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ORIGINAL RESEARCH

Research Trends and Hotspots of Gut Microbiota and Its Metabolites in Cardiovascular Diseases: A Bibliometric Analysis

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Purpose: This study leverages quantitative analysis to delve into the current state, key focal points, and developmental trajectory of research on gut microbiota and its metabolites in relation to cardiovascular diseases, offering guidance for future exploration.

Methods: Utilizing software tools such as VOSviewer, CiteSpace, and Scimago Graphica, we conducted a multidimensional analysis. This analysis aimed to accurately evaluate the current research landscape and emerging focal points in the field of gut microbiota and cardiovascular disease research, both domestically and internationally. Moreover, it also uncovers the future trends of gut microbiota in cardiovascular disease research.

Results: We included 4,348 articles and reviews examining the relationship between gut microbiota and cardiovascular diseases. Researchers from 105 countries and regions, 4,411 institutions, and 20,600 authors have contributed to this field. Key research topics include the Mediterranean diet, gut microbiota metabolites, coronary heart disease, myocardial infarction, atherosclerosis, probiotics, and prebiotics. Recently, there has been a significant increase in the frequency of specific keywords such as bile acid, trimethylamine oxide, and coronary artery disease.

Conclusion: This study underscores the promising research prospects of gut microbiota and its metabolites in cardiovascular disease research. Their potential application value is expected to promote the sustainable development and innovation of related fields.

Keywords: bibliometric analysis, gut microbiota, cardiovascular diseases, VOSviewer, CiteSpace, research trends

Introduction

The human intestine is home to a vast microbial community, comprising billions of bacteria. These bacteria constitute the largest microbiome in the body, designated the intestinal microbiome.[1] It plays a significant role in regulating metabolic processes, immune function and the nervous system, while maintaining a delicate equilibrium with the human host.[2] In their metagenomic analysis, Eckburg et al identified six phyla of intestinal microbial organisms, namely Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Clostridia and Verrucomicrobia, most of which are anaerobic.[3] In a healthy bacterial community, the dominant phyla are Firmicutes and Bacteroidetes, which account for more than 90% of the total population.[4] Cardiovascular diseases encompass a range of conditions affecting the heart and blood vessels, including coronary atherosclerotic heart disease, diabetic cardiomyopathy, heart failure, stroke, hypertension and peripheral vascular disease.[5]

Given the growing prevalence of cardiovascular disease alongside the increasing prevalence of unhealthy lifestyles, elevated stress levels and accelerated population ageing, it is evident that the prevention and treatment of cardiovascular disease have become significant public health concerns. With the rapid advancement of molecular biology and bioinformatics, an increasing number of studies have established a correlation between the onset and progression of

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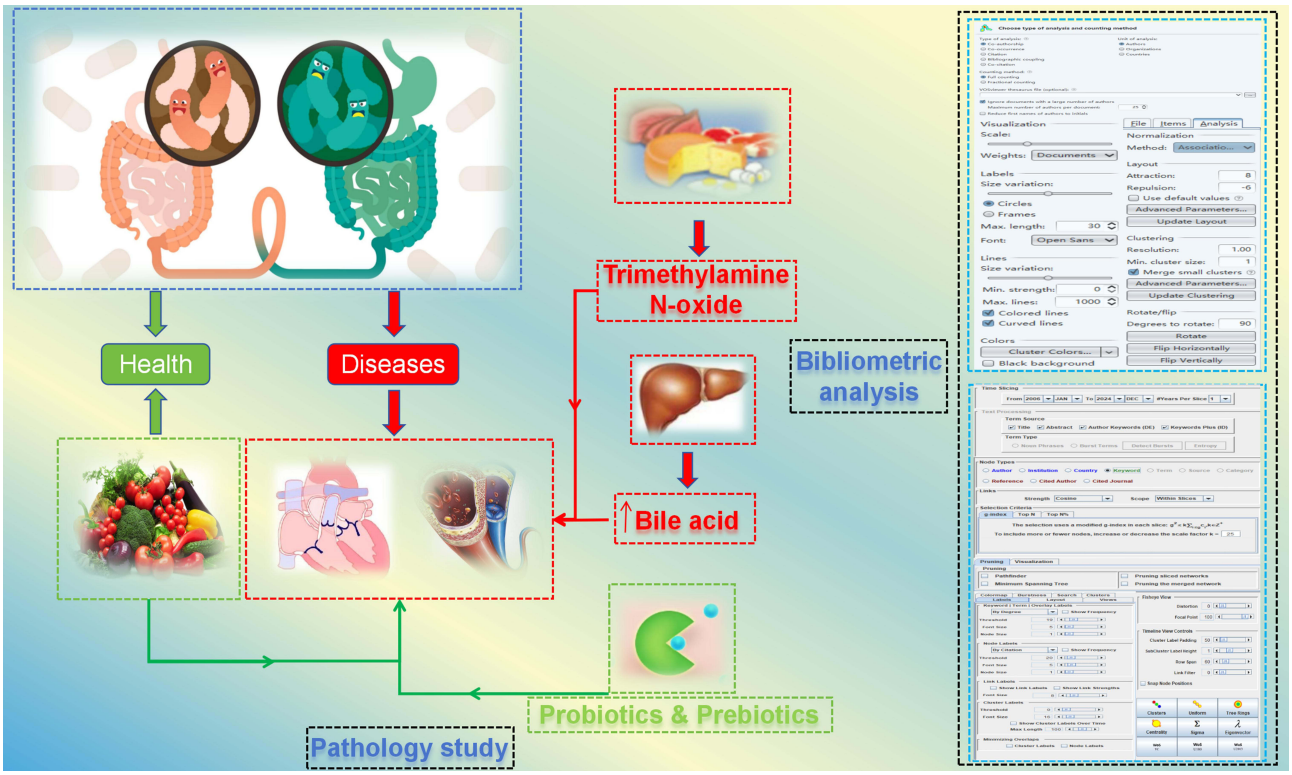
Graphical Abstract



cardiovascular disease and the composition of the human intestinal flora. Recent studies have indicated that an imbalance in the intestinal flora may be associated with the occurrence and development of atherosclerosis, myocardial infarction, hypertension, diabetes and hyper lipidaemia. It is possible that microbiota metabolites may exert a protective or aggravating influence with respect to cardiovascular disease.[6–8] In 2020, Ying Zhu et al analyzed metabolites produced by intestinal flora, including trimethylamine, trimethylamine N-oxide, bile acids, short-chain fatty acids and aromatic amino acids. They elucidated the effects of these metabolites on cardiovascular diseases and identified effective methods for treating cardiovascular diseases with intestinal flora metabolites.[9] It has been reported that the abundance of Collin Sella in patients with atherosclerosis has increased, as has the Firmicutes/Bacteroidetes ratio. Species such as Eubacterium and Rosebury are more prevalent in the intestines of healthy individuals, whereas the intestinal flora composition is disrupted in patients with atherosclerosis.[10]

Probiotics, derived from the *Greek* words "pro" (meaning "for") and "biotic" (referring to life), are defined as "living microorganisms that confer health benefits on the host when administered in adequate amounts".[11] Prebiotics are substances that are commonly used to maintain a normal intestinal microbiota and restore body balance when it is disturbed.[12–14] Studies have demonstrated that consuming probiotics and prebiotics can restore intestinal flora equilibrium by promoting the growth of beneficial bacteria, thereby reducing the risk of chronic diseases such as cardiovascular disease. However, research in this area is still in its infancy. It is imperative for the scientific community to clarify the mechanisms of probiotics and prebiotics and develop robust modelling and prediction tools to establish them as a new therapeutic approach for cardiovascular diseases.[15]

Bibliometrics is a research method that uses literature, systems and related media analysis to identify research hotspots and development trends in various fields.[16,17] This method combines mathematical and statistical techniques with visual analysis, offering valuable insights for academic research and innovation. Scientific analysis methods are commonly used to identify active authors, cooperative networks among countries or institutions, current research

hotspots and frontiers, and to guide researchers into related fields.[18–20] In the field of gut microbiota and cardiovascular disease research, a knowledge gap exists in comprehensively understanding research trends and hotspots through bibliometric analysis. While individual studies offer valuable insights, a systematic review of the entire research landscape is lacking. Bibliometric analysis can fill this gap by providing a comprehensive view of research activities over the past 19 years, helping to identify key topics, influential authors, and prominent research institutions. This study employs software tools such as VOSviewer, CiteSpace, and Scimago Graphica to summarize the latest research progress on gut microbiota and its metabolites in cardiovascular diseases. It also reveals research hotspots and future trends, providing references for future studies and a foundation for identifying hotspots and trends. Bibliometric analysis has been successfully applied in other fields. For instance, it has revealed research trends in Alzheimer's disease and other neurodegenerative diseases in the field of neuroscience.[21] In traditional Chinese medicine research, it has identified research hotspots and trends in the field of Maca, offering important references for subsequent studies on its chemical composition, pharmacological mechanisms, and clinical applications.[22] In the field of traditional Chinese medicine research, the hotspots and trends in maca research have been revealed, providing important references for subsequent studies on its chemical composition, pharmacological mechanisms, and clinical applications,[23] Additionally, the research hotspots and trends of licorice in the field of traditional Chinese medicine resources have been unveiled. Clarifying the chemical composition, pharmacological effects, and clinical applications of licorice is a key area of research, offering crucial references for future studies. This helps to further explore the value of licorice and promotes its application in the field of traditional Chinese medicine.[24] These examples demonstrate that bibliometric analysis is effective in providing valuable insights and guiding future research. Thus, applying bibliometric analysis to the field of gut microbiota and cardiovascular diseases is well-founded and promising, offering strong theoretical support and innovative perspectives for in-depth research in this area.

Materials and Methods

Data Source and Search

In the field of bibliometrics, the majority of scholars concur that the Web of Science (link: http://apps.webofknowledge.com) is the most authoritative database of scientific publications.[25–28] In addition to the fundamental details such as titles, authors, institutions, countries or regions, and author keywords, the database also incorporates the references information.[29,30] Accordingly, it is regarded as the most suitable database and has been employed in numerous previous bibliometric studies.[31]

We searched for terms on 31 December 2024 and completed the data download on the same day. A comprehensive literature search was conducted using the Web of Science database to analyze papers published between 2006 and 2024 that investigate the impact of gut microbiota on cardiovascular disease. The search strategy was as follows: Topic Search (TS) = cardiovascular disease and TS = "gut microbiota" or "gut microbiome" or "gut microflora" or "gut bacteria" and Language (LA) = English and Document Type (DT) = article or review.

A total of 4513 articles were retrieved from the initial literature search and identified as potential inclusion objects. Subsequently, 165 papers were excluded, comprising non-English papers and other types of publications (eg proceedings, papers, corrections, editorial material, connections, additions, letters, retracted publications, retractions, biographical items) that are unsuitable for bibliometric analysis. The remaining 2228 research papers and 2120 reviews were employed in the generation of the bibliometric analysis. Subsequently, the search results were exported in plain text format, and the full records and cited references of the documents were collated. Figure 1 presents a flowchart of the study's methodology.

Data Analysis

Two bibliometric software packages were employed for the analysis of the collected publications: VOSviewer (version 1.6.18) and CiteSpace (version 6.1.R3). VOSviewer is a sophisticated document visualization tool developed by Leiden University. It enables multidimensional bibliometrics and visual analysis,[32] including network visualization, coverage visualization, and density visualization. By constructing network relationship maps between authors, keywords, citations, and other entities, it facilitates the identification of cooperative relationships, research hotspots, and development trends within a given field.

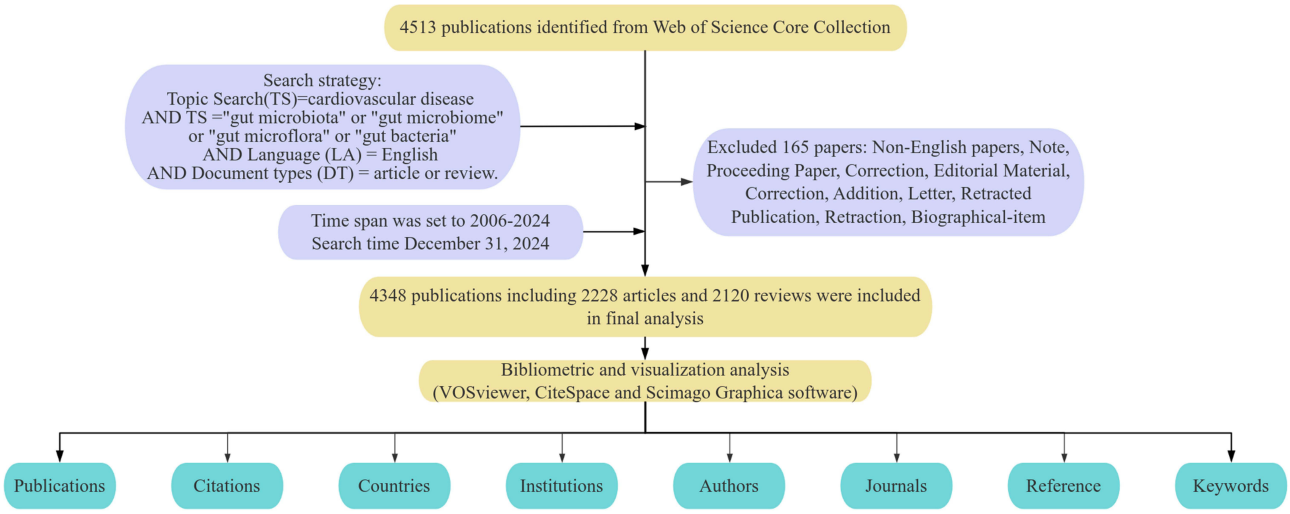


Figure 1 Analysis flow chart.

A network visualization represents the interconnections between documents, keywords and authors through the use of a network diagram. The size of the nodes is indicative of the frequency of occurrence of the corresponding unit, while clusters are indicated by the same color. The overlay visualization technique provides supplementary information to the original network diagram, thereby facilitating a more nuanced understanding of the data. Density visualization depicts the distribution of a specific attribute within the network diagram, enabling the visualization of heat distribution.

CiteSpace is a document visualization software developed by Professor Chen. It is capable of analyzing a substantial number of documents drawn from a variety of databases, including Web of Science, PubMed, and CNKI. It offers insights into a range of areas, including topics, keywords, author affiliations, collaboration networks, journals, publication time, and citations.[33] By employing spatiotemporal analysis, hot spot analysis, and cluster analysis on topics, CiteSpace is capable of identifying research hot spots and periods of heightened interest in a given field. This is achieved through the examination of keyword bursts, which facilitate the analysis of development trends within the field.[34] The present study employed this module to identify keyword outbreaks across different time periods and to investigate the research hotspots and development trends pertaining to the gut microbiota in cardiovascular diseases.

Scimago Graphica (Version 1.0.23) is a visualization tool designed for the exploration and communication of data. In this study, Scimago Graphica was employed for the purpose of visualizing the collaborative relationships between countries and regions.

Results

A total of 4513 publications were searched from Web of Science under the topic of the effect of gut microbiota on cardiovascular disease. Following the removal of publications with incomplete information and those published in languages other than English, the number of remaining publications was 4348. As illustrated in Figure 2A, the article represents the predominant publication format, with both article and review formats accounting for a similar proportion. Of the total published forms, articles constituted 51.24%, while reviews accounted for 48.76%. This suggests that the impact of gut microbiota on cardiovascular disease has garnered significant attention from scholars.

Analysis of Publications Outputs and Citations

A bar graph was constructed using the number of papers published per year in order to visualize the growth trend of publications. As illustrated in Figure 2B, the number of publications addressing the topic of the effect of gut microbiota on cardiovascular disease has increased annually over the past 19 years. From 2019 onwards, the number of annual publications has increased markedly. From the diagram, it can be observed that the number of papers published in 2019–2022 continues to increase, while the number of articles published in the past two years has demonstrated

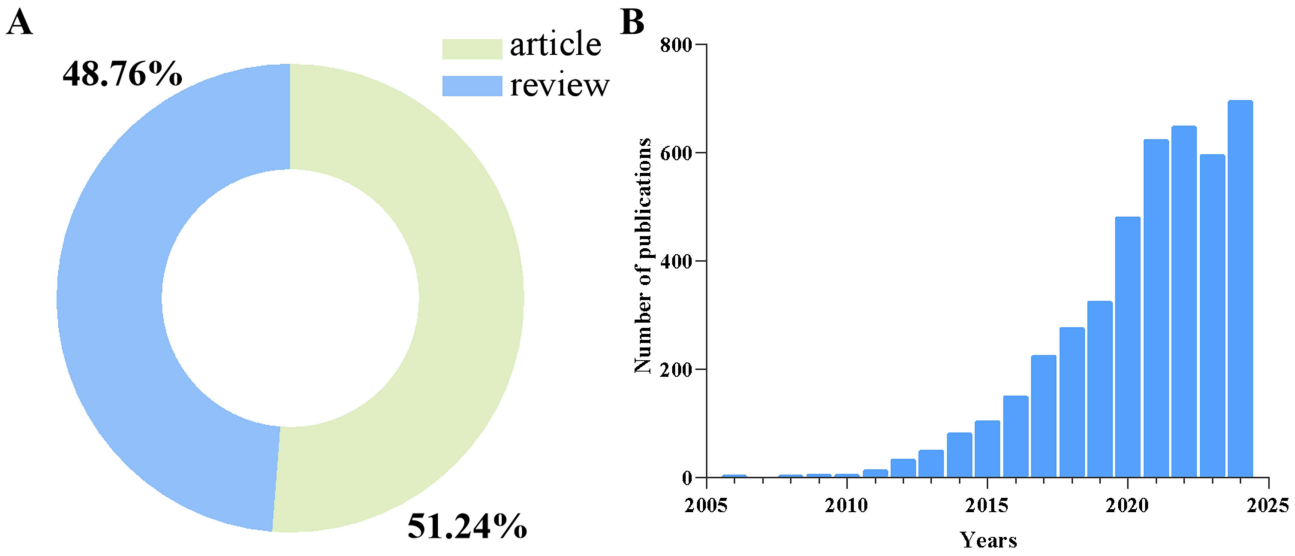


Figure 2 (**A**) Document type. Blue represents articles and Red represents reviews. (**B**) The number of annual publications from 2006 to 2024.

a downward trend. In general, the mean number of annual publications in recent years has been above 300. By the end of 2024, the number of studies on the role of gut microbiota in cardiovascular disease had reached its highest point at 697, and research interest in this area had peaked. This research demonstrates that intestinal flora plays an important role in the treatment of cardiovascular disease, which is also developing rapidly.

Discipline Categories

The subject categories of this study were predominantly distributed across three main disciplines: Biochemistry Molecular Biology (publication = 592), Pharmacology Pharmacy (publication = 416) and Microbiology (publication = 389). This indicates that the primary focus of this study is on the interdisciplinary fields of chemistry and medicine.

Analysis of Most Productive Countries/Regions

To date, a total of 105 countries or regions have published opinions on the study of gut microbiota in cardiovascular diseases. The ten countries or regions with the highest level of productivity are presented in Table 1. The parameters were evaluated by combining the literature, number of citations, total link strength, and links.

As illustrated in Figure 3A and B and Table 1, the greatest number of published documents on the impact of gut microbiota on cardiovascular disease were produced in China (documents = 1009), followed by the USA (documents = 978), Italy (documents = 388), Spain (documents = 246) and the United Kingdom (documents = 222). With regard to the

Table 1 The Top 10 Most Productive Countries or Regions

No.	Countries/Regions	Continent	Documents	Citations
1	China	Asia	1009	29,776
2	USA	America	978	73,465
3	Italy	Europe	388	18,717
4	Spain	Europe	246	12,891
5	United Kingdom	Europe	222	13,547
6	Austral	Oceania	178	9013
7	Germany	Europe	161	10,377
8	Canada	America	153	7486
9	France	Europe	136	8188
10	Sweden	Europe	128	13,195

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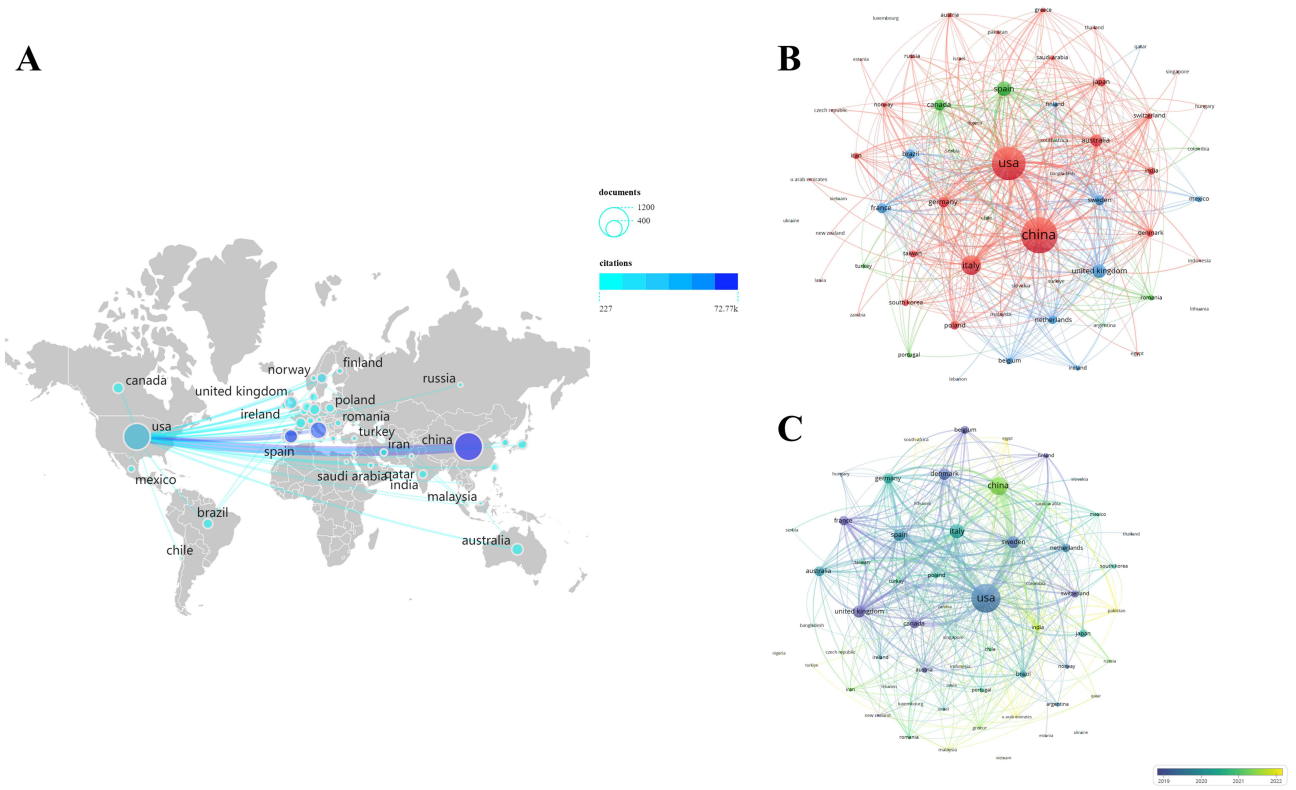

Figure 3 (**A**) Main countries/regions distribution and collaboration. Overlay visualization of (**B**) citation and (**C**) co-authorship analysis for countries/regions. The weight was (**B**) document and (**C**) citation. The color indicates the average publication year.

number of citations, a similar trend is observed to that seen in the number of publications, with the USA ranking first, followed by China and Italy. The next highest number of citations is that of Spain and the United Kingdom. In terms of the number of citations, the United States of America (USA) is the country with the highest number of citations (73,465), while other countries have a significantly lower number of citations. Furthermore, the centrality of the network between different countries or regions, as illustrated in Figure 3C, indicates that it is a pivotal element in the collaborative relationship between countries. As illustrated in Figure 3C, the USA occupies a more central position in the network and has a higher number of citations, which suggests that it plays a pivotal role in the cooperative relationship.

It is worthy of mention that the relationship between China and the USA is characterized by a notable degree of collaboration. Despite China's considerable output of publications, the number of citations per publication is significantly lower than that of the USA (Figure 3C).

Analysis of the Most Prolific Institutions

The VOSviewer analysis revealed that a total of 4411 institutions worldwide have contributed to research publications on the relationship between gut microbiota and cardiovascular disease. Table 2 presents the ten most productive institutions, ranked by the number of publications and related parameters. The Cleveland Clinic is the most prolific institution, with 83 documents, and is one of the largest private hospitals globally, as well as ranking among the top four hospitals in the United States in terms of quality and reputation. The institution treats patients from over 100 countries annually. The following institutions are worthy of note: the University of Copenhagen (documents = 65), which is one of Denmark's most esteemed higher education institutions and has a commendable ranking in the global university rankings, thereby attesting to its academic and research excellence; and the University of Murcia (documents = 55) (Figure 4A). With regard to the number of citations, Cleveland Clin occupies the leading position with 16,290 citations, while Univ Copenhagen (citations = 11,379) and Univ Gothenburg (citations = 9663) are slightly lower.

Table 2 The Top 10 Institutions of Publications

No.	Institution	Country	Documents	Citations
1	Cleveland Clin	USA	83	16,290
2	Univ Copenhagen	Denmark	65	11,379
3	Inst Salud Carlos Iii	Spain	58	3372
4	Capital Med Univ	China	54	2437
5	Sun Yat Sen Univ	China	54	2049
6	Harvard Med Sch	USA	48	2206
7	Southern Med Univ	China	47	1908
8	Chinese Acad sci	China	43	2339
9	Karolinska Inst	Denmark	42	1227
10	Shanghai Jiao Tong Univ	China	41	1886

The network of institutional collaboration constructed by VOSviewer is presented in Figure 4B. The earliest publications were from Cleveland Clinic, followed by those from University of Copenhagen and then University of Gothenburg, which respectively had the first three citations. Conversely, certain Chinese institutions, including Capital Medical University, Sun Yat-Sen University and Southern Medical University, have published a greater number of papers in the 2020 period, yet the number of citations is comparatively low.

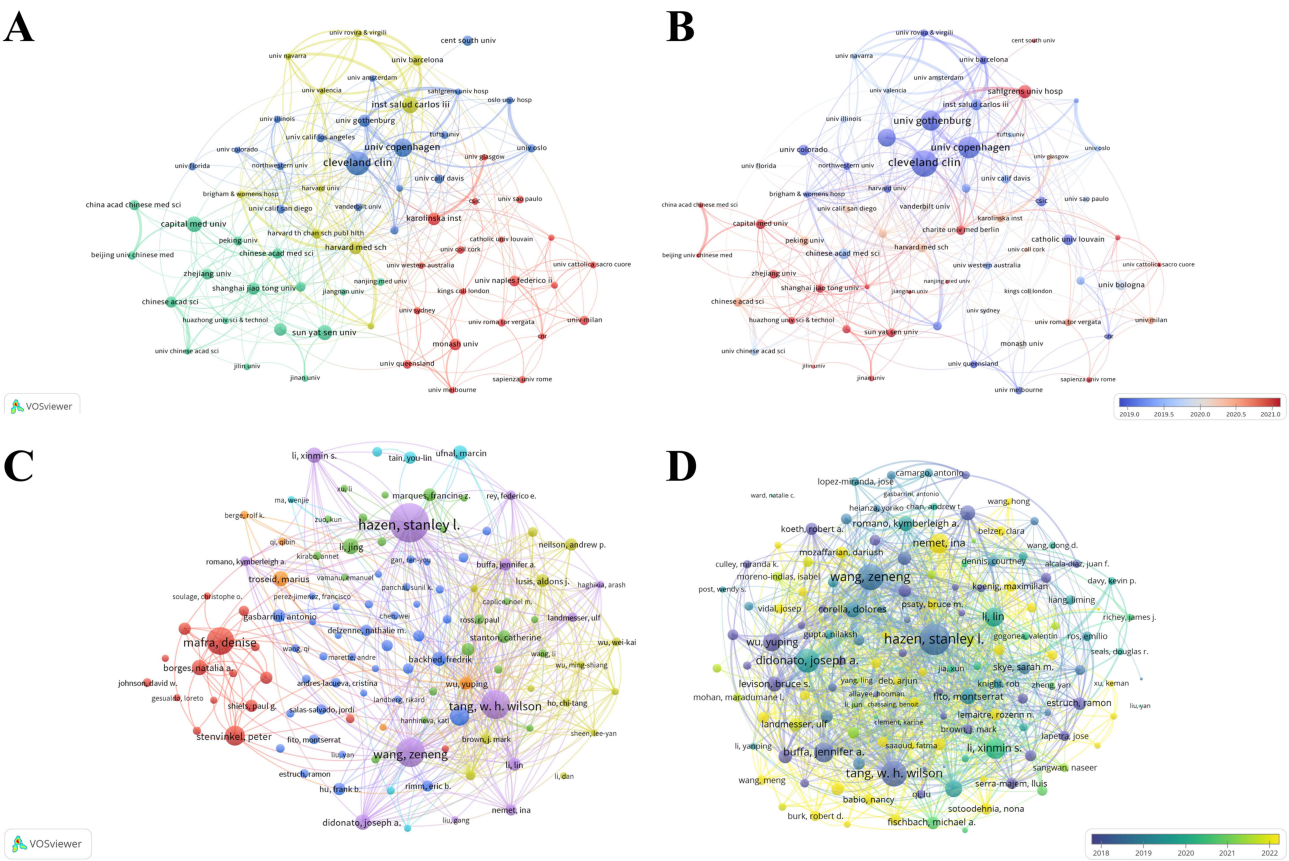

Figure 4 Overlay visualization of institutional (**A**) citations and (**B**) co-authorship analysis. Weights are for (**A**) literature and (**B**) citations. Color indicates mean year of publication. Overlay visualization of author (**C**) citations and (**D**) co-authorship analysis. Weights are for (**A**) literature and (**B–D**) citations. Color indicates mean year of publication.

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Analysis of the Most Influential Authors

A total of 20,600 authors are responsible for the creation of the 4348 identified publications. In terms of the number of publications (Table 3 and Figure 4C), Stanley L. Hazen from Cleveland State University is the most prolific author (documents = 54), followed by Tang Wai Hong Wilson (documents = 38, Heart Vasc & Thorac Inst), Wang Zeneng (documents = 37, Cleveland Clinic Foundation) and Mafra Denise (documents = 36, Fed Fluminense Univ UFF). Furthermore, Stanley L. Hazen (citations = 14,897), Tang Wai Hong Wilson (citations = 11,984) and Wang Zeneng (citations = 11,168) are the three authors with the highest number of citations in Figure 4D.

The formation of collaborative relationships among authors is an effective strategy for investigators in navigating existing partnerships. In the author collaboration clusters created by VOSviewer, it can be observed that one or two core authors exert a dominant influence within each cluster, as indicated by their high centrality scores. These include Stanley L. Hazen, Tang Wai Hong Wilson, Wang Zeneng, Bruce S. Levison, Backhed Fredrik, and Patrice D. Cani, along with Knight Rob. Furthermore, Nemet Ina is situated within a cluster of relatively young researchers in the field, as indicated by the color mapping of the average year of publication per author in the network. As demonstrated by the co-citation network (Figure 5A and Table 4), Tang Wai Hong Wilson is the most frequently cited author, with 2139 citations, followed by Wang Zeneng (citations = 1602) and Patrice D. Cani (citations = 1390).

Analysis of Co-Citation Journals

A journal co-citation analysis allows for the identification of those journals that have played a pivotal role in the advancement of cardiovascular disease research. Following the visualization of the journal co-citation network by VOSviewer, the ten most frequently cited journals are presented in Table 5. As illustrated in Figure 5B, the network visualization map of the journal co-citation analysis was subsequently conducted using VOSviewer. The journals that have been cited together most frequently are Nature (citation = 9265), Nutrients (citation = 8340), and PLoS One (citation = 7169). The aforementioned journals represent the top three in terms of citation frequency and are all classified as Q1 in the JCR ranking.

Analysis of Highly-Cited Studies

A citation analysis of the documents was conducted to ascertain the most influential part of the studies published (Figure 5C). The ten most frequently cited papers are presented in Table 6. The studies in question were published between 2011 and 2021, with eight of them receiving in excess of 500 citations. Of the ten studies, seven were research articles, while the remaining three were reviews.

Co-Citation Analysis of Cited References

A similar approach was employed in the analysis of literature citations, with the objective of identifying those works that have had a significant influence on the development of gut microbiota in the context of cardiovascular disease research (Figure 5D). Table 7 presents a list of the ten most frequently cited references in the included publications. The most

Table 3 The Top 10 Productive Authors

No.	Author	Country	Documents	Citations
1	Stanley L. Hazen	Cleveland State University	54	14,897
2	Tang Wai Hong Wilson	Heart Vasc & Thorac Inst	38	11,984
3	Wang Zeneng	Cleveland Clinic Foundation	37	11,168
4	Denise Mafra	Fed Fluminense Univ UFF	36	957
5	Peter Stenvinkel	University of Alberta	24	458
6	Max Nieuwdorp	Diabeter Ctr Amsterdam	24	1401
7	Li Jing	Nanjing University of Chinese Medicine	18	1701
8	Didonato Joseph A.	Cleveland Clinic Foundation	18	5557
9	Xinmin S. Li	Cleveland Clinic Foundation	17	2029
10	Marius Troseid	National Hospital Norway	17	636

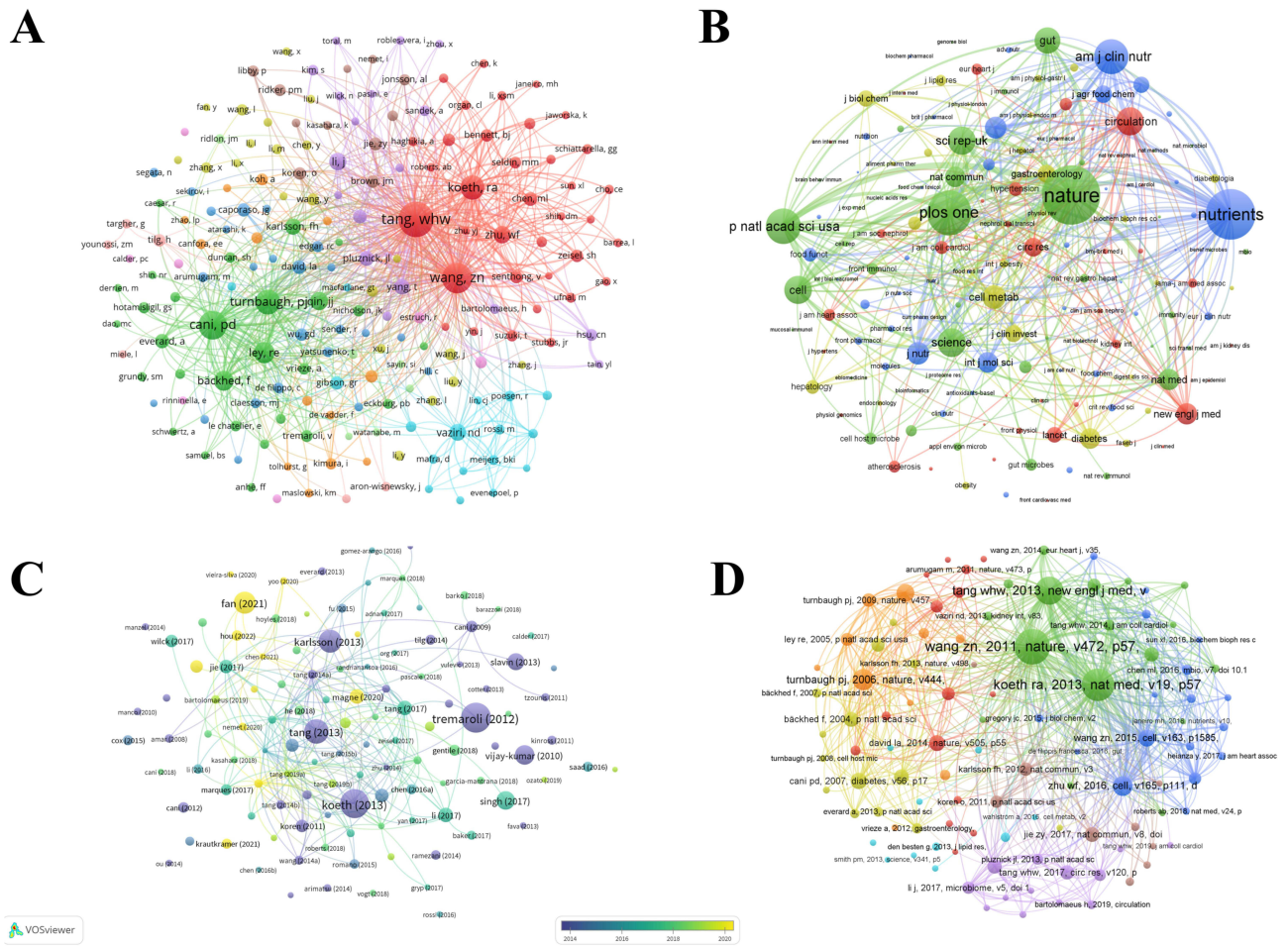

Figure 5 Network visualization of co-citation analysis for (**A**) authors and (**B**) journals. (**C**) Overlay visualization of citation analysis for references. (**D**) Network visualization of co-citation analysis for references. The weight was citation. For (**C**), the color indicates the average publication year.

highly cited study is that of "Gut flora metabolism of phosphatidylcholine promoting cardiovascular disease". The number of citations is 836, from the highly cited author Wang Zeneng. The second most cited article was "Intestinal Microbiota Metabolism of L-Carnitine, a Nutrient in Red Meat, Promoting Atherosclerosis", published by Robert A. Koeth in 2012, with a number of citations of 743. Additionally, Tang Wai Hong Wilson from the Heart Vasc & Thorac Inst. published "Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk" in 2013, which has been cited 637 times.

Table 4 The Top 10 Co-Citation Authors

No.	Author	Citations	Total Link Strength
1	Tang Wai Hong Wilson	2139	37,174
2	Wang Zeneng	1602	28,903
3	Patrice D. Cani	1390	19,715
4	Turnbaugh P. J.	1018	18,877
5	Robert A. Koeth	987	15,958
6	Ley R. E.	739	11,492
7	Backhed F.	647	11,259
8	Qin J J	566	10,919
9	Li j	543	9791
10	Zhu W F	533	9488

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Table 5 The Top 10 Co-Citation Journals

No.	Journal	Citations	Quartile in Category
1	Nature	9265	Q1
2	Nutrients	8340	Q1
3	Plos One	7169	Q1
4	Am J Clin Res	5407	Q4
5	P Natl Acad Sci USA	5290	Q1
6	Sci repuk	4681	Q3
7	Circulation	4543	Q1
8	Science	4136	Q1
9	Cell	4100	Q1
10	Gut	3842	Q1

Table 6 The Top 10 Frequently Cited References

No.	Title	First Author	Type	Year	Citation	Ref.
1	Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis	Robert A. Koeth	Article	2013	3017	[35]
2	Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk	Tang W. H. Wilson	Article	2013	2297	[36]
3	Gut microbiota in human metabolic health and disease	Fan Y	Review	2021	2013	[37]
4	Gut Microbiota in Cardiovascular Health and Disease	Tang W. H. Wilson	Review	2017	987	[7]
5	Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis	Wang Zeneng	Article	2015	907	[38]
6	The gut microbiome in atherosclerotic cardiovascular disease	Jie Z Y	Article	2017	899	[39]
7	Human oral, gut, and plaque microbiota in patients with atherosclerosis	Koren O	Article	2011	789	[40]
8	Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota	Chen M L	Article	2016	534	[41]
9	Prognostic Value of Elevated Levels of Intestinal Microbe-Generated Metabolite Trimethylamine-N-Oxide in Patients with Heart Failure Refining the Gut Hypothesis	Tang W. H. Wilson	Article	2014	481	[42]
10	The contributory role of gut microbiota in cardiovascular disease	Tang W. H. Wilson	Review	2014	462	[43]

Table 7 The Top 10 Frequently Co-Cited References

No.	Title	Journal	First author	Type	Year	Citation	Ref.
1	Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease	Nature	Wang Zeneng	Article	2011	836	[44]
2	Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis	Nature Medicine	Robert A. Koeth	Article	2013	743	[35]
3	Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk	New England Journal of Medicine	Tang W. H. Wilson	Article	2013	637	[36]
4	Gut Microbial Metabolite TMAO Enhances Platel-et Hyperreactivity and Thrombosis Risk	Cell	Zhu Weifei	Article	2016	431	[45]
5	Nonlethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis	Cell	Wang Zeneng	Article	2015	339	[38]
6	The gut microbiome in atherosclerotic cardiovascular disease	Nature Communications	Jie Z Y	Article	2017	277	[39]
7	Gut Microbiota in Cardiovascular Health and Disease	Circulation Research	Tang W. H. Wilson	Review	2017	300	[7]

(*Continued*)

Table 7 (Continued).

No.	Title	Journal	First author	Type	Year	Citation	Ref.
8	Gut Microbiota-Dependent Trimethylamine N-Oxide (TMAO) Pathway Contributes to Both Development of Renal Insufficiency and Mortality Risk in Chronic Kidney Disease	Circulation Research	Tang W. H. Wilson	Article	2015	285	[46]
9	Gut Dysbiosis Is Linked to Hypertension	Hypertension	Yang Tao	Article	2015	289	[47]
10	Symptomatic atherosclerosis is associated with an altered gut metagenome	Nature Communications	Fredrik H Karlsson	Article	2012	272	[48]

Analysis of Co-Occurrence Keywords

Keywords encapsulate the principal content and central theme of the field of concern. In the field of bibliometrics, keyword co-occurrence analysis is frequently employed as a means of identifying research topics that are currently receiving significant attention.[49–51] In the co-occurrence network, the appearance of the Occurrences parameter represents the number of documents in which specific keywords appear, thereby reflecting the degree of attention paid to those keywords. The complete co-occurrence network of keywords is presented in Figure 6A. Combined with Figure 6A and Table 8 lists the top 10 keywords and their centrality. Centrality is the most direct measure of node centrality in network analysis. The higher the centrality of a node is, the more important the node is in the network. In general, most of these keywords frequently appear in the context of gut microbiome and cardiovascular disease. It is worth noting that most of these keywords focus on gut microbiota and their metabolites in the treatment and pathogenesis of cardiovascular diseases, such as frequent metabolism, chain fatty acids and trimethylamine n oxide, and oxidative stress.

These keywords can be divided into eight clusters using the Log Likelihood (LLR) method in CiteSpace (Figure 6B). As illustrated in the figure, heart failure, coronary heart disease and chronic kidney disease represent the most significant diseases in terms of the impact of intestinal flora and its metabolites on cardiovascular diseases. They also constitute inherent challenges in the study. Furthermore, metabolic syndrome represents a significant area of investigation within this research domain. In addition to the aforementioned prominent disease keywords, there are also several internal pathological mechanisms, such as L-carnitine and phosphatidylcholine. These two clusters may provide valuable insights for the study of intestinal flora and its metabolites on cardiovascular diseases. CiteSpace can be used to perform statistical and correlational analysis of co-cited references into clusters. In this study, we identified eight distinct clusters in the network of co-cited references, with significant modularity and silhouette scores indicating highly credible clusters. The eight clusters are displayed in Figure 6C.

Analysis of Keywords with Citation Burst

The application of keyword burst analysis allows for the identification of periods of accelerated popularity for specific keywords. This approach offers a practical method for exploring the evolution of research hotspots across different academic fields. Figure 7 presents the top 25 burst keywords. It can be seen that coronary heart disease (2011–2012), metabolic syndrome (2014–2015), phosphatidylcholine related to intestinal flora metabolism (2014–2018), l-carnitine and other keywords related to cardiovascular disease emerged in the early stage and attracted attention. The role of trimethylamine-n-oxide (2021–2022) in the incidence of cardiovascular disease and typical cardiovascular diseases, such as atherosclerosis and myocardial infarction, will be discussed in greater detail later on. In recent years, there has been a growing interest among scholars in the field of coronary artery disease (2021–2024) and bile acid metabolism (2022–2024). It is possible that these areas may become the main focus of future research.

Analysis of Regulation Mechanism and Emerging Technologies

Exploring the regulatory mechanisms of gut microbiota on cardiovascular diseases can aid in developing new prevention and treatment strategies. This study summarizes and analyzes research results on these mechanisms in Table 9. Research

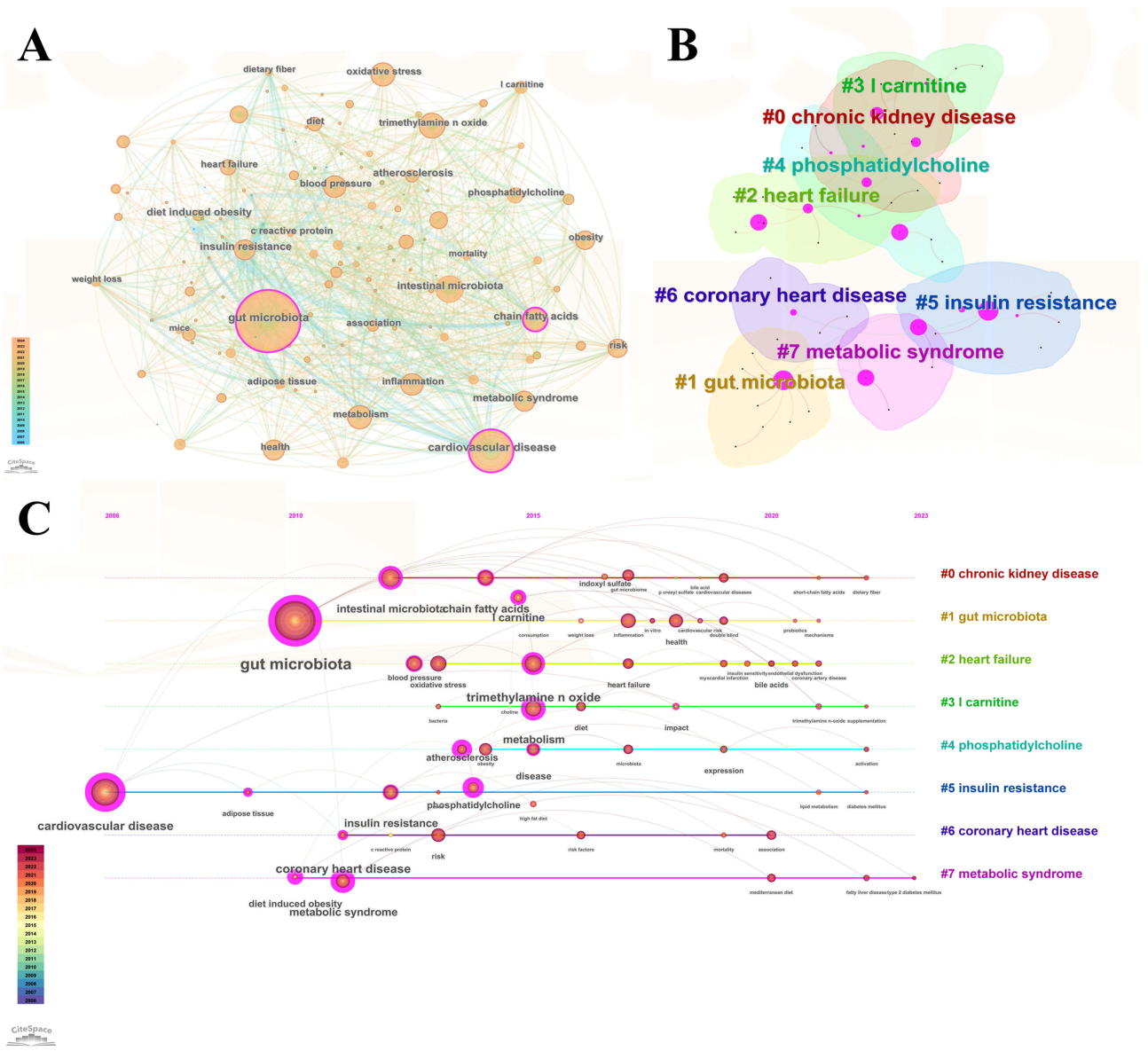

Figure 6 (**A**) The keyword co-occurrence network of the field. Node size: the number of publications; line thickness: the strength of association. (**B**) The first eight clustering terms of the study. Node color: different clusters. (**C**) The timeline of eight clusters.

on metabolism is central, with a total link strength of 1612, indicating its high frequency and prominence in the field. Immune function-related keywords have a total link strength of 871, showing high research interest. The total link strength for vascular function is 420, for intestinal barrier function is 376, and for cardiac dysfunction is 160. This indicates that metabolism is the core research area, closely related to the important role of gut microbiota in nutrient metabolism. Research on immune function, vascular function, intestinal barrier function, and cardiac dysfunction is also active, showing that gut microbiota affects the cardiovascular system through multiple pathways. Table 10 summarizes strategies for regulating cardiovascular diseases through gut microbiota. Research on prebiotics and probiotics is prominent, with a total link strength of 3220. The keyword metabonomic has a total link strength of 1083; fecal microbiota transplantation has 996; metagenomics has 478; and dietary intervention has 306. This shows that prebiotics and probiotics are key strategies. Metabonomic and metagenomics can explore the complex relationship between gut microbiota genes and host metabolism. Fecal microbiota transplantation can rapidly change gut microbiota composition, and dietary intervention can indirectly affect gut microbiota by adjusting dietary components, offering new ideas for

Table 8 The Top 10 Keywords

No.	Occurrences	Centrality	Keywords
1	2211	0.14	Gut microbiota
2	1118	0.15	Cardiovascular disease
3	756	0.03	Inflammation
4	587	0.07	Intestinal microbiota
5	544	0.04	Metabolism
6	441	0.06	Trimethylamine n oxide
7	437	0.05	Oxidative stress
8	430	0.11	Chain fatty acids
9	414	0.07	Insulin resistance
10	387	0.08	Metabolic syndrome

treating cardiovascular diseases related to gut microbiota imbalance. Thus, integrating bibliometric analysis enhances understanding of the key research directions and hotspots in this field. It provides new insights into the pathogenesis, diagnosis, and treatment of cardiovascular diseases and serves as a reference for future studies.

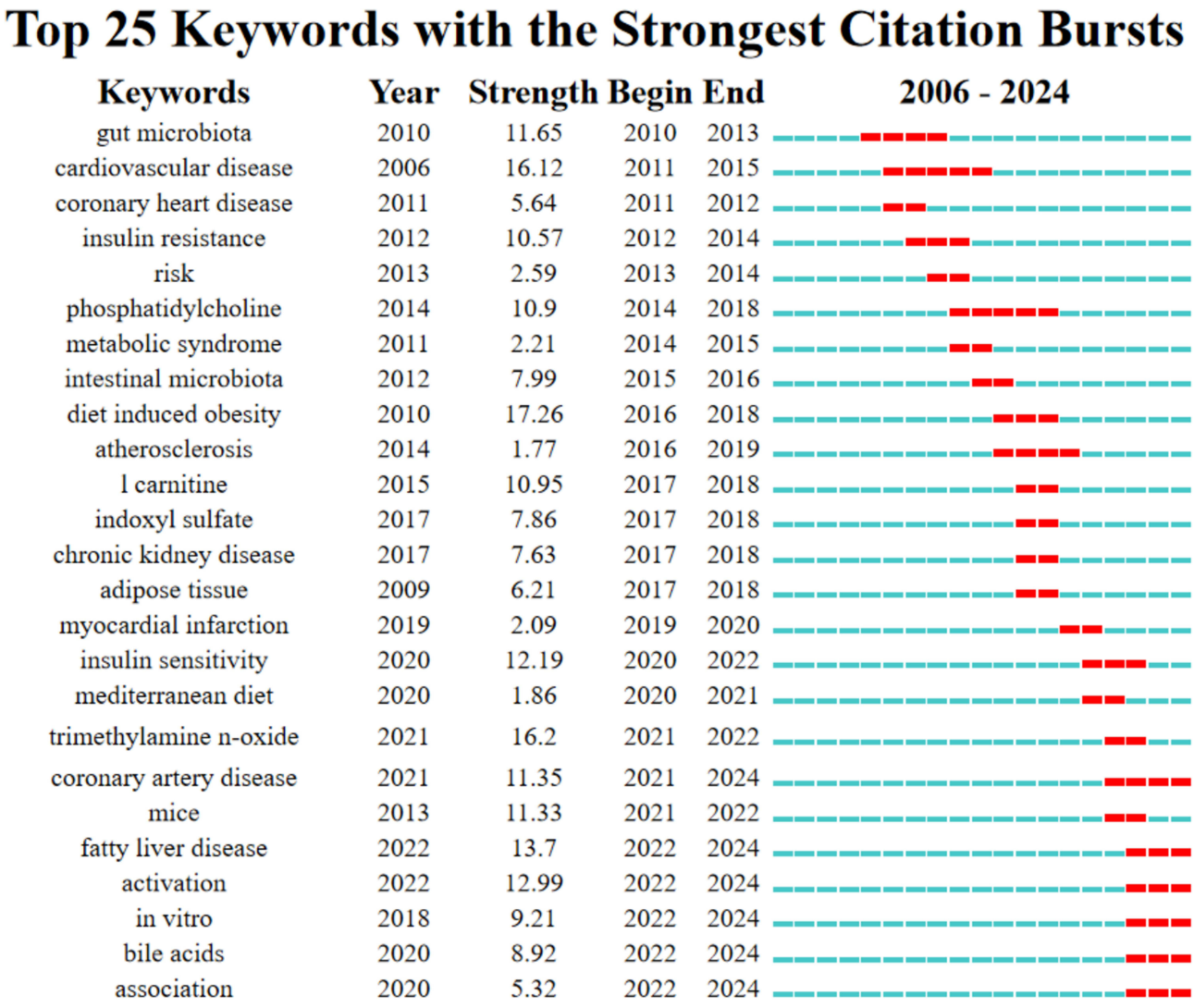

Figure 7 CiteSpace visualization map of the top 25 keywords with the strongest citation bursts. The strongest citation burst means that a variable changes greatly in a short period. Red bars indicate the duration of the burst.

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Table 9 The Regulatory Mechanism of Gut Microbiota on Cardiovascular Diseases

No.	Total link strength	Keywords
1	1612	Metabolism
2	871	Immune function
3	420	Vascular function
4	376	Intestinal barrier function
5	160	Cardiac dysfunction

Table 10 Exploring Novel Strategies for Regulating Cardiovascular Diseases Through Gut Microbiota

No.	Total link strength	Keywords
1	3220	Prebiotics and probiotics
2	1083	Metabonomic
3	996	Fecal microbiota transplantation
4	478	Metagenomics
5	306	Dietary intervention

Discussion

General Data

Over the past few decades, researchers have dedicated a significant amount of effort to investigating the relationship between intestinal flora and cardiovascular diseases,[52] resulting in numerous publications in this field. The average annual publication volume is increasing, and there are also frequent exchanges and discussions between researchers and countries and regions. In this study, statistical cluster analysis was conducted using VOSviewer, CiteSpace and Scimago Graphica software on the main countries/regions, institutions, journals, authors, citations and keywords related to the study of intestinal flora on cardiovascular diseases at home and abroad. The research hotspots and development trends were then analyzed and summarized.

Research Strength Analysis

China and the United States have a robust collaborative relationship, yet the number of Chinese citations is considerably lower than that of the United States. This suggests that the United States has conducted more comprehensive and high-quality research on the impact of gut microbiota on cardiovascular disease, and is therefore a more prominent source of attention for scholars in related fields. In this regard, further research is required in China to enhance the depth of research on the role of gut microbiota in cardiovascular disease and the quality of published papers in this field.

The preceding indicates results that four of the ten institutions with the highest number of published papers are located in China, while the most frequently cited institutions are from the United States. It is noteworthy that, despite the relatively limited number of publications, Gothenburg University has a considerably higher number of citations (documents = 40, citation = 9663) than the majority of other institutions. Gothenburg University is held in high esteem in Sweden and internationally. Notably, Gothenburg University has made significant contributions to scientific research, particularly in the field of gut microbiota and its role in cardiovascular disease.

The findings indicate that institutions in select high-income European and American countries, particularly the USA, Spain and Denmark, engage in close collaboration with other organizations. Researchers specializing in cardiovascular disease are particularly attentive to their research. In light of these findings, it can be posited that the USA has consistently demonstrated a leading role in cardiovascular disease research, characterized by high productivity and paper quality. Moreover, institutions situated on the left side of the network in China frequently engage in collaborative endeavors but have comparatively limited

academic exchange with institutions in other countries, a phenomenon also observed in some other Asian countries. It is therefore vital to enhance communication and collaboration between different regions and organizations.

The majority of high-impact authors in the field of cardiovascular disease research are affiliated with the relevant staff of Chinese medical schools and some medical institutions in the United States. These individuals play a vital role in the study of the disease in their respective countries. A meticulous examination of the findings of these researchers offers significant clinical insights. Furthermore, the three authors with the highest number of citations are Stanley L. Hazen (citations = 14,897), Tang Wai Hong Wilson (citations = 11,984) and Wang Zeneng (citations = 11,168). This illustrates that the three authors have produced outstanding research results on gut microbiota in cardiovascular diseases, and that their number of publications and citations are among the top three, which is crucial to the contribution of this study. In particular, Tang Wai Hong Wilson from the Heart Vasc & Thorac Inst. addressed the role of gut microbiota in cardiovascular health and disease in 2017, emphasizing the intricate interactions between microbiota, metabolites and the development and progression of cardiovascular disease. Additionally, he is the second author of the greatest number of papers published in the field of cardiovascular disease research.

A co-citation relationship is defined as a reference to a study in which two authors or studies are cited simultaneously.[53] The analysis of author co-citations is a method typically employed to identify the most influential authors within a given field. In general, authors who are frequently cited demonstrate a greater level of engagement with the subject matter and exert a more significant influence. In a joint effort, Stanley L. Hazen and Wang Zeneng undertook a review of the impact of gut microbiota on phosphatidylcholine and its implications for cardiovascular disease. Their findings revealed a correlation between the gut flora-dependent metabolism of dietary phosphatidylcholine and the pathogenesis of cardiovascular diseases. This discovery offers potential avenues for the development of novel diagnostic tools and therapeutic strategies for atherosclerotic heart disease.[44] It is noteworthy that the majority of authors with high productivity are affiliated with American institutions. Additionally, the United States is the highest cited country/region, indicating that high-yield countries/regions have the potential to establish influential institutions that can facilitate more productive researchers. Furthermore, the number of author citations is relatively high. It can therefore be surmised that the impact of excellent gut microbiota research on cardiovascular disease can enhance the status of the institutions in which it is conducted, and even that of the countries in which they are based.

Hotspots Analysis

The journal citation frequency ranking reveals that Nature, Nutrients and Plos One are the three journals with the highest citation frequency. This indicates that these journals have received greater international recognition and attention in this field.[36,44,54] In particular, the most frequently referenced article is that of Robert A. Koeth, published in 2013. The metabolism of L-carnitine, a nutrient found in red meat, by the intestinal microbiota promotes the development of atherosclerosis. It has been demonstrated in detail that the metabolism by the intestinal microbiota of dietary L-carnitine, a trimethylamine abundant in red meat, also produces Trimethylamine-N-Oxide and accelerates atherosclerosis in mice. Furthermore, it can be posited that the intestinal microbiota may be a contributing factor in the well-established correlation between high levels of red meat consumption and an increased risk of cardiovascular disease.

In order to analyze the publications, it is necessary to begin with the first highly cited study, which is entitled “Gut flora metabolism of phosphatidylcholine promoting cardiovascular disease”. The study has been cited 836 times, primarily by Wang Zeneng, a highly cited author. Zeneng’s discovery of a relationship between gut-flora-dependent metabolism of dietary phosphatidylcholine and cardiovascular disease pathogenesis has provided opportunities for the development of new diagnostic tests and therapeutic approaches for atherosclerotic heart disease.[44] In the second article, Robert A. Koeth posited that intestinal microbiota may contribute to the well-established link between high levels of red meat consumption and cardiovascular disease risk. Furthermore, Zhu Weifei and Tang W. H. Wilson et al identified a potential correlation between Trimethylamine-N-Oxide, a metabolite of intestinal flora, and the development of cardiovascular disease.

By further analyzing the co-occurrence characteristics of keywords, they can be classified into eight distinct clusters. Further analysis of the keywords in clusters #5 and #7 revealed that there is a theoretical basis for cardiovascular disease research in numerous research fields, including insulin resistance, metabolic diseases and even kidney diseases, which can be attributed to the role of intestinal flora and its metabolites. Furthermore, the intestinal flora plays a role in

metabolic processes that regulate the development of diabetic cardiomyopathy, a specific form of cardiomyopathy that occurs in the absence of other cardiovascular diseases, such as hypertension, coronary heart disease, and congenital heart disease. The prevalence of this condition is rising in clinical practice. Cluster #2 Heart failure and #6 coronary heart disease showed some common cardiovascular diseases. Heart failure (HF) is a disease caused by abnormal pumping function of the heart, which makes the heart unable to meet the basic metabolic needs of the whole body. Common causes include myocardial infarction, cardiomyopathy, myocarditis, etc. The high-risk population includes the elderly over 70 years old, with an incidence of more than 10% and a 5-year mortality rate of up to 50%. Coronary atherosclerotic heart disease, commonly referred to as coronary heart disease, is an ischemic heart disease. The prevalence of coronary artery disease was 12.3 and 8.1 in urban and rural areas, respectively, and it was more common in adults over 40 years old. The incidence of male was earlier than that of female, and it showed a younger trend in recent years. These diseases can often be prevented or alleviated by changing lifestyle habits, including watching blood pressure, quitting smoking and drinking alcohol, reducing the intake of foods high in fat, sugar and salt, and getting enough exercise. Cluster #3 L-carnitine and #4 phosphatidylcholine indicates a correlation between the metabolism of phosphatidylcholine by the intestinal flora and the pathogenesis of cardiovascular diseases. The trimethylamine-n-oxide produced by the metabolites of intestinal flora has been demonstrated to have a certain degree of efficacy in the treatment of cardiovascular diseases.

Coronary heart disease represents the earliest citation outbreak and is a relatively clear keyword, reflecting its initial state in the study of intestinal flora and cardiovascular disease. The crucial point regarding the role of intestinal flora in the etiology of coronary heart disease is that dysbacteriosis and its metabolites can in result the development of coronary atherosclerosis. A comparison of the metabolites presents in Tibetan subjects by Qi Cheng et al revealed a significant reduction in the enzymes K01714 and K00821, which are involved in the lysine biosynthesis pathway, in the coronary heart disease group. The findings of the study enhanced the Tibetan people's comprehension of the correlation between the etiology of coronary heart disease and the gut microbiota, and furnished some direction for the advancement and enhancement of diagnostic and therapeutic modalities for Tibetan Coronary heart disease patients.[55] A substantial body of research has demonstrated that probiotics and prebiotics can play a role in the prevention of cardiovascular disease by influencing the composition of the intestinal microbiota and modulating the inflammatory response. In 2021, Wu Haicui discussed and summarized the potential of probiotics or prebiotics as a new mechanism for preventing cardiovascular disease. This may indicate a novel approach for the future prevention of cardiovascular disease, whereby probiotics or prebiotics may prevent or improve cardiovascular disease through immune homeostasis.[56] The findings of three studies conducted by Raygan et al indicate that the administration of probiotics in conjunction with vitamin D or selenium can lead to a notable improvement in the biomarkers of mental health and metabolic characteristics in diabetic patients with coronary heart disease. This includes a reduction in hypersensitive C-reactive protein, nitric oxide, low density lipoprotein or total cholesterol, as well as a decrease in parameters associated with inflammation oxidative and stress.[57–59]

Phosphatidylcholine represents a medium-term keyword outbreak content. The intestinal flora produced by phosphatidylcholine in meat has been demonstrated to produce an endothelial toxicity factor, trimethylamine N-oxide. This has been in a keyword outbreak state for the previous two years (approximately 2022) and has attracted the attention of numerous scholars. Trimethylamine N-oxide has been identified as a key factor in endothelial cell dysfunction and is a major contributor to cardiovascular disease. The two principal forms are coronary artery disease and coronary microvascular disease.[60] In 2019, Chittim et al observed the ability of the intestinal microflora to produce choline through the action of the phospholipase D enzyme.[61] In a study published in 2017, Mohammed A. I. Al-Obaide et al found that elevated levels of Trimethylamine-N-Oxide and increased intestinal permeability may contribute to an increased risk of cardiovascular disease through the promotion of chronic inflammation and endothelial dysfunction.[62]

Myocardial infarction is a key term for a specific disease that emerged around 2020, with high morbidity and mortality rates. Lu Li et al demonstrated that the consumption of intestinal microflora negated the beneficial effects of spironolactone on myocardial infarction Myocardial infarction-induced cardiac dysfunction and cardiac dilatation in mice. The findings indicated that Lactobacillus vaginalis administration enhanced cardiac function and diminished the infarct area following myocardial infarction surgery in mice.[63] In the context of keyword analysis, insulin resistance and insulin sensitivity emerged as key terms in the significant outbreak observed in 2013 and 2021. These terms were found to be interrelated and associated with diabetic cardiomyopathy. In their 2018 article, Jia Guanghong et al defined diabetic

cardiomyopathy as the presence of abnormal myocardial structure and performance in patients with diabetes mellitus without other cardiac risk factors, such as hypertension, coronary artery disease, and significant valvular disease.[64] A proteomics analysis conducted by Heiko Bugger et al demonstrated that the proteins involved in fatty acid oxidation in cardiomyocyte deletion of insulin receptors mitochondria, which had been induced by diabetes, exhibited a decrease in expression. Similarly, the proteins associated with the tricarboxylic acid cycle and oxidative phosphorylation also demonstrated a reduction in expression in cardiomyocyte deletion of insulin receptors mitochondria in the presence of diabetes. It can be concluded that the congenital absence of an insulin signal will significantly damage cardiac efficiency when diabetes is induced. This may be achieved by mitochondrial uncoupling and increased fraction absorbed utilization.[65] Saad M. J. A. et al (2022) discussed the promotion of insulin resistance in diet-induced obesity through mechanisms independent of and dependent on gut microbiota. They also highlighted the potential for this field to facilitate the development of new therapeutic approaches for obesity/insulin resistance and its complications in the near future.[66] The terms "Mediterranean diet" and "diet-induced obesity" are both related to dietary habits and are therefore considered keywords in this field of study. In 2020, Ilias Attaye et al highlighted the potential for certain microbial metabolites derived from dietary sources to regulate the human body's metabolism, thereby influencing the risk of developing coronary microvascular disease. The researchers concentrated on the part played by macronutrients (carbohydrates, proteins and fats) and dietary formulas (such as vegetarian/vegan and diets the Mediterranean diet) in the composition and function of gut microbiota in the context of coronary microvascular disease.[67]

In 2020, Jose Rodriguez-Morato et al presented a discussion and conclusion regarding the significant impact of dietary regulation of gut microbiota on bile acid metabolism, which in turn affects host physiological responses.[68] Although studies have demonstrated that the relationship between diet, gut microbiome and cardiovascular disease risk may be influenced by the effects of bile acids on a range of metabolic pathways, further research is required to confirm, expand upon and translate these findings into clinical practice.[69–72]

Innovative technologies and strategies for studying gut microbiota in cardiovascular disease research hold great promise. Among these, prebiotics and probiotics stand out as core elements in novel strategies to modulate cardiovascular diseases through gut microbiota. This is closely tied to their wide-ranging applications and significant effects in regulating gut microbiota and enhancing host health.[73] Metabolomics can identify and quantify metabolic biomarkers linked to cardiovascular diseases and has revealed that trimethylamine N-oxide, produced by gut microbiota, is a key risk factor for atherosclerosis and cardiovascular diseases. This provides a basis for developing early diagnostic markers and treatment targets grounded in metabolomics.[74] Metagenomics can identify specific bacterial groups and functional genes associated with cardiovascular diseases and has found that certain bacterial species and functional gene expressions in the gut microbiota of cardiovascular disease patients are altered, which may be closely related to disease pathogenesis. These findings suggest the potential for developing diagnostic tools and therapeutic strategies based on metagenomics.[39] Fecal microbiota transplantation, a treatment involving the transfer of fecal bacteria from a healthy donor to a patient's gut to restore microbial balance, has shown promise in treating various diseases, including cardiovascular diseases.[75,76] Preliminary research indicates that Fecal microbiota transplantation can improve the gut microbiota structure in cardiovascular disease patients, reduce inflammation, and enhance cardiovascular function.[77]

Trend and Perspective

One of the current research trends is the analysis of the effects of intestinal flora on cardiovascular diseases from the perspective of the microbiome and its metabolites. There is a growing interest in the impact of intestinal flora composition and its metabolites (such as short-chain fatty acids and bile salt metabolites) on cardiovascular health. These metabolites may exert an influence on inflammatory processes, lipid metabolism and endothelial function. Additionally, some researchers are investigating the potential efficacy of regulating intestinal flora through dietary modifications, probiotics, or other interventions in reducing the risk of cardiovascular disease.

As a consequence of the growing understanding of the role of the gut microbiota in health and disease, it is possible that in the future, personalized diet and lifestyle intervention programmers will be developed to effectively prevent and manage cardiovascular diseases. In the context of future clinical applications, products regulating intestinal flora, such as probiotics and prebiotics, may be further developed and applied to the prevention and treatment of cardiovascular diseases. Metabolomics and metagenomics technologies can further deeply analyze the molecular mechanisms and

signaling pathways linking gut microbiota and cardiovascular diseases, thereby strongly supporting the development of new diagnostic biomarkers and therapeutic targets.[78] Fecal microbiota transplantation, despite showing some initial clinical success, requires further validation of its safety and efficacy, as its underlying mechanism remains incompletely understood. Additional basic research and clinical trials are needed to further explore its potential. Despite the growing depth of understanding of host-microbiome interactions, there remains a paucity of knowledge regarding the function of the majority of gut microbiota metabolites. A comprehensive understanding of the interaction mechanism between the gut microbiome and host metabolism remains a crucial and indispensable area of research. This understanding will facilitate the elucidation of disease pathophysiology and the mechanisms of drug intervention. Furthermore, it will establish a foundation for the development of innovative therapeutic methods and drugs.

Conclusion

In conclusion, this study presents a synthesis of the research findings on the impact of intestinal flora on cardiovascular diseases over the past 19 years. It may therefore be surmised that the field of intestinal flora research in relation to cardiovascular diseases is a broad and promising one, with the potential to drive sustainable development and innovation in related disciplines. The impact of metabolites on cardiovascular disease will remain a subject of investigation. In these research fields, future research may focus on metabolism and its associated product regulation, as well as immune function regulation, etc. In emerging technologies and therapeutic strategies, metabolomics and metagenomics technologies can be further combined to gain deeper insights into the key metabolic products and functional genes linking gut microbiota and cardiovascular diseases. This could potentially lead to the development of new diagnostic tools and therapeutic drugs based on gut microbiota. In addition, large-scale, multi-center clinical trials of fecal microbiota transplantation could be conducted to evaluate its long-term safety and effectiveness, as well as to explore its mechanism of action. Probiotics and prebiotics also represent promising avenues for further development, with potential application value in the prevention and treatment of cardiovascular diseases.

Data Sharing Statement

All datasets presented in this study can be found in the article and Web of Science database.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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