Original Article

Research progress of mitochondria in chronic obstructive pulmonary disease: a bibliometric analysis based on the Web of Science Core Collection

Naer An[#], Jing An[#], Tingting Zeng, Shuyan Wang, Ping Li, Xueru Hu, Yongchun Shen, Lian Liu, Fuqiang Wen

Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy, Chengdu, China

Contributions: (I) Conception and design: N An, J An; (II) Administrative support: Y Shen, L Liu, F Wen; (III) Provision of study materials or patients: T Zeng, S Wang; (IV) Collection and assembly of data: N An, J An; (V) Data analysis and interpretation: N An, J An, P Li, X Hu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Yongchun Shen, MD; Lian Liu, PhD. Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy, No. 37, Guoxue Road, Chengdu 610041, China. Email: shen_yongchun@126.com; desertfoxliu@hotmail.com.

Background: Due to its high morbidity and mortality, chronic obstructive pulmonary disease (COPD) has become a major global healthcare issue. Although there is abundant research regarding COPD, a bibliometric analysis of the literature related to mitochondria and COPD is lacking. Thus this study aimed to summarize the research status, research direction, and research hotspots of the published articles concerning COPD and mitochondria.

Methods: A literature search for included publications related to COPD and mitochondria was carried out on the Web of Science Core Collection from the date of database establishment to December 15, 2022. A subsequent bibliometric and visual analysis of the included publications was conducted via Microsoft Excel, R software, CiteSpace, and VOSviewer.

Results: A total of 227 published articles on COPD and mitochondria from 139 journals were included. Over the study period, the annual publication number and citation frequency in this field both showed a trend of continuous growth. The United States had the highest centrality and was the most productive country. The frequently occurring keywords were “oxidative stress”, “obstructive pulmonary disease”, “dysfunction”, “mitochondria”, “inflammation”, and “cigarette smoke”, among others. Recent research hotspots included autophagy, model, mitochondria, health, and extracellular vesicles (EVs). Despite an abundance and variety of research, there is still relatively little academic communications between scholars and institutions.

Conclusions: This bibliometric study can help researchers gain a quick overview of the research into mitochondria and COPD and thus inform novel ideas and directions for future research in this field.

Keywords: Mitochondria; chronic obstructive pulmonary disease (COPD); bibliometric analysis; CiteSpace; VOSviewer

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by persistent and progressive airflow obstruction and respiratory symptoms due to damage and remodeling of the airways, lung parenchyma, and pulmonary vasculature (1), resulting in increased dyspnea, disability, and death. In 2017, the number of people with chronic respiratory disease was about 544 million, with COPD accounting for approximately 55% of these cases (2). According to the mortality statistics published by the World Health Organization (WHO), there are about 3 million deaths per year due to COPD (3), making it second only to ischemic heart disease and cerebrovascular disease in the global ranking of age-standardized mortality for both sexes (4). Because of its high global morbidity and mortality, COPD is considered a major health burden, which seriously endangers the health of individuals worldwide (5). The pathogenesis of COPD is complex, as it involves a combination of dynamic and cumulative gene-environment interactions (6), such as smoking, inhalation of other pollutants, respiratory infections, and malnutrition. These interactions regulate the development, maintenance, and function of the lungs through a variety of complicated biological mechanisms, including oxidative stress, inflammation, aberrant cell proliferation, cell apoptosis, and senescence, and may also impact other important organs to induce systemic and multimorbid syndromes (7). The complexity of the pathogenesis presents a considerable challenge to the clinical management of COPD. Current clinical treatments of COPD mainly focus on the control of symptoms, and there are no effective preventive or curative measures. Therefore, it is necessary to acquire an in-depth understanding of the pathophysiological processes and pathogenesis of COPD to develop new strategies for improving the health and prognosis of patients.

Mitochondria is an essential organelle involved in cellular energy supply, cell metabolism adjustment, calcium homeostasis maintenance, substances synthesis, gene expression, signal transduction, and cell death program regulation (8), all of which critically influence COPD through a variety of pathways. As the most fundamental and essential function of mitochondria, energy supply is involved in all physiological processes. Mitochondrial bioenergetic dysfunctions, such as mitochondrial respiratory chain inhibition, mitochondrial leakage, and uncoupling contribute to pulmonary dysfunction (9). Excessive production of mitochondrial reactive oxygen species (ROS) leads to an oxidant-antioxidant imbalance that induces and promotes chronic airway inflammation (10). Mitochondrial calcium homeostasis and redox regulation contribute to cellular signaling, gene expression, regulation of the contraction, and proliferation of airway smooth muscle, which are crucial determinants in the pathophysiology of chronic lung disease (11). Mitochondria maintain normal morphology and function through a dynamic balance of cleavage, fusion, and mitosis, resulting in quality control and stress adaptations known as "mitochondrial dynamics", the disruption of which may exacerbate inflammatory response and airway injury in patients with COPD (12). These facts suggest that studies on mitochondria can generate novel ideas concerning the pathogenesis of COPD and provide ideas for its rational and effective treatment. Therefore, this bibliometric study, which summarized and visualized the research status and trends on COPD and mitochondria, was conducted to clarify the relationship between these elements and provide new research directions for improving the prevention and treatment of COPD.

Bibliometrics is a means quantitative statistical analysis that can be used to describe the status in a given research field by summarizing the collected literature data (13). As the number of research results and academic papers increases dramatically and as researchers communicate

Highlight box

Key findings

- This study systematically summarized the research status, direction, and hotspots of published articles on mitochondria in chronic obstructive pulmonary disease (COPD) and identify several key problems in the field.

What is known and what is new?

- Mitochondria are highly involved in the process of COPD through a variety of pathways. However, the distribution of literature related to mitochondria in COPD is scattered.
- This bibliometric analysis was conducted to provide a visual, empirical, and clear overview of the current research situation and characteristics concerning COPD and mitochondria, with the ultimate aim of providing new ideas and directions for future research.

What is the implication, and what should change now?

- This study's findings offer a reference for researchers interested in the field to easily apprehend the research trends and hotspots and to accurately formulate future research directions and strategies. Academic communication and collaboration should be improved to explore the connection between COPD and mitochondria.

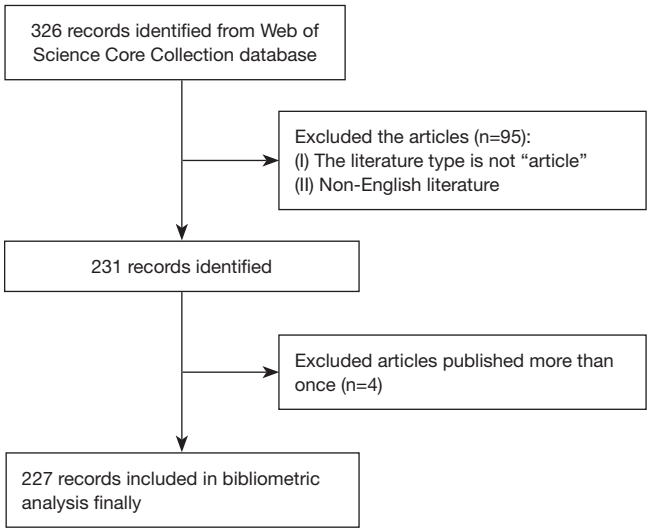

Figure 1 Flowchart of literature screening.

more frequently through reading and citing published research results, bibliometrics is playing an increasingly important role in academic research and has been applied in many research areas to evaluate countries, institutions, authors, journals, keywords, and cited references (14). It can not only extract valuable information and display it in different dimensions through data mining techniques, but it can also construct knowledge graphs to visualize the research data (15), which is difficult to achieve via traditional methods. Bibliometrics is also capable of predicting the hotspots, directions, and trends in scholarly research activity and of providing a macroscopic perspective on aspects of the research output in a field (16). Citation is a crucial aspect that reflects the scientific impact of literature (17). As a unique component of bibliometric analysis, citation analysis makes it possible to assess the comparative importance of articles or journals and to establish links between researchers, institutions, and specific fields (18). Although bibliometric analysis is deficient in terms of detailed analysis compared to the traditional literature review method, it has advantages in terms of comprehensiveness (19). In this study, CiteSpace software and VOSviewer were used to conducted a bibliometric analysis on articles about COPD and mitochondria published on the Web of Science Core Collection. So that researchers can quickly identify the literature characteristics, understand the research developments, discover research hotspots, and offer clues and directions for future studies and clinical treatment.

Methods

Data sources

This bibliometric analysis was based on the Web of Science Core Collection [indexes: Science Citation Index Expanded (SCI-Expanded), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), Conference Proceedings Citation Index-Science (CPCI-S), Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH), Emerging Sources Citation Index (ESCI), Current Chemical Reactions-Expanded (CCR-Expanded), and Index Chemicus (IC)]. As one of the world's most comprehensive and authoritative academic resource databases, Web of Science Core Collection is the most commonly used database for bibliometric analysis at present (20), contains high-quality and constantly updated literature collections (21), and provides comprehensive citation indexing records.

Search strategy

All published articles related to COPD and mitochondria were searched from the time of database establishment to December 15, 2022. The search terms under the Medical Subject Headings (MeSH) were set as follows: TS = ("chronic obstructive pulmonary disease" OR "COPD" OR "chronic airflow obstruction" OR "chronic obstructive lung disease") AND TS = (mitochondria OR mitochondrion OR mitochondrial). In order to reduce selection bias, two researchers (N.A. and J.A.) conducted the literature search independently at the same time (December 15, 2022). The concordance of screening results exceeded 0.9, thus indicating relative confidence. Researchers further excluded the retrieved articles based on the following criteria: (I) a literature type other than an article; (II) non-English language literature; and (III) duplicate articles. Every downloaded article included fully documented and cited references. *Figure 1* shows the literature screening process.

Analysis methods

After completing the search, we exported all included records of the results in text format as the original dataset and retrospectively analyzed the collected literature using R software v.3.1.4 (The Foundation for Statistical Computing), VOSviewer, and CiteSpace v.6.2.2. The analysis included the annual number of publications and citations; the distribution of published literature including

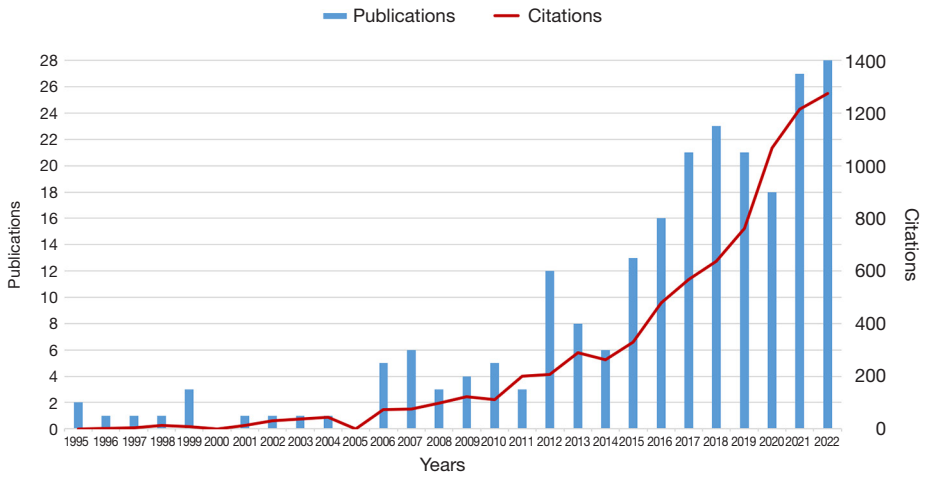

Figure 2 Publications and citations on COPD and mitochondria between 1995 and 2022. COPD, chronic obstructive pulmonary disease.

journals, countries, institutions, and authors; reference citations; keywords; and collaboration between countries, institutions, and authors. Microsoft Excel 2016 was used to describe line and bar charts, while the R package "bibliometrix", VOSviewer, and CiteSpace were used to perform bibliometric and visual analyses.

Results

Time analysis

From 1995 to 2022, a total of 231 original articles (four articles were duplicated) related to COPD and mitochondria were obtained, and 8,013 citations were reported with an h-index of 48. Each article was cited with average of 34.69 times. From 1995—the year the first article was published—to 2005, 12 articles were published with a total citation frequency of 152. From 2006 to 2022, 219 articles were published with a total citation frequency of 7,861. Since 2006, the number of publications on COPD and mitochondria has shown a trend of continuous growth, and the number of citations each year has increased significantly (*Figure 2*). In the last 2 years of the study period, especially, there has been a surge in the number of publications and citations, demonstrating that an increasing number of researchers are focusing on this field, indicating the great potential for future research.

Journal analysis

There were 227 articles published in 139 journals in the field of mitochondrial and COPD. The majority of the published journals and cocited journals were respiratory and biology journals from the United States and Europe. *American Journal of Respiratory Cell and Molecular Biology* published the highest number of articles with 12. *American Journal of Respiratory and Critical Care Medicine* had the highest number of cocitations at 170. *Table 1* lists the top 10 journals in terms of number of published articles and frequency of cocitations. The impact factors of these journals ranged from 3.65 to 33.801.

Country and institution analysis

The literature search identified 227 articles from 452 institutions in 31 countries (*Figure 3A*). *Table 2* lists the information of the 10 countries and institutions with the highest article output. The United States was the country that produced the most articles and had the highest centrality (0.68). China's intermediary centrality (0.02) was much lower than that of other productive countries. In *Figure 3*, nodes with purple outer circles indicate a centrality greater than or equal to 0.10 (22) and suggests that these countries assume a key role in the research cooperation network. Both the University of Groningen and Imperial College London had nine publications, and four institutions had an intermediate centrality greater than 0.10, with the National Institute of Health and Medical Research (INSERM) having the highest centrality of 0.14. There were significantly more collaborative links between countries than between institutions (*Figure 3B*), indicating academic communication has been more common between

Table 1 Top 10 most productive journals and cocited journals in the field of COPD and mitochondria

Rank	Most productive journals			Most cocited journals		
	Content	Publication	IF [2021]	Content	Publication	IF [2021]
1	*American Journal of Respiratory Cell and Molecular Biology*	12	7.748	*American Journal of Respiratory and Critical Care Medicine*	170	30.528
2	*American Journal of Physiology Lung Cellular and Molecular Physiology*	10	6.011	*European Respiratory Journal*	146	33.801
3	*European Respiratory Journal*	8	33.801	*American Journal of Physiology Lung Cellular and Molecular Physiology*	122	6.011
4	*American Journal of Respiratory and Critical Care Medicine*	7	30.528	*PLOS ONE*	114	3.752
5	*Respiratory Research*	6	7.162	*Journal of Biological Chemistry*	114	5.485
6	*Free Radical Biology and Medicine*	5	8.101	*American Journal of Respiratory Cell and Molecular*	113	7.748
7	*Advances in Experimental Medicine and Biology*	4	3.65	*Journal of Clinical Investigation*	106	19.477
8	*Cells*	4	7.666	*Chest*	100	11.393
9	*Chest*	4	11.393	*Respiratory Research*	96	7.162
10	*Journal of Applied Physiology*	4	3.881	*Proceedings of the National Academy of Sciences of the United States of America*	90	12.779

COPD, chronic obstructive pulmonary disease; IF, impact factor.

institutions from different countries than between research institutions in the same country.

Author analysis

As can be seen in *Table 3*, only five authors published five or more articles among all 514 authors. All authors had very low centrality, with a maximum of only 0.01. Barnes PJ was cited frequently (about 54 times) and had the highest centrality, indicating that his articles were widely accepted by researchers in this field. The relatively sparse and scattered contact between authors (*Figure 3C*) indicates a lack of collaboration among most researchers, and thus the intensity of academic communication should be increased in the future.

Discipline analysis

The 227 retrieved articles covered 44 subdisciplines, including those related to the respiratory system (69, 29.870%), cell biology (44, 19.048%), biochemistry molecular biology (44, 19.048%), physiology (31, 13.420%), experimental medicine research (25, 10.823%), pharmacology (20, 8.658%), and general internal medicine (18, 7.792%) among others. *Table 4* shows the top 10 disciplines in terms of total articles.

Cocitation analysis

Table 5 shows the top 10 articles in terms of cocitation frequency (23-32), 50% of which were from the United States, indicating that this country has contributed

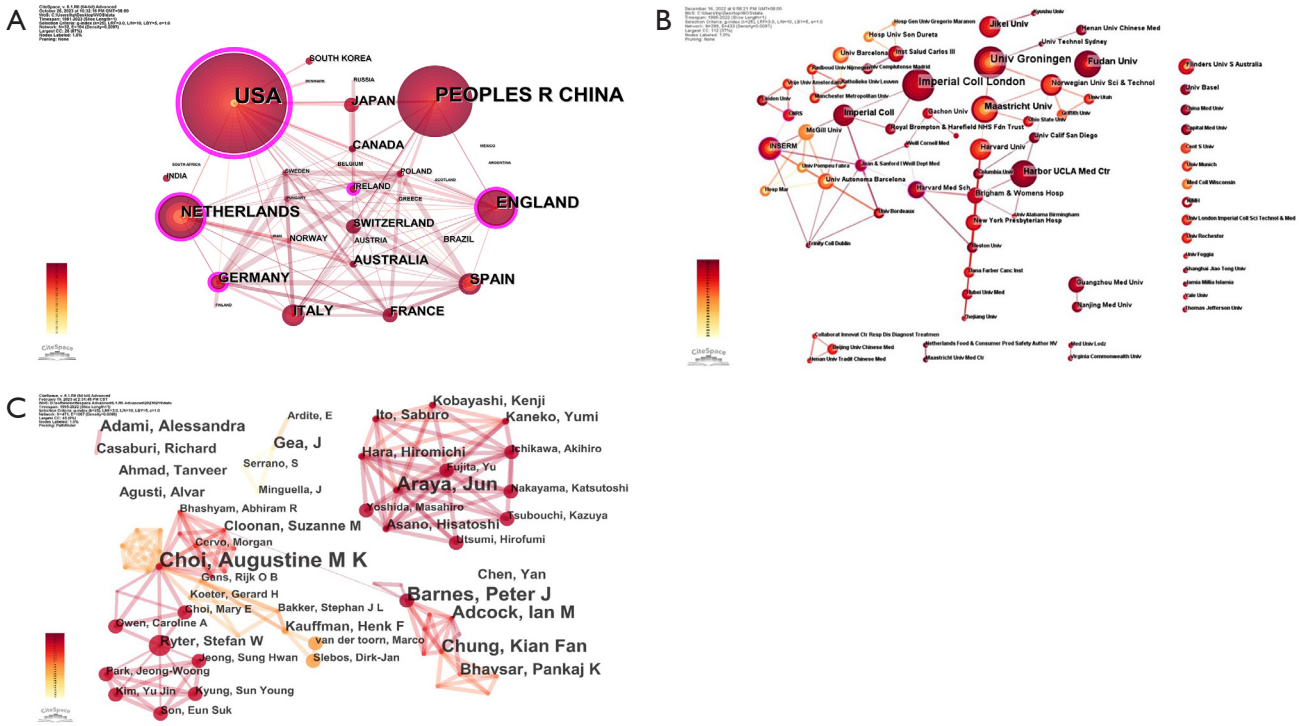

Figure 3 Distribution of publications related to COPD and mitochondria. (A) The visual map of the countries. (B) The visual map of the institutions. (C) The visual map of the authors. The size of nodes is positively correlated with the frequency of occurrence or co-occurrence of analyzed objects. Lines between nodes represent cooperative relationships, and the thickness of lines represent the strength of the relationship. The color of nodes indicates the year in which the object occurs as shown in the color bar of figure. COPD, chronic obstructive pulmonary disease.

Table 2 Top 10 most productive countries/regions and institutions in field of COPD and mitochondria

Rank	Country/region				Institution		
	Content	Publication	Centrality	Year	Content	Publication	Centrality
1	USA	82	0.68	1995	University of Groningen	9	0.05
2	China	55	0.02	2012	Imperial College London	9	0.02
3	UK	24	0.17	2006	Maastricht University	6	0.03
4	The Netherlands	21	0.14	2006	Fudan University	6	0.00
5	Spain	15	0.03	1996	Imperial College	5	0.03
6	Germany	13	0.12	2004	Harbor-UCLA Medical Center	5	0.01
7	Italy	13	0.10	2010	Jikei University	5	0.00
8	Australia	11	0.02	2003	INSERM	4	0.14
9	France	10	0.02	1999	Harvard University	4	0.08
10	Japan	10	0.00	2013	Brigham Women's Hospital	4	0.04

COPD, chronic obstructive pulmonary disease; UCLA, University of California, Los Angeles; INSERM, National Institute of Health and Medical Research.

Table 3 Top 10 most productive and cocited authors in field of COPD and mitochondria

Rank	Author			Cocited author		
	Content	Publication	Centrality	Content	Publication	Centrality
1	Choi AM	7	0.01	Barnes PJ	54	0.36
2	Barnes PJ	6	0.01	Mizumura K	45	0.03
3	Araya J	6	0.00	Hoffmann RF	39	0.04
4	Chung KF	5	0.00	Hara H	33	0.08
5	Adcock IM	5	0.00	van der Toorn M	30	0.05
6	Bhavsar PK	4	0.00	Aravamudan B	29	0.03
7	Adami A	4	0.00	Ahmad T	29	0.07
8	Gea J	4	0.00	Wiegman CH	28	0.03
9	Asano H	3	0.00	Gosker HR	28	0.15
10	Agusti A	3	0.00	Cloonan SM	27	0.04

COPD, chronic obstructive pulmonary disease.

Table 4 Top 10 disciplines in field of COPD and mitochondria

Rank	Disciplines	Publication	Percent (%)
1	Respiratory system	69	29.870
2	Cell biology	44	19.048
3	Biochemistry molecular biology	44	19.048
4	Physiology	31	13.420
5	Experimental medicine research	25	10.823
6	Pharmacology	20	8.658
7	General internal medicine	18	7.792
8	Immunology	12	5.195
9	Science technology and other topics	12	5.195
10	Endocrinology metabolism	10	4.329

COPD, chronic obstructive pulmonary disease.

significantly to the field of mitochondria and COPD. The publication dates of the highly cocited articles were concentrated in the period of 2013–2016, which can be considered an essential phase of research progression in this field. Most of the highly cocited articles focused on the pathogenesis of COPD in terms of autophagy, cigarette smoke (CS), oxidative stress, and mitochondrial dysfunction.

Keyword analysis

Keywords can reflect the hotspots and frontiers of the area to be studied and is thus one of the most valuable aspects of bibliometric analysis (33). *Table 6* shows the top 18 keywords with the highest frequency of occurrence and the high centrality. In addition to "oxidative stress" and "obstructive pulmonary disease", the terms "dysfunction", "mitochondria", "inflammation", and "cigarette smoke" also occurred frequently in the articles. A keyword visualization map (*Figure 4A*) was also drawn to show the direct connection between keywords. A trend analysis of keywords (*Figure 4B*) indicated that the high-frequency terms most commonly appeared between 2013 and 2021. Keyword co-

Table 5 Top 10 cocited references in field of COPD and mitochondria

Rank	Title (reference)	Year	Author	Journal	Country	Cocitations
1	Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD (23)	2014	Mizumura *et al.*	*Journal of Clinical Investigation*	USA	25
2	Oxidative stress–induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease (24)	2015	Wiegman *et al.*	*Journal Allergy Clinical Immunology*	UK	20
3	Prolonged cigarette smoke exposure alters mitochondrial structure and function in airway epithelial cells (25)	2013	Hoffmann *et al.*	*Respiratory Research*	The Netherlands	16
4	Impaired mitophagy leads to cigarette smoke stress-induced cellular senescence: implications for chronic obstructive pulmonary disease (26)	2015	Ahmad *et al.*	*FASEB Journal*	USA	15
5	Mitochondria in lung disease (27)	2016	Cloonan *et al.*	*Journal of Clinical Investigation*	USA	13
6	Cigarette smoke-induced mitochondrial fragmentation and dysfunction in human airway smooth muscle (28)	2014	Aravamudan *et al.*	*American Journal Physiology Lung Cellular and Molecular Physiology*	USA	12
7	PARK2-mediated mitophagy is involved in regulation of HBEC senescence in COPD pathogenesis (29)	2015	Ito *et al.*	*Autophagy*	Japan	12
8	Mitochondrial fragmentation in cigarette smoke-induced bronchial epithelial cell senescence (30)	2013	Hara *et al.*	*American Journal Physiology Lung Cellular and Molecular Physiology*	Japan	11
9	Mitochondria in lung diseases (31)	2013	Aravamudan *et al.*	*Expert Review Respiratory Medicine*	USA	10
10	Skeletal muscle mitochondrial dysfunction during chronic obstructive pulmonary disease: central actor and therapeutic target (32)	2013	Meyer *et al.*	*Experimental Physiology*	France	9

COPD, chronic obstructive pulmonary disease.

occurrence refers to the simultaneous occurrence of more than two keywords in the same article (34). A co-occurrence cluster atlas (*Figure 4C*) was created to show the top 10 most highly related co-occurrence keyword clusters. *Table 7* shows the characteristics of the 10 largest keyword clusters, whose silhouette values were all greater than 0.85, indicating the clustering was reliable (35). The keyword timeline diagram (*Figure 4D*) shows the longest research cycles (#4, #6) and the most recent research hotspots (#7). For high-frequency keywords, we performed citation burst detection, which is visualized in *Figure 5*, where the red segments on the blue timeline represent the outbreak period. We found that the most recent hotspots were autophagy, model, mitochondria, health, and extracellular vesicles (EVs). The keyword that had the first burst and longest burst duration [1996–2009] was "respiratory muscle". The keyword with the largest strength was "exercise", which first appeared in 1999. In 2 recent years [2021–2022], the keywords that emerged were

Table 6 Top 18 most frequent keywords related to COPD and mitochondria

Rank	Keywords	Frequency	Year	Centrality
1	Oxidative stress	79	1997	0.18
2	Obstructive pulmonary disease	71	1997	0.27
3	COPD	47	2008	0.17
4	Chronic obstructive pulmonary disease	37	1995	0.31
5	Dysfunction	35	2006	0.15
6	Mitochondria	32	1997	0.14
7	Inflammation	32	2007	0.08
8	Cigarette smoke	30	1995	0.15
9	Skeletal muscle	28	2007	0.13
10	Apoptosis	26	2004	0.17
11	Autophagy	22	2015	0.05
12	Expression	21	2007	0.12
13	Pathogenesis	21	2016	0.05
14	Exercise	19	1995	0.12
15	Mitochondrial dysfunction	16	2004	0.03
16	Activation	16	2015	0.07
17	Emphysema	14	2007	0.03
18	Cell	13	1998	0.08

COPD, chronic obstructive pulmonary disease.

"mitochondria", "health" and "extracellular vesicles".

Discussion

As a common respiratory disease, COPD has become major threat to human health due to its substantial and increasing morbidity and mortality (36). Therefore, exploring new and cognitive research avenues is necessary to gain insight into the pathogenesis and better management of COPD. A series of mitochondrial-based studies on the pathogenesis of COPD has discussed new possibilities for the prevention and treatment of the disease, but there is no systematic evaluation of the abundant research in this subfield. In this study, a bibliometric analysis on COPD and mitochondria was conducted using R software, VOSviewer, and CiteSpace to visualize the various aspects of the included publications, showing their characteristics, distribution, research direction, and hotspots. The overarching aim of this study was to provide researchers with a reference to systematically understand the current research status and the ongoing trends in COPD and mitochondria research, gain new ideas concerning the pathogenesis and prevention of COPD, and thus better benefit patients with this disease.

A total of 227 publications on the relationship between COPD and mitochondria from 139 journals in the Web of Science Core Collection published from 1995 to 2022 were included. The first relevant article was published in the *Journal of Applied Physiology* in 1995 (37). In this article, the authors reported that oxygen availability in patients with COPD significantly limits intramuscular oxygen metabolism. Since 2006, both the number of publications and the frequency of citations annually have increased each year. In the past 2 years especially, there has been a surge in research, indicating that an increasing number of researchers believe mitochondria to be critical to the understanding of COPD.

According to our analysis, the United States was the most productive country with the highest centrality. It is worth mentioning that the number of articles published from China ranked second in the world. The reason for

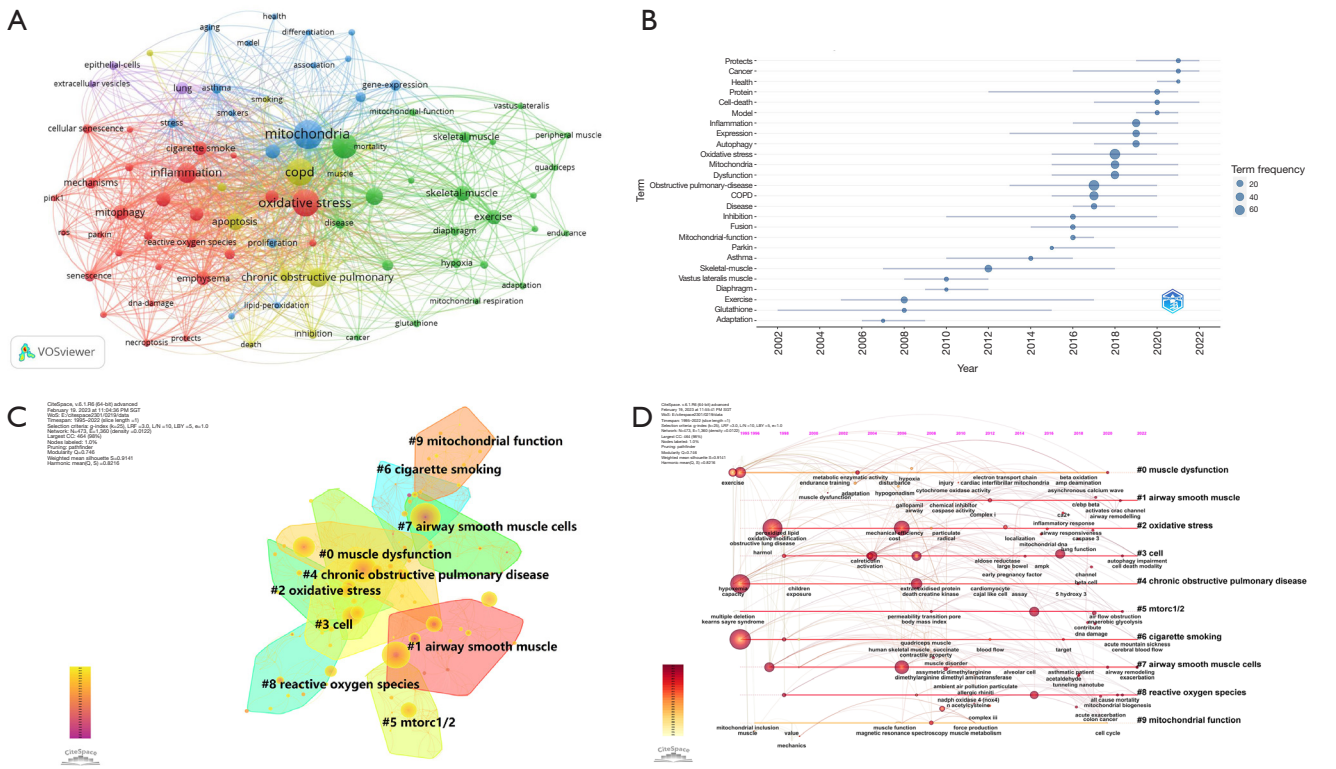

Figure 4 Analysis of keywords in the literature related to COPD and mitochondria. (A) The visualization map of keywords. (B) The time trend of keywords. (C) Co-occurrence cluster atlas of keywords. (D) Keyword timeline diagram based on the clustering results. #0–9: 10 co-occurrence clusters (# indicates keyword cluster number). COPD, chronic obstructive pulmonary disease.

this may be related to the epidemiological characteristics of COPD in the United States and China, and the high priority given to the management of the disease by the governments of these two countries. The United Kingdom, the Netherlands, Germany, and Ireland had high intermediary centralities, indicating their strong potential in this field. The United States and European countries maintained a degree of academic communication and cooperation. In contrast to its high production, China's centrality was only 0.02, and we assume this may be due to the fact that the global academic influence of Chinese researchers was not yet as high as that of their European and American colleagues. Among institutions, universities in the United States and Europe contributed to the majority of the articles. There were frequent academic information exchanges between institutions in different countries, but a relatively low level of collaboration between research institutions within each country. From the author collaboration network (*Figure 3C*), it was clear that although many researchers had published articles on COPD and mitochondria, there was little collaboration among them in this area. Academic communication and collaboration should be improved to further explore the connection between COPD and mitochondria.

Most of the highly cocited articles were from the academically active European and American regions, which made significant contributions to the field. It is worth noting that two articles from Japanese researchers were also cited several times. Highly cocited articles were concentrated in the period of 2013–2016, which can be considered a critical phase of growth in this field. The most frequently cocited article emphasized that mitophagy-dependent necroptosis induced by CS exposure is related to the pathogenesis of COPD (23). The second most frequently cocited article proposed that mitochondrial ROS overproduction in patients with COPD leads to an increased inflammatory response and excessive cell proliferation that results in mitochondrial dysfunction. Therefore, this mechanism may be a source for developing novel therapeutic approaches targeting mitochondrial ROS in patients with COPD (24).

Table 7 Characteristics of the 10 main clusters in the cluster atlas of keywords

Cluster ID	Size	Silhouette	Mean (year)	Cluster (LLR)	Main keywords
#0	45	0.908	2007	Muscle dysfunction	Muscle dysfunction; oxidative phosphorylation; glutathione; endurance training; skeletal muscle
#1	40	0.936	2014	Airway smooth muscle	Airway smooth muscle; airway hyperresponsiveness; proliferation; metabolic reprogramming; PHB1
#2	40	0.891	2007	Oxidative stress	Oxidative stress; ACOS; mitochondrial DNA; chronic obstructive pulmonary disease (COPD); pulmonary artery
#3	39	0.92	2013	Cell	Cell; dexamethasone; airway epithelial cells; airway epithelial cell; phosphodiesterase 4
#4	37	0.878	2005	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease; skeletal muscle; fibroblasts; acetaldehyde; interstitial cells
#5	32	0.899	2010	mTORC1/2	mTORC1/2; DNA deletion; nucleotide primer extension; Kearns-Sayre syndrome; progressive external ophthalmoplegia
#6	30	0.879	2008	Cigarette smoking	Cigarette smoking; cigarette smoke; quadriceps muscle; fiber type; adaptation
#7	30	0.933	2013	Airway smooth muscle cells	Airway smooth muscle cells; asthma; alveolar epithelial cell; oxygen consumption; skeletal muscle
#8	29	0.863	2014	Reactive oxygen species	Reactive oxygen species; tiotropium; acute exacerbation; NLRP3 inflammasome; lipopolysaccharide
#9	26	0.908	2007	Mitochondrial dysfunction	Mitochondrial function; respiratory muscle; normal human bronchial epithelial BEAS-2b cells; mitochondrial inclusions; magnetic resonance imaging

# indicates keyword cluster number. LLR, log-likelihood rate; ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease.

The third-ranked article in terms of cocitation found a marked increase in the expression of mitochondrial fission/fusion markers, oxidative phosphorylation proteins, and oxidative stress markers in the airway epithelial cells of patients with COPD due to long-term CS exposure from smoking (25). The abovementioned highly cocited articles all arrived at a similar conclusion concerning the effects of CS and ROS on COPD: CS-induced oxidative stress overload and mitochondrial ROS overproduction disrupt the balance of the oxidative-antioxidant system, resulting in structural and functional changes of mitochondria that induce and promote chronic airway inflammation diseases. Mitochondria-targeted antioxidant therapies, such as mitochondria-targeted peptide SS-31 (38) and mitochondrial quinone (MitoQ) (39), are important for ameliorating the CS-induced chronic airway inflammation. The relevant highlights mentioned in these articles are consistent with the findings of other studies conducted by our team (38,39) and the keyword analysis in this article.

As the most valuable part of bibliometric analysis, keyword analysis can relate the basic content of articles and identify the concerns of researchers over different periods to reveal the key themes of clinical research (40). In our study, CiteSpace and VOSviewer were used to analyze the co-occurrence, clustering, and bursting of keywords to characterize the research hotspots, frontiers, and trends in this field (41). In these articles, high-frequency keywords changed significantly over time according to the burst detection. During the 1996–2007 period, frequent keywords mainly focused on respiratory muscle, exercise, skeletal muscle, adaptation, fiber type, and the diaphragm. Researchers mainly considered respiratory muscle dysfunction to be associated with the progression of COPD during this period. The keyword emergence

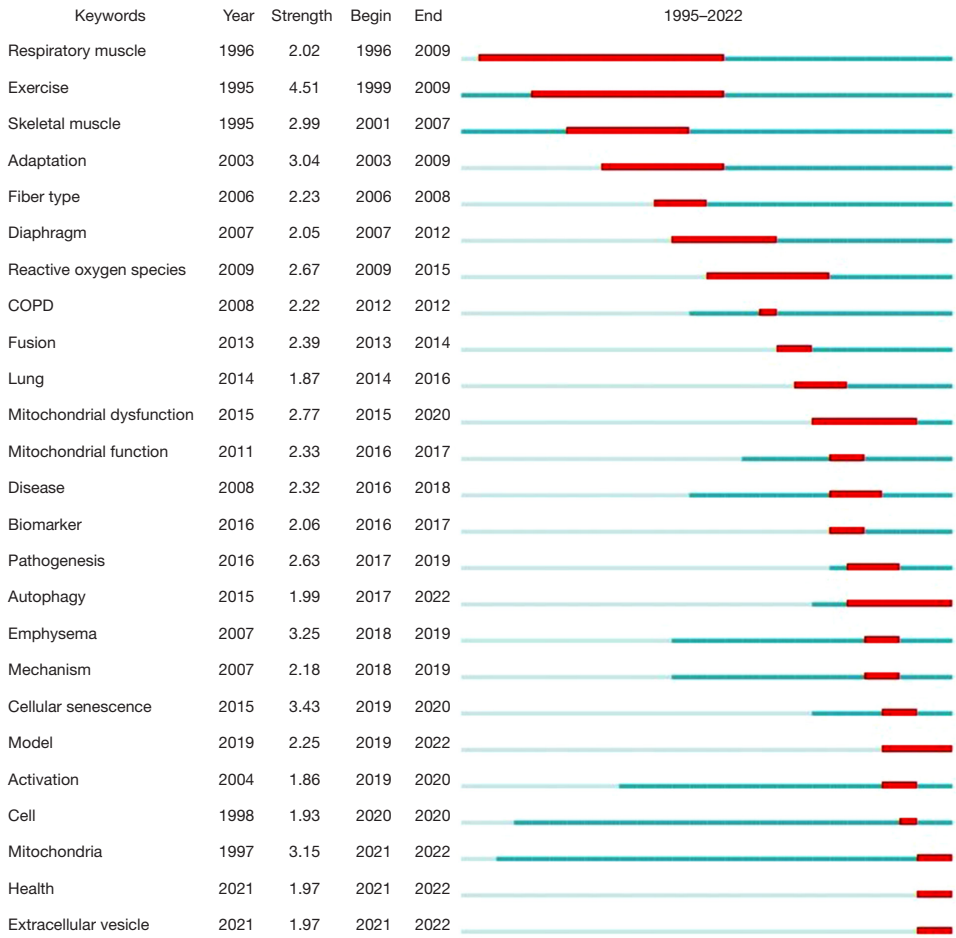

Figure 5 Top 25 keywords with the strongest citation burst. Blue lines represent the timeline, and red segments represent the burst period.

analysis also showed that the keyword that had the first and longest burst duration was "respiratory muscle". Orozco-Levi *et al.* (42) reported that pulmonary dysfunction of patients with COPD is related to the subcellular changes in the diaphragm, namely the shortening of sarcomere length and the increase of mitochondrial concentration. During the 2009–2018 period, most common keywords then shifted to "reactive oxygen species", "COPD", "fusion", "lung", "mitochondrial dysfunction", "mitochondrial function", and "disease". Puente-Maestu *et al.* (43) reported that the skeletal muscle mitochondria in patients with COPD showed blocked electron transmission chain and overproduction of ROS. Hara *et al.* (30) demonstrated that CS causes the overproduction of mitochondrial ROS, which induces mitochondrial rupture and contributes to cellular senescence, so they speculated that destruction of mitochondrial dynamics might be a part of the pathogenic mechanism of COPD. It should be noted that at this point in time, researchers' attention was increasingly focusing on the internal link between mitochondria and COPD.

From 2016 to 2022, the keyword emphasis changed to "biomarker", "pathogenesis", "autophagy", "emphysema", "mechanism", "cellular senescence", "model", "activation", "cell", "mitochondria", "health", and "extracellular vesicles". Autophagy is an important biological reaction that counters ROS and oxidative stress to maintain redox homeostasis (44). Ornatowski *et al.* (45) found that CS can result in mitochondrial dysfunction and a lack of autophagy, inducing cellular senescence and COPD progression. In investigating how mitochondrial dysfunction leads to COPD and the mechanism of its aggravation, Summer *et al.* (46) found that the critical factors are an increase of ROS, inflammatory reaction, and the possible induction of cell senescence through mitochondrial damage-associated

molecular patterns (DAMPS). In one of our previous studies, we also identified the importance of mitochondrial DAMPs in the pathogenesis of COPD and discussed the therapeutic potential of targeting DAMPS and their associated signaling pathways and receptors (47). EVs, a general term for the nanoscale lipid bilayer vesicles released by virtually all cells upon activation, injury, or apoptosis, are key mediators of intercellular communication and alter the activity of peripheral or distant lung structural cells and associated immune cells to perform a variety of functions (48). Exposure of endothelial cells, epithelial cells, macrophages, neutrophils, and T lymphocytes to CS increase the release of EVs, which promote inflammation, injury, and apoptosis and are involved in the early development of COPD (49-52). It was found that cell-free mitochondrial DNA (mtDNA) levels were both elevated in the plasma of patients with COPD and in the serum of CS-induced emphysema mice. Cell culture revealed that exposure to sublethal doses of CS decreased mitochondrial membrane potential, increased oxidative stress, triggered mtDNA release from EVs, and dysregulated mitochondrial dynamics (53). Studies are continuing to delve into the molecular biology of mitochondria and its connection to COPD.

The co-occurrence and cluster analysis of keywords revealed that COPD and mitochondrial-related research over the last 27 years can be divided into the four main categories: (I) respiratory muscle factors, including skeletal muscle, muscle dysfunction, sarcopenia, exercise, endurance training, etc.; (II) airway factors, including airway epithelial cells, airway endothelial cells, airway smooth muscle, and airway hyperresponsiveness, etc.; (III) mitochondrial factors, including mitochondrial dysfunction, dynamics, and mtDNA, etc.; and (IV) biological mechanism studies, including CS, oxidative phosphorylation, oxidative stress, ROS, inflammation, autophagy, apoptosis, senescence, and EVs, etc. Studies in the 2 most recent years tended to focus on autophagy, EVs, and mitochondrial dysfunction mediated by ROS and inflammation, indicating that research into COPD is gradually moving toward unraveling the biological mechanisms underlying the apparent phenomena.

Bibliometric analysis is a novel scientific approach that combines mathematical and statistical methods (54) and which can be used to overview the various aspects of articles and provide valuable references and recommendations. There were several strengths to present analysis. First, this study provided a visual, empirical, and clear characterization of the current research on COPD and mitochondria. Second, the study objectively revealed some of the relevant problems in this field, such as the lack of cooperation among most of researchers and institutions and uneven geographical distribution of academic research. Finally, our findings enable researchers interested in this field to easily apprehend the current research trends and hotspots to accurately formulate future research directions and strategies. The conclusions of this study will assist researchers interested in this field and help them to make further progress and engage more collaboratively in this field.

However, there are limitations in this study that should be mentioned. First, we only used the Web of Science Core Collection to carry out this bibliometric analysis, and non-SCI journals were excluded, within which there may be many publications related to COPD and mitochondria. The lack of inclusion of other database resources might have yielded incomplete results. In addition, we only included English-language articles from the Web of Science Core Collection database. Literature published in other language or databases were not included, which might have introduced a certain degree of bias in the results of this study.

Conclusions

Overall, we found an upward trend in both the annual publication number and the annual citations for articles on COPD and mitochondria. The United States, the United Kingdom, the Netherlands, Germany, Ireland, and Italy were active and influential in this research field. China had a high output but relatively low impact. There was more academic communication between countries than between institutions. A growing number of researchers are becoming engaged in the research in this field, but collaboration remains relatively fragmented. The most recent research has generally centered on autophagy, EVs, and mitochondrial dysfunction. More convincing studies, as well as exploration of mechanisms, are needed to promote the development of future research into mitochondria and COPD. We look forward to elucidating more novel and effective interventions for COPD.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-777/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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