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Clinical trial

Higher health care use before a clinically isolated syndrome with or without subsequent MS

Ruth Ann Marrie[a,b,*], José M.A. Wijnands[c], Elaine Kingwell[c], Feng Zhu[c], Yinshan Zhao[c], Okechukwu Ekuma[d], Xinya Lu[e], Charity Evans[f], John D. Fisk[g], Helen Tremlett[c]

[a] Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[b] Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[c] Department of Medicine (Neurology), University of British Columbia and The Djavad Mowafaghian Centre for Brain Health, Vancouver, Canada
[d] Manitoba Centre for Health Policy, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[e] Saskatchewan Health Quality Council Saskatoon, Canada
[f] College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada
[g] Departments of Psychiatry, Psychology & Neuroscience and Medicine, Dalhousie University, Halifax, Canada

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ABSTRACT

Background: To establish whether a unique multiple sclerosis (MS) prodrome exists by comparing health care utilization in the five-year period before initial presentation with optic neuritis (ON) or transverse myelitis (TM) among those who were and were not subsequently diagnosed with MS.

Methods: Using population-based administrative health data we conducted a retrospective cohort study in three Canadian provinces. We identified individuals with a clinically isolated syndrome (ON or TM), who were eventually diagnosed with MS (CIS-MS) or not (CIS-non MS), and a control cohort matched on age, sex and region without a CIS. We compared rates of hospitalization, physician services use and prescription drug use in the five years before the first ON or TM claim (labeled years -1,-2,-3,-4,-5) using negative binomial regression models adjusted for age, sex, socioeconomic status and index year.

Results: We identified 1,155 CIS-MS cases, 20,638 CIS-non MS cases, and 108,726 matched controls. Compared to matched controls, the CIS-MS cohort had a higher hospitalization rate (years -5 and -1), physician visits (all years) and prescription drug use (years -4 and -1). Compared to matched controls, the CIS-non MS cohort had a higher rate of hospitalizations (all years), physician visits (all years) and prescription drug use (all years).

Conclusion: Health care use was higher in individuals with a CIS than without a CIS in the five years before an incident demyelinating event, regardless of whether they were subsequently diagnosed with MS. This suggests that there is a prodromal period before CIS which is not unique to MS.

1. Introduction

The etiology of multiple sclerosis (MS) remains incompletely understood. Approximately 85% of individuals with MS present with the relapsing form of the disease in which the initial event is classified as a clinically isolated syndrome (CIS).(Miller et al., 2012) Two typical CIS presentations include optic neuritis (ON) and transverse myelitis (TM). Some individuals who present with a CIS experience a monophasic illness and are never diagnosed with MS (CIS-non MS); these individuals may not have the same risk factors as those ultimately diagnosed with MS.(van Pelt, Mescheriakova et al. 2013)

Establishing and understanding the prodromal phase of a disease facilitates earlier identification and intervention, and is essential to establish the etiologically relevant time period for research that seeks to determine the origins of disease. Recent studies have suggested the presence of a prodromal period beginning at least five years before presentation with typical symptoms of MS.(Berger et al., 2013; Wijnands et al., 2017) Generally, these studies compared individuals with MS to individuals without MS. It is unknown whether persons with CIS who do not develop MS also experience a prodromal period. We could postulate that a CIS that does not lead to MS represents a transient, self-limited illness and therefore would lack a prodrome;

* Corresponding author at: Health Sciences Center, GF-543, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada
E-mail addresses: rmarrie@hsc.mb.ca (R.A. Marrie), j.wijnands@ubc.ca (J.M.A. Wijnands), elainejk@mail.ubc.ca (E. Kingwell), feng.zhu@ubc.ca (F. Zhu), yinshan@mail.ubc.ca (Y. Zhao), okechukwu_ekuma@cpe.umanitoba.ca (O. Ekuma), xlu@hqc.sk.ca (X. Lu), charity.evans@usask.ca (C. Evans), john.fisk@nshealth.ca (J.D. Fisk), helen.tremlett@ubc.ca (H. Tremlett).

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however, a Danish study reported that persons with ON without MS had elevated medical costs up to eight years before diagnosis.(Jennum et al., 2013) This study did not examine any other common CIS presentations, nor did it examine the patterns of health care use responsible for the elevated costs.

We aimed to establish whether a unique MS prodrome exists by comparing health care utilization (hospital, physician or prescription use) in the five-year period before the first presentation with optic neuritis (ON) or transverse myelitis (TM) among those who were subsequently diagnosed with MS and those who were not. We hypothesized that there would be a prodromal period in the CIS-non MS cohort which would be less pronounced than in the CIS-MS cohort.

2. Methods

2.1. Design

We conducted this matched cohort study using prospectively collected data in three Canadian provinces, Saskatchewan, Manitoba and Nova Scotia (NS). These provinces were chosen because of the availability of the required data sources and experienced investigators.

2.1.1. Data sources

In each province, health care is universal and publicly funded. Population-based databases capture health services use of nearly all residents. Within each province we accessed the population registry, hospital discharge abstracts, physician (medical) services visits, and prescription claims. These databases were linked deterministically using an encrypted unique provincial identifier. The population registry captures date of birth, sex, region of residence (postal code), dates of health care coverage and date of death. The Discharge Abstract Database captures inpatient (hospital) admission and separation dates, and up to 25 discharge diagnoses coded using the International Classification of Diseases (ICD) system, according to ICD-9-clinical modification (CM) or ICD-10-Canada (CA) depending on the year. Physician Services capture the service date and physician-assigned diagnoses using ICD-9-CM codes. Because some provinces recorded one diagnosis and others recorded up to three, only the first diagnosis was used for consistency. Prescription databases capture drug name, drug identification number (DIN), and date dispensed; each DIN can be mapped to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System.(WHO Collaborating Centre for Drug Statistics Methodology 2011) There is no provincial prescription claims database in NS, but records of disease-modifying therapy use are available. Data availability varied by province, beginning January 1, 1996 and ending April 2014 in SK, beginning April 1, 1984 and ending December 2013 in Manitoba and beginning January 1, 1990 and ending December 2013 in NS.

We obtained ethics approval from the University of Manitoba Health Research Ethics Board, University of Saskatchewan Biomedical Research Ethics Board, NS Health Authority Research Ethics Board, and approval to access the administrative data from the relevant bodies that regulate access (Manitoba's Health Information Privacy Committee, Health Data NS, Saskatchewan Health Quality Council/Saskatchewan Ministry of Health).

2.2. Study populations

We applied validated case definitions to the linked administrative datasets to identify three study cohorts.(Al-Sakran et al., 2018; Marrie et al., 2018) First, we identified persons with MS as those with ≥ 3 hospital, physician or prescription claims specific for MS in any combination. This case definition has a sensitivity of 99.5% and specificity of 98.5%.(Al-Sakran et al., 2018) Within this group of persons with MS, we identified the date of the first demyelinating disease claim (Table e1) as the index date, and selected persons whose first claim was for ON or TM.(Marrie et al., 2018) This subgroup constituted the CIS-MS cohort. Second, we identified all persons with a first demyelinating disease claim for ON (in physician claims) or TM (in hospital or physician claims), who did not have any subsequent claims for MS or NMO within a minimum follow-up period of ≥ 5 years. This group constituted the CIS-non MS cohort.(Marrie et al., 2018) The specificity of these case definitions was 82.7% (ON) to 89% (TM) when applied within a population of patients referred to an MS clinic, but are expected to exceed 99% when applied in the general population.(Marrie et al., 2018) Third, we identified up to 5 controls matched on sex, birth year, and region of residence (first three digits of the postal code) at the index date; controls did not have any demyelinating disease claims and were assigned the index date of their matched cases. All controls were combined into one group as we did not expect differences between the controls of the CIS-MS and CIS-non MS cases after adjusting for age, sex, index year and socioeconomic status (SES). Finally, to ensure that we identified incident CIS-MS and CIS-non MS cases, all cohorts were required to have ≥ 5 years of data before the index date. We also required ≥ 5 years of data after the index date based on natural history studies suggesting that most individuals presenting with a CIS will meet diagnostic criteria for MS within 5 years of onset.(Beck et al., 2003)

2.3. Health care utilization

We assessed all-cause health care utilization in each of the five years before the index date, separately for hospitalizations (inpatient hospitalizations involving an overnight stay), physician services, and prescriptions dispensed. For physician services, all visits on the same day with the same ICD-9 code were treated as one visit. We counted the number of drug classes from which prescriptions were dispensed using level 4 of the ATC System.

2.4. Covariates

Covariates were sex (male as the reference), age at the index date (continuous), index year (grouped as 1990–1993; 1994–1998; 1999–2003; 2004–2009 [reference]), SES each year (lowest income quintile as the reference), and year of the prodromal period (categorized as year -5, -4, -3, -2, -1 before the index date with year -1 as the reference). We derived area-level SES in quintiles by linkage of postal codes to Statistics Canada enumeration area census information on household income.(Watson et al., 2005) We did not include comorbidity or other measures of health status because these could be components of the prodrome under investigation.

2.5. Analysis

We summarized categorical variables using frequency (percent), and continuous variables using mean (standard deviation [SD]). We examined the associations between study cohort (CIS-MS, CIS-non MS, controls) and each health care utilization outcome of interest (number of inpatient hospitalizations, number of physician services used, number of prescription drug classes) using negative binomial regression models to account for over-dispersion. To account for dependence of repeated measurements within individuals we used generalized estimating equations with an unstructured working correlation matrix. These models included the log of person-years as an offset, and the covariates defined above. To test temporal trends over the five-year period, we added an interaction term between study cohort and year of the prodromal period. We present the findings using adjusted rate ratios (RR) with 95% confidence intervals (95%CI).

Due to provincial regulations regarding use of individual-level data, standardized analyses were performed in parallel in each province. We pooled findings using random effects meta-analysis.(Hertzmark and Spiegelman 2012) We report I^2 as a measure of heterogeneity, and interpret values of $<25\%$ as indicating low, values of 25–50% as

indicating moderate, and values >75% as indicating high heterogeneity.(Higgins and Thompson 2002)

2.5.1. Complementary analyses

We conducted complementary analyses to explore the reasons for differences in utilization between CIS-MS and CIS-non MS cohorts; these were restricted to Manitoba due to constraints related to data approvals and study funding. We: (i) compared the proportion of ON and TM in the CIS-MS and CIS-non MS cohorts; (ii) examined the proportion of persons in the CIS-non MS cohort who developed inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), (Bernstein et al., 1999; Hitchon et al., 2019) as these are other autoimmune diseases in which prodromes are being explored (Pimentel et al., 2000; Mankia and Emery 2016); and (iii) repeated the analyses requiring members of the CIS-MS, CIS-non MS and matched cohorts to have ≥10 years of follow-up after the index date. Finally, given the increased likelihood of alternative etiologies of optic neuropathy such as ischemic optic neuropathies particularly at ages ≥50 years, (Hoorbakht and Bagherkashi 2012) we repeated the analyses among individuals with an age at the index date <50 years.

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participants

Across all provinces, we identified 1155 CIS-MS cases, 20,638 CIS-non MS cases, and 108,726 matched controls (Table 1). The proportion of women was higher in the CIS-MS cohort than in the CIS-non MS cohort ($p < 0.0001$); as expected the proportion of females in the control cohort fell between the proportions in the CIS-MS and CIS-non MS cohorts ($p = 0.025$). Table e2 shows cohort characteristics by province.

During the entire five-year period before the index date, 41% of the combined CIS (CIS-MS and CIS-non MS) cohort had ≥1 inpatient hospitalization, which was higher than the proportion of the control cohort which was hospitalized (28%, Table 1). Nearly all members of each cohort used ≥1 physician service and this did not differ between CIS and controls, but the mean number of physician services used overall was higher in the combined CIS cohort than in the control cohort.

When we examined health services use for each year before the index date, the proportion of the CIS-MS and CIS-non MS cohorts who were hospitalized, used physician services or filled a prescription increased gradually from year −5 to year −1 (Fig. 1). In contrast, the proportion of controls who were hospitalized and used physician services was stable over the five year period before the index date. All groups demonstrated an increase in the number of prescription drug classes dispensed over time, including the controls (Fig. 1C).

3.2. Multivariable results

On multivariable analysis, the CIS-MS cohort had a higher hospitalization rate than the controls; this difference was statistically significant in Year −5 and Year −1 (Fig. 2A, Table e3). The CIS-non MS cohort had a higher rate of hospitalizations than the controls in each of the five years before the index date. As compared to the CIS-non MS cohort, the CIS-MS cohort had lower hospitalization rates during each of the five years before the index date; this difference reached statistical significance in three of the years.

As compared to the controls, the CIS-MS and CIS-non MS cohorts

Table 1
Characteristics of study participants.

Characteristics	CIS-MS (N = 1155)	CIS-non MS (N = 20,638)	CIS[e] (N = 21,793)	Controls (N = 108,726)	P-value[f]
At the index date[a]					
Females, n (%)	866 (75.0)	12,187 (59.1)	13,053 (59.9)	65,117 (59.9)	1
Age, years, mean (SD)	37.0 (10.3)	48.5 (19.7)	47.8 (19.3)	47.9 (19.2)	0.48
Age group (years), n (%)					0.99
<20	51 (4.4)	1893 (9.2)	1944 (8.9)	9751 (9.0)	
20 to <30	279 (24.2)	2103 (10.2)	2382 (10.9)	11,870 (10.9)	
30 to <40	384 (33.2)	3043 (14.7)	3427 (15.7)	17,187 (15.8)	
40 to <50	324 (28.1)	3707 (18.0)	4031 (18.5)	20,115 (18.5)	
≥50	117 (10.1)	9892 (47.9)	10,009 (45.9)	49,803 (45.8)	
Index year[a], n (%)					0.99
1990–1993	189 (16.4)	1795 (8.7)	1984 (9.1)	9920 (9.1)	
1994–1998	240 (20.8)	4155 (20.1)	4395 (20.2)	21,960 (20.2)	
1999–2003	362 (31.3)	6026 (29.2)	6388 (29.3)	31,908 (29.3)	
2004–2009	348 (30.1)	8127 (49.4)	8475 (38.9)	42,214 (38.8)	
2010–2014	16 (1.4)	535 (2.6)	551 (2.5)	2724 (2.5)	
Socioeconomic status[b], n (%)					0.99
1 (lowest income quintile)	S	3962 (19.2)	4144 (19.0)	21,242 (19.5)	
2	235 (20.3)	4022 (19.5)	4257 (19.5)	21,998 (20.2)	
3	245 (21.2)	4148 (20.1)	4393 (20.2)	21,653 (19.9)	
4	237 (20.5)	4192 (20.3)	4429 (20.3)	21,642 (19.9)	
5 (highest income quintile)	254 (22.0)	4190 (20.3)	4444 (20.4)	21,689 (19.9)	
Missing	S	124 (0.6)	s	502 (0.5)	
In the five year period before the index date					
≥1 inpatient hospitalizations, n (%)	379 (32.8)	8564 (41.5)	8943 (41.0)	30,769 (28.3)	<0.0001
Any physician visits, n (%)	1155 (100)	20,616 (99.9)	21,771 (98.2)	106,803 (98.2)	<0.0001
Number of physician services used, mean (SD)	43.5 (36.2)	52.8 (47.2)	52.3 (46.6)	38.5 (36.7)	<0.0001
≥1 prescription drug dispensed[c,d], n (%)	593 (66.0)	10,802 (74.5)	11,395 (74.0)	54,535 (71.0)	<0.0001

MS: multiple sclerosis, CIS-MS: clinically isolated syndrome later diagnosed with MS, CIS-non MS: clinically isolated syndrome not later diagnosed as MS.

[a] The index dates represent the first demyelinating event.

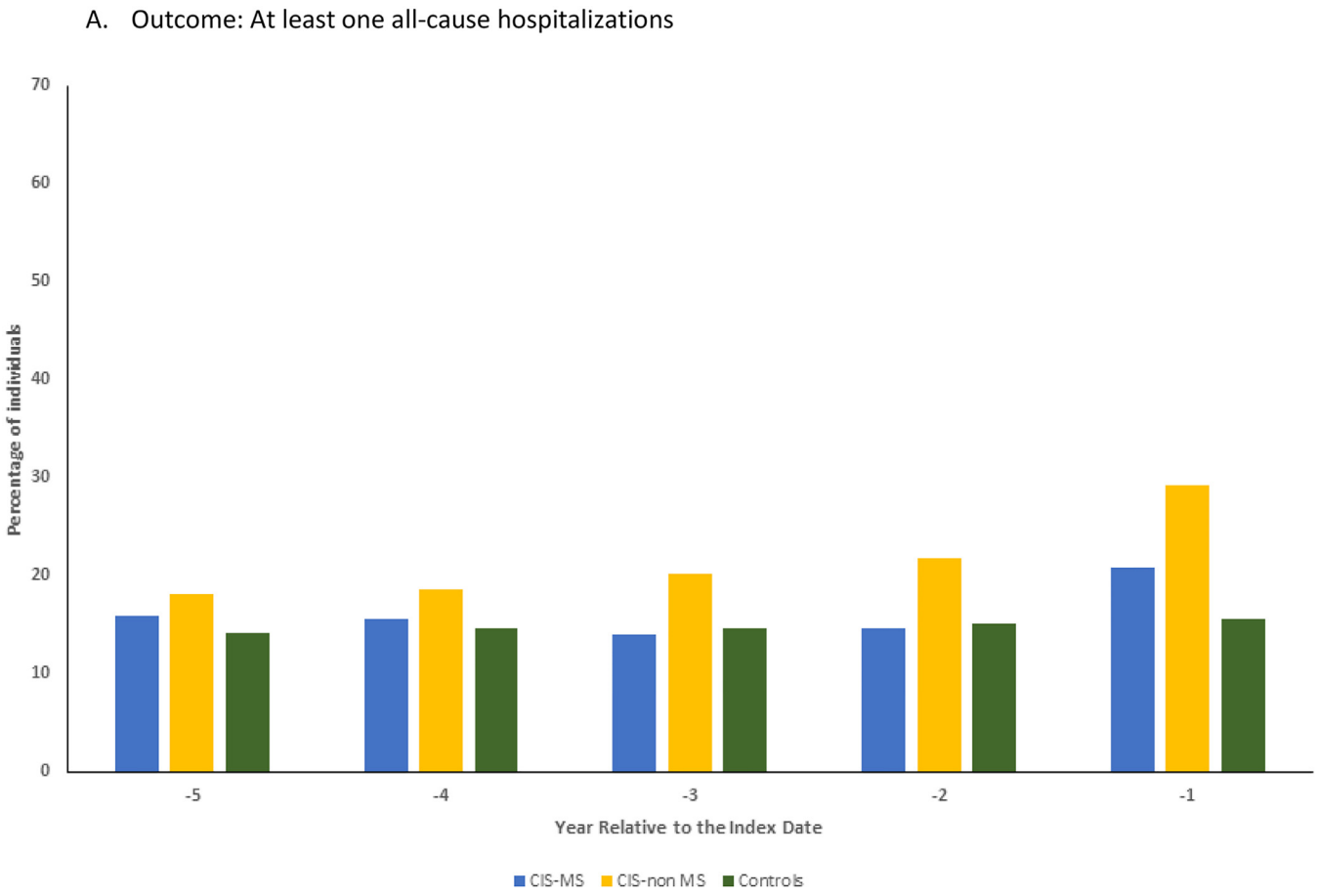
[b] Data are suppressed to prevent direct or residual disclosure of identifiable data (denoted as 's').

[c] Prescription records were available starting in 1996, except for Nova Scotia where prescription data were not available.

[d] A prescription class was defined by the Anatomical Therapeutic Chemical Classification System, level 4. The proportion with a prescription dispensed was calculated for 899 CIS-MS cases, 14,490 CIS-non MS cases and 76,771 controls.

[e] Combined CIS-MS and CIS-non MS groups.

[f] Comparison of the combined CIS cases and matched controls using student's t-test and chi-squared tests.



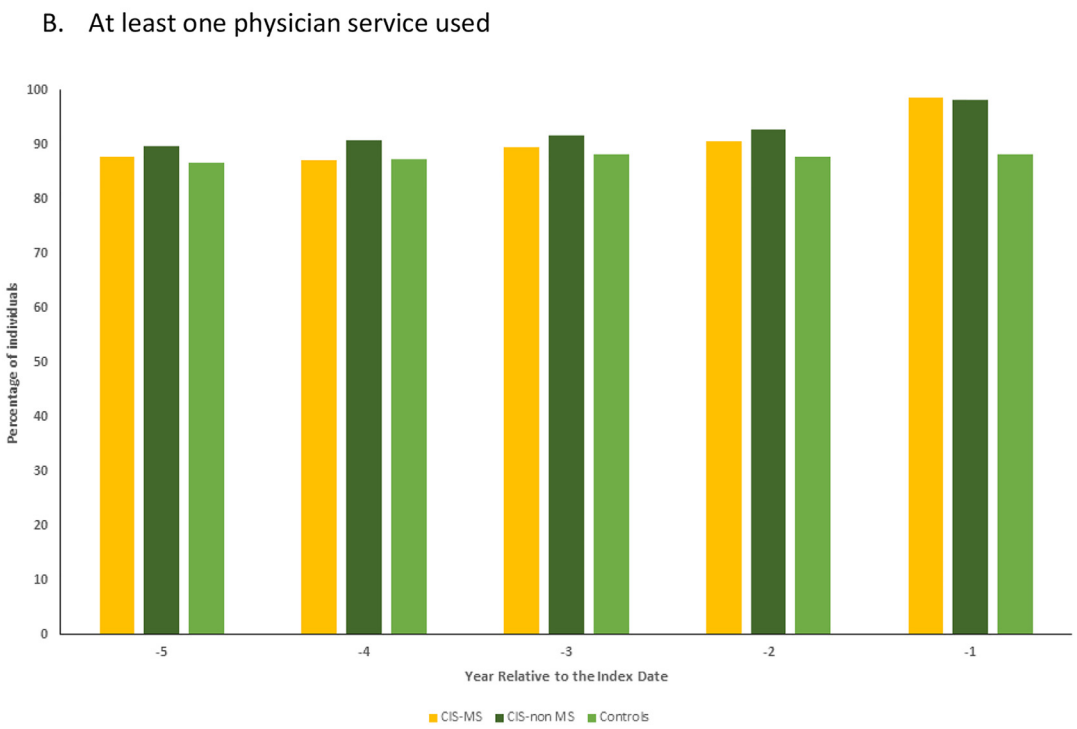


Fig. 1. Percentage of individuals with at least one hospitalization (A), physician service used (B) and prescription drug dispensed (C) in the five years before the index date, pooled across provinces.

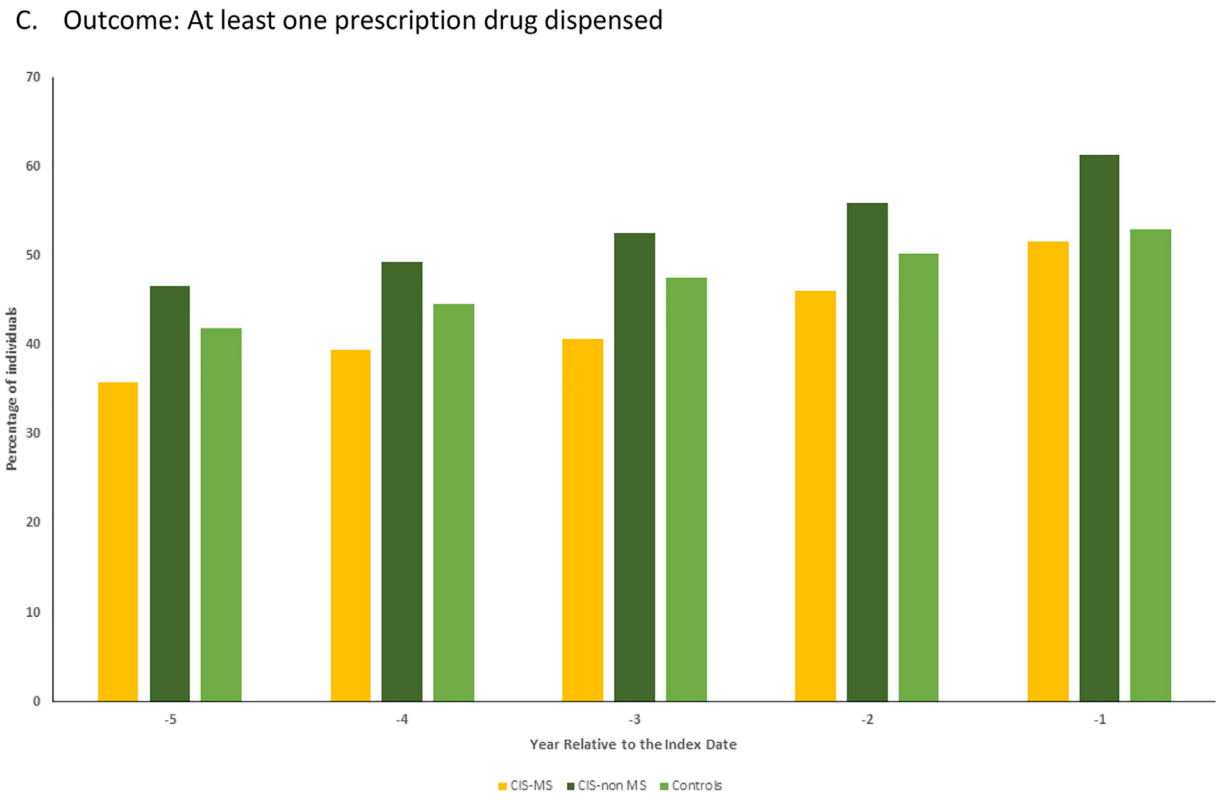


Fig. 1. (*continued*)

had higher rates of physician services use during each of the five years before the index date (Fig. 2B, Table e4). As compared to the CIS-non MS cohort, the CIS-MS cohort had lower rates of physician services use during each of the five years before the index date.

Versus the controls, the CIS-MS cohort had higher rates of prescription use by drug class during the last year before the index date (Fig. 2C, Table e5). The CIS-non MS cohort had higher rates of prescription use during each of the five years before the index date. As compared to the CIS-non MS cohort, the CIS-MS cohort had lower rates of prescription use during the last year before the index date.

3.3. Complementary analyses

The proportion of individuals with ON was lower in the CIS-MS cohort (65.9%) than in the CIS-non MS cohort (80.0%, $p < 0.0001$). As compared to the CIS-MS cohort, the frequency of RA was higher in the CIS-non MS cohort (IBD: 1.18% vs. number suppressed, $p = 0.25$; RA 4.23% vs. 1.2%, $p = 0.0002$). When we repeated the analyses among members of the cohorts (CIS-MS: 455; CIS-non MS: 2903; controls: 10,041) with ≥10 years of follow-up after the index date the pattern of observations was similar (Table e6). The CIS-MS cohort had a higher rate of hospitalizations than controls in year −1. Versus controls, the CIS-MS and CIS-non MS cohorts had higher rates of physician services use during each of the five years before the index date; the magnitude of the associations was similar to those in the larger cohorts. The CIS-MS cohort had a higher rate of prescription use during the last year before the index date as compared to controls, while the CIS-non MS cohort had a higher rate of prescription use during all 5 years before the index date. Versus the CIS-non MS cohort, the CIS-MS cohort had lower rates of hospitalizations (years −4 through −1), physician services use (all years), and prescription use than the CIS-non MS cohort (years −3, −2, −1). When we repeated the analyses in Manitoba among individuals aged ≥50 years at the index date, the findings were the same as those just described (Table e7).

4. Discussion

In this population-based study using administrative data from three Canadian provinces, health care use of people with a CIS was higher than in matched controls without a CIS during the five years before the index date (first claim for ON or TM). In the CIS-non MS cohort (those not diagnosed with MS), health care use was higher for hospitalizations, physician services use and drug prescriptions during each of the five years before the index date. In the smaller CIS-MS cohort, health care use was higher for physician services during each of the five years before the index date as compared to controls and higher for hospitalizations and filled prescriptions primarily in the final year (year −1), after adjustment for age, sex, SES and index year.

The proportion of individuals with CIS who developed MS was relatively low, but was higher in the subgroup followed for 10 years. The likelihood of being diagnosed with MS following a CIS depends strongly on the presence or absence of abnormalities on brain MRI, and duration of follow-up.(Miller et al., 2012) It also varies across regions.

Few studies have investigated a possible prodrome in MS, some of which included control groups from the general population.(Berger et al., 2013; Sinay et al., 2015; Cortese et al., 2016; Wijnands et al., 2017; Disanto et al., 2018) In a study using administrative data in the United States, one-third of individuals with MS had health claims for fatigue in the preceding three years,(Berger et al., 2013) but there was no control group making interpretation of the findings difficult. Previously, we found that people with MS had more hospitalizations, physician visits, and filled prescriptions than matched controls without MS in the five years before their first demyelinating disease claim. (Wijnands et al., 2017) A British study using the Clinical Practice Research Database found that patients with MS were more likely than matched controls to present to their general practitioner for care for a variety of symptoms, such as anxiety, depression, fatigue, pain, and urinary symptoms, up to ten years before the index date.(Disanto et al., 2018) A Norwegian study of 924 male MS cases and 19,530 matched controls who underwent a conscription examination at age 18 or 19

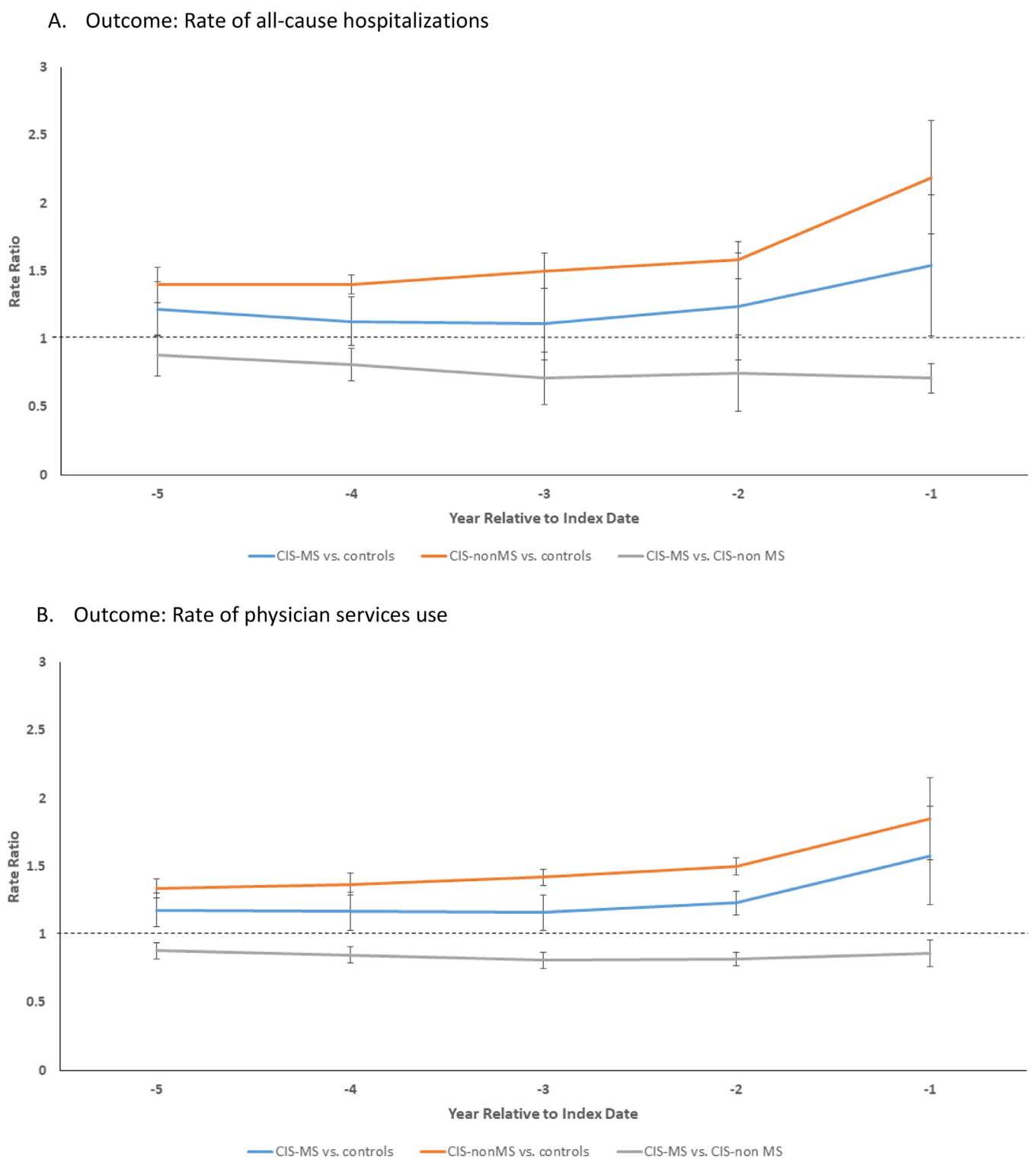


Fig. 2. Association of clinically isolated syndrome with multiple sclerosis (CIS-MS) and without multiple sclerosis (CIS-non MS) with (A) hospitalizations, (B) physician services use, and (C) prescription drug dispensations (C) in the five years before the index date, pooled across provinces.
Error bars represent 95% confidence intervals. All models were adjusted for age, sex, socioeconomic status and index year. The second cohort named in each comparison is the reference group.

years found that those who subsequently developed MS had performed worse on cognitive testing.(Cortese et al., 2016) A study of MS cases and controls in Argentina found that school performance was lower in MS cases, on average 13 years before symptom onset.(Sinay et al., 2015)

We were unable to identify studies that sought to examine a possible prodrome among individuals with a CIS who did not develop MS. However, one study has examined health care costs among individuals with ON. In a Danish study of 1677 patients with ON and 6708 age-, sex- and geographically-matched controls, patients with ON had increased average annual medical costs up to eight years before diagnosis. (Jennum et al., 2013) Costs were higher for hospitalizations, outpatient

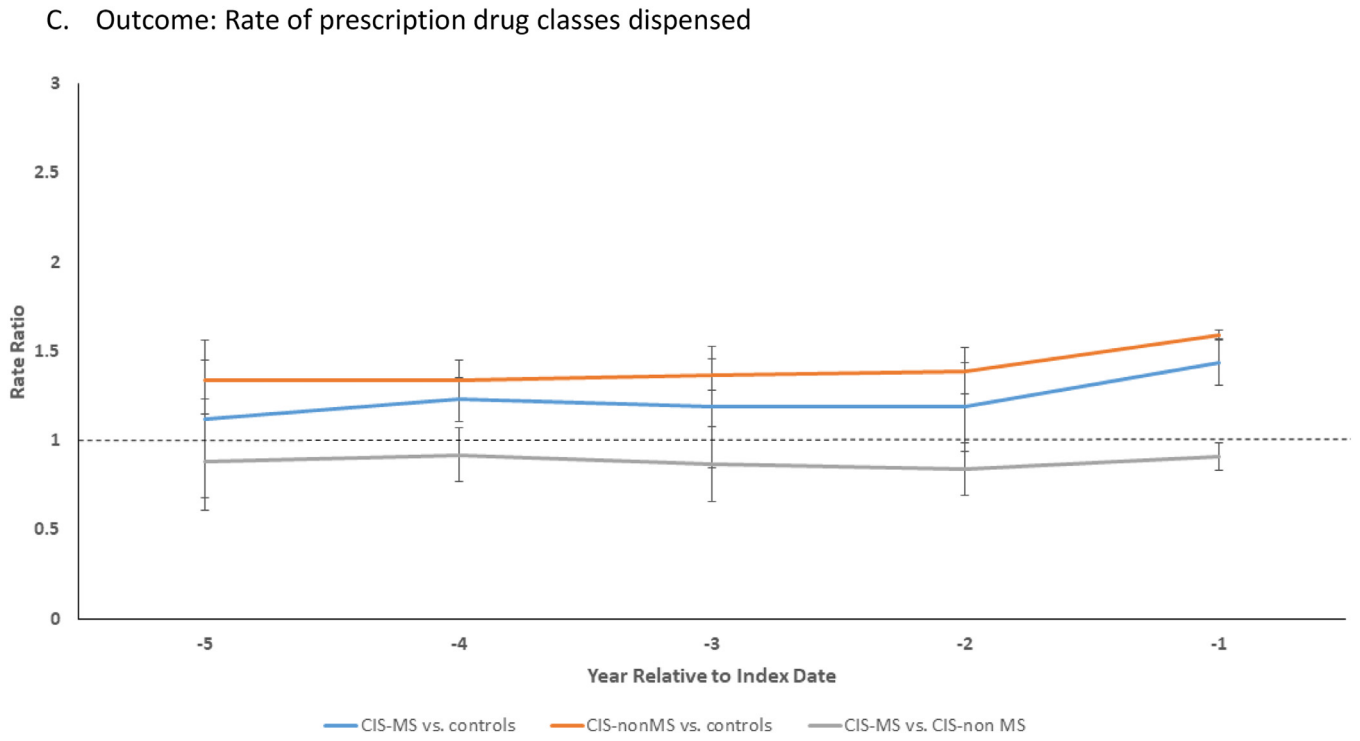


Fig. 2. (*continued*)

care and prescription medication use in individuals with ON whether they were, or were not, subsequently diagnosed with MS. Contrary to our findings, which also included individuals with TM, costs were higher in those with ON-MS than ON-non MS. Our observation of increased health care use in the CIS-non MS versus CIS-MS cohort was unexpected, particularly given the higher proportion of the CIS-non MS cohort with ON, as TM might be expected to be associated with higher health care needs. While we excluded the development of MS within five years of the onset of ON and TM (and ten years in complementary analyses), it was not feasible to exclude all other diseases potentially associated with the development of a CIS, including other autoimmune diseases (e.g. systemic lupus erythematosus, Sjogren's syndrome), or infections (e.g. Lyme disease) (Schulz et al., 2012) which could be independently associated with increased health care use. The proportion with RA was higher in the CIS-non MS cohort than the CIS-MS cohort, suggesting that higher utilization in the CIS-non MS cohort could reflect the contributions of other serious immune-mediated disorders. Future studies should explore this issue.

Our findings our extend our previous work regarding a prodromal period in MS, and suggest that there may be a prodrome among individuals with incident ON or TM regardless of whether or not MS is subsequently diagnosed. This raises questions about what factors determine whether an incident demyelinating event is monophasic or leads to a chronic illness. Prodromal phases have been described in other inflammatory and neurodegenerative disorders.(Doty et al., 1995; Pimentel et al., 2000; Mankia and Emery 2016) In Crohn's disease, an immune-mediated inflammatory disorder affecting the gastrointestinal tract, prodromal symptoms of bloating, diarrhea, stomach pain, weight loss and fatigue have been reported to precede the diagnosis for an average of 7.7 years.(Pimentel et al., 2000) In RA, signs of systemic autoimmunity, pain, stiffness and fatigue develop years before joint swelling emerges.(Mankia and Emery 2016) A clear understanding of the prodromal phase of demyelinating disease could facilitate early recognition and diagnosis, and may offer the opportunity to prevent the development of the full manifestations of disease. This approach is being tested in clinical trials in which individuals who have elevated autoantibody levels associated with future onset of RA are being randomized to placebo or an immunomodulatory agent. (National Institute of Allergy and Infectious Diseases (NIAID) 2015)

The strengths of this study include the population-based design, use of incident cases, and use of prospectively collected administrative data which limits the potential for recall bias. However, this study also had limitations. Absent a validated case definition that could identify all individuals with CIS, we focused on ON and TM, for which case definitions exist;(Marrie et al., 2018) so our findings may not generalize to other CIS presentations. Also, this resulted in a modest sized CIS-MS cohort which may have limited our power to detect differences in health care use versus the control cohort. Although we used a validated case definition the limited specificity of 3-digit diagnostic codes could have lead to the inclusion of individuals who did not have a CIS, particularly for individuals with an older age of presentation. However, when we limited the Manitoba cohort to individuals with an age <50 years our findings were similar. The diagnostic criteria for MS continue to evolve, and some individuals classified as CIS at initial presentation in the past would be diagnosed with MS immediately now. This may make it harder to identify the initial clinical presentation using administrative data in the future as codes for ON and TM may be replaced solely by MS. Nonetheless, our findings have relevance with respect to the prodromal phase for individuals presenting with ON and TM. We did not compare the reasons for health care utilization in the prodromal period between the CIS-MS and CIS-non MS cohorts but this should be investigated in future studies. We could not investigate a possible prodrome more than five years before the index date due to sample size limitations when a longer study period is required.

Health care use was more frequent in individuals with a CIS than without a CIS in the five years before an incident demyelinating event, regardless of whether they were subsequently diagnosed with MS. This suggests that there may be a prodromal period before CIS regardless of whether the individual is ultimately diagnosed with MS or not. Future studies should determine whether specific characteristics of the possible prodromal phase of CIS-MS and CIS-non MS individuals differ.

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All inferences, opinions, and conclusions drawn in this publication are those of the authors and do not reflect the opinions or policies of the Data Stewards. No official endorsement by the Saskatchewan Government or the Ministry of Health, Manitoba Centre for Health Policy, Manitoba Health or other data providers is intended or should be inferred. Some data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health. Some data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness. The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #2014–022 (HIPC# 2007/2008–51 G) and the important contribution of Yan Wang (Nova Scotia).

Disclosures

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Supplementary materials

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References

Al-Sakran, L.H., Marrie, R.A., Blackburn, D.F., Knox, K.B., Evans, C.D., 2018. Establishing the incidence and prevalence of multiple sclerosis in Saskatchewan. Can. J. Neurol. Sci. 45 (3), 295–303.

Beck, R.W., Trobe, J.D., Moke, P.S., Gal, R.L., Xing, D., Bhatti, M.T., et al., 2003. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Arch. Ophthalmol. 121, 944–949.

Berger, J.R., Pocoski, J., Preblick, R., Boklage, S., 2013. Fatigue heralding multiple sclerosis. Multiple Sclerosis J. 19 (11), 1526–1532.

Bernstein, C.N., Blanchard, J.F., Rawsthorne, P., Wajda, A., 1999. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian Province: a population-based study. Am. J. Epidemiol. 149 (10), 916–924.

Cortese, M., Riise, T., Bjørnevik, K., Bhan, A., Farbu, E., Grytten, N., et al., 2016. Preclinical disease activity in multiple sclerosis: a prospective study on cognitive performance prior to first symptom. Ann. Neurol. 80 (4), 616–624.

Disanto, G., Zecca, C., MacLachlan, S., Sacco, R., Handunnetthi, L., Meier, U.C., et al., 2018. Prodromal symptoms of multiple sclerosis in primary care. Ann. Neurol. 83 (6), 1162–1173.

Doty, R.L., Bromley, S.M., Stern, M.B., 1995. "Olfactory testing as an aid in the diagnosis of parkinson's Disease: development of optimal discrimination criteria. Neurodegeneration 4 (1), 93–97.

Hertzmark E. and Spiegelman D. (2012). The SAS METAANAL macro.

Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.

Hitchon, C.A., Khan, S., Elias, B., Lix, L.M., Peschken, C.A., 2019. Prevalence and incidence of rheumatoid arthritis in canadian first nations and non-first nations People: a population-based study. J. Clin. Rheumatol.

Hoorbakht, H., Bagherkashi, F., 2012. Optic neuritis, its differential diagnosis and management. Open Ophthalmol. J. 6, 65–72.

Jennum, P., Frederiksen, J.L., Wanscher, B., Kjellberg, J., 2013. "The socioeconomic consequences of optic neuritis with and without multiple sclerosis: a controlled national study. Acta Neurol. Scand. 127 (4), 242–250.

Mankia, K., Emery, P., 2016. Review: preclinical rheumatoid Arthritis: progress toward prevention. Arthritis Rheumatol. 68 (4), 779–788.

Marrie, R.A., Ekuma, O., Wijnands, J.M.A., Kingwell, E., Zhu, F., Zhao, Y., et al., 2018. Identifying optic neuritis and transverse myelitis using administrative data. Mult. Scler. Relat. Disord. 25, 258–264.

Miller, D.H., Chard, D.T., Ciccarelli, O., 2012. "Clinically isolated syndromes. Lancet Neurol. 11 (2), 157–169.

National Institute of Allergy and Infectious Diseases (NIAID). (2015). "Strategy to prevent the onset of clinically-apparent rheumatoid arthritis (StopRA) NCT02603146." Retrieved December 19, 2018, fromhttps://clinicaltrials.gov/ct2/show/NCT02603146.

Pimentel, M., Chang, M., Chow, E.J., Tabibzadeh, S., Kirit-Kiriak, V., Targan, S.R., et al., 2000. Identification of a prodromal period in crohn's disease but not ulcerative colitis. Am. J. Gastroenterol. 95, 3458–3462.

Schulz, S.W., Shenin, M., Mehta, A., Kebede, A., Fluerant, M., Derk, C.T., 2012. "Initial presentation of acute transverse myelitis in systemic lupus erythematosus: demographics, diagnosis, management and comparison to idiopathic cases. Rheumatol. Int. 32 (9), 2623–2627.

Sinay, V., Perez Akly, M., Zanga, G., Ciardi, C., Racosta, J.M., 2015. "School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis. Multiple Sclerosis J. 21 (7), 945–952.

van Pelt, E.D., Mescheriakova, J.Y., Makhani, N., Ketelslegers, I.A., Neuteboom, R.F., Kundu, S., et al., 2013. Risk genes associated with pediatric-onset MS but not with monophasic acquired CNS demyelination. Neurology 81 (23), 1996–2001.

Watson, D.E., Heppner, P., Roos, N.P., Reid, R.J., Katz, A., 2005. "Population-based use of mental health services and patterns of delivery among family physicians, 1992 to 2001. Can. J. Psychiatry 50, 398–406.

WHO Collaborating Centre for Drug Statistics Methodology. (2011). "Anatomic therapeutic chemical classification system." Retrieved August 9, 2012, fromhttp://www.whocc.no/atc/structure_and_principles/.

Wijnands, J.M.A., Kingwell, E., Zhu, F., Zhao, Y., Hogg, T., Stadnyk, K., et al., 2017. Health-care use before a first demyelinating event suggestive of a multiple sclerosis prodrome: a matched cohort study. Lancet Neurol. 16 (6), 445–451.