Global research production in neonatal abstinence syndrome: A bibliometric analysis

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**Abstract**

**BACKGROUND**

Recently, neonatal abstinence syndrome (NAS) emerged as a significant global concern with a dramatic increase in healthcare expenditures. The incidence of the NAS has increased notably in the past decade and emergence as a global public health problem.

**AIM**

To evaluate the development and trend of global NAS research from 1958 to 2019 by bibliometric analysis.

**METHODS**

Analyzed aspects included publication output per year, language, document types, journals, countries/territories, h-index, authors, and top research priorities. The VOSviewer was used to determine the top research priorities, and trends, and to present bibliometric networks concerning various dimensions, such as co-authorship, authors, and countries.
RESULTS
A total of 1738 articles were retrieved in the Scopus database from 1958 to 2019. It was found that the great majority of the total NAS documents (n = 1295) were original articles followed by reviews (n = 268) and letters (n = 48). The most productive countries in the NAS field were the United States (n = 833), Canada (n = 112), the United Kingdom (n = 111), and Germany (n = 77). Treatment and hospital outcomes in NAS, evidence-based nurse-driven interventions for the care of newborns with NAS, and a systematic reviews and network meta-analysis for therapeutic approaches of NAS were found in recent years (after 2010), compared with terms such as pathophysiology, mechanisms of NAS, and signs and symptoms in the early years.

CONCLUSION
Treatment and pediatric outcomes and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed in those topics.

Key Words: Neonatal abstinence syndrome; Bibliometric; Scopus; VOSviewer; Visualization

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Core Tip: This bibliometric study extracts data on Neonatal abstinence syndrome (NAS) research at a global level, aiming to provide the top-cited articles and top research priorities in NAS and to determine the most prolific countries, journals, and authors. This would enable scientists and clinicians interested in the NAS field to identify the most prevalent topics that have been used for increasing our understanding of NAS and provide a basis for future research. Treatment and pediatric outcomes and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed on these topics.

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INTRODUCTION
Neonatal abstinence syndrome (NAS) is a group of signs and symptoms that occur due to the sudden discontinuation of infants shortly after the birth of certain substances that were abused or used during pregnancy[1,2]. NAS can present with a broad range of signs and symptoms including restlessness, agitation, feeding intolerance, gastrointestinal disturbances, hypertonia, tremors, seizures, and respiratory distress[2-6].

Recently, NAS emerged as a significant global concern with a dramatic increase in healthcare expenditures[1,7-9]. The incidence of NAS has increased notably in the past decade and emergence as a global public health problem. The reported rise in antidepressant therapy during pregnancy, or the use of narcotic analgesics for pain relief in pregnant women, or the illicit use of opioids such as heroin and oxycodone[10] may play an important role in this aspect. The most clinically significant interventions in NAS management are appropriate to nonpharmacologic interventions[6,11] including promoting breastfeeding of infants when not contraindicated, rooming-in, positioning of the infant, bed type, and non-insertive acupuncture. Opioids such as morphine or methadone or buprenorphine are usually the first-line agent to treat the symptoms of withdrawal when pharmacological treatment is indicated. Although phenobarbital has been recognized as a second-line agent to be used in infants when opioids fail, clonidine may be used as a nonopioid adjunctive NAS therapy with minimal adverse effects and reduced treatment time[5,6,12,13].

Although several bibliometric analyses have been carried out on several topics related to substance abuse such as illicit drug addiction[14], cocaine intoxication[15], substance use disorders[16], drug and alcohol[17], and drug abuse and dependence[18-23], an extensive literature search did not reveal any bibliometric analysis on NAS. Therefore, this bibliometric study extracts data on NAS research at a global level, aiming to provide the top-cited articles and top research priorities in NAS and to determine the most prolific countries, journals, and authors. This would enable scientists and clinicians interested in the NAS field to identify the most prevalent topics that have been used for increasing our understanding of NAS and provide a basis for future research.
MATERIALS AND METHODS

Database used
To achieve the objectives of the current bibliometric study, we performed a generalized search using the database of Scopus (Elsevier’s citation database). The search was performed on July 17, 2020. Because the first publication related to NAS was published in 1958, the timespan was set from 1958 to 2019. The final year (2020) was omitted from the study as, at the time of data collection, certain publications from that year might not have been indexed in databases and this year’s data does not represent a complete year of publication in the field.

Search strategy
The search was thus conducted using the following search string: (TITLE-ABS (neonat* OR TITLE-ABS (newborn) OR TITLE-ABS (birth) OR TITLE-ABS (infant) AND TITLE-ABS ("Abstinence Syndrome") OR TITLE-ABS ("Abstinence Symptom*") OR TITLE-ABS ("Substance Withdrawal") OR TITLE-ABS ("narcotic syndrome") OR TITLE-ABS ("narcotic Symptom*") OR TITLE-ABS ("Withdrawal Symptom*") OR TITLE-ABS ("Withdrawal Syndrome") OR TITLE-ABS ("drug Withdrawal") OR TITLE-ABS ("Passive Addiction") OR TITLE-ABS("opioid withdrawal") OR TITLE-ABS("opioid syndrome") AND EXCLUDE (DOCTYPE) AND [EXCLUDE (PUBYEAR, 2020)]. Neonatal abstinence syndrome-related terms were selected for this string based on those identified in previous literature reviews[6,10,24-27]. The search strategy for the terms related to NAS was restricted to Title/Abstract to achieve greater accuracy in the results because many reported publications were not related to NAS (i.e., false-positive data) if applied to other search fields such as keywords. The use of title/abstract search is recommended in bibliometric studies[15,28,29] in contrast to the title-abstract-keywords search query because it substantially increases specificity with minimum loss of sensitivity. The main explanation for the generation of false-positive results by keyword search is that Scopus considers keywords such as "Medline keywords", "EMTREE medical terms" and "EMTRE drug terms" as author and indexed keywords. In the absence of false-positive and false-negative findings, the method adopted in the current study was validated[30]. No language restrictions were applied. Thus, both English and non-English documents were used.

Data analysis and visualization
The data was organized and analyzed using Microsoft Office Excel 2010. Descriptive statistics were used for data analysis, using frequencies and percentages. The downloaded document included the title, abstract, publication date, journal information, authors, country, collaboration patterns, and citations as indicators for quantity and qualitative analysis. These indicators were identified according to previous bibliometric literature[31-33]. The VOSviewer version 1.6.14[34], a software package for analyzing and visualizing large bibliographic datasets, was used for content analysis to determine the top research priority topics, and trends, and to present bibliometric networks concerning various dimensions, such as co-authorship, authors, and countries. To map the network of terms co-occurrence in the title and abstract countries, collaboration co-authorship was extracted from downloaded bibliometric records. In terms with an occurrence frequency no less than 20 authors and countries who had at least five publications were chosen for visualisation. The number of publications related to a certain word is measured by the size of circles in VOSviewer maps and the distance between the two terms means the number of co-occurrences of the terms. Moreover, words that are similar to each other or have a certain color are more likely to deal with the same topic[34]. In addition, the terms co-occurrences were analyzed to distinguish topics used by the authors’ overtime. Using the “link strength” indicator extracted from visualization maps, an international research collaboration among active countries was evaluated. The strength of the link is a measure of the strength of cooperation between any two countries in this field. The higher value of link strength means the thickness of the connecting line, which is considered the stronger research collaboration between certain countries in this field[34].

RESULTS
A total of 1738 articles were retrieved in the Scopus database from 1958 to 2019. It was found that the great majority of the total NAS documents (1295; 74.51%) were original articles followed by reviews (268; 15.42%) and letters (48; 2.76%). The yearly publication number of articles increased rapidly from 2 in 1958 to 40 in 2007 and then to 177 in 2019. Twenty-three languages of publication were identified in the 1,738 articles retrieved. The four predominant languages were English (n = 1489; 85.67%), followed by German (n = 66; 3.80%), Spanish (n = 39; 2.24%), and French (n = 38; 2.13%). There is a total of 111 countries/areas that make great contribution research publications in neonatal abstinence syndrome. Table 1 presents the 10 most productive countries in the NAS concerning total publications, h-index, as well as the collaboration pattern. The most productive countries in NAS field were the United States (n = 833; 47.93%), Canada (n = 112; 6.44%), the United Kingdom (n = 111; 6.39%)
Table 1 The top 10 countries contributed to publications in neonatal abstinence syndrome research (1958 to 2019)

| SCR | Country          | Number of documents (%) | h-index | No. of collaborated countries |
|-----|------------------|-------------------------|---------|------------------------------|
| 1st | United States    | 833 (47.93)             | 71      | 38                           |
| 2nd | Canada           | 112 (6.44)              | 29      | 14                           |
| 3rd | United Kingdom   | 111 (6.39)              | 29      | 25                           |
| 4th | Germany          | 77 (4.43)               | 17      | 23                           |
| 5th | Italy            | 65 (3.74)               | 15      | 21                           |
| 6th | Australia        | 63 (3.62)               | 26      | 7                            |
| 7th | France           | 62 (3.57)               | 20      | 23                           |
| 8th | Spain            | 59 (3.39)               | 18      | 22                           |
| 9th | Austria          | 52 (2.99)               | 19      | 19                           |
| 10th| the Netherlands  | 45 (2.59)               | 16      | 24                           |

Figure 1 Annual number of articles published in neonatal abstinence syndrome.

and Germany (n = 77; 4.43%). The h-index of the total retrieved articles was 87. Among the most productive countries, the United States achieved the highest h-index value with 71, followed by the United Kingdom with 29, and Canada with 29. A network visualization map for country collaboration is shown in Figure 2 and demonstrates that the United States is the most important collaboration country. Of the 111 countries, 33 had at least five publications; the largest set of connected countries consists of 28 countries in 8 clusters. For research collaboration, the strongest was in the United States (total link strength = 111), followed by the United Kingdom (total link strength = 72), and Netherlands (total link strength = 70). For most countries, the link strength was less than 20, suggesting insufficient international research collaboration in this field.[34]

Table 2 shows the 11 journals with more than 17 published papers with their impact factors. The journals publishing most papers are Pediatrics (n = 43), Journal of Pediatrics (n = 34), and Journal of Perinatology (n = 33).

Among the top contributive authors (Table 3), Jones Hendrée (42 publications) from the University of North Carolina at Chapel Hill (United States) was ranked first, followed by Fischer, Gabriele (29 publications) from the Medical University Vienna (Austria). Of note, 8 and 3 authors are from the United States and Austria, respectively, suggesting an important contributing role to these countries. A network visualization map for the authors’ collaboration is shown in Figure 3. Of the 5305 authors, 118 had at least five publications; the largest set of connected authors consists of 70 authors in 11 clusters.

In VOSviewer, co-occurrence analysis for the title and abstract contents was used to produce the term co-occurrence network of NAS studies (Figure 4). In Figure 4, it can be seen that the top research priorities of NAS studies form five clusters, and the terms in the same cluster show superior connection in each of the research topics. These five clusters were as follows: Cluster 1 (blue) involved terms related to “treatment and hospital outcomes in NAS” such as “hospitalization, length, stay, hospital stay, discharge, neonate outcome”; Cluster 2 (yellow) involved terms related to “evidence-based nurse-
Table 2 The top 11 most productive journals on neonatal abstinence syndrome research from 1958 to 2019

| SCR | Journal                                      | Frequency (%) | IF* |
|-----|----------------------------------------------|---------------|-----|
| 1st | Pediatrics                                   | 43 (2.47)     | 5.359 |
| 2nd | Journal of Pediatrics                        | 34 (1.96)     | 3.700 |
| 3rd | Journal of Perinatology                      | 33 (1.90)     | 1.967 |
| 4th | Drug and Alcohol Dependence                  | 31 (1.78)     | 3.951 |
| 5th | Addiction                                    | 27 (1.55)     | 6.343 |
| 6th | Advances in Neonatal Care                    | 23 (1.32)     | 1.405 |
| 6th | American Journal of Obstetrics and Gynecology| 23 (1.32)     | 6.502 |
| 8th | Acta Paediatrica                             | 22 (1.27)     | 2.111 |
| 9th | Archives in Disease in Childhood Fetal and Neonatal Edition | 19 (1.09) | 5.436 |
| 10th| Journal of Addiction Medicine                | 18 (1.04)     | 3.014 |
| 10th| Pediatric Research                           | 18 (1.04)     | 2.747 |

1If some journals receive the same ranking number, a gap is left in the next ranking numbers.

2Impact factors based on Journal Citation Reports 2019 adapted from Clarivate Analytics which was published in 2020.

IF: Impact factors.

Table 3 The first twelve authors by record count in neonatal abstinence syndrome research

| SCR | Author name  | Country   | Number of documents (%) |
|-----|--------------|-----------|-------------------------|
| 1st | Jones HE     | United States | 42 (2.42) |
| 2nd | Fischer G    | Austria   | 29 (1.67) |
| 3rd | Jansson LM   | United States | 28 (1.61) |
| 3rd | Patrick SW   | United States | 28 (1.61) |
| 5th | Finnegan LP  | United States | 24 (1.38) |
| 5th | Kaltenbach K | United States | 24 (1.38) |
| 5th | Wachman EM   | United States | 24 (1.38) |
| 8th | Davis JM     | United States | 17 (0.98) |
| 9th | Jagsch R     | Austria   | 14 (0.81) |
| 10th| Huestis MA   | United States | 12 (0.69) |
| 10th| Koren G      | Israel    | 12 (0.69) |
| 10th| Raith W      | Austria   | 12 (0.69) |

1If some authors receive the same ranking number, a gap is left in the next ranking numbers.

driven interventions for the care of newborns with NAS” such as “nurse, intervention, guideline, barrier, challenge”; Cluster 3 (red) involved terms related to “pathophysiology and mechanisms of NAS” such as “brain, onset, alteration, activity, administration, tolerance, analgesia, sedation, animal, rat”; Cluster 4 (purple) involved terms related to “systematic review and network meta-analysis for therapeutic approaches of NAS” such as “systematic review, meta-analysis, Medline, trial, search”; and Cluster 5 (green) involved terms related to “signs and symptoms” such as “jitteriness in neonates, meconium, irritability, prematurity”. In the analysis of term co-occurrence (Figure 5), we also identified terms in the titles and abstracts related to NAS over time. Treatment and hospital outcomes in NAS, evidence-based nurse-driven interventions for the care of newborns with NAS, and a systematic reviews and network meta-analysis for therapeutic approaches of NAS were found in recent years (after 2010), compared with terms such as pathophysiology, mechanisms of NAS, and signs and symptoms in the early years (before 2010).

The top 20 cited publications in the field of NAS ranked by the total number of citations are shown in Table 4. The highest cited publication in the top 20 was cited 529 times and the lowest cited article 177
times[1,2,9,35-52]. Table 5 includes the most frequently encountered agents related to NAS literature. “Methadone” (n = 629) was the most commonly occurred in NAS literature, followed by “morphine” (n = 378), “buprenorphine” (n = 313), and “phenobarbital” (n = 275).

### DISCUSSION

This study is set out with the aim of investigating the current situation of NAS research at a global level by analysing the related literature bibliometrically. In 2015, member states of the United Nations had
Table 5 List of most frequent drugs occurrences in neonatal abstinence syndrome literature

| Drug           | Number of publications |
|----------------|------------------------|
| Methadone      | 629                    |
| Morphine       | 378                    |
| Buprenorphine  | 313                    |
| Phenobarbital  | 275                    |
| Diamorphine    | 212                    |
| Heroine        | 138                    |
| Cocaine        | 138                    |
| Clonidine      | 130                    |
| Diazepam       | 124                    |
| Alcohol        | 80                     |
| Cannabis       | 79                     |
| Chlorpromazine | 76                     |
| Naloxone       | 62                     |
| Fentanyl       | 56                     |

Figure 2 Network visualization map for countries collaboration among most productive countries. Of the 111 countries, 33 had at least five publications; the largest set of connected countries consists of 28 countries in 6 clusters.

The current study is novel in describing the characteristics of research publications related to NAS across time, via bibliometric analysis, and determining the top research priorities in this field during six decades (1958–2019). Advances in the knowledge of NAS by determining the top research priorities for this complex health issue will help to improve future research for maternal and neonatal care.

Overall, the current study demonstrated an increase in the number of publications involving NAS over the period 1958–2019. In another way, the total number of publications related to NAS increased more than twofold from 437 before 2000 to 971 during the last decade (2010–2019). This was possible because of different explanations. First, research concerning substance abuse, with a focus on prevention...
and policy issues has become a rapidly emerging area in medical sciences and is recently reaching maturity. Second, this progress can be attributed largely to the trend of increasing maternal opiates and illicit drug use across the world. Third, the development of neonatal opioid withdrawal scale to measure opioid withdrawal signs and symptoms in the neonate. Fourth, the rapid growth of the global economy with the development of information technology has contributed to the progress of research to keep up this increasing trend.
In this study, the United States was found to be the leader in NAS research. This result may be explained by the fact that the United States is the most prolific country for research in general by most bibliometric studies[31,55-57]. Moreover, the United States is one of the countries that attributed largely to the trend of increasing maternal cocaine, illicit drugs, and opiate use, and subsequently escalating numbers of deaths[58]. Additionally, the United States may be leading because of its size and economic strength and has a large research system including United States institutions, individual colleges, and hospitals[59]. Seven newborns were diagnosed with NAS for every 1,000 hospital stays for newborns, according to 2016 statistics[60]. This is around one baby in the United States diagnosed with NAS every 19 minutes, or almost 80 newborns diagnosed every day[60].

Clearly, the most commonly used keyword in NAS literature was “methadone,” followed by “morphine”, “buprenorphine”, and “phenobarbital”. It is interesting to note that three studies from the top 20 cited publications in the field of NAS were evaluating the efficacy and safety of methadone vs buprenorphine therapy for treating opioid-dependent pregnant patients[42-44].

The most cited publication in the field of NAS was published in 2012 in JAMA - Journal of the American Medical Association, conducted by Patrick et al[1], where the authors found an increase in maternal opiate use and incidence of NAS in the United States. The authors analyzed information on 7.4 million discharges from 4121 hospitals in 44 states, to measure the epidemiology and economic damage associated with NAS over the past decade. The authors reported that the number of mothers using opiates rose from 1.19 to 5.63 per 1000 hospital births per year between 2000 and 2009, and that it is estimated that aggregate hospital costs for NAS cases, adjusted for inflation, rose from $190 million to $720 million between 2000 and 2009. The second most cited publication was published in 2010 in New England Journal of Medicine, conducted by Jones et al[43] resulting from the collaboration between several countries (United States, Canada, and Austria). This study considered the use of buprenorphine as the first-line treatment option instead of methadone for the treatment of opioid dependency during pregnancy. Methadone therapy for heroin addiction began in New York City in 1964[61], and then became the standard therapy for treating opioid-dependent pregnant patients in both the developed and developing worlds[62]. Methadone therapy led to several adverse pregnancy events during withdrawal[63]. After that, marked progress has been made in the area of buprenorphine research as an alternative treatment for opioid dependence[43] which gives relative superiority for buprenorphine to be associated with a lower risk of NAS severity[64]. This finding also accords with our observations, which showed that top research priorities including treatment and pediatric outcomes, and the effectiveness of pharmacological treatment were found in recent years. Furthermore, top research priorities in the field of NAS are consistent with the findings highlighted in the most highly cited publications, which provide substantial and valuable findings that open the door for new areas of research investigation.

Despite the importance of this topic, there remains a paucity of evidence on several issues related to NAS[65-68]. The most significant knowledge gaps in NAS are the long-term outcomes and the international differences between treatments of drug-using mother/infant dyads. What happens to the children...
afterward? How have they looked after? Some of the medications used to treat NAS (e.g., methadone) are not sanctioned in countries outside the United States. Opioid-exposed infants are still at significantly higher risk of dying, of being abused, and of sliding towards an unpalatable life trajectory after discharge from the hospital. Further work is needed to highlight this missing information and note the urgent need to prioritize research and clinical care towards improving and ameliorating the impact of maternal drug use. More broadly, the emphasis on the need to conduct more research into pharmacological treatment neglects other aspects of care for infants, including rooming-in, breastfeeding, etc. The medications that are used to treat NAS are not innocuous, therefore, research is also needed to avoid pharmacological treatment, rather than to see which treatment is most effective in discharging the infants out of the hospital faster.

**Strengths and limitations**

This bibliometric study is the first comprehensive investigation to explore the distribution trends and top research priorities in the field of NAS. Additionally, another strength of the current study including a large literature database (i.e., Scopus), benefits from a higher coverage than other databases[69,70], spanning multiple years of analysis to identify relevant NAS literature. Several limitations matching those observed in earlier bibliometric studies[31,71,72] should be noted. The main limitation of this study was the use of the Scopus database which expects that most perspectives of the publications in the field of NAS indexed in this database were analysed. Additionally, the current study used a comprehensive list of keywords based on those identified in previous literature reviews[6,10,24-27]; however, there is a possible slight chance that some keywords have been missed which may lead to false-negative results.

**CONCLUSION**

In conclusion, this bibliometric review defined the scientific research output in the field of NAS using bibliometric methods over the past 60 years, including publication numbers, countries, organizations, journals, top research priorities, and emerging trends. The findings from this study make several contributions to the current literature. First, this study confirmed the increase in the number of publications involving NAS over the period 1958–2019. Second, the United States, Canada, and the United Kingdom had the leading position in global research productivity in this field. Third, it was found that the comparative studies related to the safety and efficacy of methadone and buprenorphine in NAS were the mainstay of the top-cited studies. In the last treatment and pediatric outcomes, and the effectiveness of pharmacological treatment may be frontiers in the NAS field, and continued efforts from researchers are needed on these topics. This bibliometric study offers an objective and quantitative summary of the progress of research in the NAS field, which can serve as a significant guide and entry point for more scientific research. This information can be used to develop targeted interventions aimed to improve international cooperation between organizations and countries by applying useful initiatives and policies.

**ARTICLE HIGHLIGHTS**

**Research background**

Neonatal abstinence syndrome (NAS) has recently become a major global issue, resulting in a substantial rise in healthcare costs. The NAS has become a global public health epidemic in the last decade, with a rise in incidence.

**Research motivation**

Despite the fact that bibliometric studies have been conducted on a variety of topics related to substance abuse, such as illegal drug addiction, a thorough search of the literature revealed no bibliometric research on NAS.

**Research objectives**

Bibliometric analysis was used to assess the evolution and pattern of the global NAS research from 1958 to 2019.

**Research methods**

Yearly publication production, language, document types, journals, countries/territories, h-index, authors, and top research priorities were among the indicators examined. The VOSviewer was used to assess the top research priorities and patterns, as well as to present bibliometric networks on a variety of dimensions, including co-authorship, authors, and countries.
Research results
The current study is novel in that it uses bibliometric analysis to describe the characteristics of research publications relevant to NAS over time and determine the top research priorities in this field over six decades (1958-2019). Advances in NAS awareness will help to enhance future maternal and neonatal care research by identifying the top research priorities for this complex health problem.

Research conclusions
Treatment and pediatric outcome, as well as the efficacy of pharmacological treatment, may be frontiers in the NAS area, and researchers must continue to work on these topics.

Research perspectives
This will allow scientists and clinicians interested in the field of NAS to recognise the most common topics that have been used to improve our understanding of the disease and serve as a foundation for future study.

FOOTNOTES
Author contributions: Zyoud SH designed the study, collected the data, analyzed the data, made major contributions to the manuscript’s existing literature search and interpretation, and drafted the manuscript; Al-Jabi SW, Jairoun AA, and Shahwan WM were involved in interpretation of the data, and made revisions to the initial draft; all authors provided a critical review and approved the final manuscript before submission.

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