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Global research trends in the microbiome related to irritable bowel syndrome: A bibliometric and visualized study

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. Dysregulation of the gut-brain axis plays a central role in the pathophysiology of IBS. It is increasingly clear that the microbiome plays a key role in the development and normal functioning of the gut-brain axis.

AIM

To facilitate the identification of specific areas of focus that may be of relevance to future research. This study represents a bibliometric analysis of the literature pertaining to the microbiome in IBS to understand the development of this field.

METHODS

The data used in our bibliometric analysis were retrieved from the Scopus database. The terms related to IBS and microbiome were searched in titles or abstracts within the period of 2000–2019. VOSviewer software was used for data

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visualization.

RESULTS

A total of 13055 documents related to IBS were retrieved at the global level. There were 1872 scientific publications focused on the microbiome in IBS. There was a strong positive correlation between publication productivity related to IBS in all fields and productivity related to the microbiome in IBS ($r = 0.951$, $P < 0.001$). The United States was the most prolific country with 449 (24%) publications, followed by the United Kingdom ($n = 176$, 9.4%), China ($n = 154$, 8.2%), and Italy ($n = 151$, 8.1%). The h-index for all retrieved publications related to the microbiome in IBS was 138. The hot topics were stratified into four clusters: (1) The gut-brain axis related to IBS; (2) Clinical trials related to IBS and the microbiome; (3) Drug-mediated manipulation of the gut microbiome; and (4) The role of the altered composition of intestinal microbiota in IBS prevention.

CONCLUSION

This is the first study to evaluate and quantify global research productivity pertaining to the microbiome in IBS. The number of publications regarding the gut microbiota in IBS has continuously grown since 2013. This finding suggests that the future outlook for interventions targeting the gut microbiota in IBS remains promising.

Key Words: Irritable bowel syndrome; Bibliometric; Microbiota; Microbiome; Scopus; Brain gut axis

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Core Tip: This is the first study to evaluate and quantify the global research productivity pertaining to the microbiome in irritable bowel syndrome (IBS). We present a holistic picture of this emerging topic and explore future research directions. A number of abnormalities have been described within the microbiome of patients with IBS. The relationships of these abnormalities to the causality of dysfunction and associated symptomatology have not been clearly elucidated. Our finding, while preliminary, suggests that the future outlook for interventions targeting the gut microbiota in IBS remains promising.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a term used to describe a group of symptoms, including abdominal pain and altered bowel habits, that arises because of disturbances of the interactions between the diet, the brain, the gut, and the microbiome. IBS poses a significant disease burden, with 20% of adults estimated to develop IBS symptoms in any given year. Symptoms arise as a consequence of abnormal visceral sensation and or motility as a result of abnormalities within the enteric or central nervous systems, or both^[1]. This usually occurs in the absence of 'organic' disease, but the association with other gastrointestinal diseases is common. Many patients experiencing gastrointestinal inflammation due to infection or inflammatory bowel disease develop IBS symptoms^[2]. Nearly a quarter of patients with IBS without identifiable 'organic' disease appear to have low-grade intestinal inflammation as judged by faecal inflammatory markers (calprotectin)^[3]. Inflammation may lead to sensitization of peripheral nerves. Most inflammation within the gastrointestinal tract settles, but in susceptible individuals sensitization of peripheral afferents may persist. Such sensitization may be driven by ongoing mast cell activation and increased epithelial

permeability associated with low-level inflammation^[4].

The onset of symptoms in IBS is often associated with psychological stressors. A high proportion of people with IBS have psychological comorbidities. Chronic stress is associated with stress-induced hyperalgesia. This hyperalgesia is mediated *via* corticotrophin-releasing hormone and the hypothalamic-pituitary axis (HPA)^[5]. Dysfunction within these systems is well documented in patients with functional gastrointestinal disorders and other chronic pain syndromes. Furthermore, many patients have histories of traumatic events in early life. These events may result in changes that profoundly affect the microbiome and brain development, predisposing patients to visceral pain syndromes^[6-8]. In addition to direct effects on neurons proximal to the bowel, bacteria and their products have a profound effect on the development and activity of the central nervous system and, consequently, upon the psychological state and behaviors^[9]. Within the enteric nervous system, certain bacterial strains may directly promote sensitization or downregulation of peripheral afferents. Of note, low-grade inflammation seen in a proportion of patients with IBS may result from the ability of specific bacteria to enhance the production and the effects of proinflammatory cytokines. Bacteria may also be able to transmit signals *via* the enteric nervous and immune systems to the central nervous system^[10].

Although several bibliometric studies have been conducted to evaluate research productivity regarding various research aspects in the medical field^[11-18], and some bibliometric studies have focused on microbiota science^[19-25], there has not been an assessment of the research output regarding the microbiome in IBS. This study undertakes a bibliometric analysis of the literature within this field to understand the development of the literature pertaining to the microbiome in IBS and to facilitate the identification of specific areas of focus that may be of relevance to future research. This study evaluates data that will help to address the research gaps in this field. The current bibliometric study plays a significant role for researchers interested in the relationship between the microbiome and IBS, because it offers a quick reference guide for interdisciplinary researchers to know how this field has been assessed by scientific experts in previous years.

MATERIALS AND METHODS

The data used in our bibliometric analysis were retrieved from Scopus, which is a multidisciplinary database owned by Elsevier and is considered the largest and most widely used database^[26-28]. Most of the publications in this field were published between 2000 and 2019. The following term combinations were searched in the title or abstract within this period: Terms related to IBS, *i.e.*, 'adaptive colitis' OR 'colon spasm' OR 'functional bowel disease' OR 'irritable bowel' OR 'irritable colon' OR 'membranous colitis' OR 'mucous colitis' OR 'spastic colitis' OR 'spastic colon' OR 'spastic bowel' OR 'functional colonic disease' OR 'colon irritable' OR 'colon neurosis' OR 'bowel neurosis' OR 'functional colopathy' OR 'functional colonopathy' OR 'chronic catarrhal colitis' OR 'colica mucosa' OR 'colonic enterospasm' OR 'dyskinesia of the colon' OR 'dyssynergia of the colon' OR 'functional enterocolonopathy' OR 'functional diarrhea' OR 'Glarry enteritis' OR 'glutinous diarrhea' OR 'intestinal croup' OR 'irritable gut syndrome' OR 'lienteric diarrhea' OR 'Membranous catarrh of the intestine' OR 'mucomembranous colic' OR 'myxoneurosis' OR 'nervous diarrhea' OR 'neurogenic mucous' OR 'nonspecific diarrhea' OR 'tubular diarrhea' OR 'unhappy colon' OR 'unstable colon', and terms related to microbiome, *i.e.*, 'microbiome' OR 'microflora' OR 'microbiota' OR 'flora' OR 'probiotic' OR 'Saccharomyces' OR 'Lactobacillus' OR 'Bifidobacterium' OR 'Escherichia coli'. The terms were selected from related reviews on IBS^[29,30] and the microbiome^[19,20,31-33].

Data analysis

Microsoft Excel was used to analyze the retrieved data to calculate frequencies and percentages. The current bibliometric study included quantitative data about document types, language, country of the publications with their h-index and collaboration pattern, authors of the publications, journals that published papers on IBS, microbiome documents, and citation reports. In addition, we used the Statistical Package for the Social Sciences 16.0 software for Windows to assess the correlation between yearly quantitative distributions of publications related to IBS in all fields and publications related to the microbiome in IBS by using the Pearson correlation test. Analysis with $P < 0.05$ is considered statistically significant. In addition, the VOSviewer program^[34,35] was used for mapping and clustering terms according to their

occurrence in both titles and abstracts to determine hot topics in this field. Furthermore, network visualization maps for collaboration among the most productive countries and the most prolific authors in this field were prepared using VOSviewer.

RESULTS

A total of 13055 documents related to IBS in titles and abstracts were retrieved over the period of 2000–2019 at the global level. There were 1872 scientific publications focused on the microbiome in IBS. The research findings showed that English was the main research language of documents indexed in Scopus, accounting for 48.8% of the documents, followed by German (3.9%) and Chinese (2.9%). Articles were the main type of document for publications related to the microbiome and IBS, accounting for 51.9% of documents, followed by reviews (35.3%).

The number of publications related to the microbiome in IBS has increased year by year. The quantity of documents has increased each year, from 9 documents in 2000, to 84 documents in 2009, to 219 documents in 2019 (Figure 1). Published papers during the last 5 years (2015 to 2019) accounted for 47.0% of the total publications. There was a strong positive correlation between the publication productivity related to IBS in all fields and the productivity related to the microbiome in IBS ($r = 0.951$, $P < 0.001$).

In total, authors from 105 countries published their work on the microbiome and IBS topics. Table 1 lists the top 10 most prolific countries. The United States was the most prolific country with 449 (24%) publications, followed by the United Kingdom ($n = 176$, 9.4%), China ($n = 154$, 8.2%), and Italy ($n = 151$, 8.1%). The h-index for all retrieved publications related to the microbiome in IBS was 138. Figure 2 shows the network visualization map for the collaboration among the 40 most productive countries. This includes countries that published more than 5 papers on microbiome and IBS research according to the number of publications in the last two decades (2000–2019). The United States and the United Kingdom can be referred to as central countries for this network because they published research in collaboration with 40 and 31 countries, respectively. In total, 5960 authors published their work on the microbiome and IBS topics. Figure 3 shows the network visualization map for the collaboration among the 32 most productive authors (authors who published more than 10 papers) on the microbiome in IBS research according to the number of publications in the last two decades (2000–2019). EMM Quigley (United States), G Barbara (Italy), JF Cryan (Ireland), and TG Dinan (Ireland) can be considered the prolific authors of this network due to the fact that they published 61, 25, 25, and 23 documents, respectively.

Terms were extracted from the titles and abstracts of all retrieved publications related to the microbiome in IBS and analyzed by the VOSviewer software to identify the current state and hot topics in this field. Terms appearing more than 10 times were included in the map (Figure 4) and were stratified into four clusters: IBS related to the gut–brain axis (yellow cluster), clinical trials related to IBS and the microbiome (red cluster), drug-mediated manipulation of the gut microbiome (blue cluster), and the role of the altered composition of intestinal microbiota in IBS prevention (green cluster).

The top 10 journals accounted for 19.98% of all articles (Table 2). The four journals that published the most studies related to microbiome and IBS were *World Journal of Gastroenterology* ($n = 70$), *Alimentary Pharmacology and Therapeutics* ($n = 54$), *Neurogastroenterology and Motility* ($n = 52$), and the *Journal of Clinical Gastroenterology* ($n = 39$).

The sample presents an average citation rate of 42 citations per publication. However, 16.6% of the publications have never been cited. Table 3 lists the information on the top ranking of publications in terms of the highest number of citations^[36–55]. The article ‘Prebiotic Effects: Metabolic and Health Benefits’ is the most cited article with 1147 citations; it was authored by Roberfroid *et al*^[49] and published in the *British Journal of Nutrition* in 2010. This study reported that a substantial number of studies about human intervention have shown that dietary intake of food products/ingredients/supplements results in statistically important improvements in the faecal gut microbiota composition. The second most highly cited article is ‘Lactobacillus and Bifidobacterium in IBS: Symptom Responses and Relationship to Cytokine Profiles’ by O’Mahony *et al*^[44] and published in *Gastroenterology* in 2005. This study showed that intake of *Bifidobacterium infantis* over 8 wk was associated with symptomatic improvement in IBS.

Table 1 Top 10 most productive countries on the microbiome in irritable bowel syndrome research, ranked by the total number of publications in the last two decades (2000-2019)

SCR	Country	Number of documents	%
1 st	United States	449	24.0
2 nd	United Kingdom	176	9.4
3 rd	China	154	8.2
4 th	Italy	151	8.1
5 th	France	116	6.2
6 th	Germany	107	5.7
7 th	Canada	103	5.5
8 th	Ireland	102	5.4
9 th	Australia	72	3.8
10 th	Spain	69	3.7

SCR: Standard competition ranking.

Table 2 Top 10 most productive journals on the microbiome in irritable bowel syndrome research, ranked by the total number of publications in the last two decades (2000-2019)

SCR ¹	Journal	Frequency	%	IF ²
1 st	<i>World Journal of Gastroenterology</i>	70	3.74	3.665
2 nd	<i>Alimentary Pharmacology and Therapeutics</i>	54	2.88	7.515
3 rd	<i>Neurogastroenterology and Motility</i>	52	2.78	2.946
4 th	<i>Journal of Clinical Gastroenterology</i>	39	2.08	2.973
5 th	<i>American Journal of Gastroenterology</i>	34	1.82	10.171
6 th	<i>Gastroenterology</i>	33	1.76	17.373
7 th	<i>Current Opinion in Gastroenterology</i>	27	1.44	3.225
8 th	<i>PLoS One</i>	24	1.28	2.740
9 th	<i>Nutrients</i>	21	1.12	4.546
10 th	<i>Gut Microbes</i>	20	1.07	7.740

¹Equal journals have the same ranking number, and then a gap is left in the ranking numbers.

²Impact factors based on Journal Citation Reports 2019 from Clarivate Analytics.

SCR: Standard competition ranking; IF: Impact factor.

Table 4 presents the top 10 most productive institutions on the microbiome in IBS research, ranked by the total number of publications. The four institutions that have published the most studies related to microbiome and IBS are the University College Cork ($n = 87$), APC Microbiome Ireland ($n = 84$), McMaster University ($n = 45$), the Mayo Clinic ($n = 32$), and Alma Mater Studiorum Università di Bologna ($n = 38$) (Table 4).

DISCUSSION

This bibliometric study was carried out using data from Scopus for the period of 2000–2019. It presents a comprehensive review of research progress on the microbiome and IBS, identifies hot topics within this field, and indicates potential directions for future research. It is apparent that the research productivity in this field has progressively increased due to the increasing recognition of the role of the gut microbiota^[56,57]. In addition, this increase is probably linked to the growing number of

Table 3 Top 20 most cited articles on the microbiome in irritable bowel syndrome research in the last two decades (2000-2019)

SCR	Ref.	Title	Year	Source title	Cited by
1 st	Roberfroid <i>et al</i> ^[49]	"Prebiotic effects: Metabolic and health benefits"	2010	<i>British Journal of Nutrition</i>	1147
2 nd	O'Mahony <i>et al</i> ^[44]	"Lactobacillus and Bifidobacterium in irritable bowel syndrome: Symptom responses and relationship to cytokine profiles"	2005	<i>Gastroenterology</i>	1042
3 rd	Claesson <i>et al</i> ^[37]	"Composition, variability, and temporal stability of the intestinal microbiota of the elderly"	2011	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	836
4 th	Collins <i>et al</i> ^[38]	"The interplay between the intestinal microbiota and the brain"	2012	<i>Nature Reviews Microbiology</i>	735
5 th	Kassinen <i>et al</i> ^[40]	"The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects"	2007	<i>Gastroenterology</i>	684
6 th	Pimentel <i>et al</i> ^[46]	"Rifaximin therapy for patients with irritable bowel syndrome without constipation"	2011	<i>New England Journal of Medicine</i>	659
7 th	Rintilä <i>et al</i> ^[48]	"Development of an extensive set of 16S rDNA-targeted primers for quantification of pathogenic and indigenous bacteria in faecal samples by real-time PCR"	2004	<i>Journal of Applied Microbiology</i>	658
8 th	O'Mahony <i>et al</i> ^[45]	"Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses "	2009	<i>Biological Psychiatry</i>	634
9 th	Rolfe ^[50]	"The role of probiotic cultures in the control of gastrointestinal health"	2000	<i>Journal of Nutrition</i>	584
10 th	Carabotti <i>et al</i> ^[36]	"The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems"	2015	<i>Annals of Gastroenterology</i>	580
11 th	De Vrese and Schrezenmeir ^[39]	"Probiotics, prebiotics, and synbiotics"	2008	<i>Advances in Biochemical Engineering/Biotechnology</i>	575
12 th	Rajilić-Stojanović <i>et al</i> ^[47]	"Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome"	2011	<i>Gastroenterology</i>	545
13 th	Whorwell <i>et al</i> ^[55]	"Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome"	2006	<i>American Journal of Gastroenterology</i>	541
13 th	Swidsinski <i>et al</i> ^[54]	"Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease"	2005	<i>Journal of Clinical Microbiology</i>	541
15 th	Malinen <i>et al</i> ^[41]	"Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR"	2005	<i>American Journal of Gastroenterology</i>	523
16 th	Mayer <i>et al</i> ^[42]	"Gut/brain axis and the microbiota"	2015	<i>Journal of Clinical Investigation</i>	519
17 th	Simrén <i>et al</i> ^[52]	"Intestinal microbiota in functional bowel disorders: A Rome foundation report"	2013	<i>Gut</i>	510
18 th	Spiller and Garsed ^[53]	"Postinfectious irritable bowel syndrome "	2009	<i>Gastroenterology</i>	508
19 th	Rousseaux <i>et al</i> ^[51]	"Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors"	2007	<i>Nature Medicine</i>	500
20 th	Nobaek <i>et al</i> ^[43]	"Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome"	2000	<i>American Journal of Gastroenterology</i>	498

researchers who are interested in the fields of neurology and gastroenterology [e.g., EMM Quigley (the United States), JF Cryan (Ireland), TG Dinan (Ireland), G Barbara (Italy), Y Ringel (the United States), M Simrén (Sweden), M Camilleri (the United States), A Palva (Finland), M Pimentel (Canada), NJ Talley (Australia), and others]. Over the last two decades, advances in our understanding of the enteric and central nervous systems have led to an evolving understanding of their interactions and how the gastrointestinal microbiome influences their function. Disturbances in the gastrointestinal microbiome have been identified in patients with functional gastrointestinal disease, like IBS, and it is often the case that symptoms may be triggered by events that lead to changes in the microbiome, where the emotional context and the enteric nervous system function in tandem^[1].

The results of this study indicate that the United States has been the most prolific country in this field. These findings are consistent with many previous bibliometric studies^[12,58]. Research productivity in the United States is likely associated with

Table 4 Top 10 most productive institutions on the microbiome in irritable bowel syndrome research, ranked by the total number of publications in the last two decades (2000-2019)

SCR ¹	Institute	Country	<i>n</i>	%
1 st	University College Cork	Ireland	87	4.65
2 nd	APC Microbiome Ireland	Ireland	84	4.49
3 rd	McMaster University	Canada	45	2.40
4 th	Alma Mater Studiorum Università di Bologna	Italy	38	2.03
5 th	Helsingin Yliopisto	Finland	36	1.92
5 th	Mayo Clinic	United States	36	1.92
7 th	Inserm (Institut national de la santé et de la recherche médicale)	France	30	1.60
8 th	Baylor College of Medicine	United States	27	1.44
9 th	Göteborgs Universitet	Sweden	27	1.44
10 th	The University of North Carolina at Chapel Hill	United States	27	1.44

¹Equal institutes have the same ranking number, and then a gap is left in the ranking numbers.

SCR: Standard competition ranking.

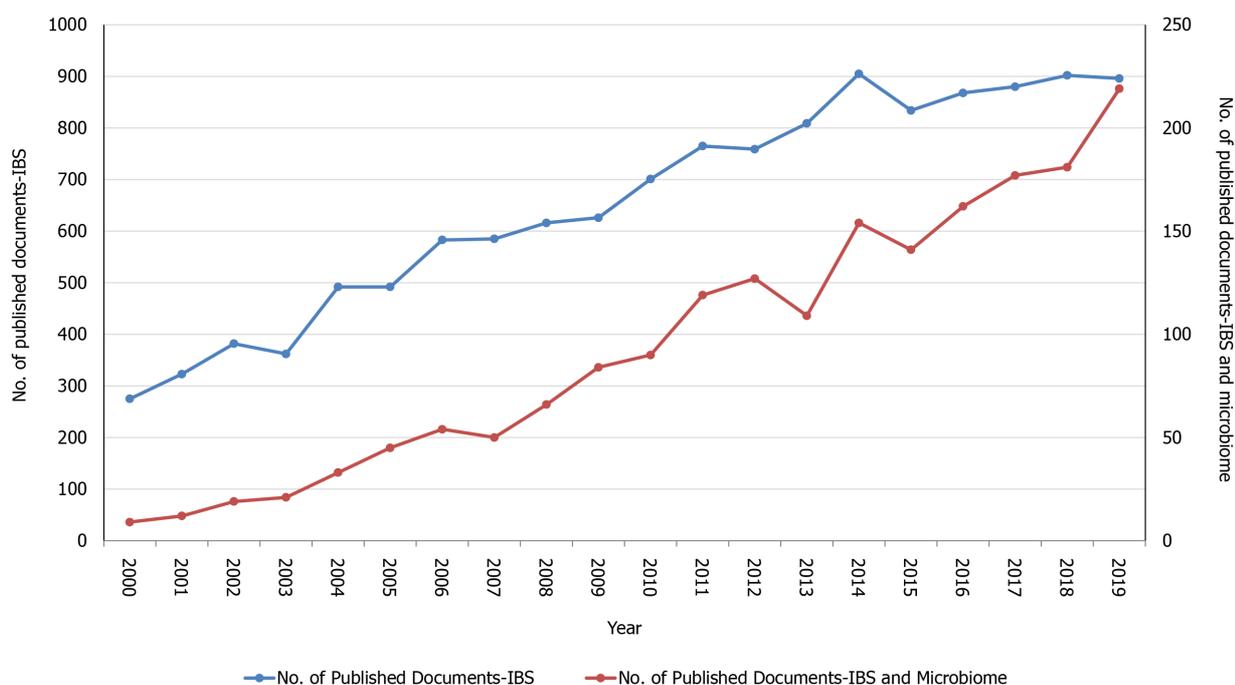


Figure 1 The annual number of publications related to irritable bowel syndrome and the microbiome from 2000 to 2019. IBS: Irritable bowel syndrome.

overwhelming support in terms of research, the wide range of researchers with an interest within this field, several well-resourced research environments, and greater availability of a well-trained workforce. In addition, the economic strength of the United States has led to a substantial amount of financial support for researchers and has enhanced the mobility of researchers^[59,60]. Furthermore, in 2013, the United States launched an exceptional research project on the gut microbiota-brain axis^[61], thus contributing to the increasing number of publications regarding the microbiome in IBS.

Our study demonstrates that the gut-brain axis has become the most prolific area for research within IBS and the microbiome globally, and several studies in a range of journals are proof of this emerging trend. According to these data, we can infer that central pain amplification occurs through a wide variety of mechanisms within the

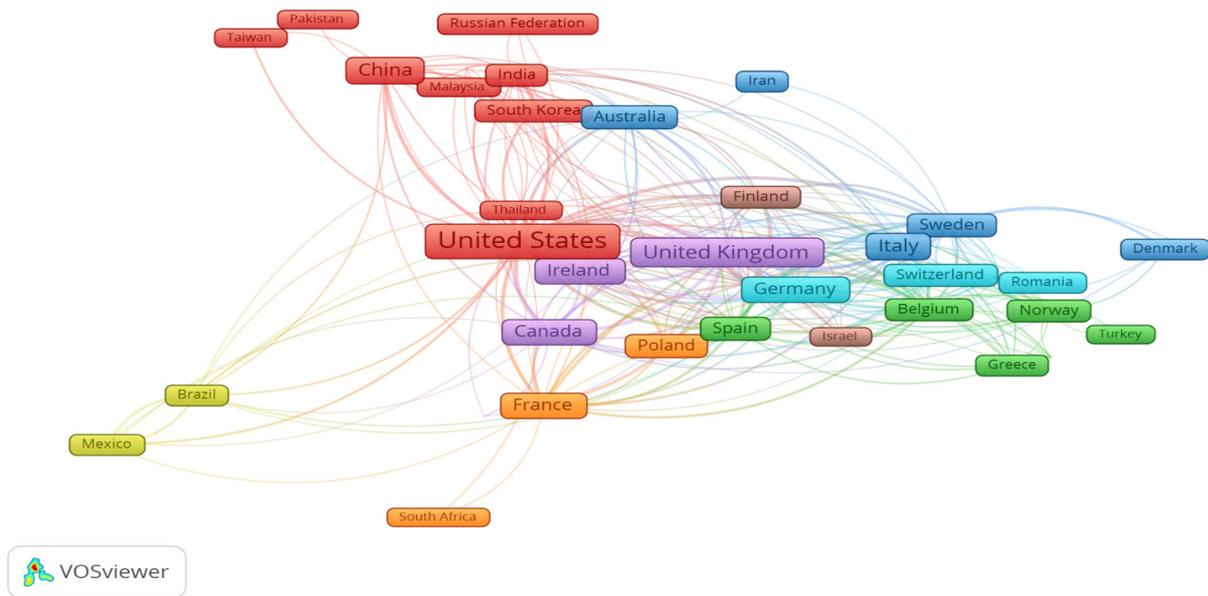


Figure 2 Network visualization map for the collaboration among the 40 most productive countries on the microbiome in irritable bowel syndrome research according to the number of publications in the last two decades (2000–2019).

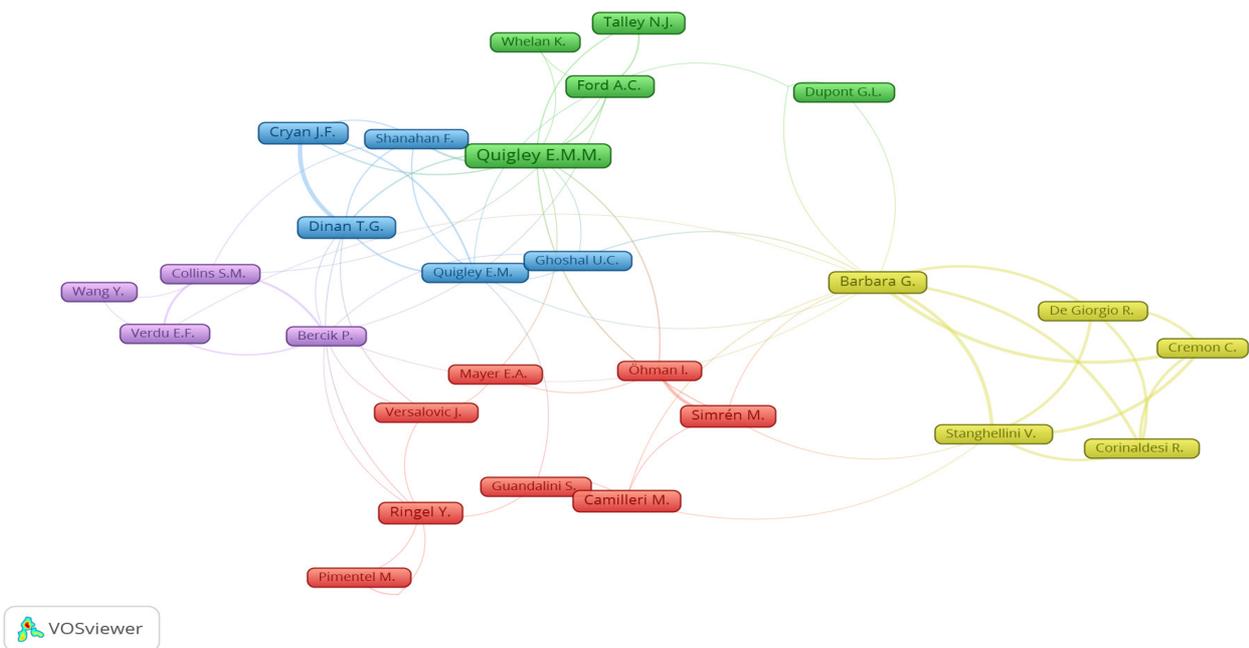


Figure 3 Network visualization map for the collaboration among the 32 most productive authors on the microbiome in irritable bowel syndrome research according to the number of publications in the last two decades (2000–2019).

central nervous system and mediates the effects of mood, emotional context, and environmental circumstances upon our central pain perception. Functional magnetic resonance imaging (fMRI) studies have demonstrated that patients with IBS often display an exaggerated response of arousal circuits associated with the HPA and activation of endogenous pain pathways in response to visceral stimulation. Similarly, studies have shown enhanced anticipation of pain in response to conditioning stimuli in patients with functional gastrointestinal disease^[62]. Neuro-immune activation within the central nervous system is associated with altered astrocyte and microglial activity that further enhances central sensitisation.

Early deprivation in patients with IBS can have profound effects on the microbiome, and researchers recognise that these factors may predispose susceptible individuals to more severe IBS^[8,63-66]. Changes in central nervous system function arise as a result of

elucidated. Our findings, while preliminary, suggest that the future outlook for interventions targeting the gut microbiota in IBS remains promising.

ARTICLE HIGHLIGHTS

Research background

The ability of specific bacteria to boost the development and the effects of proinflammatory cytokines can result in low-grade inflammation seen in a proportion of patients with irritable bowel syndrome (IBS).

Research motivation

The current bibliometric analysis plays an important role for researchers interested in the relationship between the microbiome and IBS. It provides a simple reference guide for interdisciplinary researchers to learn how scientific experts have examined this area in previous years.

Research objectives

This study aimed to carry out a bibliometric review of the IBS and the microbiome literature to explain the growth of this field and assist the identification of unique focus areas that may be important for future research.

Research methods

The information used in our bibliometric research was derived from the Scopus database. Terms related to IBS and the microbiome were searched in titles or abstracts during the period of 2000–2019. For data visualization, VOSviewer software was used.

Research results

Since 2013, the number of publications on gut microbiota in IBS has continuously increased. This result indicates that the future outlook remains optimistic for treatments targeting the gut microbiota in IBS.

Research conclusions

This is the first study to analyze and measure the global research productivity of IBS and microbiome research to provide a holistic view of this evolving subject and explore future research directions. It is evident that, due to the growing understanding of the role of the gut microbiota, research productivity in this area has steadily increased. Currently, the key hot topics are the gut–brain axis related to IBS, clinical trials related to IBS and the microbiome, drug-mediated modulation of the gut microbiome, and the role of the altered composition of the intestinal microbiome in the prevention of IBS.

Research perspectives

Our results indicate that the future outlook for IBS therapies targeting the intestinal microbiota remains promising.

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