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ORIGINAL RESEARCH

Bibliometric Analysis of Global Pediatric Research on Cow's Milk Protein Allergy

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Background: Cow's milk protein allergy (CMPA) is a prevalent food allergy in early childhood, significantly impacting the quality of life for affected children. Current palliative measures, such as specialized formula milk, offer temporary relief but are costly and fail to address the underlying issue. Thus, there is a critical need to better understand CMPA and explore new treatment options.

Methods: This study employed bibliometric methods to analyze global pediatric CMPA research and identify future directions for the first time. Visual analyses were conducted using VOS Viewer and CiteSpace software.

Results: A total of 2040 articles published between 2000 and 2023 showed increasing annual publications. In this field of research, the Icahn School of Medicine at Mount Sinai has made significant contributions, with the most influential articles published in the *Journal of Allergy and Clinical Immunology*. Current research emphasizes personalized therapy, probiotics, and gut microbiota in CMPA.

Conclusion: Future research will focus on microbiota-related personalized treatments, promising effective clinical interventions.

Keywords: Pediatric, Cow's milk protein allergy, Bibliometric analysis, Gut microbiota

Introduction

The incidence of food allergies is gradually increasing, considered as a serious public health burden.[1] Globally, an estimated 4% to 11% of children suffer from food allergies.[2] Cow's milk protein allergy (CMPA) is among the most prevalent food allergies in early childhood, affecting 2–3% of children.[2,3] While the types of common food allergens may differ due to regional dietary variations, CMPA remains the most prevalent shared allergen among children.[4]

CMPA can cause allergic clinical symptoms related to the cutaneous, gastrointestinal, and respiratory systems.[5] The occurrence, severity, and duration of symptoms vary depending on the individual. In most cases, CMPA in children is immunoglobulin E (IgE)-mediated, where the immune response triggers mast cells and basophils to release cytokines and chemokines, leading to skin, respiratory, and gastrointestinal symptoms. In some cases, CMPA is non-IgE-mediated and T cell-mediated, involving cytokines like IL-4, IL-5, and IL-13, causing chronic gastrointestinal symptoms.[6] A small percentage of children may have both types of allergies.

Currently, the elimination-challenge test remains the gold standard for diagnosing CMPA; however, it has limitations in clinical practice. Therefore, accurate diagnosis of CMPA remains a challenge. Both over-diagnosis and under-diagnosis are common, which can lead to allergic reactions, nutritional risks, and additional economic burdens for families and society.[7,8]

Simultaneously, the correlation between gut microbiota and CMPA is gaining recognition, and utilizing specific microbiota to assist in the diagnosis and treatment shows promising potential.[3] While children may become tolerant to cow's milk protein as they grow older, research indicates that 40% of children with high IgE still experience an allergic reaction to cow's milk protein at the age of 18.[9] Despite the availability of mature amino acid formulas or extensively hydrolyzed formulas as transitional options for infants and young children with CMPA, two primary obstacles remain:

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high costs and the inability to address the root cause of CMPA.[10] Research indicates that oral immunotherapy (OIT) can serve as a desensitization method for IgE-mediated CMPA patients, but it has not yet been standardized or widely used in clinical practice.[11] Therefore, it is crucial to deepen our understanding of CMPA and explore innovative approaches for early diagnosis and curative therapies.

Bibliometric analysis is a valuable tool for evaluating literature and identifying trends, enabling researchers to explore the current landscape and emerging topics in specific fields. To date, no bibliometric analysis has been conducted on pediatric CMPA in the literature. This study employs bibliometric analysis to systematically retrieve relevant literature on pediatric CMPA since the 21st century, provide a comprehensive analysis of research progress in pediatric CMPA, and identify prospective research focal points.

Materials and Methods

Data Searching and Screening Process

This study selected the high-quality Web of Science (WOS) database, widely recognized for bibliometric analysis, for subsequent literature retrieval.[12] We comprehensively searched the Science Citation Index Expanded (SCI-E) and Social Sciences Citation Index (SSCI) databases within WOS for all publications related to pediatric CMPA from January 1, 2000, to December 31, 2023. In the selected databases, the following terms were used for the search: TS = ("cow's milk protein allergy" OR "CMPA" OR "milk allergy" OR "anaphylaxis to milk") AND TS = ("infant" OR "infants" OR "infancy" OR "child" OR "children" OR "childhood" OR "newborn" OR "neonate" OR "pediatric" OR "pediatrics"). Publications that were not available in full text, were not original research articles or reviews, or were not written in English were excluded. All initially included publications meeting the above criteria were independently reviewed in full text by three authors, and any disputed articles were discussed to make a final decision on inclusion for analysis. Finally, the data was exported in plain text format for further analysis.

Data Analysis and Visualization

Our study utilized the included literature to extract information such as the publication year, publishing country, institutions, authors, journals, keywords, and references to create visualizations like charts. CiteSpace (version 5.7 R2)[13] was used to generate network visualizations, timeline views, and burst keywords. It provides an intuitive display of how research focal points evolve over time and across the historical span.[14] VOSviewer (version 1.6.20) was employed for creating network visualizations, overlay visualizations, and density visualizations to clearly present an overview of the research.[15,16] The evaluation of journals in this paper referred to the latest 2023 Journal Citation Reports (JCR) rankings and journal impact factors (IF).

Results

Annual Growth Trend of Publications

The three authors conducted a rigorous screening process based on inclusion criteria and ultimately included 2040 publications for analysis (Figure 1). Among these, 438 were review articles (21.5%), while 1602 were original research articles (78.5%). Encompassing 2616 research institutions across 87 countries, these publications were authored by 7877 individuals and appeared in 454 distinct journals. Furthermore, the referenced academic literature spanned 36,028 citations from 6197 unique journal sources.

Figure 2 illustrated the annual publication trends for pediatric CMPA from 2000 to 2023. Overall, there has been a consistent upsurge in the average number of publications per year, with a notable surge in 2012 followed by a steady rise. The year 2022 marked a milestone with a record-breaking average of 165 publications annually.

Analysis of Countries and Institutions

To explore and visually depict the contributions of 87 countries in the field of pediatric CMPA research, VOSviewer was used to create a visualization analysis of countries with at least 42 published articles. The results, shown in the overlay visualization in Figure 3A, demonstrated close collaboration among countries, with the international collaboration

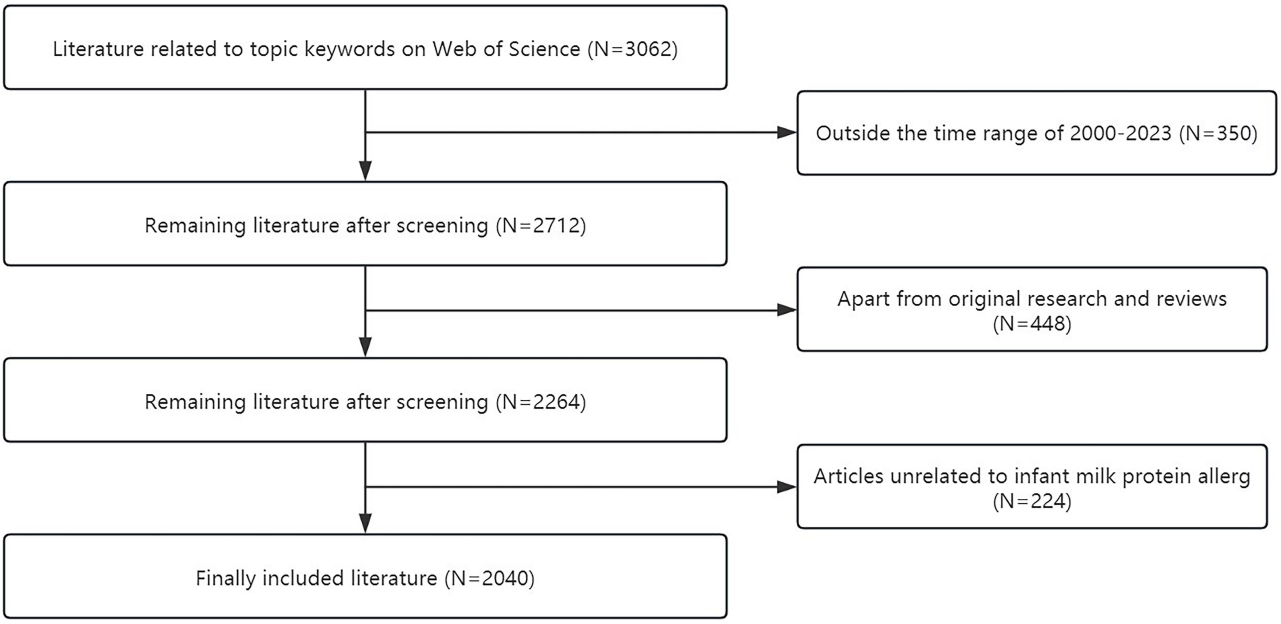

Figure 1 Flowchart of literature selection.

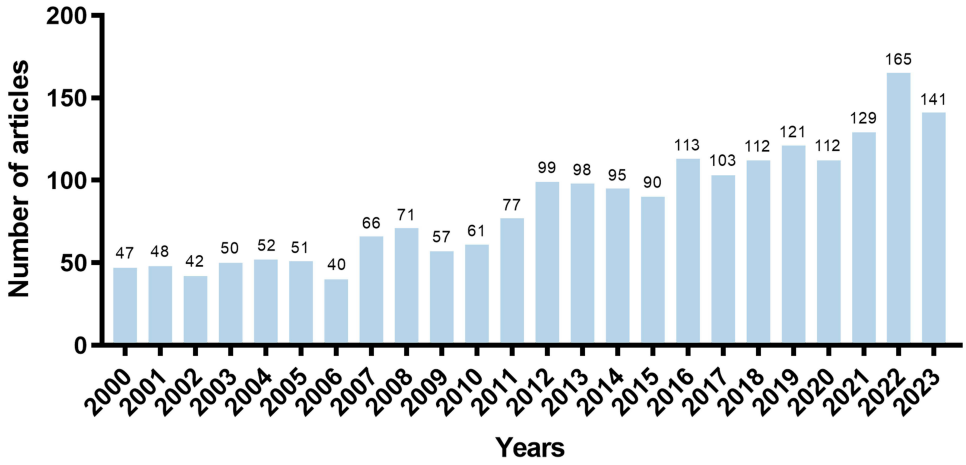

Figure 2 Annual trends of publications from the Web of Science containing pediatric CMPA from 2000 to 2023.
Abbreviation: CMPA, cow's milk protein allergy.

network of the United Kingdom being the strongest (total link strength, TLS = 511). It was worth noting that China's publications in this field predominantly appeared after 2018. Table 1 provided an analysis of the top ten countries in terms of article publication volume in this field. The United States (428 articles), Italy (317 articles), and the United Kingdom (181 articles) ranked as the top three, accounting for 45.4% of all articles, indicating significant contributions to the development of this field. In terms of average citation count per article, Germany, the United States, and the Netherlands ranked in the top three, reflecting their higher article quality and recognition.

Among the top ten institutions with the highest number of research articles, seven were from the countries in the top ten list (Table 2). The average citation count per paper for these top ten institutions was at a high level. Specifically, the Icahn School of Medicine at Mount Sinai, based in the United States, stood out with a total of 115 publications, 10,217 total citations, and an average citation per paper of 88.84, ranking first in all three categories. Additionally, there was close collaboration among institutions from different countries. Notably, the Icahn School of Medicine at Mount Sinai

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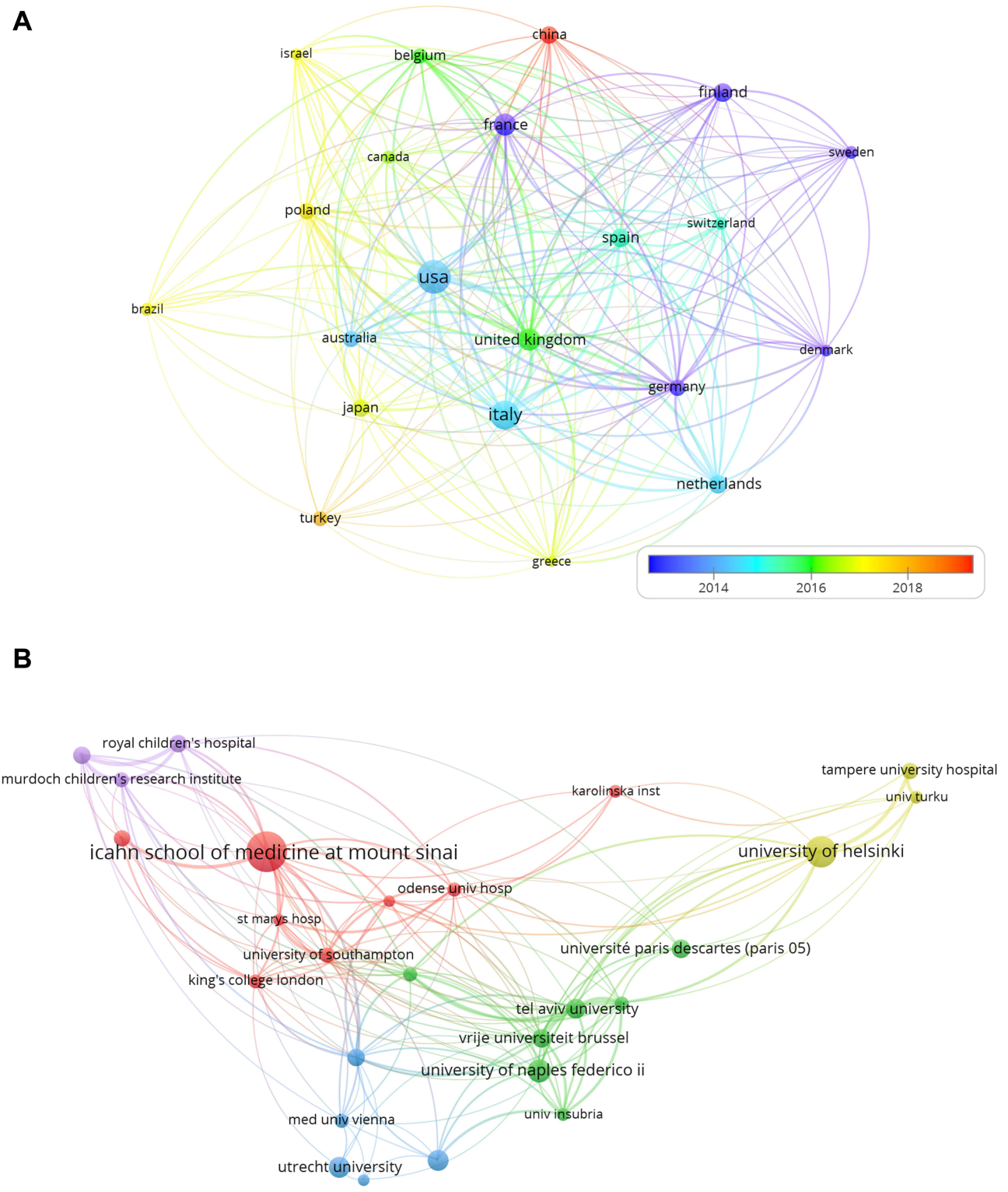

Figure 3 Visualization analysis of countries and institutions. (**A**) Overlay visualization map of countries related to pediatric CMPA from 2000 to 2023 based on VOSviewer. The size of the circular nodes represents the number of publications. The thickness of the connecting lines between nodes indicates the strength of collaboration. The color of the nodes represents different years. (**B**) Network visualization map of institutions related to pediatric CMPA from 2000 to 2023 based on VOSviewer. The size of the circular nodes represents the number of publications. The thickness of the connecting lines between nodes indicates the strength of collaboration. The color of the nodes represents different clusters.

Abbreviation: CMPA, cow's milk protein allergy.

Table 1 The Top Ten Countries in Terms of Publications on Pediatric CMPA

Rank	Country	Publications	Citations	Average Citation
1	USA	428	25,877	60.46
2	Italy	317	13,075	41.25
3	United Kingdom	181	8400	46.41
4	France	179	4618	25.80
5	Spain	134	4852	36.21
6	Netherlands	132	7189	54.46
7	Finland	129	5784	44.84
8	Japan	119	2869	24.11
9	China	114	1551	13.61
10	Germany	107	6838	63.91

Abbreviation: CMPA, cow's milk protein allergy.

Table 2 The Top Ten Institutions in Terms of Publications on Pediatric CMPA

Rank	Institution	Publications	Citations	Average Citation
1	Icahn School of Medicine at Mount Sinai	115	10,217	88.84
2	University of Helsinki	80	2863	35.79
3	University of Naples Federico II	50	2433	48.66
4	Utrecht University	45	2256	50.13
5	University of Milan	44	1629	37.02
6	Tel Aviv University	41	1673	40.80
7	Vrije Universiteit Brussel	38	1600	42.11
8	Université Paris Descartes (Paris 05)	37	1482	40.05
9	Royal Children's Hospital	35	2084	59.54
10	University of Colorado	33	1692	51.27

Abbreviation: CMPA: cow's milk protein allergy.

had the closest collaboration with other institutions, with a TLS value of 71 (Figure 3B). In terms of institutions, the Icahn School of Medicine at Mount Sinai was leading in contributions to this field.

Analysis of Journals and Authors

The density visualization map (Figure 4A) illustrated the distribution of publications across journals in this field. In conjunction with Table 3, the top ten journals in this field had collectively published 704 articles, accounting for 34.5% of the total publications. Both the *Journal of Allergy and Clinical Immunology* and *Allergy* were ranked in JCR Q1, with impact factors of 14.2 and 12.4, and average citations per paper of 190.08 and 89.76, reflecting the high quality of articles in these journals. Figure 4B displayed the network view of journal co-citation. The top ten most frequently cited journals were all ranked in JCR Q1 or Q2. Additionally, eight of these journals also appeared in the top ten journals with the highest publication volume in this field (Table S1). The top three most frequently co-cited journals were the *Journal of Allergy and Clinical Immunology* (14,817 citations), *Allergy* (5417 citations), and *Clinical and Experimental Allergy* (4333 citations).

In the field of pediatric CMPA, the top ten authors with the highest publication volumes collectively contributed 344 papers, accounting for 16.9% of the total publications (Table 4). Among them, Yvan Vandenplas from Belgium had the highest number of publications (51 articles), followed by Anna Nowak-Węgrzyn from the United States (45 articles) and Alessandro Fiocchi from Italy (36 articles), respectively. It was noteworthy that Anna Nowak-Węgrzyn and Hugh A. Sampson from the Icahn School of Medicine at Mount Sinai in the United States not only had a high publication volume but also had high average citations per paper, reaching 79.27 and 148.11, respectively. Figure 4C illustrated the co-cited network view of authors, where the size of the nodes represents the frequency of co-citation, with Hugh

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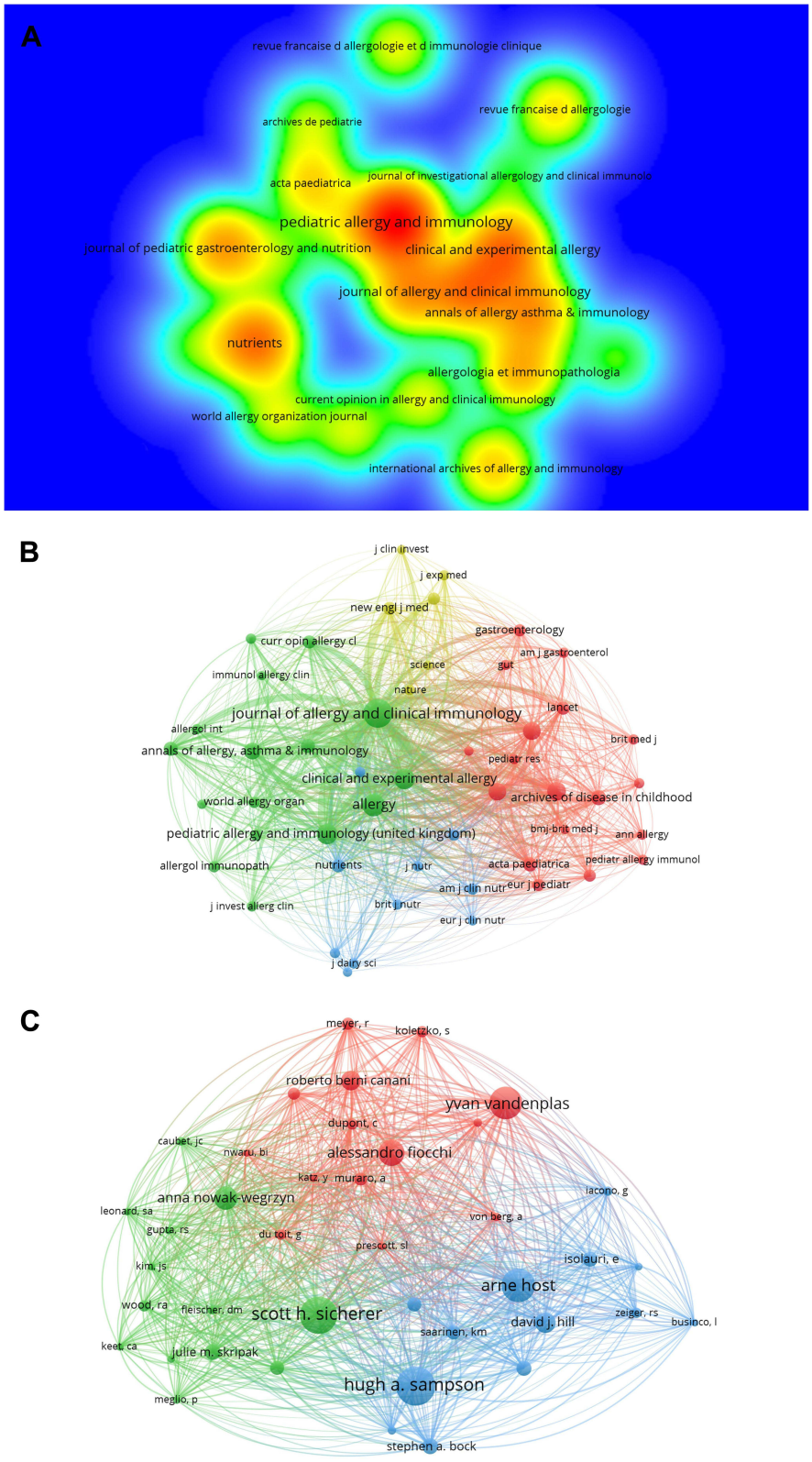

Figure 4 Visualization analysis of journals and authors. (**A**) Density visualization of journals. The more intense the red color, the larger the number of related publications; the more intense the blue color, the smaller the number of related publications. (**B**) Network visualization of co-cited journals. (**C**) Network visualization of co-cited authors. The size of the circular nodes represents the number of co-citations. The thickness of the connecting lines between nodes indicates the strength of the co-citation relationship between nodes. The color of the nodes represents different clusters.

Table 3 The Top Ten Journals in Terms of Publications on Pediatric CMPA

Rank	Journal	Publications	Citations	Average Citation
1	Pediatric Allergy and Immunology	141	6053	42.93
2	Nutrients	83	1696	20.43
3	Clinical and Experimental Allergy	81	4019	49.62
4	Journal of Allergy and Clinical Immunology	75	14,256	190.08
5	Allergy	62	5565	89.76
6	Journal of Pediatric Gastroenterology and Nutrition	62	1994	32.16
7	Annals of Allergy, Asthma & Immunology	60	2278	37.97
8	Allergologia et Immunopathologia	53	629	11.87
9	International Archives of Allergy and Immunology	45	1140	25.33
10	Acta Paediatrica	42	1029	24.50

Abbreviation: CMPA, cow's milk protein allergy.

Table 4 The Top Ten Authors in Terms of Publications on Pediatric CMPA

Rank	Author	Publications	Citations	Average Citation
1	Yvan Vandenplas	51	1320	25.88
2	Anna Nowak-Węgrzyn	45	3567	79.27
3	Alessandro Fiocchi	36	1024	28.44
4	Hugh A. Sampson	35	5184	148.11
5	Rosan Meyer	32	642	20.06
6	Carina Venter	32	648	20.25
7	Roberto Berni Canani	30	1218	40.60
8	Christophe Dupont	29	858	29.59
9	Johan Garssen	28	770	27.50
10	Rita Nocerino	26	1131	43.50

Abbreviation: CMPA, cow's milk protein allergy.

A. Sampson being the most co-cited author with 1246 citations. Half of the top ten prolific authors also appear in the top ten co-cited authors list, highlighting their significant contributions to the field in both quantity and quality (Table S2).

Visual Analysis of Co-Cited References

The analysis of co-cited references provides valuable insights into the research focus and its evolution in a specific field during a certain period. Table 5 listed the top ten co-cited references. Among them, "Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management" by Scott H. Sicherer published in the *Journal of Allergy And Clinical Immunology* was the most co-cited reference. This article provided a comprehensive review of the latest developments in the epidemiology, pathogenesis, diagnosis, and treatment of food allergies in recent years. Among the top ten co-cited reference source journals, only one was in JCR Q2, while the rest were in JCR Q1. The network view of co-cited references was visualized in Figure 5A, where the color of the annual ring represented the year of citation and the node size represented the co-citation frequency. Subsequent clustering and timeline visualization analysis evaluated the dynamic evolution process in this research field (Figure 5B). We observed a modularity Q value of 0.78 and a mean silhouette S value of 0.90, confirming the reliability of clustering. The research focus in this field has evolved from the early stages of simply reducing antigen exposure, to later stages that focused on the clinical symptoms of pediatric CMPA and the initiation of desensitization therapy, and then shifted towards precision medicine and explored the role of gut microbiota and prebiotics in CMPA.

Analysis of Keywords

After merging similar keywords and visualizing them, we could observe the evolution of hot topics through an overlay visualization (Figure 6A). Around 2012, the focus was primarily on clinical symptom-related research keywords such as

Table 5 The Top Ten Co-Cited References Related to Pediatric CMPA

Rank	Title	Counts	First Author	Journal
1	Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management	83	Scott H Sicherer	Journal of Allergy And Clinical Immunology
2	Dietary baked milk accelerates the resolution of cow's milk allergy in children	80	Jennifer S Kim	Journal of Allergy And Clinical Immunology
3	Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines	76	S Koletzko	Journal of Pediatric Gastroenterology And Nutrition
4	The natural history of IgE-mediated cow's milk allergy	74	Justin M Skripak	Journal of Allergy And Clinical Immunology
5	The natural history of milk allergy in an observational cohort	69	Robert A Wood	Journal of Allergy And Clinical Immunology
6	Incidence and natural history of challenge-proven cow's milk allergy in European children-EuroPrevall birth cohort	68	A A Schoemaker	Allergy
6	World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines	68	Alessandro Fiocchi	Pediatric Allergy And Immunology
8	EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy	66	A Muraro	Allergy
9	Epidemiology of Cow's Milk Allergy	64	Julie D Flom	Nutrients
10	BSACI guideline for the diagnosis and management of cow's milk allergy	58	D Luyt	Clinical And Experimental Allergy
10	The safety and efficacy of sublingual and oral immunotherapy for milk allergy	58	Corinne A Keet	Journal of Allergy And Clinical Immunology
10	Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment	58	Scott H Sicherer	Journal of Allergy And Clinical Immunology

Abbreviation: CMPA, cow's milk protein allergy.

"clinical course", "atopic dermatitis", and "atopic disease". Gradually, the emphasis shifted towards keywords related to mechanism and treatment like "IgE", "immunotherapy", and "infant formula". From 2018 onwards, the research spotlight mainly concentrated on emerging research directions and treatment methods such as "oral immunotherapy" and "gut microbiota", as well as keywords related to standardized management throughout the process, like "management" and "guidelines". Similarly, the burst words analysis also suggested that future focal points in this field might revolve around "gut microbiota" (strength=10.93) and "management" (strength=14.19) (Figure 6B).

Discussion

Perspective of the Current Global Publication Landscape

This study represents the first systematic analysis of the global research landscape and the historical evolution of research focal points on pediatric CMPA using bibliometric methods. A total of 2040 relevant articles published since 2000 were analyzed, showing an overall increasing trend in annual publications. This growth is undoubtedly linked to the growing interest of global researchers in this field. The focus on allergic diseases is associated with local economic, social, and environmental factors.[17] As society progresses over time, people's awareness of health is inevitably raised, leading to increased focus on such diseases. The surge in publication volume since 2012 can largely be attributed to the authoritative and comprehensive practical guidelines for the diagnosis and management of pediatric CMPA published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition.[18] These guidelines have greatly fueled research enthusiasm in the field. Additionally, that year witnessed numerous highly cited studies on immunotherapy[19–21] and the role of microbiota[22–24] in CMPA. These studies not only provide a comprehensive summary and prospects for research on immunotherapy for CMPA but also pave the way for investigations into the relevance of gut microbiota in CMPA.

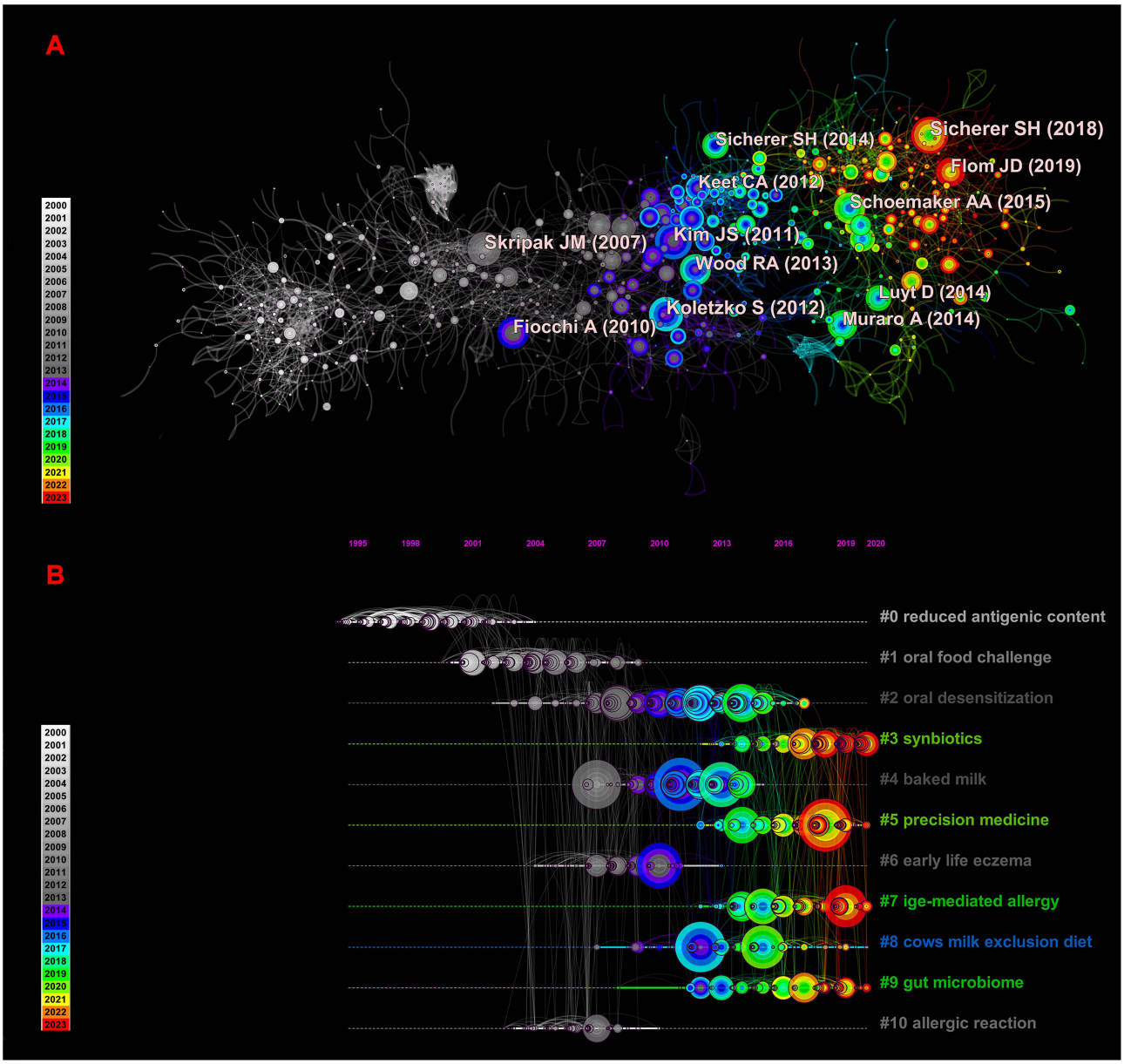

Figure 5 Visualization analysis of co-cited references related to pediatric CMPA. (**A**) Visualization of co-cited references based on CiteSpace. Node size represents the frequency of co-citations. The color of each ring around the node indicates different years, and the size of each ring reflects the frequency of co-citations in that year. The thickness of the connecting lines shows the strength of the co-citation relationship between nodes. (**B**) Timeline view of co-cited references. The x-axis of the graph represents the time intervals, while the colors represent different years of co-citation. Node size represents the frequency of co-citations for the reference. The color of each ring around the node indicates different co-citation years, with the size of each ring reflecting the frequency of co-citations in those years. The thickness of the connecting lines shows the strength of the co-citation relationship between nodes.
Abbreviation: CMPA, cow's milk protein allergy.

As mentioned above, attention to allergic diseases is closely related to the local economic situation,[25] in addition to the need for funding and technical support. It is not surprising that nine out of the top ten countries in terms of publications on pediatric CMPA are developed countries, with only China being a developing country. Similarly, our overlay view indicates that early and mid-term publications were primarily concentrated in economically mature countries. However, with societal progress and increased awareness of pediatric CMPA, countries such as Greece,[26] Poland,[27] Brazil,[28] Turkey,[29] and China,[30] which are classified as emerging or developing economies, have gradually joined research in this field.

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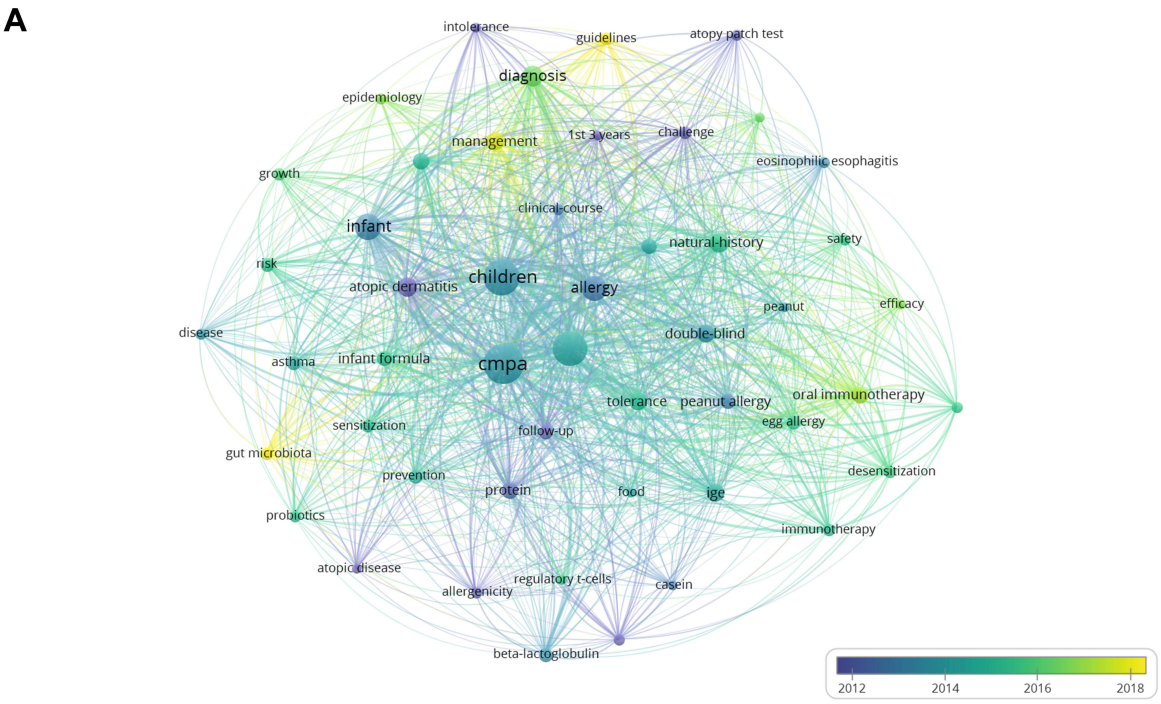

B

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2000 - 2023
hypersensitivity	2000	22.49	**2000**	2012	
1st 3 year	2000	14.02	**2000**	2009	
intolerance	2000	14	**2000**	2009	
atopic disease	2000	12.81	**2000**	2010	
young children	2000	9.83	**2000**	2011	
skin prick	2000	9.63	**2000**	2008	
dermatiti	2000	10.8	**2002**	2010	
oral tolerance induction	2000	13.07	**2009**	2015	
egg allergy	2000	10.69	**2011**	2018	
tolerance induction	2000	9.45	**2012**	2017	
oral immunotherapy	2000	12.98	**2015**	2018	
baked milk	2000	9.1	**2015**	2019	
gut microbiota	2000	10.93	**2017**	2023	
management	2000	14.19	**2018**	2023	
cows milk protein allergy	2000	13.26	**2018**	2023	

Figure 6 Visualization analysis of keywords related to pediatric CMPA. (**A**) Overlay visualization of co-occurrence keywords. Node size represents the frequency of keyword occurrences, color indicates the average year of occurrence, and the thickness of the connecting lines reflects the strength of relationships between nodes. (**B**) Burst keywords.

Abbreviation: CMPA, cow's milk protein allergy.

In terms of institutions, the leading ones in publication volume mostly came from the top ten publishing countries, and their average citation counts per paper were at a relatively high level. The Icahn School of Medicine at Mount Sinai, based in the United States, stood out with the highest publication volume, citation counts, average citations per paper, and collaboration strength, making it undoubtedly the most influential institution in this field.

Yvan Vandenplas, the most prolific author in the field, has made significant contributions by participating in numerous authoritative guideline developments,[18,31,32] driving advancements in the field. Hugh A. Sampson and Anna Nowak-Węgrzyn, both from the Icahn School of Medicine at Mount Sinai, are also among the top ten highly productive and co-cited authors in this field. Their multidimensional research on the diagnosis, treatment, and management of pediatric CMPA, particularly their studies on the relationship between IgE and CMPA, has been instrumental. In a prospective study, they validated and established decision thresholds for specific IgE concentrations to predict clinical reactions to CMPA.[33] Subsequently, they identified that the recognition of different IgE epitopes was associated with the natural history of pediatric CMPA and could be utilized to predict the persistence of milk protein allergy.[34] Furthermore, they found an association between the decrease in time-specific IgE concentrations and the development of tolerance in pediatric CMPA.[35] The aforementioned studies on the relationship between IgE and CMPA were published in the prestigious *Journal of Allergy and Clinical Immunology*, which boasts the highest average citations per article and total co-citation count in the field. Moreover, these studies have been widely cited, establishing a strong foundation for research in this particular subfield.

Evolution of Focal Points and Future Prospects

Articles that are most commonly co-cited can be regarded as the main focal points of the field, as they are frequently referenced by other research.[36] Among the top ten co-cited references, there are four guidelines and three review articles, with the rest being original research articles. The four guidelines,[18,37–39] as well as the three reviews,[40–42] published in different periods, provided comprehensive overviews on the epidemiology, natural history, diagnosis, treatment, and management of pediatric CMPA or food allergy for the respective publication years. They have become key reference points and influential sources of information for researchers and professionals working in that specific field. The high co-citation rates of these articles reflect their impact and recognition within the academic community, highlighting their importance in shaping research and practice in the field. Other original research primarily focuses on the natural history of CMPA, highlighting the positive correlation between high specific IgE antibody levels and increasing difficulty in achieving milk protein tolerance over time.[43–45] Additionally, one study demonstrates the clinical efficacy of consuming baked milk in accelerating the resolution of CMPA,[46] while another explores the safety and effectiveness of sublingual and oral immunotherapy for milk allergy through a randomized controlled trial.[19] These co-cited references to some extent showcase the research focus at a certain stage of pediatric CMPA.

To further clarify the evolution pattern of research hotspots and potential future research directions in pediatric CMPA, we utilized a timeline view (Figure 5B) to roughly divide the emergence of clustered research focal points into three periods: before 2000, 2000–2007, and after 2007. In the early phase, before 2000, the research focus in this field was on "reduced antigenic content." The best method to prevent allergic diseases is to avoid contact with allergens. However, for infants and young children, besides accidental exposure and cross-reactions, the main impact is on their quality of life and nutritional status.[47,48] For example, at that time, some viewpoints suggested that breastfeeding could help prevent CMPA, but the mother's diet may need to be restricted.[49,50] However, the latest viewpoint remains that breastfeeding is still the first recommendation, and there is a lack of strong evidence to support the need for maternal cow's milk dietary elimination.[51] In addition, some studies indicate that rice-based hydrolyzed formulas can effectively address pediatric CMPA issues.[52,53] However, in terms of dietary substitutes, more research has focused on hydrolyzed formula and amino acid-based formula.[54–56] By using these formula milks, not only can the restrictions of breastfeeding be eliminated, but also the clinical symptoms caused by CMPA can be alleviated without compromising nutritional needs or impeding growth and development.[57,58] Despite years of research on these alternative formulas, challenges in processing and high costs hinder their widespread clinical use and global popularity.[59,60]

As the field of research into CMPA entered its mid-stage between 2000 and 2007, the focus of studies began to concentrate on "oral food challenge", "oral desensitization", "baked milk", "early-life eczema", "cow's milk exclusion diet", and "allergic reaction". As research in this area deepened, investigators began to systematically observe the clinical symptoms associated

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with CMPA. CMPA can cause various clinical symptoms, including, but not limited to skin conditions (such as hives and eczema), respiratory issues (such as coughing and wheezing), gastrointestinal problems (such as diarrhea, abdominal pain, and vomiting), and systemic allergic reactions (such as anaphylactic shock). The appearance of these symptoms may vary among individuals and the clinical presentation may also change with age.[6,61,62] A significant proportion of atopic dermatitis (eczema) is believed to be caused by CMPA, thought to be IgE-mediated, and may have the potential for spontaneous resolution as age increases.[63–66] However, it may transition to other allergic conditions such as rhinitis and asthma.[64,65] Meanwhile, neither clinical symptoms, skin prick tests, nor serum IgE measurements can accurately diagnose CMPA. Only the "oral food challenge" is considered the gold standard for diagnosis.[64,67] However, during this period, in treatment, the focus is often on managing the allergic symptoms that arise.[68] While various commercial formula milks have been introduced, they are not only expensive and not widely accessible worldwide but also only provide relief for CMPA symptoms without addressing the root cause. As a result, researchers are exploring more suitable alternative methods on one hand and investigating potential approaches to curing CMPA on the other. The "cow's milk exclusion diet" can be seen as a continuation of an early trend that has persisted to this day. To eliminate the impact of cow's milk protein, researchers have been tirelessly searching for new alternative products.[69–71] "Baked milk" has been considered a simple method to accelerate the resolution of CMPA,[46,72] but over time, there seems to be no further well-designed research evidence to support this view,[73] and it has gradually faded from prominence. Research on "oral desensitization" can be roughly divided into two categories: milk ladder therapy and oral immunotherapy. Milk ladder therapy mainly targets mild to moderate non-IgE-mediated cow's milk allergy,[74,75] and there is less research on IgE-mediated cow's milk allergy treatment.[76] Overall, there may be mild allergic reactions when attempting higher ladders, but the implementation process is relatively complex and requires good compliance from the parents of the allergic child. As for oral immunotherapy, there is moderate-certainty evidence suggesting that in IgE-mediated CMPA children, oral immunotherapy can effectively induce immune tolerance to cow's milk protein, relieve related clinical symptoms, but also increase the risk of severe adverse reactions.[9,77] Both methods can treat CMPA from the root cause and have good protective effects against accidental exposure, but more prospective studies are needed to confirm the advantages and disadvantages of these two methods.[78]

In the later stages of research in this field, post-2007 studies have increasingly focused on "synbiotics", "precision medicine", "IgE-mediated allergy", and "gut microbiome". A significant amount of research indicates that IgE concentration is closely associated with the prognosis of CMPA.[7,33–35] Moreover, IgE-mediated CMPA often has a longer natural history and a higher probability of evolving into other allergic diseases.[64–66] In addition to the currently recommended oral or sublingual immunotherapy,[19,79] some clinical trials combining omalizumab with treatment have shown promising results in the management of IgE-mediated CMPA.[80–82] However, the choice of treatment options and the customization of individualized treatment plans have become practical challenges in clinical practice. With the development of omics technologies, more biomarkers have been discovered to differentiate subtypes of milk allergy, determine individual baseline immune characteristics and threshold doses, and predict the safety and efficacy of immunotherapy.[83–85] By utilizing patient data and combining it with medical history, precision medicine tailored specifically to each patient can be implemented, providing a potential solution to the current challenges of over-diagnosis and under-diagnosis. Meanwhile, researchers are gradually shifting their focus towards synbiotics and the gut microbiota. Azad, MB was among the first to systematically demonstrate the correlation between changes in the gut microbiota and the occurrence of food allergies,[86] followed by a plethora of descriptive studies highlighting the association between variations in the gut microbiota and the development of immune tolerance in CMPA.[87] In terms of diagnosis, the involvement of the gut microbiota may help overcome the challenges in distinguishing between IgE-mediated and non-IgE-mediated CMPA.[88] In terms of treatment, incorporating synbiotics to modulate the gut microbiota has emerged as one of the potential strategies for the prevention and treatment of CMPA.[3,89–91] Furthermore, one or several prebiotics may not be sufficient to alter the gut microbiota towards the desired phenotype, while fecal microbiota transplantation may be more conducive to achieving this goal, although the related research in this area remains lacking. In conclusion, with an understanding of the core gut microbiota profiles and the diet-microbe interactions in infants with CMPA, intervening with engineered active microbial communities and customizing personalized diets based on comprehensive multi-omics data and clinical characteristics emerges as a potential therapeutic strategy for CMPA.

The analysis results of keywords and burst words are similar to the timeline view of co-cited references, all depicting a comparable evolution process with a current and future focus on gut microbiota. In the coming years, research on combination therapy for CMPA involving microbiota will enter an outbreak period. However, just as it took decades of research on formula milk before it could be widely used in clinical practice today, it is foreseeable that a significant investment will still be required before comprehensive therapy including gut microbiota can truly applied to clinical application.

Limitation

Due to the inclusion of literature from a single English database and exclusion decisions made by three reviewers simultaneously, these studies may not fully encompass all relevant research on pediatric CMPA and there is a possibility of erroneous exclusions. However, by strictly adhering to established criteria and including over 2000 articles, we have significantly reduced the margin of error.

Conclusion

We have conducted a comprehensive bibliometric analysis of academic research on pediatric CMPA worldwide for the first time. Global interest in this field is growing, with regional focuses aligning with local economic conditions. The Icahn School of Medicine at Mount Sinai in the United States has made outstanding contributions to this field, with a notable number of high-quality articles published in the *Journal of Allergy and Clinical Immunology*. Since the turn of the century, research in this field has evolved from focusing on reducing antigen exposure and seeking alternative diets to gradually addressing clinical symptom treatment, diagnosis, and therapeutic approaches. Presently, there is a shift towards targeted personalized therapy and management, along with theoretical and applied research on probiotics and gut microbiota. In the future, comprehensive, microbiota-based personalized treatment strategies will be further explored and are expected to become effective clinical practices.

Data Sharing Statement

The datasets used and analyzed during the current article are available from the corresponding author on reasonable request.

Author Contributions

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

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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