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Review Article

Visualizing the Research Hotspots and Emerging Trends in Neural Tube Defects: A Review

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Abstract

Background: Neural tube defects (NTDs) are among the second most common serious birth defects and constitute a major cause of infant death. Research about NTDs has achieved tremendous progress over the last 50 years.

Methods: Visualization analysis has been used to explore the hot topic and their emerging trends in NTDs research domain. The scientific literature of research for NTDs has been retrieved from Web of Science™ Core Collection (1966–2014) databases, and final acquire 9125 related bibliographic records, then analyze time trend, distribution of journals, hot keywords, and try to explore the hot topic and their emerging trends in NTDs research domain using Histcite and CiteSpace.

Results: The number of publications about NTDs have shown an increased tendency over the last 50 years although there was on a slight decline. Birth Defects Research Part A published the most articles on NTDs research, followed by Lance and Teratology, and the Lancet had the greatest number of total citations. The largest cited frequency keywords was the "Folate", followed by "Pregnancy", "Prevention", and "Spina bifida". The research hotspots in NTDs research were homocysteine, anencephaly, and screening.

Conclusion: With the help of visualization analysis, we explore a quantitative and efficient way of understanding the NTDs knowledge field.

Keywords: Visualization analysis; Neural tube defects; Scientometrics; CiteSpace

Introduction

Neural tube defects (NTDs) are among the second most common serious birth defects (1), including anencephalia, encephalocele, rachischisis, et al. affecting approximately 0.2-10 per 1000 established pregnancies in worldwide (1). They result from failure of the neurulation process and constitute a major cause of still birth, and infant death, which remains a major public health burden in developing country (especially in rural areas)(2-4), although the prevalence of NTDs decreased in high-income countries (5, 6). Research about the NTDs has achieved tremendous progress over the last 50 years, which has been the subject of a variety of publications, including epidemiologic studies, clinical reports, and systematic review. However, the scientometric profile and the emerging trends in NTDs are still unknown.

Scientometric studies are important to make comprehensive evaluation of the development of certain research fields. In recent years, document co-citation analysis and mapping knowledge has been widely used to explore the hot topic and their emerging trends in a science research domain. A generic approach was provided to visualizing emerging trends using science mapping tool CiteSpace (7), and a lot of literature about visualizing analysis have been published. However, almost none research has been done in NTDs research field.

In this study, we conducted a nearly 50-years (1966-2014) scientometric analysis on NTDs retrieved from Web of Science, in order to visualize the intellectual landscapes of NTDs and identify the hotspots and emerging trends of NTDs over the last 50 years.

Materials and Methods

Bibliographic Records

The related bibliographic records were downloaded from the Web of Science on Nov 16, 2015. We searched the Web of Science™ Core Collection (1966–2014) databases, and used "neural tube defect*", “neural tube closure defect*”, “NTD”, “NTDs”, “anencephalus”, “anencephaly”, “kenencephalocele”, “encephalocele”, “cephalocele”, “craniocele”, “meningomyelocele”, “myelomeningocele”, “spine bifid”, “bifid spine”, “atelomyelia”, “spinal meningocele”, “rachischisis”, “schistorachis”, “dysrhaphism”, “hemirachischisis”, “cleft lips”, “amyelia”, “cryptomerorachischisis”, “meningocele”, “anencephalia”, “harelip*”, “lagocheilus”, “lagentomum”, “cheiloschisis”, “palatoschisis”, “uranocoloboma”, “uranoschisis”, “diastematomyelia”, “diastomyelia”, “diplomyelia”, “hydrocephalus”, “hydrocephaly”, “hydrocrania”, “hydromyelia”, “myelatelia”, “atelomyelia”, separately as subject terms to search the literatures, and chose OR to combine them. The publication time ranged from 1966 to 2014. Overall, 10788 records were found, then we delete the irrelevant records which also use “NTD” or “NTDs” as abbreviation, the dataset was reduced to 9125.

CiteSpace and Visualization Analysis

CiteSpace was a Java-based scientific visualization software package, developed by Dr. Chaomei Chen at Drexel University (USA)(7), which provide data gathering, survey, exploring, and synthesis. It supports the visualization of knowledge fields from bibliographic records in terms of cited reference, co-occurring keywords, cited journal, cited author, and also could track the trend of development of knowledge fields and imply the potential hotspots(8). Through its co-citation network analysis, we can explore the knowledge domains in a specific topic. In the network visualization map, the nodes represent burst co-citation from the bibliographic records, the radius of the node represents the frequency cited, the thickness of a ring is proportional to the number of citations in a given time slice, and the links in the network represent co-occurrence links among them: oldest in blue, and newest in orange, purple ring outlined the node indicated the nodes play the joint role to combine the different development stage of this knowledge domain.

In this study, we used CiteSpace III to carry out the visualized network, and the basic analysis was performed using Histcite 12.03.17. First of all, we collected data from Web of Science using the technical terms, including titles, abstracts, and cited references. Each bibliographic record represents a citing article, CiteSpace collects n-grams or terms and identifiers of citing articles in a dataset. Secondly, the software performed analyses after users specify three sets of threshold levels for citation counts, co-citation counts, and co-citation coefficients. Thirdly, the software implements a concurrent version of the algorithm to process multiple networks simultaneously and supports a standard graph view and a time-zone view to present the results(9).

Ethical considerations

This manuscript does not contain any studies with human participants or animals performed by any of the authors.

Results

Profile of Data

Overall, 9125 publications on NTDs were retrieved from the Web of Science from 1966 to 2014. Of these records, 5929 (64.98%) were articles, 970(10.63%) were review, 574 (6.29%) were letter, 483(5.29%) were meeting abstract, 440(4.82%) were proceedings paper, the rest of others (729) accounts for 7.99%. The total number of citations was 223795 and the average citations per article was 24.53. The number of publications about NTDs has shown an increased trend from 1 paper in 1966 to 512 in 2010 although in 1990 was on a slight decline, and trended to decrease since 2011 (Fig. 1).

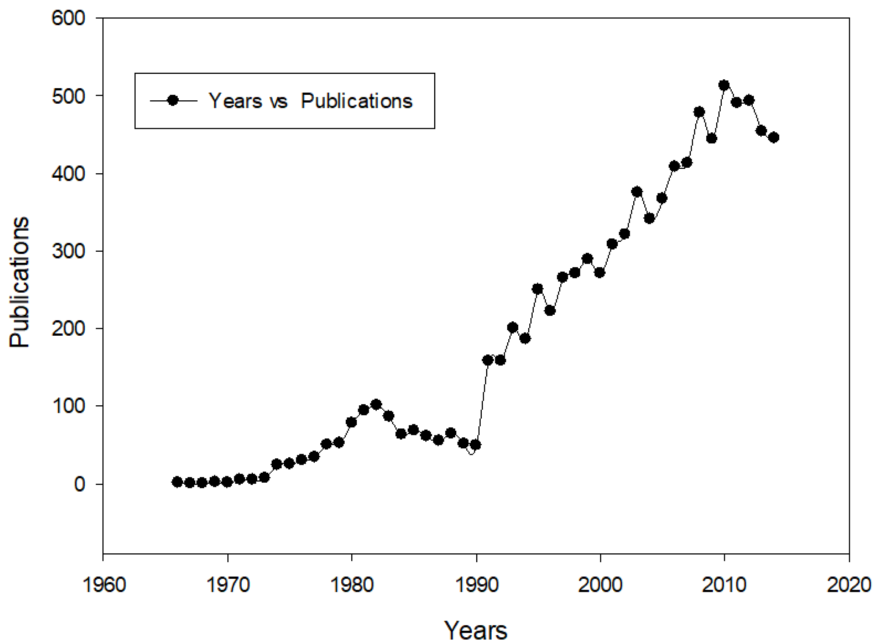

Fig. 1: The trend of publication number in worldwide on the topic of NTDs research, 1966-2014

Hot Keywords

Keywords co-citation were considered as two or more keywords occur simultaneously in one article or on field, where the number of times being cited is called the frequency or strength of co-citation(10). Figure 2 illustrates a keywords co-citation network of the literatures appeared in NTDs knowledge field. The first keywords, with the largest cited frequency 2144, was the "Folate", followed by three other keywords with more than 1000 cited frequency, "Pregnancy", "Prevention", and "Spina bifida" (Table 1).

Table 1: Top 20 Keywords in NTDs research, 1966-2014

Rank	*Keywords*	*Cited Frequency*	*Rank*	*Keywords*	*Cited Frequency*
1	Folate	2144	11	Mice	468
2	Pregnancy	1050	12	Supplementation	432
3	Prevention	1011	13	Folic acid supplementation	419
4	Spina bifida	1008	14	Prevalence	383
5	Congenital abnormalities	899	15	United States	377
6	Risk factor	761	16	Vitamin	376
7	Risk	731	17	Vitamin supplementation	303
8	Homocysteine	609	18	Malformations	301
9	MTHFR	561	19	Prenatal Diagnosis	301
10	Women	477	20	Expression	297

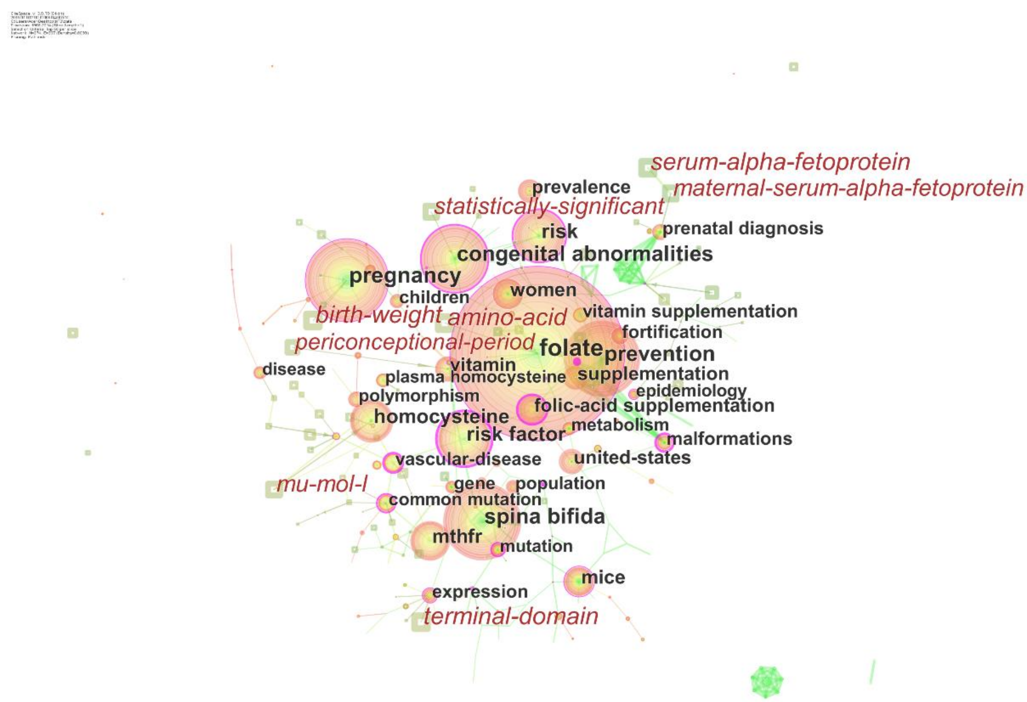

Fig. 2: Keywords co-citation network visualization map in NTDs research, 1966-2014

The terms with purple ring outlined the node were "Folic acid", "Risk factor", "Risk", "Congenital abnormalities", "Malformations" revealing those terms already paid much attention to joint different process and evolution, highly accorded with the research trend as we know.

Most Cited Papers

The complete set of 9125 bibliographic records were visualized and analyzed using CiteSpace. The related parameters were as follows: (1) Timespan: 1966-2014 (Slice Length=1); (2) Selection Criteria: Top 50 per Slice; (3) Network: N=887, E=4093(Density=0.0104); (4) Pruning: the pathfinder method was used to streamline the network. The top 50 most cited or occurring items from each slice were selected, and there are 887 unique nodes and 4093 links for one slice. The largest citation rings of the nodes is an original articles by Czeizel, with 1479 citations, published in NEW ENGL J MED. By that analogy, the top ten cited articles associated with NTDs were presented in Table 2. The second ranking articles were published in Lancet and received 1475 citations. The third also was an original articles by Frosst, with 614 citations, published in NAT GENET. Purple ring outlined the node that indicated the nodes play the joint role to combine the different time periods in this research domain.

Co-Citation Clusters Analysis

Cluster analysis is a collective term covering a wide variety of techniques for delineating natural groups or clusters in data sets. It could group a set of objects in the same groups (called a cluster) are more similar to each other than to those in other groups. In CiteSpace, three different metrics (LLR, TF*IDF, and MI) can be used to extract noun phrases from the titles of articles cited the cluster, and LLR would often be considered the best choice to describe the themes related with a cluster(11). The silhouette score reflected the quality of a cluster, which represents its consistency or homogeneity. The values of the silhouette for a consistency cluster tend to close to 1. There are total 48 cluster in the network. The largest cluster was homocysteine (#0), followed by anencephaly (#1) and screening (#2), the oldest cluster was neurulation (#9), and the youngest cluster was tissue polarity gene (#7). Most of the silhouette values in top 10 clusters were greater than 0.8, except the second largest cluster (#9) with a values of 0.634, suggesting meaningful results (Fig. 3).

References with Strong Citation Bursts

A citation burst visualization shows which references have the strongest citation bursts and which periods of time the strongest bursts took place within a scientific research domain. Figure 4 shows the top 10 essential references with strong citation bursts in NTDs research from 1966 to 2014. Among them, three references started to burst in 1996, two references started to burst in the year of 1990, and others started to burst in different times. The strongest citation burst was the article study by MRC Vitamin Study Research Group(12) with the highest strength of 123.85. Followed by De et al(5), Milunsky et al.(13), Mills et al(14), which were the representative references for different groups by the beginning time of burst.

Table 2: Top ten critical articles in NTDs research, 1966-2014

Rank	*Cited Frequency*	*Title*	*Author*	*Year*	*Betweenness Centrality*	*Journal*
1	1479	Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation	Czeizel et al	1992	0.10	NEW ENGL J MED
2	1475	Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study	Wald et al	1991	0.08	LANCET
3	614	A candidate genetic risk factor for vascular disease: a common mutation in methylenete-trahydrofolate reductase	Frosst et al	1995	0.05	NAT GENET
4	580	Prevention of neural-tube defects with folic acid in China	Berry et al	1999	0.01	NEW ENGL J MED
5	428	Mutated methylenetetrahydrofolate reductase as a risk factor for spina-bifida	Vanderput et al	1995	0.03	LANCET
6	426	Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects	Honein et al	2001	0.02	JAMA-J AM MED ASSOC
7	404	Homocysteine metabolism in pregnancies complicated by neural-tube defects	Mills et al	1995	0.02	LANCET
8	389	Multivitamin folic-acid supplementation in early-pregnancy reduces the prevalence of neural-tube defects	Milunsky et al	1989	0.02	JAMA-J AM MED ASSOC
9	372	Double-blind randomized controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects	Laurence et al	1981	0.17	BRIT MED J
10	371	A second common mutation in the methylenetetrahydrofolate reductase gene: An additional risk factor for neural-tube defects?	Van et al	1998	0.01	AM J HUM GENET

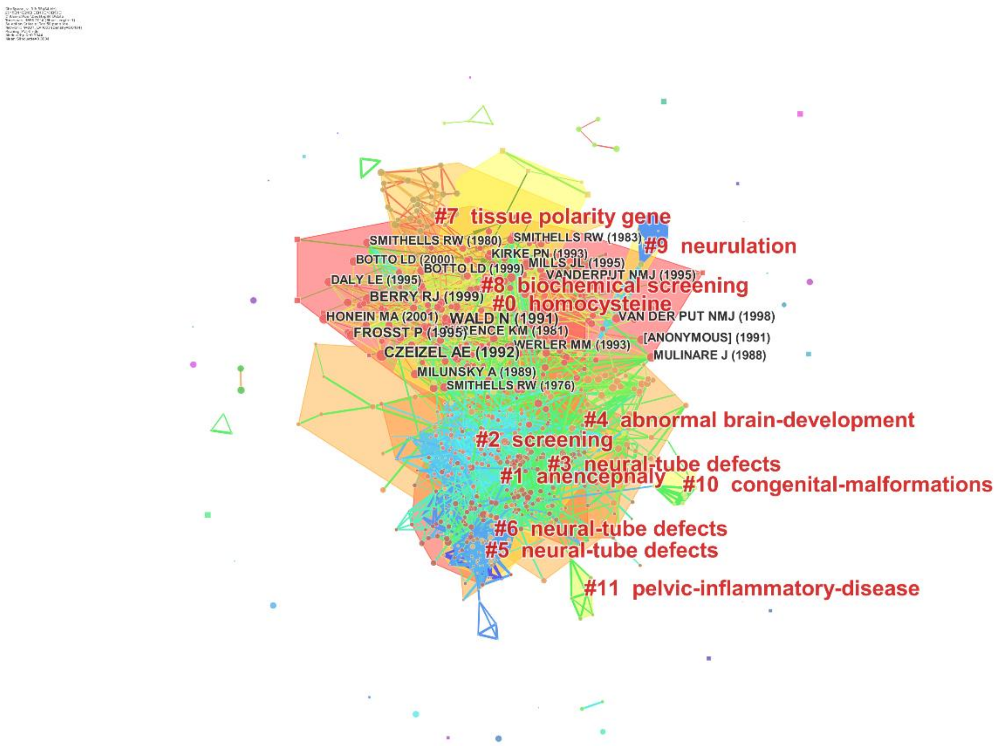

Fig. 3: Cluster visualization based on NTDs research, 1966-2014

Top 10 References with Strongest Citation Bursts

References	Year	Strength	Begin	End
BROCK DJH, 1972, LANCET, V2, P197	1972	51.9582	**1974**	1990
[ANONYMOUS], 1977, LANCET, V1, P1323	1977	51.6783	**1977**	1995
SMITHELLS RW, 1981, ARCH DIS CHILD, V56, P911	1981	51.3104	**1982**	1995
MILUNSKY A, 1989, JAMA-J AM MED ASSOC, V262, P2847, DOI	1989	62.0054	**1990**	1998
MILLS JL, 1989, NEW ENGL J MED, V321, P430, DOI	1989	58.2794	**1990**	1998
[ANONYMOUS], 1991, LANCET, V338, P131	1991	123.8487	**1992**	1996
STEEGERSTHEUNISSEN RPM, 1994, METABOLISM, V43, P1475, DOI	1994	51.8702	**1996**	2003
VANDERPUT NMJ, 1995, LANCET, V346, P1070, DOI	1995	51.0564	**1996**	2003
MILLS JL, 1995, LANCET, V345, P149, DOI	1995	50.9424	**1996**	2003
DE WALS P, 2007, NEW ENGL J MED, V357, P135, DOI	2007	77.0607	**2008**	2014

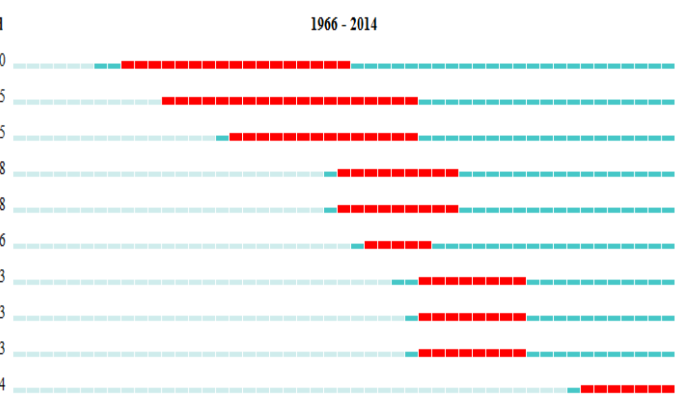

Fig. 4: Top 10 references with strong citation bursts

Discussion

In this study, we analyzed the publication time trend, distribution of journals, most cited papers, hot keywords, co-citation clusters, and strong citation bursts according to the bibliographic records on NTDs research domain from 1966 to 2014. To our knowledge, this was the first bibliometric research on the topic of NTDs. Our result found that the number of publication articles have a uptrend since the 1990s and there was a peak in 2010, hinting that more attention was paid to NTDs research during this period. The top five journals of NTDs research were Birth Defects Research Part A, Lancet, Teratology, Prenatal Diagnosis, and American Journal of

Medical Genetics. These journals had published 1193 accounting to 13.07% of 9125 papers. Meanwhile, one third of papers were approximately found in top 20 most productive journals, indicated that there was a high concentration on NTDs research publications in these top journals, which follows Bradford's law(15).

A keywords co-word network analysis can be used to monitor research topics, as well the evolving research frontiers of a knowledge domain (16). Using keywords co-word analysis, the top 20 most frequently keywords were "Folate", "Pregnancy", "Prevention", "Spina bifida" et al (Table 1), suggesting core content of NTDs research during this period. Since the folate supplementation before conception was proved to prevent the recurrence of neural tube defects in 1981(17), that "Folate", "Supplementation", "Prevention", "Pregnancy", "Women" have become the hot topics in NTDs research. Meanwhile, "Homocysteine" and "MTHFR" show that folate metabolism was also the emphasis of research in NTDs. "United States" indicated that the USA paid more attention to the NTDs research.

The top-cited is an article, which demonstrated that before conception vitamin use reduces the incidence of a first occurrence of NTDs. The second one found that folic acid supplementation before pregnancy showed a significant protective effect (RR: 0.28, CI95%: 0.12-0.71) for NTDs. The other two (18, 19) of the top five articles focus on genetic mutation in methylenetetrahydrofolate reductase (MTHFR), and found that the 677C --> 7 mutation was associated with high plasma homocysteine, low plasma folate, decreased MTHFR activity, and should be regarded as a genetic risk factor for spina bifida. The other one (20) also discussed the links between folic acid supplementation and NTDs, which reported that periconceptional intake of 400mg of folic acid daily can reduce the risk of NTDs. The highest betweenness centrality (0.17) article, with a purple ring outlined the node, was a randomize controlled double-blind trial study by Laurence et al.(17), which found that the risk of a recurrence of fetal NTDs could be reduced by taking folate supplements or improving women diet. In sum, all these papers help reveal the major points of interest in research on NTDs.

The emerging trends and research patterns in NTDs research field were also explored. Our research showed that the largest cluster, homocysteine (#0), consists of 231 articles and an average publication year of 1997 (Fig. 3). The three most citing articles in this cluster were Czeizel et al.(21), Wald et al.(22), and Frosst et al.(18) , and it mainly concerned about the relationship between folic acid and NTDs, which demonstrated that take folic acid during the periconceptional period decreases the risk of NTDs through change the levels of plasma homocysteine. Obviously, this is the main focus of NTDs research field. The second-largest cluster was anencephaly (#1) which has 135 articles and an average publication year of 1975. Top three citing articles in this cluster were Khoury et al.(23), Holmes et al. (24), Hall et al. (25), which mainly investigated the epidemiological, genetic, and clinical factors in NTDs. The oldest cluster, neurulation (#9), has 14 member articles and an average publication year of 1960. According to the major citing articles (26, 27), the mechanisms of neural tube formation were mainly being discussed in earlier researches. The youngest cluster has 38 articles, with an average publication year of 2006. The three most citing articles in this cluster were Copp et al. (28), Kibar et al. (29), Juriloff et al.(30), all these researches mainly analysis of the genetic influences on neurulation, and the availability of many genetic mutants with neurulation phenotypes provides an opportunity for a rigorous analysis of the molecular mechanisms of mammalian neurulation. No doubt, it reflect the recent knowledge domain in NTDs research.

Significant increase of research interests within the NTDs research field were characterized by related bibliographic records that experienced citation bursts. We found the top 10 references with the strongest citation bursts from 1966 to 2014, indicating that citations of this papers increased rapidly in a given time period. Furthermore, seven of tenth articles belongs to homocysteine (#0), suggested the cluster might absorb most research interest. The article(31) with the earliest citation bursts starting from 1974 discussed that amniotic fluid alpha-fetoprotein measurements will be valuable in the early antenatal diagnosis of spina bifida and anencephaly. The key article(12) with the highest strength of 123.85 found that folic acid supplement around the time of conception can prevent NTDs (anencephaly, spina bifida, encephalocele) through conducted a randomized double-blind trial at 33 centers in seven countries. In these articles started to burst in year 1996, a disorder reported in the re-methylation of homocysteine to methionine due to an acquired or inherited derangement of folate or vitamin B-12 metabolism (32). An abnormality in homocysteine metabolism was present in many women who give birth to children with NTDs (33). The last paper (5) with the most recent citation bursts starting from 2008 demonstrated that the prevalence of NTDs decreased from 1.58 per 1000 births before food fortification with folic acid to 0.86 per 1000 births during the full food fortification period in Canada, and the observed reduction in rate was greater for spina bifida (decrease of 53%) than for anencephaly (decreases of 38%). These observations indicated that the emerging trends in NTDs research domain.

The top cited articles and the keywords reflected the recognition of NTDs were a gradual course. After the correlation between folate intake and the decrease the incidence of NTDs had explored, the role of folate in maternal metabolism during pregnancy draw most attention in this area, and studies found an association between elevated levels of blood circulating homocysteine in women during pregnancy with NTDs, folic supplements can reduce homocysteine levels, helping to reduce the risk of NTDs. The ongoing studies found genetic mutation of folate-metabolizing enzymes were associated with high plasma homocysteine, low plasma folate, increase the risk of NTDs. However, the mechanism is not entirely clear. Further study need focus on the role of folate-metabolizing enzymes genetic polymorphism and identify a candidate genetic risk factor for NTDs, influenced by nutrient intake, represents a critical step in the design of an effective prevention strategy for the NTDs.

Conclusion

The study on NTDs have made huge developments over the last 50 years. There has been shown a mild increased trend in the number of publications. According to the network visualization analysis supported by CiteSpace, we dig out the hot topics in NTDs research field and the key cluster of articles. The first keywords were the “Folate”, followed by “Pregnancy” and “Prevention”, which represents the hot topic in NTDs research. The top two clusters were labeled as “homocysteine” and “anencephaly”, which reflect the most prominent knowledge field in NTDs research. Similarly, the emerging trends and research patterns were also identified in the literature, the persistent cluster, “folic acid”, represents a continuation of an existing trend, the emergence of a new cluster indicates the beginning of a trend, and the citation burst demonstrate a changing in NTDs research interests over the last nearly 50 years. Obviously, with the help of visualization analysis, we explore a quantitative and efficient way of understanding the NTDs knowledge field.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interests

The authors declare that there is no conflict of interest.

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