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RESEARCH ARTICLE

Gastrointestinal conditions in the multiple sclerosis prodrome

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Abstract

Objective: To investigate gastrointestinal (GI)-related physician visits and drug dispensations in the 5 years preceding a first recorded demyelinating event or multiple sclerosis (MS) onset. **Methods**: Using linked administrative and clinical data from British Columbia (1996–2013), Canada, we identified an administrative cohort via a validated algorithm (n = 6863), a clinical cohort diagnosed at a MS clinic (n = 966), and matched controls (administrative cohort: n = 31,865; clinical cohort: n = 4534). In each cohort, the 5 years before a first demyelinating event or MS symptom onset (i.e., index date) were examined. We compared rates of GI-related physician visits and risk of ≥1 GI-related dispensation between MS cases and controls using negative binomial and robust Poisson models. Sex differences were tested using interaction terms. **Results**: The administrative cohort MS cases had higher rates of physician visits related to gastritis and duodenitis (adjusted rate/risk ratio (aRR):1.42, 95% CI: 1.10–1.83) and diseases of the esophagus (aRR: 1.46, 95% CI: 1.06–2.02) prior to the index date. MS cases also had greater risk of at least one dispensation for several drug classes, including constipation-related (aRR: 1.82, 95% CI: 1.50–2.22), antiemetics/antinauseants (aRR: 1.64, 95% CI: 1.43–1.89), and propulsives (promotility drugs; aRR: 1.62, 95% CI: 1.47–1.79). Men had a disproportionally higher relative risk for propulsives than women (aRR: men = 2.32, 95% CI: 1.79–3.00; women = 1.54, 95% CI: 1.36–1.72). Several findings were similar in the smaller clinical cohort though none reached statistical significance. **Interpretation**: GI-related physician visits and drug dispensations were more common in the 5 years before the first demyelinating event versus matched controls. GI symptoms are a measurable feature of the prodromal or early phase of MS, with a sex difference evident.

Introduction

Multiple sclerosis (MS) is a highly heterogeneous, chronic, immune-mediated disorder of the central nervous system. Current evidence suggests that MS has a prodromal phase consisting of nonspecific or nonclassical symptoms before the onset of characteristic MS symptoms.[1–7] As recent studies have implicated the gut microbiome as a potential player in MS development,[8,9] determining whether gastrointestinal (GI) symptoms are a prodromal feature of MS is of major interest. Better understanding of GI symptoms in the prodromal phase of MS may provide further insights into its pathogenesis and facilitate its earlier recognition and treatment,[6,10] but few such studies exist. One study of

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385 MS patients seeking health care for bowel symptoms in the United States, reported that 32% experienced bowel symptoms before MS onset, but interpretation of the findings is hampered by the lack of any formal analyses with a comparator group.[11] In a UK nested case–control study, MS cases were more likely to present with GI-related issues (e.g., 'gastric' or 'intestinal' symptoms) than general population controls up to 10 years before a first diagnostic code for MS or CIS, as recorded by the patient's general practitioner.[7] However, this study was restricted to the primary care setting.[5,7] Uncertainty remains as to whether GI symptoms constitute part of the MS prodrome. In this study, we used population-based data to investigate GI-related physician visits and drug dispensations in the 5 years preceding (i) the first diagnostic code (claim) for a demyelinating disease, as captured in health administrative data, and (ii) MS symptom onset, as recorded by the MS patients' specialist neurologists.

Methods

Data sources

We conducted a matched cohort study to investigate GI conditions in the MS prodrome.[4] Linked health administrative, pharmacy and clinical data were accessed in British Columbia (BC), the westernmost province of Canada that compromises approximately 13% of the Canadian population. Health administrative data consisted of demographics (sex, date of birth, and socioeconomic status [SES] quintiles, derived from the neighborhood-level income associated with each person's postal code), information on registration in BC's universal healthcare system (to determine residency in the province), as well as physician claims/visits, hospitalizations, and prescriptions filled.[12–16] Physician claims and hospital admission data included the dates and reasons for the health service use, recorded using the International Classification of Diseases (ICD)-9/10 diagnostic codes. Prescriptions filled in community and out-patient pharmacies were available as unique drug identification numbers, as assigned by Health Canada. These were mapped to the World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification system and reported as drug classes (3rd level).[17] We capitalized on an existing linked dataset; thus, these health administrative data were accessible from April 1991 through December 2013, with the prescription information available from January 1996. Clinical data were accessed for the MS cases who had visited an MS clinic in BC from April 1991 to December 2008 (including the date of MS symptom onset, as recorded by the patient's MS neurologist after a face-to-face clinic visit) and linked to health administrative data.

Study population

This study population comprised of a population-based health administrative cohort for the primary analysis, and a smaller, overlapping clinical MS cohort for the secondary analysis.[2–4] In the administrative cohort, MS cases were identified using a validated case definition requiring at least three MS-specific hospitalizations, physician visits or prescription-fills occurring ever, in any combination (Table S1).[18,19] In the clinical cohort, MS cases were required to have visited an MS clinic in BC and have a neurologist-confirmed MS diagnosis, using the prevalent diagnostic criteria at the time of diagnosis.[20] The index date for MS cases in the administrative cohort was the date of the first demyelinating disease-related diagnostic code (Table S1), and in the clinical cohort it was the date of MS symptom onset recorded by the MS specialist neurologist after evaluating a patient's prior medical history.

General population controls with no evidence of MS (i.e., no diagnostic codes for MS, other demyelinating diseases or prescriptions filled for an MS-specific drug) were randomly selected from the BC population. Up to five controls were matched to each MS case by age, sex, calendar-year, and geographical location. Controls were then assigned the same index date as their matched case. Both the MS cases and controls were required to be resident in BC for at least 90% of the days in each of the 5 years pre-index date through until the case's third MS-specific diagnostic code or prescription filled for the administrative cohort (i.e., the case finding algorithm was fulfilled), or the first visit to a MS clinic for the clinical cohort.

Outcomes

We assessed the number of physician visits per ICD subchapter (grouped according to the WHO's classification system structure), as well as two select GI conditions that have previously been assessed prior to MS onset in a non-comparative study,[11] constipation and irritable bowel syndrome. The ICD subchapters comprised individual or groups of 3-digit ICD codes, while the ICD codes for constipation and irritable bowel syndrome were 4 digits. In addition, we assessed prescription-fills per GI-related drug class (ATC third level), categorized as "yes/no," over the same periods.[2,7,11] All ICD codes and ATC drug classes are shown in Tables S2 and S3.

Statistical analysis

The characteristics of the MS cases and controls in the health administrative cohort were described at the index date. The rates of GI-related physician visits were compared between MS cases and controls using negative binomial models, and

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the risk of a GI-related prescription-fill (yes/no) was compared via Poisson regression models with robust error variances. Models were adjusted for sex, age, SES quintiles (reference category = lowest quintile), and calendar year (grouped as 1996–2000, 2001–2005, 2006–2008/2010, 2011–2013; reference category = 1996–2000), as measured at the index date. Sex-disaggregated analyses were conducted for the GI-related outcomes that were found to significantly differ between MS cases and controls. Interaction terms between disease status (MS or control) and sex were introduced separately and, models with and without the interaction term were compared using likelihood ratio tests with a significance level of 0.05. Models included offsets to account for any differences in the length of each individual's time spent resident in BC and the number of controls per case. Findings were reported as overall and sex-specific risk ratios (RR) and 95% confidence intervals (CIs). We repeated the analyses in the clinical cohort for those GI outcomes with sufficient data. Data were analyzed in R version 4.0.3.[21]

Results

Administrative cohort (primary analysis)

We identified 6863 MS cases and 31,865 matched controls in the administrative cohort (Table 1). Women accounted for 73% of the MS cases and controls. At the index date, the average age was 44 years and SES was evenly distributed across the quintiles.

Before a first demyelinating event, the most frequent GI-related conditions that prompted a physician visit among MS cases were gastritis and duodenitis (52.3 visits per 1000 person-years), followed by diseases of the esophagus (23.3 visits per 1000 person-years). Physician visits were 42% higher among the MS cases compared to controls for gastritis and duodenitis, and 46% higher for diseases of the esophagus. Visits classified as the ICD9/10 code for "other diseases of the intestines and peritoneum" were 74% higher among MS case (Fig. 1). Included in this were constipation and irritable bowel syndrome; both conditions were observed to have physician visit rates that were more than 200% greater among MS cases, though these estimates did not reach statistical significance. We did not identify statistically significant differences between MS cases and controls for any other GI condition, and the strengths of the observed associations did not significantly differ by sex (i.e., interaction terms were not significant; Figure S1).

For the drug classes (prescription fills), the highest risk of a dispensation among MS cases was observed for drugs treating peptic ulcer and gastroesophageal reflux disease (GORD), with 46 persons who filled a prescription per

Table 1. Characteristics of the multiple sclerosis (MS) cases and controls in the administrative and clinical cohorts at the respective index dates in British Columbia, Canada.

	Administrative cohort		Clinical cohort	
Characteristics	MS cases *N* = 6863	Controls[b] *N* = 31,865	MS cases *N* = 966	Controls[b] *N* = 4534
Women, *N* (%)	5039 (73.4)	23,311 (73.2)	728 (75.4)	3398 (74.9)
Age at index date, years, *N* (%)				
<30	859 (12.5)	4080 (12.8)	232 (24.0)	1082 (23.9)
30 to <50	3827 (55.8)	17,899 (56.2)	639 (66.1)	2992 (66.0)
≥ 50	2177 (31.7)	9886 (31.0)	95 (9.8)	460 (10.1)
Mean (SD)	44.4 (13.5)	44.2 (13.4)	37.0 (10.2)	36.9 (10.1)
Index year, *N* (%)				
1996–2000	2001 (29.2)	9216 (28.9)	589 (61.0)	2764 (61.0)
2001–2005	2149 (31.3)	9914 (31.1)	344 (35.6)	1618 (35.7)
2006–2008/2010[a]	2078 (30.3)	9736 (30.6)	33 (3.42)	152 (3.35)
2011–2013	635 (9.3)	2999 (9.4)		
SES at index date, *N* (%)				
1 (least affluent)	1184 (17.3)	5476 (17.2)	145 (15.0)	763 (16.8)
2	1286 (18.7)	5950 (18.7)	180 (18.6)	812 (17.9)
3	1413 (20.6)	6329 (19.9)	204 (21.1)	895 (19.7)
4	1465 (21.3)	6826 (21.4)	194 (20.1)	962 (21.2)
5 (most affluent)	1365 (19.9)	6591 (20.7)	210 (21.7)	952 (21.0)
Missing	150 (2.2)	693 (2.2)	33 (3.4)	150 (3.3)

The index date = first demyelinating disease-related diagnostic code (health administrative cohort) or MS symptom onset (clinical cohort). SES, socioeconomic status, based on each individual's neighborhood-level income.

[a]The index year category was 2006–2008 for the clinical cohort and 2006–2010 for the administrative cohort.

[b]Five controls matching on sex, birth year and postal code were not available for each MS case. Therefore, some MS cases were matched to fewer than 5 controls.

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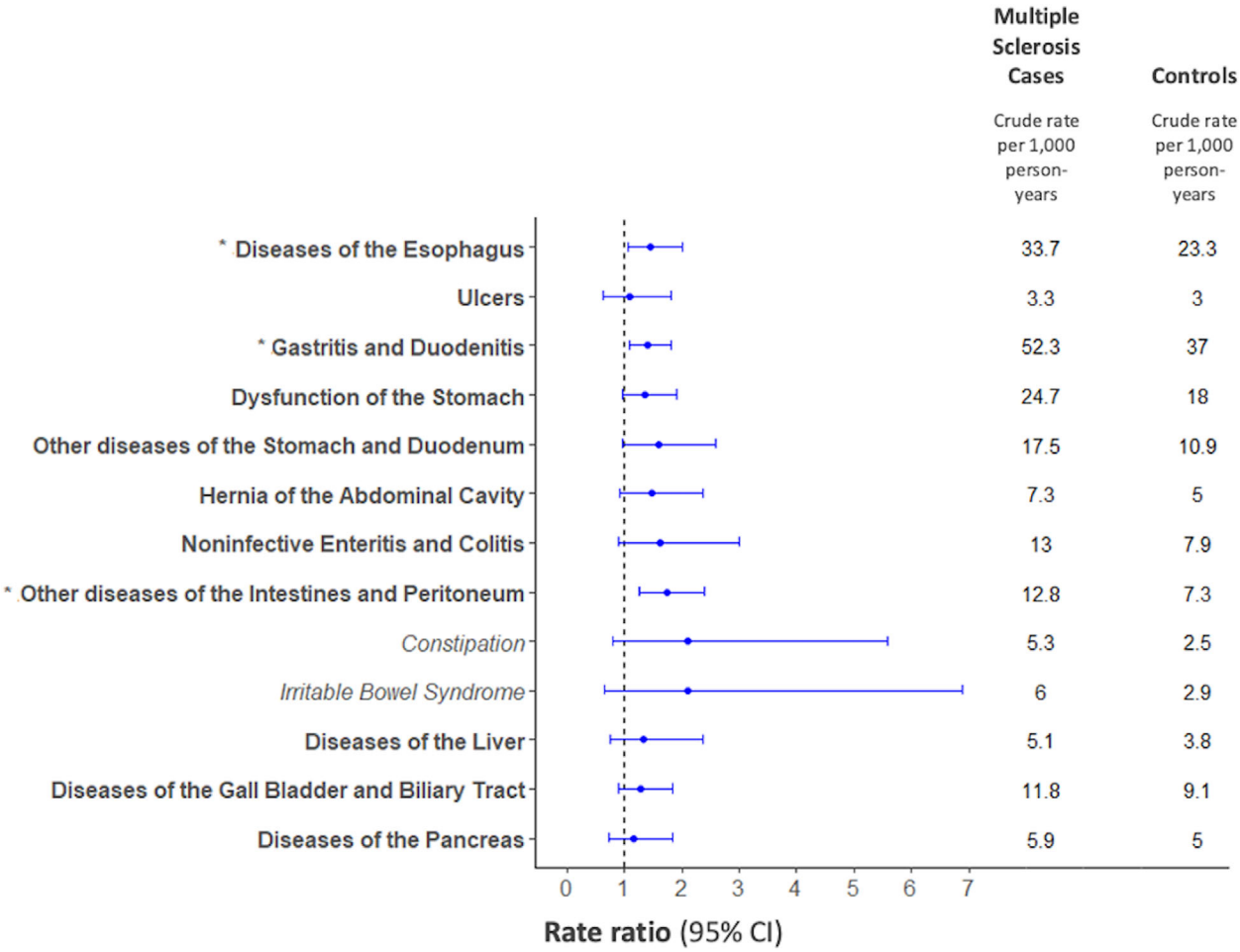

Figure 1. Multiple sclerosis (MS) cases versus controls in the administrative cohort: number of gastrointestinal-related physician visits in the five years before a first demyelinating disease-related diagnostic code ('MS onset'). The ICD subchapters are ordered according to the original structure of the coding system, corresponding to the order shown in Table S2. Italicized text is used for constipation, and irritable bowel syndrome as they are conditions that are also included under "other" diseases of the intestines and peritoneum. Crude rate is the number of physician visits per 1000 person-years. $*P < 0.05$ indicates that the rates between the MS cases and controls were statistically different. A rate ratio greater than 1 indicates that the visit rate was greater among MS cases, and a rate ratio less than 1 indicates that the visit rate was greater among controls. All rate ratios were adjusted for sex, age, SES quintiles and year (grouped as 1996–2000, 2001–2005, 2006–2010, 2011–2013), as measured at the index date. CI, confidence interval.

1000 person-years, representing a 35% greater risk than that of controls (Fig. 2). Elevated risks for MS cases, ranging from 55% to 103% higher than that of controls, were also seen for antacids, drugs for functional gastrointestinal disorders (e.g., serotonin receptor antagonists), antispasmodics, propulsives (i.e., promotility agents), antiemetics and antinauseants, drugs for constipation, intestinal anti-infectives, intestinal anti-inflammatory agents, anti-obesity preparations, and digestives.

Among men, MS cases had a 132% higher risk for promotility drugs than controls. This was disproportionately higher than the 54% elevated risk observed among women ($P_{\text{interaction}} = 0.0049$, Figure S2). No other sex differences reached significance for the GI-related prescription fills (all $P > 0.05$).

Clinical cohort (secondary analysis)

The clinical cohort comprised 966 MS cases and 4534 controls. Similar to the administrative cohort, about three-quarters were women (Table 1). However, MS cases had a mean age of 37 years at their index date, and were 7 years younger than their counterparts in the administrative cohort.

Before MS symptom onset, the most frequent reason (diagnostic claim) for a GI-related physician visit among

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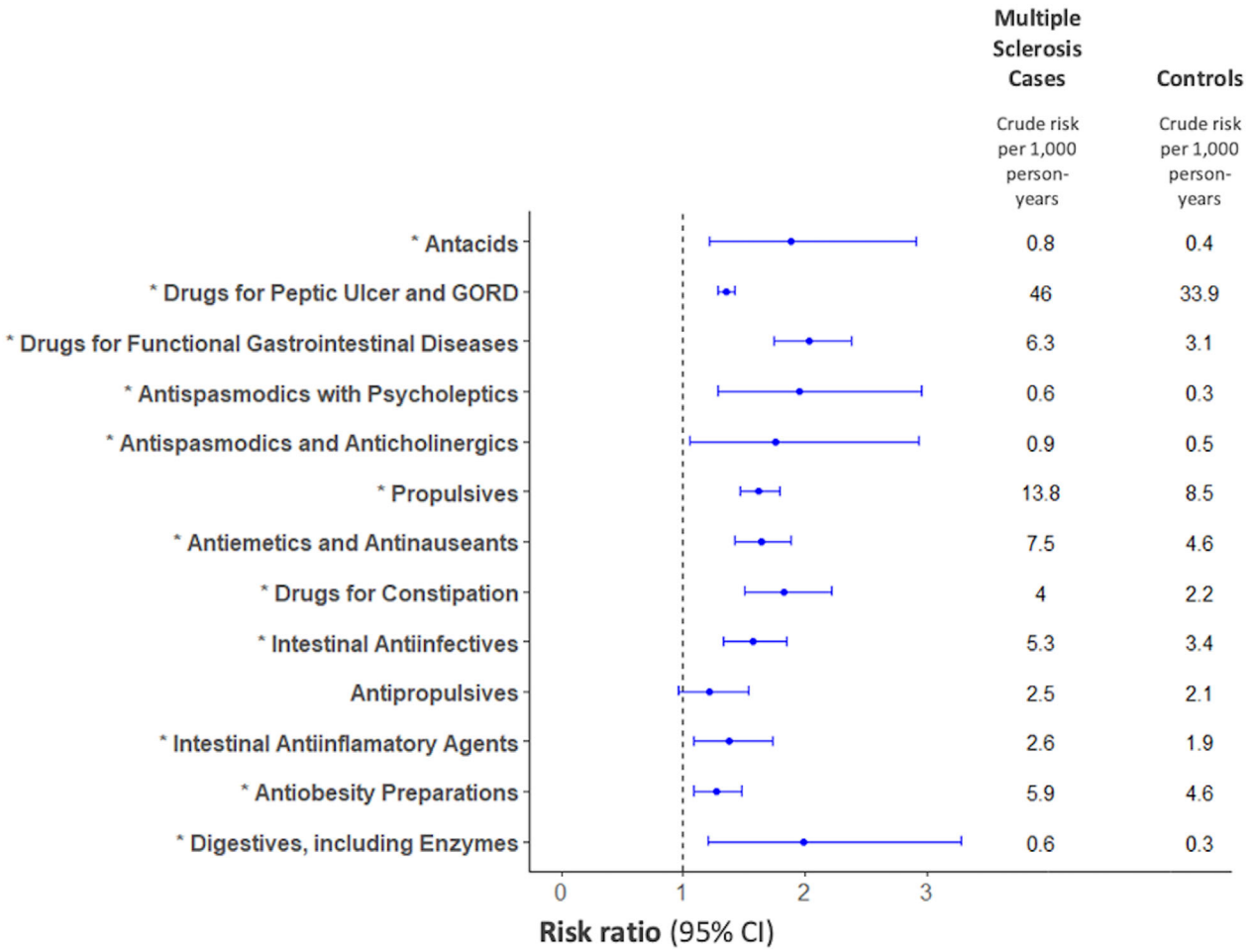

Figure 2. Multiple sclerosis (MS) cases versus controls in the administrative cohort: at least one (or more) prescription fills for a gastrointestinal-related medication (shown as drug classes‡) in the five years before a first demyelinating disease-related diagnostic code. ‡ The gastrointestinal-related drug classes are ordered and grouped according to Level 3 of the Anatomic Therapeutic Chemical Classification (Table S3). Crude risk is the number of persons that filled at least one prescription per 1000 person-years. *$P < 0.05$ indicates that the rates between the MS cases and controls were statistically different. A rate ratio greater than 1 indicates that the visit rate was greater among MS cases, and a rate ratio less than 1 indicates that the visit rate was greater among controls. All rate ratios were adjusted for sex, age, SES quintiles and year (grouped as 1996–2000, 2001–2005, 2006–2010, 2011–2013), as measured at the index date. GORD, gastroesophageal reflux disease; CI, confidence interval.

MS cases was gastritis and duodenitis (26.1 visits per 1000 person-years), and the most common drug class dispensed was peptic ulcer and GORD drugs (124.7 prescription fills per 1000 person-years; Figures S3 and S4). None of the GI-related conditions and drug classes examined differed significantly between the MS cases and controls therefore sex differences were not examined. However, the magnitudes of associations were similar to those observed in the administrative cohort for some GI-related outcomes. For example, rate ratios were 1.5 or higher for physician visits related to "other" diseases of the intestines and peritoneum (aRR: 1.71, 95% CI: 0.65–4.49) and diseases of the esophagus (aRR: 1.64, 95% CI: 0.47–5.73). The corresponding confidence intervals were wide, reflecting the low counts.

Discussion

In this population-based study, we found that GI-related physician visits and prescription fills were elevated in the 5 years preceding the first demyelinating disease claim among people with MS. Specifically, compared to the matched population, MS cases had more frequent physician visits for diseases of the esophagus, gastritis and duodenitis, and "other" diseases of the intestines and peritoneum (including constipation and irritable bowel syndrome). Elevated risk of a dispensation among MS cases were also observed for several GI-related drugs, including drugs to treat constipation, antiemetics and antinauseants, antiobesity preparations, antispasmodics,

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and promotility drugs. A sex difference was evident in that men with MS had a disproportionately higher risk of a prescription fill for a promotility agent than women. Our study demonstrates that gut-related issues may be an early feature of MS, pre-dating clinical recognition of MS and should be considered as a prodromal feature of MS.

As expected, MS cases were on average older at the administrative index date (the first demyelinating disease claim) than the clinical index date (MS symptom onset). This is in part due to the date of MS symptom onset being recorded retrospectively by the MS neurologist with the benefits of hindsight and the patients prior medical history. This contrasts with the administrative data and the demyelinating disease-related claim which was captured prospectively as the patient moved through the health system. Also, and as an example, less specific symptoms, such as sensitivity disturbances, that were not recognized or recorded by the care provider as potentially related to CNS demyelination, would not have contributed to the administrative index date (the first demyelinating disease claim).

Prior research assessing GI-related health use before MS onset, or a first demyelinating event, or diagnosis has been limited. Consistent with our findings, a nested case–control study in the United Kingdom found the odds of presenting with intestinal symptoms, including diarrhea, flatulence, and constipation, to a primary care general practitioner (GP) were 132%, 80%, and 41% higher among MS cases in the 0- to 2-, 2- to 5-, and 5- to 10-year periods before a first recorded diagnostic code for MS than among general population controls.[7] These MS cases were also observed to have 1.5–2.3 times the odds of gastric symptoms, including nausea and vomiting, versus controls, up to 10 years before MS diagnosis. In that study authors were only able to consider visits to GPs and were also not able to access prescription information. As the diagnostic coding structure used (Read codes) is also specific to UK GP's, direct comparability with our study is somewhat limited. A US-based retrospective study of 385 MS patients with at least one bowel-related outpatient visit found that 32% had this visit before a first demyelinating event.[11] Of these patients, 50% had constipation as the first bowel-related symptom, almost 30% had diarrhea and 17% had irritable bowel syndrome (IBS). Similarly, our study found constipation and IBS were common before a first demyelinating event. Authors of a Polish case–control study used national health claims data to assess the period before the date of the first MS-specific claim (i.e., MS diagnosis), though not the earlier date of MS onset.[22] They found that rates of health claims for any disease related to the digestive system were 11% higher among their 815 MS cases than 952,434 matched controls in the 7 years before MS diagnosis.[22] The authors were unable to look at individual GI conditions (or related medications) and it remains unclear how much of the 7-year period overlapped with the pre-MS onset/prodromal phase. Contrary to our results, the Polish study found females with MS had a greater risk for digestive system diseases than females without MS before MS diagnosis, while no difference was detected for males.[22] Few other studies have examined sex differences. In our current study, a significantly higher relative risk among men was only observed for promotility drugs. No further sex differences reached statistical significance. Our findings may reflect sex differences in the underlying MS pathology occurring even before a first demyelinating event.

Gut-related issues are known to pre-date other neurological conditions, particularly Parkinson's disease (PD). Constipation can occur 5–10 years before classical motor-onset PD[23] and is well-recognized as a prodromal feature of PD.[24] Combined with other observations, this has led to the suggestion of a gut origin and involvement of the gut microbiota for at least some portion of persons with PD.[25] Although our study did not directly examine the role of the gut microbiota in MS pathophysiology during the prodromal period, dysregulation of the gut–brain axis is one potential hypothesis for our findings.[26] Studies accessing health administrative and primary care data have suggested that the prodromal phase of MS lasts up to 5–10 years preceding MS onset.[2–4,7] For example, over this time period, studies found that MS cases had higher rates of health service use for issues such as anxiety, depression, fatigue, pain, fibromyalgia, headache, migraine, and sleep disorders.[2,3,7] Some of our results may be driven by unrecognized underlying MS pathology (i.e., demyelination) manifesting prior to onset of classical MS symptoms. For example, swallowing difficulties (dysphagia) due to cranial nerve damage are common in the MS population after diagnosis,[27] and may account for the observed increase in disorders of the esophagus before MS onset. Reduced gastrointestinal motility, including delayed gastric and colonic transit due to dysfunction in the autonomic nervous system that is present in MS[28,29] would also concur with our finding of increased dispensations for antacids, digestives and promotility drugs among cases before MS onset. Antispasmodics, a common treatment for MS spasticity stemming from damage of the upper motor neurons of the corticospinal tract,[30] were also filled more often by MS cases in our study. Our study is one of the first to demonstrate that such features occur before a first demyelinating event. Some of the GI symptoms and drugs used to treat them may be a consequence of autonomic nervous system abnormalities.[31] While not directly linked to GI symptoms, studies have shown that autonomic nervous system-related abnormalities, such as orthostatic intolerance and urogenital symptoms, can be

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present before MS onset.[2,7,32,33] Interestingly, we found prescriptions for anti-obesity preparations were more common before a first demyelinating event, consistent with evidence that obesity is a risk factor for MS onset.[34] However, other findings were less expected, such as higher rates of physician visits for gastritis and duodenitis, and prescription fills for peptic ulcer drugs.[35] However, a previous study accessing our same health administrative cohort found higher rates of prescriptions for musculoskeletal drugs among people who went on to develop MS than general population controls,[2] and these included nonsteroidal anti-inflammatory drugs (NSAIDs) which are known to increase the risk of gastritis.[36] As well, autoimmune atrophic gastritis has also been linked to several autoimmune conditions, including thyroiditis and Type 1 diabetes,[37] although its relationship with MS is less understood. Further work is required to investigate the potentially intriguing relationships between MS and these GI conditions. For example, future studies could interrogate the timing and inter-relationships between pain, NSAID use, and GI symptoms in the prodromal period. Finally, given that the effect estimates were attenuated in the clinical cohort, it is also possible that GI symptoms manifest early after clinically recognized onset of MS symptoms for some, rather than during the prodromal period.

Our study had several strengths. This was a population-based study that used a matched design to account for confounding by age, sex, calendar year, and geographic variation. The use of prospectively collected health administrative data minimized the influence of recall bias. The clinical cohort enabled capture of the date of symptom onset, as recorded retrospectively by the MS neurologist which arguably enables a truer assessment of the prodromal period. There were some study limitations. None of the findings reached statistical significance in this smaller cohort; the modest sample size may have limited our ability to detect differences between MS cases and controls. However, the direction and magnitude of the estimates in the clinical cohort for some of the GI-related outcomes were similar to those of the administrative cohort. We were underpowered to evaluate yearly differences in the GI-related outcomes. We recommend future studies employ a larger cohort of MS cases to detect trends over the pre-index period. We were unable to adjust for potential confounders, such as relevant (co)morbidities before the study period, as we could only access health administrative data over the 5 years pre-index date. We also could not adjust for lifestyle variables that were not available in the data, such as smoking status. We did not have access to information on the use of over-the-counter GI medications, and only required one occurrence of a single ICD or drug code to identify the respective GI condition or drug class. However, validated algorithms were not available for most of the GI outcomes. Also, given that most ICD codes in physician claims data are reported to the third digit, visits for constipation and irritable bowel syndrome were likely under-reported, possibly reducing precision and biasing our results towards the null. We did not evaluate the inter-relationships between GI-related conditions and other prodromal symptoms such as psychiatric disorders. However, in the general population, GI-related conditions such as irritable bowel syndrome are associated with several psychiatric conditions, including generalized anxiety disorder and major depressive disorder.[38,39] Further studies are required to interrogate these interrelationships in the MS prodrome. Finally, due to limited data availability, we only accessed data through 2013.

To conclude, GI-related physician visits and drug dispensations were more common than expected in the MS population 5 years before a first demyelinating event. GI symptoms appear to be an early feature of MS and may form part of the prodromal phase.

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Author Contributions

Conception and design of the study: F.Y., H.T. Acquisition and analysis of data: F.Y., F.Z., C.E., J.D.F., Y.Z., R.A.M., H.T. Drafting a significant portion of the manuscript or figures: F.Y., F.Z., C.E., J.D.F., Y.Z., R.A.M., H.T.

Potential Conflicts of Interest

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Multiple sclerosis-specific and demyelinating disease related International Classification of Diseases-9/10 (ICD-9/10) codes and Drug Identification Numbers used to identify people with MS and their respective index date (i.e., first recorded demyelinating event).
Table S2. Gastrointestinal conditions as coded in the International Classification of Diseases (ICD)-9 Classification system.
Table S3. Gastrointestinal drug classes in the Anatomical Therapeutic Chemical Classification System, 3rd level.
Figure S1. Multiple sclerosis (MS) cases versus controls in the administrative cohort: sex-specific rate ratios for gastrointestinal-related physician visits in the 5 years before a first demyelinating disease-related diagnostic code.
Figure S2. Multiple sclerosis (MS) cases versus controls in the administrative cohort: sex-specific rate ratios for at least one gastrointestinal-related prescription dispensations in the 5 years before a first demyelinating disease-related diagnostic code.
Figure S3. Multiple sclerosis (MS) cases versus controls in the clinical cohort: number of gastrointestinal-related physician visits in the 5 years before MS symptom onset.
Figure S4. Multiple sclerosis (MS) cases versus controls in the clinical cohort: at least one (or more) prescription fills for a gastrointestinal-related medication (shown as drug classes‡) in the 5 years before MS symptom onset.

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