# Bibliometric Analysis of Literature on Acute Respiratory Distress Syndrome Treatments Published Between 2000 and 2019

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**Research**

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# Abstract

**Background:** Acute respiratory distress syndrome (ARDS) is a common and extensively researched condition, and treatment modalities are continuously being developed and improved. Although the literature on ARDS treatment is vast, there have not been any bibliographic analyses examining trends in this area. We aimed to systematically evaluate the literature on ARDS treatments published between 2000 and 2019, from the perspective of bibliometrics.

**Methods:** Literature retrieval was performed in PubMed and in the Web of Science Core Collection, and analyzed for publication and temporal trends. CiteSpace was used to perform co-occurrence analysis for institutions, and reference co-citation analysis for research topics. Burst keyword detection was used to predict future areas of research interest in the field.

**Results:** A total of 13,933 articles were retrieved. The journal *Critical Care Medicine* published the largest number of articles (956, 6.86%). The University of Toronto was affiliated with the most publications (574, 4.28%) and had the highest degree of betweenness centrality, indicating extensive inter-institution collaboration. The papers on ARDS treatment published between 2000 and 2019 were grouped into 10 major clusters, 3 of which indicated recent activity ("acute lung injury," "long-term outcome" and "extracorporeal membrane oxygenation"). Fifteen burst keywords/terms were identified, including extracorporeal membrane oxygenation, meta-analysis and oxidative stress.

**Conclusions:** On the basis of the literature published in the preceding 20 years, the exploration of ARDS treatment is an ongoing concern. Extracorporeal membrane oxygenation was an active focus of research in this field. It and oxidative stress are likely to become major topics of research interest in the near future. Meta-analysis will be a popular method in analyzing the efficacy of ARDS treatments.


# Background

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by non-cardiogenic pulmonary edema, diffuse endothelial injury and bilateral pulmonary infiltrates, which can be devastating to critically ill patients in the intensive care unit, and places a burden on the healthcare system. The LUNG SAFE study reported that 23.4% of patients receiving mechanical ventilation were ARDS cases and that the hospital mortality rate in patients with severe ARDS was 46.1% [1]. The first report of the syndrome was published in 1967 [2], and discussions of how best to define the new clinical entity have been going on for many decades, from the American-European Consensus Conference definition to the Berlin definition, and the same is true regarding the development of ARDS treatment. In 1969, a treatment with continuous positive-pressure breathing was proposed [3], and positive end-expiratory pressure (PEEP) therapy was evaluated in 11 ARDS patients in 1973 [4].Ventilation with a low tidal volume (6 mL/kg predicted body weight) and a plateau pressure of 30 cm of water or less was shown to improve survival in patients with ARDS [5], and these strategies are recommended in clinical practice guidelines. ARDS management strategies began to take shape, but more therapies need to be developed. Recruitment maneuvers, the technique that sustained high airway pressure for a period of time in order to expand the collapsed alveoli during mechanical ventilation, are still under debate, although they can reverse hypoxemia [6]. The findings of a recent randomized clinical trial did not support the routine use of recruitment maneuvers and titrated PEEP because of increased 28-day mortality in patients with moderate-to-severe ARDS [7]. These examples illustrate the evolution in thinking and clinical practice around the treatment of ARDS, but individual examples cannot provide a comprehensive overview of this evolution. The entire published literature on ARDS, however, contains a detailed history of this evolution in terms of: trends; leading journals in the publication of ARDS research; and the investigators and institutions behind this research, along with their interrelationships and influences.

A detailed and comprehensive overview of this nature may provide policy makers, funding agencies and researchers with important information to facilitate identification of key research topics, financial support for meaningful research and collaboration possibilities in this field. Although ARDS treatments have been reviewed [8, 9], there have not been any bibliographic analyses examining trends in topics, journals and research institutions. Recognizing the absence of such a published survey, we undertook to perform a bibliographic analysis of papers related to ARDS therapy published over the last 20 years. Bibliometric analysis is a useful method for identifying impactful authors and regions, constructing collaboration networks, and distilling key research topics in particular areas [10]. In this study, bibliometric analysis was used to achieve three goals: map the overall layout of ARDS research from the perspective of publication dates, journals, keywords and citations; identify core research institutions and their direct collaborative networks; and highlight current and potential future areas of research focus.

## Methods

# Data collection

Literature retrieval was performed in both PubMed and the Web of Science Core Collection on Aug 3, 2020. We selected “respiratory distress syndrome, adult” as a subject heading, which was combined in PubMed searches with several subheadings (therapy, diet therapy, drug therapy, nursing, prevention and control, and surgery). We then searched for ARDS-treatment articles in Web of Science using the same strategy. Both sets from the literature were merged, and duplicates were removed. Articles, reviews and letters published between 2000 and 2019, inclusive, were kept for further analysis. Figure 1 shows a flowchart of the literature retrieval strategy. More details on the retrieval process are given in Online Supplement 1. Informed consent was not necessary as our study analyzed published literature without any identifying information about participants in the research reported.

# Analysis and visualization

The identified articles were systematically analyzed using the Web of Science website and CiteSpace (5.7.R1, Chaomei Chen) [11]. Web of Science has built-in statistics tools to graph publication trends by year, language and journal. CiteSpace is a tool for visualizing and analyzing scientific literature, by constructing the knowledge structure based on citation relationship among literatures in the research field. Among the bibliometric analysis methods, we selected reference co-citation analysis [12] and analysis of institutional collaboration networks for articles published between 2000 and 2019 [13]. The indicators used in the evaluation were "modularity" and "betweenness centrality," as follows. The degree to which a network can be divided into several independent blocks is measured by modularity [14]. Its value ranges from 0 to 1, and a relatively high value means a well-structured network [15]. Betweenness centrality is a quantitative indicator of the influence of institutions, calculated as the fraction of shortest paths going through a given node that denotes an institution in the cooperative network [16]. A citation is regarded as a reasoned and solid index of scientific communication. Co-citation analysis enables the identification of the inner structure of research disciplines. A co-citation exists if two references or authors appear in the same bibliography, and is interpreted as the measure for similarity of content of the two references or authors [17]. In this study, the 50 most cited articles in successive 3-year intervals (e.g., 2000–2002, 2003–2005) were collected, and all references from each 50-article block were used to create the individual networks. Log-likelihood ratio weighting was used to analyze the contents of each cluster. "Burst keyword detection," a computing technique used to identify mutations in information, was used to determine new research foci in the field [18]. A keyword burst is characterized by the intensity of the burst and by its duration.

## Results

# Temporal distribution of papers

A total of 13,933 papers were collected for analysis. Figure 2 graphs the number of articles published by year, and indicates a general upward trend in research into ARDS treatments, from 466 articles in 2000 to 918 in 2019.

# Publication language

The articles returned in the search had been published in 15 languages. Of the 13,933 papers, 13,460 (96.61%) were published in English, 221 (1.59%) in German, 121 (0.87%) in French, 89 (0.64%) in Spanish, 15 (0.11%) in Portuguese and 27 (0.2%) in other languages.

# Core journals

A total of 1,592 scholarly journals published articles on ARDS treatment during the period of interest. The top 10 journals (Table 1) accounted for 28.1% of all documents published (3,914 articles). The journals publishing the most ARDS research were *Critical Care Medicine*, *Intensive Care Medicine*, *American Journal of Respiratory and Critical Care Medicine*, and *Critical Care*.

Table 1
The 10 journals publishing the most research articles on the treatment of acute respiratory distress syndrome

| Journal | N (%) | Country | Impact factor in 2019 |
|---|---|---|---|
| *Critical Care Medicine* | 956 (6.86%) | USA | 7.414 |
| *Intensive Care Medicine* | 601 (4.31%) | USA | 17.679 |
| *American Journal of Respiratory and Critical Care Medicine* | 479 (3.44%) | USA | 17.452 |
| *Critical Care* | 460 (3.30%) | England | 6.407 |
| *American Journal of Physiology-Lung Cellular and Molecular Physiology* | 309 (2.22%) | USA | 4.406 |
| *Respiratory Care* | 260 (1.87%) | USA | 2.066 |
| *Chest* | 254 (1.82%) | Netherlands | 8.308 |
| *Current Opinion in Critical Care* | 200 (1.44%) | USA | 2.92 |
| *Journal of Critical Care* | 200 (1.44%) | USA | 2.685 |
| *Shock* | 195 (1.40%) | USA | 2.96 |

N (%), number of articles published by the journal and percentage of the total articles assessed in this study. Country refers to the country associated with the publisher. Impact factors are derived from *Journal Citation Reports* (2019) published by the Institute for Scientific Information of the United States.

# Research institutions

The researchers who published the literature included in this study were affiliated with a total of 9,468 institutions. Table 2 lists the top 15 institutions, which accounted for 28.64% of the total articles. The University of Toronto was associated with the most publications, followed by the University of California, San Francisco, and Harvard University. Extensive collaborations were observed between institutions (Fig. 3). The University of Toronto, the University of California, San Francisco, Harvard University and the University of Washington had high betweenness centrality.

Table 2
Ranking of the 15 institutions most active in researching treatments for acute respiratory distress syndrome, based on numbers of publications

| Institution | N (%) | Betweenness centrality |
|---|---|---|
| University of Toronto | 574 (4.28%) | 0.29 |
| University of California, San Francisco | 395 (2.95%) | 0.17 |
| Harvard University | 327 (2.44%) | 0.15 |
| Massachusetts General Hospital | 257 (1.92%) | 0.12 |
| University of Pennsylvania | 237 (1.77%) | 0.07 |
| University of Sao Paulo | 229 (1.71%) | 0.04 |
| Johns Hopkins University | 228 (1.70%) | 0.07 |
| Vanderbilt University | 217 (1.62%) | 0.1 |
| University of Washington | 216 (1.61%) | 0.14 |
| University of Pittsburgh | 210 (1.57%) | 0.09 |
| University of Milan | 203 (1.52%) | 0.02 |
| University of Michigan | 201 (1.5%) | 0.03 |
| St. Michael's Hospital | 195 (1.46%) | 0.09 |
| University Colorado | 179 (1.34%) | 0.08 |
| Mayo Clinic | 170 (1.27%) | 0.03 |

N (%), number of articles and percentage of the total articles assessed in this study. Betweenness centrality is a quantitative indicator of the influence of institutions in a collaborative network of academic institutions.

# Analysis of reference co-citation

We used all references from the 50 most-cited publications in each successive 3-year grouping to construct each individual network, and then synthesized the individual networks for a total of 243,830 references. We performed reference co-citation analysis to generalize clusters and construct a knowledge map in timeline view, which grouped publications on ARDS treatment into nine major clusters (Fig. 4).

The network in this study had a modularity of 0.717, which is typically considered relatively high. We focused on the major clusters that were sorted and tagged by the number of co-cited references. A total of 10 clusters were included in the analysis (Table 3). Three of these clusters (key terms “acute lung injury,” “long-term outcome” and “extracorporeal membrane oxygenation”) have been active in recent years.

Table 3
Characteristics of co-citation clusters

| Cluster | Size[a] | Beginning year | Ending year | Activity[b] | Tag name[c] |
|---|---|---|---|---|---|
| #0 | 46 | 2001 | 2010 | inactive | ventilatory strategies |
| #1 | 38 | 2013 | 2017 | active | acute lung injury |
| #2 | 37 | 2007 | 2015 | active | long-term outcome |
| #3 | 31 | 1995 | 2002 | inactive | high-frequency ventilation |
| #4 | 27 | 2006 | 2018 | active | extracorporeal membrane oxygenation |
| #5 | 19 | 1999 | 2002 | inactive | computed tomography |
| #6 | 17 | 1996 | 1999 | inactive | inhaled nitric oxide |
| #7 | 7 | 2001 | 2004 | inactive | severe sepsis |
| #8 | 7 | 2003 | 2008 | inactive | pharmacological treatment |
| #9 | 6 | 2009 | 2012 | inactive | mesenchymal stem cell |

[a]Number of published articles. [b]Persistence of a theme over the past 5 years (yes/no). [c]Typical word assigned to represent the main content of the cluster using a log-likelihood ratio algorithm.

The timeline view of reference co-citation analysis (Fig. 4) shows that the duration of research into extracorporeal membrane oxygenation was the longest, lasting from 2006 to 2018. The use of nitric oxide in treatment was no longer a topic of research papers after 1999. Some references were included in multiple clusters, acting as a link. Table 4 lists the core articles in the main co-citation clusters.

Table 4
Core articles in the main co-citation clusters

| Cluster and tag name | Lead author | Publishing year | Theme |
|---|---|---|---|
| #4 ECMO | Peek GJ [20] | 2009 | ECMO, severe adult respiratory failure |
| #4 ECMO | Davies A [21] | 2009 | ECMO, influenza A |
| #4 ECMO | Bein T [22] | 2013 | Extracorporeal carbon dioxide removal, ultraprotective ventilation |
| #4 ECMO | Schmidt M [23] | 2013 | ECMO, outcome assessment |
| #0 Ventilatory strategies | Meade MO [25] | 2008 | Open-lung strategy, ARDS |
| #0 Ventilatory strategies | Mercat A [26] | 2008 | PEEP setting strategy, ARDS |
| #2 Long-term outcome | Briel M [29] | 2010 | Higher versus lower PEEP, ARDS |
| #2 Long-term outcome | Papazian L [35] | 2010 | Neuromuscular blocker, ARDS |
| #2 Long-term outcome | Ranieri VM [36] | 2012 | Berlin definition, ARDS |
| #2 Long-term outcome | Ferguson ND [37] | 2013 | High-frequency oscillatory ventilation, ARDS |
| #2 Long-term outcome | Young D [38] | 2013 | High-frequency oscillatory ventilation, ARDS |
| #2 Long-term outcome | Guérin C [30] | 2013 | Prone positioning, ARDS |
| #1 Acute lung injury | Amato MBP [33] | 2015 | Driving pressure, ARDS |
| #1 Acute lung injury | Bellani G [1] | 2016 | Epidemiology, patterns of care, mortality, ARDS |
| #1 Acute lung injury | Slutsky AS [31] | 2013 | Ventilator-induced lung injury |
| #1 Acute lung injury | Frat JP [34] | 2015 | High-flow oxygen, acute hypoxemic respiratory failure |
| #1 Acute lung injury | Calfee CS [32] | 2014 | ARDS subphenotypes |

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure.

| Cluster and tag name | Lead author | Publishing year | Theme |
|---|---|---|---|
| #0 Ventilatory strategies | Gattinoni L [28] | 2001 | Prone positioning, acute respiratory failure |
| #0 Ventilatory strategies | Brower RG [39] | 2004 | Higher versus lower PEEP, ARDS |
| #0 Ventilatory strategies | Rubenfeld GD [40] | 2005 | Incidence and outcomes, acute lung injury |
| #0 Ventilatory strategies | Wiedemann HP [27] | 2006 | Fluid-management strategy, acute lung injury |
| ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure. | | | |

# Analysis of burst keywords

Keyword co-occurrence analysis returned 59 keywords. The keyword citation burst (citation increase over a given period) identified 15 keywords with strong citation bursts over the past decade (Table 5). Extracorporeal membrane oxygenation, listed in both full and abbreviated forms, was an area of active research between 2013 and 2018. Meta-analysis and randomized controlled trials also had high burst strength, especially meta-analysis in recent years. Two active keywords related to basic ARDS research were NF-kappa B, a key nuclear transcription factor regulating inflammatory responses in ARDS [19], and oxidative stress. Recruitment, protective ventilation, and noninvasive ventilation were often-used keywords connected to ARDS treatment between 2013 and 2016. Keywords relating to pathogenic factors such as risk, infection, pneumonia and sepsis are still in use.

Table 5
Keywords with the strongest citation burst in papers on treatment of acute respiratory distress syndrome in the past two decades

| Keywords | Strength | Beginning year | Ending year |
|---|---|---|---|
| extracorporeal membrane oxygenation | 67.91 | 2013 | 2018 |
| ECMO | 54.72 | 2015 | 2018 |
| meta-analysis | 50.56 | 2015 | 2018 |
| oxidative stress | 31.35 | 2015 | 2018 |
| noninvasive ventilation | 29.57 | 2015 | 2016 |
| risk factor | 29.35 | 2009 | 2014 |
| randomized controlled trial | 27.84 | 2009 | 2010 |
| infection | 27.54 | 2011 | 2012 |
| protective ventilation | 17.35 | 2013 | 2014 |
| NF-kappa B | 13.44 | 2013 | 2018 |
| survival | 12.37 | 2013 | 2014 |
| recruitment | 10.06 | 2013 | 2014 |
| randomized controlled trial | 7.4 | 2013 | 2015 |
| pneumonia | 7.11 | 2009 | 2011 |
| severe sepsis | 6.62 | 2013 | 2016 |

Strength denotes the rate of increase in citations over a given period. Higher strength values denote more active research. ECMO, extracorporeal membrane oxygenation.

# Discussion

We have presented a visual analysis of the research literature into the treatment of ARDS, which revealed the following epistemological characteristics. The body of literature has grown over time, with *Critical Care Medicine* and *Intensive Care Medicine* publishing multiple papers on the topic. Many of the researchers publishing on the topic were affiliated with the University of Toronto, St. Michael’s Hospital, the University of Washington, and the University of California, San Francisco. Co-citation analysis grouped the references into eight major co-citation clusters indicating research interests within the field of ARDS therapy. The 15 keywords thus identified may be helpful in formulating future research.

The growth in the number of publications indicates that an increasing number of researchers were studying ARDS treatments, frequently in collaboration with researchers in other institutions. Nearly onethird of the literature was published in just 10 journals, indicating that ARDS treatment was within the scope of research published by these journals.

Reference co-citation analysis was used to assess the co-citation relevance between papers, and to categorize the data into major clusters representing research interests. In our study, the reference network was grouped into eight clearly defined co-citation clusters. Active research in this field appears to be dominated currently by extracorporeal membrane oxygenation and acute lung injury. Extracorporeal membrane oxygenation, as an approach to cardiopulmonary support, has been shown to improve the survival of patients with severe respiratory failure [20], and was used in influenza A (H1N1)-associated ARDS [21]. Related topics of research discussion were criteria for extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal and long-term outcomes of this approach [22, 23]. However, the most recent study (EOLIA trial) in patients with severe ARDS showed no benefit, in terms of 60-day mortality, with extracorporeal membrane oxygenation [24]. The ventilatory strategies cluster, which contained the most articles, including comprehensive topics involving the open lung [25], PEEP level setting [26] and fluid-management strategy [27], short-term prone positioning, and the burden of ARDS [28], has been inactive since 2010. The clusters marked with long-term outcome and acute lung injury have developed and remain active. In particular, the former was in an inherent relationship with the cluster of ventilatory strategies, and we found some overlapping topics in their core literature, such as PEEP [29] and prone positioning [30]. Treatment outcome has always been the focus of attention in research into ARDS and, perhaps for this reason, the long-term outcome cluster kept in close contact with the acute lung injury cluster and extracorporeal membrane oxygenation, which served as a bridge among the clusters. The core articles targeting prognosis of ARDS were contained in the aforementioned clusters. From the timeline view, “acute lung injury” was the recent cluster, and is still active. The themes of core articles contained ventilator-induced lung injury [31], the exploration on sub-phenotypes of ARDS [32], driving pressure [33], the effect of high-flow oxygen on acute hypoxemic respiratory failure [34], and the reassessment of ARDS burden [1]. These topics seemed to be unfocused but involved basic data, issues of wide concern, and exploration of new direction, which were often co-cited in the papers to provide basic support and guide the elaboration, and probably developed over time.

A heavily cited keyword is considered an indicator of a topic of research interest, or an emerging trend. Extracorporeal membrane oxygenation and its abbreviation (ECMO) take the top two spots in the ranking of citation burst strength in recent years, indicating that this topic will continue to be studied. Meta-analysis can comprehensively analyze the results of previous randomized controlled trials on ARDS, to come to more-objective conclusions, and it is still expected to be the popular research methodology based on the strength value obtained. In the field of basic research, oxidative stress has become a popular topic of investigation in ARDS therapy. Table 5 shows the progress in ARDS research through the evolution of burst keywords over the past decade. Factors that can precipitate ARDS, which appeared in the literature we analyzed, were pneumonia, infection and severe sepsis, in chronological order. A similar evolution was reflected in the therapeutic methods, from lung recruitment and protective ventilation, to noninvasive ventilation, to extracorporeal membrane oxygenation.

To perform the co-citation clustering analysis, we selected the Web of Science as our final literature source, which may have excluded some studies. Valuable articles can also be found in evidence-based medicine databases such as the Cochrane Library and citation databases such as Scopus. When constructing the retrieval strategy, we listed a large number of technical terms related to ARDS treatment, and limited the scope to treatment, possibly ignoring the literature related to diagnosis, prevention and control of ARDS, which may influence treatment. We selected as many search terms as possible, to cover as much of the relevant literature as we could. Research topics that are deemed exciting are often pursued intensively during a given period and result in multiple publications, but the findings may not be clinically valuable with the passage of time and further investigation, weakening the value of the research topic. Finally, we did not include conference abstracts in our search, which may have influenced the weighting of results.

# Conclusions

On the basis of the bibliographic analysis of the literature in the last 20 years, the research into ARDS treatment has been receiving continuous attention. Extracorporeal membrane oxygenation is currently a topic of active research, and it and oxidative stress are likely to be the research interests in the near future. Meta-analysis of original studies will still be a popular research method in this field.

# Abbreviations

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; ECMO, extracorporeal membrane oxygenation.

# Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

The supporting data are provided in the online supplementary material.

### Competing interests

None declared.

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### Authors' contributions

Z.Y.W. designed the study and manuscript content and contributed to drafting the manuscript. Z.C.Z. contributed to the manuscript content, collected and analyzed the data, and drafted the manuscript. J.Z. contributed to the manuscript content. X.Z. contributed to the study concept and critical evaluation of the manuscript. All authors approved the submission of this version for publication.

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X.Z. takes responsibility for the content of the manuscript, including the data and analysis.

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# Figures

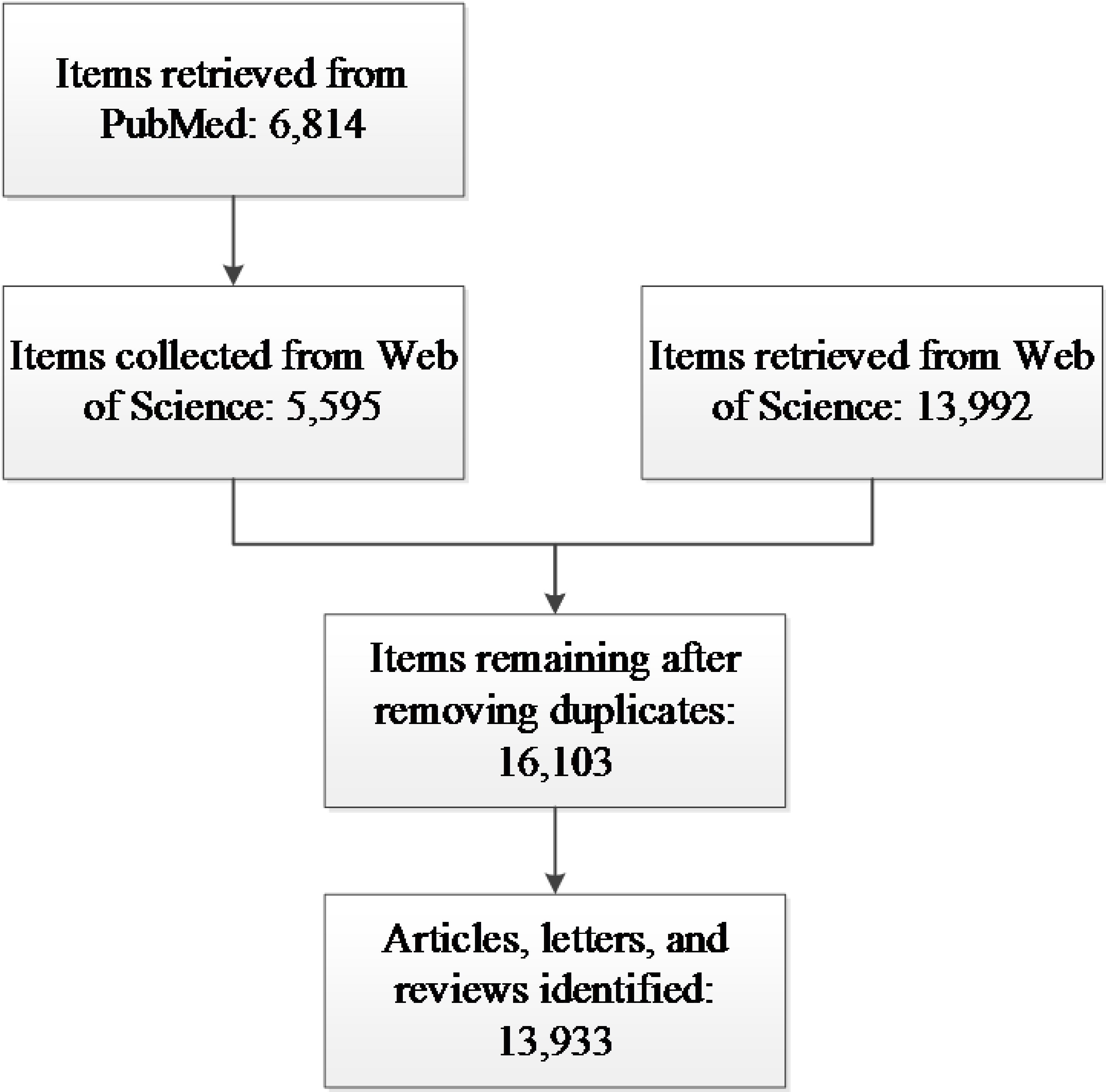
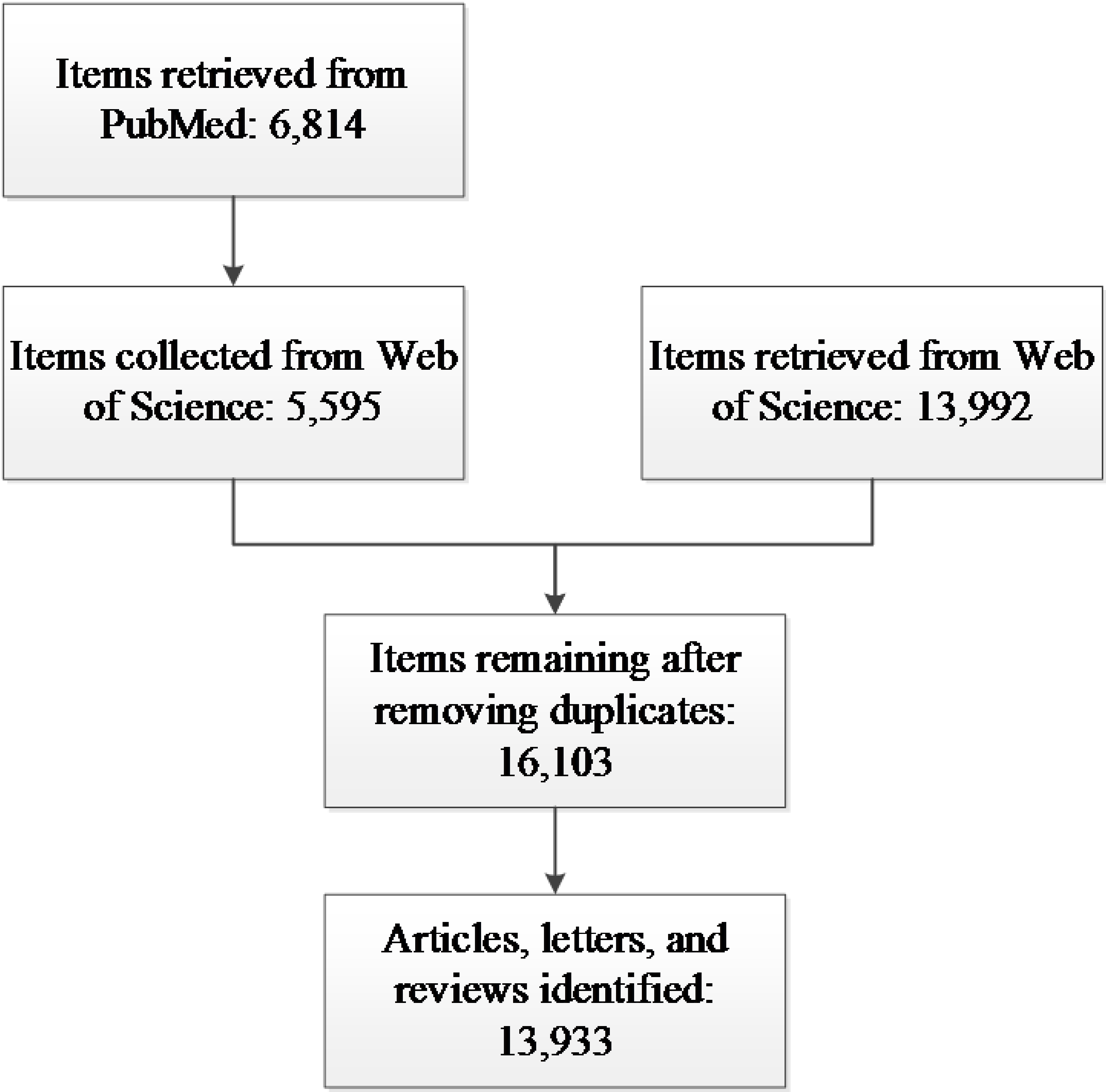



**Figure 1**

Flowchart of literature selection.

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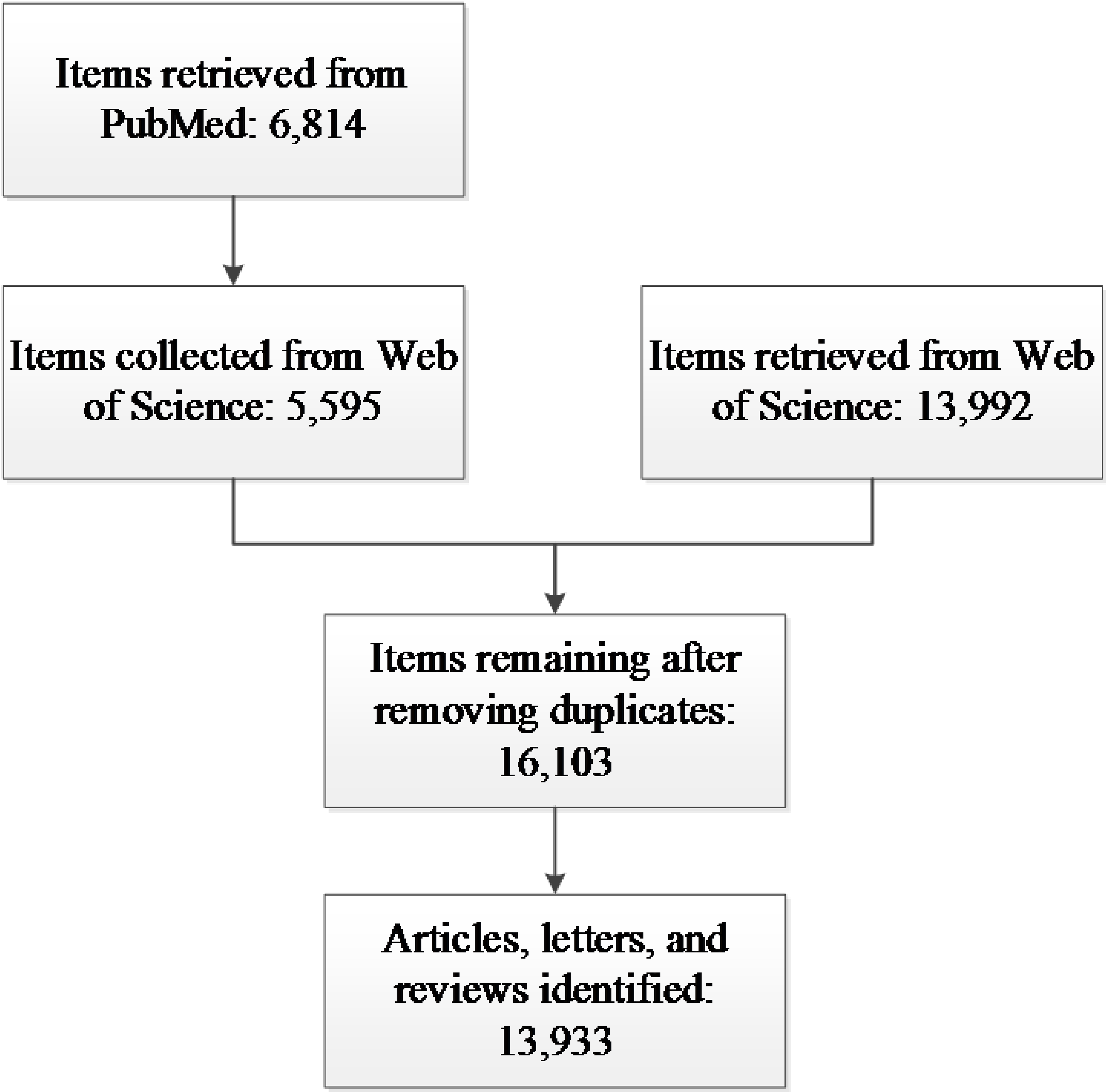


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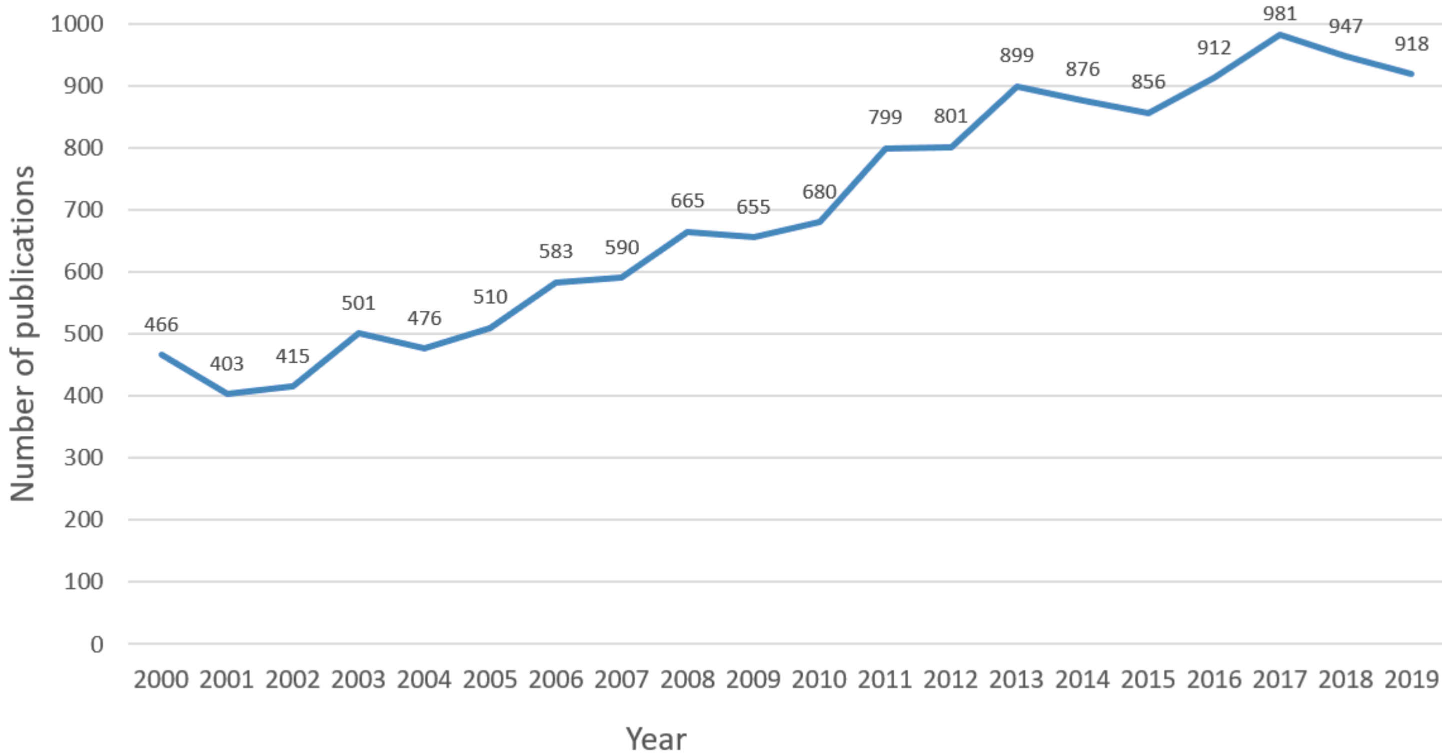
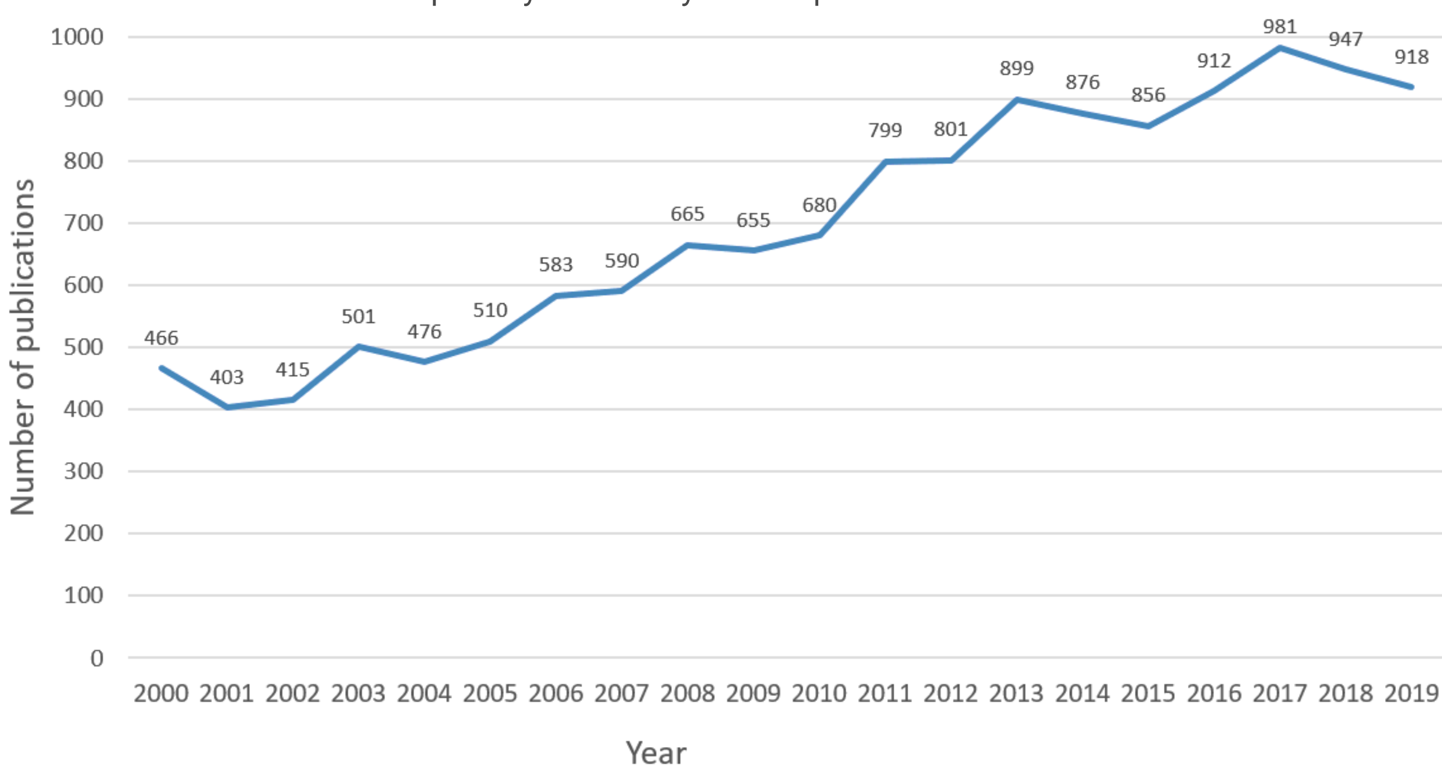



## Figure 2

Numbers of articles on acute respiratory distress syndrome published over time.



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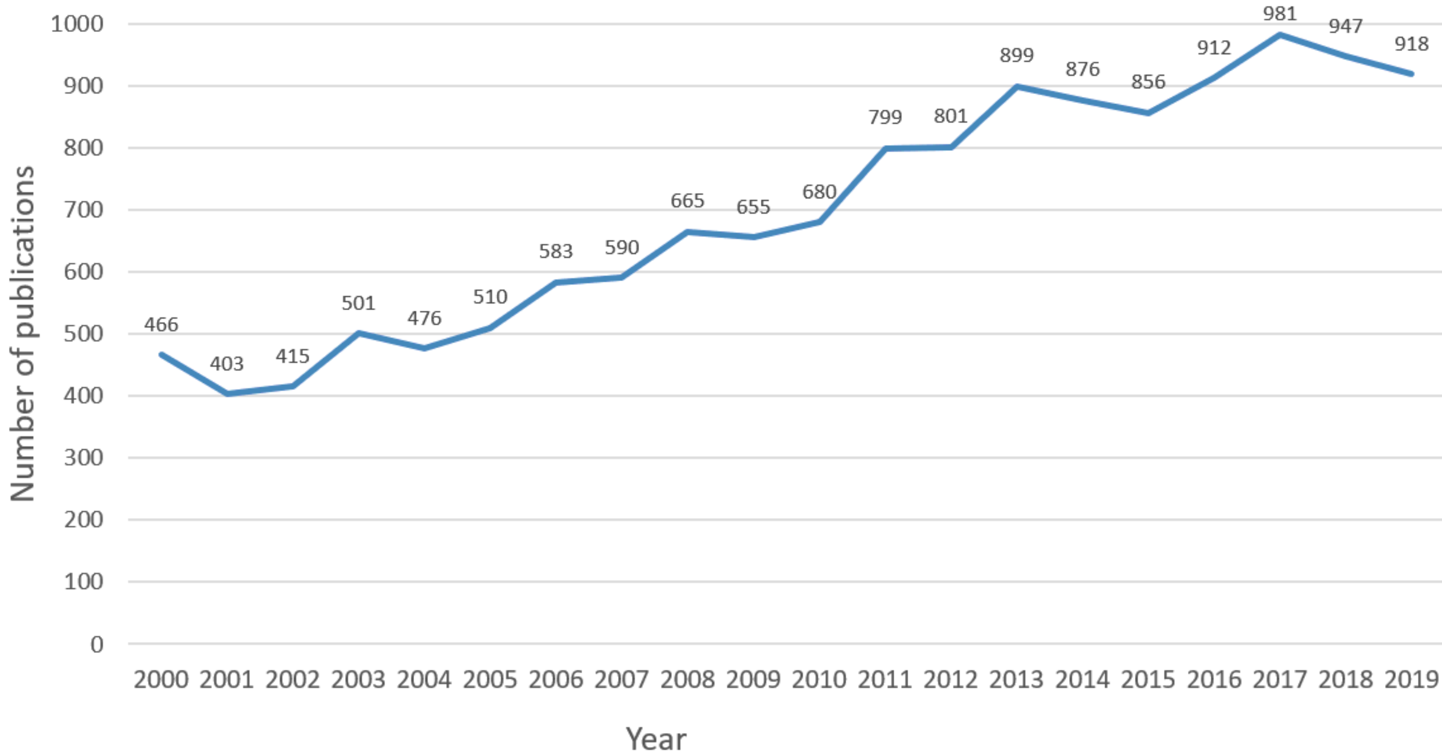


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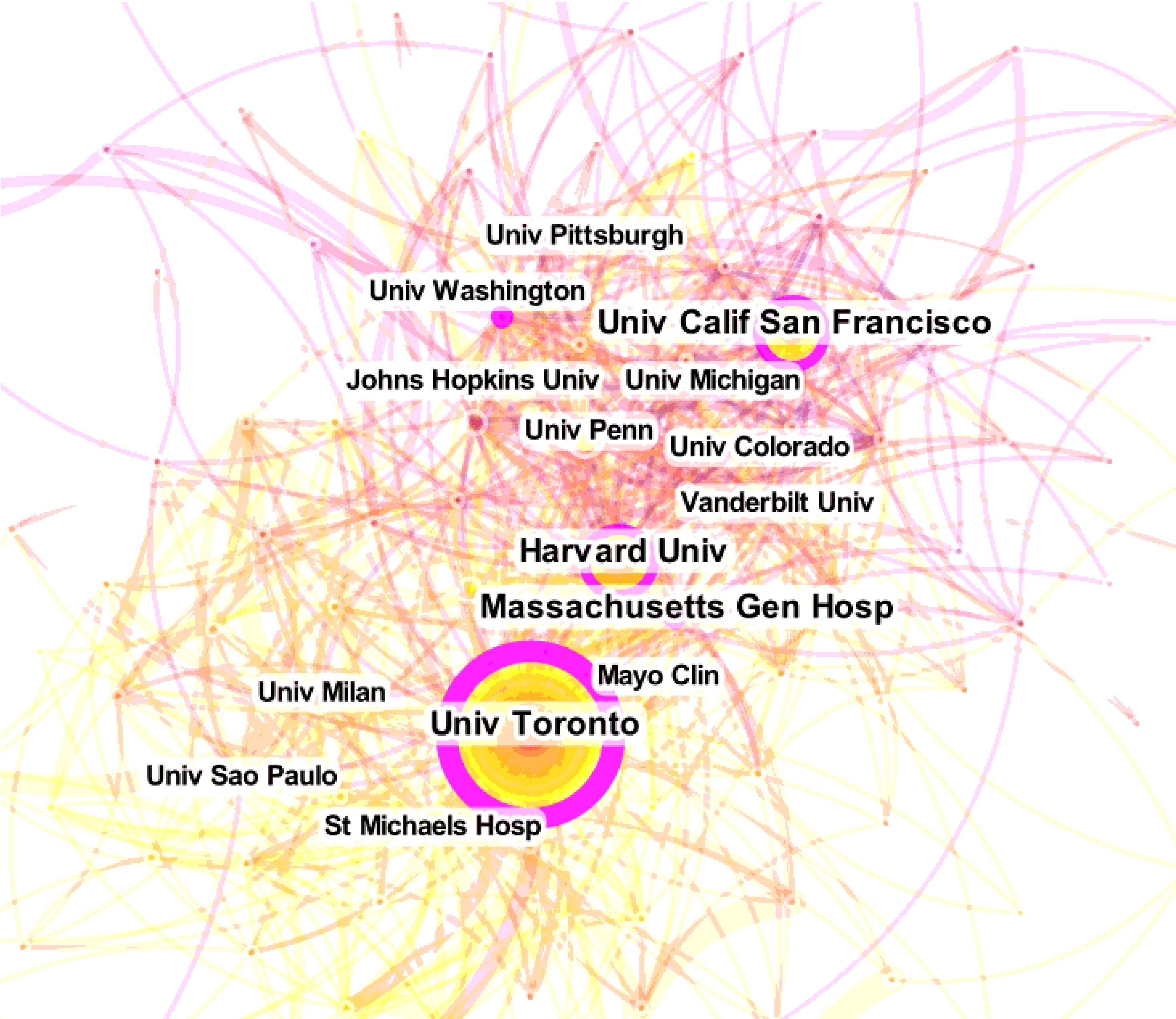
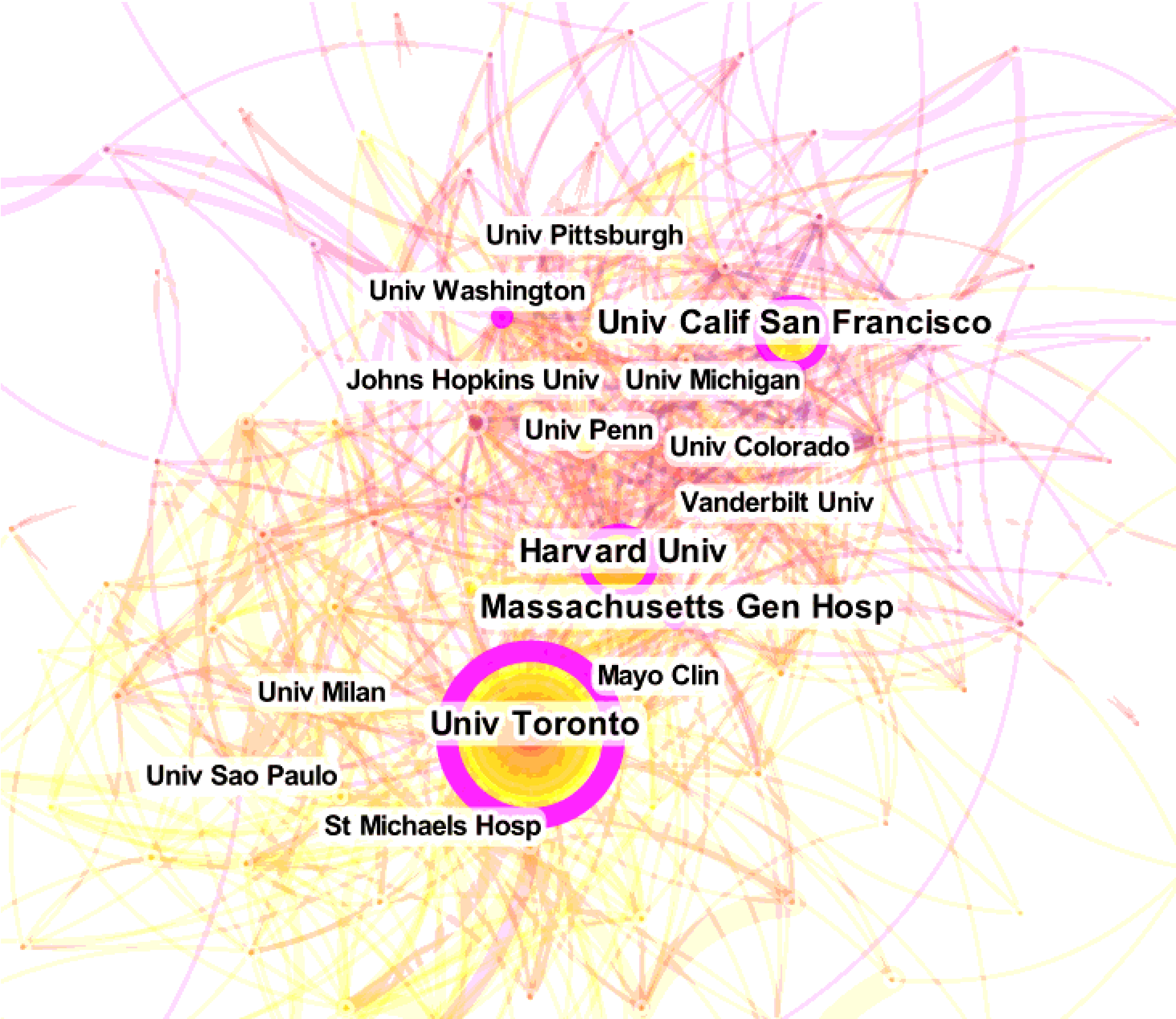



## Figure 3

Map of institutions active in publishing research on the treatment of acute respiratory distress syndrome between 2000 and 2019. Larger typeface indicates a larger number of articles published by researchers affiliated with the institution. Core institutions are marked with a purple ring and greater width of the ring indicates high centrality. The thickness of the curve in connecting lines represents collaborative intensity between institutions, with thicker lines denoting more-intense collaborations. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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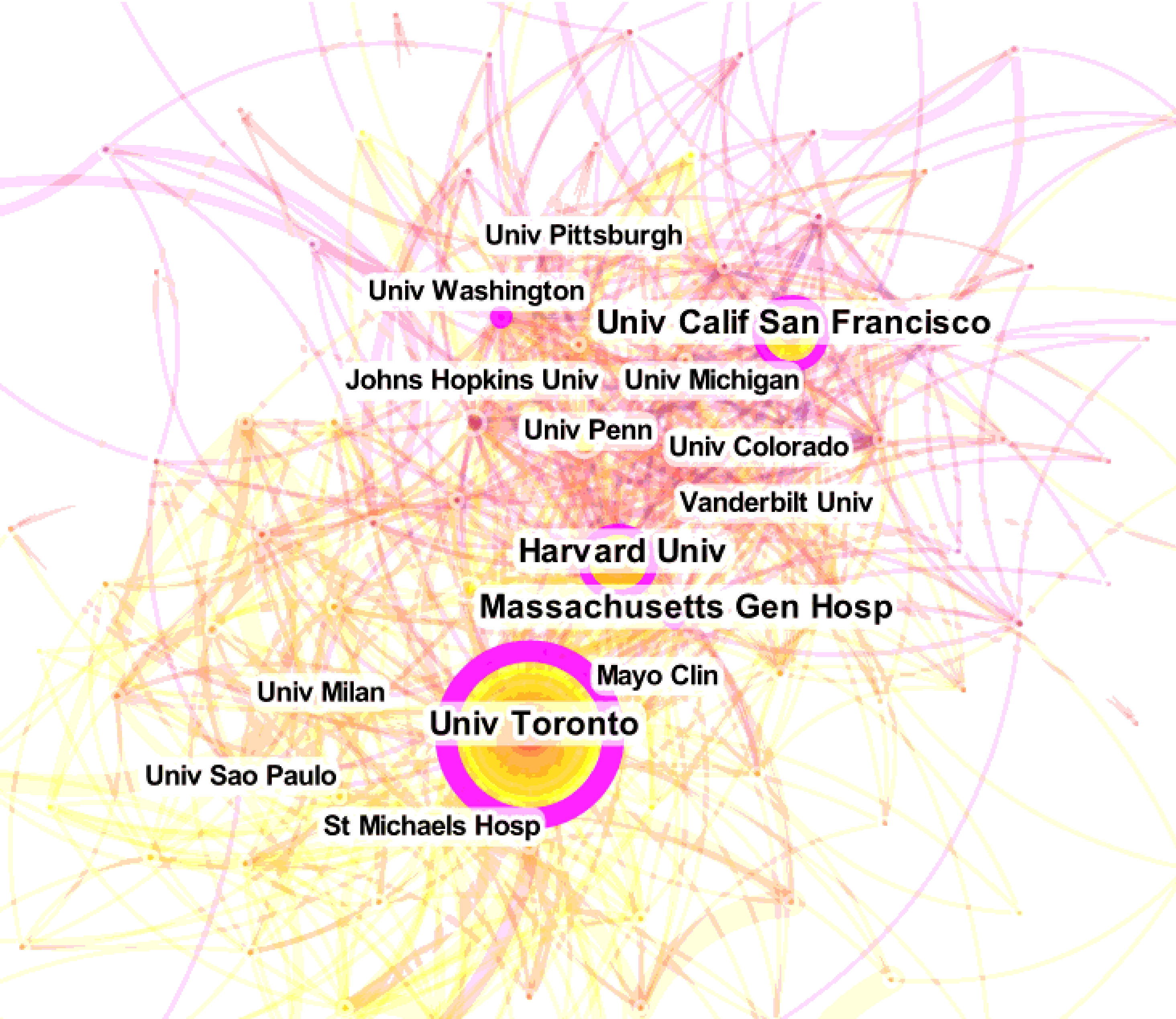


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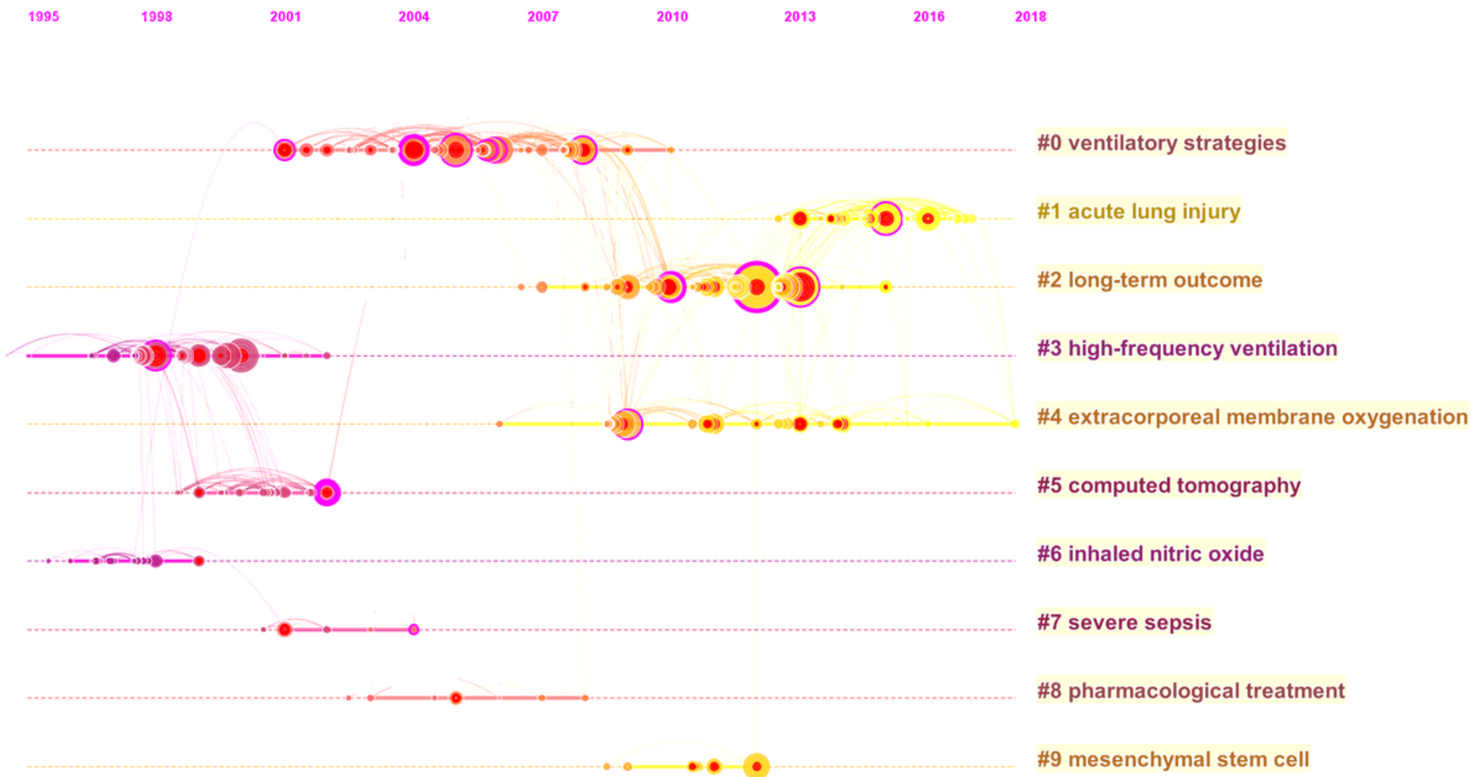
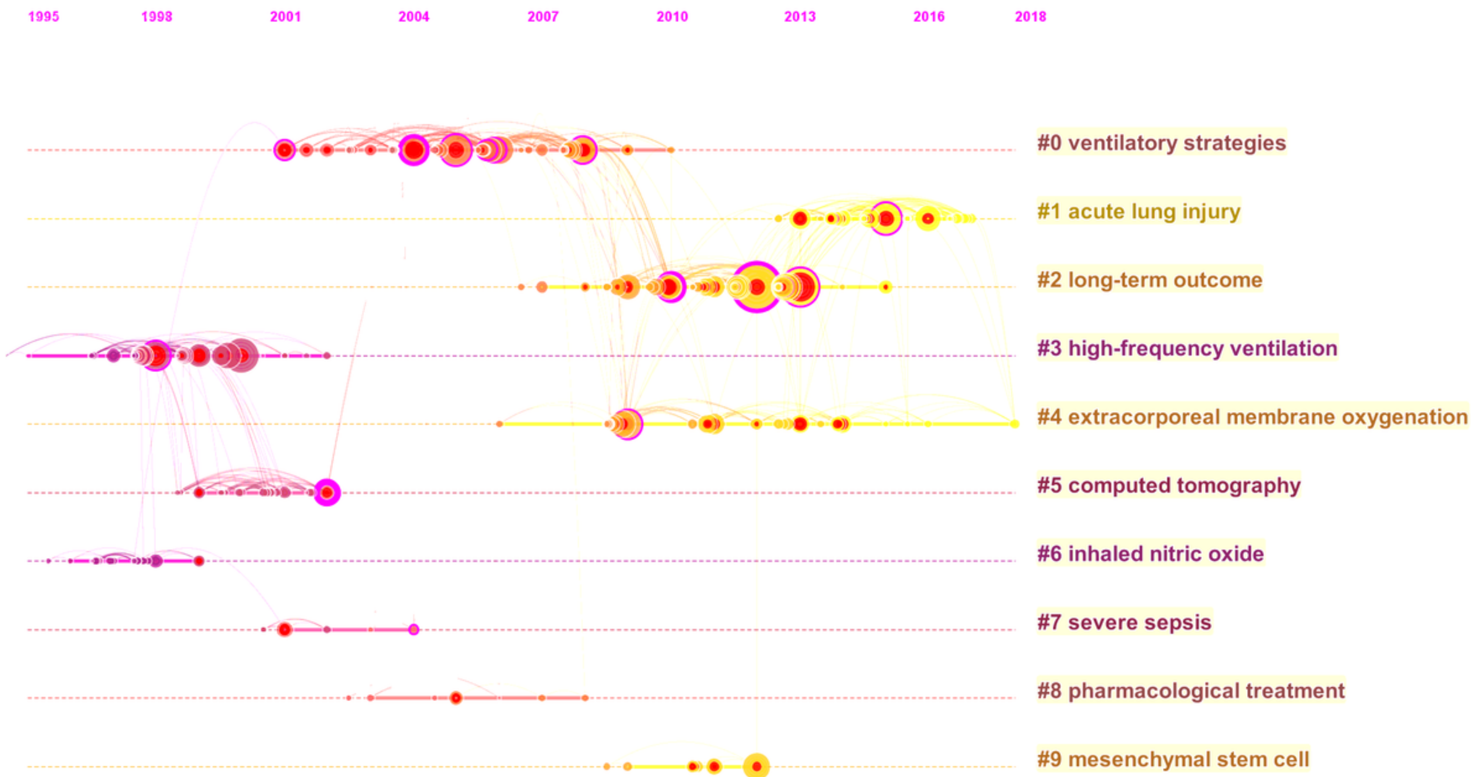



## Figure 4

Timeline view of the knowledge map from reference co-citation analysis of research into treatments for acute respiratory distress syndrome published between 2000 and 2019. Ten classified clusters, tagged with characteristic names, are represented by colored line segments and numbered from 0 to 9 (from the largest to smallest number of references). Tag names were assigned by a tag word extraction algorithm (log-likelihood ratio algorithm). The left endpoints of colored horizontal lines indicate the year when co-citation links in the fields appeared for the first time, and their length denotes the duration of publication of relevant research articles. Lines connecting the clusters reflect the co-citation relationship, and often-cited articles are highlighted by dots or rings.

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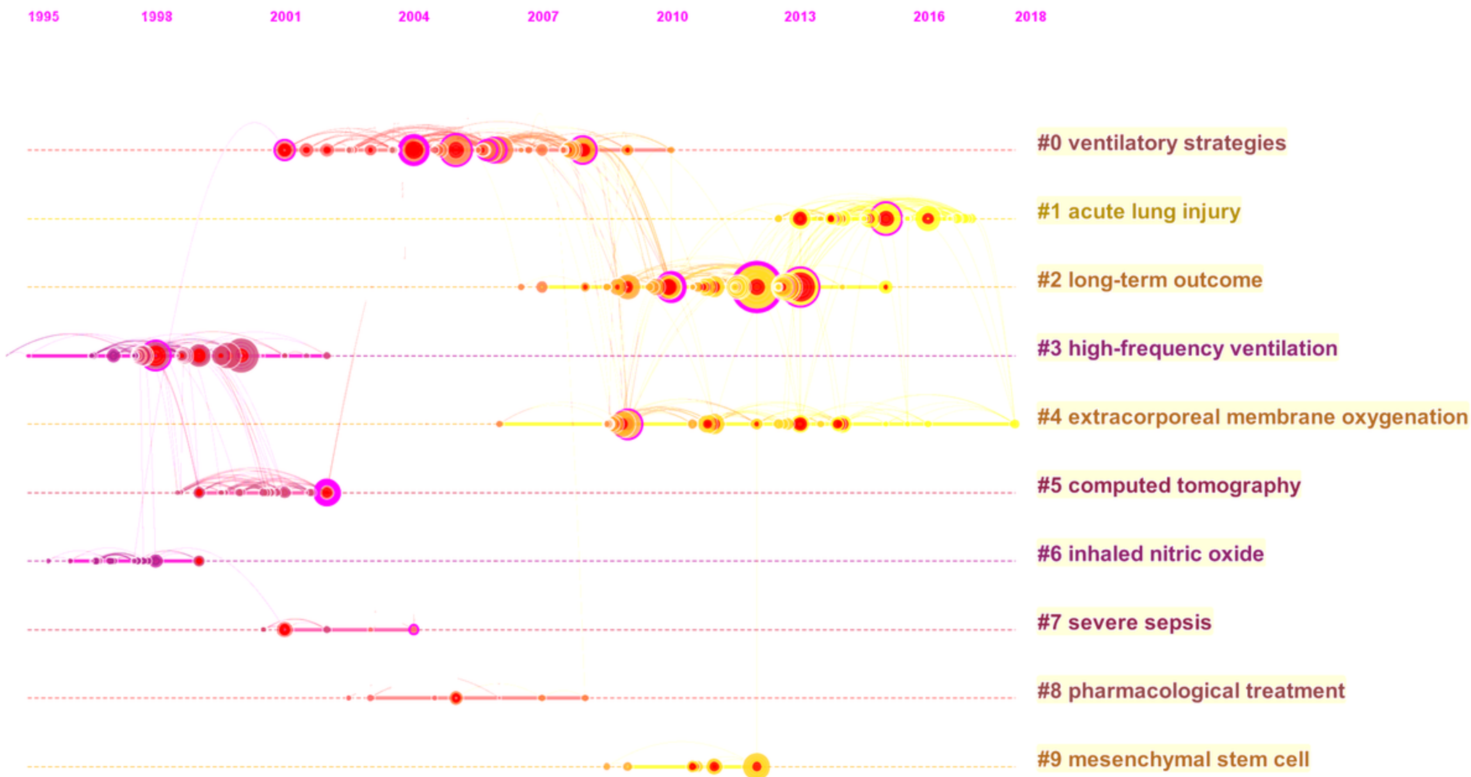


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