


Relationship Between COPD and GERD: A Bibliometrics Analysis

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Purpose: A growing body of evidence links chronic obstructive pulmonary disease (COPD) to gastroesophageal reflux disease (GERD). In spite of the lack of understanding of the specific cause-effect relationship between COPD and GERD, GERD has been shown to be a significant predictor of acute exacerbations of COPD. In this study, we examined the evolution of the relationship between COPD and GERD over the past decades and provided valuable insights into this topic.

Methods: The Web of Science Core Collection (WoSCC) was searched since its inception until 19 August 2022 to obtain publications related to COPD and GERD. The data was analyzed in Microsoft Excel (version 2021), HisCite (version 2.1), Scimago Graphica (version 1.0.23), VOSviewer (1.6.17), and CiteSpace (version 5.8.R3).

Results: We extracted 545 documents from the WoSCC database. Since 2002, there have been rapid increases in publications. Among countries and institutions, the United States and the University of Manchester were most prolific. The most cited journal was Chest, while Respiratory Medicine had the most publications. Among 2870 related authors, Hasenfuss, Gerd, Lange, Peter, and Martinez, Gerd were the top 3 contributing authors in this field. Aside from “gastroesophageal reflux disease” and “chronic obstructive pulmonary disease”, the terms “quality of life”, “cough”, and “inflammation” were frequently occurred in the title and abstract of articles. Keywords co-occurrence overlay visualization indicated that “refractory chronic cough” was hot topics in recent years.

Conclusion: Research on COPD and GERD has flourished, and its content topics have become more in-depth over time. In the future, this hot topic deserves more attention.

Keywords: chronic obstructive pulmonary disease, gastroesophageal reflux disease, knowledge graph, disease connections

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive condition in which the airways are inflamed, and airflow is limited in a nonreversible manner.¹ There is a high likelihood of acute exacerbations, which increase the risk of COPD morbidity and mortality and contribute to worsening quality of life.² It has been shown that COPD is increasing in prevalence, particularly among people aged 65 and older.³ Comorbid conditions may complicate the clinical presentation of COPD and impact mortality and morbidity.

A normal physiological occurrence, gastroesophageal reflux (GER) is influenced by the integrity of the gastroesophageal junction. Symptoms of gastroesophageal reflux disease (GERD) result from the reflux of gastric contents.⁴ Approximately 33% of the general population has this condition, which can either be esophageal or extraesophageal in nature.⁵ A number of factors have been proposed as contributing to GERD, including increased compliance of the gastroesophageal junction.⁶ Importantly, it appears that chronic cough associated with GERD is becoming more common as GER itself becomes more prevalent.

There is a long history of recognition of the likelihood of an interaction between COPD and GERD due to their high prevalence.⁷⁻⁹ GERD may aggravate COPD's clinical status, while mechanical changes caused by COPD may exacerbate GERD's severity. It is therefore crucial to understand the relationship between the two conditions and the potential

consequences of their co-occurrence. Bibliometrics analysis is a quantitative method for evaluating research characteristics and trends within a specific period of time by analyzing published academic literature. With this approach, we can identify the research hotspots and emerging trends associated with a specific field. In this study, the overall status of COPD and GERD research was analyzed using bibliometrics.

Materials and Methods

Data Sources and Search Strategy

The literature search was performed using Web of Science Core Collection (WoSCC) with no specified starting date, but up to 19 August 2022. We limited our search to English-language literatures, and [Table 1](#) details our search strategy. A total of 591 records were retrieved, and we examined only two types of documents: articles and reviews. As a result, 545 retrieval records were analyzed. The flow chart of literature screening is shown in [Figure 1](#).

Data Analysis

The WoSCC was used to obtain the information needed, such as the number of publications per year and the number of articles published per country/region, institution, journal, and author. A further evaluation of the scientific impact of a journal was based on the impact factor (IF) and quartiles of the journal categories in the 2021 Journal Citation Reports (JCR). We presented the data in tables or charts using Microsoft Excel (version 2021) and Origin software (version 2021).

VOSviewer and Citespace are bibliometric visualization tools that can help analyze the current state of scientific research and detect its frontiers.^{10,11} In this study, VOSviewer and Citespace were used to perform (1) countries/regions and institutions co-authorship, (2) authors co-authorship and co-citation, (3) journals citation and co-citation, (4) keywords co-occurrence, (5) citation-burst analysis of references.

History of Cite (HisCite, version 2.1) is an analysis software developed by Garfield for analyzing citation maps.¹² Generally, it is used to illustrate relationships between different pieces of literature within a field of study. The software can locate the important literature and depict the field's developmental process. This study used the HisCite software to analyze GERD's development in COPD. In this study, we used the HisCite software to analyze the developmental process of the relationship between COPD and GERD.

We also used the Scimago Graphica tool (version 1.0.23) to create collaboration networks between institutions and countries/regions.

Since this was a bibliometric analysis, no approval was required from the Internal Review Board.

Results

Analysis of Publications

The development profile of a field can be reflected in annual publications. [Figure 2](#) shows a general upward trend in this field. In spite of a brief decline phase, publication numbers in this field have exploded since 2002. Researchers have increasingly focused on the relationship between COPD and GERD.

Analysis of Collaborations

Five hundred and forty-five documents on COPD and GERD have been co-authored by 1085 institutions from 50 countries/regions. [Tables 2](#) and [3](#) list the top 10 most productive countries/regions or institutions. Our study indicated that

Table 1 Search Strategy

Rank	Search Phrases	Result
#1	(((TS=(gastroesophageal reflux)) OR TS=(GERD)) OR TS=(GORD)) OR TS=(heartburn)) OR TS=(esophagitis)) OR TS=(oesophagitis)	87,426
#2	(TS=(chronic obstructive pulmonary disease)) OR TS=(COPD)	143,504
#3	#1 AND #2	591

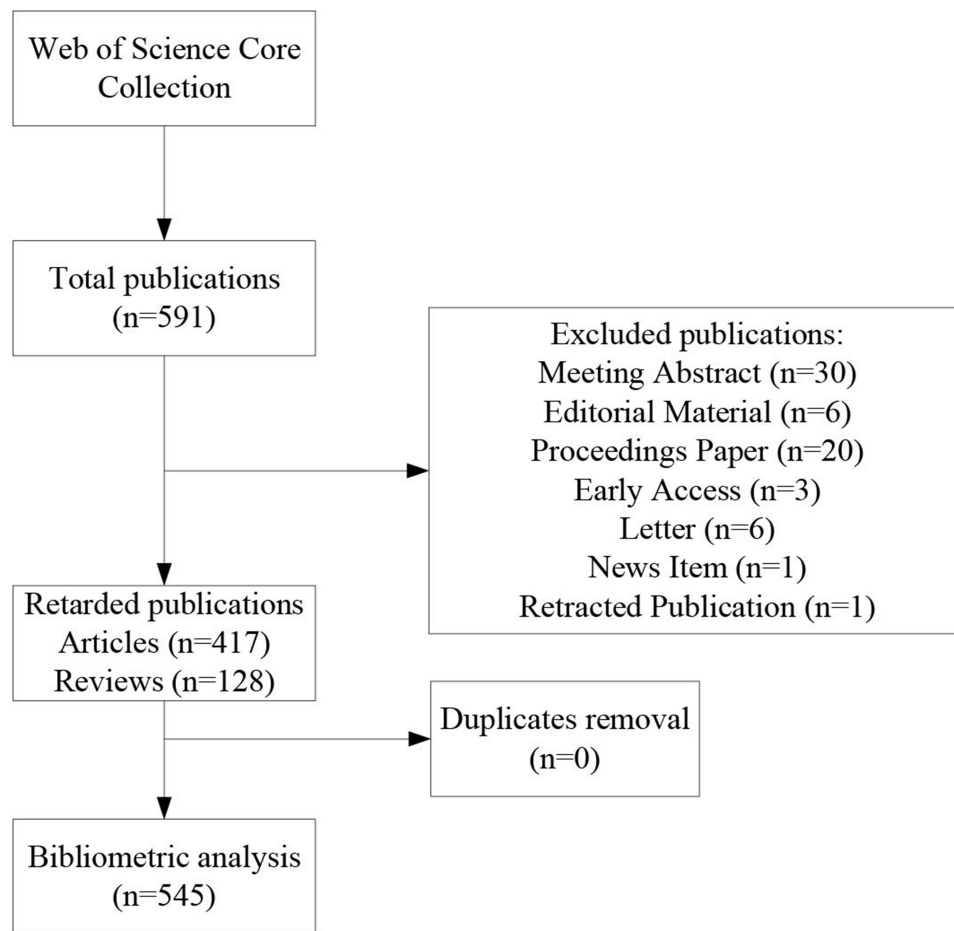


Figure 1 The flowchart of literature selection.

United States (158, 28.99%) was the most productive country, followed by United Kingdom (46, 8.44%), Germany (35, 6.42%), Japan (28, 5.14%), and Italy (27, 4.95%). The most active affiliate was Univ Manchester (16, 2.94%), followed by Univ Michigan (13, 2.39%), Mayo Clin (12, 2.20%), Univ Copenhagen (12, 2.20%), and Brigham & Womens Hosp (11, 2.02%). Our analysis of the total link strength of countries/regions and organizations identifies the United States and Brigham & Womens Hosp as the most influential in this field.

Figures 3 and 4 show the cooperation maps for each country/region and institution. The size of each node correlates with the number of documents, while the link line width and color reflect the degree of cooperation between them. It is readily apparent that the United States works closely with a number of countries, but the United Kingdom is the most important. Furthermore, many research institutions, including Brigham & Womens Hosp, Univ Manchester, and Temple Univ, cooperated actively.

Analysis of Journals

There were 283 journals that published the documents included. The majority of the top ten relevant journals (Table 4) had IF above 3 and these journals were classified in the top two quartiles (Q1 and Q2): Respiratory Medicine (N = 28, IF = 4.582, JCR = Q2), Chest (N = 24, IF = 10.262, JCR = Q1), International Journal of Chronic Obstructive Pulmonary Disease (N = 21, IF = 2.893, JCR = Q2), European Respiratory Journal (N = 11, IF = 33.795, JCR = Q1), Respiratory Research (N = 11, IF = 7.162, JCR = Q1).

The co-citation analysis of journals is concerned primarily with the relationship between the journals, which reveals whether a journal acts as a bridge in this field.¹³ As can be seen from Table 4, there were two academic journals with more than 2000 citations, one is Chest (IF = 10.262) and the other is American Journal of Respiratory and Critical Care Medicine (IF = 30.528). The co-citation relationship between Chest and other journals is clearly demonstrated in Figure 5.

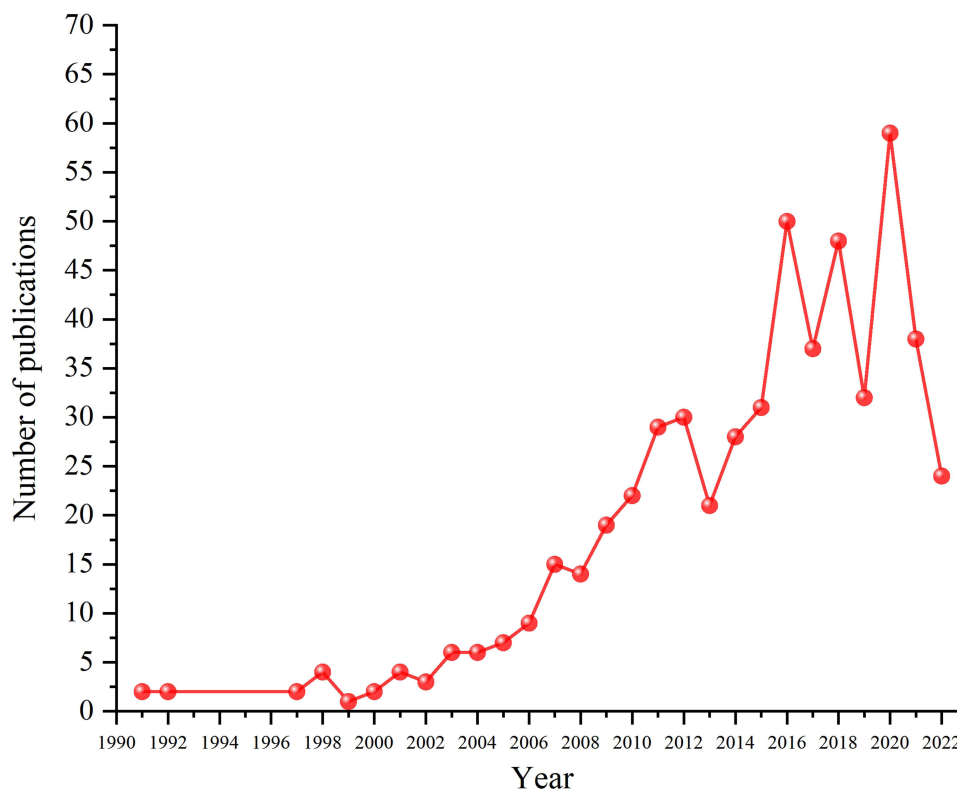


Figure 2 Annual trends in publications.

Analysis of Authors

In total, 2870 authors contributed to this field. [Table 5](#) lists the top 10 authors who contributed and were cited the most, with 6 authors working in the Univ Manchester. Hasenfuss, Gerd (12, 2.20%), Lange, Peter (11, 2.02%), and Martinez, Gerd (11, 2.02%) are the top three most prolific authors. This field has been the subject of many academic teams, as shown in the author collaborative map ([Figure 6](#)). Author co-citation can reveal highly influential scholars. A list of the 10 most co-cited scholars is presented in [Table 5](#). As far as citations are concerned, Irwin, *RS* ranked first, with 156 citations, followed by Raghu, G (citations = 140), Morice, AH (citations = 103), Hurst, JR (citations = 99), and Terada, K (citations = 94).

Table 2 The 10 Countries/Regions with the Highest Number of Outputs and the Highest Degree of Cooperation

Rank	Country/Region	Counts (%)	Co-Authorship Country/Region	Total Link Strength
1	United States	158 (28.99%)	United States	24
2	United Kingdom	46 (8.44%)	United Kingdom	19
3	Germany	35 (6.42%)	Sweden	9
4	Japan	28 (5.14%)	Germany	8
5	Italy	27 (4.95%)	Spain	7
6	China	19 (3.49%)	Brazil	6
7	Australia	18 (3.30%)	Italy	5
8	Canada	18 (3.30%)	Australia	4
9	South korea	16 (2.94%)	Japan	3
10	China Taiwan	16 (2.94%)	Canada	3

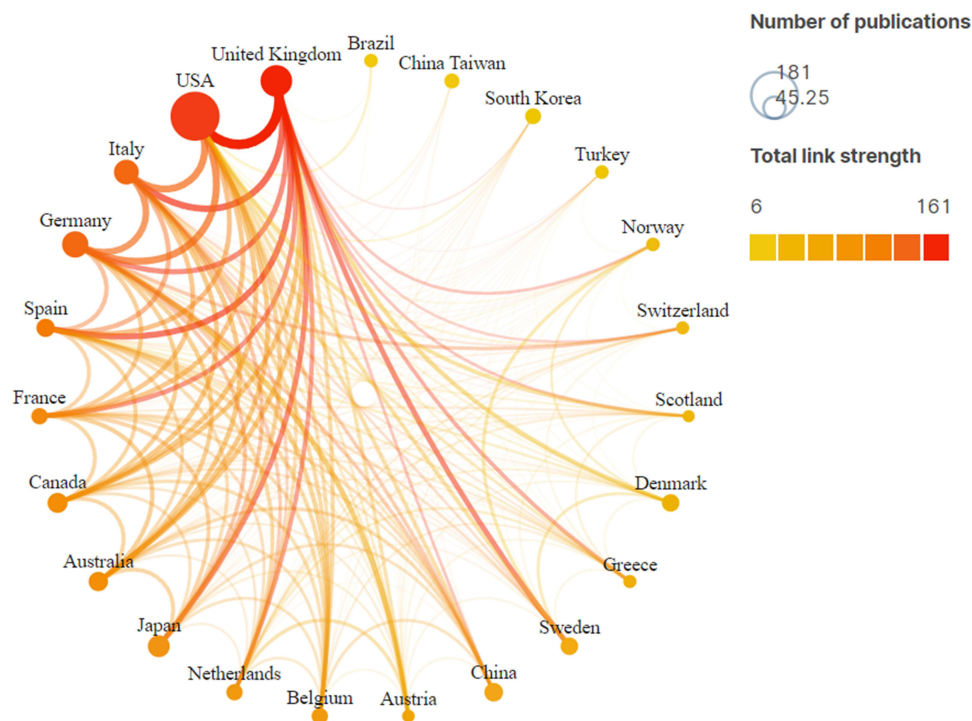
Table 3 The 10 Institutions with the Highest Number of Outputs and the Highest Degree of Cooperation

Rank	Institution	Counts (%)	Co-Authorship Institution	Total Link Strength
1	Univ Manchester	16 (2.94%)	Brigham & Womens Hosp	61
2	Univ Michigan	13 (2.39%)	Univ Manchester	59
3	Mayo Clin	12 (2.20%)	Temple Univ	58
4	Univ Copenhagen	12 (2.20%)	Univ Hosp	51
5	Brigham & Womens Hosp	11 (2.02%)	New York Presbyterian Hosp	50
6	Hannover Med Sch	10 (1.83%)	Univ Marburg	46
7	Kings Coll London	10 (1.83%)	Univ Barcelona	45
8	Univ Hosp	10 (1.83%)	Mcgill Univ	45
9	Ewha Womans Univ	9 (1.65%)	Univ British Columbia	45
10	Haukeland Hosp	8 (1.47%)	Univ Modena & Reggio Emilia	45

Keywords Co-Occurrence Analysis

The keywords in an article indicate the topic of the article, and they can be used to identify research hotspots and frontiers within a field. A co-occurrence map of 62 high-frequency keywords (more than 10 times) was constructed using VOSviewer software (Figure 7). The top 30 keywords associated with COPD and GERD are presented in Table 6. Aside from “gastroesophageal reflux disease” and “chronic obstructive pulmonary disease”, the terms “quality of life”, “cough”, and “inflammation” frequently occurred in the abstract and title of articles.

In VOSviewer, keywords were colored based on the average time they appeared in the document. We can find the research hotspots over time in a specific field based on the average time of keywords appearance. Using a co-occurrence

**Figure 3** Countries/regions collaboration map.

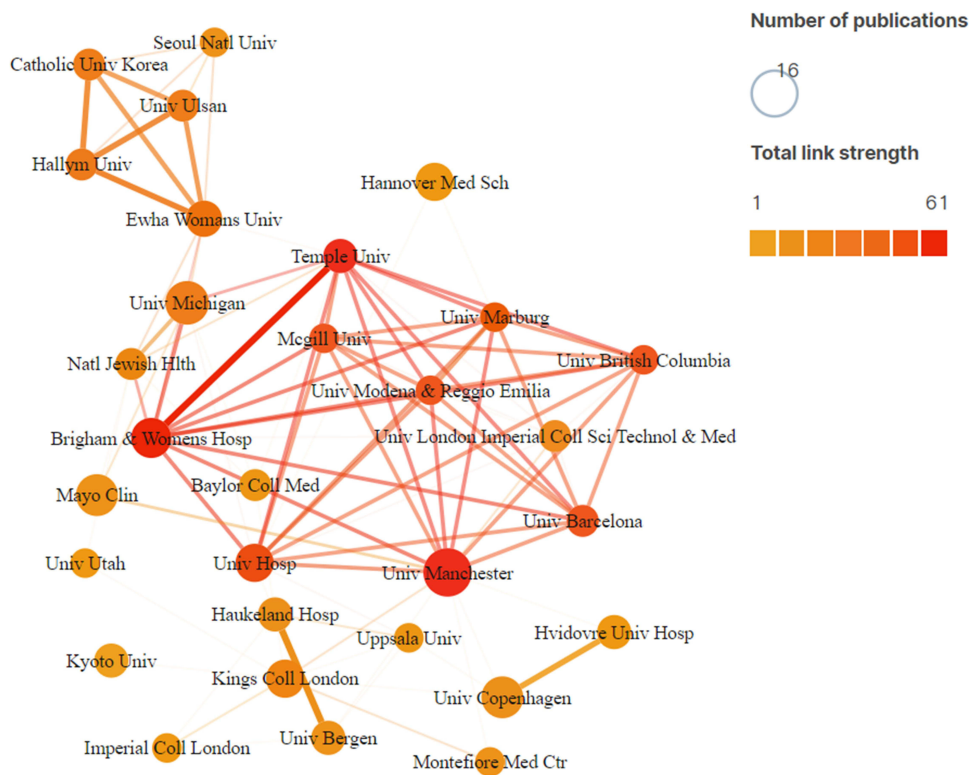


Figure 4 Institutions collaboration map.

overlay visualization, Figure 8 shows the top 15 keywords from 1991 to 2022. In comparison to yellow keywords, blue keywords appeared earlier. Among these keywords, “refractory chronic cough”, “chronic rhinosinusitis”, and “adults” generated the most interest in recent years.

Table 4 The Top Ten Journals and Co-Cited Journals

Rank	Journal	Count (%)	Total Citations	IF (2021)	JCR	Co-Cited Journal	Total Citations	IF (2021)	JCR
1	Respiratory Medicine	28 (5.14%)	615	4.582	Q2	Chest	2442	10.262	Q1
2	Chest	24 (4.40%)	2094	10.262	Q1	American Journal of Respiratory and Critical Care Medicine	2408	30.528	Q1
3	International Journal of Chronic Obstructive Pulmonary Disease	21 (3.85%)	651	2.893	Q2	European Respiratory Journal	1849	33.795	Q1
4	European Respiratory Journal	11 (2.02%)	2268	33.795	Q1	Thorax	1298	9.102	Q1
5	Respiratory Research	11 (2.02%)	465	7.162	Q1	New England Journal of Medicine	884	176.079	Q1
6	BMC Pulmonary Medicine	10 (1.83%)	168	3.32	Q2	Respiratory Medicine	806	4.582	Q2
7	Lung	10 (1.83%)	138	3.777	Q3	Journal of Allergy and Clinical Immunology	545	14.29	Q1

(Continued)

Table 5 The Top Ten Authors and Co-Cited Authors

Rank	Author	Count (%)	Co-Cited Author	Citation
1	Hasenfuss, Gerd	12 (2.20%)	Irwin, RS	156
2	Lange, Peter	11 (2.02%)	Raghu, G	140
3	Martinez, Gerd	11 (2.02%)	Morice, AH	103
4	Andreas, Stefan	9 (1.65%)	Hurst, JR	99
5	Martinez, Fernando J.	9 (1.65%)	Terada, K	94
6	Vestbo, Jorgen	9 (1.65%)	Casanova, C	80
7	Han, Meilan K.	8 (1.47%)	Harding, SM	75
8	Lee, Jin Hwa	8 (1.47%)	Mokhlesi, B	71
9	Ringbaek, Thomas	8 (1.47%)	Birring, SS	70
10	Criner, Gerard J.	7 (1.28%)	Rascon-Aguilar, IE	70

significantly associated with exacerbation risk.¹⁵ The later study reviewed the possible causes of GERD in COPD, such as gastroesophageal mechanisms, respiratory mechanisms, respiratory medications, and non-COPD factors.¹⁶

Burst Detection of References

In over time, burst detection of references reflects a shift in research focus. Among the top 25 references (Figure 10), the article authored by Baumeler et al¹⁷ with a burst strength of 4.92 and another article authored by Broers et al¹⁸ with a burst strength of 3.93 were frequently cited in recent years. Despite receiving acid-suppressive therapy, Baumeler et al found that patients with stable COPD were still highly vulnerable to frequent and severe exacerbations. As discussed by Broers et al, there has been a contradictory and inconsistent response to anti-reflux therapy when considering pulmonary outcomes. They call for further research to identify subgroups of COPD patients who would benefit from anti-reflux therapy. Obviously, scholars are taking a more active interest in the relationship between COPD and GERD and examining treatment options.

Discussion

Over the past decade, the role of GERD in the pathogenesis of chronic pulmonary diseases has garnered a lot of attention. There is a possibility that GERD and chronic respiratory disease are bidirectional, or that the relationship can be caused by changes in latent variables that are correlated. GERD drives respiratory disease, while respiratory mechanics contribute to GERD, making it important to better understand their relationship and possible consequences.

General Information

The current analysis indicates that the relationship between COPD and GERD has not received much attention before 2002. However, the rise in annual publications from 2002 to the present shows that this field of study is a hotspot and continues to draw interest.

Using a map analysis of the distribution of countries/regions and institutions, it is evident that COPD and GERD research has been conducted in many countries and regions. With 158 publications, the United States has contributed the most to this field, followed by the United Kingdom with 46 and Germany with 35. Again, from the Table 2, the United States ranked highest in total link strength, suggesting that articles published in the United States may be more influential. Globally, over 1000 institutions study the relationship between COPD and GERD. The most productive institution was Univ Manchester, according to Table 3. It is likely that the contributions of scholars at this institution, such as Lange, Peter, Martinez, Gerd, Martinez, Fernando J, Vestbo, Jorgen, Ringbaek, Thomas, and Criner, Gerard J, have contributed to this result. Although some of these institutions have collaborated closely, others have not, as seen in Figure 4. Thus, the breadth and depth of cooperation between countries and institutions with similar research topics should be strengthened, and this field should be further developed jointly.

In Table 4, it is evident that most of the top 10 journals are from JCR Q1 or Q2, and most of them have IFs higher than 3.0, showing that this field has relatively high levels of research. In our analysis, articles with high co-citations were

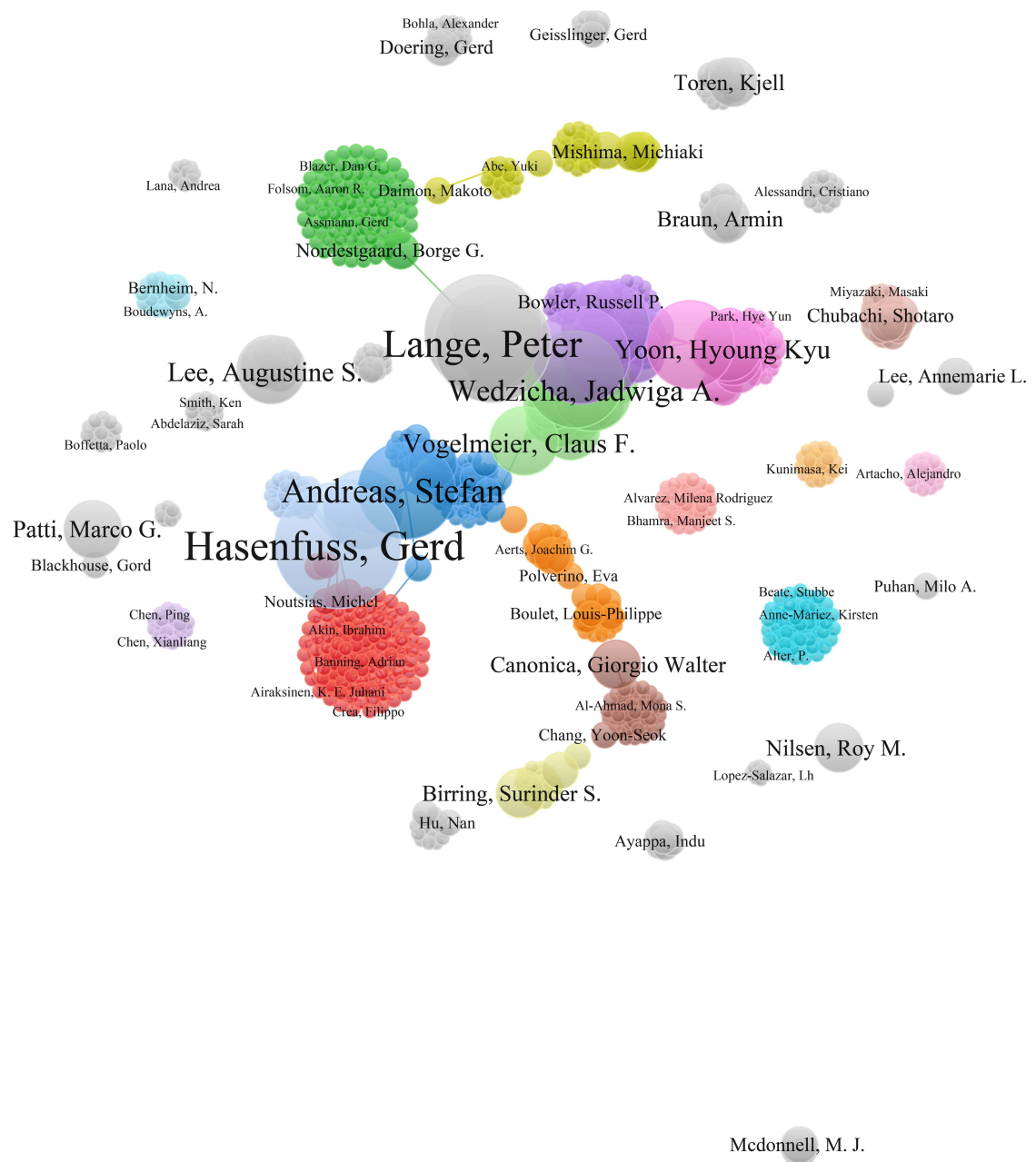


Figure 6 Inter-author collaborative map.

published in multiple prestigious journals, such as *Chest*, *American Journal of Respiratory and Critical Care Medicine*, *European Respiratory Journal*, *New England Journal of Medicine*, and *Lancet*. Due to COPD and COPD's potential impact, top scholars have shown a keen interest in the topic. It is important, therefore, to pay more attention to these journals in order to acquire new research advancements or discoveries.

Among numerous scholars in this field, Hasenfuss, Gerd, Lange, Peter, and Martinez, Gerd have contributed the most. It is apparent from the network of author cooperation that, while many academic teams have been formed in this field, there is little cooperation. Efforts should be made by all academic teams to improve scholarly communication, investigate the link between COPD and GERD, and promote its rapid development. A particular note of note is Irwin, RS, the most

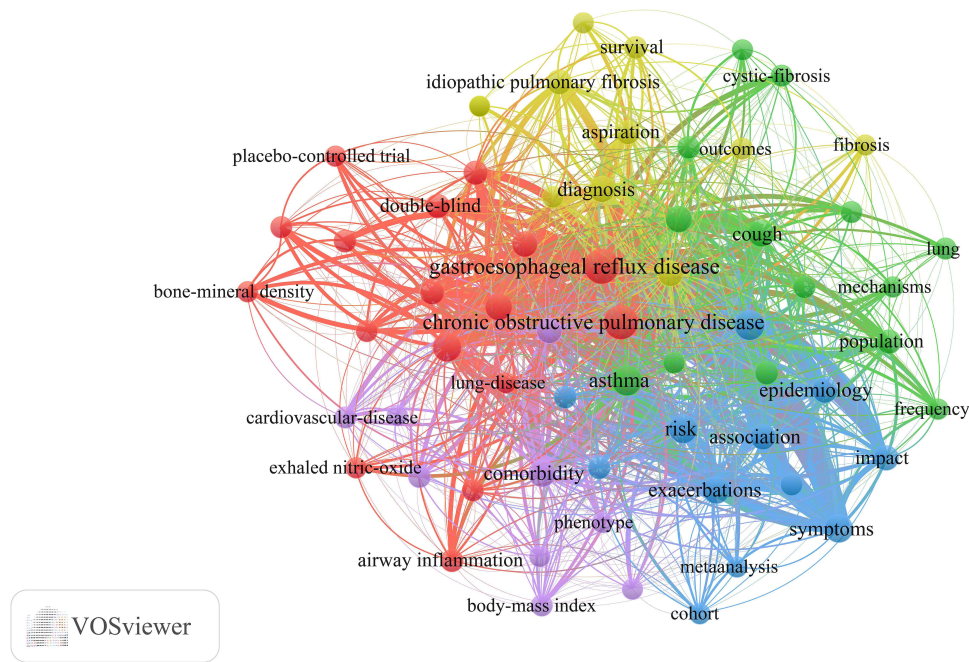


Figure 7 Keywords co-occurrence visualization map.

co-cited author in this field who has made significant contributions to this field. An analysis of diagnosis and treatment algorithms of acute, subacute, and chronic cough in adults was carried out by Irwin et al.¹⁹

Hotspots and Frontiers

Keyword analysis can provide valuable information about research frontier in a particular field, which is the most valuable aspect of bibliometrics analysis. The top frequency keywords related to COPD and GERD, including quality of

Table 6 The Top 30 Keywords Related to COPD and GERD

Rank	Keyword	Count	Total Link Strength	Rank	Keyword	Count	Total Link Strength
1	Gastroesophageal reflux disease	286	1150	16	Smoking	18	99
2	Chronic obstructive pulmonary disease	262	1033	17	Airway inflammation	17	73
3	Quality of life	89	409	18	Bronchiectasis	17	82
4	Exacerbations	64	325	19	Positive airway pressure	17	69
5	Obstructive sleep apnea	60	287	20	Cardiovascular-disease	15	68
6	Cough	54	264	21	Chronic rhinosinusitis	14	68
7	Inflammation	43	201	22	Cystic-fibrosis	14	58
8	Mortality	41	174	23	Body-mass index	13	70
9	Idiopathic pulmonary fibrosis	31	147	24	Inhaled corticosteroids	13	62
10	Lung-function	29	130	25	Lung	13	40
11	Acute exacerbation	28	153	26	Pneumonia	13	65
12	Survival	20	71	27	Allergic rhinitis	12	71
13	Obesity	19	89	28	Bone-mineral density	12	61
14	Air-flow obstruction	18	76	29	C-reactive protein	12	46
15	Depression	18	87	30	Health	12	79

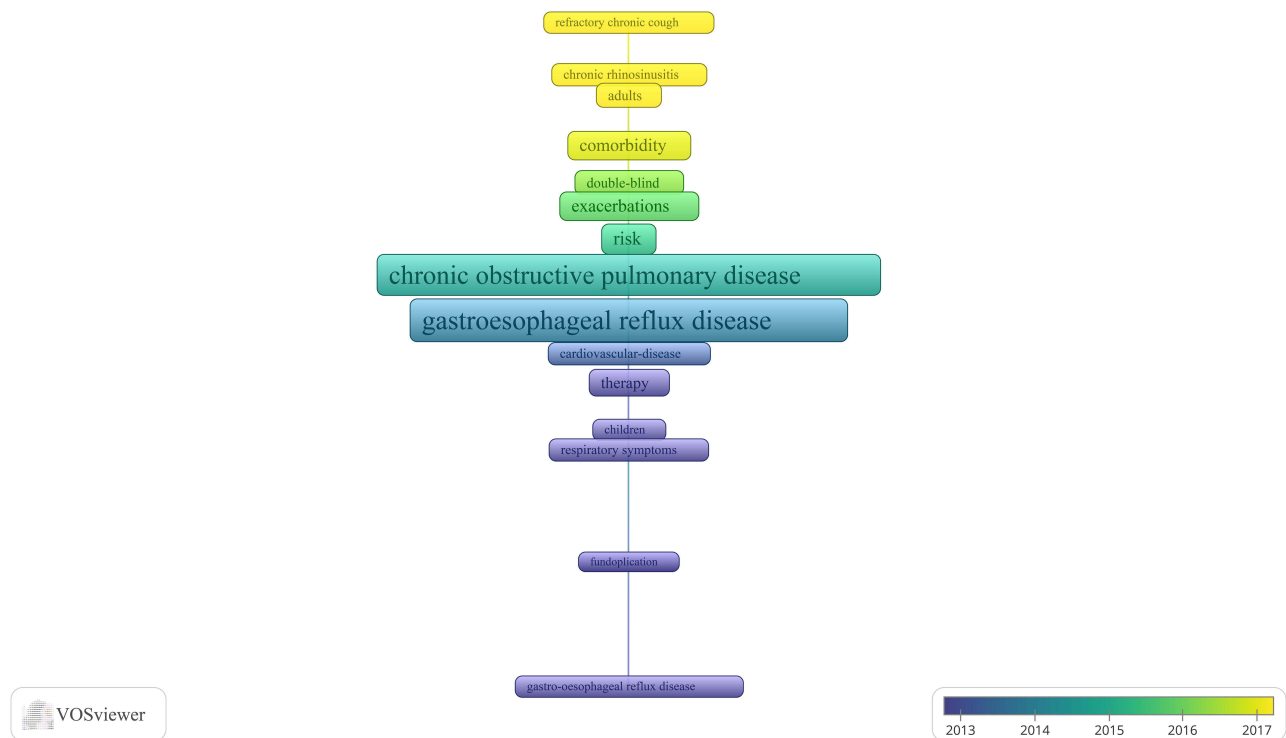


Figure 8 Keywords co-occurrence overlay visualization map.

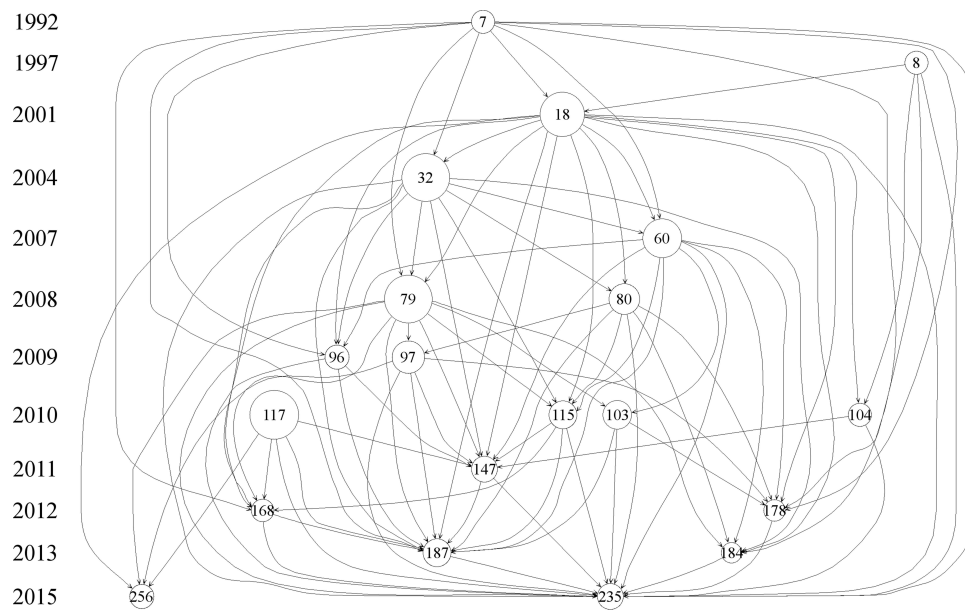


Figure 9 Network of the top 20 articles in literature on COPD and GERD based on the LCS.

life, cough, inflammation, obstructive sleep apnea, obesity, depression, smoking, cardiovascular-disease, and inhaled corticosteroids, are shown in Table 6. According to Figure 8, research in this area has been shifting over time, with recent attention being paid to refractory chronic cough and chronic rhinosinusitis.

COPD comorbidities may negatively impact health-related quality of life (HRQOL). Some studies with a larger group of COPD patients reported poorer HRQOL and more anxiety and depression when self-reported GERD was present.^{20–22}

Table 7 The Detailed Information of the Top 20 Articles in Literature on COPD and GERD Based on the LCS

Rank	ID	Title	LCS
1	117	Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease.	70
2	79	Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation.	69
3	32	Increased gastro-oesophageal reflux disease in patients with severe COPD.	67
4	18	Increased prevalence of gastroesophageal reflux symptoms in patients with COPD.	59
5	60	High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD.	45
6	97	A Randomized, Single-Blind Study of Lansoprazole for the Prevention of Exacerbations of Chronic Obstructive Pulmonary Disease in Older Patients.	32
7	80	Relationship Between Gastroesophageal Reflux Disease and COPD in UK Primary Care.	28
8	103	Abnormal Swallowing Reflex and COPD Exacerbations.	25
9	115	Association of Gastroesophageal Reflux Disease Symptoms with Exacerbations of Chronic Obstructive Pulmonary Disease.	23
10	187	Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis.	23
11	147	Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire	20
12	235	Gastroesophageal reflux disease in COPD: links and risks.	20
13	96	Incidence and treatment results of laryngopharyngeal reflux in chronic obstructive pulmonary disease.	18
14	256	Associations between gastro-oesophageal reflux, its management and exacerbations of chronic obstructive pulmonary disease.	18
15	7	Esophageal function and gastroesophageal reflux during sleep and waking in patients with chronic obstructive pulmonary disease	17
16	8	Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans.	17
17	104	Prevalence of gastroesophageal reflux disease in patients with asthma and chronic obstructive pulmonary disease	17
18	168	Association of Gastroesophageal Reflux Disease Symptoms with Stable Chronic Obstructive Pulmonary Disease.	15
19	178	Esophageal Motility Pattern and Gastro-Esophageal Reflux in Chronic Obstructive Pulmonary Disease.	14
20	184	Study of gastro-oesophageal reflux disease in patients with mild-to-moderate chronic obstructive pulmonary disease in India.	13

Increased anxiety is known to exacerbate GERD symptoms by increasing acid production.²³ Anxiety is common in COPD, and this may contribute to GERD.

A change in respiratory mechanics may contribute to GERD. Severe hyperinflation requires increased respiratory muscle inspiratory effort to overcome the increased inspiratory load at high lung volume. During severe hyperinflation, respiratory muscles must exert increased inspiratory effort to overcome an increased inspiratory load. It is well known that transient relaxation of the lower esophageal sphincter (LES) is one of the primary causes of GERD. In this case, increased negative pressure enhances the pressure gradient between the thorax and abdomen, which affects the tone of the LES and makes reflux more likely.^{24,25} During COPD exacerbations, airflow reductions and coughing can exacerbate this pressure gradient.

Vagally mediated reflex bronchoconstriction may influence the severity of COPD by GERD. Bronchoconstriction is innervated by the autonomic innervation between the esophagus and the tracheobronchial tree. Airway irritation and inflammation caused by esophageal acid in the distal esophagus trigger the release of bronchoconstrictors.²⁶

There has also been evidence that certain comorbidities can increase the risk of GERD, including cardiac disease and sleep apnea.²⁰ A higher intrathoracic pressure during an apneic episode is accompanied by a higher transdiaphragmatic pressure, which causes the gastric contents to migrate up the esophagus.²⁷ Additionally, repetitive pressure changes can lead to LES insufficiency.²⁷

COPD patients with a higher body mass index (BMI) are at greater risk of GERD, and this risk increases as the BMI increases.^{20,28} Having a high BMI affects the contour of the diaphragm and thus affects breathing elastically.²⁹ Hence, GERD may become more likely when respiratory-related factors are combined with a high BMI for people with COPD.

An association has been found between smoking and a reduction in LES tone. As a result of nicotine-induced relaxation of the circular muscle of the LES, there is an increase in acid exposure in the upright position.^{30,31} In addition, nicotine also interferes with esophageal clearance. A high smoking index has been shown to increase the severity of

Top 25 References with the Strongest Citation Bursts

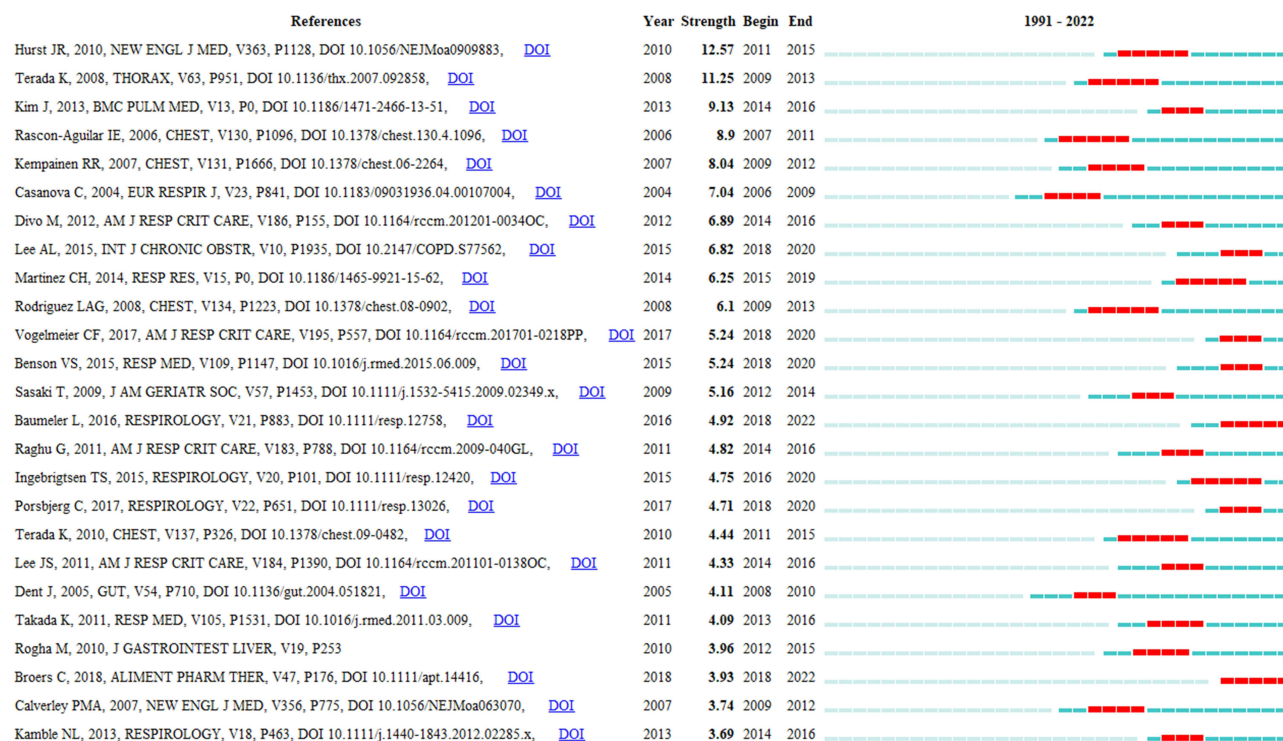


Figure 10 Burst detection of references.

GERD in COPD patients.²⁸ Due to smoking being a risk factor for GERD as well as a leading cause of COPD, smoking may contribute to GERD in COPD.³²

Corticosteroids, anticholinergics, and theophylline preparations are some of the respiratory medications considered to be associated with GERD.^{20,33,34} Although these medications may reduce LES pressure or esophageal motility, their specific impact on GERD risks varies. In addition, the correlation between GERD and respiratory medications may also reflect the severity of lung disease rather than a physiological reaction to these medications. In COPD, further investigation is needed into the cause-and-effect relationship between respiratory medications and GERD.

In our study, some limitations exist. First, the study retrieved only literature from WoSCC database, so there is a risk of overlooking related studies, resulting in biased results. Our second limitation was that we only included reviews and articles in English, which could lead to bias. Additionally, the downloaded data may also have omitted some important details since it is not in full text.

Conclusion

Our study identified 545 publications on COPD and GERD, revealing influential countries, institutions, and authors that made significant contributions to this field. Moreover, we concentrated on specific topics in order to investigate research trends. According to our analysis, quality of life, cough, and inflammation have been the research frontier in this field. In summary, COPD and GERD are subjects of ongoing research.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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