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Unveiling the hidden world of gut health: Exploring cutting-edge research through visualizing randomized controlled trials on the gut microbiota

Zyoud S *et al*. Randomized controlled trials on the gut microbiota

Abstract

BACKGROUND

The gut microbiota plays a crucial role in gastrointestinal and overall health. Randomized clinical trials (RCTs) play a crucial role in advancing our knowledge and evaluating the efficacy of therapeutic interventions targeting the gut microbiota.

AIM

To conduct a comprehensive bibliometric analysis of the literature on RCTs involving the gut microbiota.

METHODS

Using bibliometric tools, a descriptive cross-sectional investigation was conducted on scholarly publications concentrated on RCTs related to gut microbiota, spanning the years 2003 to 2022. The study used VOSviewer version 1.6.9 to examine collaboration networks between different countries and evaluate the frequently employed terms in the titles and abstracts of the retrieved publications. The primary objective of this analysis was to identify key research areas and focal points associated with RCTs involving the gut microbiota.

RESULTS

A total of 1061 relevant articles were identified from the 24758 research articles published between 2003 and 2022. The number of publications showed a notable increase over time, with a positive correlation (R^2 = 0.978, P < 0.001). China (n = 276, 26.01%), the United States (n = 254, 23.94%), and the United Kingdom (n = 97, 9.14%)

were the leading contributing countries. *Københavns Universitet* (*n* = 38, 3.58%) and *Dankook University* (*n* = 35, 3.30%) were the top active institutions. The co-occurrence analysis shows current gut microbiota research trends and important topics, such as obesity interventions targeting the gut microbiota, the efficacy and safety of fecal microbiota transplantation, and the effects of dietary interventions on humans.

CONCLUSION

The study highlights the rapid growth and importance of research on RCTs that involve the gut microbiota. This study provides valuable insight into research trends, identifies key players, and outlines potential future directions in this field. Additionally, the co-occurrence analysis identified important topics that play a critical role in the advancement of science and provided insights into future research directions in this field.

Key Words: Gut microbiota; Microbiome; Randomized clinical trials; Bibliometric analysis

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Core Tip: This bibliometric analysis provides valuable insights into the growing research on randomized clinical trials (RCTs) involving the gut microbiota. The study identifies key research areas, prominent contributors, and collaboration networks. The analysis reveals that interventions targeting the gut microbiota for managing obesity, fecal microbiota transplantation, and the impact of diet interventions on the gut microbiota are important focal points. The study underscores the significance of RCTs

in understanding the gut microbiota and offers directions for future research in this field.

INTRODUCTION

The gastrointestinal microbiota is a crucial organ contributing significantly to gastrointestinal and general health. Over the past few decades, understanding of this organ has improved substantially thanks to abundant influential research on the gastrointestinal microbiome[1-4].

"Microbiome" is the genetic material of microorganisms in a given environment. "Intestinal microbiome" refers to the various bacteria present in the human digestive system[5,6], where the host-microorganisms interact with each other. Bacteria dominate these microbial communities, especially in the intestines[7], interact with the host, and are considered a vital regulator of digestion in the gastrointestinal tract. Many genes in microorganisms create metabolites that affect host cell function and physiology[8,9]. Many studies demonstrate that gut microbial makeup and function can affect human health and disease. This affects metabolism, immunity, and neurobehavior. Numerous scholarly sources stress how crucial it is to understand the role of the microbiome in human health[10-12].

Clinical trials are the most reliable way to evaluate medicines' safety and efficacy[13-15], minimize biases, and influence medical practice more than other study designs; as a result, they continue to be valued and applied by medical research more than other study designs[16]. Randomized clinical trials (RCTs) are an experimental approach and essential for assessing the impact of treatment interventions on the gut microbiota[17]. This unique investigation of RCTs on the gut microbiota is growing as evidence-based medicine evolves and is needed to understand and assess intestinal tract microbial therapies and is needed to understand and assess intestinal tract microbial therapies[18,19]. RCTs can evaluate intestinal microbiota composition, function and demonstrate responses after probiotic supplementations, food modifications, or alternative therapy. The interpretation of research and scientific discoveries related to

RCTs involving gut microbiota is not fully studied. However, ongoing research in this area will probably persist, as suggested by studies that are akin to those centered on microbiota[20-22], including investigations into the role of the gut microbiota in schizophrenia[23], nutrition[24], bone metabolism[25], cardiovascular diseases[26-28], atherosclerosis[29], diabetes (both type 1 and type 2)[30,31], irritable bowel syndrome[32,33], depression[34], autoimmune diseases[35], rheumatoid arthritis[36], attention deficit and hyperactivity disorder[37], cancer[38-42], the microbiome-gut-brain axis[38-42], and fecal microbiota transplantation[43-47].

These findings show that RCTs on the intestinal microbiota may be comparable. Thus, this study's major goal is a comprehensive bibliometric analysis of RCTs on intestinal microbiota. This analysis identifies focus areas that can influence future research to understand this specialty's evolution better. This study could become a crucial academic reference for scholars studying current trends and relevant subjects in this field by rigorously evaluating data and identifying research needs. It also helps multidisciplinary scholars comprehend sector professionals' recent assessments.

MATERIALS AND METHODS

Study design

A descriptive cross-sectional study was performed in publications that used bibliometric tools to focus on RCTs involving the gut microbiota between 2003 and 2022.

Data source

The researchers accessed specialized scientific documents through SciVerse Scopus. Scopus is Elsevier's premier abstract and citation database. It allows users to search for academic articles, books, conference papers, and patents that have been published. Scopus is distinguished from other databases such as Web of Science, PubMed, and Google Scholar by its superior quality and breadth of coverage[48,49]. Using the SciVerse Scopus database, the researchers conducted a bibliometric study. Bibliometric studies

analyze patterns of scientific publication and citation using quantitative methods. Unlike systematic and scoping reviews, bibliometric studies do not require researchers to peruse and evaluate individual articles[50-53]. Instead, bibliometric studies can be utilized to identify trends in research output, patterns of collaboration, and citation rates.

Search strategy

To find RCTs that were relevant to the topic of gut microbiota, we did a thorough search of the Scopus database from January 1, 2003 to December 31, 2022. We collected all of the necessary articles on the same day, May 5th, 2023, to eliminate the possibility of biases produced by database upgrades and revisions. Our search method was precise and extensive, utilizing complicated search engines and combining various terms and phrases related to RCTs and gut microbiota. The following steps were followed to retrieve the data for this study.

Step 1: We entered the terminology associated with the gut microbiota, derived from various sources, including PubMed Medical Subject Headings (MeSH), previous systematic and meta-analyses of the gut microbiota[54-59], and bibliometric studies[24,31,42,60,61], into the Scopus research engine. All selected terms were placed in the "Article Title" section.

Step 2: We narrowed down the search results from step 1 to include only documents with the phrase "randomized controlled trials" and related terms in their titles or abstracts. Relevant MeSH terms for RCTs were obtained from MeSH and previous systematic reviews and meta-analyses[62-67].

Step 3: The search was limited to primary research articles, excluding other forms of publications such as errata, editorials, letters, and proceedings.

Validation of the search strategy

It is well known that no search query is 100% perfect, and false positive and negative results are always possible. Instead of conducting a simultaneous search in the title, abstract, and keywords, a deliberate search approach was implemented, focusing solely on the chosen terms within the title. This specific search strategy was adopted to ensure reliability. Using this method, the likelihood of retrieving a negligible number of documents with inaccurate positive results is minimized, thus improving the trustworthiness of the findings[68-72]. In contrast, conducting a search of titles, abstracts, and keywords is likely to generate a significant number of false positives. This is because the main focus of these studies is not directly related to RCTs that specifically focus on gut microbiota but rather on various other topics.

The study used a research strategy that was validated to ensure reliable and precise results. To avoid false positive outcomes, documents with even numbers (10, 20, 30, 40, *etc.*) up to the end of the retrieved document list were scrutinized by evaluating their titles and abstracts. The research strategy was continuously refined until a completely accurate set of randomly selected outcomes was achieved.

To ensure the absence of false negative results, we validated our research strategy by examining the research productivity of 20 active authors in the field. We manually reviewed their publications to identify relevant RCTs on the gut microbiota. We then compared the number of publications identified with those obtained through our research strategy using the Spearman correlation test[73]. The study found a robust and statistically significant correlation ($P < 0.001$; $r = 0.963$) between the two sets of findings, highlighting the high level of validity. Notably, Sweileh *et al*[74,75] previously used this validation method.

Bibliometric analysis

Bibliometric indicators were collected using an Excel spreadsheet. Key bibliometric indicators that were analyzed include the following: publication trends, citation patterns, h-index and the top 10 countries, journals, institutions, funding agencies, and

cited publications. The displayed *Impact Index Per Article* indicates the ten most frequently referenced papers, sourced from the *Reference Citation Analysis* (RCA) database available at https://www.referencecitationanalysis.com/. RCA is an openly accessible citation analysis repository spanning diverse academic domains, and it is under the ownership of Baishideng Publishing Group Inc. The organization is headquartered in Pleasanton, CA 94566, United States[76-78].

Visualization analysis

The network maps in this study were generated using version 1.6.9 of the VOSviewer software developed by Leiden University in the Netherlands. These maps visually represent the interconnection of terms extracted from article titles or abstracts of articles, highlighting the collaborative relationships between different countries. By utilizing VOSviewer, a tool for creating knowledge networks based on scientific research, we can observe the advancements made in various research fields and potentially predict future research trends. VOSviewer employs co-occurrence analysis, grouping terms into clusters with different colors. Consequently, analyzing clusters within the co-occurrence network of terms found in titles and abstracts enhances the effectiveness of identifying research hotspots. This approach enables the illustration and identification of developing trends[79,80].

RESULTS

Volume of publications

Between 2003 and 2022, a total of 24758 research articles were published on the topic of gut microbiota. However, when the search was limited to articles specifically related to RCTs involving the gut microbiota, Scopus identified 1061 relevant articles.

Growth and productivity trends

Figure 1 presents the growth and productivity trends in research related to RCTs involving the gut microbiota over the past two decades. The graph illustrates an

upward trend in the number of publications, with a remarkable increase from 1 in 2003 to 249 in 2022. The growth occurred in two phases: The first was a period of relatively slow publication from 2003 to 2017, followed by a rapid increase from 2018 to 2022. A linear regression analysis conducted in this study shows a strong positive correlation (R^2 = 0.978, P < 0.001) between the annual publication count and the respective year of publication.

Performance of countries/regions

In the field of study, Table 1 provides a ranking of the top ten countries based on their research activity. Our analysis revealed that among a total of 1061 publications released in 77 countries, the ten countries with the highest research activity contributed 830 publications. These top 10 countries collectively represent 78.23% of the total publications. In particular, China holds the highest position with 276 publications, accounting for 26.01% of the total. Following closely, the United States secures the second spot with 254 publications (23.94%), followed by the United Kingdom with 97 publications (9.14%) and the Netherlands with 76 publications (7.16%). Figure 2 illustrates the international research collaboration between countries, showing a minimum contribution of 10 articles to the study field. The map encompasses 28 countries, and those positioned centrally, such as the United States, the United Kingdom, and China, possess larger node sizes, signifying a greater number of documents with international collaboration.

Active institutions/organizations

Table 2 presents the top ten institutions among 4793 that have actively participated in the production of research publications related to RCTs and gut microbiota. The findings suggest that these institutions have collectively contributed to 22.43% of the total documents published in this field. Københavns University has secured the top spot by producing 38 documents, accounting for 3.58% of the total publications. Dankook University follows closely behind with 35 publications (3.30%), and the

Ministry of Education China and Wageningen University & Research have produced 30 publications (2.83%) and 28 publications (2.64%), respectively. The majority of active institutions were based in the United States, with three institutions represented. China had two institutions, while Denmark, South Korea, Canada, France, Finland, and Spain each had one institution represented.

Top funding agencies

Table 3 presents the top 10 funding agencies that have contributed significantly to this field. The findings suggest that these institutions have collectively contributed to 23.84% of the total documents published in this field. In particular, the National Natural Science Foundation of China (n = 91; 8.58%), the National Institutes of Health (n = 67; 6.31%), the National Institute of Diabetes and Digestive and Kidney Diseases (n = 32; 3.02%), and the National Key Research and Development Program of China (n = 32; 3.02%) emerged as key players in funding. It is worth mentioning that the United States has made the largest contribution to this field, with the majority of active funding agencies being based in the country. In fact, four of the represented funding agencies are from the United States.

Top active journals

Table 4 presents the top 10 journals ranked by number of publications. In total, these journals have published 228 articles, representing approximately 21.49% of all publications. The journal with the highest number of articles is *Nutrients*, which has published 50 articles. *Plos One* follows with 26 articles, *Scientific Reports* with 24 articles, and European *Journal of Nutrition Clinical Nutrition* with 20 articles.

Analysis of citations

Based on citation analysis, it was found that the retrieved articles had received an average of 40.9 citations, resulting in an h-index of 96 and a total of 43393 citations. Among these articles, 102 did not receive any citations, while 92 received more than 100

citations. The number of citations for these articles ranged from 0 to 1977. Table 5 presents the top ten publications[81-90] related to RCTs and the gut microbiota, which collectively received 7894 citations with a citation range of 414 to 1977.

Co-occurrence analysis

By examining the frequency of terms in article titles and abstracts, a co-occurrence network was generated with the aim of identifying current research trends and important topics that play a critical role in the advancement of science. Figure 3 illustrates the network that comprises 222 terms that were selected from a pool of 24653 terms based on a minimum frequency of 30 occurrences. These terms were further classified into three distinct clusters, with the most frequent terms assigned to specific categories, namely: (1) Interventions targeting the gut microbiota to manage obesity (red cluster); (2) the efficacy and safety of fecal microbiota transplantation (green cluster); and (3) the impact of dietary interventions on the gut microbiota in humans (blue cluster).

Future research direction analysis

Figure 4 of VOSviewer employs a color-coded system to represent each term uniquely based on its average frequency in all retrieved publications. The color spectrum varies from yellow for the latest terms to blue for the older ones. Previous studies in this field focused mainly on exploring the effects of dietary interventions on the human gut microbiota before 2019. However, in recent years, new avenues of study have surfaced, including "managing obesity by targeting the gut microbiota" and "assessing the safety and efficacy of fecal microbiota transplantation".

DISCUSSION

In this investigation, we used information visualization techniques to analyze primary research articles that examined RCTs and gut microbiota published between 2003 and 2022. Based on the trends we observed, which demonstrated a steady increase in

scientific publications over the two-decade period, we have concluded that the gut microbiota has emerged as a rapidly growing and increasingly important area of research. The surge of research activity that followed 2017 can be attributed to seminal publications that have significantly contributed to our understanding of intestinal microbiota diversity, enterotype, sequencing data analysis, and their associations with digestive disorders, particularly inflammatory bowel disease (IBD) and obesity. These publications, which were published between 2009 and 2017[81-90], attracted considerable attention from researchers in this field, leading to an exponential increase in the number of publications.

The annual number of publications on the gut microbiota exhibits exponential growth (Figure 1), indicating that this research area is a vibrant and continuously expanding research field. This observation is consistent with previous studies[20-22,91]. Researchers should keep a constant focus on the trends in this field to reveal additional connections between humans and the gastrointestinal microbiome. China is the leading contributor to publications, which may be attributable to the emphasis placed on studying the human microbiome highlighted by the National Natural Science Foundation of China, the 14th Five-Year National Key Research and Development Plan, and the Outline of the 2035 Vision Goals[21]. The United States is the second most productive country in terms of publication output, which may be related to the Human Microbiome Project (HMP) programme launched by the National Institutes of Health in 2007 and the Gut Microbiota Brain AXIS programme initiated in 2013[92,93].

The current study reveals that researchers have paid great attention to publications related to RCTs involving the gut microbiota, especially in recent years. They have published several outstanding articles in leading journals in the medical field, including *Gastroenterology*[85,89], *Nature Medicine*[90], *Nature*[88], *Lancet*[86], *Nature Reviews Gastroenterology and Hepatology*[82], and *JAMA-Journal of the American Medical Association*[84].

The article by Vrieze *et al*[89] published in *Gastroenterology* is the most cited, where the authors suggest a connection between alterations in the intestinal microbiota, insulin

resistance, and obesity. In this study, researchers looked at what would happen if they gave men with metabolic syndrome the gut microbiota of lean donors. The goal was to see how the microbiota and receivers' glucose usage changed. The people who took part were given either allogeneic or autologous microbiota infusions in their small intestines. Six weeks after getting a microbiota infusion from lean donors, the insulin sensitivity of the people who got the infusion improved (the median rate of glucose leaving the body went from 26.2 mol/kg/min to 45.3 mol/kg/min; P 0.05)[89]. Furthermore, the levels of the intestinal microbiota that produce butyrate also showed an increase. These findings suggest that the intestinal microbiota may be developed as a therapeutic agent to improve human insulin sensitivity.

Moayyedi et al[85] published the second most cited article in Gastroenterology in 2015. In their study, the authors proposed that fecal microbiota transplantation induces remission in a considerably higher proportion of patients with active ulcerative colitis compared to placebo, with no notable variation in adverse effects. The outcomes are affected by the fecal donor and the duration of ulcerative colitis.

In 2017, Wu et al[90] published an article in Nature Medicine, which is the third most cited article. The authors discovered that their findings offer evidence to support the idea that the modified gut microbiota mediates certain antidiabetic effects of metformin.

The current study identified, visualized, and described three research hotspots in publications related to RCTs involving the gut microbiota. Among these, evaluating the safety and efficacy of fecal microbiota transplantation (FMT) was the main topic and received greater attention. FMT is a new therapy[46,94] being tested for autoimmune diseases[95], IBD[96,97], liver encephalopathy[98], and neurological disorders[99]. It has been extensively examined for recurrent Clostridium difficile infections[100-104]. FMT may assist patients with metabolic syndrome[105,106] and insulin resistance[107], especially when employing lean donors. This therapy increased gut microbiota diversity and insulin sensitivity.

The gut microbiome has been targeted to manage obesity in recent years. Weight gain and related comorbidities can be prevented or treated by manipulating gut flora[108].

Prebiotics, probiotics, synbiotics, FMT, and other therapies can be used[17]. These therapies depend on the structure and composition of the resident microbiota and a thorough understanding of the dynamic changes that occur over time[109,110]. Through intensive research, some processes of the gut microbiota have been better studied in relation to their association with obesogenic mechanisms. For example, one such process involves the participation of the gut microbiota in bile acid metabolism, which ultimately contributes in different ways to increased glucagon-like peptide 1 production. These effects result in improved glucose homeostasis, decreased fat absorption, reduced insulin resistance, and a decreased likelihood of weight gain[111]. The gut microbiota's impact on immune function modifications may also influence body weight control[112,113]. Numerous studies have also explored the impact of physical activity on the gut microbiota with the aim of improving body weight management[114,115].

Strengths and limitations

This study represents the first bibliometric analysis to evaluate the performance of scientific publications focused on RCTs involving the gut microbiota. Our findings provide valuable information for researchers seeking to identify research subjects, research hotspots, and development trends related to RCTs and the gut microbiota. However, it is important to acknowledge certain limitations. First, the study was conducted exclusively on publications in the Scopus database. Although Scopus is widely recognized as the most commonly used and trusted[116-120], a small number of outlier publications from alternative sources such as PubMed and Web of Science may have been omitted. However, this bibliometric study presents the initial comprehensive analysis of global publications on RCTs and gut microbiota using Scopus and VOSviewer. It showcases the advantages of bibliometric analysis in evaluating research productivity in this field in a standardized way. Second, although we used a comprehensive list of keywords based on previous systematic reviews and meta-analyses[54-59] and bibliometric studies[24,31,42,60,61], it is possible that certain pertinent

keywords could be overlooked, which could result in false negative results. Third, our selection of the ten most highly cited papers may have been influenced by the time-dependent nature of citation searches, which tend to favor older publications. Fourth, our analysis was limited to searching for titles and specific search phrases related to RCTs and gut microbiota, potentially missing relevant articles that used these terms as keywords or included them in the text. Finally, it is important to acknowledge that the results generated by Scopus reflect the nature and scope of the data it encompasses, which may lead to the scattering of research output from active institutions and the underrepresentation of certain funding agencies. To ensure the accuracy and impartiality of our results, we followed a specified methodology and avoided any manipulations or merging of the Scopus output.

CONCLUSION

Based on the results presented, the study of publications related to RCTs involving the gut microbiota has experienced a significant increase in research activity in the past two decades. A robust positive correlation is observed between the annual count of publications and the respective year of publication. International research collaboration has been depicted on a map with the United States, the United Kingdom, and China as the countries with the largest node sizes, indicating greater collaboration. China leads research, followed by the United States and United Kingdom. The co-occurrence analysis shows current gut microbiota research trends and important topics, such as obesity interventions targeting the gut microbiota, the efficacy and safety of fecal microbiota transplantation, and the effects of dietary interventions on humans. The findings imply that future research could focus on generating new therapies, researching the possibilities of fecal microbiota transplantation to treat various diseases, and studying the effects of dietary interventions on gut microbiota and human health.

ARTICLE HIGHLIGHTS

Research background

The gut microbiome contains bacteria, fungi, and viruses. Recent research reveals that the gut microbiota, the microbial community in the gastrointestinal tract, affects immune system function and host inflammation.

Research motivation

Clinical investigations have provided evidence of connections between the human microbiome and various diseases. However, fundamental inquiries still need to be addressed regarding the generalizability of this knowledge.

Research objectives

To identify and assess the current state and trends in global research output on randomized clinical trials (RCTs) centered on gut microbiota. Additionally, this study aimed to analyze the key areas of research visually focused within this particular sector.

Research methods

The body of literature on RCTs centered on the gut microbiota was compiled using the Scopus database and *Reference Citation Analysis* (RCA). In addition, VOSviewer software was utilized to assess the collected data from relevant scholarly articles visually.

Research results

This study is the first bibliometric analysis of worldwide research patterns on RCTs centered on gut microbiota. There has been a notable increase in scholarly works focusing on RCTs and gut microbiota in recent years. The results of our study indicate that future research will focus on interventions targeting obesity by manipulating the gut microbiota, evaluating the efficacy and safety of fecal microbiota transplantation, and exploring the impact of dietary interventions on the human gut microbiota.

Research conclusions

The report shows the tremendous expansion and importance of gut microbiota RCTs. Identifies major actors, research trends, and future prospects in this subject. The co-occurrence analysis also revealed key themes that promote science and suggested future study options.

Research perspectives

Over the past decades, a series of investigations have yielded compelling findings regarding the considerable significance of the gut microbiota in human health and its correlation with various diseases. The intricate and interconnected dynamics of gut fungi, bacteria, and the host's immune system play a crucial role in preserving the equilibrium of the host's physiological processes while also exerting an impact on the progression, advancement, and potential therapeutic outcomes of diseases.

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Table 1 The ten most active countries from 2003 to 2022 in research related to randomized controlled trials involving gut microbiota

Ranking	Country	No. of documents	%
1st	China	276	26.01
2nd	United States	254	23.94
3rd	United Kingdom	97	9.14
4th	Netherlands	76	7.16
5th	Italy	61	5.75
5th	South Korea	61	5.75

7[h]	Canada	60	5.66
8th	Spain	54	5.09
9th	Australia	53	5.00
10th	Denmark	52	4.90

Table 2 The top ten active institutions in research related to randomized controlled trials involving gut microbiota from 2003 to 2022

Ranking	Institute	Country	No. of documents	%
1st	Københavns Universitet	Denmark	38	3.58
2nd	Dankook University	South Korea	35	3.30
3rd	Ministry of Education China	China	30	2.83
4th	Wageningen University & Research	United States	28	2.64
5th	Harvard Medical School	United States	21	1.98
6th	University of Calgary	Canada	20	1.89
7th	Helsingin Yliopisto	Finland	19	1.79
7th	Chinese Academy of Sciences	China	19	1.79
9th	University of California, Davis	United States	18	1.70
10th	INSEM	France	17	1.60
10th	Instituto de Salud Carlos III	Spain	17	1.60

Table 3 The top ten funding agencies that have published the most research on randomized controlled trials involving gut microbiota between 2003 and 2022

Ranking	Funding agencies	Country	No. of documents	%
1st	National Natural Science Foundation of China	China	91	8.58
2nd	National Institutes of Health	United States	67	6.31
3rd	National Institute of Diabetes and Digestive and Kidney Diseases	United States	32	3.02
3rd	National Key Research and Development Program of China	China	32	3.02
5th	European Regional Development Fund	European Union	20	1.89
6th	Instituto de Salud Carlos III	Spain	18	1.70
6th	National Center for Advancing Translational Sciences	United States	18	1.70
8h	National Health and Medical Research Council	Australia	14	1.32
8th	National Research Foundation of Korea	South Korea	14	1.32
10th	National Cancer Institute	United States	13	1.23

Table 4 The leading journals with the most publications in research on randomized controlled trials involving gut microbiota from 2003 to 2022

Ranking	Journal/source title	No. of documents	%	IF[1]
1st	*Nutrients*	50	4.71	6.706
2nd	*Plos one*	26	2.45	3.752
3rd	*Scientific Reports*	24	2.26	4.996
4th	*European Journal of Nutrition*	20	1.89	4.865
5th	*American Journal of Clinical Nutrition*	19	1.79	8.472
5th	*Clinical Nutrition*	19	1.79	7.643
7th	*BMJ Open*	18	1.70	3.006
7h	*Journal of Nutrition*	18	1.70	4.687
9th	*Frontiers in Nutrition*	17	1.60	6.59
9th	*Gut*	17	1.60	31.793

[1]2021 *Journal Citation Reports™* (Clarivate, 2022).

IF: Impact factor.

Table 5 The ten most-cited articles that cited research involving randomized controlled trials on gut microbiota between 2003 and 2022

Ref.	Title	Year	Source title	Cited by	Impact index per article[1]
Vrieze *et al*[89], 2012	"Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome"	2012	*Gastroenterology*	1977	171.0
Moayyedi *et al*[85], 2015	"Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial"	2015	*Gastroenterology*	1012	116.3
Wu *et al*[90], 2017	"Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug"	2017	*Nature Medicine*	892	137.3
Subramanian *et al*[88], 2014	"Persistent gut microbiota immaturity in malnourished Bangladeshi children"	2014	*Nature*	773	89.7

Paramsothy et al[86], 2017	"Multidonor intensive fecal microbiota transplantation for active ulcerative colitis: A randomised placebo-controlled trial"	2017	*The Lancet*	754	118.3
Gareau et al[82], 2010	"Probiotics and the gut microbiota in intestinal health and disease"	2010	*Nature Reviews Gastroenterology and Hepatology*	596	43.5
Cani et al[81], 2009	"Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal"	2009	*American Journal of Clinical Nutrition*	534	36.6
Queipo-Ortuño et al[87], 2012	"Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers"	2012	*American Journal of Clinical Nutrition*	481	41.7
Lee et al[84], 2016	"Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with	2016	*JAMA-Journal of the American Medical Association*	461	62.3

	recurrent *clostridium difficile* infection a randomized clinical trial"				
Ianiro *et al*[83], 2018	"Randomised clinical trial: Faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection"	2015	*Alimentary Pharmacology and Therapeutics*	414	47.8

[1]The impact index per article is presented based on *Reference Citation Analysis* (Source: Baishideng Publishing Group Inc. Pleasanton, CA 94566, United States).

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