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RESEARCH ARTICLE

Multiple sclerosis and inflammatory bowel disease: A systematic review and meta-analysis

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Abstract

Background: Multiple sclerosis (MS) and inflammatory bowel disease (IBD) are two autoimmune diseases that seriously affect patients' quality of life. Previous studies have established an association between MS and IBD, including Crohn's disease (CD) and ulcerative colitis (UC), but the results were inconsistent. The aim of this study was to quantify the prevalences of and the association between MS and IBD. **Methods**: The PubMed, Web of Science, and Embase databases were searched through November 2020 for studies reporting data on MS among patients with IBD and vice versa. The main outcomes were the proportion of MS in patients with IBD and vice versa, as well as the association (risk ratio [RR]) of IBD in MS and that of MS in IBD. **Results**: Based on the analysis of 17 studies, the prevalence of MS in patients with IBD was 0.2% (95% CI 0.1–0.4%), while the prevalence of IBD in patients with MS was 0.6% (95% CI 0.4–0.9%). Patients with MS had a higher prevalence of IBD than controls (RR = 1.53, 95% CI 1.38–1.70, $p < 0.00001$). There was a similarly high risk of developing CD (RR 1.41, 95% CI 1.14–1.74, $p = 0.001$) or UC (RR 1.42, 95% CI 1.17–1.71, $p = 0.0003$) in patients with MS (p for subgroup differences: 0.97). Patients with IBD had a higher prevalence of MS than controls (RR = 1.91, 95% CI 1.06–3.45, $p = 0.03$). **Conclusions**: Clinicians should be aware of the increased risk of IBD or MS comorbidity during the diagnostic process. Systematic diagnosis and management at an earlier stage are suggested.

Introduction

Multiple sclerosis (MS) is the most prevalent inflammatory disease of the central nervous system (CNS), and it affects approximately 2.3 million people in the world.[1] It leads to impaired ambulation, loss of bladder control, and slowed cognitive processing. Genetic and pathological studies indicate that the adaptive immune system, composed of T and B cells, plays a key role in the pathogenesis of disease.[2] Inflammatory bowel disease (IBD) is a common chronic inflammatory disease of the gastrointestinal tract that contains both Crohn's disease (CD) and ulcerative colitis (UC).[3] The prevalence of IBD is on the rise, reaching approximately 0.3–0.5% in Western countries.[4]

Some case–control studies have found a relationship between MS and IBD.[5,6] MS was found to have a higher prevalence among IBD patients, and the prevalence of IBD among MS patients is also higher than that in the general population.[7] An association between MS and IBD has been suggested due to their common epidemiological and immunological

patterns.[8] Although the risk for MS or IBD comorbidity is increasingly being recognized, few specialized studies have focused on the association between MS and IBD. Kosmidou et al[8] reported an increased risk of MS and IBD comorbidity, but their study did not show the pooled prevalence. The prevalence of MS among IBD patients and the prevalence of IBD among MS patients are still unknown. Therefore, we conducted a systematic review and meta-analysis to quantify the association between IBD and MS.

Materials and Methods

Search strategy and studies selection

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9] Jian Wan and Xuan Wang designed the search strategy. Both Kaichun Wu and Fang Yang approved the final search strategy. Jian Wan and Xuan Wang independently searched the PubMed, Embase, and Web of Science databases for literature published up to November 9, 2020. The following search terms were used: "(Multiple Sclerosis) AND (inflammatory bowel disease OR Crohn Disease OR Crohns Disease OR Crohn's Disease OR ulcerative colitis)". Studies meeting all the following criteria were included: (a) reported data on MS among patients with IBD or vice versa; and (b) original studies, written in English, and available in full-text. The exclusion criteria were as follows: (a) research data were missing; (b) duplicate data or paper; (c) case report, letters, editorials, reviews, and meta-analyses not presenting original data; and (d) abstracts from conferences and commentary articles. We also reviewed the references of the included articles to guarantee the comprehensiveness and accuracy of our research. If different publications presented data from the same population, the newest or most comprehensive study was included.

Data extraction

After performing the literature search independently, the two investigators (Xuan Wang and Jian Wan) used EndNote X 9.0 software to exclude duplicate records. After independently screening the titles and abstracts of the articles, the two authors (Xuan Wang and Jian Wan) reviewed the full texts to select potentially eligible studies and then used predesigned standard forms to extract data from the eligible studies. The following data were extracted: the names of the authors, published year, country, study period, number of patients with IBD, including CD and UC, number of patients with MS, and number of controls. Any disagreements were resolved by discussion with the third reviewer (Kaichun Wu).

Quality assessment

The 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) for cross-sectional/prevalence study quality[10] was used when we assessed the quality of each included study. The AHRQ checklist consists of 11 items, with classifications of 'yes', 'no', or "unclear'. Article quality was assessed as follows: low quality (0–3 items with a 'yes' response), moderate quality (4–7 items with a 'yes' response), and high quality (8–11 items with a 'yes' response). Xuan Wang and Jian Wan assessed the quality of each included study independently. Disagreements were resolved by discussion with the third researcher (Kaichun Wu).

Statistical analysis

The data on all outcomes of interest were analyzed using Review Manager version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software version 12.0 (Stata Corporation, College Station, TX). Heterogeneity among studies was tested using the Cochran chi-square test and I^2. We used a random effects model when heterogeneity among the studies was high (heterogeneity $p < 0.10$ or $I^2 > 50\%$). A fixed effects model was used when heterogeneity among the studies was low (heterogeneity $p \geq 0.10$ or $I^2 \leq 50\%$). Data are presented as risk ratios (RRs) and 95% confidence intervals (CIs) using forest plots. The statistical significance level was set at $p \leq 0.05$. Statistical heterogeneity was set at $p < 0.10$ for the Q test and $I^2 > 50\%$ for the I^2 value.[11]

Results

Based on the search strategy, a total of 6278 studies (3970 from Embase, 1361 from PubMed, 947 from Web of Science) were obtained from the databases. After deleting duplicate records and screening the abstracts and titles, 70 articles were selected for full-text assessment. Ultimately, 17 studies[6,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27] were included in the meta-analysis. A flow diagram of the search results and study selection process is shown in Figure 1. The main characteristics and quality assessment of the included studies are shown in Table 1. Among the 17 studies included in our meta-analysis, 11 studies were of high quality, and 6 studies were of moderate quality.

Prevalence of MS in patients with IBD

The pooled results of 5 studies[6,15,20,22,27] (125,687 IBD patients) showed that the prevalence of MS in patients with IBD was 0.2% (95% CI 0.1–0.4%, $I^2 = 98.6\%$, heterogeneity $p < 0.001$) (Table 2). Sensitivity analysis revealed that after

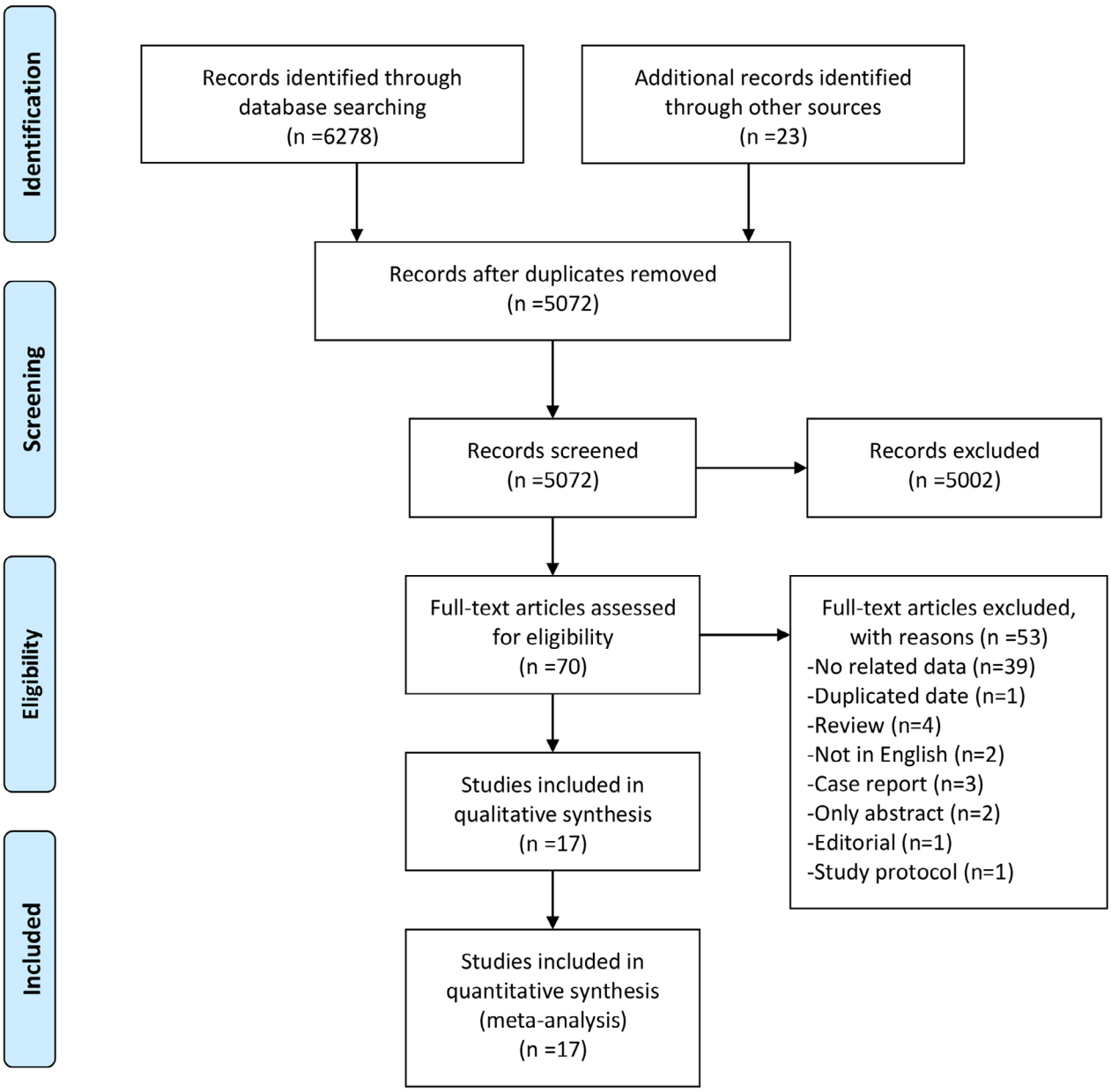

Figure 1. Flow diagram of the search results and study selection.

excluding two moderate-quality studies, the prevalence of MS in patients with IBD was 0.3% (95% CI −0.1% to 0.6%, I^2 = 95.8%, heterogeneity $p < 0.001$), which was similar to the primary estimate. Since only two studies reported the prevalence of MS in patients with UC or CD,[15,27] no meta-analysis was conducted.

Prevalence of IBD in patients with MS

Overall, 12 studies[12,13,14,16,17,18,19,21,23,24,25,26] reported data on the prevalence of IBD in 96,478 patients with MS. The pooled prevalence of IBD in patients with MS was 0.6% (95% CI 0.4–0.9%, I^2 = 96%, heterogeneity $p < 0.001$) (Table 2). After excluding four moderate-quality studies, the prevalence of IBD in patients with MS was 0.7% (95% CI 0.4–1.0%, I^2 = 91.9%, heterogeneity $p < 0.001$), which was similar to the primary estimate. Three studies[13,14,17] reported the prevalence of UC in 25,965 MS patients, resulting in a pooled prevalence of 0.4% (95% CI 0.1–0.8%, I^2 = 91.7%, heterogeneity $p < 0.001$) (Table 2). Four studies[13,14,17,19] reported the prevalence of CD in 26,176 MS patients, resulting in a pooled

Table 1. Characteristics of included studies.

Author, year	Country	Study period	Primary disease (*n*)	Female (*n*, %)	Age (mean)	Concomitant disease (*n*)	Controls (*n*)	Concomitant disease (*n*)	Quality score
Kimura, 2000[6]	USA	1950–1995	IBD (474)	232 (48.9)	NA	MS (4)	NA	NA	8
Weng, 2007[15]	USA	1996–2005	IBD (12,601) UC (7525) CD (4021) Unspecified (1055)	6216 (52.5)	43	MS (49) MS (28) MS (16) MS (5)	50,404	MS (74)	9
Nyboe Anderson, 2015[20]	Denmark	1999–2012	IBD (20,933)	NA	NA	MS (7)	NA	NA	7
Card, 2016[22]	UK	1987–2011	IBD (56,097)	29,814 (53.1)	47.2	MS (265)	280,382	MS (913)	7
Park, 2019[27]	South Korea	2012–2013	IBD (35,581) UC (23,737) CD (11,803)	13,663 (38.4)	41.7 ± 16.4	MS (6) MS (3) MS (3)	142,324	MS (NA)	9
Tremlett, 2002[12]	UK	1995–1999	MS (320)	211 (65.9)	46.7 (range 17–84)	IBD (5)	320	IBD (0)	7
Edwards, 2004[13]	UK	2002–2003	MS (658)	454 (69.0)	45 (range 18–80)	UC (5) CD (2) IBD (8)	136,000	UC (330) CD (196) IBD (526)	8
Ramagopalan, 2007[14]	Canada	1993–2004	MS (5031)	3634 (72.2)	55.2 ± 12.6	UC (9) CD (11)	2707	UC (4) CD (4)	9
Langer-Gould, 2010[16]	USA	1994–2004	MS (5296)	3972 (75.0)	54.5 ± 13.7	IBD (42)	26,478	IBD (120)	8
Roshanisefat, 2012[17]	Sweden	1964–2005	MS (20,276)	13,218 (65.2)	35.1	UC (113) CD (93) IBD (206)	203,951	UC (819) CD (669) IBD (1488)	8
Fromont, 2013[18]	France	1995–2004	MS (22,087)	NA	NA	IBD (23)	NA	NA	7
Farez, 2014[19]	Argentina	NA	MS (211)	163 (77.3)	40.4 ± 10	CD (1)	211	CD (1)	6
Deretzi, 2015[21]	Greek	2000–2011	MS (2140)	1450 (67.8)	33.7 ± 10.2*	IBD (9)	1580	IBD (9)	8
Marrie, 2016[23]	Canada	1990–2011	MS (23,382)	16,803 (71.9)	44.0 ± 14.1	IBD (131)	116,638	IBD (390)	7
Marrie 2, 2016[24]	Canada	1994–2011	MS (9624)	6635 (68.9)	42.9 ± 13.3	IBD (30)	41,194	IBD (75)	9
Abbasi, 2017[25]	Iran	2013–2014	MS (660)	558 (84.5)	Median 37	IBD (5)	421	IBD (1)	9
Wijnands, 2018[26]	Canada	1996–2013	MS (6793)	4999 (73.6)	45.4 ± 13.3	IBD (72)	NA	NA	8

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; MS, multiple sclerosis; NA, not available.
*Age at diagnosis.

prevalence of 0.3% (95% CI 0.2–0.5%, $I^2 = 66.3\%$, heterogeneity $p = 0.031$) (Table 2). After excluding one moderate-quality study, the prevalence of CD in patients with MS was 0.3% (95% CI 0.1–0.5%, $I^2 = 77.4\%$, heterogeneity $p = 0.012$), which was similar to the primary estimate.

Association between MS and IBD

Ten studies[12,13,14,16,17,19,21,23,24,25] reported the prevalence of IBD in patients with MS and controls. Compared to controls, those with MS had a higher prevalence of IBD (RR = 1.53, 95% CI 1.38–1.70, $p < 0.00001$, $I^2 = 26\%$, heterogeneity $p = 0.20$) (Fig. 2). After excluding three moderate-quality studies, the RR was 1.47 (95% CI 1.30–1.66, $p < 0.00001$, $I^2 = 35\%$, heterogeneity $p = 0.16$), which was similar to the primary estimate. The RRs for UC and CD in patients with MS were 1.42 (95% CI 1.17–1.71, $p = 0.0003$, $I^2 = 38\%$, heterogeneity $p = 0.20$, 3 studies[13,14,17]) and 1.41 (95% CI 1.14–1.74, $p = 0.001$, $I^2 = 0\%$, heterogeneity $p = 0.94$, 4 studies[13,14,17,19]), respectively (Fig. 3). After excluding one moderate-quality study, compared to the controls, those with MS had a higher prevalence of CD (RR = 1.41, 95% CI 1.14–1.74, $p = 0.001$, $I^2 = 0\%$, heterogeneity $p = 0.85$), which was the same as the primary estimate. No difference was found in the prevalence of CD or UC in patients with MS (p for subgroup differences: 0.97) (Fig. 3).

Table 2. Results of meta-analysis (random effects model).

Characteristics	Studies	Patients	Events	I^2 %	Heterogeneity *p*	Pooled prevalence (%)	95% CI (%)
Prevalence of MS in IBD patients	5	125,687	331	98.6	<0.001	0.2	0.1–0.4
Prevalence of IBD in MS patients	12	96,478	552	96	<0.001	0.6	0.4–0.9
Prevalence of UC in MS patients	3	25,965	127	91.7	<0.001	0.4	0.1–0.8
Prevalence of CD in MS patients	4	26,176	107	66.3	0.031	0.3	0.2–0.5

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; MS, multiple sclerosis.

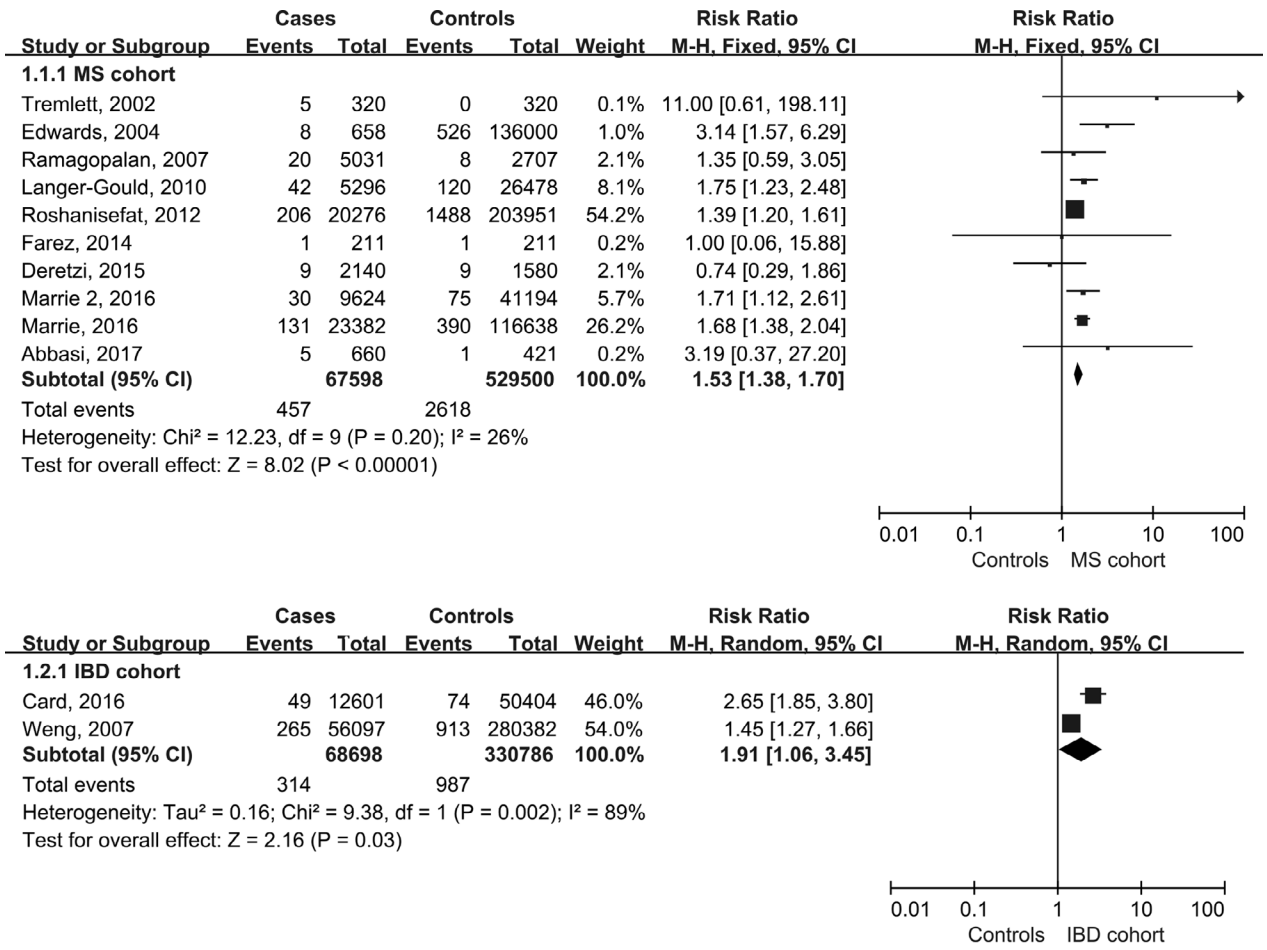

Figure 2. Analysis of the prevalence of multiple sclerosis in patients with IBD compared to controls, and vice versa. IBD, inflammatory bowel disease; MS, multiple sclerosis.

Two studies[15,22] reported the prevalence of MS in patients and controls. Compared to controls, those with IBD had a higher prevalence of MS (RR = 1.91, 95% CI 1.06–3.45, $p = 0.03$, $I^2 = 89\%$, heterogeneity $p = 0.002$) (Fig. 2).

Publication bias

No publication bias was found in the prevalence of MS in patients with IBD (Begg's test $p = 0.806$, Egger's test $p = 0.941$) or the prevalence of IBD in patients with MS (Begg's test $p = 0.436$, Egger's test $p = 0.196$).

Discussion

In this meta-analysis, we showed an association between MS and IBD, with the pooled prevalence of MS in patients with IBD being 0.2% and the prevalence of IBD in patients with MS being 0.6%. There was a similarly high risk of developing CD or UC among patients with

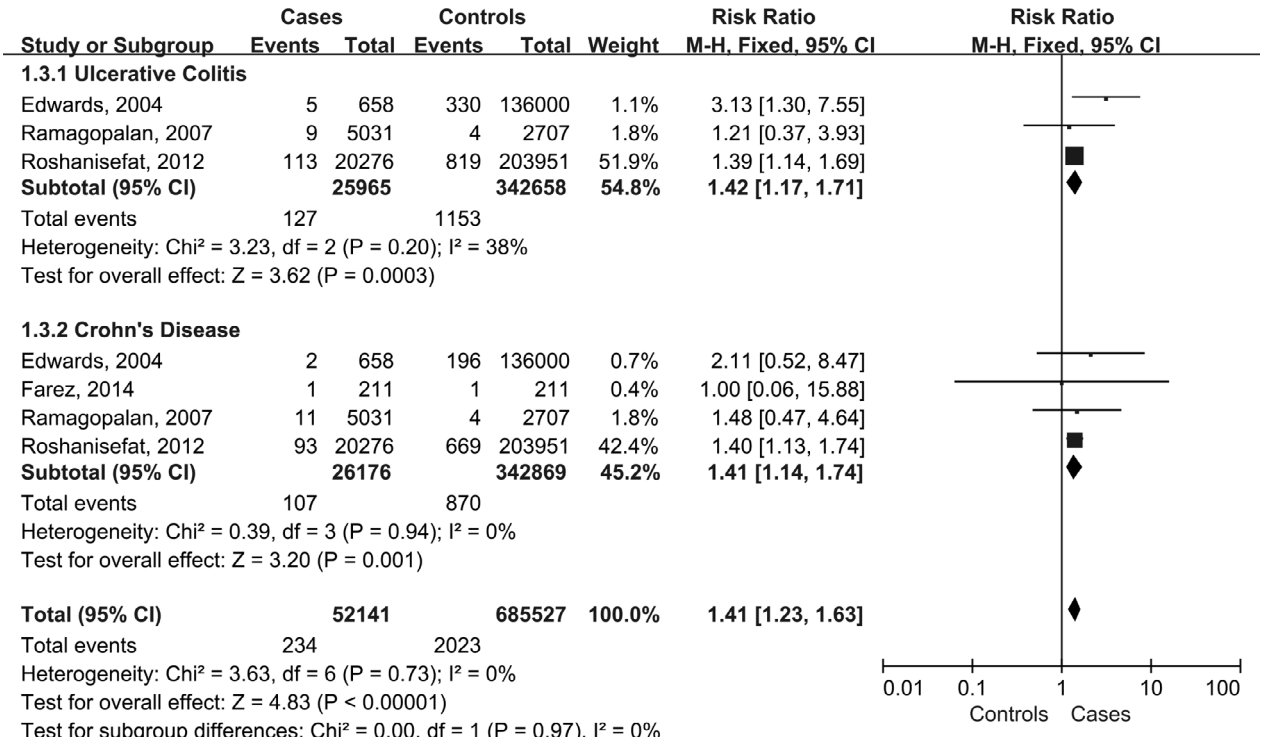

Figure 3. Subgroup analysis on the prevalence of Crohn's disease or ulcerative colitis in patients with multiple sclerosis compared to controls.

MS. This outcome emphasizes the risk of MS or IBD comorbidity. Systematic diagnosis and management at an earlier stage are suggested.

In our study, we showed that MS patients had an increased risk of IBD and vice versa. This association might be due to similar environmental risk factors for these diseases, including smoking, higher socioeconomic status, vitamin D deficiency, and cold climate.[28] In addition, consistent genetic relationships that existed between MS and IBD were also described. Yang et al identified three single-nucleotide polymorphisms shared between MS and IBD (rs13428812), UC (rs116555563) and CD (rs13428812, rs9977672).[29] Brain–gut interactions are another factor that cannot be ignored. Lange and Shiner performed jejunal biopsies in 12 patients with MS and found subtle histological changes, such as some cases of intestinal inflammatory cell infiltration and two cases of villous atrophy.[30] Inflammation plays an essential role in the pathophysiology of IBD and causes increased permeability of the intestinal barrier.[30] Experimental autoimmune encephalomyelitis (EAE) is a widely accepted animal model of MS. Secher et al found that the degree of intestinal permeability disturbance is closely associated with EAE severity.[31] The transmucosal passage of injurious or immunogenic antigens increases when intestinal permeability is altered, which modulates or perpetuates neuroimmune dysregulation.[30] The gut microenvironment was found to have the ability to modulate the activation and differentiation of autoreactive T cells and guide them to the CNS.[37]

In the pathogenesis of IBD, the intestinal mucosal barrier is damaged and breaches, and the luminal microflora initiates a sustained and uninhibited inflammatory response.[35,36] Interestingly, microbiome alterations have also been observed in EAE.[32] The microbiome makes a significant contribution to maintaining intestinal barrier homeostasis, which is thought to be central in accounting for its regulation of neuroinflammation.[30] Previous studies showed that the microbiome regulates the shift back-and-forth of immune cells from pro- to anti-inflammatory phenotypes in germ-free mice.[33,34]

Therefore, both neurologists and gastroenterologists should be vigilant of MS or IBD comorbidity during clinical practice. For MS, the median age of disease onset was approximately 29 years, and the female/male ratio was approximately 3:1.[38] Typical clinical symptoms of MS include loss of vision due to optic neuritis, limb weakness or loss of sensation due to transverse myelitis, diplopia due to brainstem lesion, or ataxia due to cerebellar dysfunction. MRI is the key diagnostic test in MS patients. MRI showed lesions in the periventricular white matter, spinal cord, thalamus, brainstem, and

optic nerve.[39] If IBD patients have neurological symptoms, brain or/and spinal cord MRI is suggested. In turn, if MS patients experience bloody diarrhea or abdominal pain, colonoscopies are recommended. It is also worth noting that some individuals whose MRI findings are strongly suggestive of MS lesions but with no neurological manifestations are considered to have radiologically isolated syndrome (RIS). Approximately one-third of individuals with RIS are diagnosed with MS within 5 years of presentation, and some researchers agree that individuals with RIS might already exhibit evidence of putative pathobiology.[40] Hence, the prevalence of MS in patients with IBD may be underestimated.

Regarding treatment strategies, steroids in acute relapses are crucial for both MS and IBD patients, but there are many differences in the methods and doses of steroids used. High-dose intravenous methylprednisolone is recommended for MS patients with acute relapses.[2] However, for IBD patients, the selection of medications is based on the disease severity and extent.[35] The treatments in the remitting course also show their value in achieving good long-term outcomes. As of 2017, the US Food and Drug Administration has approved 15 disease-modified drugs to treat MS.[39] Recently, new so-called immune reconstitution therapies, such as hematopoietic stem cell transplantation and the monoclonal antibodies alemtuzumab, rituximab, and ocrelizumab, have been expected to induce long-term or even permanent drug-free remission in MS patients.[41] However, clinicians should be aware that interferon-β, which is commonly used to treat MS, could increase the severity of IBD symptoms,[42] and alemtuzumab might alter the gut microbiome, which has detrimental effects on the integrity of the intestinal barrier.[30] There are also many drugs that are expected to induce and maintain remission in IBD.[35,36] It is worth noting that anti-TNFα biologics (e.g., infliximab and adalimumab) are some of these drugs, but these medicines were found to have the possibility of worsening MS.[28] Similarly, we speculate that if anti-TNFα biologics are given to RIS patients, it may lead to accelerated disease progression to MS. Therefore, we suggest that if IBD patients receive anti-TNFα biologics, neurological examination may be necessary. If there are clinical findings, patients should receive brain/and spinal cord MRI. The most appropriate treatment regimen for patients with MS and IBD comorbidities remains to be explored.

The major strengths of this study are as follows. First, we excluded studies from the same population to make our results more reliable. Second, we included a larger number of studies and different study populations. In addition, there were some limitations in our study. First, six studies included in our meta-analysis were of moderate quality, and high heterogeneity was found in several analyses, primarily in the analyses of the prevalence of IBD in MS patients and vice versa. The sensitivity analysis did not change the high heterogeneity and pooled results. We speculated that the high heterogeneity might be ascribed to the differences in the geographical area, study design and study populations between the included studies. The different prevalences of IBD and MS in different geographical areas also suggested that our results were likely to be generalizable to the global prevalence of MS among IBD patients and vice versa. Second, the percentage of IBD patients under treatment with anti-TNFα drugs is not clearly presented in the included studies.

In conclusion, clinicians should be vigilant regarding the increased risk of MS or IBD comorbidity. During clinical practice, it seems to be necessary to obtain regular neurological examinations for patients with IBD, especially those patients requiring anti-TNFa drugs, and perform routine gastroenterological monitoring for patients with MS.

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Conflict of Interest

None.

Author Contributions

K. W. and F. Y. designed the study. J. W., X. W., and M. W. collected the data. J. W. and X. W. analyzed the data. Y. Z. and K. W. revised the statistical analyses. J. W. and X. W. wrote the paper. M. W., K. W., and F. Y. revised the paper. All the authors approved the final version of the manuscript.

Data Sharing and Data Accessibility

Data sharing is not applicable to this article.

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