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ORIGINAL RESEARCH

Bibliometric Analysis of Cow's Milk Protein Allergy Research in the Past Two Decades

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Background: Cow's Milk Protein Allergy (CMPA) is a prevalent food allergy in children with a rising global incidence. Despite extensive research, a comprehensive bibliometric analysis that links CMPA research trends to inflammation and immunological mechanisms is lacking.

Methods: This study conducted a bibliometric analysis of CMPA-related literature from 2004 to 2024, utilizing the Web of Science database and tools such as Vosviewer, CiteSpace, and bibliometrix. The analysis explored publication trends, country/institution/author contributions, collaboration networks, journal impacts, high-frequency keywords, co-cited references, and citation bursts.

Results: Recent years have seen significant growth in CMPA research, with publications peaking in 2022. Key contributors are the US, Italy, and China; Europe and America collaborate closely, while Asia, especially China, could enhance international cooperation. Leading authors like Vandenplas Y and Nowak-Wegrzyn A guide research and enjoy academic recognition. Core institutions, e.g. Icahn School of Medicine, have extensive networks. High-quality research appears in journals like Pediatric Allergy and Immunology, and Nutrients shows interdisciplinary trends. Hotspots include CMPA and oral immunotherapy (OIT). Foundational guidelines and reviews are key references. Citation bursts highlight research frontiers. Future research directions identified include immunotherapy, prevention strategies, and specific milk protein components, with OIT emerging as a key immunological intervention associated with immune tolerance induction.

Conclusion: This analysis provides a comprehensive overview of CMPA research, emphasizing growth trends, hotspots, and future directions. By integrating bibliometric insights with immunological perspectives, it underscores the interplay between clinical management and mechanistic studies, particularly in the context of inflammation and immune regulation.

Keywords: cow's milk protein allergy, bibliometric, immunotherapy, primary prevention, lactoglobulin

Introduction

CMPA is a common food allergy among children, caused by the body's abnormal immune response to milk proteins. Epidemiological studies on CMPA have shown that its prevalence varies globally but generally exhibits an increasing trend. It is estimated that about 2–3% of infants and young children worldwide are affected by CMPA, and the incidence rate has indeed been rising in recent years.[1]

CMPA manifests in a variety of ways, including but not limited to skin symptoms (such as eczema and urticaria), gastrointestinal symptoms (such as vomiting, diarrhea, and abdominal pain), and respiratory symptoms (such as asthma and rhinitis). In severe cases, it can lead to anaphylactic shock, posing a serious threat to the health of the affected children.[2] Additionally, long-term CMPA may also affect the growth and development of the children, increasing the medical burden on families and society. Although numerous studies on CMPA have emerged in recent years, covering various aspects such as pathogenesis, diagnosis methods, and treatment strategies, there has not been a systematic bibliometric study to comprehensively analyze the research status and development trends in this field.

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Importantly, CMPA is fundamentally an immune-mediated condition characterized by aberrant inflammatory responses to dietary proteins. The pathogenesis involves complex immunological mechanisms, including IgE-mediated mast cell degranulation, Th2-skewed immune responses, and dysregulation of regulatory T cells, all of which contribute to the clinical manifestations of inflammation in target organs such as the skin, gastrointestinal tract, and respiratory system.[2] Despite the centrality of these immunological and inflammatory processes to CMPA, previous reviews have not systematically examined how research trends in this field align with advances in understanding these mechanisms. Although numerous studies on CMPA have emerged in recent years, covering various aspects such as pathogenesis, diagnosis methods, and treatment strategies, there has not been a systematic bibliometric study to comprehensively analyze the research status and development trends in this field, particularly from the perspective of immunological and inflammatory mechanisms.[3] Bibliometric analysis offers a unique opportunity to bridge the gap between research activity and mechanistic understanding by quantifying the evolution of research foci related to immune tolerance induction, inflammatory biomarkers, and immunological pathways. By mapping publication patterns, citation networks, and keyword co-occurrence, this approach can reveal how immunological concepts—such as oral immunotherapy (OIT), regulatory T cell function, and epithelial barrier integrity—have gained prominence over time. Furthermore, tracking the emergence of inflammation-related keywords and co-citation clusters can identify pivotal studies that have shaped our current understanding of CMPA as an inflammatory disorder.

This study aims to fill this gap and comprehensively review the research progress in the field of CMPA over the past two decades through bibliometric analysis, with particular attention to immunological and inflammation-focused themes. Based on the Web of Science Core Collection (WoSCC) database, this study conducted a systematic analysis of CMPA-related literature from 2004 to 2024 using bibliometric tools such as Vosviewer, CiteSpace, and the R package bibliometrix. The research includes various aspects such as literature publication trends, contributions by countries/institutions/authors, collaboration networks among countries/institutions/authors, journal publication volume and impact, high-frequency keywords, co-cited references, and citation burst analysis of references and keywords, aiming to reveal the current research status, hotspots, and frontiers in this field. Through bibliometric analysis, this study aims to provide comprehensive and systematic reference information for researchers in the field of CMPA, promoting further development in this area, particularly by highlighting the interplay between clinical management and mechanistic studies in the context of inflammation and immune regulation.

Materials and Methods

Data Source and Search Strategy

WoSCC database as one of the most famous and the most influential scientific literature database, is the first selection of bibliometrics analysis database. The search strategy is as follows: TS= “Milk Hypersensitivity” OR “Milk Hypersensitivities” OR “Milk Allergy” OR “Milk Allergies” OR “Cow’s Milk Protein Allergy” OR “Cow’s Milk Allergy” OR “Cow Milk Allergy” OR “Cow’s Milk Allergies” OR “Cows Milk Allergy”.The search date is set to 2004.1.1–2024.6.21,the publication type limit is “article and review article”, and the language limit is “English”. A total of 2349 articles were included (As shown in Figure 1). This study did not involve animal or human experiments, so no ethical claims are shown here.

Analysis Method

Download complete records and cited references from WoSCC database and import them into VOSviewer, CiteSpace and Bibliometrix in different formats for analysis.

VOSviewer

VOSviewer is one of the commonly used quantitative analysis tools in bibliometrics,developed by the Science and Technology Research Center of Leiden University in the Netherlands. It can be used for cluster view, overlay view and density view of literature to evaluate the research direction and hot spots of literature.[4] A collaborative network, co-citation network, or co-occurrence network is developed using this method.[5,6] This paper utilizes VOSviewer (ver.1.6.20) to construct country/institution/author collaboration network maps, aiming to reveal collaboration patterns and identify key contributors. It also conducts keyword co-occurrence visualization analysis to recognize research hotspots and core

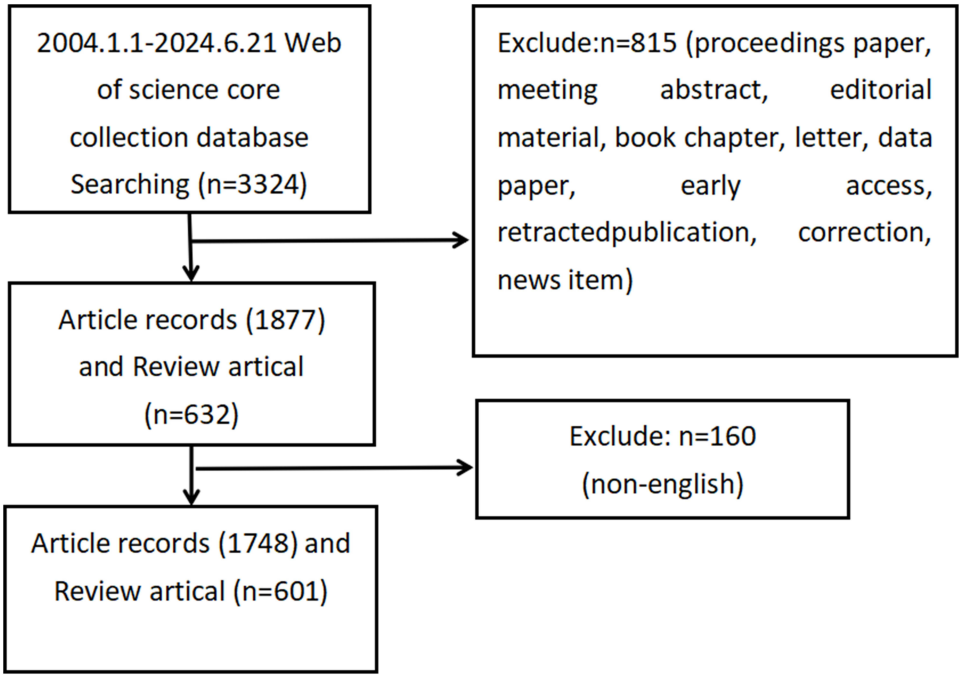

Figure 1 Flow chart for the inclusion and exclusion of literature.

topics. Additionally, co-cited reference visualization is implemented to explore the knowledge base and significant research outcomes.

VOSviewer (version 1.6.20) was configured to construct collaboration and co-occurrence networks with the following settings:

1) Network type: Co-authorship (for country/institution/author networks) and co-occurrence (for keyword analysis).
2) Thresholds: Minimum occurrence frequency of keywords was set to 47 to filter noise while retaining sufficiently representative terms; this threshold was selected based on iterative testing to balance inclusiveness and visual clarity. For country/institution collaboration, only entities with ≥10 publications were included to ensure meaningful network representation.
3) Normalization method: Association strength for link weighting, which corrects for differences in publication counts across nodes.
4) Clustering algorithm: Default VOS clustering with resolution parameter = 1.0, providing a balance between cluster granularity and interpretability.
5) Visualization: Layout optimization for clarity, with node size proportional to publication count and link thickness reflecting collaboration strength.

CiteSpace

Invented by Professor Meichao Chen of Drexel University, CiteSpace, a Java-based software tool, facilitates visual exploration and knowledge discovery within bibliometric datasets, serving as a robust platform for bibliometric analysis and visualization.[7,8] Its analytical framework revolves around three core principles: burst detection, intermediary centrality, and heterogeneous network analysis. By identifying burst terms derived from titles, abstracts, and metadata, the software effectively maps emerging research frontiers within a field.[9] In the strongest citation bursts analysis, the intensity of the burst is represented by a numerical value. The greater the value, the greater the intensity of the burst, and the more obvious the development trend of the theme related to the burst word.In this study, CiteSpace (ver.6.3.1) was utilized to conduct references,keywords analysis through citation bursts.[10]

CiteSpace (version 6.3.1) was utilized for burst detection and timeline analysis with the following parameters:

1) Time slicing: 2004–2024, divided into 1-year intervals to capture annual fluctuations in research activity.
2) Node types: References and keywords for co-citation and burst analysis.
3) Pruning: Pathfinder algorithm applied to simplify network complexity while preserving the most salient connections; this approach reduces visual clutter and highlights structural patterns.
4) Term source: Keywords extracted from titles, abstracts, and author keywords to maximize coverage of relevant concepts.
5) Burst detection: Kleinberg's algorithm with $\gamma = 0.5$ to identify significant citation bursts; this parameter setting balances sensitivity and specificity in detecting emergent trends.
6) Top N per slice: Top 50 most cited references/keywords per year retained for analysis, ensuring that highly influential items are captured while excluding low-impact publications.

Bibliometrix (R Package)

Bibliometrix is a comprehensive bibliometric analysis package in R language, designed specifically for scientific evaluation and visualization. It supports data processing and analysis from multiple databases, greatly simplifying the analysis of complex literature data.[11] This study employs the Bibliometrix package in R language to analyze the annual number of research literature on cow's milk protein allergy over the past 20 years, revealing research trends. It also counts and analyzes the top 10 countries, institutions, authors, and journals by publication volume to identify the main research forces. Furthermore, it conducts additional statistical analysis on the annual publication volume and citation counts of the top 10 authors by publication volume to assess research output and impact, and analyzes the annual publication volume of the top 10 journals by publication volume to understand the main publication channels for research outcomes.

The Bibliometrix R package (version 4.0.0) was employed for productivity and impact analysis using:

1) Data filtering: Articles and reviews published in English between 2004–2024.
2) Field tagging: Metadata fields (eg., AU = authors, C1 = affiliations, CR = citations) mapped to WoSCC export formats.
3) Analysis modules:
4) biblioAnalysis() for annual trends and top contributor statistics.
5) couplingMap() for institutional collaboration networks.
6) citationAnalysis() for reference co-citation and H-index calculations.
7) Visualization: Custom ggplot2 scripts for line/bar charts, with smoothing applied to annual trends.

In addition, Utilizing Microsoft Office Excel 2021 software, bar charts/line graphs were created based on the annual publication volume to demonstrate the annual development trends of the research. The top 10 institutions and journals with the highest publication volume were selected, their annual publication volume was counted, and line graphs were drawn accordingly.

Results and Analysis

Quantitative Analysis of Publication

From 2004.1.1 to 2024.6.21, a total of 2349 articles were published by article (1748) and review article (601). As shown in Figure 2, from 2004 to 2024, the annual publication volume of CMPA showed an increasing trend year by year, reaching a peak of 173 in 2022. This growing trend reflects the increasing research interest and importance of this field.

Country and Affiliations Analysis

A total of 68 corresponding author countries and 1648 institutions were involved in research in the field of CMPA. Analysis of the data revealed that the United States (n=399) emerged as the leading contributor, with Italy (n=271) and China (n=207) following closely behind, as indicated in Table 1. Data from 43 countries, each with at least 10 publications, were further analyzed to construct a collaborative network. (As shown in Figure 3). The weight was

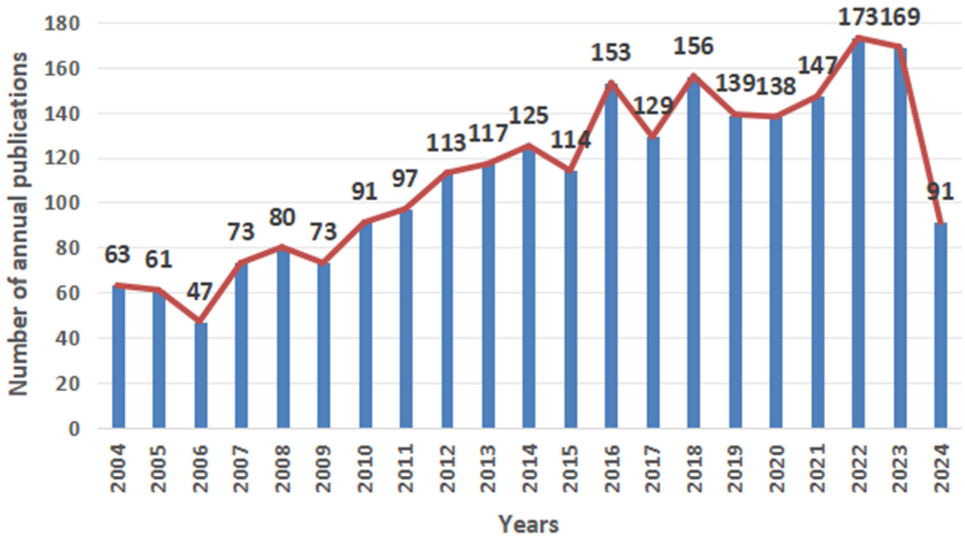

Figure 2 Number of publications per year in the field of Milk Protein Allergy from 2004 to 2024.

adjusted to Toal link strength, indicating a positive correlation between circle size and the level of cooperation with other countries. Scores is set to avg.pub.years.The figure illustrates that European and American countries such as the United States, Britain, Italy, Germany, Spain, Ireland, and Finland engage in close cooperation with other nations. Conversely, Asian countries like China and Japan, despite their high publication rates, exhibit lower levels of international cooperation. Taiwan is shown to have a limited cooperative relationship solely with the United States. Concurrently, a notable concentration of publications from the United States was observed around the year 2015. Subsequently, there has been a notable increase in the publication of research papers by scholars in China and Russia in the years following 2020.

Table 1 presents the top 10 institutions with the highest number of publications, with Icahn School of Medicine at Mount Sinai leading the list with 223 publications. Following closely behind were the University of Helsinki with 178 publications and the University of Naples Federico Ii with 173 publications. A line chart illustrating the annual publication volume of these top 10 institutions is shown in Figure 4.The line chart clearly illustrates that the publication rates of Icahn School of Medicine at Mount Sinai, University of Naples Federico II, and Nanchang University have experienced notably accelerated growth compared to other academic institutions over the past decade. Notably, Nanchang University has observed a particularly rapid surge in publications within the last three years.Data from 38 institutions, each with at least 20 publications, were further analyzed to construct a collaborative network (As shown in Figure 5). The weight was adjusted to Toal link strength, indicating a positive correlation between circle size and the level of cooperation with other institutions. Scorses is set to avg.pub.years. As shown in Figure 5, Collaboration among

Table 1 Top 10 Countries and Affiliations in Terms of Publications

Rank	Country	Articles	Affiliations	Articles
1	USA	399	Icahn School Of Medicine At Mount Sinai	223
2	Italy	271	University Of Helsinki	178
3	China	207	University Of Naples Federico Ii	173
4	Japan	141	Nanchang University	129
5	United Kingdom	119	Utrecht University	127
6	Netherlands	111	University Of London	116
7	Spain	93	Tel Aviv University	103
8	Finland	80	Universite Paris Cite	94
9	France	80	Harvard University	91
10	Poland	66	Imperial College London	85

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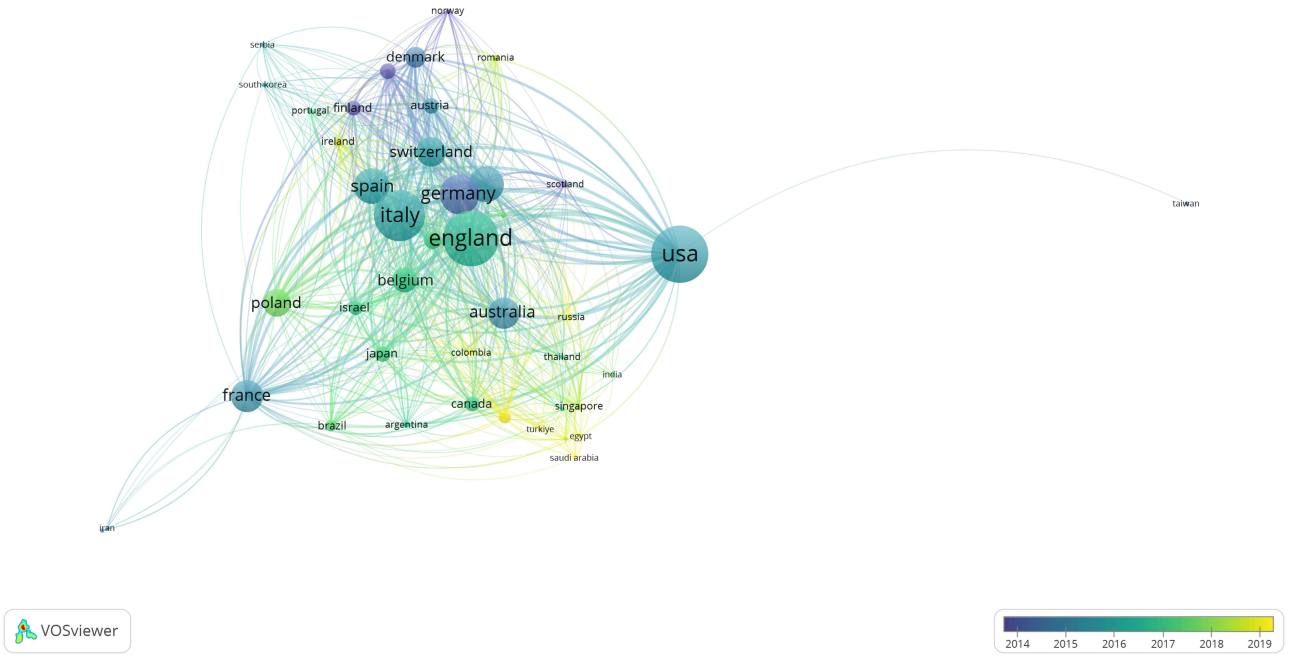

Figure 3 The visualization of 43 countries/regions collaborative network.

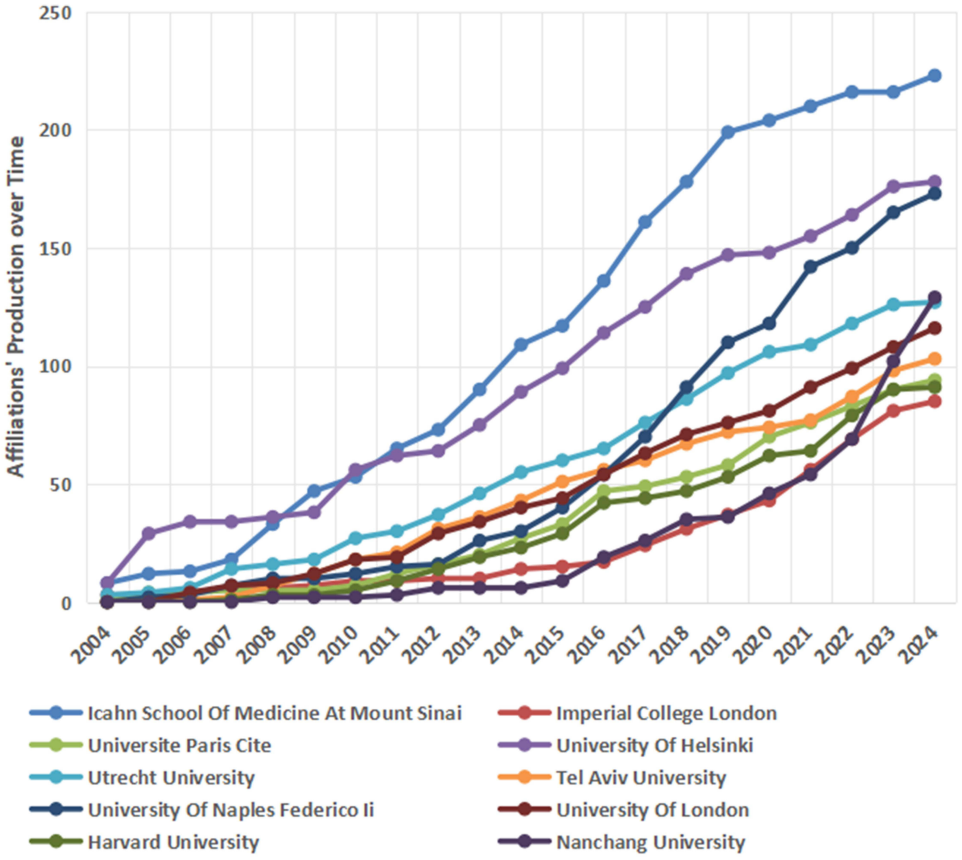

Figure 4 The top 10 institutions's production over the years.

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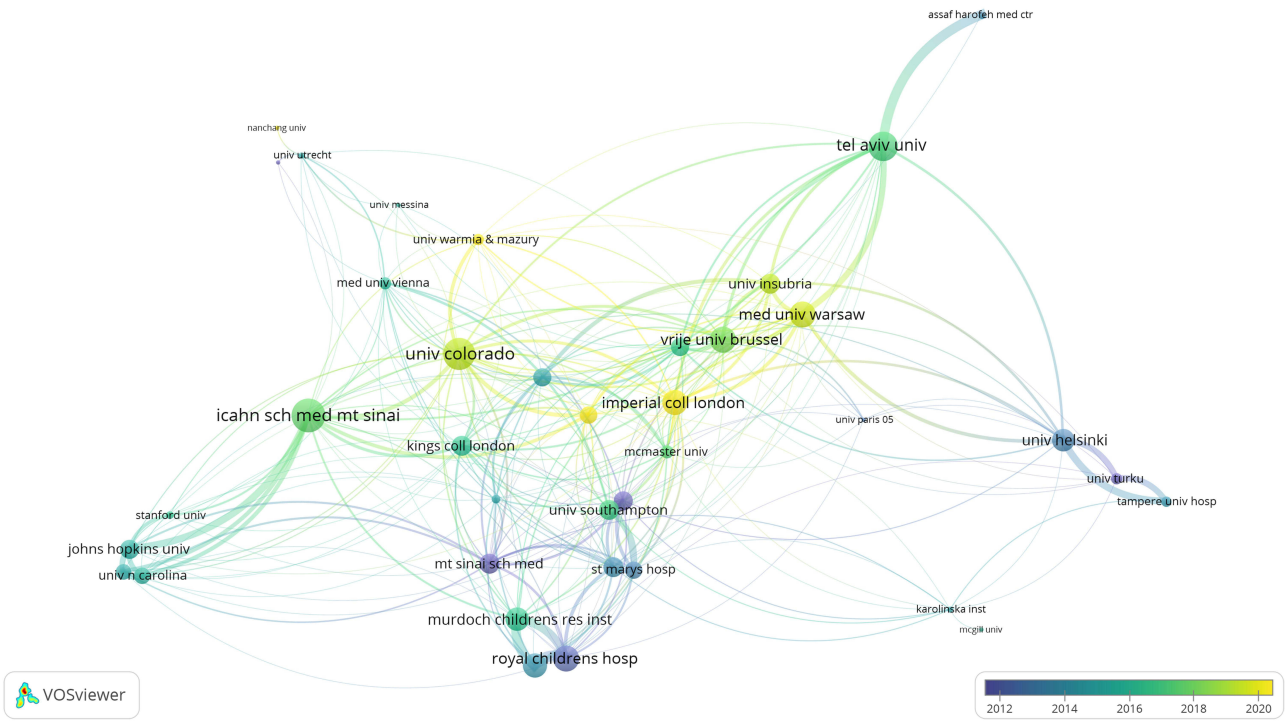

Figure 5 The visualization of 38 institutions collaborative network.

institutions is intricate and strong, with top institutions like Icahn School of Medicine at Mount Sinai and University of Helsinki at the core of the network. However, Nanchang University, despite publishing many articles, only collaborated with Utrecht University.

Authors Analysis

A total of 8552 authors participated in studies related to CMPA. We identified the top 10 authors and conducted an in-depth analysis of their publication volume, H-index and G-index. Vandenplas Y ranked first in terms of the number of papers published with 66, followed closely by Fiocchi A and Nowak-Wegrzyn A, each with 65 papers. The H-index is an important index to measure the academic influence of scholars, which takes into account the number of papers and citations of scholars.The G-index focuses more on the contribution of highly cited papers and can evaluate the academic achievements of scholars more comprehensively. Among the 10 authors, Nowak-Wegrzyn A has the highest H-Index and G-Index, which reflects the author's high academic influence and recognition.As shown in Figure 6 illustrates the publication output of the 10 authors across various years, along with the corresponding total citations per year. The size of each circle corresponds to the number of publications in a given year, with larger circles indicating a higher volume of publications. Additionally, the color intensity of each circle reflects the number of citations received in that particular year. Fiocchi A authored a notable total of 12 articles in 2022, representing the highest volume of annual publications by any author in multiple years, resulting in a cumulative total of 77 citations. Sampson HA ranked second with 11 articles in 2014, but had the highest total citations at 209.Data from 25 authors, each with at least 20 publications, were further analyzed to construct a collaborative network. (As shown in Figure 7 and Table 2).The weight was adjusted to toal link strength, indicating a positive correlation between circle size and the level of cooperation with other institutions. Scorses is set to avg.pub.years. Vandenplas Yvan, Meyer Rosan, Garssen johan have the largest nodes because they have the strongest relationships with other authors.Besides, we observed close collaboration among multiple authors.For example, Nowak-wegrzyn Anna has close cooperation with Sampson Hugh A, Flocchi Alessandro and Salvatore Silvia, etc.

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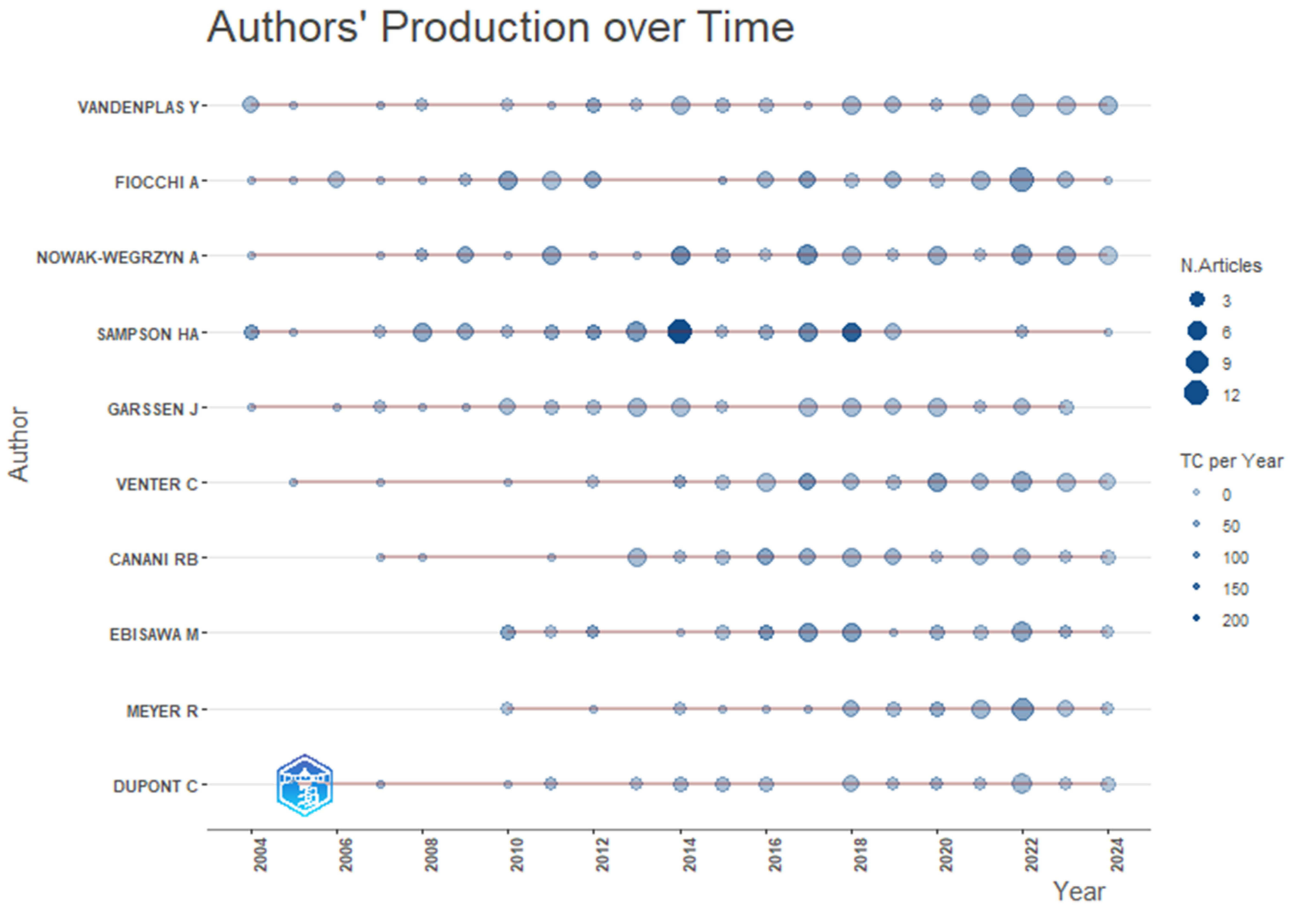

Figure 6 Top 10 authors'production over time.
Abbreviation: TC, Total Citations.

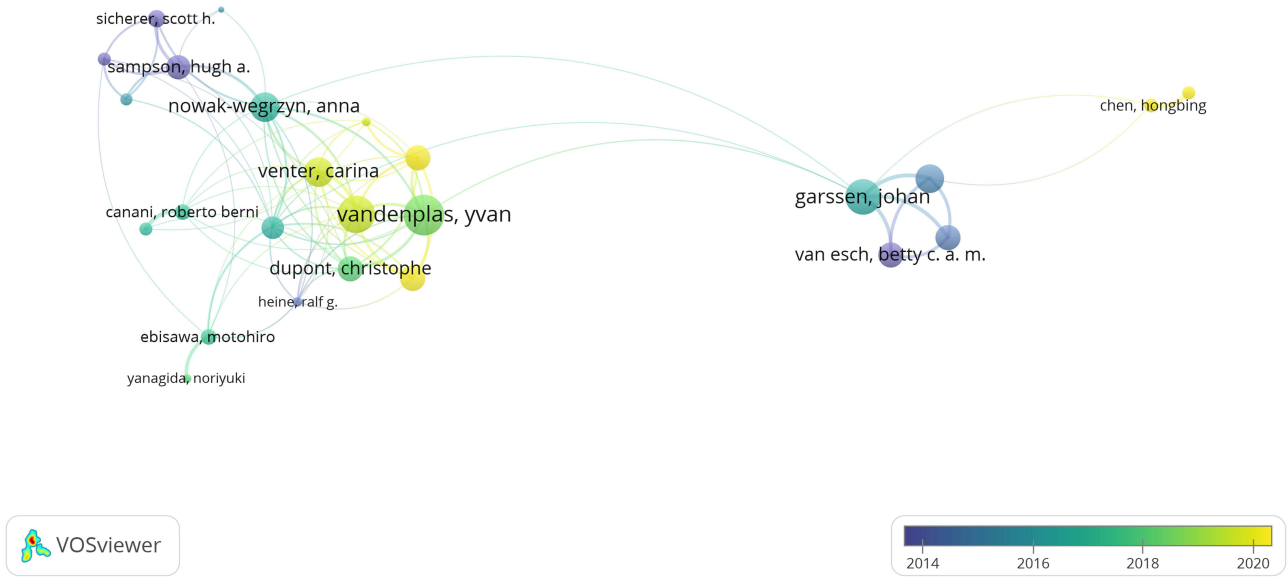

Figure 7 The visualization of 25 institutions collaborative network.

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Table 2 Top 10 Authors with the Most Published Articles

Rank	Authors	Articles	H-Index	G-Index
1	Vandenplas Y	66	24	40
2	Fiocchi A	65	24	55
3	Nowak-Wegrzyn A	65	33	64
4	Sampson Ha	64	4	4
5	Garssen J	57	22	32
6	Venter C	52	18	37
7	Canani Rb	45	21	36
8	Ebisawa M	43	21	40
9	Meyer R	39	18	30
10	Dupont C	38	15	32

Journal of Publication

A total of 444 journals have published articles in the field of CMPA. As shown in Table 3 lists the top 10 journals by volume of publications. Pediatric Allergy And Immunology ranked first with 148 publications, followed by Nutrients (n=108) And Journal Of Allergy And Clinical Immunology (n=96).The journal impact factor rankings indicate that Allergy (IF=12.6) has the highest impact factor, while Journal of Pediatric Gastroenterology and Nutrition (IF=2.4) has the lowest. There are five journals in Zone 1, followed by one in Zone 2 and four in Zone 3.As shown in the Figure 8 shows the publication growth of the top 10 journals over the years.The journal Nutrients experienced significant growth in publication output after 2015, initially ranking last but subsequently rising to second place by 2023.

Author Keywords

A total of 3792 author keywords were analyzed in this study. As shown in Table 4 lists the top 20 keywords by frequency. High-frequency keywords such as food allergy (n=628), cow's milk allergy (n=415), milk allergy (n=195), allergy (n=169), cow's milk protein allergy (n=110), cow's milk (n=74), food hypersensitivity (n=66), and milk (n=64) were excluded from the table due to their limited analytical significance. The frequencies of the words "Infant" and "infants" were combined. The keywords co-occurrence network diagram (As shown in Figure 9) was created using VOSViewer software, with a minimum frequency of occurrence set at 47, resulting in a co-occurrence network diagram of 29 high-frequency keywords.Set the weight of the circle size to occurrence. The size of the circle represents the number of keyword occurrences. The larger the circle, the more keyword occurrences.Scorses is set to avg.pub.years.As shown in the figure, several keywords in yellow, such as cow's protein allergy, prevention. Infant formula, and oral immunotherapy, have appeared more frequently since 2017.

Table 3 Top 10 Journals for Research in Terms of Publications

Rank	Journal	Articles	IF (2023)	Quartile Score
1	Pediatric Allergy And Immunology	148	4.3	2
2	Nutrients	108	4.8	1
3	Journal Of Allergy And Clinical Immunology	96	11.4	1
4	Clinical And Experimental Allergy	83	6.3	1
5	Allergy	79	12.6	1
6	Allergologia Et Immunopathologia	61	2.5	3
7	International Archives Of Allergy And Immunology	56	2.5	3
8	Annals Of Allergy Asthma & Immunology	54	5.8	1
9	Journal Of Pediatric Gastroenterology And Nutrition	51	2.4	3
10	Current Opinion In Allergy And Clinical Immunology	49	3	3

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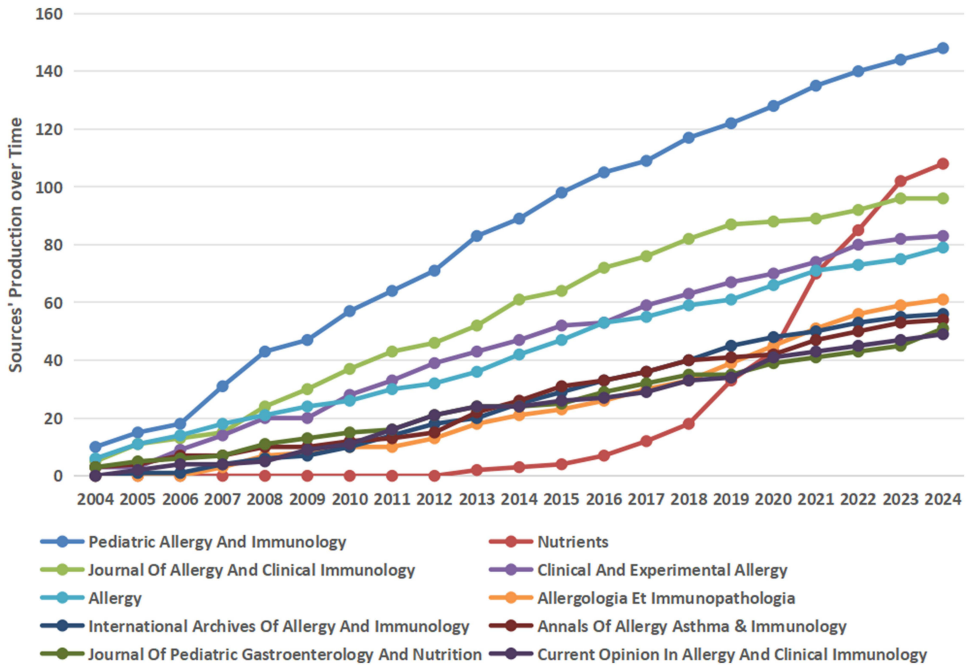

Figure 8 The top 10 journals's production over the time.

Co-Cited References

Over the past two decades, 52,342 co-cited references were identified in CMPA-related research. Among the top 10 co-cited references (As shown in Table 5), all were cited at least 169 times, with four exceeding 200 citations. To construct the co-citation network (As shown in Figure 10), 42 references meeting a minimum co-citation threshold of 100 were selected. The co-cited references network reveals three major thematic clusters, distinguished by color: clinical guidelines (red cluster), oral immunotherapy trials (blue cluster), and epidemiological studies (green cluster). Within the red cluster, the WAO DRACMA guidelines by Fiocchi et al[12] and the NIAID guidelines by Boyce et al[13] emerged as central nodes with high co-citation frequencies. The blue cluster centers on key OIT trials, including Skripak et al's 2008 randomized controlled trial[14] and Longo et al's 2008 specific oral tolerance induction study,[15] which show strong co-citation relationships with each other and with Nowak-Wegrzyn et al's 2008 baked milk study.[16] The green cluster includes epidemiological and natural history studies, such as Skripak et al's 2007 prognosis study[17] and Rona et al's 2007 meta-analysis.[18]

Table 4 Top 20 High-Frequency Author Keywords

Rank	Journal	Articles	Rank	Journal	Articles
1	Children	219	11	Immunotherapy	72
2	Oral immunotherapy	137	12	Desensitization	70
3	Anaphylaxis	106	13	Probiotics	64
4	Infants	106	14	Oral tolerance	63
5	Tolerance	100	15	Oral food challenge	62
6	Beta-lactoglobulin	91	16	Asthma	58
7	Ige	83	17	Prevention	55
8	Atopic dermatitis	79	18	Infant formula	51
9	Egg allergy	73	19	Casein	49
10	Children	219	20	Diagnosis	47

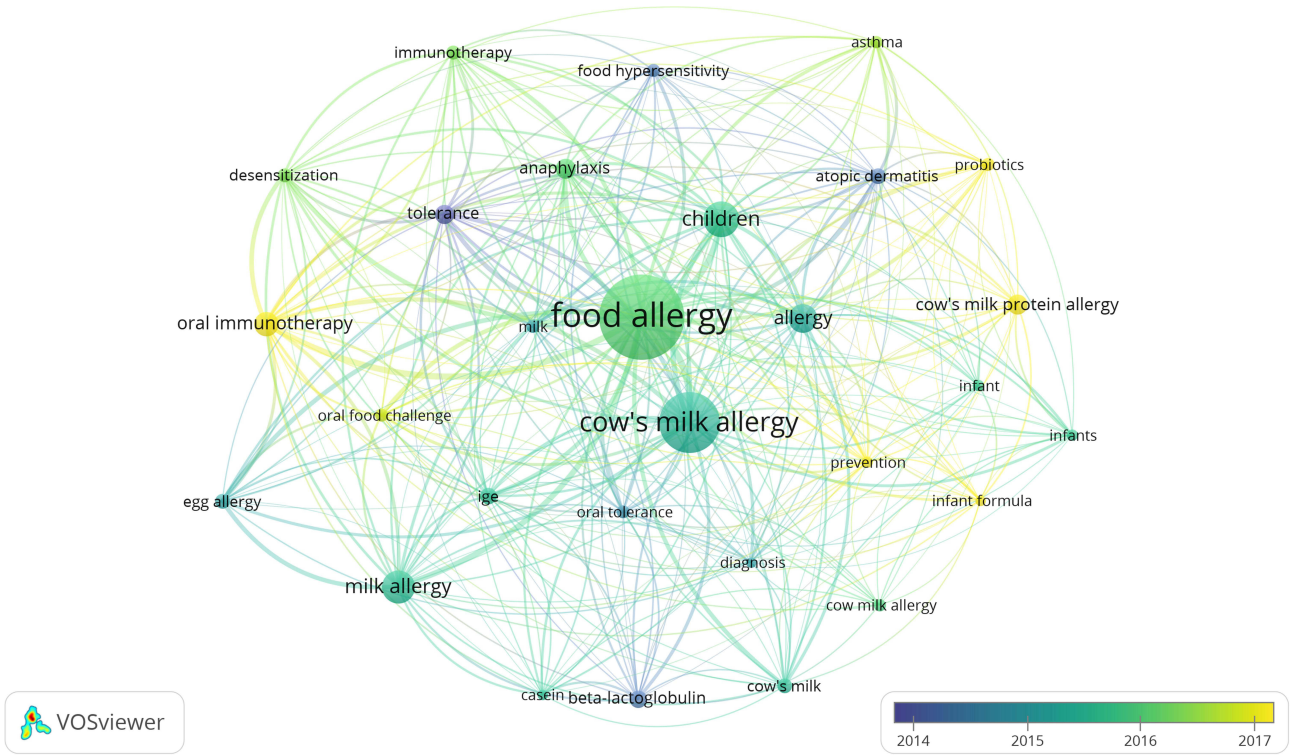

Figure 9 The visualization of 29 high-frequency keywords co-occurrence.

Reference with Citation Bursts

The term citation burst refers to references that receive a large number of citations in the course of a short period of time, indicating a high level of academic interest. We have established a time slice from 2014 to 2024.In this analysis, CiteSpace identified 20 references with notable citation bursts (As shown in Figure 11). Red bars represent periods of significant citation activity. These 20 references had burst strengths ranging from 13.17 to 30.49, and their burst durations varied from 1 to 4 years.The strongest citation burst of 30.49 was attributed to "Epidemiology of Cow's Milk Allergy" by Flom JD et al, which garnered extensive citations from 2021 to 2024.

Hotspots and Frontiers

Keywords citation bursts is a tool to quickly identify research hotspots in the field.Keyword citation bursts is analyzed using Citespace. We have established a time slice from 2014 to 2024, and we have identified the top 20 strongest citation

Table 5 Top 10 Co-Cited References on Research of CMPA

Rank	Co-Cited Reference	Citations
1	Skripak jm,2007, j allergy clin immun, v120, p1172	279
2	Fiocchi a,2010, pediat allerg imm-uk, v21,p1	257
3	Koletzko s,2012,jpediatr gastr nutr,v55,p221	256
4	Anonymous,2010,j allergy clin immun,v126,ps5	243
5	Skripak jm,2008,jallergy clin immun,v122,p1154	197
6	Nowak-wegrzyn a,2008,jallergy clin immun,v122,p342	196
7	Kim js,2011,jallergy clin immun,v128,p125	184
8	Rona rj,2007,jallergy clin immun,v120,p638	184
9	Longo g,2008,jallergy clin immun,v121,p343	176
10	Muraro a,2014,allergy,v69,p1008	169

https://doi.org/10.2147/JIR.S584283

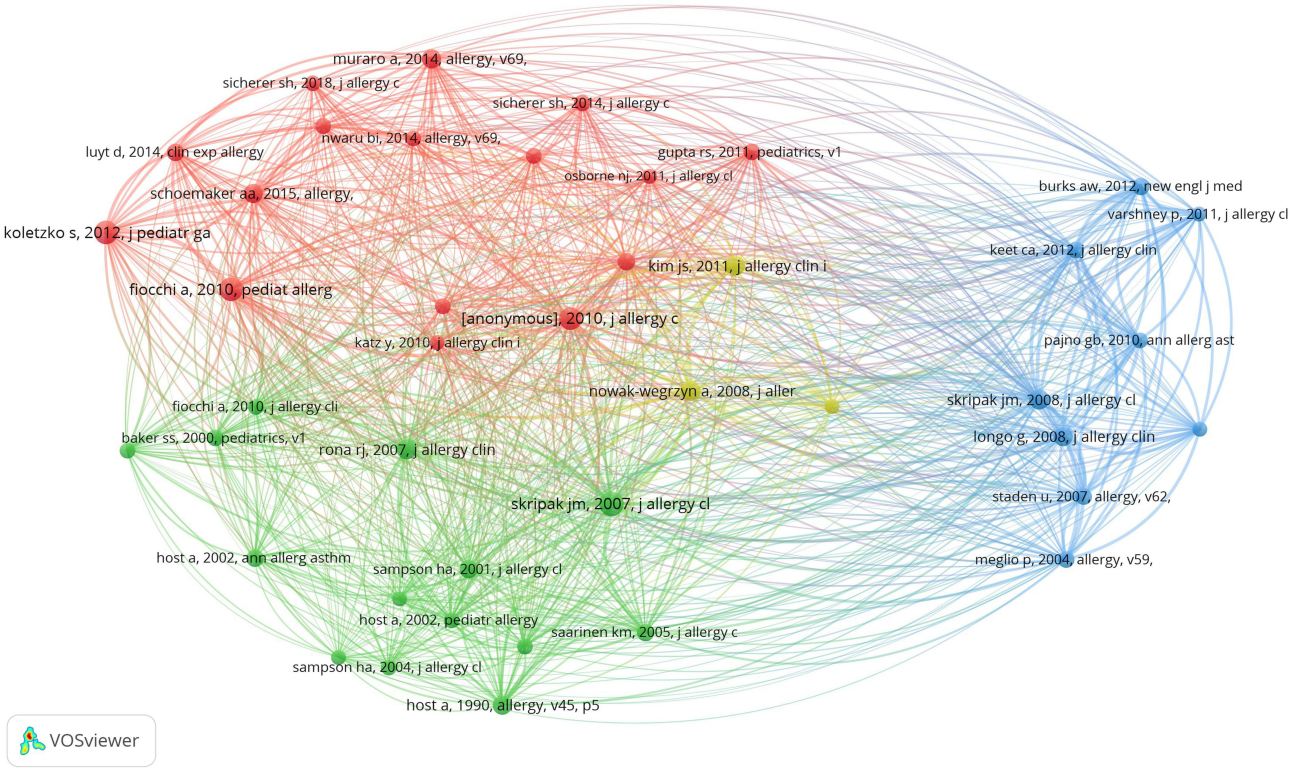

Figure 10 The visualization of co-cited references on research of of CMPA. Nodes represent references cited together in the literature; node size is proportional to co-citation frequency (minimum threshold = 100 co-citations). Colors indicate different clusters identified by CiteSpace, representing thematic groupings in the literature. Key nodes with high centrality or citation counts are labeled. For improved readability, readers may focus on the major clusters: red = clinical guidelines, blue = oral immunotherapy studies, and green = epidemiology and natural history research. A detailed list of the top 10 co-cited references with full bibliographic information is provided in Table 5.

Top 20 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2024
Unknown -, 2010, J ALLERGY CLIN IMMUN, V126, PS5, DOI 10.1016/j.jaci.2010.10.007, DOI	2010	27.97	2014	2015	
Kim JS, 2011, J ALLERGY CLIN IMMUN, V128, P125, DOI 10.1016/j.jaci.2011.04.036, DOI	2011	23.69	2014	2016	
Burks AW, 2012, NEW ENGL J MED, V367, P233, DOI 10.1056/NEJMoa1200435, DOI	2012	18.4	2014	2017	
Koletzko S, 2012, J PEDIATR GASTR NUTR, V55, P221, DOI 10.1097/MPG.0b013e31825c9482, DOI	2012	17.61	2014	2017	
Keet CA, 2012, J ALLERGY CLIN IMMUN, V129, P448, DOI 10.1016/j.jaci.2011.10.023, DOI	2012	15.24	2014	2017	
Gupta RS, 2011, PEDIATRICS, V128, PE9, DOI 10.1542/peds.2011-0204, DOI	2011	14.98	2014	2016	
Fiocchi A, 2010, PEDIAT ALLERG IMM-UK, V21, P1, DOI 10.1111/j.1399-3038.2010.01068.x, DOI	2010	14.11	2014	2015	
Leonard SA, 2012, J ALLERGY CLIN IMMUN, V130, P473, DOI 10.1016/j.jaci.2012.06.006, DOI	2012	13.17	2014	2016	
Sicherer SH, 2014, J ALLERGY CLIN IMMUN, V133, P291, DOI 10.1016/j.jaci.2013.11.020, DOI	2014	13.37	2015	2019	
Schoemaker AA, 2015, ALLERGY, V70, P963, DOI 10.1111/all.12630, DOI	2015	14.54	2016	2020	
Luyt D, 2014, CLIN EXP ALLERGY, V44, P642, DOI 10.1111/cea.12302, DOI	2014	13.4	2016	2019	
Muraro A, 2014, ALLERGY, V69, P1008, DOI 10.1111/all.12429, DOI	2014	13.94	2017	2019	
Bunyavanich S, 2016, J ALLERGY CLIN IMMUN, V138, P1122, DOI 10.1016/j.jaci.2016.03.041, DOI	2016	13.79	2018	2021	
Sicherer SH, 2018, J ALLERGY CLIN IMMUN, V141, P41, DOI 10.1016/j.jaci.2017.11.003, DOI	2018	27.48	2019	2024	
Pajno GB, 2018, ALLERGY, V73, P799, DOI 10.1111/all.13319, DOI	2018	16.1	2019	2022	
Nowak-Wegrzyn A, 2017, J ALLERGY CLIN IMMUN, V139, P1111, DOI 10.1016/j.jaci.2016.12.966, DOI	2017	15.43	2020	2022	
Meyer R, 2020, ALLERGY, V75, P14, DOI 10.1111/all.13947, DOI	2020	14	2020	2024	
Flom JD, 2019, NUTRIENTS, V11, P0, DOI 10.3390/nu11051051, DOI	2019	30.49	2021	2024	
Meyer R, 2018, J ALLER CL IMM-PRACT, V6, P383, DOI 10.1016/j.jaip.2017.09.003, DOI	2018	13.81	2021	2024	
Halken S, 2021, PEDIAT ALLERG IMM-UK, V32, P843, DOI 10.1111/pai.13496, DOI	2021	16.34	2022	2024	

Figure 11 Top 20 References with the Strongest Citation Bursts.

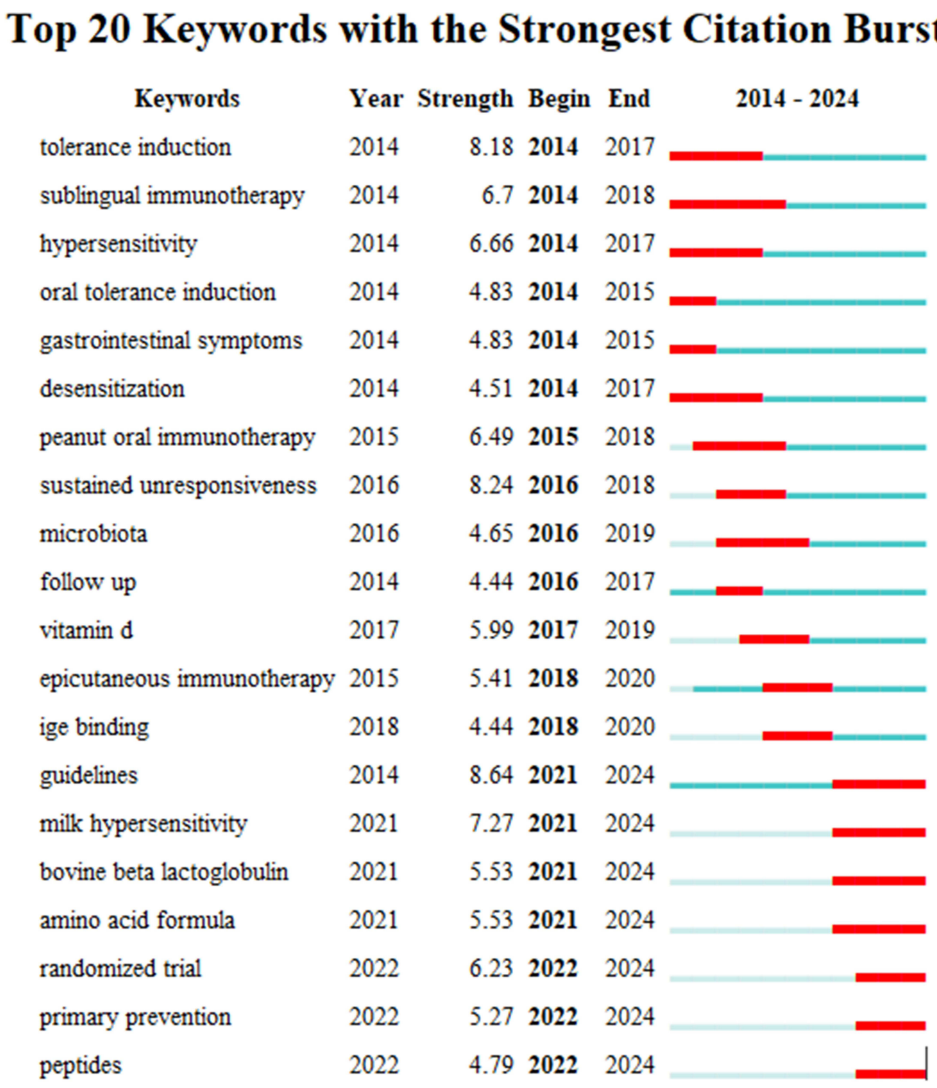

Figure 12 Top 20 Keywords with the Strongest Citation Bursts.

bursts keywords from approximately the past decade (As shown in Figure 12).These 20 Keywords had burst strengths ranging from 4.44 to 8.64, and their burst durations varied from 1 to 4 years. "bovine beta lactoglobulin", amino acid formula, "randomized trial", "primary prevention" and "peptides" were the key words with high citation intensity in recent 3 years,suggesting its potential as a current research hotspot in CMPA.

Discussion

General Information

Since 2004, there has been a consistent upward trend in the annual publication output within the realm of CMPA, culminating in a peak of 173 articles in 2022. This trend not only signifies the heightened research activity in this area, but also indicates a growing global awareness of CMPA. The surge in research on CMPA can be attributed to factors such as heightened public health consciousness, clinical demands, increased research funding and policy backing, as well as interdisciplinary collaboration and integration.

The dominance of Western countries, particularly the United States and Italy, in CMPA research output reflects not only scientific capacity but also longstanding investment in allergy research infrastructure, favorable regulatory environments for clinical studies, and established patient registries. In contrast, the relatively lower international collaboration observed for Asian countries like China, despite their increasing publication volume, may limit the global generalizability of findings from

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these regions. This geographic disparity has important implications: genetic, environmental, and dietary factors influencing CMPA pathogenesis may vary across populations, yet the current literature predominantly reflects Western cohorts. The recent surge in Chinese publications since 2020 may signal an emerging research capacity, but without parallel increases in international collaboration, the integration of these findings into global knowledge frameworks remains limited. Future research should prioritize multicenter international collaborations that include diverse populations to enhance the translational relevance of findings across different genetic backgrounds and environmental exposures.

From the perspective of author contributions, prolific authors such as Vandenplas Yvan, Fiocchi Alessandro, and Nowak-Wegrzyn Anna lead the way in CMPA research with their outstanding publications. In particular, Nowak-Wegrzyn Anna's remarkable performance on the H-Index and G-Index highlights its pre-eminence and widespread influence in academia. The analysis of cooperation network reveals the cooperation pattern and trend in CMPA research field. Core authors such as Vandenplas Yvan, Meyer Rosan and Garssen Johan have built a tight and productive research network through extensive collaborative contacts.In the 2023 publication of "World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA)," six of the authors involved in updating the guidelines were ranked among the top 10 authors, including Vandenplas Y, Fiocchi A, Nowak-Wegrzyn A, Sampson HA, Venter C, and Meyer R.

The top-ranking journal in the first 10 journals is "Pediatric Allergy and Immunology" (IF = 4.3, Q2), which published 148 articles, demonstrating its depth of knowledge in the field of pediatric allergy and immunology and its wide-reaching impact. Following closely behind is "Nutrients" (IF=4.8, Q1), which has experienced a notable surge in publications since 2015, with 108 articles, moving from the bottom to the second position. This journal specializes in nutrition, making a distinctive contribution to the intersection of nutrition, allergy, and immune health.The Journal of "Allergy and Clinical Immunology" (IF = 11.4, Q1) and "Allergy" (Q1, IF = 12.6) are esteemed publications within the field of allergy and clinical immunology, having published 96 and 79 articles, respectively. These journals have significantly advanced scientific research and clinical practice in this specialized area. Additionally, "Clinical and Experimental Allergy", with an impact factor of 6.3 and 83 published articles, maintains a prominent position in allergic experimentation and clinical research. Furthermore, journals such as "Allergologia Et Immunopathologia," "International Archives of Allergy and Immunology," and "Annals of Allergy, Asthma & Immunology," despite having a modest impact factor, are significant contributors within their respective fields. These publications offer comprehensive research and clinical guidance, facilitating the dissemination and advancement of knowledge in the areas of allergy and immunology. The journals "Journal of Pediatric Gastroenterology and Nutrition" and "Current Opinion in Allergy and Clinical Immunology" offer valuable insights and references pertaining to pediatric gastrointestinal nutrition and current developments in allergy and clinical immunology, serving as important resources for scholars and clinicians in these respective fields.

In this study, we analyzed 3,792 author keywords and created a network map to explore trends in research fields. Children and oral immunotherapy were the top two high-frequency keywords, suggesting they are core topics in current research.As a vulnerable group, children's health problems, especially allergic diseases such as CMPA, have always received high attention. OIT is a new therapy, and its efficacy and safety have been widely studied and discussed in recent years. The frequency of key words, including anaphylaxis, infants and tolerance, further highlights the high prevalence of allergic diseases in infants and young children and the urgency of research. Anaphylaxis, in particular, is a condition that researchers are constantly seeking better prevention and treatment, given its serious clinical consequences.In addition, the mention of certain food proteins, such as beta-lactoglobulin and casein, also shows researchers' efforts to identify and avoid food allergens. These proteins are common food allergens, and studying their sensitization mechanisms could help develop more accurate allergy diagnosis and treatment strategies.Notably, the frequency of keywords such as cow's protein allergy, prevention, infant formula and OIT has increased significantly since 2017. This may reflect the rising incidence of allergic diseases, especially CMPA, worldwide in recent years, as well as researchers' increasing emphasis on early prevention and intervention strategies.As an important part of the infant diet, the composition and safety of infant formula has also become a hot topic of research.

The dominance of Western countries, particularly the United States and Italy, in CMPA research output reflects not only their scientific capacity but also longstanding investment in allergy research infrastructure and favorable regulatory environments for clinical studies. In contrast, the relatively lower international collaboration observed for Asian countries like China, despite their increasing publication volume, may limit the global generalizability of findings from these

regions. This geographic disparity has important implications for understanding CMPA as a global health issue, as genetic, environmental, and dietary factors influencing CMPA pathogenesis may vary across populations. Future research should prioritize multicenter international collaborations that include diverse populations to enhance the translational relevance of findings across different genetic backgrounds and environmental exposures.

Knowledge Base

References that are co-cited are those that are cited by multiple other publications, so they could be considered as the research basis in a particular field. To determine the research basis of CMPA, we selected the 10 most co-cited references. In top 10 co-cited references, four pivotal guidelines[12,13,19,20]—World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines, Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel, Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines, and EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and Management of Food Allergy—exhibit distinct perspectives and emphases, exerting profound impacts on clinical practice and research. Specifically, The WAO DRACMA guidelines by Fiocchi et al comprehensively outline the diagnostic and therapeutic principles of cow's milk allergy, particularly focusing on IgE-mediated and non-IgE-mediated forms in children and adults. The guidelines emphasize standardized diagnostic methods and alternative feeding strategies, providing a unified framework for global healthcare professionals.[12] The NIAID guidelines authored by Boyce et al concentrate on the diagnosis and management of food allergy in the United States, addressing the growing public health concern of food allergies. The guidelines detail diagnostic protocols and delve into management strategies, including environmental control, patient education, and emergency treatment plans.[13] The ESPGHAN guidelines by Koletzko et al offer specific diagnostic and management recommendations for CMPA in infants and children. The guidelines emphasize a comprehensive diagnostic approach based on clinical manifestations and allergy tests, proposing a stepped management strategy from allergen avoidance to tolerance challenges.[19] The EAACI guidelines by Muraro et al represent the latest comprehensive guidance on the diagnosis and management of food allergy and anaphylaxis, encompassing patients of all ages. The guidelines update diagnostic techniques and delve into effective strategies for acute and long-term management.[20] Collectively, these four guidelines, each unique in content, target audience, and geographical focus, contribute to the international consensus on cow's milk allergy management, providing invaluable references for clinical practice and research endeavors.Meta-analysis by Rona RJ et al in 2007 indicate that there is significant variation in self-reported prevalence of cow's milk allergy, ranging from 1.2% to 17%, and self-reported prevalence is higher compared to objective measures.[18] Skripak et al (2007) observed that the prognosis of cow's milk allergy (CMA) in pediatric populations was less favorable than previously assumed, though some patients developed tolerance during adolescence. Their findings emphasized the prognostic value of cow's milk-specific IgE (cm-IgE) levels.[17] Subsequent work by the same team demonstrated through a randomized, double-blind trial that oral immunotherapy (OIT) significantly enhanced milk protein tolerance thresholds in children with CMPA.[14] Longo et al (2008) reported that 36% of children with severe systemic reactions achieved full tolerance after one year of specific oral tolerance induction (SOTI), while 54% tolerated limited milk intake (5–150 mL), underscoring SOTI's clinical utility.[15] Concurrently, Nowak-Wegrzyn et al (2008) revealed that 75% of children with milk allergy could safely consume heat-treated milk.[16] Further research by Kim et al (2011) indicated that incorporating baked milk into diets accelerated tolerance development to unheated milk compared to strict avoidance, though such tolerance often proved transient.[21] In general, these 10 most-cited references mainly involve the epidemiology, diagnosis and management strategies of CMPA. How to induce oral immune tolerance in the management of milk proteins is the focus of research.

The main research contents of the 20 references with strong citation bursts are summarized in Table 6, highlighting their pivotal roles in shaping foundational theories and clinical practices in CMPA research.

The predominance of clinical guidelines among the most co-cited references underscores the field's strong emphasis on standardized clinical management. However, this pattern also reveals a potential knowledge gap: fundamental mechanistic studies, while essential, may be cited less frequently despite their critical role in advancing understanding. The four major guidelines[12,13,19,20] share common elements but also reflect different regional priorities and healthcare

Table 6 The Main Research Contents of the 20 References with Strong Citations Bursts

Rank	Strength	Main Research Content	Type
1	27.97	Clinical guidelines developed by the National Institute of Allergy and Infectious Diseases aim to standardize the diagnosis and management of food allergy, addressing misconceptions, providing recommendations for healthcare professionals, and highlighting areas for future research[19](2010).	Guideline
2	23.69	Incorporating baked milk into the diet of tolerant children accelerates the development of tolerance to unheated milk, indicating a transient IgE-mediated allergy, while reactivity suggests a persistent phenotype[17] (2011).	Article
3	18.4	In a clinically significant subset of children with egg allergy, oral immunotherapy can desensitize them and induce sustained unresponsiveness[14](2012).	Article
4	17.61	This guideline provides recommendations for diagnosing and managing suspected CMPA in Europe, emphasizing strict allergen avoidance, controlled oral food challenges, dietary substitutions, and regular reevaluation to assess tolerance development and avoid unnecessary dietary restrictions[20](2012).	Guideline
5	15.24	The effectiveness of oral immunotherapy for milk protein desensitization is higher than that of sublingual immunotherapy alone, but the side effects are more systemic[15] (2012).	Article
6	14.98	Childhood food allergies are more prevalent and severe than previously reported in the United States, with racial and economic disparities in diagnosis[16] (2011).	Article
7	14.11	World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines[1] (2010).	Guideline
8	13.17	The development of regular egg tolerance is more rapid after initiation of a baked egg diet as compared with strict avoidance. Higher levels of serum EW-specific IgE are linked with persistent and initial reactivity to baked eggs[21] (2012).	Article
9	13.37	This review covers recent progress in food allergy research, including its prevalence, causes, diagnosis, and treatment[22](2014).	Review
10	14.54	Less than 1% of children under 2 years old had confirmed cow's milk allergy through a gold standard diagnostic test. Infants without specific antibodies to cow's milk were likely to tolerate it a year after diagnosis, while only half of those with antibodies outgrew their allergy quickly[23](2015).	Article
11	13.4	This guideline provides comprehensive advice on the diagnosis and management of cow's milk allergy, including recommended diagnostic methods, avoidance of cow's milk, and treatment options, with a focus on graded exposure for reintroduction and distinguishing it from lactose intolerance[2](2014).	Guideline
12	13.94	The guidelines for Food Allergy and Anaphylaxis provide evidence-based recommendations for the diagnosis and management of food allergy, addressing manifestations, diagnostic tests, and effective management strategies for patients of all ages, while emphasizing the need for reference to the related Anaphylaxis Guidelines for emergency management[24](2014).	Guideline
13	13.79	The gut microbiota during early infancy can influence the outcome of food allergies in childhood. Clostridial and Firmicute bacteria may be viable candidates for studies into probiotics to treat milk allergies[25](2016).	Article
14	27.48	This review summarizes recent advances in understanding food allergy, including epidemiology, pathogenesis, diagnosis, and treatment, highlighting a growing prevalence, improved risk factor identification, complex pathophysiology, evolving diagnostic tools, prevention strategies, and promising treatment options in clinical trials[26] (2018).	Review
15	16.1	This guideline recommends food allergen immunotherapy as an active treatment option for IgE-mediated food allergy, especially for allergies to cow's milk, hen's egg, and peanuts, while emphasizing its potential risks and the need for treatment in experienced centers[27](2018).	Guideline
16	15.43	This consensus document from an international workgroup highlights the need for improved awareness, diagnosis, and management of Food Protein-Induced Enterocolitis (FPIES), emphasizing the need for further research to advance patient care[28](2017).	Guideline
17	14	This article summarizes the findings of a European Academy for Allergy and Clinical Immunology Task Force, which aimed to establish diagnosis and management guidelines for non-IgE-mediated allergies in breastfed infants, highlighting the importance of breastfeeding and providing practical points for healthcare professionals[29] (2020).	Guideline
18	30.49	This review summarizes the epidemiology of cow's milk allergy (CMA), highlighting variations in prevalence, natural history, demographic patterns, and long-term outcomes among different populations, while considering the complexities of assessing IgE-mediated and non-IgE-mediated reactions to cow's milk[30](2019).	Review

(*Continued*)

Table 6 (Continued).

Rank	Strength	Main Research Content	Type
19	13.81	The paper offers an evidence-based guide for healthcare professionals regarding the utilization of amino acid formula (AAF) in pediatric patients diagnosed with CMPA, highlighting its utility in various clinical scenarios including growth faltering, multisystem manifestations, severe gastrointestinal reactions, eosinophilic esophagitis, and symptoms during breastfeeding[31](2018).	Guideline
20	16.34	Significant revisions in the 2014 guideline involve recommending peanut and well-cooked egg in complementary feeding and avoiding regular cow's milk formula in the first week of life.[32]	Guideline

contexts, suggesting that while international consensus exists on core principles, implementation strategies may require adaptation to local settings.

The strong citation burst of Flom JD et al's 2019 epidemiology review from 2021–2024 indicates renewed interest in understanding CMPA prevalence and risk factors, possibly driven by rising global incidence rates and the need for updated epidemiological data to inform public health policy. Similarly, the sustained citation activity surrounding Skripak et al's OIT trials[14,17] reflects the translational impact of this research—moving from mechanistic understanding of tolerance to clinical application. This pattern illustrates how bibliometric analysis can track the journey of scientific discoveries from bench to bedside.

Hotspots and Frontiers

Through a deep analysis of high-frequency keywords, keyword citation bursts, and reference citation bursts, we have uncovered three hotspot directions in CMPA research. These directions not only represent the current research foci but also indicate future research trends.

Immunotherapy and Tolerance Induction

Immunotherapy and tolerance induction, including OIT and sublingual immunotherapy (SLIT), have seen significant research advances in recent years as emerging strategies for the treatment of CMPA.

OIT, as a treatment method that gradually increases the intake of allergens, has shown potential in inducing long-term tolerance in CMPA patients. The Spanish guideline provides an exhaustive elaboration on OIT for CMPA, covering not only the complete treatment process from the initial build-up phase to the dose escalation phase and the maintenance phase, but also delving into the theoretical basis, current research status, clearly defined indications and contraindications of the therapy, and offering a variety of special treatment dosing schedules for selection. The core of this therapy lies in gradually and safely increasing the intake of cow's milk protein to induce a non-responsive state to the antigen, thereby helping patients achieve desensitization, reduce or eliminate allergic symptoms, and improve their quality of life.[22] Recent years have witnessed significant progress in OIT for CMPA. Studies consistently demonstrate that OIT not only substantially enhances patients' tolerance to cow's milk proteins[23,24] but also improves their quality of life. Notably, the generation of specific CD137+ FOXP3 + regulatory T cells induced by successful milk OIT underscores its underlying immune regulatory mechanisms,[25] providing a biological rationale for desensitization therapy. Furthermore, the combination of heat-killed Lactiplantibacillus plantarum and OIT has been shown to augment desensitization effects,[26] and systematic reviews and meta-analyses support the efficacy of OIT in IgE-mediated CMPA in children.[27] Intriguingly, the impact of OIT on gut microbiota and fecal metabolites sheds light on the maintenance of long-term desensitization.[28] While heated milk and unheated milk display comparable efficacy in inducing tolerance through OIT,[29] low-dose OIT protocols exhibit good effectiveness and safety, particularly in pediatric patients.[23,24] Importantly, early introduction of OIT has been confirmed as a safe and appealing approach for parents,[30] albeit with potential risks of severe anaphylactic reactions.[31] Long-term follow-up studies reveal that fixed low-dose OIT can sustain desensitization in children with severe CMPA,[24] and long-term changes in milk component immunoglobulins reflect the treatment outcomes of OIT.[32] Patients with elevated cow's milk-specific IgE levels prior to OIT are less likely to achieve the maintenance dose,[33] emphasizing the need for individualized treatment strategies. Moreover, age and oral challenge outcomes

may aid in identifying high-risk patients during OIT,[34] and the long-term adherence to cow's milk OIT is superior to that of peanut or sesame OIT.[35]

The prominence of OIT as a research hotspot reflects a paradigm shift in CMPA management from strict allergen avoidance toward active immune modulation. From an immunological perspective, the growing body of OIT research has advanced our understanding of oral tolerance mechanisms, particularly the role of regulatory T cells (Tregs) in suppressing Th2-mediated inflammation. Studies demonstrating that successful OIT induces casein-specific CD137+ FOXP3+ regulatory T cells[25] provide mechanistic evidence for immune reprogramming rather than mere desensitization. This mechanistic insight has translational implications: it suggests that OIT may offer disease-modifying potential rather than temporary symptom control, supporting its integration into clinical practice guidelines. Furthermore, the observation that OIT outcomes vary based on baseline characteristics such as specific IgE levels[33] highlights the need for personalized approaches, moving the field toward precision medicine in allergy treatment.

In recent years, SLIT has garnered considerable attention for the treatment of CMPA. However, when compared to OIT, SLIT has consistently demonstrated inferior desensitization efficacy, with allergic reactions tending to relapse shortly after therapy cessation. This observation underscores the significance of tailoring treatment approaches based on individual patient characteristics and the pursuit of long-lasting therapeutic effects.[36] Despite its limited efficacy relative to OIT, sublingual immunotherapy (SLIT) exhibits unique immunomodulatory properties. It regulates dendritic cell (DC)-mediated innate and adaptive immune responses by suppressing TLR-induced IL-6 secretion in myeloid DCs and enhancing IL-10 production in mature DCs, mechanisms that may attenuate allergic inflammation and foster immune tolerance.[37] Furthermore, the sublingual administration of Brucella abortus outer membrane protein Omp16 in combination with cow's milk proteins has shown promise in inducing a buccal Th1 immune response, modulating intestinal allergic responses, suppressing symptoms, reducing IgE and IL-5 levels, and upregulating IgG2a and IFN-γ, suggesting its potential to enhance the clinical and immune efficacy of SLIT for food allergies.[38] In conclusion, while SLIT may generally exhibit lower desensitization efficacy in CMA compared to OIT, its unique immune modulatory mechanisms and effectiveness in select patient populations underscore its importance as a complementary treatment modality. Future research endeavors should focus on exploring optimized SLIT protocols and their potential synergistic effects when combined with other therapies, aiming to provide more personalized and effective treatment options for patients.

Primary Prevention

The primary prevention of CMPA emerges as one of the current research hotspots, highlighting its importance and complexity. Primary prevention aims to reduce the incidence of CMPA in high-risk populations before the onset of the disease, particularly crucial in infant and young child populations. In recent years, with the deepening understanding of the pathogenesis of CMPA, primary prevention strategies have received widespread attention.

Primary prevention strategies for CMPA emphasize interventions beginning before conception, including maternal adherence to a balanced diet and lifestyle to promote placental transfer of IgG-allergen immune complexes. This approach is particularly relevant for mothers with allergic histories or planned cesarean deliveries.[39] Prenatal sensitization is suggested by studies showing cord blood cell proliferation in response to cow's milk proteins (eg., α-lactalbumin, β-lactoglobulin).[40] While maternal dietary factors, such as fatty acid intake, showed no overall correlation with offspring CMPA risk, α-linolenic acid supplementation may reduce risk in children of non-atopic mothers.[41] However, there is inconsistent evidence regarding whether mothers avoiding specific foods (such as milk and eggs) during pregnancy can effectively prevent CMPA, and such practices may increase the risk of malnutrition.[42] Therefore, ensuring adequate nutrition for pregnant women rather than restricting specific food intake has become a consensus.

In terms of infant and young child feeding, partially hydrolyzed formula (pHF) has been explored for the primary prevention of CMPA, but its effectiveness is controversial. Some studies suggest that pHF may reduce the risk of atopic dermatitis and asthma, but its specific preventive effect on CMPA is not yet clear.[39] Furthermore, the strategy of early introduction of food allergens to induce oral tolerance is gradually gaining attention. Studies support the benefits of early introduction of eggs and peanuts in preventing allergies, but the conclusion for early introduction of milk is inconsistent.[43–45]

The role of breastfeeding in primary preventing CMPA remains controversial, with studies yielding inconclusive results regarding its direct preventive effect on food allergies due to variability across individuals and genetics. More

rigorous research is required to establish its definitive effectiveness.[46] Additionally, while exclusive breastfeeding is generally advised, no specific association has been found between it and the prevention of any particular food allergy.[47]

Specific Milk Protein Components

We have added similar interpretative content linking structural findings to immunological mechanisms and clinical applications throughout the β-lactoglobulin, casein, and peptides subsections.

Beta-Lactoglobulin

In recent years, another prominent research focus in the field of CMPA has been the study of specific milk protein components, such as beta-lactoglobulin(βLg), casein, and peptides. βLg, as a major whey protein in milk, has seen significant research progress and attention, primarily focusing on the analysis of IgE-binding epitopes and the exploration of methods to reduce its allergenicity. Multiple studies have confirmed the presence of multiple IgE-binding epitopes on bovine βLg, including both linear and conformational epitopes. These epitopes are key to triggering allergic reactions in children with CMPA. The recognition of these epitopes does not depend on the clinical symptoms of patients, but individuals may experience varying degrees of allergic reactions due to personal differences. With modern immunological analysis techniques, scientists can now precisely map these epitopes, providing new directions for the diagnosis and treatment of allergies. These research findings not only enhance our understanding of the mechanism of milk allergy but also provide a scientific basis for developing more effective immunotherapy and diagnostic tools.[48–54] Current research on methods to reduce the allergenicity of βLg primarily focuses on two techniques: heat treatment and enzymatic hydrolysis. Heat treatment can reduce allergenicity by altering the protein's structure,[55] while enzymatic hydrolysis involves breaking down the protein into large molecular weight polypeptides or small peptides, thereby reducing or eliminating its allergenicity.[56] In addition, according to the latest research in 2024, fermentation[57] and supercritical CO_2 treatment[58] can also reduce the allergenicity of βLg. Studies on these methods not only provide a theoretical basis for the development of hypoallergenic foods but also offer more dietary options for patients with CMPA.

In summary, βLg, as a major whey protein in cow's milk, drives IgE-mediated allergic reactions through its structural stability and epitope diversity. Its compact globular conformation harbors both linear and conformational IgE-binding epitopes, which directly activate mast cell degranulation and Th2 immune polarization. Individual variability in epitope recognition underscores the clinical heterogeneity of CMPA symptoms. Current strategies to mitigate βLg allergenicity leverage structural disruption via heat, enzymatic hydrolysis, fermentation, or supercritical CO_2 treatment, which either degrade epitopes or mask their immunogenicity. Future research should prioritize the development of hypoallergenic βLg variants with retained nutritional value and explore synergistic approaches combining epitope-targeted therapies with microbiome modulation to enhance oral tolerance induction.

The focus on β-lactoglobulin epitope mapping[48–54] reflects a broader trend toward precision medicine in allergy—identifying specific molecular targets for diagnosis and therapy. From a mechanistic standpoint, understanding which epitopes are recognized by patient IgE enables more accurate diagnostic testing and potentially personalized immunotherapies. However, the translation of these findings into clinical tools remains limited; while epitope mapping has advanced our understanding of allergenicity, clinically available diagnostics still rely on whole-protein extracts. This gap between mechanistic research and clinical application represents an opportunity for future translational research.

Casein

As the primary protein component in milk, the allergenicity of casein and its influencing factors have been a research hotspot in recent years. Research has found that κ-casein can elicit a higher IgE response compared to βLg, indicating its stronger allergenic potential. This reveals the impact of different casein components on the immune system.[59] Furthermore, casein can be more effectively taken up by dendritic cells, inducing a stronger immune response in dendritic cells and Th2 cells, leading to increased degranulation of mast cells.[60] The structural modification of casein has a significant effect on its allergenicity. For instance, studies on glucose-glycosylated casein have shown that glycosylation can significantly reduce allergic reactions, helping to restore immune balance.[61] This discovery provides new ideas for the development of hypoallergenic dairy products. There are differences in the allergenicity of casein from

different types of milk. Cow's milk casein has the strongest allergenicity, which is related to its specific amino acid sequence and structural characteristics.[62,63] Therefore, when selecting dairy products suitable for patients with allergies, the allergenicity of casein from different milk sources should be fully considered. Physical and chemical treatments such as dielectric barrier discharge plasma pretreatment,[64] ultrasonic treatment,[65] and enzymatic hydrolysis[66] can also effectively reduce the allergenicity of casein. These methods reduce allergenicity by altering the structure of casein or degrading allergenic epitopes. The results of these studies provide technical support for the production of hypoallergenic dairy products. As an emerging treatment method, OIT has shown significant effects in reducing allergic reactions to casein.[67] Cow's milk OIT can promote the generation of casein-specific regulatory T cells, which can reduce Th2 reactions, and is expected to provide a new treatment strategy for patients with cow's milk allergies.[25] Additionally, the application of probiotics in the management of casein allergies has also received widespread attention. For example, Lactobacillus rhamnosus GG can not only reduce the incidence of functional gastrointestinal disorders but also improve patients' tolerance to cow's milk.[68] This provides strong support for the development of new dairy products to improve allergic symptoms.

In summary, exhibits heightened allergenicity due to Casein's disordered structure, efficient uptake by dendritic cells, and activation of Th2-inflammatory pathways. Its subtypes, particularly κ-casein, trigger robust IgE responses through epitope exposure and TLR4/NF-κB-mediated immune activation. Structural modifications—such as glycosylation, ultrasonic treatment, or enzymatic hydrolysis—reduce allergenicity by altering epitope accessibility or promoting immune tolerance. Comparative studies highlight that cow's milk casein surpasses goat or camel counterparts in allergenic potential, linked to unique amino acid motifs and aggregation properties. Emerging therapies like casein-focused OIT aim to reprogram immune responses via regulatory T-cell induction, though challenges persist in balancing efficacy and safety. Moving forward, integrating multi-omics approaches to decode casein-immune interactions, optimizing hybrid processing techniques, and validating clinical scalability of hypoallergenic formulations will be critical to advancing patient-centered solutions.

Peptides

In the study of CMPA, research on peptides has become a core area in recent years, especially in exploring their allergenicity, immunogenicity, and potential immunological tolerance. The hydrolysates of whey and casein exhibit significant differences in immunogenicity. Whey protein hydrolysates exhibit greater immunogenic potential compared to casein hydrolysates, eliciting elevated IgG1 antibody levels. This divergence stems from factors like hydrolysis degree, peptide size distribution, aggregation tendencies, nanoparticle formation, and surface hydrophobicity. Hydrophobic peptides are strongly associated with increased IgE antibody titers, highlighting hydrophobicity as a critical determinant of allergenicity.[69]

There is a certain relationship between peptide size and immunogenicity. The IgG reactivity of low molecular weight peptides (<3 kDa) in skim milk treated with Alcalase, Protamex, and Flavourzyme was significantly lower ($p < 0.05$) than that of higher molecular weight peptides (10–30 kDa and >30 kDa).[70] The study found significant variability in the molecular weight distribution of peptides in extensively hydrolyzed infant formula. The proportion of peptides with a molecular weight greater than 1200 Da was positively correlated with the residual BLG content, suggesting that these larger peptides may have higher immunogenicity. The larger molecular weight peptides induced a significant RBL cell degranulation response, indicating their residual allergenicity.[71] However, peptide size is not always directly correlated with reduced allergenicity in vitro or induction of oral tolerance in vivo, as the immunogenicity of specific peptides may vary due to structural differences.[72,73] Studies have shown that the determining factor for whey hydrolysates is not the degree of hydrolysis, but the presence and stability of IgE and T-cell epitopes recognized by individual patients in the hydrolysates.[74] Additionally, research has identified IgE sensitization to cryptic peptide epitopes in some children, which exist even without detectable allergen-specific IgE.[75] Therefore, despite in vitro and animal studies suggesting the potential of partially hydrolyzed proteins to reduce allergenicity and increase oral tolerance, clinical trial results have been inconsistent and cannot prove that hydrolyzed protein formulas significantly reduce the prevalence of allergic diseases.[73]

Human milk is rich in bioactive peptides, which are produced by proteolytic activity within the mammary gland. This means that breastfed infants receive pre-digested proteins and a variety of bioactive peptides. In fact, human milk contains about 1,100 unique peptides derived from the hydrolysis of 42 human milk proteins, including 306 peptides with potential bioactive properties.[73] This discovery further highlights the complexity of breastfeeding and its potential profound impact on infant health. Most specific IgE antibodies from infants and children with cow's milk allergy can recognize at least one human milk peptide, and this recognition has practical functionality. Interestingly, infants who do not respond to maternal avoidance of cow's milk are more likely to recognize more human milk peptides.[76] Using high-performance liquid chromatography-high-resolution mass spectrometry, two peptides derived from bovine βLg and one peptide from αs1-casein were identified in the milk of mothers who drink a glass of milk every day. However, these peptides were not found in the milk of mothers on a strict dairy-free diet. This suggests that milk-derived peptides from cow's milk proteins, rather than intact cow's milk proteins, may cause or induce allergic reactions in newborns through breast milk.[77]

Significant progress has been made in the identification and degradation of potentially allergenic peptides. Ye M et al successfully isolated seven potentially allergenic peptides from milk using bioinformatics prediction, protease hydrolysis, and LC-MS/MS identification techniques. These peptides include P1 [αs2-casein (AA189-197)], P2 [β-casein (AA106-113)], P3 [αs2-casein (AA71-80)], P4 [αs2-casein (AA150-158)], P5 [αs1-casein (AA84-90)], P6 [αs1-casein (AA96-102)], and P7 [β-casein (AA170-176)]. It's worth noting that the AA84-90 peptide of αs1-casein still retains a small amount of potentially allergenic peptide after alkaline protease treatment combined with lactic acid bacteria fermentation, but it demonstrates potential for immune tolerance.[78] Another study obtained 113 peptides from the major allergens in milk and yogurt digests, of which 38 peptides were present in all digests. Thirteen of these peptides exhibited specific biological functions, such as ACE inhibition, antibacterial activity, and DPP-IV inhibitory properties. Most importantly, the study identified 11 peptides that contain T-cell epitopes but not IgE epitopes, suggesting their potential to induce immune tolerance to CMPA.[79] Wan et al detected two peptide sequences, VLPVPQK and FFVAPFPEVFGK, from allergenic peptides of bovine casein, finding that the combination of M1 and M24 aminopeptidases was most effective for degrading these allergenic peptides.[80] Using the SPOT™ peptide array method, Li et al identified linear epitopes of βLg, obtaining three common peptide sequences: AA77-82 (KIPAVF), AA126-131 (PEVDNE), and AA142-147 (ALPMHI).[81]

Processing methods such as low-temperature (60°C) and high-temperature (130°C) dry heat treatments have a significant impact on the immunoreactivity of milk protein hydrolysates. The highest number of specific immunoglobulin E binding epitopes is found in unheated samples, while T-cell epitopes are present in equal amounts in all samples. Transport studies involving glycosylated peptides indicate a preference for glucosyl-lysine and lactosyl-lysine modified peptides. The restricted transport of peptides containing epitope structures suggests that the release of immunoreactive peptides is influenced by heating conditions, but the availability of epitope-containing peptides may be limited.[82] Additionally, research has shown that compared to the use of βLg-derived peptide nanoparticles, CpG nanoparticles, or a mixture of the two, pretreatment with nanoparticles co-encapsulating BLG-Pep and CpG can effectively prevent whey-induced allergic skin reactions and inhibit the rise of BLG-specific IgE in the serum.[83] Cow's milk OIT demonstrates potential for treating CMPA by rapidly increasing IgG4 binding epitopes and slowly reducing IgE binding epitopes.[84,85] IgE-binding peptides screened through bioinformatics analysis can serve as biomarkers to predict the safety and efficacy of Cow's milkvOIT.[86] Furthermore, studies have revealed that during the hydrolysis of βLg, chymotrypsin activity inhibits the formation of βLg102-124, a peptide containing a T-cell epitope. This inhibitory effect intensifies with increasing hydrolysis time. The prepared edible βLg hydrolysate, which preserves βLg102-124 and exhibits a reduced molecular weight distribution and antigenicity towards IgG and IgE, emerges as a novel candidate for peptide-based OIT.[48]

Enzymatic Polymerization: A Clinically Accessible Approach to Allergenicity Reduction

Enzymatic polymerization, particularly through the action of transglutaminase, catalyzes cross-linking between protein molecules, resulting in the formation of high-molecular-weight polymers. This technique is widely employed in the dairy industry for the production of cheese and yogurt from whey, making it readily available in conventional food markets.[87] The polymerized proteins exhibit reduced allergenicity through several mechanisms: (1) cross-linking can mask or alter conformational IgE-binding epitopes, reducing recognition by IgE antibodies; (2) polymerization may decrease protein

solubility and digestibility, potentially affecting immune cell accessibility; and (3) the formation of large protein aggregates may reduce intestinal uptake of allergenic peptides.[88,89]

Importantly, enzymatic polymerization offers practical advantages over more complex processing methods. The technology is already established in commercial dairy production, meaning that hypoallergenic products could potentially be developed without requiring entirely new manufacturing infrastructure. Furthermore, polymerized milk proteins retain functional properties that make them suitable for incorporation into a variety of food products, enhancing their potential for dietary management strategies.[90]

From a clinical perspective, the inclusion of polymerized milk proteins in tolerance induction protocols represents an intriguing possibility. Similar to the stepwise approach using baked milk products to gradually introduce allergens,[16,21] polymerized proteins could serve as an intermediate step between strict avoidance and exposure to native proteins. The reduced allergenicity of polymerized proteins might allow for safer introduction in patients with severe CMPA, potentially facilitating desensitization with lower risk of adverse reactions. Moreover, their availability in conventional food products could improve accessibility and adherence to dietary management strategies, particularly in settings where specialized hypoallergenic formulas are unavailable or unaffordable.

Future research should investigate the immunological mechanisms underlying tolerance induction with polymerized milk proteins, evaluate their safety and efficacy in clinical trials, and explore optimal protocols for incorporating them into stepwise tolerance induction strategies. Additionally, studies examining the potential synergistic effects of combining enzymatic polymerization with other allergenicity-reducing techniques (eg., hydrolysis, heat treatment) could further optimize hypoallergenic product development.

Knowledge Gaps and Future Directions Identified Through Bibliometric Analysis

While bibliometric analysis identifies what has been studied, it also reveals what remains underinvestigated. Several knowledge gaps emerge from our analysis: First, non-IgE-mediated CMPA is markedly underrepresented in the literature compared to IgE-mediated disease. Despite clinical recognition that non-IgE-mediated presentations (eg., food protein-induced enterocolitis syndrome, allergic proctocolitis) are common, particularly in infants, these conditions appear infrequently in keyword and citation analyses. This disparity may reflect diagnostic challenges, lack of validated biomarkers, or limited research funding, but it represents a significant gap given the clinical burden of these conditions. Second, research in diverse populations is limited. The dominance of Western countries in publication output means that findings may not be generalizable to populations with different genetic backgrounds, dietary practices, and environmental exposures. Studies from Asia, Africa, and South America are underrepresented, yet these regions may have unique CMPA epidemiology and management challenges. Third, mechanistic research appears less frequently in citation burst analyses than clinical studies. While clinical trials and guidelines are essential for improving patient care, the field's long-term progress depends on fundamental understanding of immune mechanisms, genetic predisposition, and environmental triggers. The relative undercitation of mechanistic work may reflect citation practices rather than scientific importance, but it nonetheless suggests opportunities for better integration of basic and clinical research. Fourth, implementation science is notably absent from identified hotspots. Even as clinical guidelines and efficacious treatments emerge, research on how to implement these findings in real-world healthcare settings—particularly in low-resource environments—remains limited. This gap between efficacy and effectiveness represents a critical barrier to improving global CMPA outcomes.

Future research should address these gaps through: (1) dedicated studies on non-IgE-mediated CMPA, including biomarker development and treatment trials; (2) multicenter international collaborations including underrepresented regions; (3) enhanced integration of mechanistic and clinical research; and (4) implementation science research to translate efficacy findings into real-world effectiveness.

Advantages and Shortcomings

This study, through the first systematic bibliometric analysis of CMPA research, comprehensively uncovers hotspots and frontiers in the field using multiple widely recognized tools, providing scholars with in-depth and intuitive guidance. The application of data visualization techniques further enhances the results' clarity, facilitating a quick grasp of research

dynamics and collaboration networks.Finally, bibliometric analysis provides more complete insight into the hotspots and frontiers than traditional reviews.

Despite the study's efforts for comprehensiveness, it should be noted that bibliometric analyses are subject to certain inherent limitations. First, our reliance on the Web of Science Core Collection (WoSCC), while justified by its comprehensive coverage and widespread use in bibliometric studies, may introduce database bias by excluding regionally published journals and non-English language publications. Second, citation-based analyses inherently favor older publications, which have had more time to accumulate citations, and may underestimate the impact of recent high-quality research (citation time-lag bias). Additionally, citation patterns can be influenced by factors unrelated to scientific merit, such as self-citation practices and publication language. While these biases do not undermine the validity of our descriptive findings, they should be considered when interpreting the results. Future studies could enhance robustness by incorporating multidisciplinary databases such as Scopus, PubMed, and Embase, and by applying normalization techniques to account for citation disparities across publication years and research fields.

While our bibliometric approach provides a comprehensive overview of research trends, it is inherently descriptive and cannot assess the quality, rigor, or clinical impact of individual studies. The identification of research hotspots should therefore be interpreted as reflecting academic activity rather than validated clinical utility. Future research should combine bibliometric insights with systematic reviews and meta-analyses to evaluate the evidence base underlying these trends. Additionally, the underrepresentation of non-IgE-mediated CMPA in our keyword analysis may reflect either true research gaps or indexing limitations, warranting targeted investigation in future studies.

Conclusion

This study systematically analyzed CMPA research over the past two decades, unveiling global trends and hotspots in this domain. Publications show a consistent upward trend, peaking in recent years, reflecting growing global interest. The United States, Italy, and China emerged as leading contributors, with strong collaboration among European and American nations. Research hotspots identified through bibliometric analysis include pathogenesis, diagnosis, prevention, and treatment strategies, particularly OIT and SLIT. Significant attention has also focused on specific milk protein components (β-lactoglobulin, casein, and peptides), advancing understanding of their allergenic properties.Through bibliometric analysis, this study provides a structured overview of the field and identifies trends that may inform future research directions.

Abbreviations

CMPA, Cow's Milk Protein Allergy; OIT, Oral Immunotherapy; SLIT, Sublingual Immunotherapy; WAO, World Allergy Organization; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy; NIAID, National Institute of Allergy and Infectious Diseases; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; EAACI, European Academy of Allergy and Clinical Immunology; βLg, Beta-Lactoglobulin; pHF, Partially Hydrolyzed Formula; DC, Dendritic Cell; IgE, Immunoglobulin E; IFN-γ, Interferon Gamma.

Data Sharing Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Ethics Approval

This bibliometric study was conducted based on published literature and did not involve direct interaction with human or animal subjects. Accordingly, it did not require review or approval by the Institutional Review Board of Yuebei People's Hospital. All methods were carried out in accordance with Declaration of Helsinki.

Author Contributions

Haizhi Tan: Conceptualization, Investigation, Writing – original draft, Data curation, Visualization, Project administration.
Xiaobing Xiao: Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.
Jianrong Deng: Investigation, Data curation, Visualization, Formal analysis.

Haizhi Tan and Xiaobing Xiao They are the co-first authors, contributed equally to this work.

All authors 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 declared that they have no conflicts of interest regarding this work.

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