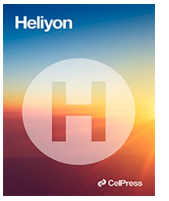
Heliyon 10 (2024) e37139

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Gut microbiota and myocardial infarction: A bibliometric analysis from 2004 to 2023

Pan Guo [a,*,1], Fang Tao [b,1], Chunpeng Ma [a], Xile Bi [a], Aihong Zhu [a], Wenguang Wang [a,**], Hongmei Yang [a,***]

[a] Department of Cardiology, Qinhuangdao First Hospital, Qinhuangdao, Hebei Province, 066000, China
[b] Medical Department, Qinhuangdao First Hospital, Qinhuangdao, Hebei Province, 066000, China

ARTICLE INFO

Keywords:
Gut microbiota
Myocardial infarction
Metabolites
Bibliometric analysis
CiteSpace
VOSviewer

ABSTRACT

Background: In recent years, numerous studies have suggested that the gut microbiota and its metabolites are closely related to myocardial infarction. Utilizing insights from these research findings may be advantageous in the prevention, treatment, and prognosis of myocardial infarction. We have employed bibliometric methodology to summarize the progress made in this research area over the past 20 years, identify the hotspots, and highlight the developmental tendencies, providing a reference for future research in this field.

Methods: We searched the content related to this field in the Web of Science Core Collection database, with a time range from 2001 to 2023. We used VOSviewer, CiteSpace, and Scimago Graphica software to visualize the search results.

Results: We included 889 reports in this study. The country with the most publications was China, while the country with the greatest influence was the United States. An analysis of institutions showed that the Chinese Academy of Medical Sciences had the largest volume of publications, whereas the Cleveland Clinic had the most influential ones. An author analysis showed Stanley L Hazen to have published the most and to also have been the most influential researcher. An analysis of all the journals publishing articles related to the search terms showed that PLoS One journal had the highest number of publications (18 articles), while Atherosclerosis journal had the most influential articles. The results of our reference analysis showed a strong association between Trimethylamine N-oxide and myocardial infarction. We found that increased intestinal permeability may be related to the progression of cardiovascular diseases, a high-fiber diet may help in the prevention of diseases such as myocardial infarction, and populations with a high intake of red meat may have an increased risk of myocardial infarction. Keyword analysis suggested that 'cardiac fibrosis' and 'major bleeding' were promising research directions in the future, and supplementing food intake with short-chain fatty acids was looked upon as a promising approach to treating coronary heart disease.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: guopan@tmu.edu.cn (P. Guo), 279549072@qq.com (W. Wang), qhddryhm@163.com (H. Yang).
[1] These authors have contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.heliyon.2024.e37139
Received 16 May 2024; Received in revised form 22 August 2024; Accepted 28 August 2024
Available online 30 August 2024

Conclusion: The gut microbiota are closely related to myocardial infarction, and investigating this relationship is crucial for the prevention and treatment of myocardial infarction, where interdisciplinary research and international cooperation are indispensable.

1. Introduction

Cardiovascular diseases (CVD) continue to pose a significant health burden globally, accounting for a substantial proportion of morbidity and mortality [1]. Amongst them, Acute Myocardial Infarction (AMI), more commonly known as heart attack, represents the severe end of the spectrum of diseases caused by coronary artery atherosclerosis [2]. Human health is severely affected by myocardial infarction, which remains a significant unsolved health concern. The mechanisms of occurrence and development of myocardial infarction have always been a hot topic of research.

Emerging research over recent years has implicated the gut microbiome, often referred to as the 'second genome' of the body [3], as a contributing factor to the development and progression of CVD, including AMI [4]. In adults, the gut microbiota are primarily composed of five main phyla: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia. Collectively, Bacteroidetes and Firmicutes represent over 90 % of the bacterial species present in the gut microbiota of healthy individuals [5]. Variations in the populations of Bacteroides and Firmicutes have been frequently linked to specific pathological conditions in the human body. Research has revealed a rise in the Firmicutes to Bacteroides ratio in some individuals with CVD [6]. The instability of coronary artery plaques is a prominent feature of myocardial infarction. Studies have shown that mucinous *Akkermansia* spp. facilitated a reduction in plasma lipopolysaccharide (LPS) levels in obese individuals with metabolic syndrome, and this has been linked to the promotion of atherosclerosis and the development of vulnerable plaques [7]. The formation of vulnerable arterial plaques may be influenced by gut microbiota because DNA from gut bacteria can activate macrophages. This activation occurs through Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4), which in turn stimulates the immune system and compromises plaque stability [8,9].

The metabolic products of the gut microbiome also play an important role in the occurrence and development of myocardial infarction. Research suggests that the structure of the gut microbial community may lead to the destruction of the mucosal epithelial barrier and an increase in permeability, thereby promoting the transfer of some endotoxins, microbial elements, and microbial metabolites into the systemic circulation. In particular, the metabolic products of the gut microbiome, such as trimethylamine N-Oxide (TMAO) [10], short-chain fatty acids (SCFAs) [11] and LPS [12], have been identified as crucial mediators in the occurrence and development of coronary heart disease [13]. Regarding TMAO, within the human body, TMAO can trigger the activation of heat shock protein 60 (HSP60) and contribute to foam cell formation by engaging toll-like receptors, particularly TLR2 and TLR4. Further, TMAO can enhance the production of inflammatory mediators such as IL-1, TNF-α, and C-reactive protein through the MAPK and NF-κB signaling pathways, thereby driving the inflammatory response in vascular endothelium. Additionally, TMAO can activate NLRP3, upregulate IL-18 and IL-1β expression, and cause vascular endothelial damage, leading to reduced plaque stability [14–16]. As for LPS, when the intestinal barrier is compromised, a condition referred to as "intestinal leakage" develops, substances from the gut that enter the bloodstream can trigger the activation of cytokines and helper T cells, resulting in chronic inflammation of the vascular endothelium. This process damages the stability of atherosclerotic plaques and encourages the development of vulnerable plaques. The underlying molecular mechanisms may involve LPS binding to toll-like receptors that activates monocytes and increases Nox2 expression. Additionally, LPS drives Th1 cell-mediated inflammation and boosts systemic immune cell activity, leading to both systemic and localized vascular inflammation. Inflammation is central to the formation of vulnerable plaques [16]. Regarding SCFAs, these substances have been found to directly or indirectly slow the progression of atherosclerosis and enhance plaque stability. Among the SCFAs, butyrate is most closely associated with the formation of stable plaques. Butyric acid can lead to a reduction in CD36 molecules in macrophages and endothelial cells, lower levels of pro-inflammatory cytokines, and decreased activation of NFkB [17]. Butyrate is also capable of preventing atherosclerosis by inhibiting the proliferation of vascular smooth muscle cells, a process that is widely recognized as essential to the pathogenesis of atherosclerosis [18].

Despite significant progress in understanding the relationship between the gut microbiome and CVDs, many anomalies and controversies remain in this field. For instance, the exact mechanisms employed by gut-derived metabolites to influence plaque stability and endothelial function are not yet fully elucidated. Further, there is ongoing debate about whether changes in gut microbiota are a cause or merely an association in the pathogenesis of coronary artery disease. The inconsistency in study results regarding the direction and extent of microbiota changes adds another layer of complexity to the conclusions drawn in this area. Therefore, more in-depth research is needed to uncover these intricate interactions and to determine whether modulating the gut microbiome could be a viable strategy for preventing and treating CVDs. Currently, there is a lack of systematic summaries of research in this field. Therefore, we applied bibliometric methods to systematically summarize past research, highlight current research hotspots in the field, and reveal directions for future research and development.

2. Methods

2.1. Data sources and search strategies

We collected data from the Web of Science Core Collection (WoSCC), encompassing the period from 2004 to 2023, by conducting a systematic search employing specific search terms on March 18, 2024: (TS=((microbiota OR microflora OR "intestinal flora" OR "intestinal microbiology" OR "gut microbiome" OR "gut flora" OR "intestinal bacteria" OR "enteric microbiota" OR "Bacteroides" OR "Firmicutes" OR "Actinobacteria" OR "Lactobacillus" OR "Bifidobacterium" OR "*Escherichia coli*" OR "Clostridium" OR "*Helicobacter pylori*" OR "Akkermansia muciniphila" OR "microbiota-derived metabolites" OR "microbial metabolites" OR "trimethylamine N-oxide" OR "TMAO"))) AND TS=(("myocardial infarction" OR "cardiac infarction" OR "coronary thrombosis" OR "coronary occlusion" OR "Coronary Myocardial Infarction")). The WoSCC provides general statistics for bibliometric software, and its labeling of document types has been demonstrated to be more accurate than other databases [19]. The English language articles and reviews were searched among the various forms of relevant publications (published papers, reprints, book chapters and reviews, conference abstracts, news items, letters, editorial material, corrections, data files, early access articles, bibliographies, and biographical entries). Our inclusion criterion was literature published in WoSCC, while the exclusion criteria comprised literature not published within the 2004–2023 study period, literature not classified as articles or reviews, and non-English language literature. Our approach to sourcing and collecting these articles and reviews is illustrated in Fig. 1. We acknowledged the possibility of biases during the data collection process. To minimize these biases, we implemented several strategies. The search strategy was refined through multiple iterations by two researchers (PG and FT) to fortify its sensitivity and precision. The criteria for inclusion and exclusion were established through collaborative discussions among team members and peer groups.

2.2. Statistical analysis

The sourced text data were harnessed from WoSCC, and bibliometric metrics like NP (Number of publications), NC (number of citations) and NCWSC (number of citations without self-citations) were extrapolated from this data, signifying publication quality. In specific instances, the h-index is leveraged to gauge the publishing prowess of a geographical region, journal, institute, or individual academic success [20]. In this study, the analyses correspond to the following software tools: VOSviewer (Leiden University, Version 1.6.20) was used for the density map analysis of research authors and institutions; CiteSpace (Drexel University, Version 6.3.R1) was utilized for the two map overlays analysis of journals, reference analysis, and keyword analysis; Scimago Graphica (SCImago Lab, Version 1.0.40) was employed for the chord diagrams analysis of national publication activity and research authors and institutions, as

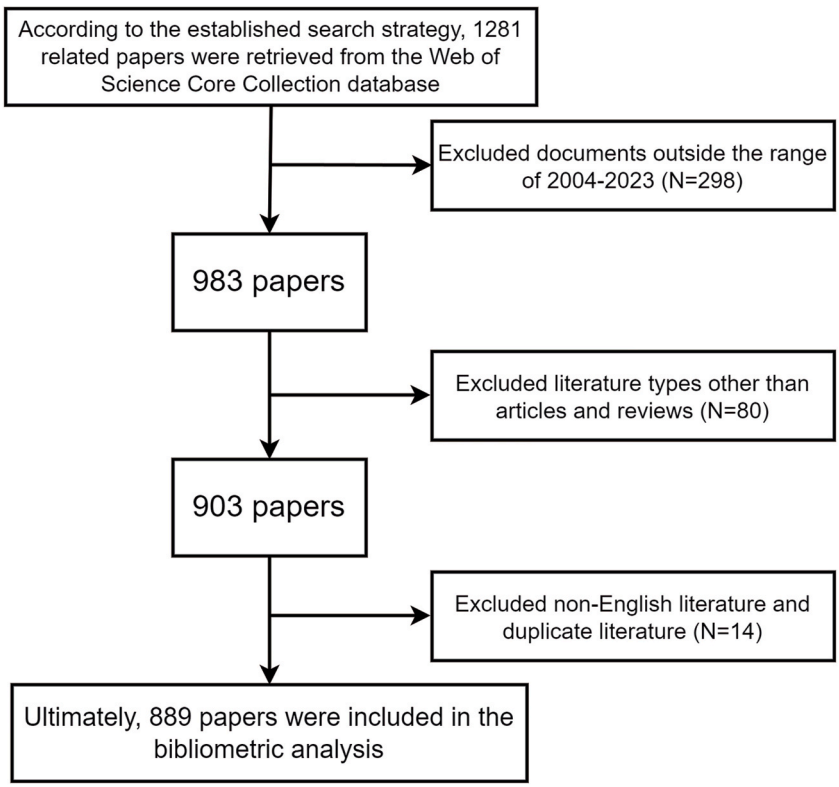


Fig. 1. Flowchart depicting literature inclusion and exclusion criteria.

well as global citation score analysis; and Microsoft Office Excel 2019 was used for analyzing the annual trend in publication numbers.

3. Results

3.1. General characteristics of the study

Strictly adhering to our search strategy, a total of 889 articles were included for analysis in our study, as detailed in Fig. 1. Overall, the articles incorporated in the present study had been cited 36,710 times, with 34,404 instances of being without self-citations. The mean citation per article stood at 41.29, and the h-index was 85.

3.2. Annual trend in publication numbers

The changes in the number of annual publications in the field of gut microbiota and AMI reflect the speed and progress of research on this topic, as well as the degree of attention devoted to studies in this field [21]. The number of annual publications focused on the correlation between myocardial infarction and gut microbiota showed no significant fluctuations, ranging between 30 and 50 from 2004 to 2018. However, after 2019, such research experienced an explosive growth, with the annual number of publications exceeding 100 in both 2022 and 2023, as specifically illustrated in Fig. 2A. Fig. 2B shows that the number of citations in this field has been increasing rapidly year by year.

3.3. Analysis of national publication activity

Examining the publications emerging from various nations can offer some insight into the value attributed to a particular field of research by that country, as well as the extent of its influence. VOSviewer clustering revealed the four groupings present within the international cooperation networks that constitute the cooperative network clusters. Fig. 3A shows that the research related to gut microbiota and myocardial infarction is geographically extensive, involving all five continents with mutual cooperation. Fig. 3B illustrates that China, United States, Italy, Canada, United Kingdom, and Germany have particularly close collaboration with other countries, whereas the countries listed in the right half of the chart need to strengthen their cooperation with other nations. The bubble chart effectively illustrates the annual publication trends of the top ten countries. Notably, in 2019, China experienced a significant surge in research output within this field. Since then, its annual number of publications has surpassed that of the United States, positioning China as the global leader. In contrast, the United States and Italy have exhibited slower growth rates in their research outputs (Fig. 3C). China boasts the highest total volume of publications, with 237 papers, accounting for 26.66 % of the global total. Meanwhile, the United States leads in both H-index and average citations per paper, underscoring its authoritative status in this domain. For more detailed information, refer to Table 1.

3.4. Analysis of research authors and institutions

Given the large number of publishing institutions, only those with more than seven articles are shown in Fig. 4, with a total of 31 institutions that met this criterion. The volume of publications from these institutions is portrayed in Fig. 4A. The color gradient in the density map, with shades closer to red, indicates a higher quantity of publications. This clearly shows that the Chinese Academy of Medical Sciences, the Cleveland Clinic, and Harvard University have the highest number of publications. Additionally, institutions such as the Cleveland Clinic, the Chinese Academy of Medical Sciences, and the University of Minnesota exhibit extensive collaborations with other entities, as depicted in Fig. 4B. The metric 'Average Publication Year' illuminates the chronology of papers published within the research domain or specific topics, where the Southern Medical University, the Chinese Academy of Medical Sciences, and the Nanjing Medical University in China appear to have the greatest contemporary research. The University of California, Los Angeles,

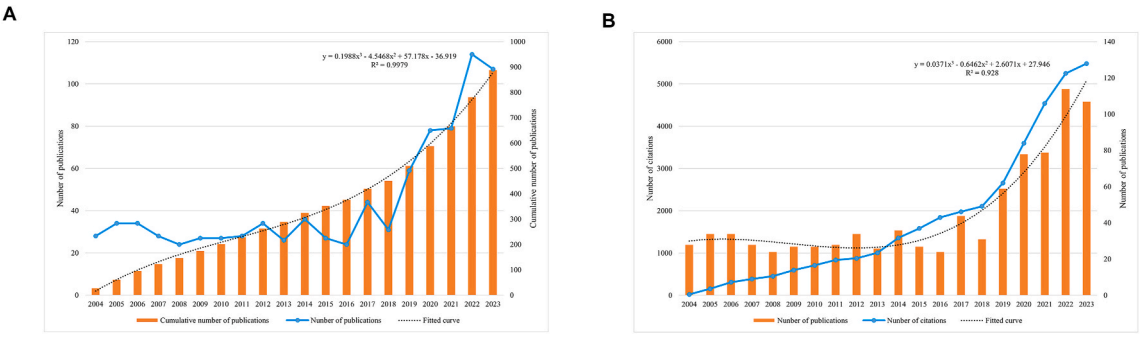


Fig. 2. Annual trends in publication numbers. (A) Changes in the annual publication numbers of articles focused on the correlation between myocardial infarction and gut microbiota from 2004 to 2023. (B) Changes in the citation numbers of articles focused on the correlation between myocardial infarction and gut microbiota from 2004 to 2023.

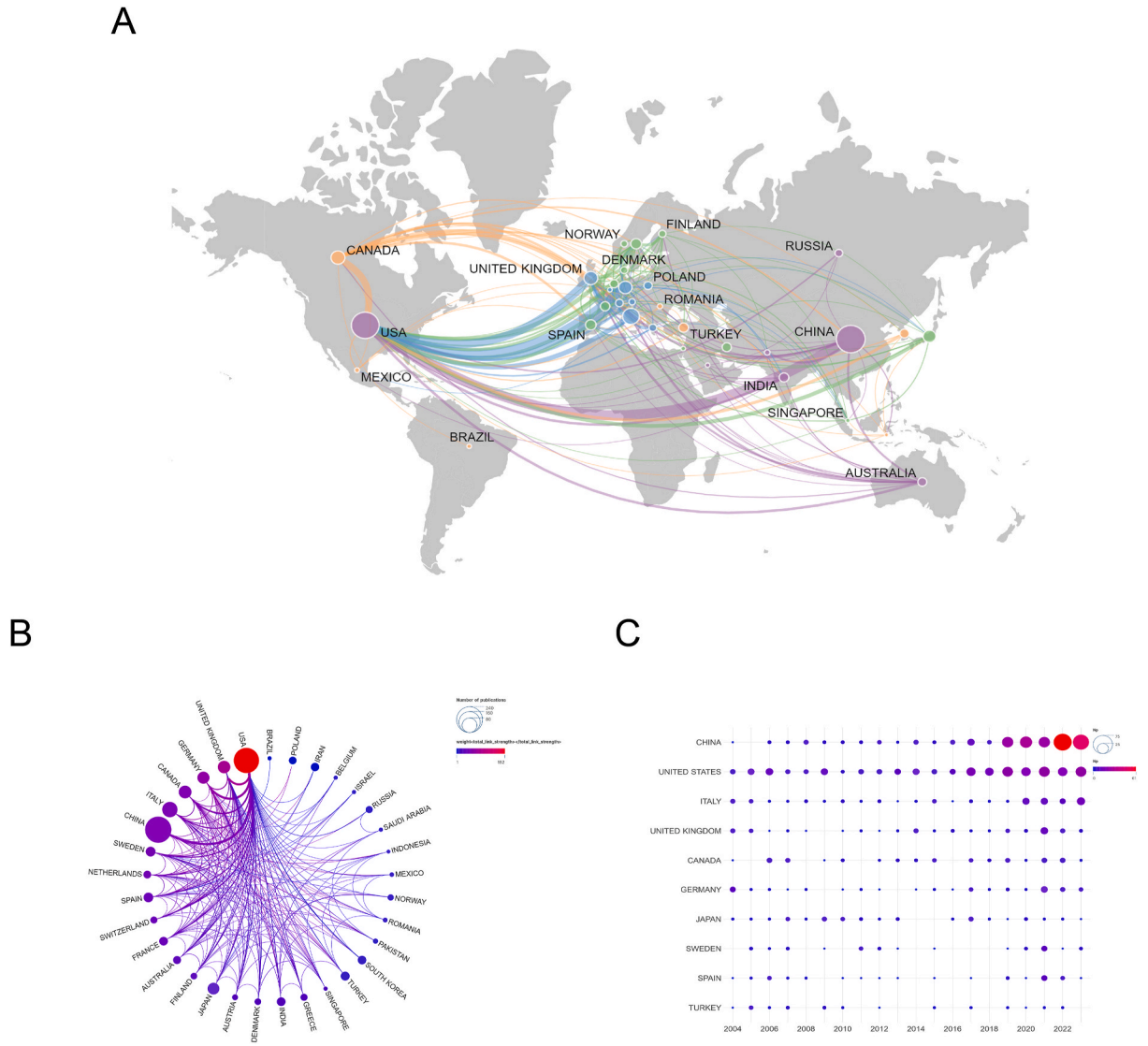


Fig. 3. Analysis of national publication activity. (A) Map of International Cooperation Networks. The node size reflects the volume of publications, while the line thickness indicates the level of cooperation. (B) Chord diagrams depicting global collaborations. (C) Bubble chart of annual publication volumes for the top ten countries.

Table 1
Publication status of the top 10 countries by volume of publications.

Country	Np	Proportion (%)	Nc	Ncwsc	Average citations	H-index
CHINA	237	26.66 %	4723	4454	19.93	38
UNITED STATES	219	24.63 %	18159	17900	82.93	56
ITALY	80	9.00 %	3085	3037	38.56	28
UNITED KINGDOM	58	6.52 %	4381	4366	75.53	29
CANADA	56	6.30 %	2537	2509	45.3	26
GERMANY	48	5.40 %	2165	2150	45.1	20
JAPAN	47	5.29 %	1746	1739	37.15	23
SWEDEN	33	3.71 %	2082	2073	63.09	19
SPAIN	31	3.49 %	2046	2038	66	16
TURKEY	27	3.04 %	495	486	18.33	14

NP: Number of publications; NC: number of citations; NCWSC: number of citations without self-citations.

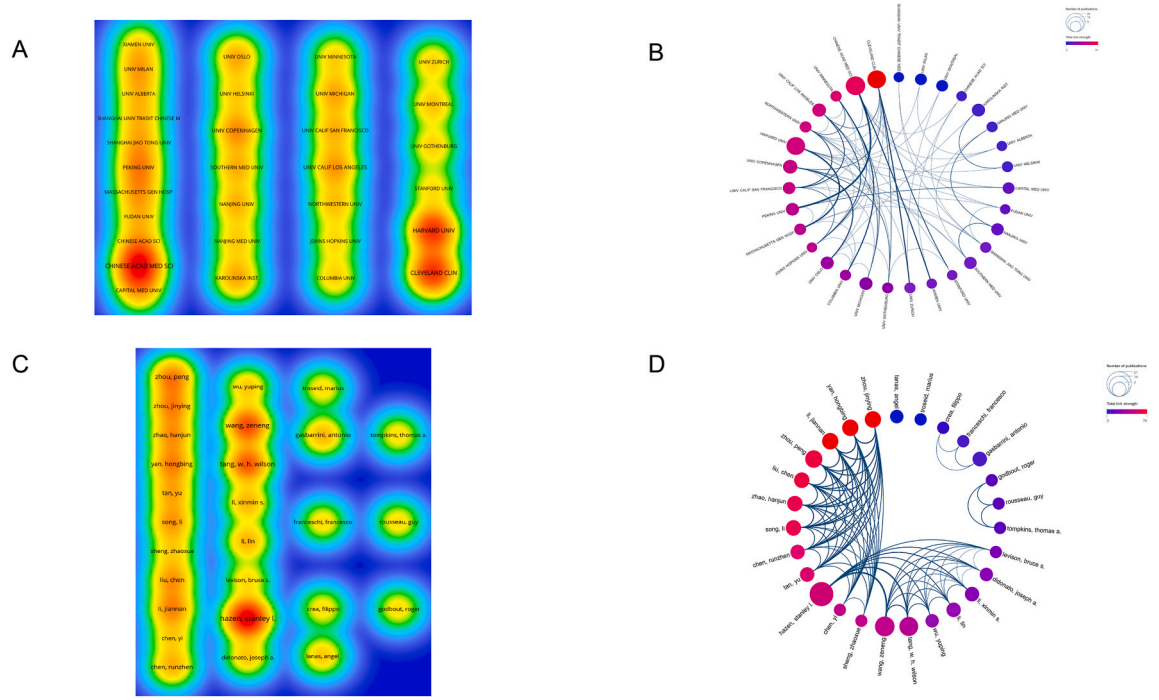


Fig. 4. Analysis of research authors and institutions. (A) Institutional publications density map. (B) Chord diagrams depicting institutional collaborations. (C) Author publication density map. (D) Chord diagrams depicting author collaborations.

Table 2
Institution publication status.

Institutions	NP	Total link strength	Average publication year	Average citations	Average normalized citation
CHINESE ACAD MED SCI	24	14	2020.92	19.79	0.81
CLEVELAND CLIN	22	16	2018.00	354.32	4.04
HARVARD UNIV	22	12	2017.86	48.73	1.16
UNIV COPENHAGEN	13	11	2016.46	51.23	1.46
UNIV CALIF LOS ANGELES	12	12	2013.17	373.67	3.30
KAROLINSKA INST	11	3	2013.45	35.27	0.74
PEKING UNIV	11	10	2020.55	27.18	0.72
UNIV MICHIGAN	11	7	2013.36	17.55	0.64
UNIV OSLO	11	8	2016.82	41.45	0.95
NANJING UNIV	10	4	2019.80	38.90	1.79
SOUTHERN MED UNIV	10	5	2021.20	19.10	1.45
UNIV CALIF SAN FRANCISCO	10	11	2017.20	95.20	1.71
CAPITAL MED UNIV	9	4	2020.22	42.56	1.86
MASSACHUSETTS GEN HOSP	9	10	2016.56	61.11	1.25
NORTHWESTERN UNIV	9	12	2014.00	109.22	2.29
UNIV MILAN	9	2	2018.33	52.11	1.37
UNIV MONTREAL	9	2	2016.11	51.89	1.03
COLUMBIA UNIV	8	8	2012.75	110.25	2.61
NANJING MED UNIV	8	3	2020.75	23.75	0.96
SHANGHAI JIAO TONG UNIV	8	5	2018.63	18.50	0.70
UNIV GOTHENBURG	8	7	2019.25	153.00	2.94
UNIV HELSINKI	8	3	2013.88	23.63	0.42
UNIV MINNESOTA	8	13	2013.75	88.75	1.90
UNIV ZURICH	8	6	2019.25	103.63	2.64
CHINESE ACAD SCI	7	3	2017.71	10.43	0.38
FUDAN UNIV	7	4	2018.86	15.71	0.58
JOHNS HOPKINS UNIV	7	10	2014.00	134.29	2.50
SHANGHAI UNIV TRADIT CHINESE MED	7	2	2019.86	12.43	0.46
STANFORD UNIV	7	5	2017.71	94.43	3.19
UNIV ALBERTA	7	3	2012.00	68.86	1.76
XIAMEN UNIV	7	5	2020.57	10.43	0.45

the Cleveland Clinic, and the University of Gothenburg exhibit the highest mean citations value, placing them in the top three positions. Average Normalized Citation is a crucial measure of citation impact, calculated based on citation frequency but also factoring in significant disparities in citation distribution across various disciplines and study fields. The standardized citation index provides a more fair and precise reflection of the academic impact of a paper or journal, implying that under equal citation instances, those papers or journals with higher normalized citation counts have a greater influence. As evident, the Cleveland Clinic, the University of California, Los Angeles, and Stanford University have the highest Average Normalized Citation, thus playing a key role in this field. Details can be found in Table 2.

Authors with at least five publications are displayed in Fig. 4C, totaling 27. The most prolific authors are Hazen, SL, Wang, Z, and Tang, WHW who are all from the U.S., as seen in Fig. 4C. In terms of collaboration, Li, J, Yan, H, and Zhou, J, have the closest cooperation, being colleagues at the Chinese Academy of Medical Sciences, as detailed in Fig. 4D. Hazen, SL has the highest NC and h-index values, indicating significant influence, and Wang, Z has the highest average citations, as shown in Table 3.

3.5. Analysis of journals

A total of 503 journals have published studies related to gut biome correlation with AMI, and the top ten journals in terms of number of publications are shown in Table 4. PLoS One has the most publications in this field, reaching 18 articles. The Impact Factor of the European Heart Journal is the highest at 39.30. The mean number of citations (51.63) and h-index score (15) of the Atherosclerosis journal are the highest. An examination of the source journals of the references reveals the contribution of each journal to the knowledge base of this field. The top three in this regard are Circulation (1477), New England Journal of Medicine (696), and Lancet (590). We investigated the citing and cited journal overlay maps that were created on the Global Scientific Journal Map. These maps encompass all comprehensive journal data on our chosen research topic, published from 2003 to 2023. The dual-map overlay analysis uncovers patterns across the global scientific journal landscape, illustrating the scientific composition [21]. The dual-map overlay on gut microbiota and myocardial infarction-related studies is shown in Fig. 5. The lines between the citing journal on the left and the cited journal on the right trace the trajectory of citation connections. It is evident that the journals publishing on this topic are concentrated in the areas of clinical and basic medicine: There are two main citation paths for MEDICINE/MEDICAL/CLINICAL category journals, namely HEALTH/NURSING/MEDICINE ($Z = 4.69$, $F = 4465$), and MOLECULAR/BIOLOGY/GENETICS ($Z = 4.72$, $F = 4499$); The main citation path for MOLECULAR/BIOLOGY/IMMUNOLOGY category journals is MOLECULAR/BIOLOGY/GENETICS ($Z = 5.16$, $F = 4895$) and HEALTH/NURSING/MEDICINE ($Z = 2.52$, $F = 2523$). Journals in the categories of PHYSICS/MATERIALS/CHEMISTRY and ECOLOGY/EARTH/MARINE might be paying more attention to the research field of gut microbiota and myocardial infarction.

3.6. Reference analysis

The co-citation analysis feature in CiteSpace plays a pivotal role [22], by generating a network of co-cited references. This network delineates cluster labels derived from cited works, portraying the research forefront and foundational knowledge through the literature that cites and is cited [23]. Analyzing these prominent clusters facilitates insights into the critical aspects of research concerning gut microbiota and myocardial infarction. A scaling parameter of $k = 25$ was established, leading to the extraction of 889 cited works of significance through the application of the g-index that facilitated the recognition of cohesive clusters of frequently cited literature related to research on gut microbiota and myocardial infarction (Fig. 6A). In this visualization, the sphere sizes, cumulatively represented across annual rings, correspond to their frequencies of co-citation. The gradient of colors ranges from purple, denoting earlier instances of citation, to yellow, for more recent citations. Spheres that feature a blend of colors signify continuous citation throughout the specified years, while the lines linking the spheres highlight the co-citation connections between different research articles and reviews. An assessment of co-citations among the references was also carried out, displaying labels that indicated the first author of the 10 most cited references along with the year of publication. Significantly, nodes marked in magenta represent crucial points within the network, distinguished by having a centrality value greater than 0.1. The study authored by Zhu et al. and collaborators, titled “Gut

Table 3
Author publication status.

Author	Country	Np	Nc	Ncwsc	Average citations	H-index
Stanley L Hazen	UNITED STATES	17	7729	7674	454.65	16
Zeneng Wang	UNITED STATES	14	6697	6647	478.36	12
Tang W. H. Wilson	UNITED STATES	9	1270	1264	141.11	9
Jiannan Li/ Jingyang Zhou/ Hongbin Yang	CHINA	9	160	148	17.78	6
Grieco Antonio	ITALY	9	337	336	37.44	7
Angel Lanas	SPAIN	9	743	737	82.56	9
Chen Liu	CHINA	7	148	140	21.14	5
Sharmila Fagoonee	ITALY	7	127	119	18.14	6
Li Xinmin S	UNITED STATES	7	688	676	98.29	7
Hanjun Zhao	CHINA	7	153	145	21.86	6

NP: Number of publications; Nc: number of citations; Ncwsc: number of citations without self-citations.

Table 4
The top 10 journals by publication volume cited journals.

Journal	NP	IF and JCR division (2022)	NC	NCWSC	Average citations	H-index	Cited Journal	NC	IF and JCR division (2022)
PLoS One	18	3.70, Q2	762	758	42.33	12	Circulation	1477	37.80, Q1
Frontiers in Cardiovascular Medicine	17	3.60, Q2	132	132	7.76	7	New England Journal of Medicine	696	158.50, Q1
Atherosclerosis	16	5.30, Q2	826	819	51.63	15	Lancet	590	168.90, Q1
Helicobacter	13	4.40, Q2	350	344	26.92	10	Journal of Biological Chemistry	354	4.80, Q1
Nutrients	12	5.90, Q2	318	317	26.50	6	Atherosclerosis	336	5.30, Q2
Frontiers in Microbiology	11	5.20, Q2	217	213	19.73	5	Journal of the American Medical Association	330	120.70, Q1
International Journal of Molecular Sciences	10	5.60, Q2	113	113	11.30	7	Journal of the American College of Cardiology	319	24.00, Q1
American Heart Journal	9	4.80, Q1	208	208	23.11	7	Stroke	290	8.30, Q1
European Heart Journal	9	39.30, Q1	1343	1339	149.22	9	British Medical Journal	264	105.70, Q1
Digestive Diseases and Sciences	8	3.10, Q3	233	232	29.13	6	Arteriosclerosis Thrombosis and Vascular Biology	263	8.70, Q1
Frontiers in Pharmacology	8	5.60, Q1	98	98	12.25	6	Gastroenterology	255	29.40, Q1

NP: Number of publications; NC: number of citations; NCWSC: number of citations without self-citations.

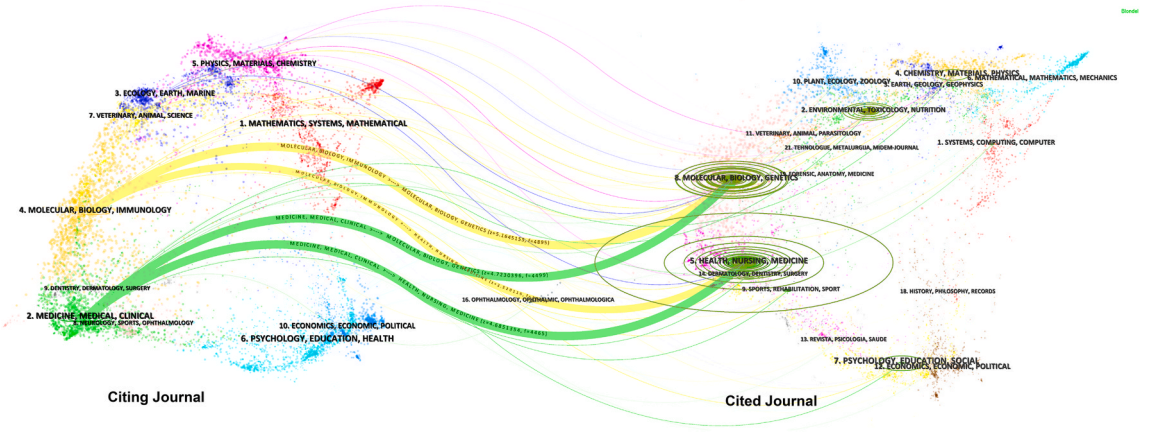


Fig. 5. Two map overlays showing citing journals and cited journals. Colored paths indicate citation relationships.

Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk," published in 2016 in Cell, is extraordinary due to its extensive citations, with the greatest number of co-citations (n = 56) [24]. In second place is the Li et al., 2017 multicenter study [25] titled "Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors," published in the European Heart Journal. The third recognized research article is titled "The gut microbiome in atherosclerotic cardiovascular disease" by Jie et al. [26], published in Nature Communications.

Through the use of cluster analysis, an evaluation of knowledge structures can be carried out and research boundaries in the particular domain can be delineated. This analysis of co-citations in the literature can provide a summary of domains investigated and showcase both prominent areas and emerging research trajectories [27]. A total Q value of 0.7173 and an average cluster weight profile of 0.8822 imply an acceptable clustering quality. An exhaustive clustering examination of every cited article is depicted in Fig. 6B. The item with the highest centrality ranking is 'Pasini E, 2016, JACC-HEART FAIL, V4, P220' in Cluster #2, boasting a centrality of 0.16. Following it is 'Zhu Q, 2018, PHYSIOL GENOMICS, V50, P893' in Cluster #0, with a centrality of 0.11. In third place is 'Marques FZ, 2017, CIRCULATION, V135, P964' in Cluster #6, with a centrality of 0.10. The fourth position is held by 'Ma GH, 2017, BIOSCIENCE REP, V37, P0' in Cluster #3, with a centrality of 0.09. Occupying the fifth rank is 'Organ CL, 2016, CIRC-HEART FAIL, V9, P0' in Cluster #2, with a centrality of 0.08. The sixth spot is taken by 'Roberts AB, 2018, NAT MED, V24, P1407' in Cluster #3, also with a centrality of 0.08. The seventh slot is held by 'Tang WHW, 2019, NAT REV CARDIOL, V16, P137' in Cluster #8, with a centrality value of 0.08. The eighth rank goes to 'Lam Vy, 2016, PLOS ONE, V11, Pe0160840' in Cluster #2, with a centrality of 0.08. 'Wang ZN, 2015, CELL, V163, P1585' in Cluster #2 occupies the ninth position, with a centrality of 0.07. Finally, the tenth rank is taken by 'Brown JM, 2018, NAT REV MICROBIOL, V16, P171' in Cluster #0, holding a centrality of 0.07. The top ten most cited references in each cluster revealed via reference clustering and co-citation analysis are listed in Supplementary Table 1.

Noun phrases commonly extracted from the titles of the cited publications, using the log-likelihood ratio (LLR) algorithm,

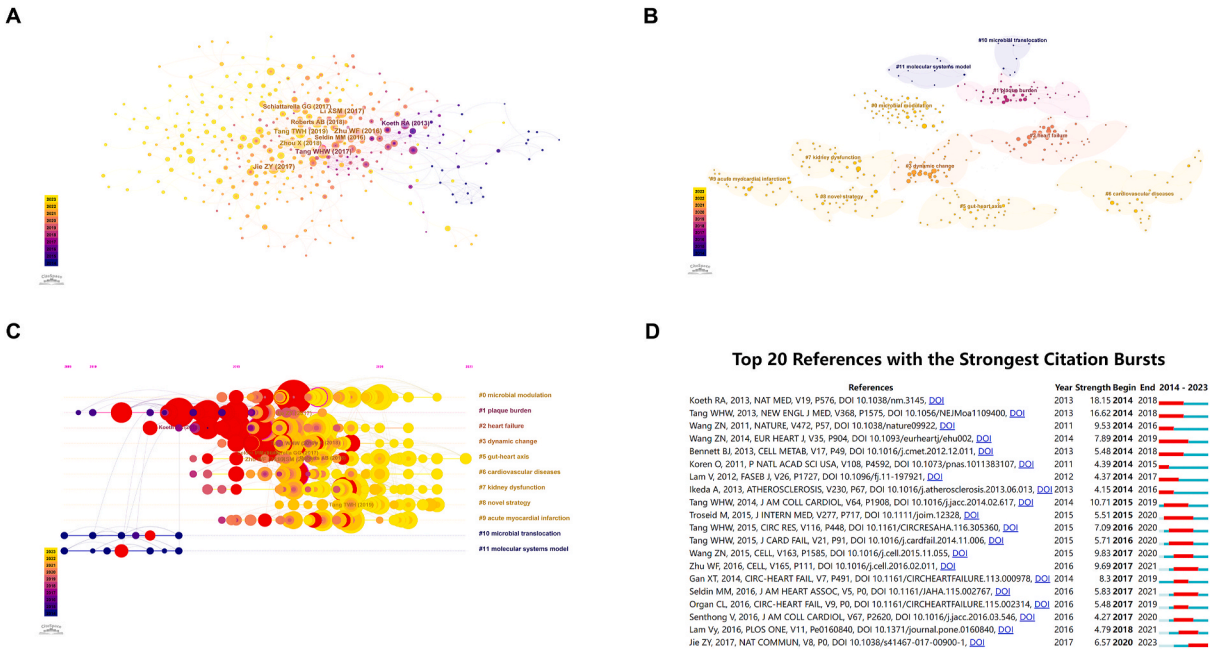


Fig. 6. Reference analysis. (A) Reference co-citation analysis. (B) Reference clustering analysis. (C) Burst analysis of each reference cluster. (D) Top 20 references with the strongest citation bursts.

oftentimes serve as cluster labels. For the specific names of these labels, refer to Fig. 6C. The blue contours symbolize initial cluster categories, such as #10 (microbial translocation) and #11 (molecular systems model), whereas the yellow contours signify the latest cluster designations, like #5 (gut-heart axis) and #9 (acute myocardial infarction). The nodes exhibiting significant bridging centrality often occupy positions either between two distinct clusters or at the core of several clusters, thereby linking various clusters or bridging

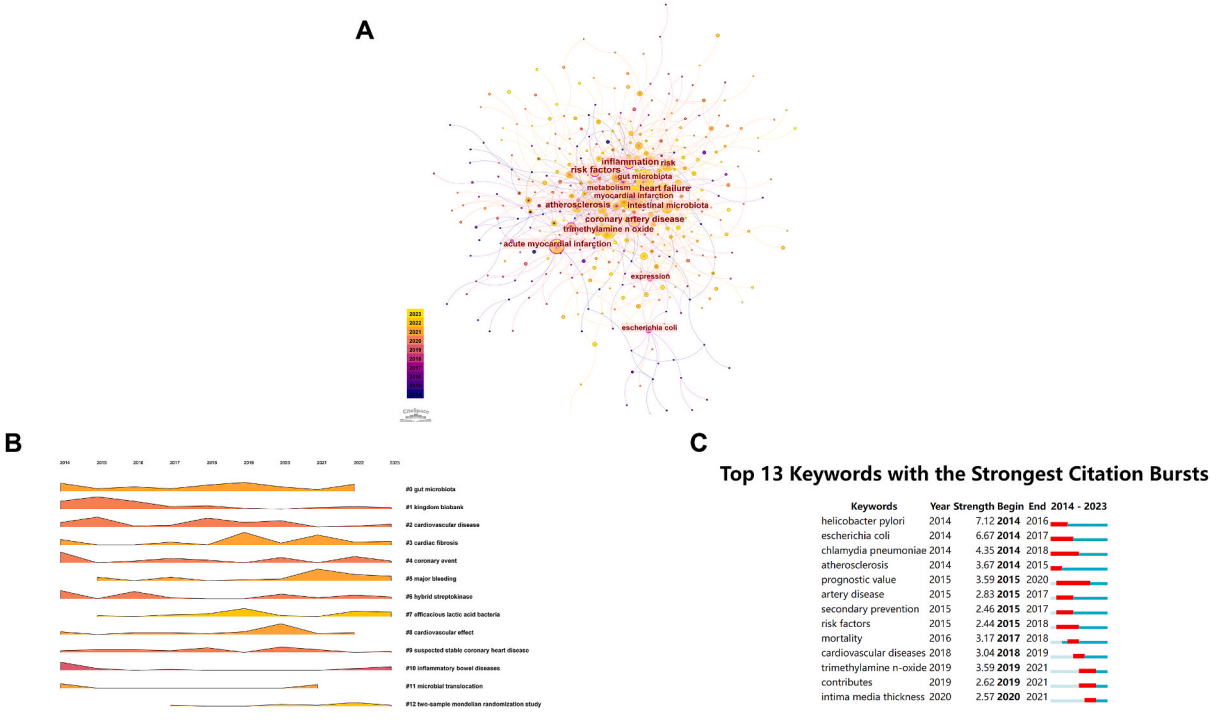


Fig. 7. Keywords analysis. (A) Keyword relevance analysis. (B) Ridgeline plot for keyword clustering analysis. (C) Top 13 keywords with the strongest citation bursts.

articles within the same cluster. This strategic placement enhances the transition between research topics and the evolution of research paradigms, among other functions [28].

As shown in Fig. 6D, burst detection has been implemented to uncover abrupt surges in frequently cited references over time. In this visual representation, nodes stand for references, while those marked with red circles symbolize the recognition of citation bursts within this cluster. For an illustration of the 20 most burst citations, see Fig. 6D. In Cluster #1, the item with the highest burst rate is 'Koeth RA, 2013, NAT MED, V19, P576,' with a burst value of 18.15. Following closely is 'Tang WHW, 2013, NEW ENGL J MED, V368, P1575,' also in Cluster #1, with a burst value of 16.62. In third place in the same cluster is 'Tang WHW, 2014, J AM COLL CARDIOL, V64, P1908' with a burst value of 10.71. In Cluster #2, 'Wang ZN, 2015, CELL, V163, P1585,' holds the fourth place with a burst value of 9.83. The next one in Cluster #3 is 'Zhu WF, 2016, CELL, V165, P111,' with a burst value of 9.69. Back to Cluster #1, 'Wang ZN, 2011, NATURE, V472, P57,' holds the sixth place with a burst of 9.53. 'Gan XT, 2014, CIRC-HEART FAIL, V7, P491,' appears seventh in Cluster #2 with a burst value of 8.30. Continuing in Cluster #1, 'Wang ZN, 2014, EUR HEART J, V35, P904' and 'Tang WHW, 2015, CIRC RES, V116, P448' come next with bursts of 7.89 and 7.09 respectively. Finally, in Cluster #0 is 'Jie ZY, 2017, NAT COMMUN, V8, P0,' coming in tenth with a burst value of 6.57.

3.7. Keyword analysis

Through keyword analysis of 889 articles included in our study using CiteSpace, as described in section 3.4 above, we set a scaling factor of k = 25 and identified influential references using the g-index, incorporating 375 of the most influential keywords into the analysis, as shown in Fig. 7A. It is clear that keywords such as inflammation risk, risk factors, gut microbiota, metabolism, heart failure, myocardial infarction, atherosclerosis, intestinal microbiota, coronary artery disease, trimethylamine n-oxide, acute myocardial infarction, expression, and *Escherichia coli* occur frequently, with colors closer to yellow indicating the most recently emerging keywords. We also conducted a cluster analysis as shown in Fig. 7B. The ridgeline plot illustrates the annual fluctuation in the number of publications for the top 12 clusters. After normalization for improved visualization, the data indicates a declining trend in research within Cluster #1 'kingdom biobank'. Meanwhile, there has been a significant emergence of research in areas such as Cluster #3 'cardiac fibrosis' and Cluster #5 'major bleeding' in recent years. Research in areas such as Cluster #11 'microbial translocation' and Cluster #12 'two-sample mendelian randomization study' has started to gradually increase. The highest centrality in Cluster #1 is attributed to 'chlamydia pneumoniae', with a centrality of 0.17. 'Acute myocardial infarction' from Cluster #9 takes the second spot, with a centrality of 0.14. Following that, 'expression' in Cluster #4 has a centrality of 0.12, ranking third. The fourth rank is held by 'risk factors' in Cluster #1, with a centrality of 0.11. 'Inflammation' from Cluster #2 takes the fifth spot, also with a centrality of 0.11. 'Coronary artery disease' in Cluster #2 claims the sixth position, with a centrality of 0.10. Ranked seventh in Cluster #0 is 'chain fatty

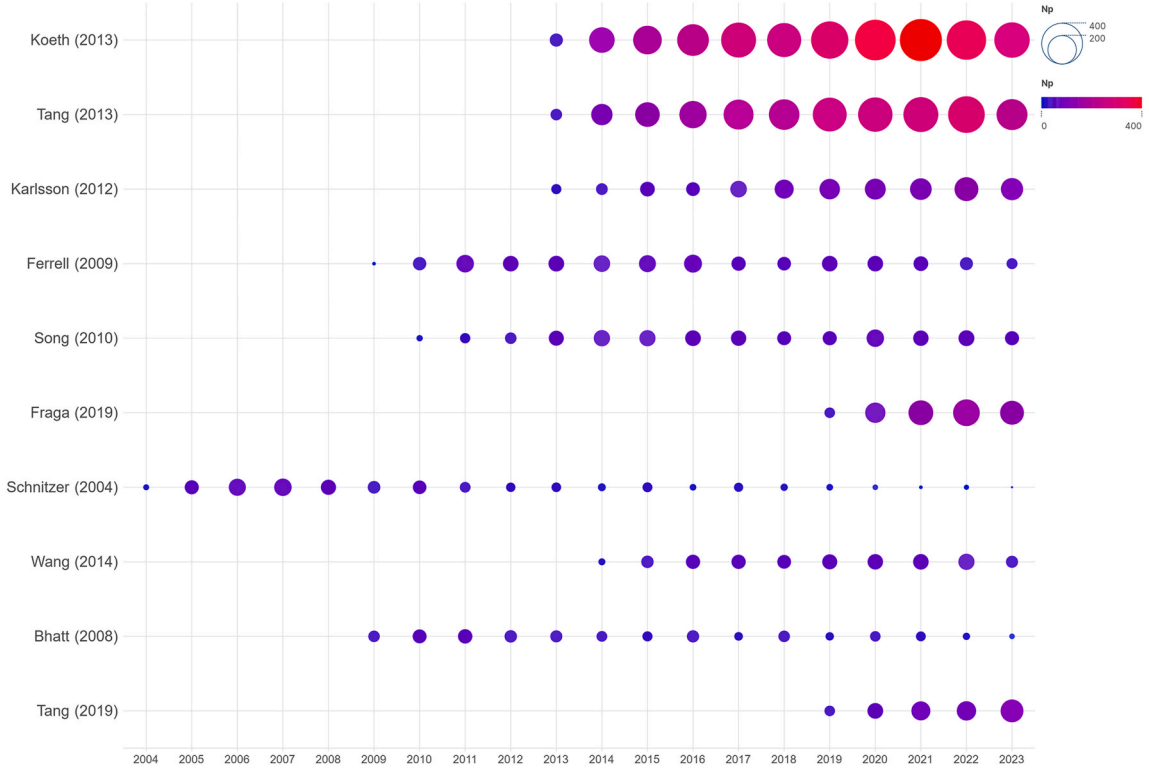


Fig. 8. Bubble chart for global citation score analysis.

acids', with a centrality of 0.10. '*Escherichia coli*' from Cluster #6 holds the eighth rank, with a centrality of 0.10. 'Meta-analysis' within Cluster #2 captures the ninth spot, with a centrality of 0.09. Completing the list at the tenth mark is 'heart failure' from Cluster #0, with a centrality of 0.09. Regarding the 13 most burst keywords, as seen in Fig. 7C, the term showing the most pronounced burst strength is 'helicobacter pylori' in Cluster #4, measured at 7.12. Following closely is 'escherichia coli' from Cluster #6, with a burst strength of 6.67. 'Chlamydia pneumoniae' in Cluster #1 is third, showing a burst value of 4.35. In fourth place, 'atherosclerosis' from Cluster #2 displays a burst magnitude of 3.67. The fifth rank is held by 'trimethylamine n-oxide' in Cluster #2, with a burst level of 3.59. Claiming the sixth slot is 'prognostic value' also in Cluster #2, with a burst strength of 3.59. Ranked seventh is 'mortality' within Cluster #2, showing a burst value of 3.17. The eighth strongest burst is found with 'cardiovascular diseases' in Cluster #0, at 3.04. Ninth in the sequence is 'artery disease' from Cluster #1, presenting a burst of 2.83. Concluding the list at the tenth place is the term 'contributes' in Cluster #3, with a burst intensity of 2.62.

3.8. Global citation score analysis

We conducted a detailed analysis of the top 10 studies ranked by the Global citation score, and a graphical presentation of these results is shown in Fig. 8, illustrating that the studies by Koeth et al. [29] (2013) and Tang et al. [30] (2013) are the intersecting point of research between gut microbiota and myocardial infarction. Recent years have also seen a potential surge in citation frequency for Fraga et al. [31] (2019) and Tang et al. [32] (2019). As shown in Table 5, out of the 10 studies, six are categorized as Articles, and only Fraga et al. (frequency = 16) (2019) is classified in the Journal Citation Reports (JCR) Q2 division, while the remaining nine fall within the Q1 category. The studies by Koeth et al. [29] (2013) and Tang et al. [30] (2013) have a Global citation score exceeding 2000, while the third-ranked study has only 831 points.

4. Discussion

In this study, we applied bibliometric methods for the first time to systematically elaborate on the correlation between the gut microbiome and myocardial infarction, covering a broad period of 20 years (2004–2023). This approach helped to capture the current state of research and trends of research on this topic, providing a reference for future studies in this field.

Fig. 2A shows a steady annual output of publications on the correlation between myocardial infarction and gut microbiota from 2004 to 2018, indicating sustained scholarly interest with consistent publication numbers. Post-2019, however, the field has seen a remarkable surge in research endeavors. This acceleration in research momentum is beneficial for advancements in the field. Fig. 2B suggests that the research interest in this field has been increasing continuously.

The research area of correlation between gut microbiota and myocardial infarction is internationally recognized, featuring collaborations across continents and significant research integration among countries including China, the US, Italy, Canada, the UK, and Germany. Countries on the right half of Fig. 3B should focus on strengthening cooperation with other nations. The Chinese research output in this area surged in 2019, surpassing the US in terms of publications. The determined efforts of researchers in China have resulted in 26.66 % of the total publications on this topic globally, demonstrating their focus on this area of study. However, the highest h-index and Average Citations are held by the US, reflecting the impact and authority of American research. While the US emphasis seems to be on depth and solid grounding, China aims to broaden the scope of research. This is beneficial for the sustained development of the field.

Fig. 4A presents a visual depiction of publication volume, notably highlighting the Chinese Academy of Medical Sciences, the Cleveland Clinic, and Harvard University, and points to their considerable contributions to the research on gut microbiome association with myocardial infarction. As shown in Fig. 4B, the Cleveland Clinic, the Chinese Academy of Medical Sciences, and the University of Minnesota are pivotal collaborators, setting an example for other institutions researching this field. The 'Average Publication Year' is an indicator of how recently that study was published. The 'Average Publication Year' serves as an indicator of the recency of research. Chinese institutions such as Southern Medical University, the Chinese Academy of Medical Sciences, and Nanjing Medical University rank highly in this regard, indicating potential for future advancements. Additionally, the high Average Normalized Citation scores at

Table 5
Display of the top ten studies on global citation scores.

Author (year)	Journal	Document Type	IF and JCR division (2022)	Global citation score (2023)
Koeth [29] (2013)	NATURE MEDICINE	Article	82.90, Q1	2861
Tang [30] (2013)	NEW ENGLAND JOURNAL OF MEDICINE	Article	158.50, Q1	2172
Karlsson [33] (2012)	NATURE COMMUNICATIONS	Article	16.60, Q1	831
Ferrell [34] (2009)	JOURNAL OF THE AMERICAN GERIATRICS SOCIETY	Review	6.30, Q1	736
Song [35] (2010)	HEALTH TECHNOLOGY ASSESSMENT	Review	3.60, Q1	656
Fraga [31] (2019)	FOOD & FUNCTION	Review	6.10, Q2	547
Schnitzer [36] (2004)	LANCET	Article	168.90, Q1	489
Wang [37] (2014)	EUROPEAN HEART JOURNAL	Article	39.30, Q1	433
Bhatt [38] (2008)	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	Article	24.00, Q1	401
Tang [32] (2019)	NATURE REVIEWS CARDIOLOGY	Review	49.60, Q1	366

the Cleveland Clinic, the University of California, Los Angeles, and Stanford University underscore the profound impact of their research. This emphasizes that, in studies originating from China, research quality should be given equal importance along with research quantity.

The predominance of American scholars such as Hazen SL, Wang Z, and Tang WHW in this field underscores the leadership position of the United States in this area of research. The collaboration patterns, particularly among Li J, Yan H, and Zhou J from the Chinese Academy of Sciences, as shown in Fig. 4D, emphasizes the importance of intramural cooperation. According to our analysis, Hazen SL emerges as a leading figure with the highest h-index and NC, signifying a substantial influence on research in this field. Wang Z, another American scholar, has the highest average citations. These details collectively highlight the significant impact that the research originating from the United States exerts in this field, suggesting that countries with high publication volume like China could further bolster their international influence by enhancing research quality.

Our analysis of the bibliometrics data from 503 journals indicates that the top three journals in terms of publication volume are all in the JCR Q2 section, suggesting that there is still room for improvement in research quality in this field. Our overview of the dual-map overlay reveals a concentrated effort in the fields of clinical and basic medicine, with journal categories like MEDICINE/MEDICAL/CLINICAL and MOLECULAR/BIOLOGY/IMMUNOLOGY forming the core citation paths. This indicates that the organic combination of basic and clinical medicine is beneficial for the development of the field. Journals that are highly cited, such as Circulation, New England Journal of Medicine, and Lancet, are renowned for contributing valuable knowledge to the field. This further emphasizes the importance of enhancing research quality. Looking ahead, the involvement of journals from the fields of PHYSICS/MATERIALS/CHEMISTRY and ECOLOGY/EARTH/MARINE will increase, indicating that interdisciplinary exchange in this field will deepen further.

In Reference analysis, the citation counts, centrality, and bursts can illustrate the significant research directions in the field. The study led by Zhu et al. [24] highlights the role of gut microbes in contributing to platelet hyperreactivity and increased thrombosis potential through the production of TMAO. In addition, research by Li et al. found that plasma TMAO levels in patients experiencing chest pain can predict both short-term and long-term risks of cardiovascular events [25]. This offers potential clinical value in risk assessment for individuals suspected of having acute coronary syndrome. These first two studies confirm the significant role of TMAO in the progression of coronary heart disease, backed by extensive research. The third study, conducted by Jie et al. [26], discovered notable differences in the gut microbiota composition and function between individuals with atherosclerotic CVD and healthy controls, suggesting a close relationship between the gut microbiome and myocardial infarction. Centrality correlates positively with the impact of research. The study with the highest centrality ranking by Pasini et al. [26] showed that individuals with chronic heart failure could have an intestinal overgrowth of pathogenic bacteria and *Candida* species, along with increased intestinal permeability, correlating with clinical severity, venous blood congestion, and inflammation. Ranked second in centrality is research by Zhu et al. [39][39] revealing that gut microbiota in patients with coronary artery disease had decreased diversity and richness. The microbial community composition in the gut microbiome shifted: *Faecalibacterium* dominated in healthy controls, whereas *Escherichia-Shigella* was prevalent in the coronary artery disease (CAD) group. This suggests that reducing the number of *Escherichia-Shigella* in the intestines of CAD patients might aid their treatment and prognosis. The third-ranked study by Marques et al. [40] found that a high-fiber diet led to gut microbiota changes that protected against CVD, providing new insights for prevention and treatment strategies, including high-fiber diets and related alternative medications. Citation burst reflects sudden attention to specific research. The highest burst rate was observed in the study by Koeth et al. [29] that highlighted the significant role played by gut microbiota-driven metabolism of choline, phosphatidylcholine, and L-carnitine in CVD development. This highlights the impact of dietary choices and gut microbial composition on CVD risk, especially in individuals with high red meat consumption. This research received significant attention between 2014 and 2018, indicating that it was a significant research topic during this period. The second highest burst was in research by Tang et al. (2013) [30], showing a correlation between elevated TMAO levels and an increased risk of adverse cardiovascular events. This study, too, gained considerable attention between 2014 and 2018, leading to numerous subsequent studies on TMAO and CVDs. These citation bursts demonstrate the explosive growth in research on TMAO and coronary heart disease between 2014 and 2018, indicating significant attention to studies on TMAO during this period. The third-ranked burst was a 2014 study by Tang et al. [41], again highlighting that high TMAO levels in heart failure patients indicated an increased risk of long-term mortality, independent of conventional risk factors and cardiorenal indices, with notable attention received between 2014 and 2016. We performed a comprehensive analysis of the ten most frequently cited articles within the initial three clusters (Supplementary Table 1), which can be summarized as follows: Cluster #0 microbial modulation, underscores the pivotal role of gut microbiota in cardiovascular health and disease. The studies within this cluster elucidate that dysbiosis, an imbalance in gut flora, is associated with various cardiovascular conditions, including hypertension, heart failure, and myocardial infarction. Furthermore, specific alterations in microbial composition are correlated with the severity of these diseases. High-fiber diets and short-chain fatty acids, particularly propionate, exhibit protective effects against cardiovascular disorders by fostering beneficial gut microbiota. The administration of probiotics has shown potential in attenuating the progression of heart failure following myocardial infarction. Collectively, these findings imply that sustaining a healthy gut microbiome may be crucial for the prevention and management of cardiovascular diseases. Cluster #1 plaque burden: Recent studies underscore the pivotal role of gut microbiota in atherosclerotic CVD. The principal findings indicate a heightened prevalence of pathogenic bacteria, such as Enterobacteriaceae and Streptococcus spp., in patients with CVD, which may adversely affect metabolic processes and cardiovascular health. Intervening in the production of TMAO by gut microbiota emerges as a promising therapeutic strategy for the treatment of atherosclerosis. Furthermore, dysbiosis, characterized by reduced microbial diversity and specific alterations in bacterial populations, is associated with CVD and systemic inflammation. Overall, these insights suggest that gut microbiota could serve as both diagnostic markers and therapeutic targets in managing cardiovascular diseases. Cluster #2 Heart Failure: Recent research underscores the adverse effects of choline and its gut microbiota-derived metabolite, TMAO, on heart failure. Elevated TMAO levels have been correlated with increased severity and mortality risk in heart failure patients,

independent of conventional risk factors. A Western diet has been shown to elevate TMAO levels, thereby contributing to cardiac inflammation and dysfunction. Additionally, TMAO has been implicated in the induction of cardiac hypertrophy and endothelial dysfunction. Alterations in gut microbiota are associated with the progression of heart failure, indicating that targeting TMAO and its microbial production may present novel therapeutic strategies for improving outcomes in cardiovascular diseases.

Keyword-based bibliometric analysis summarizes the current state and progress in this field. The ridgeline plot (Fig. 7B) reveals the year-on-year variation in the volume of publications for the 12 primary clusters, showcasing a decline in studies within cluster #1, namely 'kingdom biobank'. This decline indicates the pivotal early contributions of the 'kingdom biobank' database to the field. Simultaneously, the topics 'cardiac fibrosis' and 'major bleeding' have exhibited pronounced upward trends in recent years. Cardiac fibrosis, a common end-stage manifestation in numerous CVDs like coronary heart disease, atrial fibrillation, heart failure, and primary cardiomyopathy, significantly impacts the inception and evolution of these conditions [42]. A profound link has been identified between cardiac fibrosis and shifts in the diversity of the gut microbiome, and microbial community structure [43]. Numerous studies have demonstrated a correlation between the gut microbiome and major bleeding. For instance, in research conducted by Chen et al. [44], the effect of antibiotics on changes in the gut microbiome and their impact on the efficacy of warfarin was explored. They found that alterations in the gut microbiome significantly reduced the expression of drug-processing liver enzymes CYP1A2, CYP2C9, and CYP3A4. This led to a decreased metabolism of warfarin in the liver, extended bioavailability, and increased bleeding risk. Additionally, assessing centrality highlights the importance and growing interest in specific topics. Keywords demonstrating higher centrality, for example, *Chlamydia pneumoniae*, inflammation, and SCFAs, stand out as especially emblematic. *Mycoplasma pneumoniae* can directly lead to localized thrombotic occlusion by impacting the vascular wall, bypassing systemic hypercoagulability. It can also induce thrombotic vessel occlusion via systemic hypercoagulability through the activation of chemical mediators, such as the complement system. Additionally, *Mycoplasma pneumoniae* is often detected within atherosclerotic plaques [45]. The morphology and permeability of the intestines, along with changes in the abundance and composition of the intestinal microbiota, disrupt the intestinal barrier function, stimulate inflammatory responses, and are detrimental to the recovery from myocardial infarction [46,47]. Research indicates that supplementing with SCFAs can potentially improve heart function and inhibit the development of overload-induced cardiac fibrosis and hypertrophy by regulating inflammatory responses [48]. In future, supplementing food intake with SCFAs may be used in the treatment of patients with myocardial infarction. Fig. 7C shows that the newly emerged keywords with higher burst strength include: TMAO, whose influence showed explosive growth from 2019 to 2021, closely associated with CVDs as mentioned before; and intima-media thickness (IMT) that received significant attention within the span of 2020–2021. IMT is a commonly used measurement in vascular ultrasonography examinations, particularly of the carotid arteries, to assess the degree of atherosclerosis and the risk of CVDs. It refers to the combined thickness of the intimal and medial layers of the blood vessel wall. An increase in IMT is typically associated with the progression of atherosclerosis and thickening of the arterial wall and is considered an early marker of CVDs such as CAD and stroke. Measuring the IMT of the carotid arteries using ultrasonography technology serves as a non-invasive method to evaluate the degree of arterial hardening in an individual and to predict the potential for future cardiovascular events [49].

Our meticulous examination of the leading studies underscored by the Global citation score revealed that the research conducted by Koeth et al. (2013) [29] and Tang et al. (2013) [30][30] may be considered foundational in this field. Notably, these two foundational researchers are colleagues, both hailing from the Department of Cellular and Molecular Medicine at the Cleveland Clinic, USA, and this underscores the leading role of this institution in the field. Recent studies, particularly the works of Fraga et al. [31] and Tang et al. [32], have demonstrated a burgeoning citation frequency, indicating a sustained interest and continued relevance in the research community. Fraga et al. found that consuming foods high in polyphenols is associated with various health benefits, including improved cardiometabolic health and, to a lesser extent, enhanced brain function in humans. These benefits stem from the interactions between polyphenols and the gut microbiota. Supplementing diet with polyphenols may become a means of preventing and treating CVDs in the future. Tang et al. discovered that metabolites produced by gut microbes from dietary substances are linked to conditions such as atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity, and type 2 diabetes. They emphasized that the gut microbiome functions similarly to an endocrine organ, generating bioactive compounds that directly or indirectly influence host physiology. This open-minded approach highlights the significance of the endocrine function of the gut that will be further validated in subsequent research.

There exists a previous study similar to ours. Dan et al. [50] conducted a bibliometric analysis of the correlation between coronary heart disease (CHD) and gut microbiota. However, our research focuses on myocardial infarction that is a severe stage of CHD. Their study covered the time period from January 1, 2002, to July 31, 2022, and this duration is less recent, while our research encompasses literature from 2004 to 2023. We found that the number of studies in this field peaked in 2022 and declined slightly in 2023. They identified the United States as the most authoritative country in this field, while China published the most studies, and this is consistent with our findings. They concluded that metabolites such as TMAO, SCFAs, and LPS are closely related to CHD, a conclusion we also reached. Additionally, we identified polyphenols, IMT, and cardiac fibrosis as current research hotspots, which were not highlighted in their study.

5. Limitations

This study has several limitations: First, relying on CiteSpace that is confined to WoSCC publications may have introduced a selection bias due to the inherent constraints of the software. Second, citation bursts, affected by factors such as publication date and journal quality, may not accurately represent the impact of an article. Third, the challenge of thoroughly reviewing and analyzing all articles and their subfields required equal consideration of both high-quality and low-quality publications, potentially affecting the credibility of this study. Fourth, restricting the analysis to English-language research studies may have introduced publication bias. Fifth, an incomplete retrieval of recent literature and keywords may have resulted in gaps in the retrieved bibliometric data, impacting the overall findings. Lastly, automatic extraction of author names by VOSviewer may not always be accurate, as some authors use different spellings or multiple names, potentially leading to inaccuracies in the research results.

6. Conclusion

This study systematically summarized the research on the relationship between the gut microbiome and myocardial infarction over the past 20 years and underscored the key role of the gut microbiome in myocardial infarction. This field of research is expected to continue its rapid development that will help deepen the understanding of the pathophysiological mechanisms of myocardial infarction, potentially benefiting its clinical treatment.

Data availability statement

Data will be made available upon reasonable request to the corresponding authors.

Ethics statement

This is a bibliometric study, and no ETHICS STATEMENT is required.

CRediT authorship contribution statement

Pan Guo: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fang Tao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation. **Chunpeng Ma:** Writing – original draft, Conceptualization. **Xile Bi:** Writing – review & editing, Writing – original draft, Methodology. **Aihong Zhu:** Writing – review & editing, Formal analysis. **Wenguang Wang:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Hongmei Yang:** Writing – review & editing, Supervision, Funding acquisition, Data curation.

Declaration of competing interest

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.

Acknowledgments

The authors wish to thank the Home for Researchers editorial team (www.home-for-researchers.com) for their language editing assistance. This work was supported by the Key Research and Development Program of Qinhuangdao (grant number [202301A267]).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37139.

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