

# World Journal of *Clinical Cases*

*World J Clin Cases* 2020 July 6; 8(13): 2674-2892



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Semimonthly Volume 8 Number 13 July 6, 2020

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Electronic Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaojian Wu, Editorial Office Director: Jin-Lei Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Semimonthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

July 6, 2020

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Bibliometric analysis of subject trends and knowledge structures of gut microbiota

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**Supported by** the Liaoning Provincial Key R and D Guidance Plan Project in 2018, No. 2018225009 and the Liaoning Colleges and Universities Basic Research Project, No. LFWK201710.

**Conflict-of-interest statement:** All the authors declare that they have no competing interests.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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### Abstract

#### BACKGROUND

Gut microbiota is an emerging field of research, with related research having breakthrough development in the past 15 years. Bibliometric analysis can be applied to analyze the evolutionary trends and emerging hotspots in this field.

#### AIM

To study the subject trends and knowledge structures of gut microbiota related research fields from 2004 to 2018.

#### METHODS

The literature data on gut microbiota were identified and downloaded from the PubMed database. Through biclustering analysis, strategic diagrams, and social network analysis diagrams, the main trend and knowledge structure of research fields concerning gut microbiota were analyzed to obtain and compare the research hotspots in each period.

#### RESULTS

According to the strategic coordinates and social relationship network map, Clostridium Infections/microbiology, Clostridium Infections/therapy, RNA, Ribosomal, 16S/genetics, Microbiota/genetics, Microbiota/immunology,



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**Manuscript source:** Unsolicited manuscript

**Received:** April 7, 2020

**Peer-review started:** April 7, 2020

**First decision:** April 28, 2020

**Revised:** May 5, 2020

**Accepted:** May 30, 2020

**Article in press:** May 30, 2020

**Published online:** July 6, 2020

**P-Reviewer:** Antaki N, Lion M, Pavlovic M

**S-Editor:** Zhang H

**L-Editor:** Filipodia

**E-Editor:** Liu JH



Dysbiosis/immunology, Inflammation/immunology, Fecal Microbiota Transplantation/methods, Fecal Microbiota Transplantation can be used as an emerging research hotspot in the past 5 years (2014-2018).

## CONCLUSION

Some subjects were not yet fully studied according to the strategic coordinates; and the emerging hotspots in the social network map can be considered as directions of future research.

**Key words:** Gut microbiota; Bibliometric analysis; Co-word analysis; Strategic coordinates; Social relationship network analysis

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**Core tip:** In this study, the co-word analysis method was used for the first time to study the subject trends and knowledge structures of gut microbiota related research fields from 2004 to 2018. Our results indicate that some subjects have not been not fully studied yet, and the emerging hotspots in the social network map can be considered as a direction of future research.

**Citation:** Yue YY, Fan XY, Zhang Q, Lu YP, Wu S, Wang S, Yu M, Cui CW, Sun ZR. Bibliometric analysis of subject trends and knowledge structures of gut microbiota. *World J Clin Cases* 2020; 8(13): 2817-2832  
**URL:** <https://www.wjgnet.com/2307-8960/full/v8/i13/2817.htm>  
**DOI:** <https://dx.doi.org/10.12998/wjcc.v8.i13.2817>

## INTRODUCTION

The microbiota is a collection of all microbe groups in a microbial community, such as bacteria, archaea, fungi, and protists. The gut microbiota is a collection of all microbe groups in the intestinal microbial community<sup>[1,2]</sup>. Gut microbiota is composed of thousands of different types of bacteria, of which more than 98% include four bacterial phyla: *Firmicutes*, *Bacteroides*, *Proteobacteria*, and *Actinobacteria* (dominantly *Firmicutes* or *Bacteroides*)<sup>[3-5]</sup>. Various important functions are executed by gut microbiota, such as production of vitamins, metabolism of dietary compounds, and prevention of distension and systemic infiltration by gut pathogens<sup>[6-8]</sup>. The microbiome plays a potential role in human health, including early in life<sup>[9,10]</sup> and in some special diseases such as cardiac metabolic disorders, inflammatory bowel diseases, nervous/mental diseases, and cancer<sup>[11-13]</sup>. As shown by numerous recent studies, gut microbiota is very relevant to infection<sup>[14-17]</sup>. As a new therapy, fecal microbiota transplantation has been applied increasingly to treat *Clostridium difficile* infection, inflammatory bowel diseases, irritable bowel syndrome, and colon cancer<sup>[18-21]</sup>. In the past 15 years, there has been great progress in understanding various physiological and pathological functions of gut microbiota<sup>[22-24]</sup>. With the recent development of bibliometrics, the effects of gut microbiota in obesity and the research hotspots of gastrointestinal microbiota have been further studied<sup>[5,25]</sup>.

In this study, the trends in the research field of gut microbiota were revealed by bibliometric analysis. As a set of special methods, bibliometrics can be used for quantitative analysis of hotspots in the literature. Co-word analysis, as the most common method, can estimate the relationship between two specialized words in relevant literature. In the present study, the specialized words extracted were first classified using biclustering analysis, and then their evolutionary trend and subjects were analyzed by strategic diagram and social network analysis (SNA)<sup>[26,27]</sup>.

## MATERIALS AND METHODS

### Data collection

Literature data on gut microbiota were identified and downloaded from the PubMed database. As a source of medical words collected by the American National Library of

Medicine, Medical Subject Heading (MeSH) was applied in the search index and catalog articles of PubMed. Language was limited to English, literature type was limited to journal article, and human was designated to exclude other species. Relevant articles in PubMed were searched through the following strategies: Gut microbiome OR Gut microflora OR Gut microbiota OR Gut flora OR Intestinal microbiome OR Microbiome microbiota OR Intestinal microflora OR Intestinal flora. In order to analyze the subject trend and knowledge structure of gut microbiota over the past 15 years, literature was divided into three 5-year-periods according to publication date: from 1 January 2004 to 31 December 2008; from 1 January 2009 to 31 December 2013; and from 1 January 2014 to 31 December 2018. The search results were screened by two investigators according to title, abstract, and full text. Finally, data of 1057, 2757, and 7648 articles were obtained from these three periods, respectively.

### **Data extraction and bibliographic matrix setup**

The data of the three periods were accurately extracted by Bibliographic Item Co-Occurrence Matrix Builder. The following information was extracted: Year of literature, journal, country, author, first author, and major MeSH terms/MeSH subheadings. Finally, the term-source article and co-occurrence matrixes were generated as the data basis for subsequent bibliometric analysis<sup>[28,30]</sup>. The high-frequency major MeSH terms/MeSH subheadings were firstly counted using the Donohue equation; then the lexical matrix and co-occurrence matrix were constructed through Bibliographic Item Co-Occurrence Matrix Builder according to the high-frequency major MeSH terms/MeSH subheadings<sup>[29]</sup>.  $T = [1 + (1 + 8i)^{1/2}]/2$ . Wherein,  $i$  represents major MeSH terms/MeSH subheadings occurring in all extracted data only once.

### **Biclustering analysis of high-frequency major MeSH terms/MeSH subheadings**

Biclustering analysis was performed for high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifiers of searched articles on gut microbiota. Through the repeated dichotomization method in gCLUTO software, mountain visualization was clustered, and a visual matrix constructed<sup>[30]</sup>. In the mountain visualization, one cluster was represented by a peak. The position, volume, height, and color of each peak corresponded to the cluster and its relevant information. The color of each peak indicated the effect of biclustering analysis: A good effect was indicated by red and a poor effect by blue.

### **Strategic diagram analysis**

The intra-field relations and inter-field interactions in the research field of gut microbiota were analyzed by strategic diagram, and then the research hotspot problems in this field were further analyzed. In strategic diagrams, there are two axes: The X axis indicates the density to represent the capability of this cluster for self-maintenance and self-development; and the Y axis indicates the centrality to represent the interaction degree between the research field of gut microbiota and other fields. In 1991, the calculation methods for density and centrality were given by Callon *et al.*<sup>[30]</sup>. Four quadrants are formed by the X and Y axes. The biclustering analysis allocates the major MeSH terms/MeSH subheadings into different quadrants. The changes in the research field of gut microbiota were clearly shown by comparing the strategic diagrams in the three periods. The strategic diagrams were generated by GraphPad 5 software (La Jolla, CA, United States).

### **Social network analysis**

The knowledge structure data were analyzed by SNA. Centrality measurement is the most important research method for social relationship network analysis. The closeness centrality of a node is associated with the number of its connections with other nodes in this network and to a certain degree represents the importance of this node for the network. The higher the betweenness index is, the stronger is the capability for controlling other nodes. In this study, the betweenness index was selected as an evaluation index. The research field of gut microbiota was clearly shown in the SNA diagram.

The SNA network was constructed by Ucinet 6.0 software (Analytic Technologies Co., Lexington, KY, United States) based on the co-occurrence matrix of high-frequency major MeSH terms/MeSH subheadings and displayed in a 2D map by NetDraw 2.084 software. Major MeSH terms/MeSH subheadings were represented by the nodes, and their co-occurrence frequency was represented by the links.

## RESULTS

### ***Distribution characteristics of related publications***

From the three periods (1 January 2004 to 31 December 2008; 1 January 2009 to 31 December 2013; and 1 January 2014 to 31 December 2018), 1057, 2757, and 7648 articles were obtained, respectively, and a comparison analysis was performed. The annual number of articles on gut microbiota increased by nearly 10 fold, from 159 in 2004 to 1545 in 2018 (Figure 1). It was noteworthy that the number of articles on gut microbiota in 2018 decreased compared with 2017. The top 10 publication countries, journals, and authors of articles in each period (Table 1) showed the core change of literature in the research field of gut microbiota in the past 15 years. The first and second highest publication rates in these three periods were in the United States and the United Kingdom; the proportion of publications decreased gradually in the Russian Federation; and increasing numbers of contributions were made in Australia and the United Arab Emirates.

During 2004–2008, the top three journals were *Journal of Nutrition*, *British Journal of Nutrition*, and *Journal of Clinical Gastroenterology*, accounting for 8.1% of all publications. During 2009–2013, the first and third journals were replaced by *PLoS One* and *Gut Microbes*. During 2014–2018, the top three journals were *PLoS One*, *Scientific Reports*, and *Nutrients*. Overall, most articles in this field were published by *PLoS One* during the 15 years. In terms of authors, the greatest contributors were Isolauri E during 2004–2008, de Vos WM during 2009–2013, and Wang J during 2014–2018.

### ***Identification of hotspots based on the clusters of major MeSH terms***

In this study, 50, 44, and 66 high-frequency major MeSH terms/MeSH subheadings were extracted from relevant literature in the three periods, with occurrence frequencies of 33.6886%, 33.8091% and 33.8794%, respectively. These major MeSH terms/MeSH subheadings were regarded as research hotspots of gut microbiota in the recent 15 years.

The MeSH terms in the articles during 2004–2008 were classified into five clusters by biclustering analysis. The mountain and matrix visualization of these major MeSH terms/MeSH subheadings are shown in Figure 2. According to the matrix visualization, 50 high-frequency major MeSH terms/MeSH subheadings were allocated into five groups. The relationship of these major MeSH terms/MeSH subheadings with articles is shown by the hierarchical tree at the left and top. The representative articles are clearly indicated by the identified subjects in these clusters. Fifty high-frequency major MeSH terms/MeSH subheadings are shown in the right part, representing the MeSH terms involved in each cluster; the mountain visualization is shown at the right upper corner. Clusters 1 and 3 with red peaks indicate the most significant results.

The biclustering analyses of high-frequency major MeSH terms/MeSH subheadings during the periods 2009–2013 and 2014–2018 are shown in Figure 3 and Figure 4, respectively. In these two periods, 44 and 66 high-frequency major MeSH terms/MeSH subheadings were classified into four and six clusters, respectively. The biclustering analysis results on high-frequency major MeSH terms/MeSH subheadings in the research field of gut microbiota in three periods are shown in Table 2.

### ***Subject trend of gut microbiota***

Strategic diagrams were defined by Callon *et al*<sup>[30]</sup>. As shown in Figure 5, the motor-themes lie in quadrant I (at the right upper corner), which has strong centrality and high density. As well as these themes generally have high development and strong internal relationship with each other. The specialized themes lie in quadrant II (at the left upper corner), which has insufficient external interaction and high density. These themes are generally considered as close to perfection. The subjects in quadrant III (at the left lower corner) have a low density and insufficient centrality, and are generally considered as emerging or disappearing subjects. The subjects in quadrant IV (at the right lower corner) have very strong centrality but low internal density, and the internal clusters are mature to a certain degree.

In the strategic diagram, the subjects are identified in different quadrants by spheres according to the density and centrality that separately represent the internal and external cohesiveness. The development trends of gut microbiota in the different periods are shown in three strategic diagrams. The clusters in the strategic diagrams show the results of biclustering analysis from Table 2. The areas of spheres represent



**Table 1 Temporal distribution of gut microbiota related publications in PubMed (during the periods of 2004-2008, 2009-2013 and 2014-2018)**

Period	Rank	Country	Publications, n (%)	Top journal	Publications, n (%)	Author, number of papers
2004-2008	1	United States	406 (37.3)	<i>The Journal of Nutrition</i>	35 (3.2)	Isolauri E (27)
	2	England	307 (28.2)	<i>The British Journal of Nutrition</i>	30 (2.7)	Salminen S (25)
	3	Netherlands	73 (6.7)	<i>Journal of Clinical Gastroenterology</i>	25 (2.2)	Gibson GR (20)
	4	Russia (Federation)	45 (4.1)	<i>Applied and Environmental Microbiology</i>	23 (2.1)	Doré J (17)
	5	Germany	40 (3.6)	<i>Zhurnal Mikrobiologii, Epidemiologii, I immunobiologii</i>	20 (1.8)	Knol J (14)
	6	Switzerland	31 (2.8)	<i>Journal of Agricultural and Food Chemistry</i>	19 (1.7)	Blaut M (13)
	7	France	27 (2.4)	<i>Journal of Pediatric Gastroenterology and Nutrition</i>	19 (1.7)	Gordon JI (13)
	8	Japan	26 (2.3)	<i>Alimentary Pharmacology and Therapeutics</i>	15 (1.3)	Boehm G (11)
	9	China	18 (1.6)	<i>The American Journal of Gastroenterology</i>	12 (1.0)	Shanahan F (11)
	10	Italy	12 (1.1)	<i>Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology</i>	12 (1.0)	Kim DH (10)
	Total		985 (90.5)		210 (19.2)	
2009-2013	1	United States	1174 (40.4)	<i>PLoS One</i>	145 (4.9)	de Vos WM (44)
	2	England	884 (30.4)	<i>Gut Microbes</i>	57 (1.9)	O'Toole PW (34)
	3	Netherlands	177 (6.1)	<i>The British Journal of Nutrition</i>	53 (1.8)	Doré J (32)
	4	Switzerland	125 (4.3)	<i>Journal of Agricultural and Food Chemistry</i>	48 (1.6)	Knight R (28)
	5	Germany	99 (3.4)	<i>Anaerobe</i>	38 (1.3)	Gordon JI (25)
	6	Russia (Federation)	49 (1.6)	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	36 (1.2)	Gibson GR (25)
	7	France	46 (1.5)	<i>Inflammatory Bowel Diseases</i>	33 (1.1)	Shanahan F (24)
	8	China	32 (1.1)	<i>Digestive Diseases (Basel, Switzerland)</i>	31 (1.0)	Raoult D (24)
	9	United Arab Emirates	26 (0.8)	<i>Current Opinion in Gastroenterology</i>	31 (1.0)	Salminen S (24)
	10	Spain	26 (0.8)	<i>Nature Reviews. Gastroenterology and Hepatology</i>	27 (0.9)	Isolauri E (23)
	Total		2638 (90.9)		499 (17.1)	
2014-2018	1	United States	3013 (39.4)	<i>PLoS One</i>	247 (3.2)	Wang J (87)
	2	England	2394 (31.3)	<i>Scientific Reports</i>	149 (1.9)	Li J (80)
	3	Netherlands	467 (6.1)	<i>Nutrients</i>	148 (1.9)	Wang X (68)
	4	Switzerland	446 (5.8)	<i>Gut Microbes</i>	138 (1.8)	de Vos WM (60)
	5	Germany	312 (4.0)	<i>World Journal of Gastroenterology</i>	132 (1.7)	Wang Y (59)
	6	China	119 (1.5)	<i>Microbiome</i>	100 (1.3)	Li Y (58)
	7	Japan	105 (1.3)	<i>Food and Function</i>	93 (1.2)	Zhang X (50)
	8	France	97 (1.2)	<i>Gut</i>	80 (1.0)	Gasbarrini A (49)
	9	United Arab Emirates	76 (0.9)	<i>International Journal of Molecular Sciences</i>	67 (0.8)	Li L (49)
	10	Australia	62 (0.8)	<i>Journal of Agricultural and Food Chemistry</i>	67 (0.8)	Cryan JF (48)
	Total		7091 (92.8)		1221 (15.9)	

the number of high-frequency major MeSH terms/MeSH subheadings in each cluster.

In 2004-2008, cluster 0 was in quadrant I with strong centrality and high density, indicating that intestinal mucosa and intestines metabolism and probiotics pharmacology were at the core of all aspects of research during this period. Clusters 1-4 in quadrant III showed that studies in inflammatory bowel diseases microbiology

**Table 2 Results of biclustering analysis on high-frequency major Medical Subject Heading terms/Medical Subject Heading subheadings in the research field of gut microbiota in three periods**

Period	Cluster	Number of MeSH terms <sup>1</sup>	Cluster analysis
2004-2008	0	1, 8, 12, 15, 19, 23, 31, 46	(1) Intestinal mucosa and intestines metabolism; and (2) Probiotics pharmacology.
	1	6, 7, 13, 17, 22, 28, 34, 36, 44	(1) Inflammatory bowel diseases microbiology and immunology; (2) Gut microbiota immunology; and (3) Intestinal mucosa immunology and microbiology.
	2	5, 9, 20, 25, 26, 29, 35, 39, 40, 41, 48	(1) <i>Bifidobacterium</i> metabolism, physiology and drug effects; and (2) <i>Bifidobacterium</i> growth and development.
	3	2, 10, 16, 21, 27, 32, 33, 38, 42, 49	(1) Inflammatory bowel disease drug therapy; and (2) Probiotics therapeutic use.
	4	3, 4, 11, 14, 18, 24, 30, 37, 43, 45, 47, 50	(1) Feces microbiology and gastrointestinal tract microbiology; (2) Gut microbiota isolation, purification classification, growth and development; and (3) Irritable bowel syndrome microbiology.
2009-2013	0	8, 17, 21, 25, 26, 29, 31, 34, 35	(1) Gastrointestinal tract immunology; (2) Inflammatory bowel diseases microbiology and immunology; and (3) Intestinal mucosa microbiology and immunology.
	1	10, 20, 23, 30, 33, 39, 42, 44	(1) Anti-bacterial agents pharmacology, therapeutic use and adverse effects; and (2) Gut microbiota growth and development.
	2	3, 4, 14, 15, 18, 19, 22, 28, 32, 38, 40, 43	(1) Irritable bowel syndrome microbiology; (2) Gut microbiota classification, isolation and purification; and (3) Feces microbiology.
	3	1, 2, 5, 6, 7, 9, 11, 12, 13, 16, 24, 27, 36, 37, 41	(1) Intestines and intestinal mucosa metabolism; (2) Gastrointestinal tract microbiology; (3) Obesity microbiology; and (4) Probiotics pharmacology and therapeutic use.
2014-2018	0	7, 9, 15, 17, 27, 28, 31, 46, 55, 65	(1) Gut microbiota genetics; (2) Metagenomics methods; and (3) Feces microbiology.
	1	8, 23, 30, 32, 38, 40, 57, 58, 59, 60, 66	(1) Inflammatory bowel diseases immunology; (2) Fecal microbiota transplantation methods; (3) Gastrointestinal tract and intestinal mucosa immunology; and (4) Intestinal mucosa immunology.
	2	18, 20, 21, 29, 34, 42, 44, 53, 54, 56	(1) Irritable bowel syndrome microbiology; (2) Dysbiosis microbiology; (3) Gut microbiota growth and development; and (4) Intestinal mucosa microbiology.
	3	1, 4, 5, 10, 11, 14, 19, 25, 45, 51, 61	(1) Probiotics therapeutic use; and (2) Intestines and intestinal mucosa metabolism.
	4	6, 13, 22, 24, 26, 35, 37, 41, 47, 48, 62, 63	(1) Anti-bacterial agents pharmacology, therapeutic use and adverse effects; and (2) Prebiotics therapeutic use and pharmacology.
	5	2, 3, 12, 16, 33, 36, 39, 43, 49, 50, 52, 64	(1) Gastrointestinal tract microbiology; and (2) Non-alcoholic fatty liver disease, obesity and diabetes mellitus (type2) microbiology.

<sup>1</sup>Represents the serial number of high-frequency major Medical Subject Heading (MeSH) terms/MeSH subheadings in each period which shown in Supplementary Tables 5-7.

and immunology, gut microbiota immunology, intestinal mucosa immunology and microbiology, *Bifidobacterium* metabolism, physiology and drug effects, *Bifidobacterium* growth and development, feces microbiology and gastrointestinal tract microbiology, inflammatory bowel disease drug therapy, probiotics therapeutic use, irritable bowel syndrome microbiology, gut microbiota isolation, purification classification, growth and development, and *Bifidobacterium* isolation and purification were not yet mature.

During 2009-2013, intestinal mucosa and intestine metabolism were still research emphases, and there were also some new hotspot subjects, such as gut microbiota physiology, gastrointestinal tract microbiology and metabolism, obesity microbiology, and probiotics therapeutic use. Some immature subjects in the previous period had developed continuously, and so were considered as developing subjects in this period, such as irritable bowel syndrome microbiology, feces microbiology and gastrointestinal tract microbiology, probiotics therapeutic use, and gut microbiota classification, isolation, and purification. Compared with 2009-2013, some subjects remained as key research points during 2014-2018, such as intestinal mucosa and intestine metabolism, probiotics therapeutic use, gastrointestinal tract microbiology, obesity microbiology, and irritable bowel syndrome microbiology. However, some hotspot subjects also emerged in quadrant I, such as dysbiosis microbiology, non-alcoholic fatty liver disease, and diabetes mellitus (type 2) microbiology. Likewise, some immature subjects in the previous period became mature, such as intestinal mucosa microbiology and gut microbiota growth and development. It was noteworthy

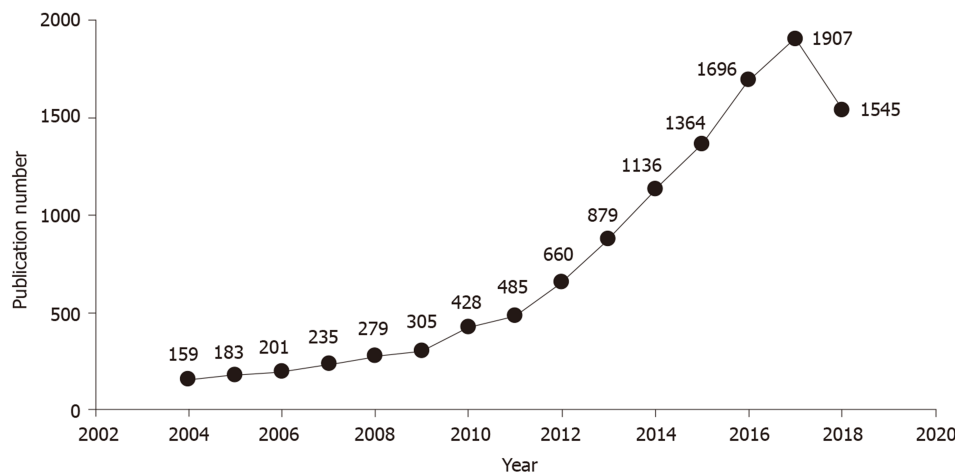


Figure 1 The number of gut microbiota related publications in 2004-2018.

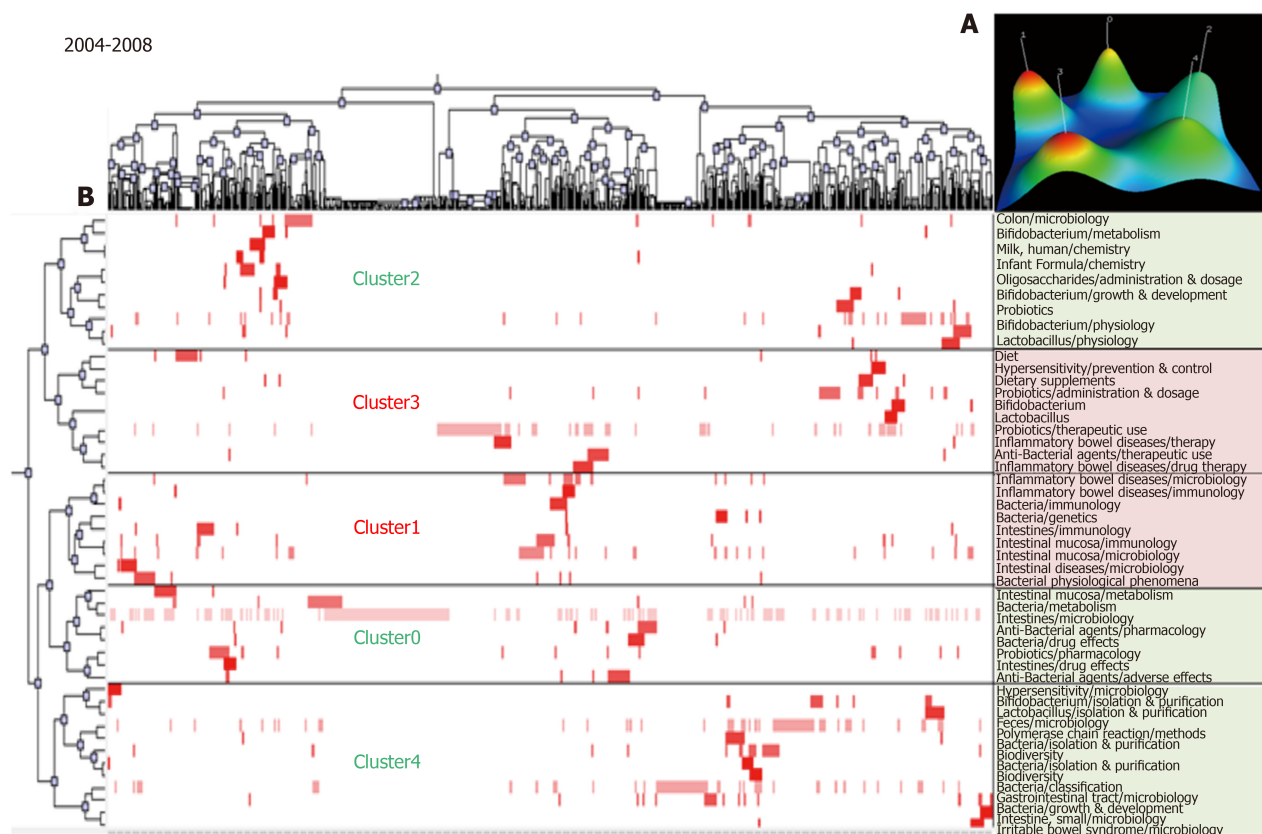


Figure 2 Biclustering analysis of 50 high frequency major Medical Subject Heading terms/Medical Subject Heading subheadings from 2004 to 2008. A: Mountain visualization of biclustering of 50 high frequency major Medical Subject Heading (MeSH) terms/MeSH subheadings and articles; B: Matrix visualization of biclustering for 50 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifiers.

that some new immature subjects occurred in quadrant III in this period, such as gut microbiota genetics, metagenomics methods, fecal microbiota transplantation methods, and prebiotics therapeutic use and pharmacology.

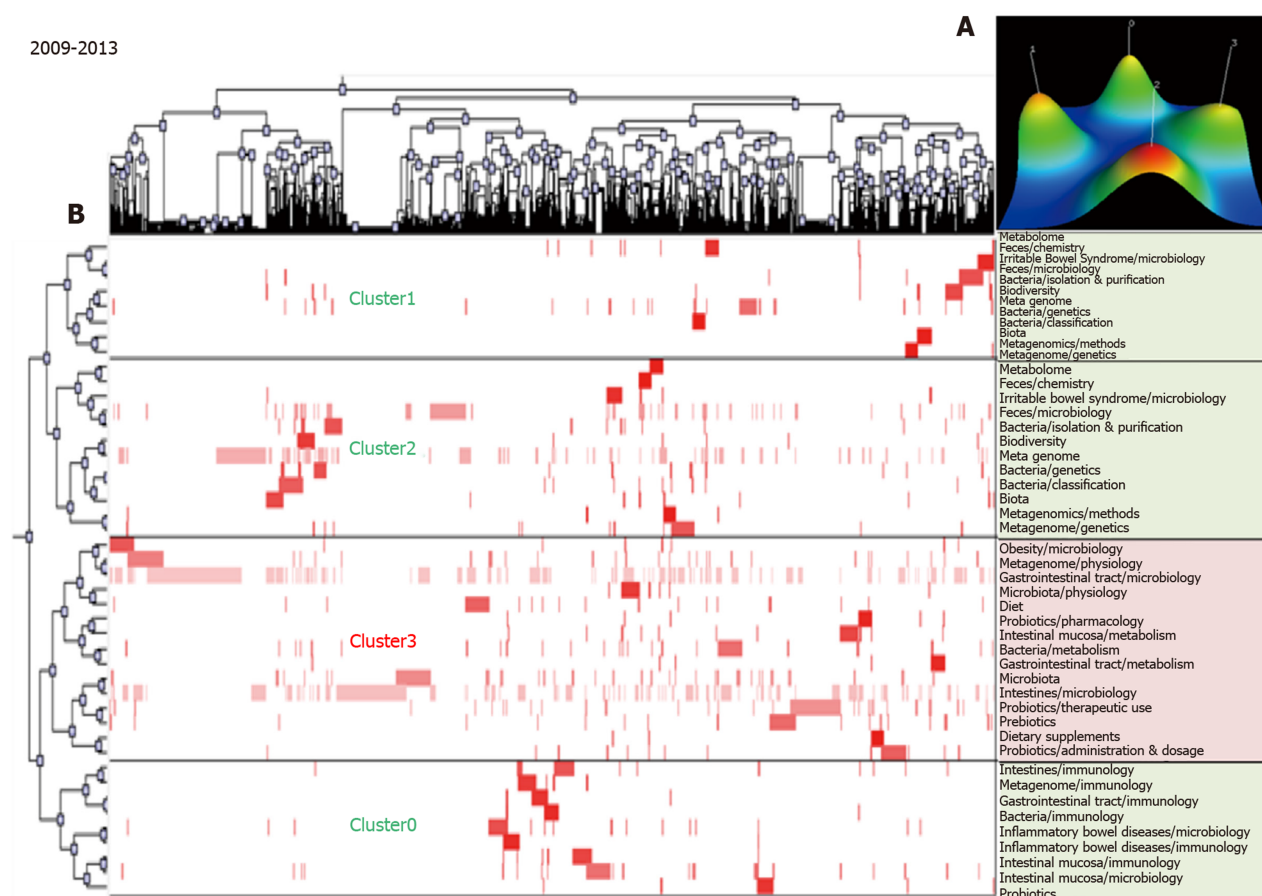
### Knowledge structure of gut microbiota

Three SNA diagrams are shown in Figure 6. In order to understand better the results, the knowledge structure of the SNA network was analyzed with three indices (*i.e.* degree, betweenness, and closeness); the dimension of nodes was directly proportional to the centrality of major MeSH terms/MeSH subheadings; and the size of lines represented collinear frequency.

In the SNA network for 2004–2008, 11 major MeSH terms/MeSH subheadings (*i.e.*



2009-2013



**Figure 3** Biclustering analysis of 44 high frequency major Medical Subject Heading terms/Medical Subject Heading subheadings from 2009 to 2013. A: Mountain visualization of biclustering of 44 high frequency major Medical Subject Heading (MeSH) terms/MeSH subheadings and articles; B: Matrix visualization of biclustering for 44 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifiers.

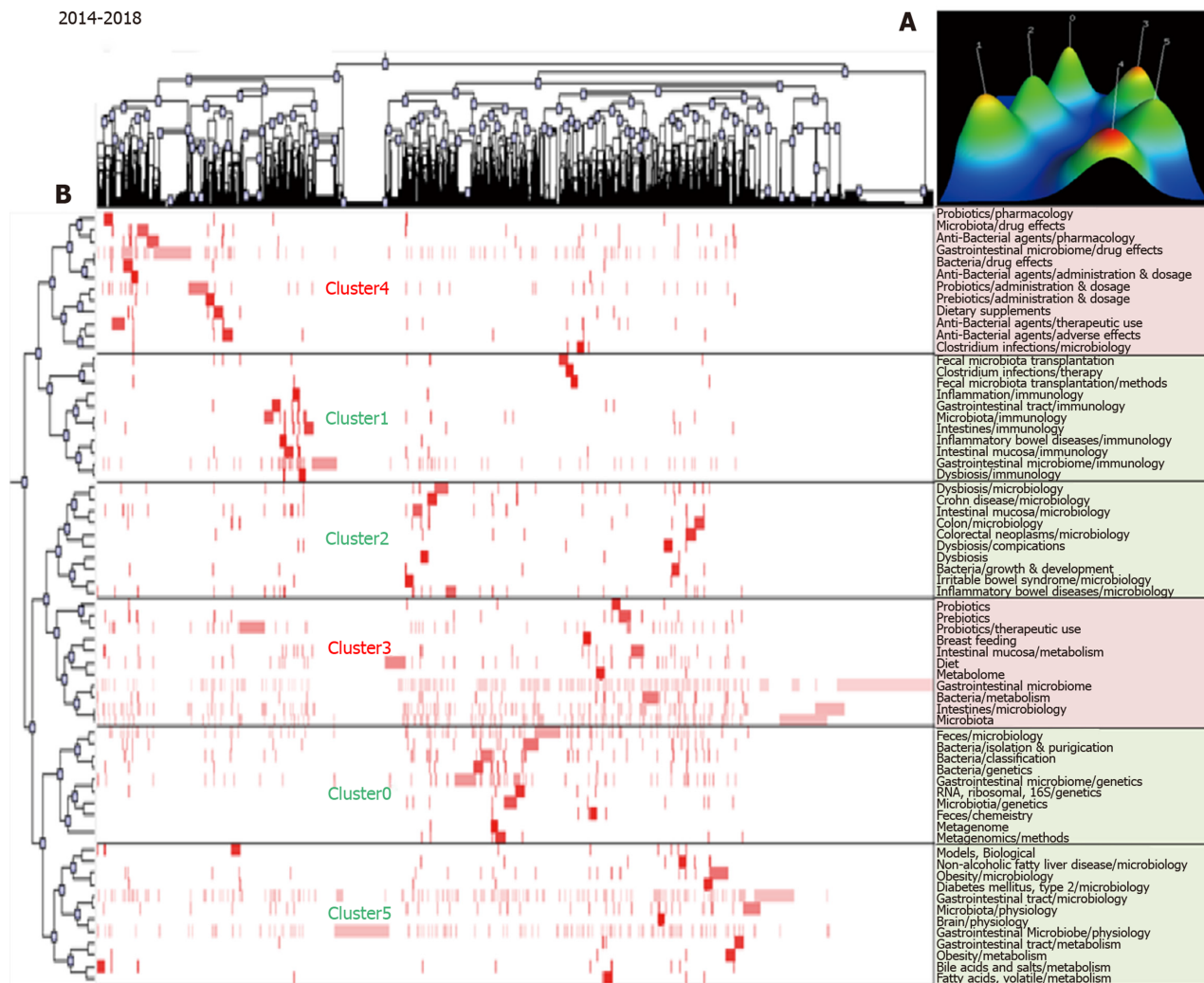
blue and yellow spheres in Figure 6A) had a high centrality ( $> 16.4$ ), of which Intestines/microbiology was the highest centrality (315, Supplementary Table 1). The first two betweenness indices were 160.08 and 73.69 (Supplementary Table 1), representing Intestines/microbiology and Feces/microbiology, respectively. These two major MeSH terms/MeSH subheadings played a strong mediation effect in the network, with closeness values of 47.50 and 42.50, respectively, indicating that they were closely connected with other nodes (Supplementary Table 1).

In addition to the above two major MeSH terms/MeSH subheadings, other major MeSH terms/MeSH subheadings had a strong mediation effect, such as Gastrointestinal tract/microbiology, Probiotics/therapeutic use, Probiotics, Intestinal mucosa/microbiology, Bacteria/growth and development, Probiotics/pharmacology, Probiotics/administration and dosage, Colon/microbiology, and Intestinal mucosa/immunology. Therefore, these terms played an important mediation role in the network. The mean betweenness value was  $16.46 \pm 1.40$  (Supplementary Table 2).

Compared with 2004-2008, seven new major MeSH terms/MeSH subheadings were added (purple circles in Figure 6B) in the SNA diagram during 2009-2013, including Metagenome/physiology, Metagenome, Bacteria/classification, Inflammatory bowel diseases/microbiology, Microbiota, and Bacteria/metabolism and prebiotics. Gastrointestinal tract/microbiology had the highest betweenness value (Supplementary Table 3).

A total of four new nodes (purple triangles in Figure 6B) emerged at the edge of the network, including Metagenome/drug effects, Crohn's disease/microbiology, Metagenome/immunology, and Gastrointestinal tract/immunology. These four terms were considered key research points of gut microbiota during 2009-2013.

In the SNA of 2014-2018, nine new major MeSH terms/MeSH subheadings (green circles in Figure 6C) were present: Gastrointestinal microbiome/drug effects, Gastrointestinal microbiome/genetics, Diet, Bacteria/isolation and purification, Microbiota/Physiology, Gastrointestinal Microbiome, Gastrointestinal Microbiome/immunology, Dysbiosis/microbiology, and Gastrointestinal



**Figure 4** Biclustering analysis of 66 high frequency major Medical Subject Heading terms/Medical Subject Heading subheadings from 2014 to 2018. A: Mountain visualization of biclustering of 66 high frequency major Medical Subject Heading (MeSH) terms/MeSH subheadings and articles; B: Matrix visualization of biclustering for 66 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifiers.

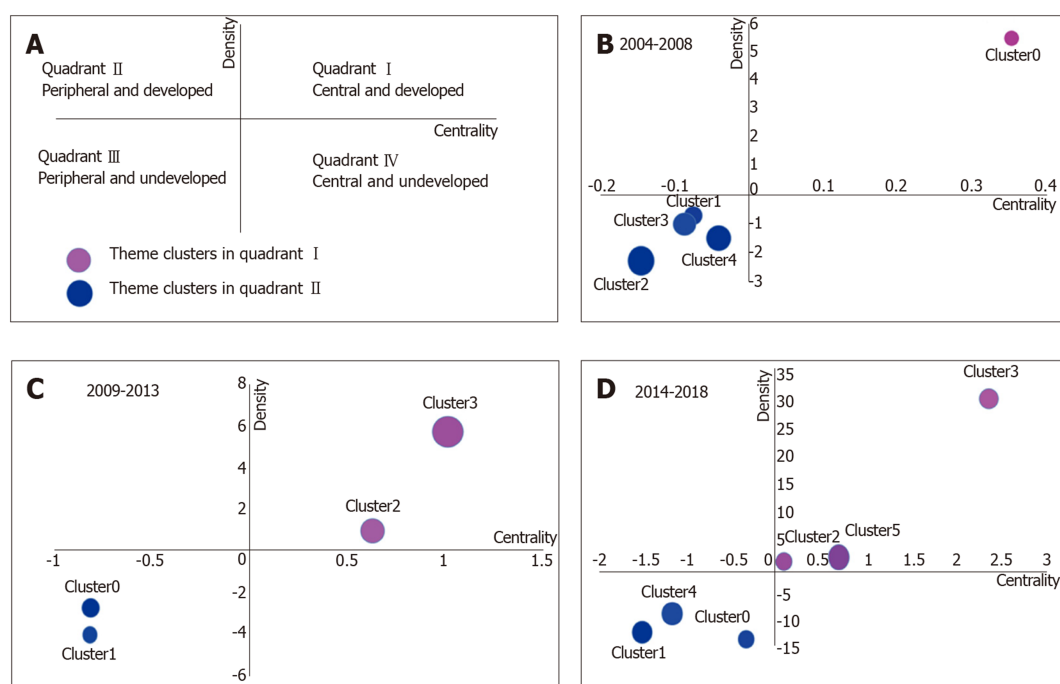
Microbiome/physiology.

There were nine new nodes in the edge of the network (green triangles in **Figure 6C**): Clostridium, Infections/microbiology, Clostridium Infections/therapy, RNA Ribosomal 16S/genetics, Microbiota/genetics, Microbiota/immunology, Dysbiosis/immunology, Inflammation/immunology, Fecal Microbiota Transplantation/methods, and Fecal microbiota transplantation. Thus, these nine terms were emerging hotspots for gut microbiota research in 2014-2018.

## DISCUSSION

As the potential clinical applications of gut microbiota are understood more deeply, the number of studies on gut microbiota has gradually increased, and this has become an emerging research field. In this study, the evolution of subject trend and knowledge structure in the past 15 years was analyzed in detail using co-word analysis, biclustering analysis, strategic diagrams, and SNA diagrams. Our assessment of global research on gut microbiota showed that relevant publications have increased rapidly in the past 15 years.

In 1977, the gut microbiota was discovered by Breznak *et al*<sup>[31]</sup> in wood-eating termites. Now, the gut microbiota is recognized as an overlooked system, and it plays an indispensable role in development of human biology. In the past 15 years, due to the rapid development of new-generation sequencing technology and metabolomics, understanding of the composition and functions of human gut microbiota is increasing



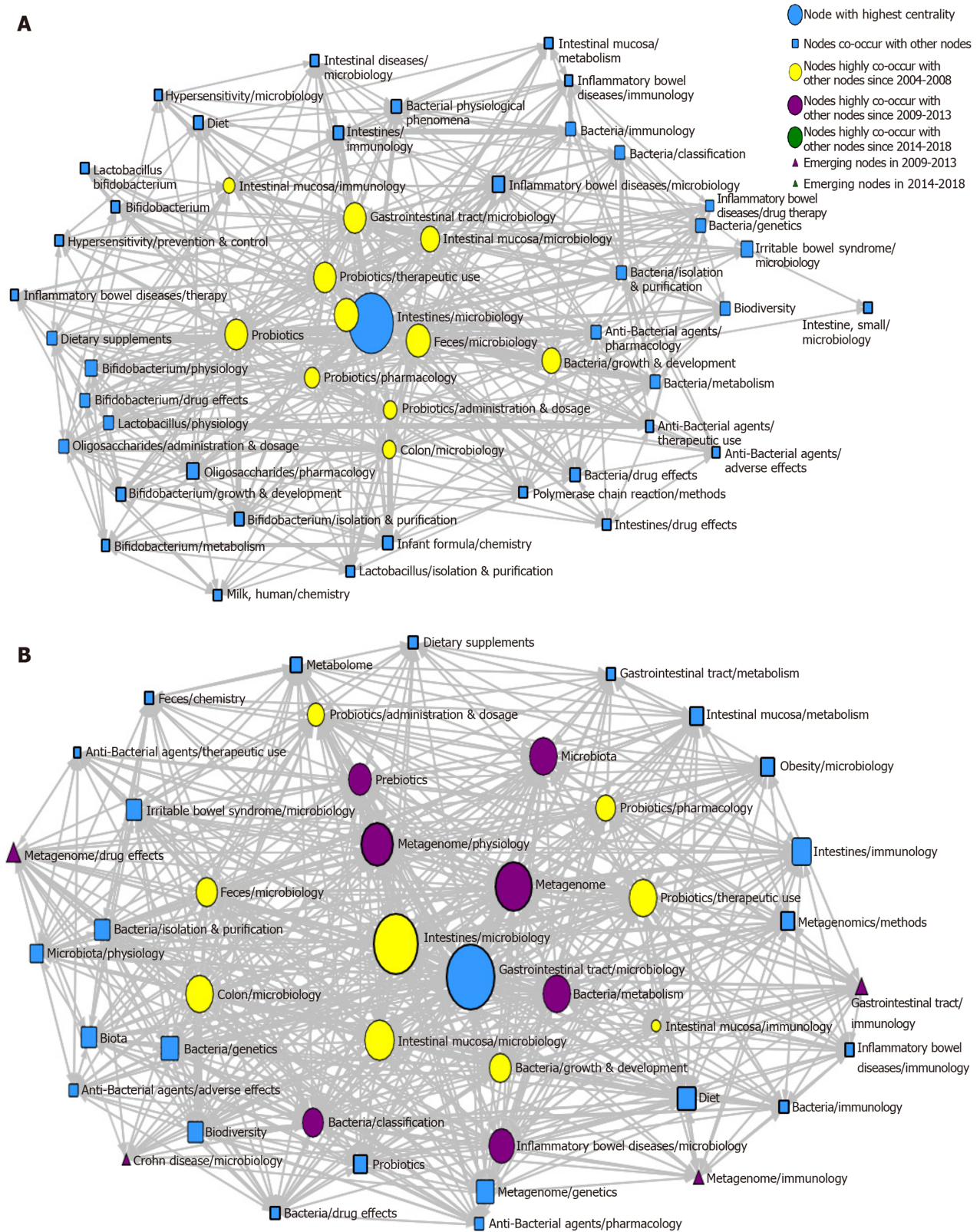
**Figure 5 Strategic diagrams of gut microbiota.** A: Signification of strategic diagrams; B: Strategic diagrams of gut microbiota in 2004-2008; C: Strategic diagrams of gut microbiota in 2009-2013; D: Strategic diagrams of gut microbiota in 2014-2018.

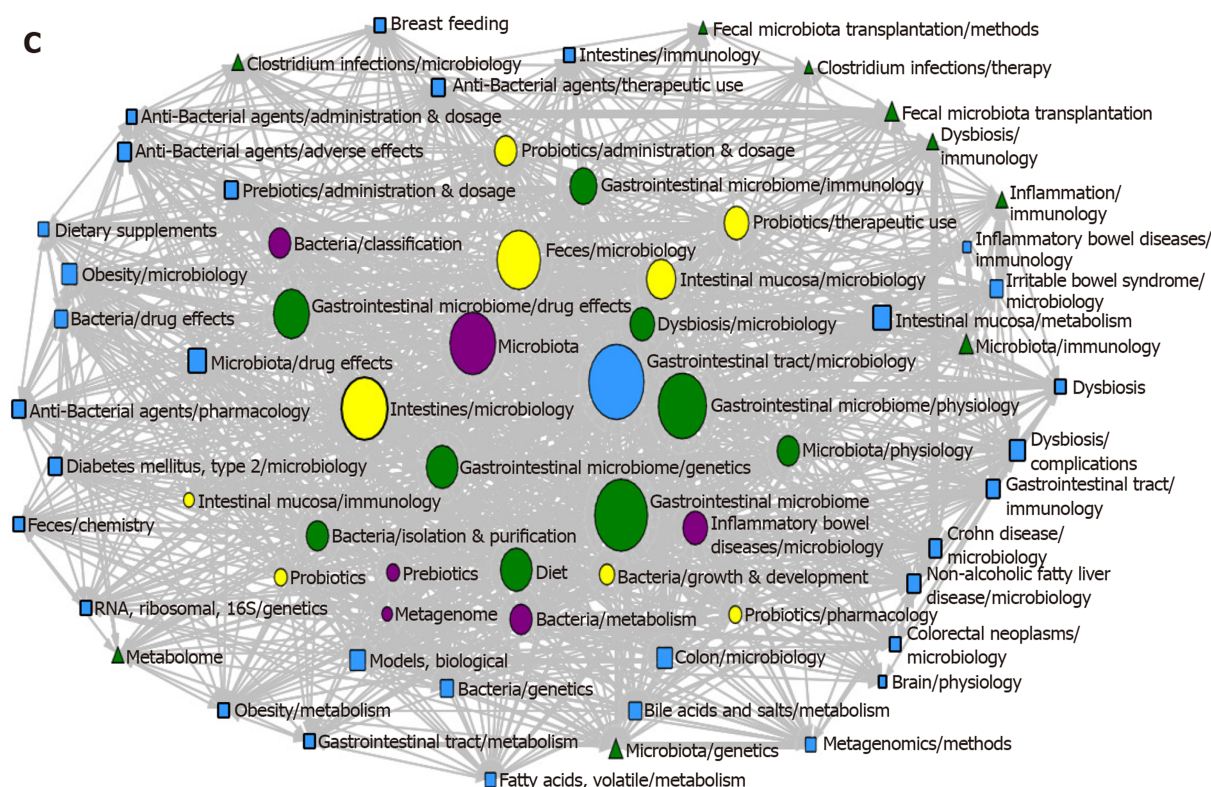
exponentially<sup>[32]</sup>. In this period, there have been numerous gut microbiota relevant publications.

In this study, the subject trends in three periods were analyzed by strategic diagrams. In quadrant I during 2004-2008, there was only one cluster, indicating that this cluster was developed very well in this period; cluster 0 represented probiotics pharmacology and intestinal mucosa and intestines metabolism, which are considered as the research focus of gut microbiota in this period. The gut microbiota plays an important role in human health and occurrence of diseases; and the adjustment of antibiotics and probiotics may become a new therapeutic method<sup>[33-35]</sup>. Clusters 1-4 were in quadrant III and included numerous studies focused on these themes: gut microbiota immunology; gut microbiota isolation, purification, classification, growth, and development; probiotics therapeutic use (*e.g.*, *Bifidobacterium*); inflammatory bowel diseases microbiology, immunology, and drug therapy; intestinal mucosa immunology and microbiology; feces microbiology; gastrointestinal tract microbiology; and irritable bowel syndrome microbiology. These subjects are immature and should be further studied. According to Noverr *et al*<sup>[34]</sup>, gut microbiota can regulate immune responses outside the gut. High-throughput diversity and functionality of gut microbiota have been increasingly analyzed, showing that *Bifidobacterium* plays an important role in the intestinal tract. Notably, gut microbiota has become more important in studies on inflammatory bowel diseases and irritable bowel syndrome<sup>[36-40]</sup>.

Some subjects in clusters 2 and 3 during 2009-2013 were still key points of research, such as probiotics pharmacology and intestines and intestinal mucosa metabolism. The interaction mechanism between gut microbiota and intestinal mucosa is still in strong dispute; and probiotics have become more popular and are used for prevention and treatment of various diseases<sup>[41,42]</sup>. However, the immature subjects during 2004-2008 had developed smoothly, such as probiotics therapeutic use, fecal microbiology, gastrointestinal tract microbiology, irritable bowel syndrome microbiology, and gut microbiota classification, isolation, and purification. The subjects from quadrant I became mature<sup>[43-46]</sup>. As reported<sup>[47]</sup>, fecal microbiota differ between patients with irritable bowel syndrome and healthy people; and microorganisms might be the basis for intestinal symptoms of irritable bowel syndrome. In addition, gastrointestinal tract immunology; inflammatory bowel diseases microbiology and immunology; intestinal mucosa microbiology and immunology; anti-bacterial agents pharmacology, therapeutic use, adverse effects; and gut microbiota growth and development are still not mature subjects. Gut microbiota were shown to be closely related to inflammatory bowel diseases<sup>[48]</sup>. In the study of Pérez-Cobas *et al*<sup>[49]</sup>, the effects and action mode of







antibiotics were found, which played an important role in regulating the composition and functions of gut microbiota. As shown in mounting evidence<sup>[30]</sup>, gut microbiota can regulate intestinal immune function, but the potential molecular mechanism has not been clarified.

The strategic diagram for 2014-2018 represented the knowledge structure for the past 5 years, and offered vast information on new hotspot problems. As a new subject in cluster 1, fecal microbiota transplantation methods were immature. In fecal microbiota transplantation methods, donor bacteria are transplanted into intestines of patients<sup>[51]</sup>; but both the controlling force and results of such transplantation remain unknown. In cluster 4, newly emerged prebiotics therapeutic use and pharmacology were immature. Human understanding of interactions among diets, microorganisms, and hosts is increased gradually and prebiotics have become an important direction of research<sup>[52]</sup>. In cluster 2, irritable bowel syndrome microbiology was a mature subject. In the study of Halkjær *et al*<sup>[53]</sup>, the change of gut microbiota did not result in clinical improvement of irritable bowel syndrome. In cluster 5, non-alcoholic fatty liver disease and diabetes mellitus (type 2) were two mature subjects. Boursier *et al*<sup>[54]</sup> showed that the severity of non-alcoholic fatty liver disease was related to ecological disorder of intestines and change in the metabolic function of gut microbiota. As shown by a study using a mouse model<sup>[55-57]</sup>, gut microbiota could be a driving factor for development of diabetes mellitus (type 2). In cluster 3, probiotics therapeutic use was a mature subject. As shown in multiple studies<sup>[58-60]</sup>, rheumatoid arthritis, *Helicobacter pylori* infection, and hepatic encephalopathy could be better treated by the intervention of gut microbiota and probiotics. In cluster 0, gut microbiota genetics was a mature subject. In the study of Lim *et al*<sup>[61]</sup>, the development of MeSH could be promoted by changing the composition of gut microbiota through the mediation of specific host genes.

The SNA diagram showed that 11, 16, and 19 major MeSH terms/MeSH subheadings had a higher centrality in the three consecutive periods, respectively. In the three periods, Intestines/microbiology and Gastrointestinal tract/microbiology were directly connected with the largest number of other nodes, indicating that they played the greatest potential role in regulating the co-occurrence of other nodes.

In addition, four MeSH terms were newly emerged and lay at the edge of the



network during 2009–2013 and were immature subjects. Crohn's disease research developed rapidly and became a mature subject during 2014–2018. Based on this phenomenon, the nine MeSH terminologies, Clostridium infections/microbiology, Clostridium infections/therapy, RNA ribosomal 16S/genetics, Microbiota/genetics, Microbiota/immunology, Dysbiosis/immunology, Inflammation/immunology, Fecal microbiota transplantation/methods, and Fecal microbiota transplantation were emerging hotspots in the third period.

This study is the first comprehensive bibliometric analysis concerning gut microbiota. Study of the gut microbiota is still in the development stage and will be studied more deeply in the future. The abovementioned emerging hotspots offer a basis and guidance for scientific researchers, clinicians, and medical educators to initiate new projects.

However, our study has certain limitations. Firstly, the inclusion and exclusion criteria only retained journals, and reviews and other types of literature were excluded; thus, some research hotspots were omitted. Secondly, since high-frequency MeSH terms were the basis for co-word analysis, the number of these terms might somewhat influence the cluster analysis results; and new subjects of low concern might not be included. Therefore, a range of databases should be used for analysis in future studies.

Aimed at high-frequency MeSH terminology, we performed co-word analysis on gut microbiota by combining bicluster analysis, strategic maps, and SNA. This study showed that gut microbiota genetics, metagenomics methods, inflammatory bowel disease immunology, fecal microbiota transplantation methods, gastrointestinal tract and intestinal mucosa immunology, intestinal mucosa immunology, anti-bacterial agents pharmacology, therapeutic use and adverse effects, and probiotics therapeutic use and pharmacology were the topics of most interest in the past 5 years. Probiotics therapeutic use, feces microbiology and gastrointestinal tract microbiology, irritable bowel syndrome microbiology, inflammatory bowel disease microbiology and immunology, intestinal mucosa microbiology and immunology, and gut microbiota isolation, purification, classification, growth, and development were core themes that evolved during 2004–2018. Clostridium infections/microbiology, Clostridium infections/therapy, RNA ribosomal 16S/genetics, Microbiota/genetics, Microbiota/immunology, Dysbiosis/immunology, Inflammation/immunology, Fecal microbiota transplantation/methods, and Fecal microbiota transplantation were emerging hotspots for gut microbiota research in the past 5 years.

## ARTICLE HIGHLIGHTS

### **Research background**

Gut microbiota is an emerging field of research, and related research has shown breakthrough development in the past 15 years. Bibliometric analysis can be applied to analyze the evolutionary trends and emerging hotspots in this field.

### **Research motivation**

As the potential clinical application of gut microbiota is understood more and more deeply, the number of studies on gut microbiota has increased rapidly. The study of gut microbiota is an emerging research field, and our findings will offer guidance to scholars in this field.

### **Research objectives**

To study the subject trends and knowledge structures of gut microbiota related research fields from 2004 to 2018.

### **Research methods**

Through the biclustering analysis, strategic diagram, and social network analysis diagram, main trends and knowledge structure of research fields concerning gut microbiota were analyzed to obtain and compare the research hotspots in each period.

### **Research results**

According to the strategic coordinates and social relationship network map, Clostridium Infections/microbiology, Clostridium Infections/therapy, RNA, Ribosomal, 16S/genetics, Microbiota/genetics, Microbiota/immunology, Dysbiosis/immunology, Inflammation/immunology, Fecal Microbiota

Transplantation/methods, and Fecal Microbiota Transplantation were emerging research hotspot in the past 5 years (2014-2018).

### Research conclusions

Using strategic coordinates, our results identified which subjects have not been not fully studied yet, and the emerging hotspots in the social network map provide a direction for future research.

### Research perspectives

This study is the first comprehensive bibliometric analysis of gut microbiota. Research on microbiota is still at the developing stage, and it will continue to be studied more deeply in the future. In our view, the abovementioned emerging hotspot problems can offer the basis for future research and can guide scientific researchers, clinicians, and medical educators to initiate new projects.

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