revision, Canadian enhancement.

Supplementary Table 3. Case definitions used to identify specific health conditions.

| Comorbidity | Algorithm | ICD-9-CM codes | ICD-10-CA codes | | Other codes |
| --- | --- | --- | --- | --- | --- |
| Anxiety | ≥1 hospitalization or ≥2 claims OR ≥1 claim and ≥2 prescription dispensations in ≤2-years | 300.0, 300.2 | F40, F41 | | *ATC drug codes:*  N05AB06, N05AB12 |
| Cardiovascular disease (any of the below) | |  |  |  | |
| Atrial fibrillation | ≥1 hospitalization or ≥2 claims in ≤2 years | 427.3 | I48.0 | |  |
| Chronic heart failure | ≥1 hospitalization or ≥2 claims in ≤2 years | 398.9, 402, 404, 425.4 –425.9, 428 | I09.9, I25.5, I42.0, I42.5–I42.9, I43, I50 | |  |
| Coronary artery disease | ≥1 hospitalization or ≥1 ambulatory care visit or ≥1 procedure or ≥2 claims in ≤2 years | 410-413 | I20–I25 | | *Procedure codes:* 1.IJ.57.GQ, 1.IJ.50, 1.IL.35, 1.IJ.76 |
| Peripheral artery disease | ≥1 hospitalization or ≥1 ambulatory care visit or ≥1 claim in any years | 440.2 | I70.2 | |  |
| Stroke | ≥1 hospitalization or ≥1 emergency department with stroke as most responsible diagnosis OR ≥1 hospitalization or ≥1 emergency department with stroke as secondary z-code as most responsible diagnosis\* in any years |  | G08, G45 (excluding subcode G45.4), H34.0, H34.1, I60, I61, I62.9 (code only applicable to fiscal years prior to 2015/2016), I63, I64, I67.6; Z50 (excluding subcodes Z50.2, Z50.3, Z50.4), Z54.8, Z54.9, \*only Z51.5 applies to ambulatory care | |  |
| Chronic obstructive pulmonary disease | ≥35 years with ≥1 hospitalization or ≥1 claim in any years | 491-492, 496 | J41–J44 | |  |
| Depression | ≥1 hospitalization or ≥2 claims in ≤2 years | 300.4, 311 | F32-F33, F34.1 | |  |
| Diabetes | ≥1 hospitalization or ≥2 claims in ≤2 years | 250 | E10-E14 | |  |
| Hypertension | ≥1 hospitalization or ≥2 claims in ≤2 years | 401–405 | I10–I13, I15 | |  |

Each participant was classified with respect to the presence or absence of these conditions as measured during the 2 year period before the index date. Abbreviations: ATC = anatomical therapeutic chemical; ICD-9-CM = International classification of diseases, ninth revision, clinical modification; ICD-10-CA = International classification of diseases, tenth revision, Canadian enhancement.

Supplementary Table 4. Health conditions included in the case definition used to estimate the expanded disability status scale among individuals in the multiple sclerosis cohort.

| Health condition | ICD-9-CM codes | ICD-10-CA codes |
| --- | --- | --- |
| Visual disturbance | 368, 269 | H53.2, H53.4, H54 |
| Other paralytic syndromes | 344.0, 344.1 | G82 |
| Spasticity | 781.0 | R25.2 |

To be considered as having one of the listed health conditions, an individual must have had ≥2 of the corresponding ICD codes ≥90 days apart. Abbreviations: ICD-9-CM = International classification of diseases, ninth revision, clinical modification; ICD-10-CA = International classification of diseases, tenth revision, Canadian enhancement.

Supplementary Table 5. Disease-modifying therapies included in this study.

|  |  |
| --- | --- |
| Disease modifying therapy | Method of identification: anatomical therapeutic chemical code or  drug identification number |
|
| *Older platform and injection therapies* |  |
| Oral |  |  |
| Dimethyl fumarate | L04AX07, N07XX09 |  |
| Teriflunomide | L04AA31 |  |
| Injection |  |  |
| Glatiramer acetate | L03AX13 |  |
| Interferon beta-1a | L03AB07 |  |
| Interferon beta-1b | L03AB08 |  |
| Peginterferon beta-1a | L03AB13 |  |
|  |  |  |
| *High-efficacy and induction therapies* |  |
| Oral |  |  |
| Cladribine | L04AA40 |  |
| Fingolimod | L04AA27 |  |
| Infusion |  |  |
| Alemtuzumab | L04AA34 |  |
| Natalizumab | L04AA23 |  |
| Ocrelizumab | L04AA36 |  |
| Rituximab | L01FA01 |  |
|  |  |  |
| *Other therapies* |  |  |
| Cyclophosphamide (infusion) | 00013544, 00013552, 00373753, 00602833, 00602949, 02094428, 02241797, 02241798, 02241800 |  |
| Daclizumab | L04AC01 |  |
| Mitoxantrone | L01DB07 |  |
|  |  |  |



Supplementary Figure 1. Cohort selection and data linkage flow diagram. Abbreviations: ACCIS = Alberta Continuing Care Information System; AHCIP = Alberta Health Care Insurance Plan; CLM = Physician Claims; DAD = Discharge Abstract Database; DMT = disease-modifying therapy; ICD-9-CM = International Classification of Disease – Version 9 – Clinical Modification; ICD-10-CA = International Classification of Disease - Version 10 - Canadian Enhancement; MS = multiple sclerosis; NACRS = National Ambulatory Care Reporting System; NRS = National Rehabilitation Reporting System; PHN = personal health number; PIN = Pharmaceutical Information Network; REG = Provincial Registry; VS = vital statistics.