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Research trends and hotspots of osteoporosis and intestinal microbiota

A bibliometric analysis

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Abstract

Background: Osteoporosis (OP) is the second most detrimental chronic disease, and thus novel diagnostic and therapeutic approaches are needed. In recent years, there has been an increased emphasis on the utilization of gut microbiota (GM) in the context of OP. However, a comprehensive bibliometric analysis on this subject is currently lacking. Furthermore, a deeper exploration of the role of GM in bone health is imperative, and there is a pressing need to foster international and inter-agency exchange and experience in this field. Accordingly, this study aimed to provide an overview of the research trends in this field and propose suggestions for related scientific and technological research and development.

Methods: The Web of Science database was searched for articles related to both GM and OP. Statistical analyses and data visualization were performed using the EXCEL and CiteSpace software.

Results: China exhibited the highest number of publications, followed by the United States. NUTRIENTS and Sichuan University were identified as the journal and institution, respectively, with the highest number of articles. Notably, the keywords "gut microbiota" and "bone loss" have been increasingly used in publications.

Conclusion: In conclusion, this study fills the existing gap in the literature and contributes valuable insights to the understanding of the relationship between GM and OP.

Abbreviations: AD = Alzheimer disease, GH = growth hormone, GM = gut microbiota, OP = osteoporosis, TLR4 = Toll-like receptor 4.

Keywords: bibliometric analysis, bone health, CiteSpace, gut microbiota, osteoporosis, visualization analysis

1. Introduction

Osteoporosis (OP) is a metabolic disease of the bone characterized by the loss of bone mass, disruption of bone microarchitecture, and reduced bone strength. Clinically, it manifests with pain, degenerative changes in the spine, and susceptibility to fractures.[1,2] Studies have indicated that patients with OP face a higher risk of fractures than the general population, with the morbidity risk reaching 40%. Consequently, OP significantly impacts the quality of life of patients.[3] Moreover, the mortality resulting from these fractures has been progressively increasing. According to epidemiological projections, the number and annual cost of OP-related fractures in 2050, as compared to 2010, are expected to increase by approximately 158% and 169%, respectively. These increases pose socioeconomic challenges worldwide, demanding attention.[4,5]

Currently, OP medications are primarily categorized as bone resorption inhibitors and bone anabolic inhibitors.[6] The former aims to mitigate bone loss and increase bone mass by inhibiting the biological activity of osteoclasts and reducing their

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This study is a retrospective literature review aimed at exploring through the analysis of previously published data. The process did not involve any new experimental procedures, nor did it directly use human or animal subjects. All analyses were based on existing, publicly available data, and hence, this study did not require the approval of an ethics review committee. We confirm that the conduct of this research is in full compliance with current ethical standards.

All relevant data are within the paper.

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numbers, while the latter impedes bone formation by interfering with the activity of bone cells (osteoblasts and osteoclasts) to regulate bone growth and reconstruction.[7,8] Inhibitors of bone resorption, such as bisphosphonates and selective estrogen-receptor modulators, have been recognized for their relatively high efficacy in OP treatment. However, studies have documented various degrees of gastrointestinal adverse effects, including esophagitis and ulcers, associated with short-term (≤3 years) bisphosphonate treatment.[9,10] Additionally, long-term use of bisphosphonates is linked to complications such as mandibular necrosis and atypical femur fractures, as well as an increased risk of atrial fibrillation. Regarding selective estrogen-receptor modulators, they mimic the physiological effects of estrogen, inhibiting bone resorption, increasing bone density, and reducing the risk of fractures. However, they can induce painful lower-extremity spasms, unstable vascular movement, and even severe stroke.[11,12]

Inhibitors of bone anabolism primarily consist of monoclonal antibodies targeting receptor activator of nuclear factor-kappa B ligand (RANKL), a key factor in osteoclast differentiation. RANKL activates the NF-KB signaling pathway by binding to RANK and thereby turns on genes involved in osteoclast differentiation, ultimately inducing the maturation of osteoclast precursor cells into mature osteoclasts.[13] However, a meta-analysis in 2023 suggested an association between these inhibitors and increased risks of neoplasm and cardiac disease.[14] In light of these complexities, an integrated strategy is essential for the effective treatment of OP.

Gut microbiota (GM) is often referred to as the "second brain" due to the crucial roles played by genomic metabolites from the GM in essential physiological processes. These processes encompass nutrient absorption, regulation of the immune system, and maintenance of bone homeostasis.[15–18] A meta-analysis in 2022 demonstrated that both the composition and abundance of GM can influence bone mass to varying degrees in OP.[19] Consequently, the interdisciplinary research field known as "bone microbiology" emerged, and aims to bridge the realms of gut microbiology and bone biology for a more in-depth exploration of the impact of the microbiome on bone metabolism. However, due to the inherent differences between these 2 disciplines, their integration remains a complex endeavor that warrants further investigation to elucidate the specific mechanisms through which the microbiome influences bone marrow density. Therefore, conducting a comprehensive analysis of the relationship between GM and bone marrow density holds immense significance as it can serve as a valuable reference for clinical diagnosis and treatment strategies.

Bibliometrics, a research field within library and information science, aims to discern trends in the scientific archive and unveil key research directions. Employing mathematical, statistical, and other scientific metrological methods, bibliometrics involves conducting quantitative analyses and reviews of various literature characteristics, such as volume as well as associated countries, author data, and databases. Through these methods, it is used for determining trends in scientific archives, thereby shedding light on crucial research directions within a particular field.[20,21]

In recent years, bibliometric analyses of various aspects of OP have been conducted. Nevertheless, a noticeable gap exists in such analyses concerning rehabilitation medicine, endocrinology, rheumatic immunity, and many other fields.[22–24] Despite the growing focus on GM in contemporary research, bibliometric studies on GM in OP are lacking. Therefore, it was attempted to use bibliometric analysis, focusing on keyword analysis to evaluate the current research hotspot and predict the possible future research trend of GM in OP. In this study, a variety of software programs and online platforms were used to map the scientific knowledge of OP-related research areas. The main objectives of this study were to (1) identify the major contributors to the field of GM in OP from 1998 to 2023, including authors, institutions, and countries; (2) analyze the research focus of each period and explore its development and evolutionary trends; (3) predict the future research frontiers in the field; (4) provide novel perspectives and ideas for subsequent research in OP; and (5) call for more attention, especially from clinical physicians and researchers on this topic.

2. Materials and methods

2.1. Literature source and search strategy

The Web of Science Core Collection served as the source database for retrieving studies published between the establishment of the library and September 6, 2023. Terms with various combinations of the following terms were searched: Osteoporosis-related terms: (OP OR OsteoPro* OR "Bone Loss"). Gut microbiota-related terms: (gut microbiota OR Microbiome* OR Flora* OR "Enteric Bacteria*"). A total of 922 publications were obtained and then exported as "full record versus cited references" and saved as text files for subsequent analysis (Supplementary Material, Supplemental Digital Content, https://links.lww.com/MD/O871).

2.2. Data collection and statistical analysis

The obtained publications were initially imported into the CiteSpace 6.1 software for processing. Subsequently, publications unrelated to the topic of this study were excluded by 2 investigators (ZHB and SJY) after reviewing the titles and abstracts. Only reports or reviews that established a connection between GM and OP and were published in English were considered.

The final selection of publications was meticulously confirmed through a comprehensive examination of both full-text content and abstracts. The 2 reviewers (ZHB and SJY) cross-verified the final results and resolved any disagreement through consensus or seeking adjudication from a third party (HWQ).

CiteSpace 6.1 and VOSviewer were employed in this study for the visual analysis of articles,[25–27] considering aspects such as annual papers, institutions, countries, journals, authors, keywords, and H-index.[28] Various visual results, including a map of publication volume; diagrams of cooperation among authors, institutions, and nations; graphs showing burst words and citations; and a map of keyword clustering, were derived. "Pathfinder" and "pruning sliced networks" were set as software parameters. Time-slicing spanned from January 1998 to September 2023, with slices set at "1" year as the minimum unit, and the remaining settings were kept at the default values. Keyword-cluster analysis was performed using the log-likelihood ratio algorithm.[29–31] The literature screening process and results are shown in Figure 1.

2.3. Quality assessment of the publications

The methodological quality assessment of the included studies was conducted using the Mixed Methods Appraisal Tool, a rigorous assessment tool within the mixed methods research field. The Mixed Methods Appraisal Tool was developed to appraise different empirical studies that were divided into 5 categories: qualitative studies, randomized controlled trials, non-randomized trials, quantitative descriptive studies, and mixed methods studies.[32] The tool comprises individual items in each category, and each item can be marked as "Yes," "No," or "No resolution," with "Yes" scoring 1, and the other answers scoring 0. High quality was defined as obtaining more than half (>50%) of the total score. The quality assessment was independently conducted by 2 researchers (DZY and ZZQ).

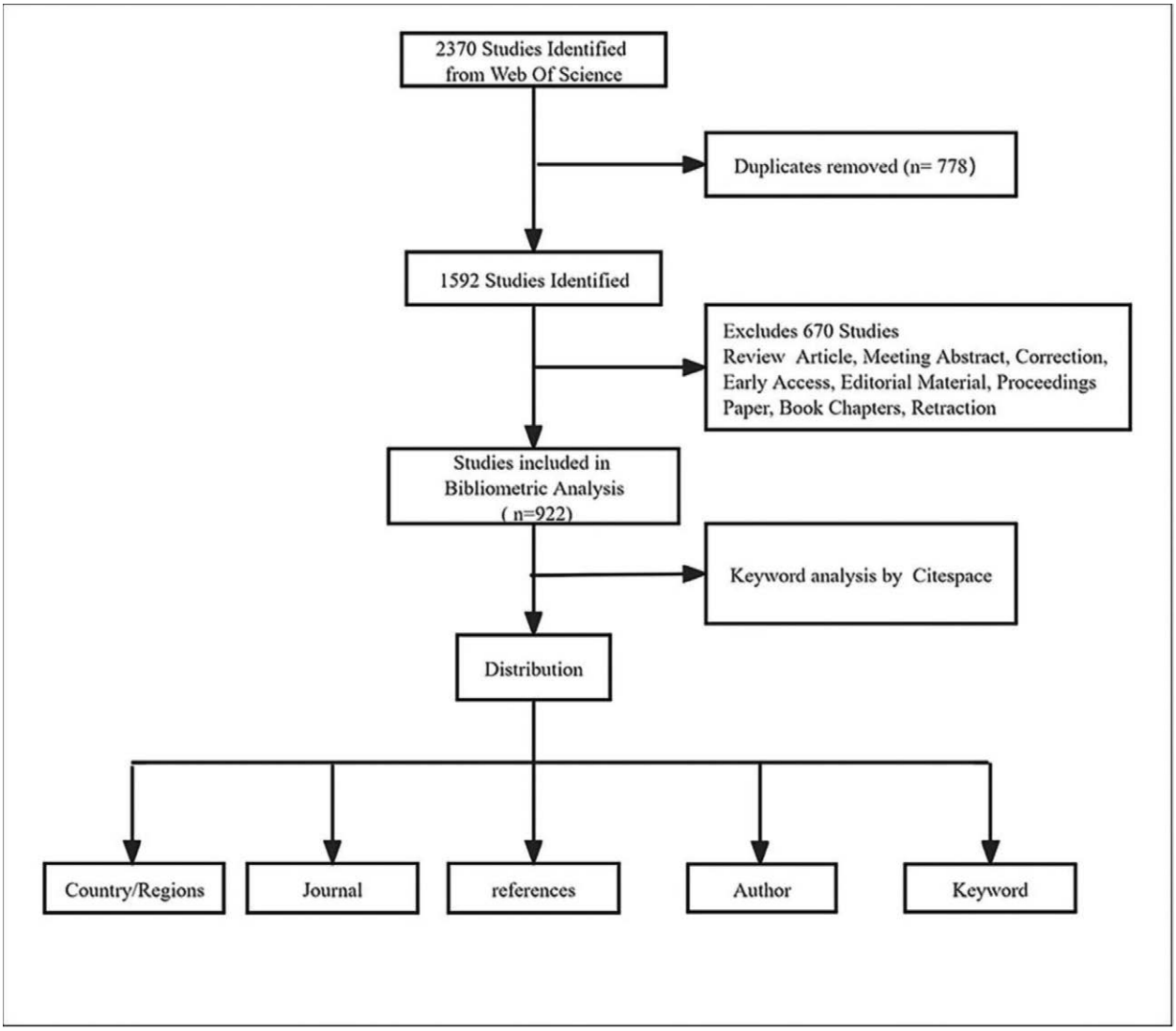

Figure 1. Literature screening process and results. The flowchart illustrates the process of literature retrieval from the Web of Science, including duplicate removal, exclusion of ineligible records, and final inclusion for bibliometric analysis. Included studies were analyzed by country/region, journal, author, and keyword distribution.

3. Results

3.1. Literature output

Annual volume of publications serves as an intuitive means to assess the current state of research and predict the future research trends in the corresponding field.[33] In total, 922 publications, comprising 625 study reports and 297 reviews, were identified in the fields of GM and OP spanning from 1998 to 2023 (Fig. 2).

A comprehensive search of databases revealed 3 distinct stages in annual publication volume. The first stage was the slow development period from 1978 to 2011 during which the yearly number of publications grew relatively slowly, never exceeding 10 per year. Roberfroid et al[34] first proposed the hypothesis that the GM plays a preventative role in the development of OP. Since then, research into the mechanism by which intestinal flora influences OP has progressively advanced, thus shedding light on this complex biological interaction.

The second phase, spanning 2012 to 2016, saw SJögren et al providing evidence that GM increases the number of CD4 + T cells and the level of TNF-α in blood and secondary lymphoid tissues. This effect occurred through changes in the intestinal mucosal immune barrier, leading to an increase in the numbers of CD4 + T cells and osteoclast precursor cells in bone marrow, as well as upregulating the osteolytic cytokine TNF-α in the bone, whereby OP was mitigated.[35]

The third phase, from 2016 to 2022, displayed exponential growth, with a subsequent decline in 2023 (Fig. 2). It is noteworthy that the retrieval time for this study was confined to September 6, 2023, potentially introducing biases due to incomplete inclusion of literature for 2023. Hence, when predicting cumulative publications, data from the years 2012 to 2023 were used. The function of the trend line set by the Excel software yielded a correlation coefficient of $y = 1E{-}232^{0.2667x}$, $R^2 = 0.9272$, $P < .01$, aligning with Price law of exponential growth in scientific literature.[36] When the coefficient of determination, R^2, approaches 1, the results are deemed more reliable. Detailed investigation of the intersection point of the 2 trend lines uncovered intriguing phenomena. During a specific timeframe, the alignment between these trend lines peaked, thereby indicating a period where the research focus in this field was exceptionally distinct, and the scholars' directions of inquiry were in high agreement. However, as time progressed, the congruence between the 2 trend lines gradually diminished, signaling a divergence in research hotspots. This trend could be attributed to the deepening of investigative efforts in the

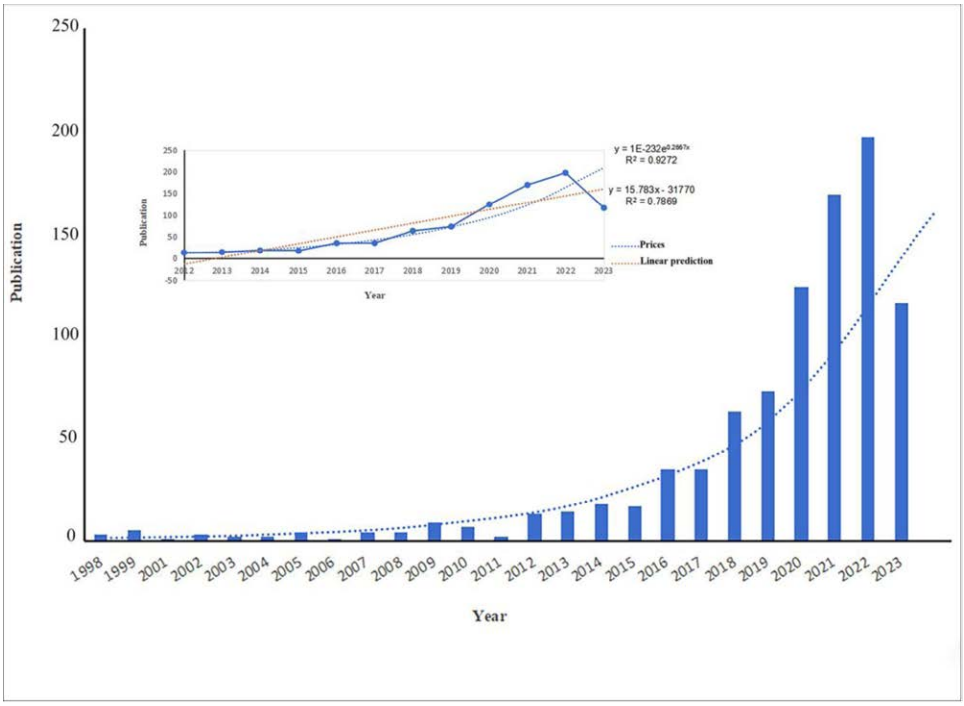

Figure 2. Annual and cumulative publications from 1998 to 2023. The bar chart shows the annual number of publications, while the dotted line indicates the cumulative trend over time. The inset provides a linear and exponential regression analysis of publication trends with corresponding equations and R^2 values.

domain, uncovering a broader array of pertinent issues, thereby diversifying the focal points of research.

In summary, the findings of this study indicated by a linear prediction coefficient R^2 of 0.7869, reveal a consistent upward trajectory in the research popularity within this field. This trend persists despite the increasingly diverse research interests, highlighting the field's extensive appeal and its significant contributions to medical advancements. The ongoing evolution of research methodologies and technologies, driven by advancements in science and technology, further solidifies the foundation for research in this domain.

Looking ahead, it is anticipated that this field will continue to sustain its research momentum. To enhance research efficiency, scholars are encouraged to actively seek interdisciplinary collaborations, fostering breakthroughs in medical science. Concurrently, investing in the development of young researchers is crucial for ensuring the field's sustainable growth. Emphasizing the integration of emerging technologies, such as artificial intelligence and gene editing, in medical research promises new opportunities and challenges for this field. In retrospect, the past decade has witnessed remarkable achievements and sustained interest in this area of study. A thorough analysis of the shifting research trend lines offers insights into the evolving hotspots and directions. To maintain this dynamism, it is imperative for scholars to explore innovative research methodologies and technologies, strengthen cross-disciplinary cooperation, and nurture the next generation of scientific talents. The field is poised to yield more substantial outcomes in future medical research endeavors.

3.2. Research areas and the journals of publication

Research areas serve as crucial nodes for distinguishing relationships between disciplines and scholars. In this study, a total of 227 journals were included in the field of research on the correlation between GM and OP (Fig. 3). This study demonstrated a multidisciplinary nature, with a primary focus on the fields of biology and medicine, encompassing immunology, microbiology, endocrinology/metabolism, orthopedics, multidisciplinary science, and geriatrics/gerontology. Given that this study is rooted in life sciences, the investigation into the correlation between GM and OP has primarily centered on the intersections of immune metabolism and bone diseases.

The volume of publications in a journal is considered representative of the research direction in the corresponding field. Table 1 enumerates the top 10 journals publishing in the field of the correlation between GM and OP. NUTRIENTS (36, 3.89%) emerged as the journal with the highest number of publications, underscoring its emphasis on this research area. The second position was shared between FRONTIERS IN CELLULAR AND INFECTION MICROBIOLOGY (20, 2.12%) and INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES (20, 2.12%). The remaining 7 journals published > 10 relevant articles. In recent years, with the deeper exploration of GM, GM has been observed to modulate bone mineral density and osteoblast function through immune regulation, as well as antioxidant and anti-apoptosis mechanisms.[37] This trend further validates the promising prospect of GM in the prevention and treatment of OP.

Regarding the impact factors of the journals, NUTRIENTS, FRONTIERS IN CELLULAR AND INFECTION MICROBIOLOGY, and INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES have all had impact factor scores > 5. Regarding the H-index, INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, JOURNAL OF BONE AND MINERAL RESEARCH, and SCIENTIFIC REPORTS have all had H-indices > 200.

A more comprehensive examination of the top 5 journals reveals their significant impact on the fields of OP and GM research. The research findings published in these journals not only left a profound imprint on the academic community but also furnished valuable references for clinical applications. Furthermore, these top journals encompass a wide spectrum of topics related to OP and gut microbiota, including mechanisms of interaction, microbiota regulation, disease treatment, and prevention.

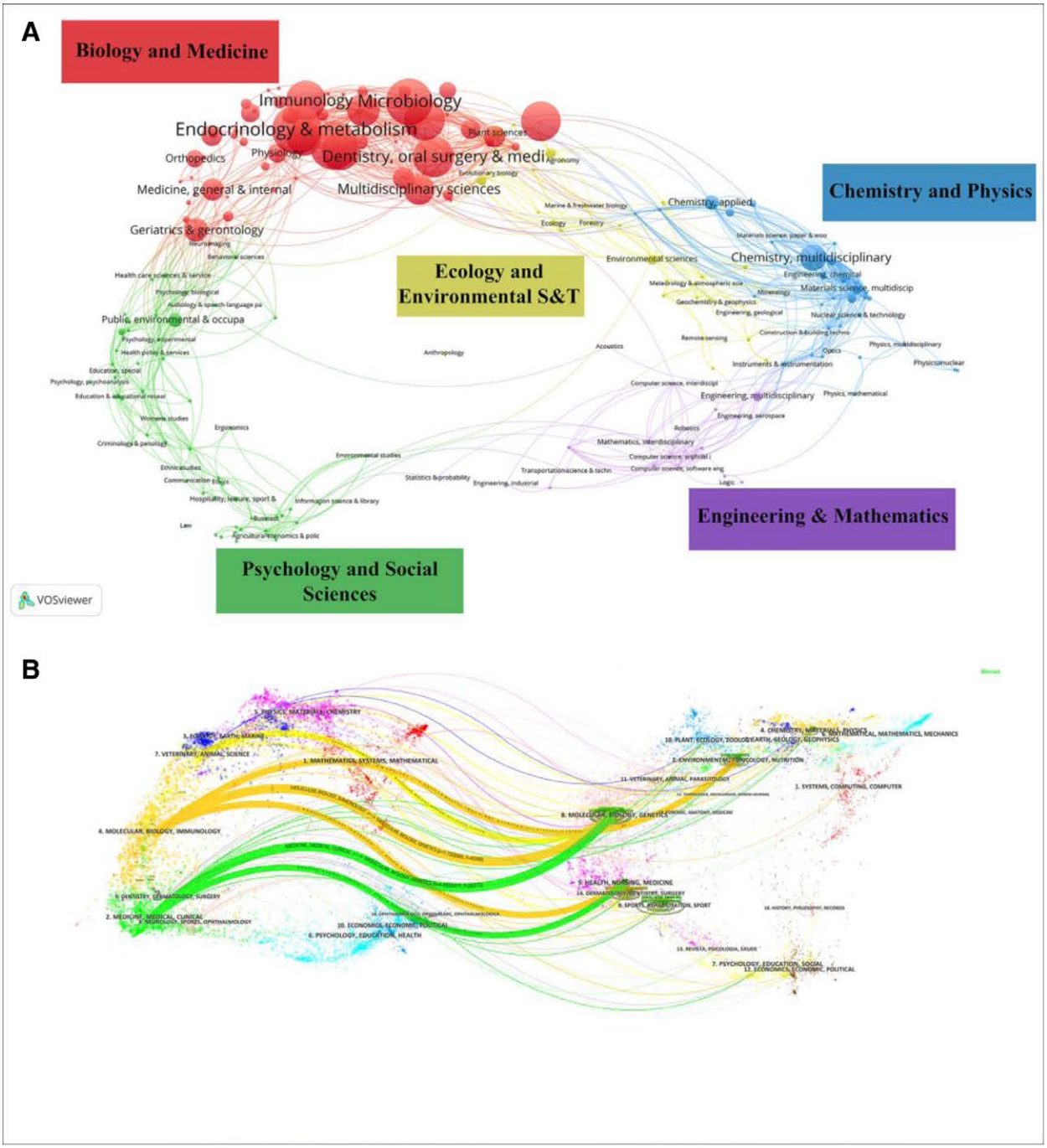

Figure 3. Research areas visualization for osteoporosis and intestinal microbiota. (A) Mapping of different research disciplines using VOSviewer, showing clusters such as Biology and Medicine, Ecology and Environmental Science, Chemistry and Physics, Psychology and Social Sciences, and Engineering & Mathematics. (B) Dual-map overlay of academic journals, illustrating citation patterns between disciplines.

It is worth noting that several of the top 10 articles reference the work of Chinese scholars. This demonstrates that China has made substantial contributions to the realms of OP and intestinal flora research and maintains close ties with the global academic community. As research in these areas continues to deepen, the prominence of China in this field is steadily ascending, with the potential to exert a more substantial global influence.

To better understand the citation relationship among the journals, a dual-map overlay of mutual journal citations was conducted, involving mainly 6 citation paths. The citation relationship among citing journals primarily focused on the following 3 domains: "Medicine, Medical, Clinical," "Molecular, Biology, Immunology," and "Veterinary, Animal, Science." Additionally, cited journals were concentrated in the following 3 domains: "Molecular, Biology, Genetics," "Health, Nursing, Medicine," and "Environmental, Toxicology, Nutrition" (Fig. 3).

3.3. Cooperation networks

3.3.1. Among nations/regions. A total of 69 countries/regions contributed to the publications on GM and OP. The top 10 countries/regions are presented in Figure 4A. China was found to be the most prolific country in terms of publications (300, 32.539%), followed by the USA (289, 31.347%) and Italy (42, 4.648%). Although the United States was behind China

Table 1

The top 10 journals in the field of osteoporosis and intestinal microbiota.

Journal	Publication numbers	IF	H-index	JCR	Ration
NUTRIENTS	36	5.9	178	Q2	3.89%
FRONTIERS IN CELLULARAND INFECTION MICROBIOLOGY	20	5.7	53	Q2	2.12%
INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	20	5.6	230	Q2	2.12%
FRONTIERS IN IMMUNOLOGY	11	7.3	190	Q2	1.19%
JOURNAL OF BONE AND MINERAL RESEARCH	11	6.2	233	Q1	1.19%
CALCIFIED TISSUE INTERNATIONAL	15	4.2	127	Q3	1.65%
SCIENTIFIC REPORTS	15	4.6	282	Q3	1.65%
BONE	14	4.1	217	Q2	1.53%
FRONTIERS IN ENDOCRINOLOGY	14	5.2	144	Q2	1.53%
CURRENT OSTEOPOROSIS REPORTS	12	4.3	70	Q2	1.30%

IF = impact factor.

in terms of the number of publications, its centrality was 0.36, significantly higher than that of other countries. Figure 4A illustrates that China entered the field relatively late but experienced rapid development and has consistently been the global leader in annual publication volume since 2019.

Subsequently, the cooperation networks between different countries were analyzed (Fig. 4B and C). The geographical map in Figure 4C illustrates international cooperation among countries, and Figure 4B depicts the specific cooperation relationships. The cooperation network map (Fig. 4B) highlights that the United States and China engaged in the most extensive international network cooperation. China collaborated most frequently with the United States and Poland, and the United States mostly collaborated with Belgium, Australia, and China.

3.3.2. Among authors/institutes. The academic influence of an institution in a specific field can be showcased through collaborative research endeavors involving scholars from diverse countries.[38] As shown in Table 2, the top 10 institutes were distributed across 3 countries, with 6 affiliated with the United States, 3 affiliated with China, and 1 affiliated with Sweden. The institutional message volume was represented by node size and exhibited a positive correlation. A total of 389 nodes and 467 connections were identified, resulting in a network density of 0.0062 (Fig. 5). This value indicates that the cooperation among these institutes was not closely interconnected.

The top 10 authors were associated with 2 countries: China and the US, further underscoring the substantial contributions to the field by these 2 countries. Additionally, other countries played various roles in advancing the field, contributing to its consistent and stable development.

However, integrated analysis of the data from Table 1 and Figure 5 revealed that some institutes were loosely connected, compared with the connections among other institutes. Subsequently, efforts should be directed toward enhancing collaboration among authors and institutes to ensure the sustained development of the field.

3.4. Citations

We also performed a co-citation analysis of the relevant articles published between 1998 and 2023. The co-cited theory of literature was initially proposed by Small H[39] and MashakovaI VI[40] in 1973. Chen CM[41] and Small HG[42] subsequently began utilizing this research method to measure the extent of literature relationships. By employing Citespace software, the "Reference" literature co-citation analysis function was selected for the included research in the literature analysis. The operational results revealed a network comprising 553 nodes and 2123 connections.

In the literature co-citation network, the key node publications were analyzed using comprehensive indices, specifically the Sigma Index, in the CiteSpace software system (Fig. 6). The Sigma index[43] represents the central idea of the leading edge and hot spot issues in literature research within the co-cited network. In this context, the nodes in the co-cited network were sorted based on the size of the Sigma index, and the top 10 items of node information were selected for analysis (Table 3).

Citation frequency indicates the academic value of the corresponding publication. In 2016, Li et al[44] from the University of Atlanta, USA, published an article in the JOURNAL OF CLINICAL INVESTIGATION, and this publication has been cited 112 times, with the largest sigma metric (3.16) in the entire co-citation network. This publication has significantly influenced the development of the field. It highlights the significance of sex-hormone deficiency as a crucial trigger for OP development. Several studies have suggested that sex hormones contribute to OP through inflammatory responses.[45–47] Research has demonstrated that reduction in sex-hormone levels downregulates the tight-junction protein ZO-1 in intestinal epithelial cells and increases the numbers of T and helper cells in the intestinal mucosa, resulting in upregulation of tumor necrosis factor and interleukin-17. This cascade activates the MAPK signaling pathway, mediating the production of osteoclastogenic cytokines and inducing osteoporosis. Furthermore, GM can regulate related response mechanisms and inhibit inflammation, thereby suppressing OP. In recent years, GM has become a focal point in the study of sex-hormone deficiency.

Among the top 10 articles ranked by their Sigma indices, articles 3, 5, and 10 addressed OP-related issues induced by deficiencies in GM-related factors. These articles were published in the journals J Cell Physiol and PLoS One by Britton RA, Ohlsson C, and Collins FL.[48–50] Article 2, authored by Sjogren et al.[35] in 2012 and published in J Bone Miner Res, was cited 14 times, with a sigma index of 2.83. This article was a pioneering work suggesting the role of GM in the prevention and treatment of OP, marking a significant advancement in the field.

It is noteworthy that in the article published in Science by Schwarzer et al[51] in 2016, the authors experimentally demonstrated that GM plays a crucial role in human growth and development, providing insightful perspectives for the prevention of bone loss. Growth hormone (GH), a single-chain polypeptide secreted from cells in the anterior pituitary gland, promotes osteoblast development, growth, differentiation, and proliferation. Additionally, GH has been shown to modulate the immune system.[52] In cases of GH deficiency, GM promotes GH receptor substrate phosphorylation by activating insulin growth factor-1 in the liver and peripheral tissues. This increases the tightness of GH binding to its receptor, inducing osteoblast differentiation and stimulating the proliferation of growing chondrocytes.

3.5. Keywords

3.5.1. Keyword co-occurrence. Serving as the essence and focal points of literature, discerning current research hotspots in this

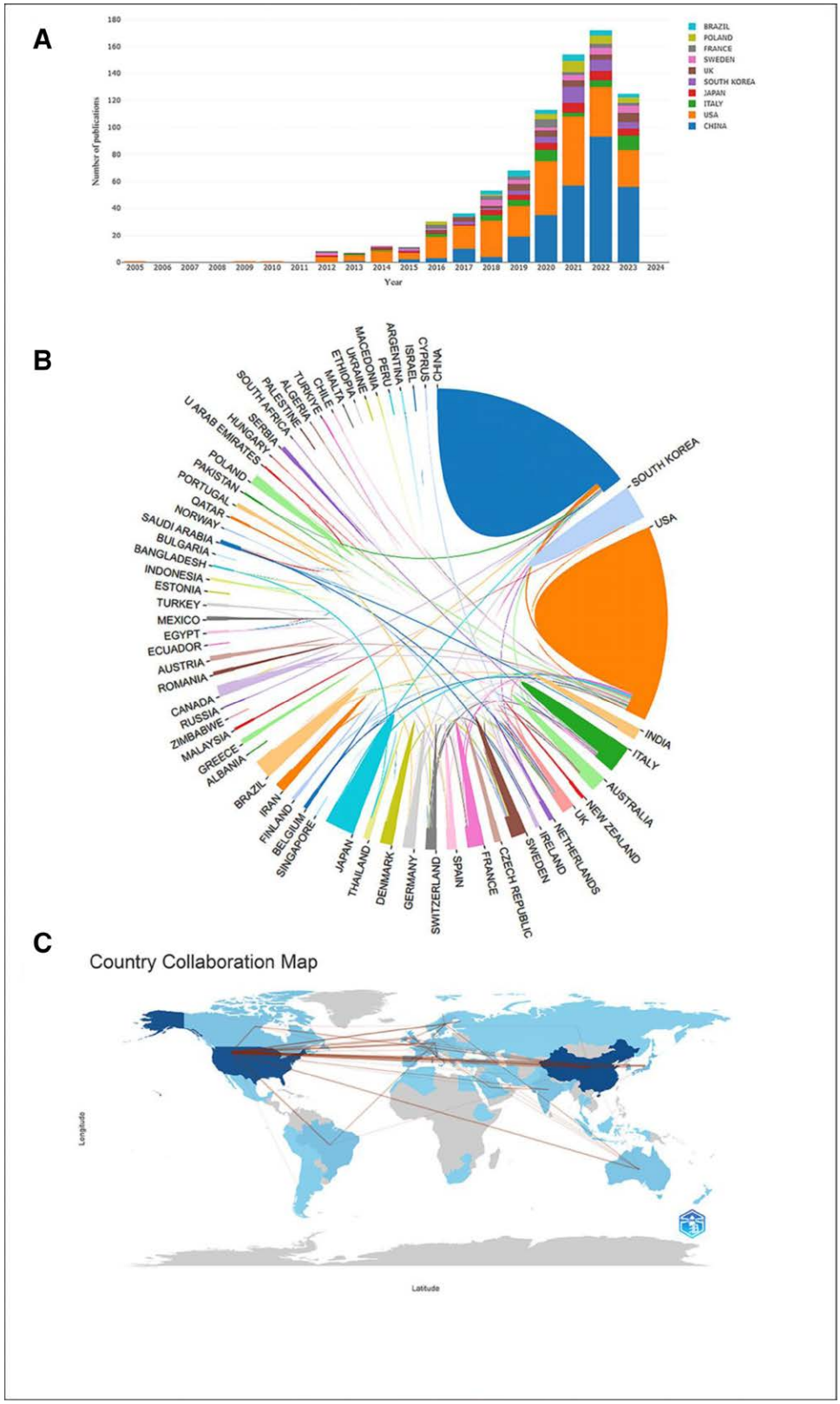

Figure 4. Top 10 countries by annual publication volume and international collaboration. (A) Annual publication volume for the top 10 countries from 2005 to 2023. (B) Collaboration network between the top publishing countries. (C) Global map showing international collaboration between countries, with lines indicating cooperative relationships.

field can be achieved through keyword co-occurrence analysis. In this analysis, a total of 920 keywords from the selected data were considered, and a visualization analysis was conducted using CiteSpace. The results showcased a network featuring 390 nodes with 2296 connections. The size of each node corresponds to the frequency of its occurrence, while the connections indicate the strength of co-occurrence. CiteSpace delineates relevant field research hotspots by assessing node size and centrality. Centrality

measures the significance and importance of a node within a network, reflecting its prominence in the overall structure. Nodes with a centrality value > 0.1 are presently regarded as holding substantial positions in the network structure.[32] In this study, analysis of Figure 7A shows that the keywords gut microbiota, bone loss, health, disease, and inflammation were frequent, had large nodes, deep fonts, and occupied prominent positions, signifying their current significance in research focus within this field. The top 10 frequent keywords are shown in Table 4.

Among the top 10 keywords, "gut microbiota" appeared most frequently (354, 0.08), and "bone mineral density" had the largest centrality (0.34), followed by "disease" (0.22) and "mineral density" (0.12). These results emphasize that the relationship between GM and OP remains a current research hotspot. This connection may be associated with the clinical characteristics of OP, which is prone to various complications and can significantly impact quality of life. The ultimate goal of OP research is to improve patient quality of life. Therefore, conducting more focused clinical research in this area is crucial to further explore related mechanisms and generate new insights for the diagnosis and treatment of OP patients.

Table 2

The top 10 authors and institutions with the largest number of publications.

Author	Count	Institution	Count
Parameswaran, Narayanan	9	Sichuan Univ	24
Hernandez, Christopher J	9	Univ Gothenburg	18
Mccabe, Laura R	9	Univ Penn	17
Pacifici, Roberto	8	Emory Univ	15
Fu, Lingjie	7	Univ Michigan	14
Xu, Xin	7	Michigan State Univ	13
Zhang, Yuan-Wei	6	Shanghai Jiao Tong Univ	13
Zhou, Xuedong	6	Cornell Univ	12
Britton, Robert A	6	Cent South Univ	9
Rui, Yun-Feng	6	Univ Calif Los Angeles	9

3.5.2. Keyword clustering and timeline. Keyword clustering aims to showcase the current major hot research directions in related fields. Based on keyword co-occurrence, the log-likelihood ratio algorithm is commonly utilized to generate cluster labels, which represent the direction of the study. A low cluster number implies a high number of keywords included in the cluster. In cluster analysis, it is widely acknowledged that Q > 0.3 indicates the significance of the cluster structure, and S > 0.5 suggests reasonable clustering.[53] In the present study, these values were Q = 0.81 and S = 0.9166, justifying the data analysis. The results indicated that most of the clusters were well-formed, signifying that all clusters were closely connected, and the study subjects were closely related. Since the search topic was GM and OP, clusters #0 and #2 to 9 corresponded to studies on OP, and clusters #1, #10, and #11 were associated with studies on GM (Fig. 7B).

3.5.3. Keyword emergence. To further understand the sudden emerging research hotspots in this field, the keyword burst analysis function of Citespace was employed (Fig. 7C). Keyword burst refers to the phenomenon where a keyword experiences a sudden increase in frequency within a specific period, reflecting the research hotspots and changing trends in the field during different periods. This analysis can also provide insights into future research trends. It is commonly accepted that when the strength is > 2, it can be considered a reference point for identifying a keyword outbreak. Based on the analysis of keywords over the past 25 years, the top 21 keywords are depicted in Figure 7C. Noteworthy, emerging keywords with a sustained presence in the past 5 years include "NF-KB, "therapy, "Alzheimer disease, "postmenopausal osteoporosis, "probiotics,

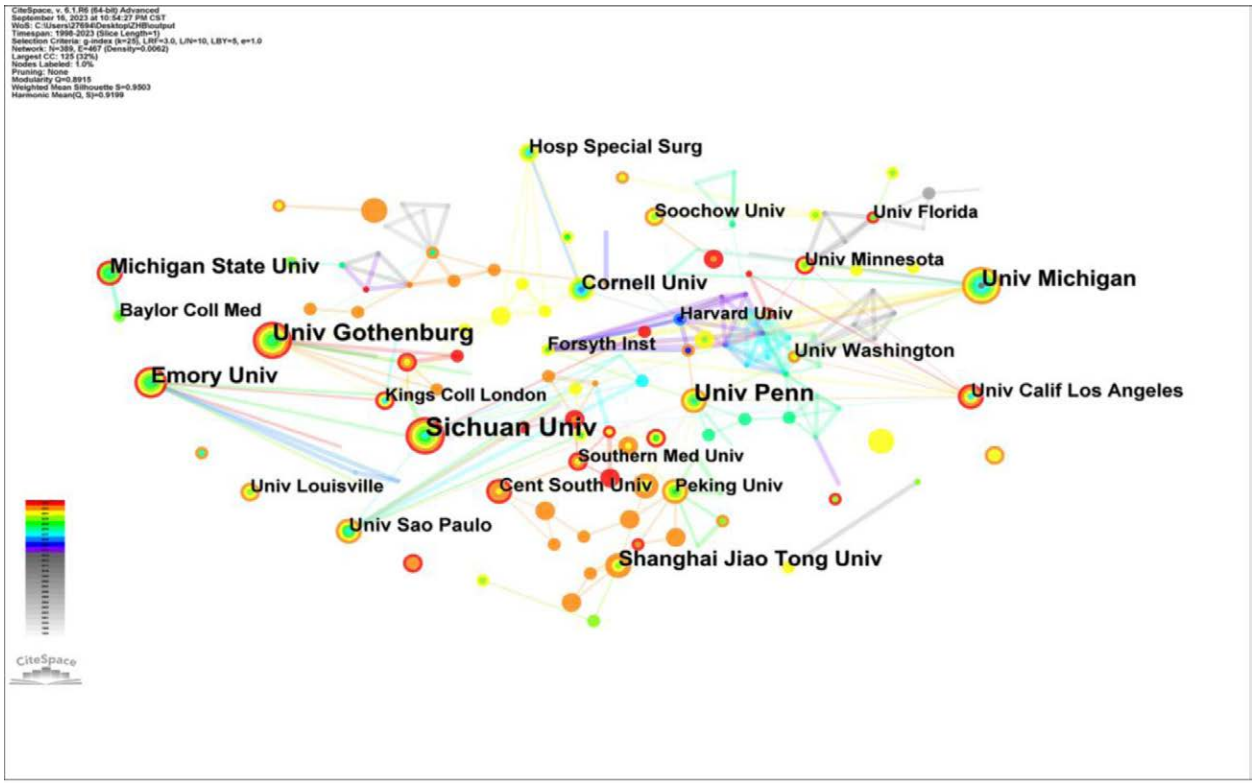

Figure 5. Collaboration among research institutions. The network map illustrates collaboration among research institutions. Node size represents publication volume, while link thickness indicates the strength of collaboration. Larger nodes, such as Sichuan Univ, Univ Penn, and Univ Michigan, represent higher productivity.

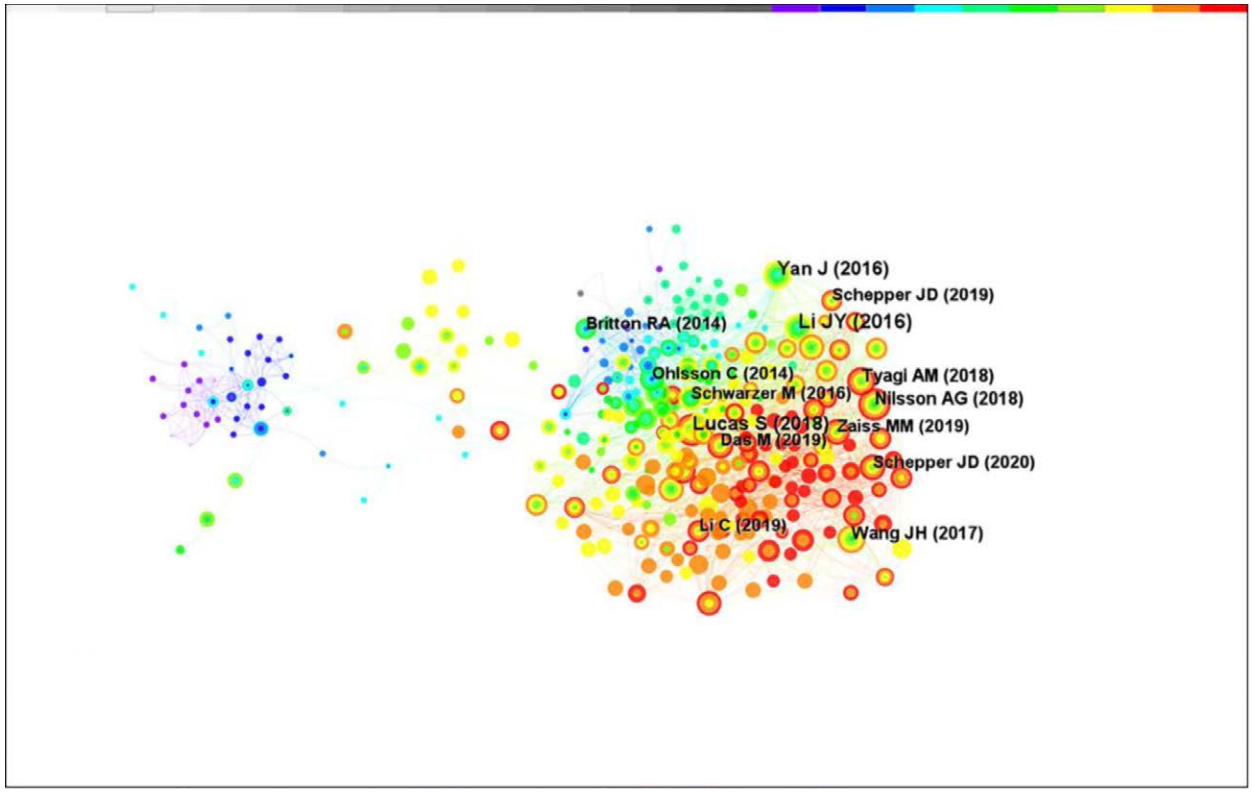

Figure 6. Co-citation network of references in osteoporosis and intestinal microbiota studies. The network shows clusters of co-cited references, with nodes representing individual references. Larger nodes indicate higher citation frequencies, while colors represent different research clusters. Key references, such as Britton RA (2014), Li JY (2016), and Schepper JD (2019), are highlighted for their influence.

Table 3

The 10 commonly cited literatures in Osteoporosis and intestinal microbiota.

Rank	Co-citations (N)	Centrality	Σ	First author	Year	Title	Journal	Cluster
1	112	0.07	3.16	Li JY	2016	Sex steroid deficiency-associated bone loss is microbiota dependent and prevented by probiotics.	J Clin Invest	1
2	14	0.13	2.83	Sjogren K	2012	The gut microbiota regulates bone mass in mice.	J Bone Miner Res	2
3	53	0.03	2.17	Britton RA	2014	Probiotic *L. reuteri* treatment prevents bone loss in a menopausal ovariectomized mouse model.	J Cell Physiol	2
4	79	0.06	1.97	Yan J	2016	Gut microbiota induce IGF-1 and promote bone formation and growth.	Proc Natl Acad Sci U S A	1
5	48	0.03	1.94	Ohlsson C	2014	Protect mice from ovariectomy-induced cortical bone loss.	PLoS One	2
6	49	0.03	1.33	Schwarzer M	2016	*Lactobacillus plantarum* strain maintains growth of infant mice during chronic undernutrition.	Science	1
7	41	0.02	1.32	Ohlsson C	2015	Effects of the gut microbiota on bone mass.	Trends Endocrinol Metab	2
8	28	0.04	1.28	Collins FL	2016	*Lactobacillus reuteri* 6475 increases bone density in intact females only under an inflammatory setting	PLoS One	1
9	22	0.02	1.25	Zhang J	2015	Loss of bone and Wnt10b expression in male type 1 diabetic mice is blocked by the probiotic *Lactobacillus reuteri*	Endocrinology	1
10	30	0.01	1.17	McCabe L	2015	Prebiotic and probiotic regulation of bone health: role of the intestine and its microbiome	Curr Osteoporos Rep	1

and "bone."[54] These keywords are anticipated to continue receiving significant attention in the coming years.

4. Discussion

This study aimed to provide a visual analysis of research conducted over the past 25 years in the field of applying GM to the diagnosis and treatment of OP using the bibliometric software CiteSpace. It offers an objective portrayal of the current status, development trends, and future research focal points in the realm of utilizing GM for OP. This endeavor presents a novel perspective to assist future scholars in gaining a better understanding of the current research landscape and developmental trends in this area.

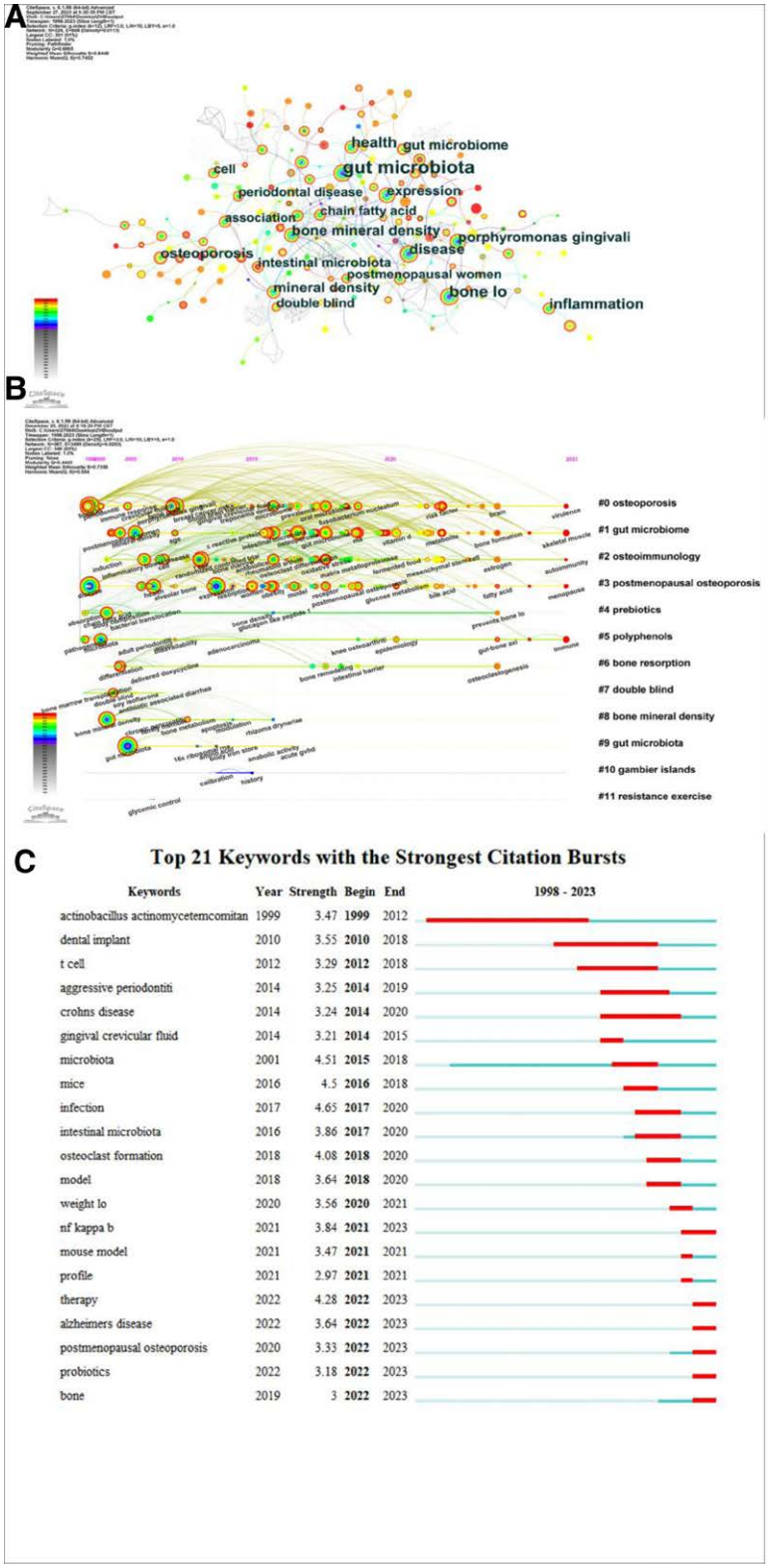

Figure 7. Keyword analysis in osteoporosis and intestinal microbiota studies. (A) Co-occurrence network of keywords, showing clusters and relationships among key terms. (B) Timeline view of keyword co-occurrence, illustrating the evolution of research focus. (C) Top 21 keywords with the strongest citation bursts, indicating periods of increased research attention from 1998 to 2023.

4.1. General information

Building on the aforementioned results, a discernible year-on-year escalation in the number of publications in this field was evident, with a more pronounced growth trend noted since 2016.[55] This upward trajectory indicates an increasing level of attention and a gradual consolidation of related research. Past studies have indicated that the scientific research output of a country is intricately linked to its social environment and economic status. Countries with higher GDP tend to prioritize scientific research, investing more in personnel training compared

Table 4

The top 10 keywords in osteoporosis and intestinal microbiota.

Rank	Count	Keywords	Centrality
1	354	Gut microbiota	0.08
2	133	Bone loss	0.07
3	102	Health	0.09
4	98	Disease	0.22
5	91	Inflammation	0.03
6	87	Bone mineral density	0.34
7	80	Osteoporosis	0.03
8	75	Mineral density	0.12
9	70	Expression	0.02
10	62	Gut microbiome	0.06

to other developing nations.[56] China embarked on its exploration in this area relatively late. However, in recent years, the investigation has experienced rapid growth, surpassing numerous developed countries (e.g., the United States and the United Kingdom) and positioning itself as a prominent contributor. As a developing country, the overall economic status of China now ranks second after the United States. Consequently, it is reasonable to assert that the recent dramatic improvement in the scientific research level of China is closely related to its rapidly developing economy. Despite the fact that China is top ranking worldwide regarding the number of scientific research papers published, there is a stark contrast in its central position in international scientific research cooperation when compared to developed countries like the United States. This phenomenon underscores a deficiency in the collaboration of China with other developed nations and highlights the need to bolster its influence in the international scientific research arena.

First, while China has achieved commendable numbers in terms of published papers, its standing in international scientific research cooperation falls short when compared to developed nations, particularly the United States. Centrality serves as a crucial metric and reflects the pivotal role of a country or region within the global research landscape. In this regard, China's relatively modest performance suggests that there is considerable room for improvement in terms of collaboration and exchanging scientific research findings with other developed nations.

Furthermore, China's network of connections in international scientific research cooperation remains somewhat inadequate. In the era of globalization, international collaboration in scientific research holds significant value in advancing scientific and technological innovation and in fostering national development. However, the limited engagement of China with other developed countries places it on the periphery of the global scientific research network. This marginal position undoubtedly hinders the progression of our scientific research capabilities and the enhancement of our international competitiveness. To further enhance the research standard, China should intensify collaboration with other nations and optimize the utilization and efficiency of research resources.

In this study, domain analysis revealed research hotspots in various directions, including animal research on the impact of GM on OP, clinical investigations into the relationship between GM and OP, and studies on probiotics and their effects on immunology. The exploration of the connection between GM and OP demonstrated a focus on the multifaceted regulation of GM on OP.[57] Additionally, the prevention and control of OP were considered through a multidisciplinary approach. In addition, it is necessary to enhance training and investments in scientific research to provide greater support and assurance for research in this field. Only through these efforts can China attain more noteworthy achievements in research within this domain and contribute significantly to the advancement of human health.

4.2. Future research and prospects

4.2.1. Experimental study on the effect of intestinal flora on osteoporosis. Based on the current keyword clustering and timeline analysis, the prevailing studies have elucidated that reshaping the GM is beneficial in mitigating the progression of OP. Notably, the terms "mice" (2016–2018) and "model" (2018–2021) highlight that empirical research analyzing the impact of GM on improving OP stands out as the primary focus of the studies in this field.

Since 2012, publications on the relationship between GM and OP have emerged, with primary research focusing on the interplay between the intestinal barrier and immune function in GM and OP.[10] Notably, increased membrane levels of Toll-like receptor 4 (TLR4) and tumor necrosis factor secreted by the endotoxin/TLR4 signaling pathway have been observed in primary cells treated with lipopolysaccharide, suggesting a regulatory role in RANKL-induced osteoclastogenesis.[58] This finding emphasizes the significance of the lipopolysaccharide/TLR4/TNF-α axis in OP and osteoclast differentiation. Since 2016, research focus has shifted to the modulation of GM and the impact of GM on bone metabolism. Mainly Shono Y and Jason D Guss from the United States have contributed to this field between 2016 and 2017.[29,30] Their data suggest that probiotics can prevent fractures and reduce the risk of OP by influencing GM and regulating the mechanical properties of the bone. As research advances and metabolomics become more prominent, a new technical platform and research approach has emerged, expanding the study of microbial community structure, including the bone microbiota. A study in 2019 revealed that astronauts experience a 5-fold reduction in Akkermansia muciniphila in space compared to pre-space conditions, resulting in diaphragm and bone density damage. Scientists propose that this phenomenon may be associated with the impact of microgravity exposure on the human body in outer space, which induces alterations in immune cytokines. It is hypothesized that these changes influence gene transcription and metabolism via the brain-gut axis, potentially triggering the production of inflammatory factors. Such cascading effects are thought to possibly expedite the aging process, thereby indirectly contributing to skeletal muscle deterioration.[59,60]

A team led by Xiehui has found that transplanting the GM from children in the rapid growth period into postmenopausal OP models effectively reduces bone loss, improves bone microstructure, and enhances bone mechanical properties. Conversely, transplanting the GM from older individuals did not exhibit a bone-protective effect. High-throughput sequencing of the 16S rRNA gene revealed a significant reduction in the probiotic Akkermansia muciniphila in the feces of ovariectomized mice compared with the level in the control mice. Following the transplantation of GM from children, which is abundant in Akkermansia muciniphila, into ovariectomized mice, the feces of the host mice exhibited an increased abundance of this bacterium. The study elucidated the mechanism whereby the GM and extracellular vesicles released by Akkermansia muciniphila directly enter the bone tissue, promoting bone growth and inhibiting osteoclast activity.[60] This mechanism helps reduce the degradation of bone microstructure and the decline in bone mass and strength caused by estrogen deficiency. The study revealed a novel "gut–bone axis" in bone metabolism regulation mediated by functional extracellular vesicles of intestinal bacteria, offering a fresh perspective for OP prevention and treatment.[61] Future research on the connection between Akkermansia muciniphila and OP is expected, fostering multi-center collaborations, refining experimental designs to meet standards, and

translating experimental results into clinical applications for improved credibility and widespread application.

4.2.2. New trends in the role of intestinal flora in osteoporosis. The emerging keywords "Alzheimer disease," "NF-KB," and "probiotics" indicate new trends in the field.

4.2.2.1. Alzheimer disease (AD). Alzheimer disease (AD) is a severe neurodegenerative condition with no effective treatment currently available. As the global population ages, the number of AD patients is expected to significantly rise, reaching an estimated 135 million by 2050, adding a new patient every 33 seconds.[62] Recent studies increasingly suggest a close connection between AD and OP. Multiple scholars have proposed that AD can be a risk factor for OP, and vice versa.

In AD patients, there is a notable increase in the risk of reduced bone mineral density and hip fractures, mirroring the pathophysiological mechanisms seen in OP. Common pathogenic factors, such as inflammation, oxidative stress, and neuroendocrine disorders, are shared between AD and OP.[63] Database mining by Liushuhua et al has established a correlation between OP and AD, identifying a common gene related to collagen deficiency. Exosomes carrying 9b-3p or pre-hsa-mir-29b have been suggested as novel treatments for both conditions.[64] A study by Zhuguangsu et al has indicated that Bifidobacterium breve may alleviate cognitive impairment in mice by modulating GM and its short-chain fatty-acid metabolites.[65]

In summary, the association between AD and OP presents new therapeutic avenues. Future research should delve deeper into the shared mechanisms of these 2 diseases to develop more effective treatments. Additionally, raising public awareness and enhancing preventive measures for both conditions should be prioritized.

4.2.2.2. NF-KB. The emergence of NF-KB as a keyword burst since 2021 indicates a significant research focus in recent years. A study by Huaiyong Zhang et al from Belgium, in particular, has garnered substantial attention in this field.[66] They experimentally showcased the efficacy of probiotic supplementation in facilitating calcium absorption, modulating GM, strengthening the integrity of the intestinal epithelial cell wall, and suppressing the activation of the NF-KB signaling pathway. These interventions were shown to reverse alterations in bone quality induced by environmental factors.

A 2019 review extensively detailed the involvement of GM in various inflammatory responses, with a focus on NF-kB.[67] The continuous development of the space industry in recent years has brought attention to the health issues faced by astronauts in space, with OP emerging as a significant concern in aerospace medicine. The NF-KB signaling pathway, crucial for bone metabolism regulation, has become a key focus in OP research. Scientists have actively explored new technologies and methods to prevent and reverse changes in bone quality induced by the space environment. For instance, interventions such as probiotic supplements to modulate the GM composition or intestinal calcium absorption and employing the gene-editing technology to interfere with the NF-KB signaling pathway, have been investigated.[68–70] These studies not only contribute to addressing the health concerns of astronauts in space but also offer novel insights and methods for promoting human bone health on Earth. However, current challenges lie in effectively regulating the production of the NF-KB signaling pathway, necessitating more clinical trials and personalized treatment plans. Future research should emphasize clinical investigations to understand the GM changes in OP through high-throughput confirmation of the role of specific intestinal microbes in the onset and progression of OP through experiments, providing robust technical support for the sustained development of the aerospace industry.

4.2.2.3. Probiotics. Probiotics and prebiotics have become common interventions in the treatment of OP. Lan et al[71] have demonstrated that Lactobacillus bl-99, owing to its capacity to shape GM and suppress the production of inflammatory cytokines, can serve as a beneficial probiotic for suppressing OP development in individuals with colitis. Similarly, Guo et al[72] have observed that L. rhamnosus LGG alleviates estrogen deficiency-induced OP by modulating GM, enhancing intestinal barrier function, and influencing Th17/Treg balance in both the gut and bone. However, despite the potential demonstrated by probiotics and prebiotics in OP treatment, the current study is not without limitations. Firstly, the majority of investigations are confined to observational studies, lacking robust evidence from randomized controlled trials. Secondly, a consensus is yet to be established regarding the optimal types, doses, and usage of probiotics and prebiotics, necessitating further research to delineate the most effective treatment strategies. Additionally, the safety of probiotics and prebiotics warrants more in-depth research and vigilant monitoring.

Consequently, although probiotics and prebiotics exhibit promising application prospects in OP treatment, further studies are imperative to substantiate their efficacy and safety. Simultaneously, to enhance the promotion and application of probiotics and prebiotics in OP treatment, it is essential to bolster research and development efforts and conduct rigorous clinical trials related to such products. These endeavors aim to yield more scientifically grounded and effective treatment methods for OP.

4.2.2.4. Use of GM for OP diagnosis. GM holds significant relevance in OP diagnosis and treatment. Li et al[36] have conducted assessments of bone mineral density in 102 elderly individuals based on 16S rRNA gene sequencing of GM. Their findings indicate a positive correlation of bone mineral density and T-cell number with abundance of Firmicutes, and a negative correlation with Bacteroides. These results suggest a discernible association between GM homeostasis and OP. Building upon these findings, Xu Z et al[57] have elucidated the regulatory mechanism of intestinal dysbiosis in OP patients through clinical studies. They have observed an increased abundance of Bacteroides and Pseudomonas in the gut of OP patients, with the GM diversity in OP patients significantly surpassing that of the healthy population. Consequently, the authors have proposed the use of GM as a novel diagnostic indicator for OP, emphasizing the need for further clinical investigations to enrich our understanding in this context.

4.3. Strengths and limitations

This study, for the first time, presents the current status and potential future research trends regarding GM and OP through bibliometric analysis. Nevertheless, it is subject to certain limitations. Firstly, the database employed in this study is confined to the Web of Science, and publications from other databases, such as Scopus or PubMed were not incorporated, potentially rendering the included literature incomplete. Secondly, the scope of literature considered in this review was limited to study articles and reviews written in English, and thus the process of study inclusion may have some bias. Lastly, the selection of informative features from the literature was rigorously controlled during the study, raising the possibility that crucial points in some publications may have been overlooked during the inclusion process.

5. Conclusions

In conclusion, this study provides an elaborate examination of the interaction between GM and OP from various perspectives.

It reveals that the investigation into the correlation between GM and OP has garnered global scholarly attention, manifesting significant clinical application value within the realm of bone microbiology. Furthermore, this avenue is anticipated to be the next frontier in bone metabolism research. Integrated studies on bone microorganisms, with an increased emphasis on the utilization of GM to identify diagnostic and prognostic biomarkers, are expected to increase. Such integrated approaches will contribute to a more comprehensive understanding of the pathogenesis and prevention of OP. In summary, this study systematically delineates the current status of research on the interplay between GM and OP, aiming to furnish researchers in this field with valuable insights and directions for future studies.

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