Review Article

The Prevalence of Inflammatory Bowel Disease (IBD) in Patients with Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis

Abstract

Background: This systematic review and meta-analysis aim to update the pooled prevalence of Inflammatory bowel disease (IBD) in patients with multiple sclerosis (MS). **Methods:** Two researchers independently and systematically searched PubMed, Scopus, EMBASE, Web of Science, and google scholar. They also searched for references of the included studies, and conference abstracts that were published up to September 2021. **Results:** The literature search revealed 5719 articles, after deleting duplicates 3616 remained. Finally, 17 studies were included. The pooled prevalence of IBD in MS was 1% (I^2 = 96.3%, P < 0.001). The pooled odds ratio of developing IBD in MS cases was 1.36 (95% CI: 1.1–1.6) (I^2 = 58.3, P = 0.01). **Conclusions:** The results of this systematic review and meta-analysis show that the pooled prevalence of IBD in MS patients was 1% and the pooled odds ratio of developing IBD in MS cases was 1.36.

Keywords: *Inflammatory bowel disease, multiple sclerosis, prevalence*

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Introduction

Multiple sclerosis (MS) is an inflammatory disease targeting the central nervous system (CNS) mostly affecting youth in productive age.[1,2] Patients with MS have a wide range of physical and psychological co-morbidities.[3-7] These comorbidities are associated with a decreased quality of life, more hospitalization, imposing a cost to both the health system and the patients, and a higher rate of mortality.[8]

Previous studies suggested that the presence of co-morbidities in MS is related to diagnostic delays, more MS-related disability, and a greater risk of disability progression during the disease.[9]

Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease, is another autoimmune disorder.[10] It is shown that the prevalence of IBD before and after diagnosis is higher in MS patients than in controls.[11] In recent years, evidence for reciprocal comorbidity of MS and IBD has increased.[12,13] Literature suggests that MS share genetic risk with IBD but the magnitude of this overlap is not clear.[14] TNF alpha play role in the pathogenesis of both diseases.[15]

In a previous systematic review and meta-analysis, Kosmidou *et al*.[16] reported that MS patients have an increased risk of having IBD of 50%. Their study was published in 2017 and in this systematic review, we want to update their results. So, the goal of this systematic review and meta-analysis is to update the pooled prevalence of IBD in MS patients.

Methods

Literature search

Two researchers independently and systematically searched PubMed, Scopus, EMBASE, Web of Science, and google scholar. They also searched for references of the included studies, and conference abstracts published up to September 2021.

Inclusion criteria were

We included cross-sectional studies which had reported the prevalence of IBD (UC/CD) in MS patients.

Exclusion criteria were

Letters to the editor, case-control, case reports, and cross-sectional studies which had no clear data.

Data search and extraction

The search strategy included the MeSH and text words such as ("Disseminated Sclerosis" OR "multiple sclerosis" OR "MS"

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OR "Acute Fulminating") AND ("IBD" OR "Inflammatory Bowel Disease" OR "Crohn's Enteritis" OR "Regional Enteritis" OR "Crohn's Disease" OR "Granulomatous Enteritis" OR "Ileocolitis" OR "Granulomatous Colitis" OR "Terminal Ileitis" OR "Regional Ileitis" OR "Regional Ileitides" OR "Idiopathic Proctocolitis" OR "Ulcerative Colitis" OR "Colitis Gravis").

Two independent researchers independently evaluated the articles.

Data regarding the total number of participants, first author, publication year, country of origin, mean age, and the number of patients with IBD (UC/CD) was recorded.

Risk of bias assessment

We evaluated the risk of potential bias with the Hoy quality assessment scale (adapted for cross-sectional studies).[17]

Statistical analysis

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We used random effects model. The pooled ODDs ratio (OR) was calculated.

To determine heterogeneity, Inconsistency (I^2) was calculated.

Results

The literature search revealed 5719 articles, after deleting duplicates 3616 remained. Finally, 17 studies were included [Figure 1].

Finally, 17 articles were included. Totally105155 MS patients and 506423 controls were evaluated.

Basic characteristics of included studies are summarized in Table 1.

The pooled prevalence of IBD in MS was 1% (I^2 = 96.3%, $P < 0.001$) [Figure 2].

The pooled odds ratio of developing IBD in MS cases was 1.36 (95%CI: 1.1-1.6) (I^2 = 58.3, P = 0.01) [Figure 3].

The results of Hoy quality assessment in seen in Table 2.

Discussion

The results of this study show that the pooled prevalence of IBD in MS is 1% and the odds of developing IBD in MS cases was 1.36 which shows that MS patients 36% have significantly higher odds of developing IBD.

Kosmidou *et al*.[16] evaluated both the risk of developing MS in IBD and IBD in MS and found that both IBD and MS patients have a fifty percent increased risk of developing MS or IBD. They estimated the pooled RR of

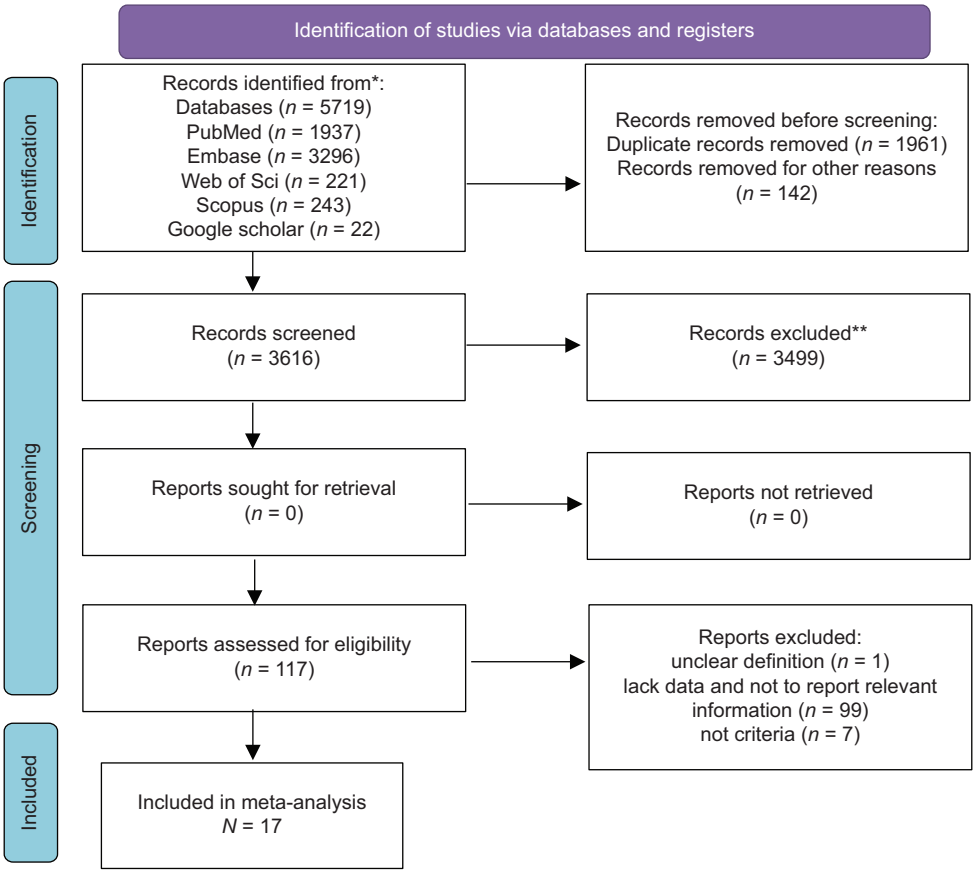

Figure 1: Flow diagram presenting the selection of eligible studies according to PRISMA 2020 flow diagram

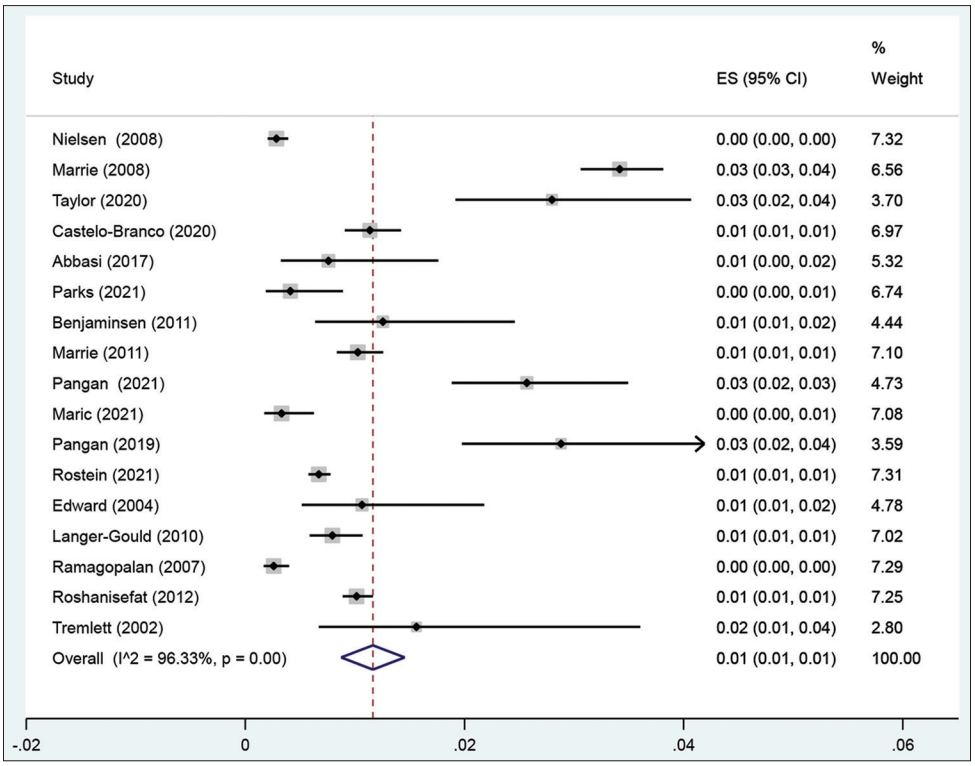

Figure 2: The pooled prevalence of IBD in MS

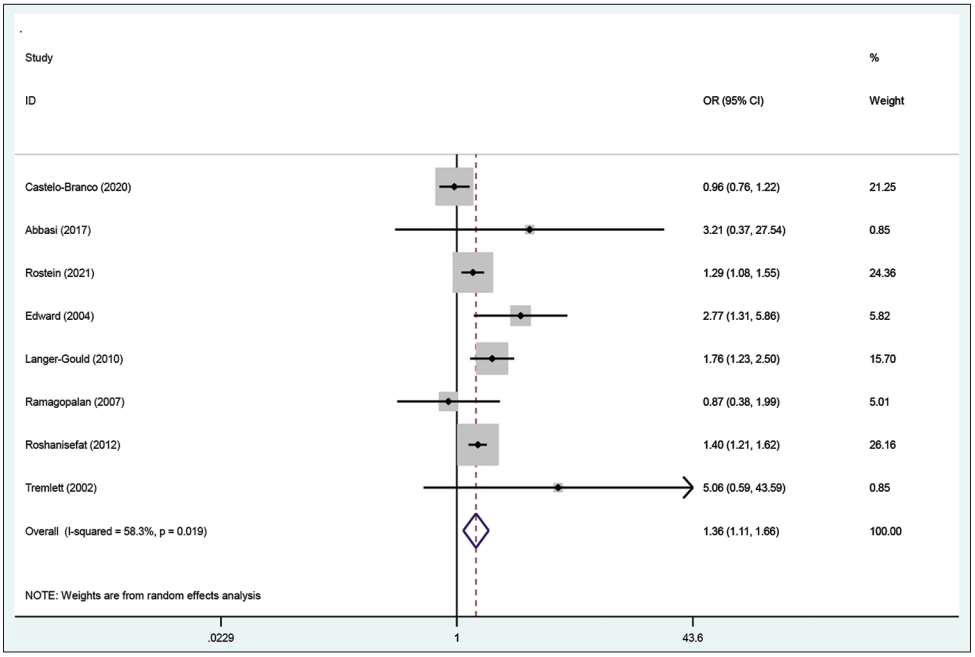

Figure 3: The pooled odds ratio of developing IBD in MS cases

IBD comorbidity in MS cases as 1.55 (95% CI: 1.32–1.88). The difference between the result of our systematic review and the previous one could be due to the higher number of included studies in our survey. A recent systematic review and meta-analysis showed the risk of developing IBD in MS as 1.53, $P < 0.001$.[18]

MS patients suffer from a wide range of comorbidities (both physical and psychological) which are associated with many adverse outcomes such as utilizing health care and imposing costs.

Kirby *et al*.[19] found that comorbid autoimmune disease is not associated with MS progression except asthma which was related to higher disability status.

Nielsen *et al*.[20] enrolled 12403 MS and 20 798 controls and found that MS patients were at higher risk of developing

Table 1: Basic characteristics of the included studies

Author	Year	Country	Study type	Male	Female	F/M ratio	Total number	Primary disease (*n*)	Number of patients with primary disease	Concomitant disease	Number of patients with concomitant disease	control (*n*)	Control disease (*n*)
Nielsen	2008	Denmark	Cohort	-	-	-	12403	MS	12403	UC	29	-	-
				-	-	-	12403	MS	12403	CD	6	-	-
Marrie	2008	United States	Cross-sectional	2172	6811	3.135819521	8983	MS	8983	IBD	307	-	-
Taylor	2020	Australia	Cohort	180	749	4.161111111	929	MS	929	IBD	26	-	-
Castelo-Branco	2020	Sweden	Cohort	2080	4522	2.174038462	68430	MS	6602	CD	34	61828	294
				2080	4522	2.174038462	68430	MS	6602	UC	41	61828	436
Abbasi	2017	Iran	Case-Control	101	558	5.524752475	1081	MS	660	IBD	5	421	1
Parks	2021	Canada	Cohort	341	1122	3.290322581	1464	MS	1464	IBD	6		
Benjaminsen	2021	Norway	Case-Control				637	MS	637	IBD	8		
Marrie	2011	North American	cross-sectional	2125	6654	3.13123E+11	8779	MS	8779	IBD	90		
Pangan	2021	Australia	Cohort	309	1204	3.896440129	1518	MS	1518	IBD	39		
Maric	2021	Serbia	cross-sectional				2725	MS	2725	IBD	9		
Pangan	2019	Australia	cross-sectional				902	MS	902	IBD	26		
Rotstein	2021	Canada	cohort	7689	17576	2.284692418	99983	MS	25265	IBD	169	74718	388
Edwards	2004	UK	Cohort	204	454	2.225490196	136658	MS	658	UC	5	136000	330
				204	454	2.225490196	136658	MS	658	CD	2	136000	196
Langer-Gould	2010	USA	Case-Control	1324	3972	3	31774	MS	5296	IBD	42	26478	120
Ramagopalan	2007	Canada	Case-Control			2.6	7738	MS	5031	UC	9	2707	4
						2.6	7738	MS	5031	CD	11	2707	4
						2.6	7738	MS	5031	UC and CD	20	2707	8
Roshanisefat	2012	Sweden	Case-Control	7058	13218	1.87276849	224227	MS	20276	UC	113	203951	819
				7058	13218	1.87276849	224227	MS	20276	CD	93	203951	669
Tremlett	2002	UK	Case-Control	109	211	1.935779817	640	MS	320	IBD	5	320	0

Table 2: Quality assessment checklist for included studies

Risk of bias items	Abbasi *et al.*	Edwards *et al.*	Benjaminsen *et al.*	Castelo-Branco *et al.*	Langer-Gould *et al.*	Marrie *et al.* (2011)	Ramagopalan *et al.*	Maric *et al.*	Nielsen *et al.*	Rotstein *et al.*	Parks *et al.*	Tremlett *et al.*	Pangan *et al.* (2021)	Pangan *et al.* (2019)	Roshanisefat *et al.*	Chen *et al.*	Marrie *et al.* (2008)
Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, and occupation?	Low risk	Low risk	high risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Was the sampling frame a true or close representation of the target population?	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	Low risk	High risk	Low risk
Was the likelihood of non-response bias minimal?	Low risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	Low risk
Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk
Was an acceptable case definition used in the study?	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Contd...

Table 2: Contd...

Risk of bias items	Abbasi *et al.*	Edwards *et al.*	Benjaminsen *et al.*	Castelo-Branco *et al.*	Langer-Gould *et al.*	Marrie *et al.* (2011)	Ramagopalan *et al.*	Maric *et al.*	Nielsen *et al.*	Rotstein *et al.*	Parks *et al.*	Tremlett *et al.*	Pangan *et al.* (2021)	Pangan *et al.* (2019)	Roshanisefat *et al.*	Chen *et al.*	Marrie *et al.* (2008)
Was the same mode of data collection used for all subjects?	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Were the numerator(s) and denominator(s) for the parameter of interest appropriate	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Summary on the overall risk of study bias	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ulcerative colitis (RR = 2). They also found that the first degree of MS patients is at higher risk of developing Crohn's disease and ulcerative colitis.

Castelo-Branco *et al*.[21] enrolled 6602 MS patients and 61,828 healthy subjects and reported no significant difference in the frequency of UC and CD between the two groups.

The co-occurrence of IBD and MS could be explained by both genetic (single-nucleotide polymorphisms such as (rs13428812), UC (rs116555563) and CD (rs13428812, rs9977672)) and environmental risk factors (smoking, cold climate, socioeconomic status).[14,22-24] Yang *et al*.,[14] using Mendelian randomization found evidence for the causal effect of MS on UC and IBD.

In a review which was conducted by Katsanos *et al*.,[25] it was suggested that IBD cases have demyelinating events in both peripheral and central nervous systems and there is no exact evidence to decide if anti-TNF-α therapies result in developing demyelination or not.

As both MS and IBD are chronic inflammatory diseases there is no exact evidence that which of them preceded the other. The role of brain-gut interaction should not be ignored.

In a study by Lange and Shiner, jejunal biopsies of MS patients demonstrated intestinal inflammatory cell infiltration and villous atrophy.[26]

Kosmidou *et al*.[16] in their systematic review and meta-analysis found that the risk of developing IBD in MS cases and vice versa is similar in included studies.

The only point is that clinicians should consider gastrointestinal manifestations in MS cases.

IBD is a group of inflammatory relapsing autoimmune diseases that is the result of dysregulation of the adaptive and innate immune systems. In both MS and IBD, IL-17 level is high which prominent the role of T helper 17 in the pathogenesis of both diseases.[27] MS and IBD have relapsing and remitting nature and evidence shows that MS medications such as interferons or rituximab could start or exacerbate the IBD in MS patients.[27,28]

Both neurologists and gastroenterologists should be aware of MS or IBD comorbidity to consider better therapy and follow-up.

This systematic review and meta-analysis have some strengths. First, it is the first study. Second, the number of included studies is high. But, prospective cohort studies should be done to assess the incidence of IBD in MS.

Conclusion

The result of this systematic review and meta-analysis shows that the pooled prevalence of IBD in MS patients was 1% The pooled odds ratio of developing IBD in MS cases was 1.36.

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Conflicts of interest

There are no conflicts of interest.

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