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Relationships Between Obstructive Sleep Apnea and Cardiovascular Disease: A Bibliometric Analysis (2010-2021)

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Obstructive sleep apnea (OSA) is a common disease that can lead to intermittent hypoxia, increased sympathetic overdrive, and excessive oxidative stress, and eventually lead to cardiovascular/cerebrovascular diseases and metabolic disorders. The prevalence of OSA is reported to be higher in people with certain cardiovascular diseases (CVD). Therefore, the relationship between OSA and CVD has been gradually favored by researchers.

Material/Methods: Data were downloaded from the Web of Science Core Collection database. Citespace was used to remove duplicated data and construct knowledge visual maps.

Results: A total of 7047 publications were obtained. The USA was the largest contributor as well as an important player in the cooperation network between nations. The leading institution was the Mayo Clinic. Our study ultimately identified the top 5 hotspots and 4 research frontiers in this field. Top 5 hotspots were: the specific types of obstructive sleep apnea-related cardiovascular and metabolic co-morbidities, the curative effects of CPAP on these co-morbidities, the specific mechanisms of co-morbidities, the importance of polysomnography on OSA and its co-morbidities with CVD, and the prevalence of OSA and its co-morbidities with CVD in particular populations. The top 4 frontiers were: the relationship between OSA and resistant hypertension, the molecular mechanisms of OSA and its co-morbidities with CVD, specific medications and treatment guidelines for the co-morbidities, and the mainstream research methods in this field.

Conclusions: This study provides insight and valuable information for researchers and helps to identify new perspectives concerning potential collaborators and cooperative institutions, hot topics, and research frontiers in this field.

Keywords: **Bibliometrics • Cardiovascular Diseases • Sleep Apnea Syndromes • Sleep Apnea, Obstructive**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/933448>

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Background

Obstructive sleep apnea (OSA) is a disease characterized by repeated episodes of upper airway closure during sleep, which results in recurrent oxyhemoglobin desaturation and sleep fragmentation. OSA can lead to intermittent hypoxia, increased sympathetic overdrive, and excessive oxidative stress, and can eventually lead to cardiovascular/cerebrovascular diseases and metabolic disorders. Recent epidemiological studies have shown that the prevalence of OSA is about 14% in men and 5% in women [1]. OSA is an independent risk factor for many cardiovascular diseases (CVD), and is also associated with obesity [2], insulin resistance [3], hypertension [4], arrhythmias [5], stroke [6], coronary artery disease [7,8], heart failure [9], and atherosclerosis [10]. Patients with CVD are susceptible to OSA-related stress factors and their associated adverse cardiovascular outcomes. The prevalence of OSA is reported to be higher in people with certain cardiovascular diseases. For example, the prevalence of OSA is 40% in patients with hypertension and rises to 90% in patients with refractory hypertension [11]. About 30–60% of OSA patients have a complicated arrhythmia, including sinus arrest, second-degree atrioventricular block, atrial flutter, atrial fibrillation, premature atrial (ventricular) contraction, ventricular (supraventricular) tachycardia, and even sudden cardiac death [12,13]. Likewise, the prevalence of OSA is conservatively estimated to be 12% to 53% in patients with HFpEF and 40% in patients with HFrEF [14]. Despite the high incidence of OSA in patients with various types of CVD, OSA is often underrecognized and undertreated in the treatment of CVD. The relationship between OSA and CVD has been gradually favored by researchers.

Bibliometric analysis contains co-word analysis and cluster analysis. It is used to present the knowledge structure, identify international collaborations and geographic distributions, as well as explore development tendency via quantitative analysis [15,16]. Citespace is a Java-based bibliometric visualization tool created by Chaomei Chen (University of Dressel). It uses programming methods to help visualize the research countries, institutions, and authors [17]. The most notable feature is that Citespace can identify research hotspots and frontiers by analyzing co-cited references and burst terms. In this review, we used Citespace to present the current research situation and future trends of OSA and CVD in a visual way, aiming to provide direction for related researchers.

Material and Methods

Search Strategies

We collected the data from the Web of Science Core Collection (WoSCC) database. These data were download on Apr 26th

(2021). We used the following topics for retrieval: (heart OR *cardi* OR “blood pressure” OR hypertension OR coronary OR “atrioventricular block”) AND (“obstructive sleep apnea” OR “obstructive sleep apnea hypopnea syndrome” OR OSAHS). Indexes: SCI-expanded, CCR-expanded, IC. Timespan: 2010–2021. Only articles and reviews were included, while other types of publications were excluded.

Data Collection and Analysis

The full record and cited references were exported from WoSCC in plain text format. First, we imported the data into Citespace (Version 5.7 R5, University of Dressel, Chaomei Chen) to remove duplication. After that, we constructed knowledge visual maps by using Citespace [17,18].

Parameters Setting

Timespan: 2005–2021 (Slice Length=1). Selection Criteria: Top 50. Term source: all selected. Node type: check one at a time. Selection criteria: 50. Pruning: pathfinder. Visualization: cluster view static, display merged network.

Analytical Method

The nodes in the map represent the countries, authors, institutions, or keywords. The link lines between the nodes indicate the collaboration relationship. The wider the line, the stronger the relationship between the 2 nodes. The size of the node represents the number of studies published. The purple ring represents centrality of more than 0.1, which means the element is considered relatively important.

Results

Search Results

The initial search resulted in 8226 publications after duplicates had been removed. These publications included articles (5678), reviews (1369), editorial materials (224), proceedings papers (89), news item (1), letters (152), book chapters (48), retracted publications (2), meeting abstracts (790), early access (86), correction (11), and retraction (1). A total of 7047 publications met the inclusion criteria – 5678 articles and 1369 reviews.

Annual Publication Output

A total of 382 papers were published in 2010. The annual publication output increased sharply from 2010 to 2014 and showed a fluctuating upward trend from 2015 to 2019. A total of 747 papers were published in 2020, which is the year with the highest number of papers. To date, a total of 178 papers

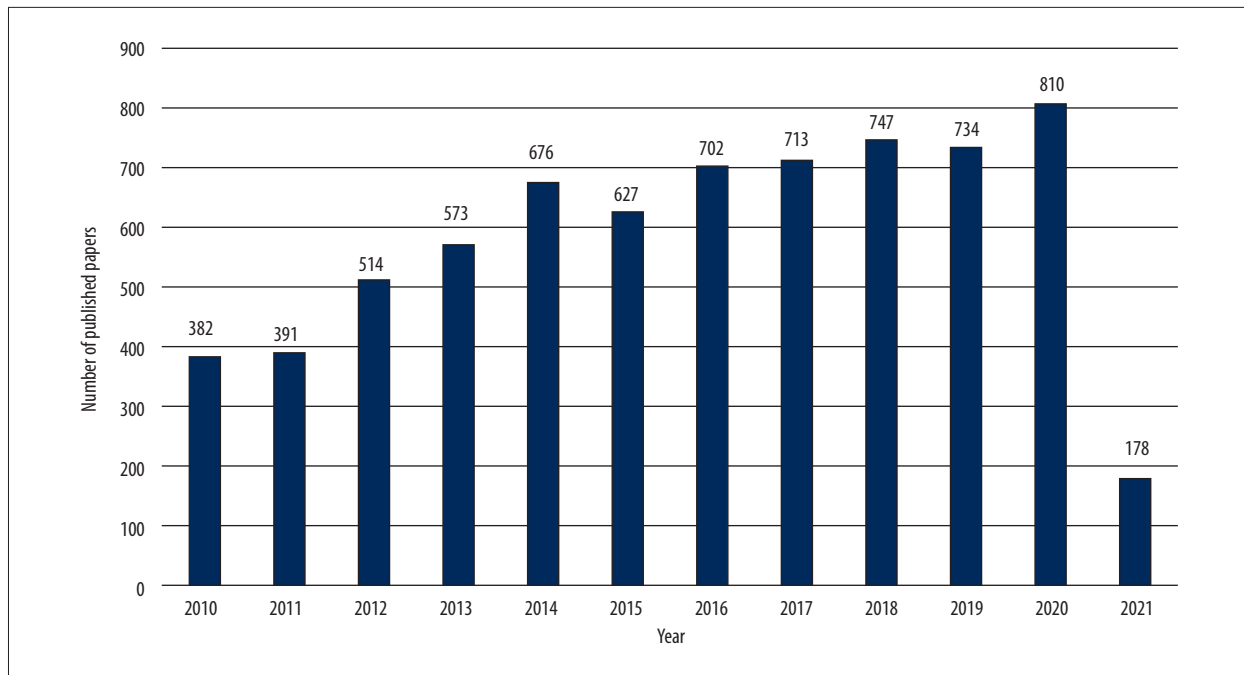


Figure 1. The number and linear growth trends of publications (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

Table 1. The top 10 productive journals.

Rank	Journals	Impact Factor	Number of published papers
1	Sleep and Breathing	2.816	449
2	Journal of Clinical Sleep Medicine	4.062	278
3	Sleep Medicine	3.490	233
4	Sleep	5.841	161
5	PLoS One	3.240	148
6	Chest	9.411	109
7	Journal of Sleep Research	3.980	83
8	Obesity Surgery	4.120	73
9	Respiratory Physiology Neurobiology	1.931	66
10	American Journal of Respiratory and Critical Care Medicine	21.405	63

have been published in 2021, and the number is expected to grow (Figure 1). The results showed that the field of the relationship between OSA and CVD had gradually developed in the past decade.

Analysis of Journals

The top 10 most productive journals are listed in Table 1. According to the results, the journal *Sleep and Breathing* published the most articles and came in first place. This journal focuses on different pathological respiratory states during sleep and covers a wide range of sub-topics. The journal has published worldwide studies of OSA on prevalence,

etiology, pathogenesis, and treatment. The *American Journal of Respiratory and Critical Care Medicine*, with the highest impact factor of 21.405, paid special attention to cardiovascular consequences of OSA and published many relevant articles. The majority of these journals are in the field of sleep, with the rest distributed among journals related to cardiothoracic, respiratory, nervous and metabolic diseases. There is still currently no specific journal on OSA and cardiovascular co-morbidities.

Analysis of Countries, Institutions, and Authors

The co-occurrence map provides valuable information and helps researchers to identify the cooperative relationship. A total of

Table 2. Top 10 countries and institutions in terms of frequency.

Rank	Count	Centrality	Country	Rank	Count	Centrality	Institution
1	2223	0.08	USA	1	154	0.05	Mayo Clin
2	707	0.00	PR China	2	142	0.03	Harvard Med Sch
3	383	0.00	Canada	3	129	0.10	Univ Toronto
4	374	0.00	Italy	4	124	0.04	Univ Chicago
5	322	0.02	Germany	5	120	0.03	Brigham & Womens Hosp
6	316	0.04	Australia	6	118	0.05	Johns Hopkins Univ
7	298	0.00	Turkey	7	117	0.18	Univ Penn
8	290	0.13	France	8	103	0.12	Univ Pittsburgh
9	270	0.00	Japan	9	101	0.05	Harvard Univ
10	261	0.00	Brazil	10	96	0.01	Univ Sao Paulo

Table 3. Top 10 countries and institutions in terms of centrality.

Rank	Count	Centrality	Country	Rank	Count	Centrality	Institution
1	36	0.72	Austria	1	66	0.41	Univ Melbourne
2	54	0.58	Singapore	2	41	0.40	Boston Univ
3	9	0.55	South africa	3	27	0.36	Univ Hosp
4	11	0.53	Pakistan	4	43	0.33	Univ Adelaide
5	51	0.33	Denmark	5	63	0.31	Massachusetts Gen Hosp
6	21	0.29	Hungary	6	56	0.30	Beth Israel Deaconess Med Ctr
7	258	0.19	England	7	35	0.26	Univ Milano Bicocca
8	50	0.19	Finland	8	6	0.26	Virginia Commonwealth Univ
9	122	0.18	Netherlands	9	2	0.26	CIBERes
10	6	0.15	Cyprus	10	19	0.24	Flinders Univ S Australia

595 researchers from more than 97 countries and 265 institutions contributed to the 7047 articles on the research of the relationship between OSA and CVD. The top 10 countries and institutions in terms of frequency and centrality are shown in **Tables 2 and 3**, respectively. The USA (2223) and China (707) were the leading countries. The Mayo Clinic (154) and Harvard Medical School (142) were the leading institutions. Australia, Singapore, Denmark, the University of Melbourne, and Boston University have high centrality, which means active cooperation has already developed (**Figures 2, 3**). Susan Redline, David Gozal, and Jeanlouis Pepin were the most productive authors (**Table 4**). We can draw a conclusion from **Figure 4** that many authors prefer to cooperate with a relatively stable group of authors to generate several major author clusters, and each of these clusters contains more than 2 core authors.

Analysis of Co-Cited References

Analysis of co-cited references can help identify the influential publications and authors, as well as development tendency in this field. A total of 420 papers were obtained. The top 10 most co-cited references are listed in **Table 5**. Three of them reported the epidemiological information of OSA. Specifically speaking, Heinzer and Peppard found a sharp increase in the prevalence of OSA in adults from Wisconsin (USA) and Lausanne (Switzerland) over the past 20 years, and pointed out the independent associations between severity of sleep-disordered breathing and hypertension [19,20]. Senaratna made a systematic review to determine the prevalence of OSA in the general population, and mentioned that the diagnostic apnea hypopnea index (AHI) level where the treatment needs to begin can be determined based on the related morbidity/mortality profile, as in the case of hypertension and hyperlipidemia [21]. Three

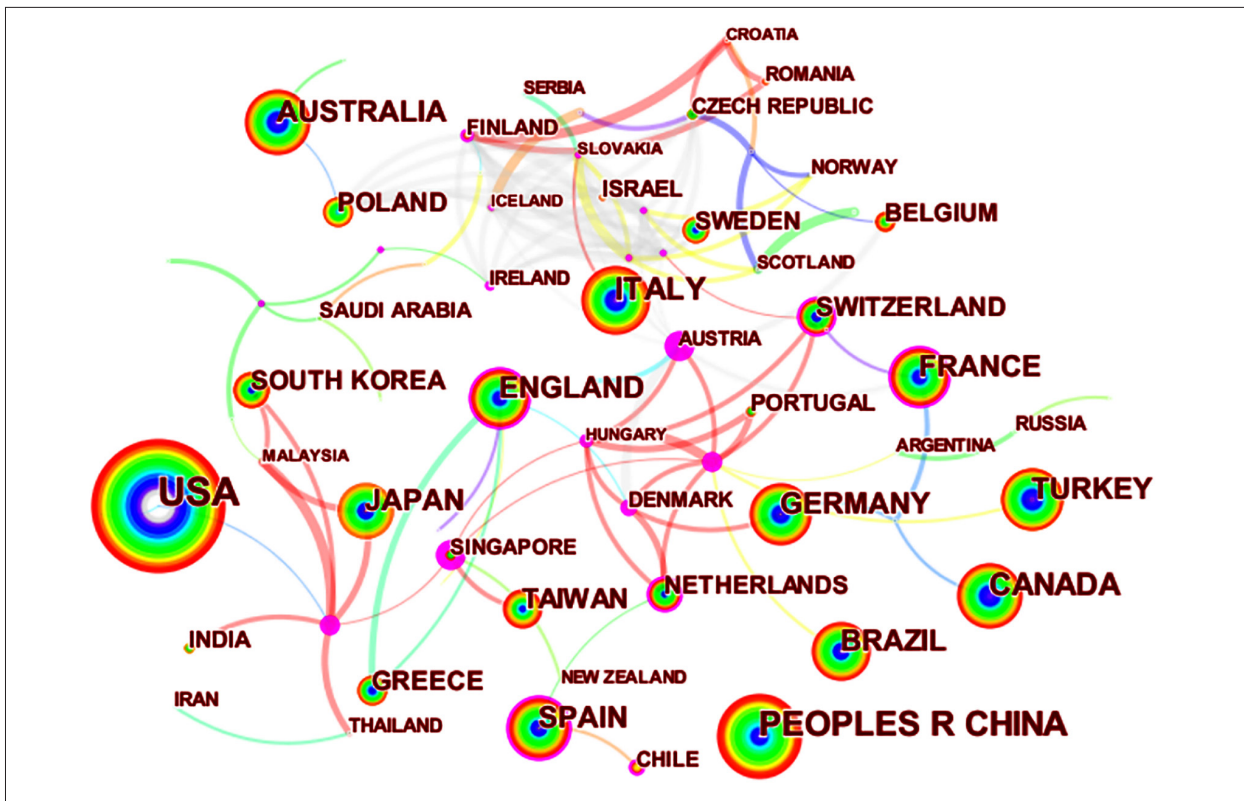


Figure 2. Co-occurrence map of countries (N97=, E=157) (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

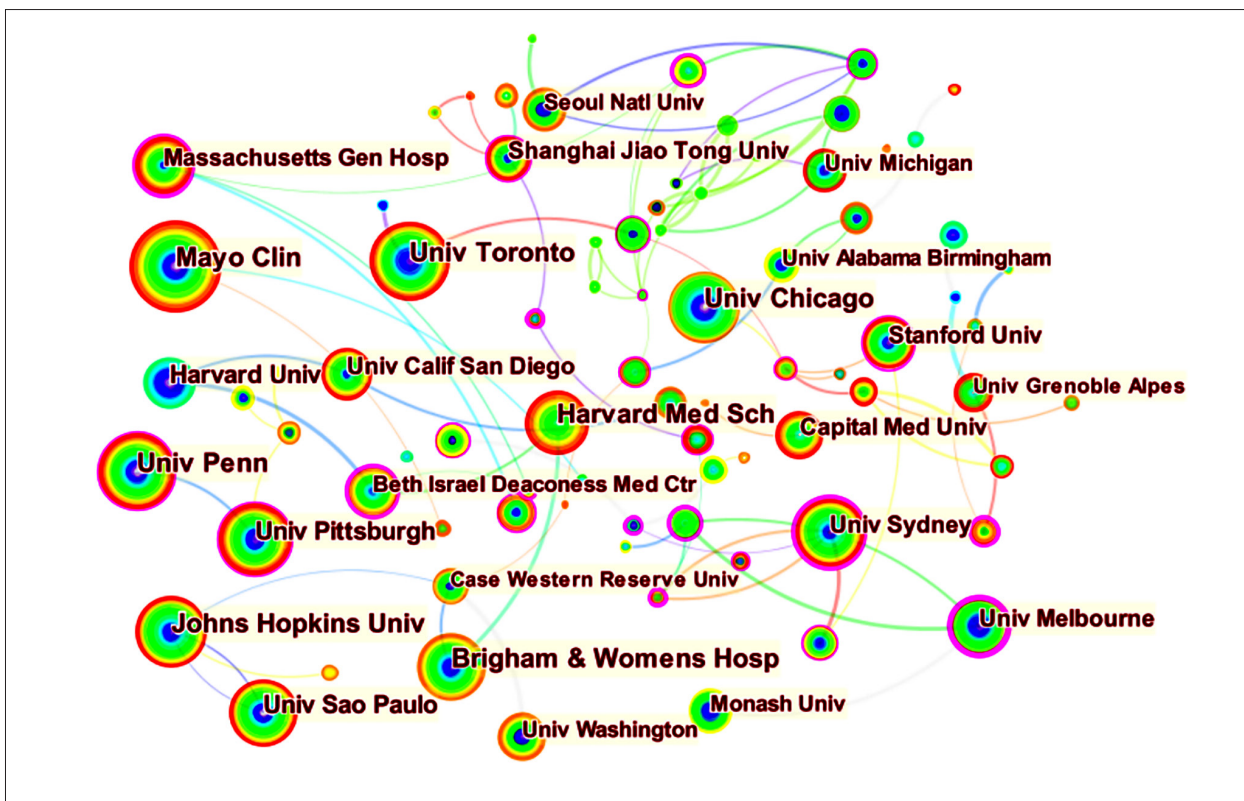


Figure 3. Co-occurrence map of institutions (N=265, E=369) (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

Table 4. Top 10 most productive authors.

Rank	Count	Centrality	Year	Author
1	68	0.03	2011	Susan Redline
2	68	0.02	2011	David Gozal
3	60	0.07	2011	Jeanlouis Pepin
4	54	0.23	2011	Atul Malhotra
5	52	0.04	2011	Luciano F Drager
6	51	0.13	2011	Ferran Barbe
7	51	0.12	2011	Virend K Somers
8	45	0.02	2011	Renaud Tamisier
9	44	0.03	2011	Geraldo Lorenzifilho
10	35	0.07	2015	Yongxiang Wei

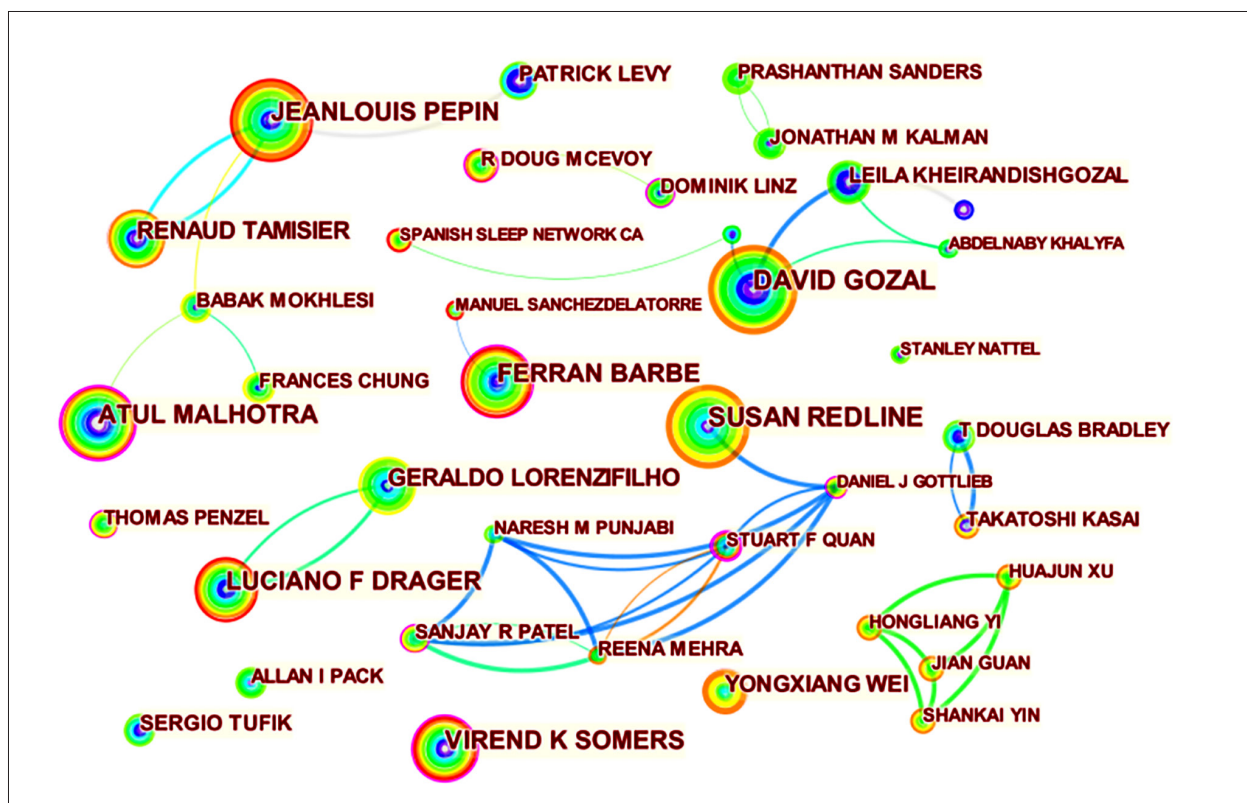


Figure 4. Co-occurrence map of authors (N=596, E=1514) (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

other studies emphasized the relationship between OSA and CVD. Gottlieb carried out a prospective study and found that OSA is associated with an increased risk of incident heart failure in community-dwelling middle-aged and older men [22]. Javaheri made a review to generalize the clinical cardiovascular consequences and molecular signatures of OSA concerning cardiocerebrovascular disorders [23]. The paper “Adult obstructive sleep apnea”, published in the Lancet, was considered to be the first comprehensive review in this field. The

authors highly summarized the diagnosis, definitions, pathophysiology, risk factors, consequences, and management of OSA. Then they cited a large number of examples to illustrate the relationship between OSA and other CVD, such as hypertension, and pointed out that the effect of continuous positive airway pressure (CPAP) on CVD in OSA patients is equivocal [24]. Similarly, the SAVE study, a large international multi-center randomized controlled study conducted by McEvoy, showed that CPAP did not prevent cardiovascular events in patients

Table 5. Top 10 co-cited references in terms of frequency.

Rank	Count	Centrality	Year	Author	Title	Journal
1	346	0.04	2013	Peppard PE	Increased prevalence of sleep-disordered breathing in adults	Am J Epidemiol (IF=4.894, 2020)
2	272	0.01	2016	McEvoy RD	CPAP for prevention of cardiovascular events in obstructive sleep apnea	New Engl J Med (IF=91.244, 2020)
3	210	0.01	2015	Heinzer R	Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study	Lancet Resp Med (IF=30.701, 2020)
4	162	0.00	2012	Berry RB	Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine	J Clin Sleep Med (IF=4.060, 2020)
5	142	0.05	2010	Gottlieb DJ	Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study	Circulation (IF=29.690, 2020)
6	141	0.04	2017	Kapur VK	Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine Clinical Practice Guideline	J Clin Sleep Med (IF=4.061, 2020)
7	119	0.13	2017	Javaheri S	Sleep apnea: Types, mechanisms, and clinical cardiovascular consequences	J Am Coll Cardiol (IF=24.094, 2020)
8	118	0.05	2010	Redline S	Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study	Am J Resp Crit Care (IF= 21.405, 2020)
9	113	0.04	2017	Senaratna CV	Prevalence of obstructive sleep apnea in the general population: A systematic review	Sleep Med Rev (IF=11.063, 2020)
10	104	0.00	2014	Jordan AS	Adult obstructive sleep apnoea	Lancet (IF=79.320, 2020)

with moderate-to-severe OSA and established cardiovascular disease [25]. Another study showed a significant positive association between ischemic stroke and AHI in men, in which each 1-unit increase in OAHl in men was estimated to increase stroke risk by 6% in the mild-to-moderate range [26]. In addition, 2 important guidelines were also obtained through our analysis: one is an update of the “2007 AASM Manual for the Scoring of Sleep and Associated Events” by the American Academy of Sleep Medicine (AASM), and the other is a clinical practice guideline for diagnostic testing for adult OSA [27,28]. These findings suggest that we still need to deepen clinical understanding of the relationship between OSA and CVD, and also emphasized the importance of treatment of OSA, especially in patients with complicated CVD. Clinical practice urgently needs therapeutic measures that have definite and significant positive effects on cardiovascular events.

A document co-citation analysis produced 10 co-citation clusters, which were marked by indexed terms from their citations. The results showed Modularity $Q=0.8333 >0.3$ and

Silhouette $=0.9504 >0.7$, which demonstrated that the cluster structure was significant, and the results were accurate, reasonable, and reliable (Figure 5). Cluster #0, labeling “hypertension”, was the largest cluster, consisting of 36 references, followed by “mandibular advancement device” (cluster #1), “atrial fibrillation” (cluster #2), and “acute coronary syndrome” (cluster #3).

Analysis of Keywords and Burst Terms

Keywords represent the main content of research. Keyword occurrence analysis provides a reasonable description of research hotspots (Figure 6). The top keywords were “obstructive sleep apnea”, “positive airway pressure”, “hypertension”, “association”, “blood pressure”, “cardiovascular disease”, “risk factor”, “prevalence”, “risk”, and “obesity” (Table 6).

Finally, we used Citespace to obtain burst terms that can represent research frontiers by counting the frequency and growth rate of keywords in this field. The larger the burst value, the

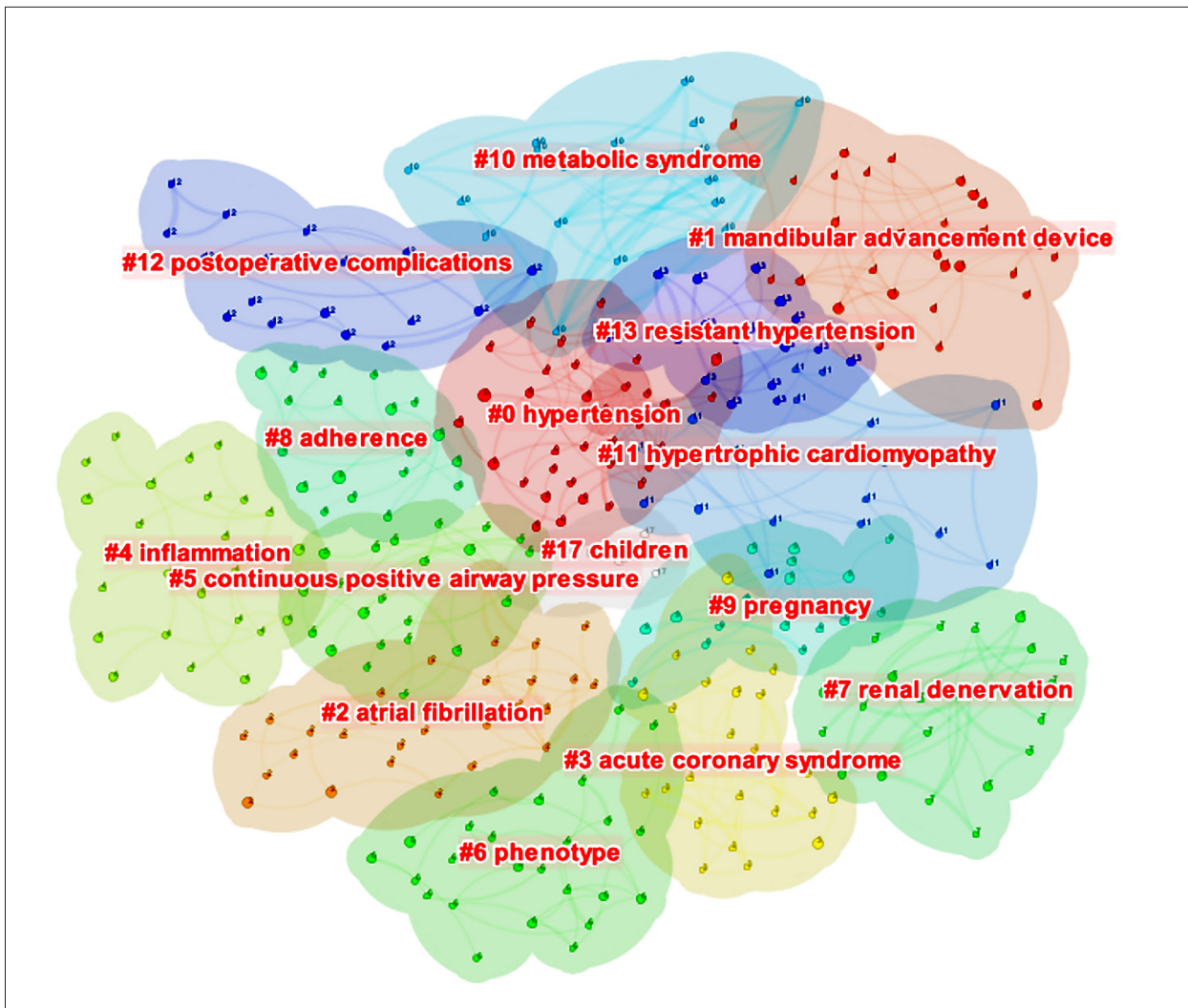


Figure 5. The clustered network map of co-cited references (N=420, E=579, Modularity Q=0.8333, Silhouette=0.9504) (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

greater the innovation of the research outcomes. Of the top 20 burst terms with the strongest citation bursts in this field (Figure 7), we were particularly interested in those keywords that related to cardiovascular health, including “coronary heart diseases”, “myocardial infarction”, “cardiovascular risk factor”, “heart health”, “resistant hypertension”, and “cardiovascular event”.

Top 5 Hotspots and 4 Frontiers

The analyses of keywords and clusters reflect the core themes and hot contents in this field. Burst terms represent the indicators of frontier or emerging trends. We summarize the top 5 research hotspots as follows: the specific types of obstructive sleep apnea-related cardiovascular and metabolic co-morbidities, the curative effects of CPAP on these co-morbidities, the specific mechanisms of co-morbidities, the importance of

polysomnography on OSA and its co-morbidities with CVD, and the prevalence of OSA and its co-morbidities with CVD in particular populations. The top 4 frontiers were: the relationship between OSA and resistant hypertension, the molecular mechanisms of OSA and its co-morbidities with CVD, specific medications and treatment guidelines for the co-morbidities, and the mainstream research methods in this field.

Discussion

Research Progress in OSA and CVD

Gastaut [29] and Jung [30] found the existence of sleep apnea in 1965. Christian Guilleminault, the founding editor of the journal SLEEP, proposed the concept of OSAHS in 1978. Since 2000, many relevant guidelines have been developed

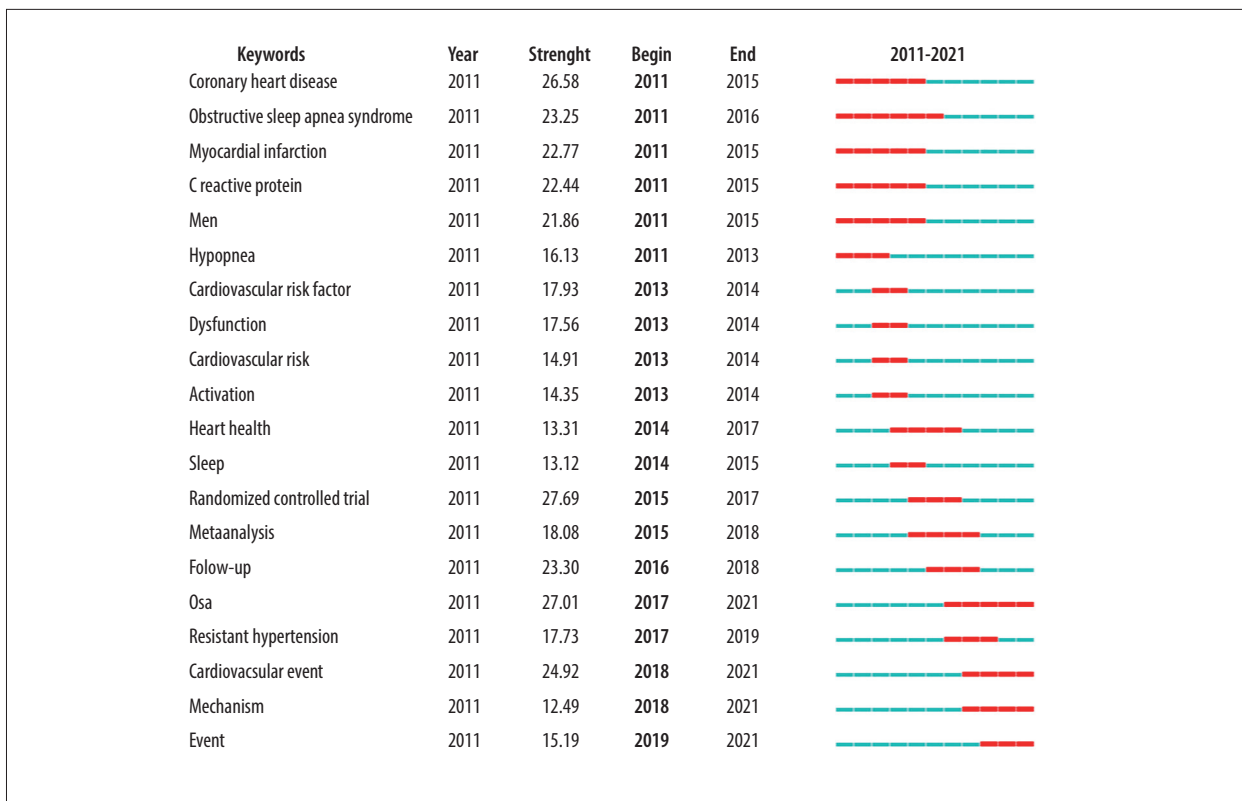


Figure 7. Top 20 keywords with the strongest citation bursts in original articles (Citespace, Version 5.7 R5, University of Dressel, Chaomei Chen).

Hot Issues in OSA and CVD Research

1. Obstructive sleep apnea-related cardiovascular and metabolic co-morbidities, including hypertension, atrial fibrillation, acute coronary syndrome, hypertrophic cardiomyopathy, heart failure, stroke, metabolic syndrome, and obesity, are a major concern for the prognosis of OSA as well as the complexity of OSA integrated care [33]. Recently, some studies have reported the association between OSA and some special diseases, like myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) and cognitive decline [8,34].
2. CPAP, the primary treatment modality for OSA [35], is highly effective at alleviating symptoms and improving quality of life, and also has positive effects on endothelial function [36] and insulin sensitivity [37]. However, many researchers hold the opinion that it has limited effect on co-morbidities.
3. The specific mechanisms related to OSA, such as hypoxia [38], inflammation [39], oxidative stress [40,41], and insulin resistance [42], are also one of the current research hotspots.
4. Polysomnography has been widely adopted as the criterion standard for diagnosing OSA, and can also be used for scales of severity.

5. Researchers are also concerned about the prevalence of OSA in particular populations, such as pregnant women and children. Studies have shown that OSA is associated with gestational hypertension, gestational diabetes, and severe maternal morbidities including venous thromboembolism and cardiomyopathy [43,44]. Many pediatric studies have shown an increased risk of pulmonary hypertension or right heart failure in children who were affected by severe OSA [45-47].

Frontiers in OSA and CVD Research

1. Resistant hypertension. There is an even stronger association between OSA and resistant hypertension [48]. The prevalence of OSA in patients with resistant hypertension is as high as 60% to 71% [49]. The HIPARCO randomized clinical trial showed that CPAP treatment for 12 weeks reduced the 24-h mean and diastolic blood pressure and improved the nocturnal blood pressure pattern [50]. However, further research is warranted to assess other health outcomes.
2. Mechanism. A more specific and nuanced mechanism at the molecular and cellular level is needed to illustrate issues related to the occurrence and treatment of OSA and CVD. For instance, many preclinical studies performed on different experimental models (cells, rodents, healthy volunteers) of intermittent hypoxia have emphasized the role

of hypoxia-inducible factor-1 (HIF-1) in the deleterious consequences of OSA and CVD [51-53].

3. Treatments. Deciphering the molecular and cellular pathways involved in OSA cardiovascular consequences is a priority to make new pharmacological targets available, in combination with or as an alternative to continuous positive airway pressure. In addition, developing practice guidelines for the detection and management of OSA for specific groups of people, such as pregnant women, should be put on the agenda.
4. Research methods. To date, randomized controlled trial (RCT) and meta-analysis, with cardiovascular events as outcomes, are still the mainstream research methods in OSA and CVD research.

Strengths and Limitations

To the best of our knowledge, this study is the first bibliometric analysis of publications focused on the relationship between OSA and CVD to provide direction concerning potential collaborators, hotspots, and frontiers. However, this study still has some limitations. The publications were all written in English and were retrieved only from WOSCC, which may not be comprehensive. Some authors' names in the literature are given by using the same abbreviation, which may cause misidentification by Citespace.

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Conclusions

Our study ultimately identified 5 hotspots and 4 research frontiers in this field through the analysis of co-cited references, clusters, keywords, and burst terms.

Department and Institution Where Work Was Done

This work was done at the Graduate School of Beijing University of Chinese Medicine, Beijing, China

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The authors would like to express their appreciation to Professor CM Chen, who invented Citespace, which is free to use.

Ethics Approval

These data were downloaded from the WoSCC database and do not involve human subjects, animals, or any related specimens. Therefore, no ethics approval was required.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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