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ORIGINAL RESEARCH

Exploring Research Trends and Mechanisms: Maternal Diabetes and Neural Tube Defects (1991–2023)

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Background: Neural tube defect (NTD) is the second most common congenital neuropathy in the world. Maternal diabetes is an important factor leading to the occurrence of NTD in offspring. However, existing studies lack a systematic analysis of the correlation between maternal diabetes and NTDs, as well as an exploration of NTD pathogenesis and associated preventive strategies. Consequently, there is a need for a thorough examination of the literature pertaining to NTDs and maternal diabetes to elucidate a comprehensive understanding, identify research focal points, and anticipate future developmental trends.

Methods: The literature related to NTDs and maternal diabetes from 1991 to 2023 was retrieved from the Web of Science Core Collection (WoSCC). Bibliometric software CiteSpace (version 6.2.6) was used for co-occurrence/citation network analysis and to draw a knowledge visualization map.

Results: A total of 382 articles and reviews were included in the final analysis. Findings revealed an increasing trend in annual publication rates. The University of Maryland Baltimore emerged as the institution with the highest number of publications, while the American Journal of Obstetrics and Gynecology and Birth Defects Research Part A-Clinical and Molecular Teratology stood out as the most prolific research journals. EA Reece was identified as the leading contributor in this domain. The United States emerged as the global leader in this field, making the most significant contribution to research endeavors. The cluster analysis of keywords obtained eight clusters, and the research focus was on the pathogenesis of NTDs induced by maternal diabetes.

Conclusion: This study employed bibliometric methods to visualize the research landscape of NTDs induced by maternal diabetes, aiming to comprehend trends and identify key areas of interest in this domain. By studying the relevant mechanisms, we will search for new key targets. Meanwhile, future research needs to further explore new treatment strategies.

Keywords: bibliometric analysis, neural tube defects, diabetes, research hotspots, cluster analyses, visualization, CiteSpace, VOSviewer

Introduction

Neural tube defects (NTDs) arise from inadequate closure of the neural tube during early pregnancy and include spina bifida, anencephaly, and encephalocele.[1,2] Spina bifida and encephalocele often result in severe disabilities for the child, and anencephaly is even outright fatal.[3] NTDs rank as the second most prevalent congenital neuropathy globally, impacting 300,000–400,000 newborns annually.[4] A retrospective study based on nursing costs in the United States showed that the estimated total per capita nursing cost for NTD patients is $791900, which imposes a serious psychological and economic burden on the families of NTD patients. Reducing the birth of NTD patients can lower expenditures on medical assistance,

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special education, and other areas.[5] Regrettably, treatment options remain highly limited at present. Genetic factors are believed to primarily underlie NTDs, with prior research highlighting folate deficiency as a significant contributing factor.[6] Nonetheless, folic acid supplementation alone may not completely eliminate the risk of NTD, underscoring the need to explore other genetic factors.

Elevated blood glucose levels resulting from total failure of insulin secretion or tolerance characterize diabetes mellitus, a metabolic illness. Miscarriage, newborn morbidity and death, and congenital deformities are among the numerous reproductive issues that women with poorly managed type I or type II diabetes mellitus frequently experience.[7] For example, a study of data from the Canadian Center for Health Policy showed that maternal diabetes status during the first 20 weeks of pregnancy caused congenital kidney and urinary tract abnormalities in the fetus.[8] Globally, the disease burden of diabetes mellitus (DM) has continued to rise, with the number of patients increasing by 62% between 1990 and 2019, and projected to increase by a further 51% by 2045.[9] To the best of our knowledge, the development of maternal diabetes mellitus is now considered to be a critically significant risk factor for the occurrence of NTDs in the progeny. In addition, the review of this area of research by Shyamasundar et al also mentions that the exact mechanism or link between how high glucose alters gene expression/transcriptome and the mechanism that induces NTDs is largely unknown.[10]

Bibliometrics is a technique for document analysis that examines the output and standing of publications from both qualitative and quantitative angles in a particular field of study. During the analysis, detailed information such as authors, keywords, journals, countries, institutions, and references can be obtained in pertinent research domains, facilitating cluster analysis to identify future research hotspots. Recent clinical studies have highlighted the absence of systematic analysis concerning the relationship between maternal diabetes and NTDs, emphasizing the importance of identifying research hotspots for advancing the field. Mother diabetes is a factor that can be intervened through pregnancy management. Different from NTD caused by some genetic factors, maternal diabetes can control the blood sugar level through diet control, exercise and necessary drug treatment. By strengthening the management of pregnant women with diabetes, such as blood glucose control before pregnancy, blood glucose monitoring during pregnancy, and adjusting treatment programs, the risk of NTD in the fetus can be effectively reduced. Therefore, maternal diabetes is one of the key focuses in preventing NTD. To address this gap in knowledge, this study aimed to bibliometric analyze publications on maternal diabetes mellitus and NTDs research from its inception to the present. The objectives were to identify key contributors, assess the current research landscape, and explore trends and future prospects in the field.

Materials and Methods

Search Strategy

A literature search was performed on December 20, 2023, on the Web of Science Core Collection (WoSCC) database (https://www.webofscience.com/wos/woscc/basic-search). The search formula was (TS = (maternal diabetes)) AND TS = (NTDs). The type of literature was not restricted too much to present a more comprehensive picture of research in the field.

Data Analysis

CiteSpace (version 6.2.6), developed by Professor Chen C, is utilized for bibliometric analysis and visualization purposes.[1] CiteSpace was utilized in our study to create a double overlap map of journals and to perform citation burst analysis on the references.

In addition, timeline diagrams and cluster analysis were also implemented through CiteSpace.

We used R language (version 4.3.1), RStudio, and R package "bibliometrix" (version 3.2.1) (https://www.bibliometrix.org) to analyze the research in this field from multiple dimensions. We designed a circular column overlay map, three real maps, and an annual production map to show the publication of different levels in the field. In addition, we also used trend topic maps, thematic maps, and Lotka's law to analyze potential hotspots and research depth in this field. With Microsoft Office Excel 2021, a quantitative study of the publication was conducted.

Results

Analysis of Annual Publications

Through literature screening, 382 publications on maternal diabetes and NTDs were obtained from the WOS database from 1991 to 2023. Figure 1 showed the quantity and trend distribution of yearly publications. Although there has been a downward trend at certain points in time, the overall number of publications has shown an upward trend, increasing from 4 in 1991 to 25 in 2015, indicating an explosive growth in research in this field. As shown in Figure 1, the maximum number of publications published in 2015 was 25, and the minimum number in 1993 was only one.

Analysis of Most Productive Countries/Regions

Using VOSviewer to draw a collaborative network diagram of various countries based on the information from published articles, Figure 2A showed the collaborative relationships between different research topics in different countries. The United States publishes the most and collaborates with other nations the closest. According to the ranking of the top five countries based on the quantity of published articles, most of the published articles on this topic were from the United States, followed by Canada, China, the United Kingdom, and Italy (Figure 2B).

Analysis of Most Productive Institutions

The following is a ranking of the top 10 research-producing institutions: University of Maryland Baltimore, University System of Maryland, Louisiana State University, Pennsylvania Biomedical Research Center, University of Toronto, Harvard University, University of California System, University of Texas Health Science Center Houston, Joslin Diabetes Center, Inc. Notably, the number of papers published by the top-ranked institution, the University of Maryland Baltimore, was nearly twice that of the second-ranked institution, the University System of Maryland (Figure 3).

The Sankey diagram revealed that the main research topics include NTDs, preheating, risk, women, birth defects, endoscopic stress, etc. Among them, NTDs, preheating, and risk rank in the top three. Among them, NTDs are the research focus of various countries and institutions. For these research topics, the United States has the most exposure, followed by China and Canada (Figure 4).

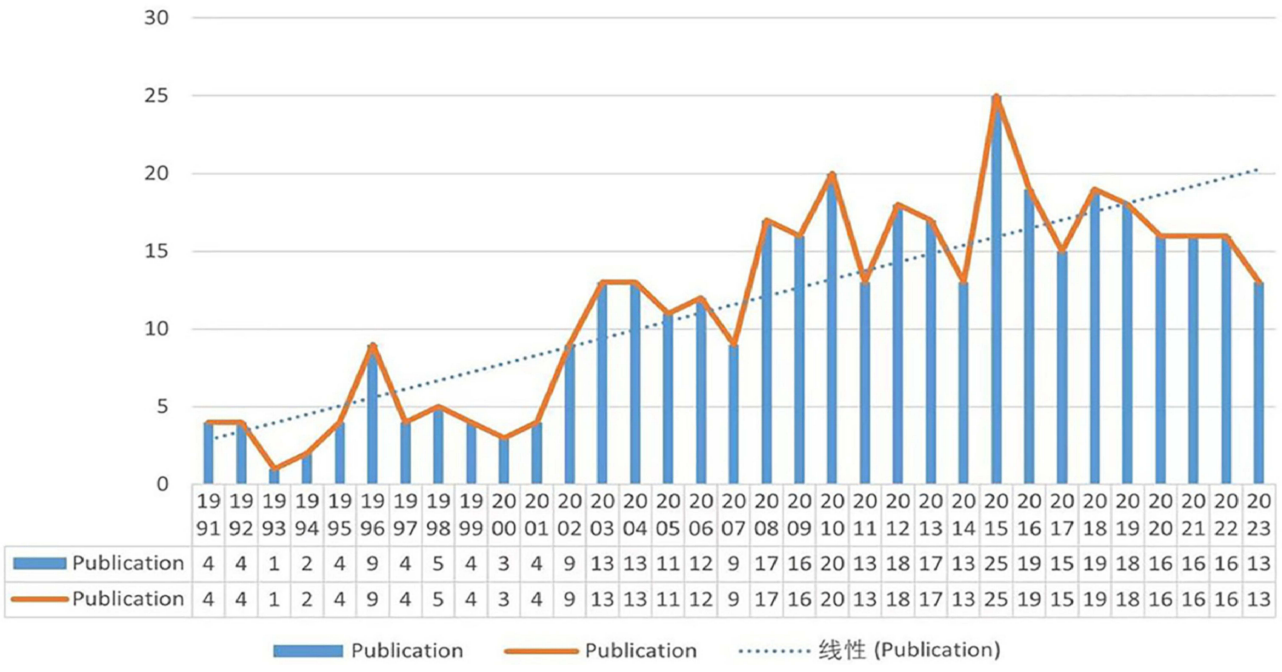

Figure 1 Annual research publications involving maternal diabetes and neural tube defects from 1991 to 2023.

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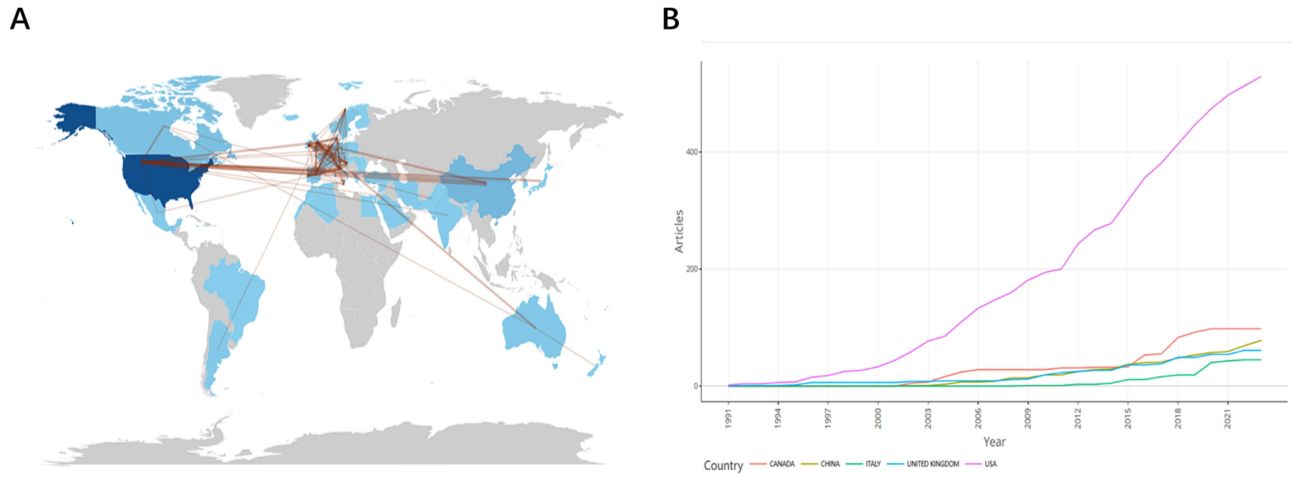

Figure 2 (**A**) Network diagram of collaborative relationships between countries, where different color depths represent different numbers of publications in different countries. (**B**) The total number of papers published in five countries or regions.

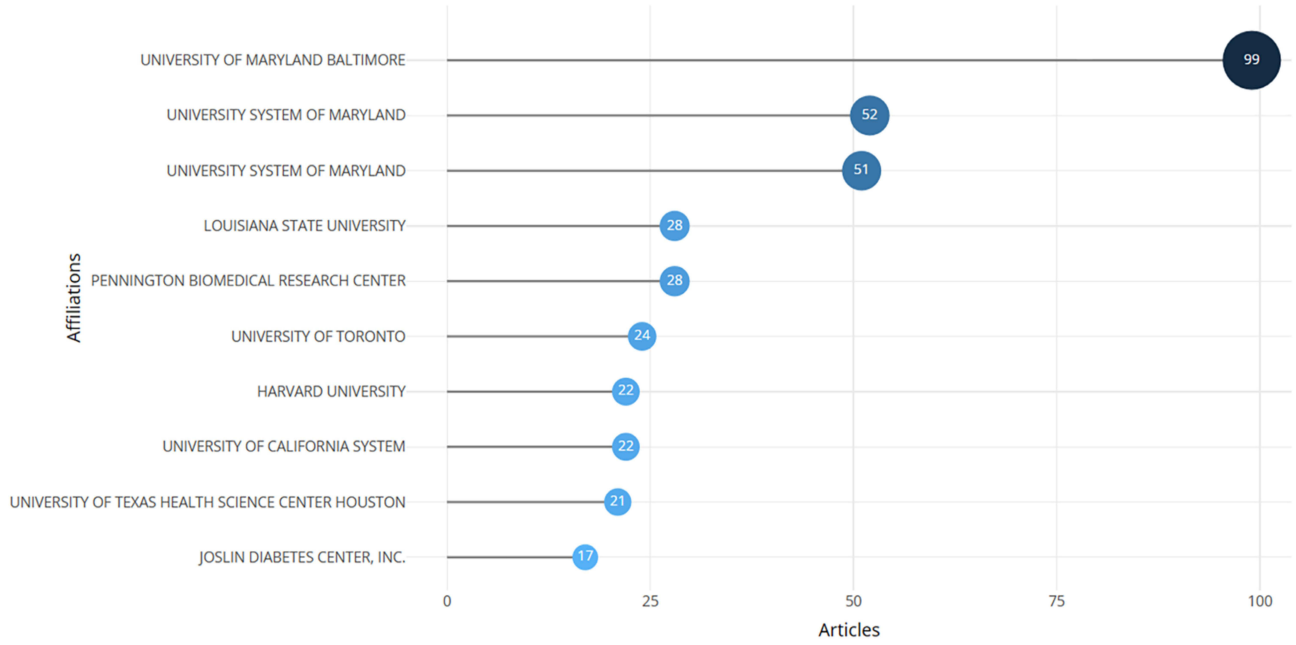

Figure 3 Institutions with the largest contribution and most published papers in the field related to maternal diabetes and neural tube defects.

Analysis of Higher-Impact Journals

The top 10 journals in terms of publication quantity were presented in Figure 5. The American Journal of Obstetrics and Gynecology and Birth Defects Research Part A-Clinical and Molecular Teratology have the highest number of articles published, making them the mainstream journal in the field, followed by Diabetes.[10,11]

Analysis of Productive Authors

Lotka's law reveals that the proportion of authors with one article published in this field was close to 80%, indicating that the field had not yet been thoroughly researched (Figure 6). Figure 7 displayed the top 10 writers with the most published articles. Among them, REE EA is the most prolific author and also the author with the highest H-index, publishing 21 papers, followed by YANG PX and SHAW GM, publishing 20 and 14 papers respectively.

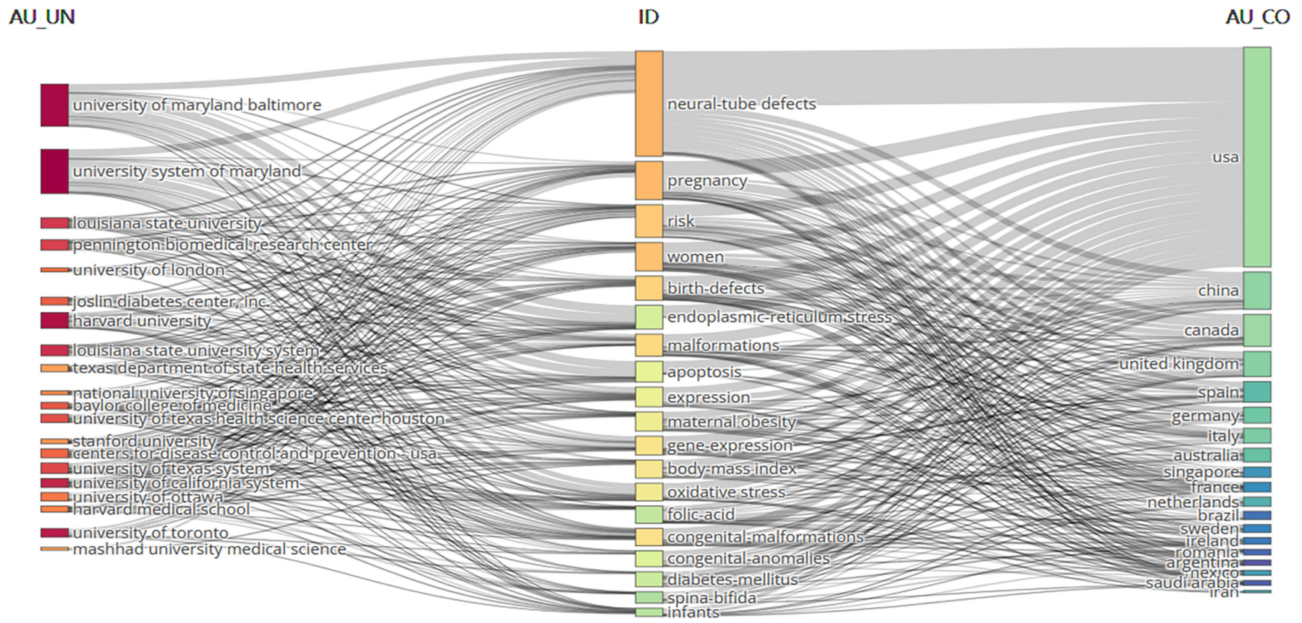

Figure 4 The institutions and countries to which high-frequency keywords appear in the article.

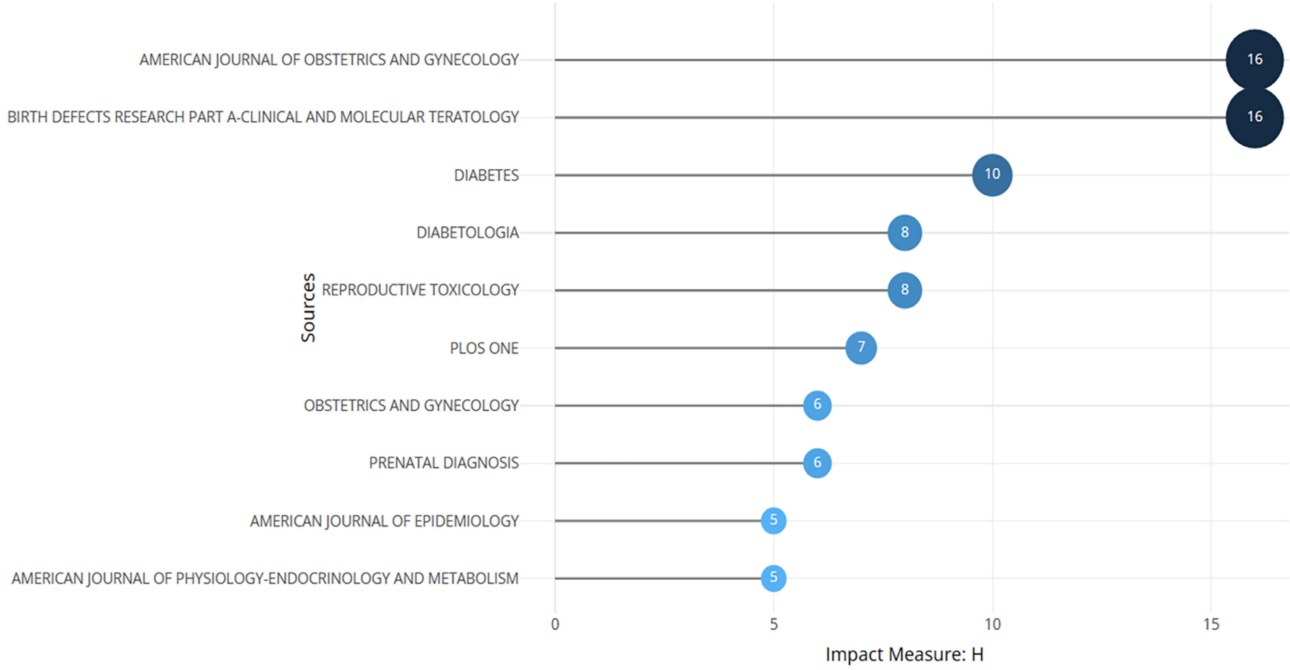

Figure 5 The top 10 journals in terms of the number of research publications.

Cluster Analyses

Trend Topic Chart

Figure 8 provided a graphical representation of the trend of theme words. The trend words added to the research focus included insulin resistance, folate, and policy aid supplementation. The size of the circle in the figure represented the proportion of each keyword based on region, with NTDs accounting for the largest proportion.

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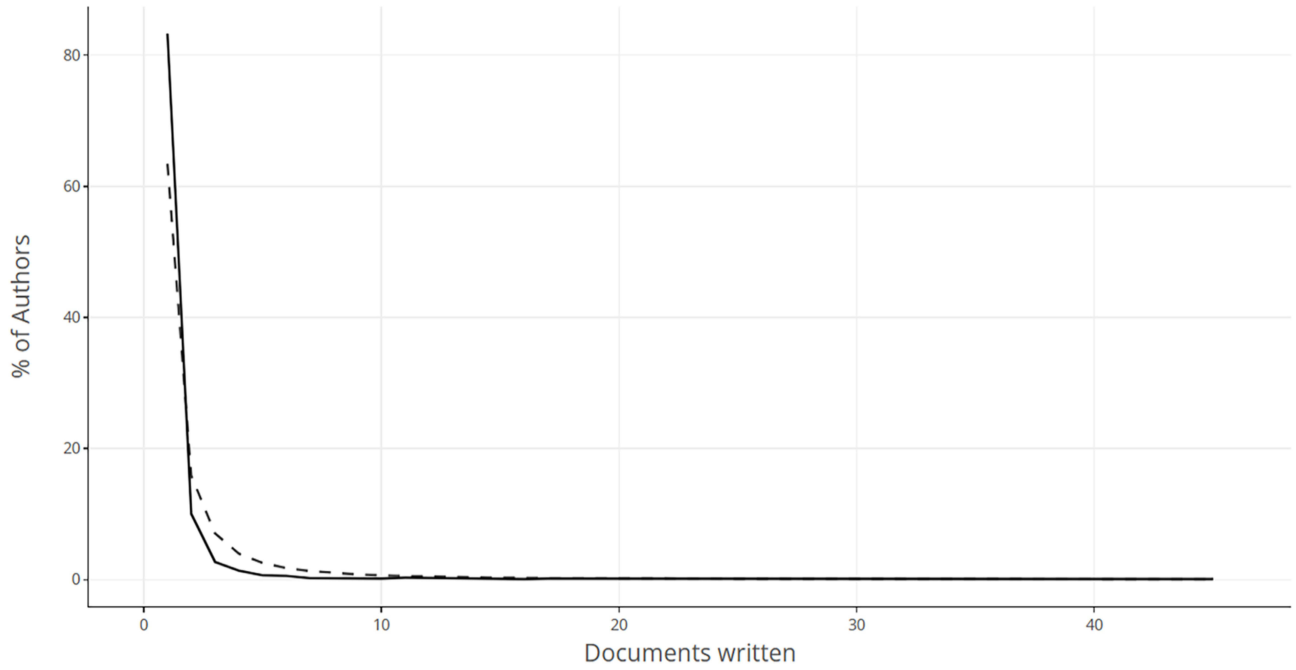

Figure 6 Lotka's Law.

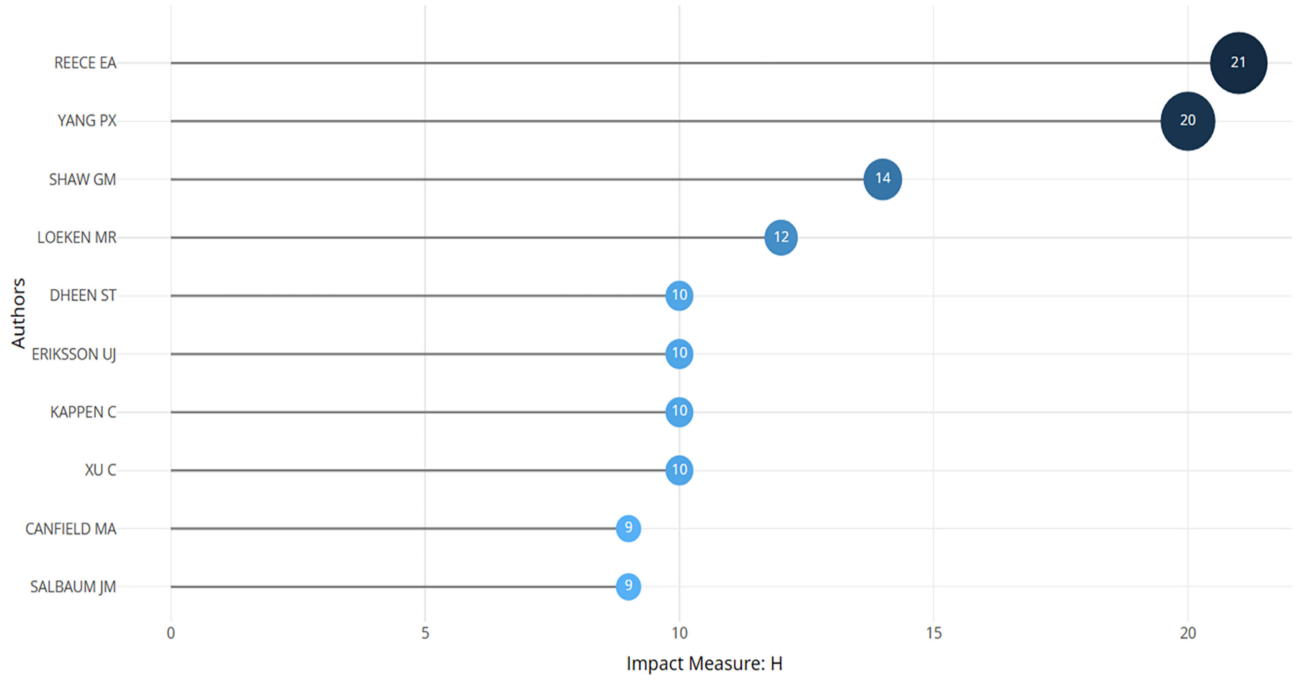

Figure 7 Top 10 high-yield authors in this field of research.

Keywords Clustering Analysis

An article's content and research focus could be briefly summarized using keywords. The co-occurrence graph of keywords can be used to analyze high-frequency keywords and display the evolution and development trends of research hotspots and frontiers over time. We constructed several clustering-based co-citation networks (Q=0.3779, S=0.7155) based on the references retrieved from 1993 to 2023, which were verified to be well-structured and sufficiently reliable. By removing irrelevant clusters and retaining highly correlated ones, a total of eight clusters were obtained, as shown in Figure 9, each

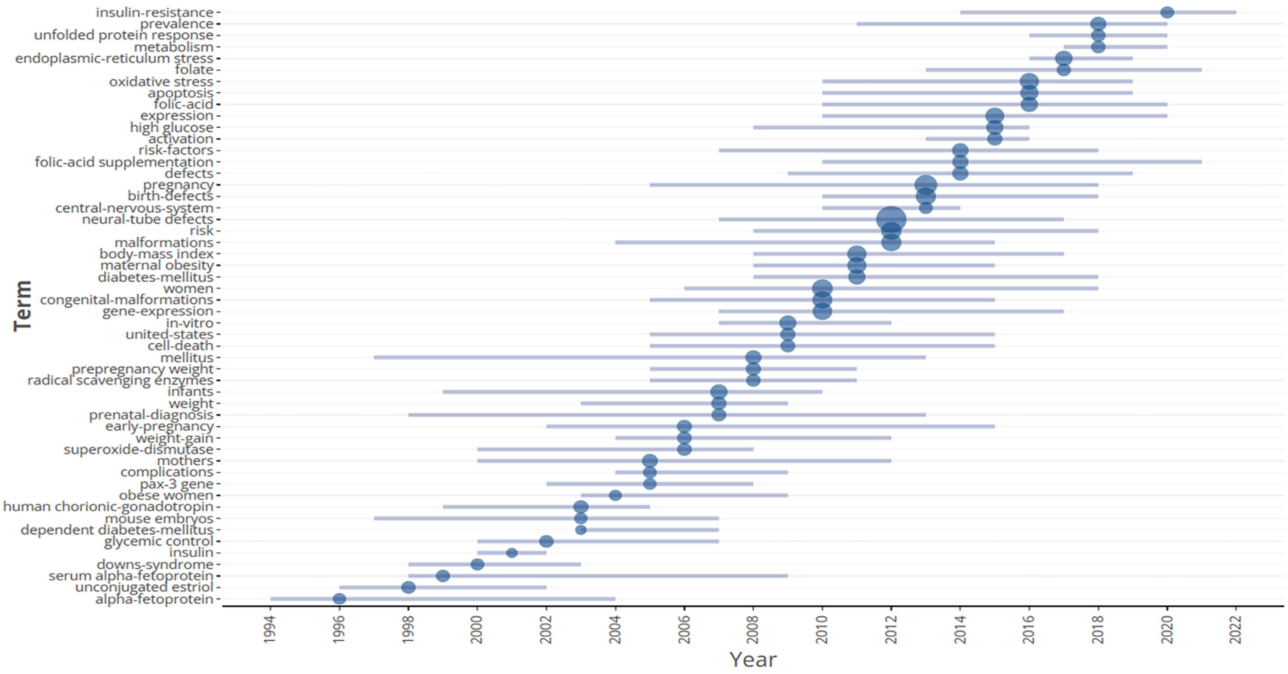

Figure 8 Map showing thematic trends over time.

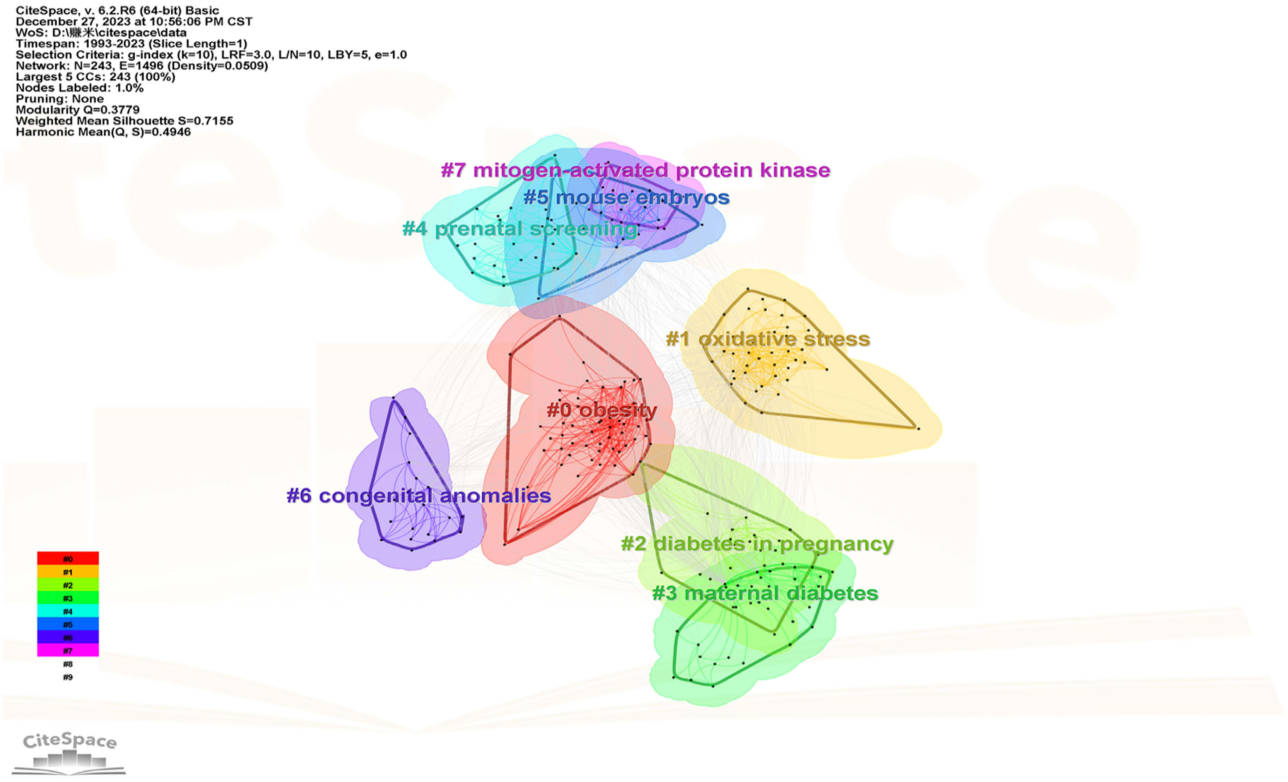

Figure 9 Cluster analysis of research hotspots and keywords.

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cluster was assigned a cluster number, which depended on its size (from maximum size (# 0) to a minimum size (# 7)): cluster # 0, "objectivity", cluster # 1, "oxidative stress", cluster # 2, "diamonds in prediction", cluster # 3, "material diamonds", cluster # 4, "preliminary screening", cluster # 5, "mouse embryos", cluster # 6, "congruent alloys", Cluster # 7, "mitogen-activated protein kinase".

Based on keyword co-occurrence and clustering, we ran the timeline module to obtain the timeline map of keywords (Figure 10). The research hotspots are mainly concentrated in three clusters, # 0, # 1, and # 3. From 2005 to 2015, the number of clustering results for # 0 and # 1 began to increase, and the nodes became dense, indicating that this cluster has received attention from researchers. In the development process of # 3 clustering, iconic keywords such as NTDs have emerged, affecting the overall trend of the clustering.

Keyword Emergence

Further keyword explosion analysis revealed the top 13 keywords with the strongest citation explosion. These keywords represent rapidly growing themes in the research field and reflect the forefront of research (Figure 11). The results showed that from 1999 to 2015, researchers mainly focused on the relationship between NTDs and maternal obesity, maternal diabetes, and hyperglycemia. Their main research directions were gene expression, endoplasmic reticulum stress, oxidative stress, and other mechanisms. Among them, "endoplasmic reticulum stress" was the word with the highest emergence intensity, and was widely considered by researchers from 2015 to 2020. Since 2016, the role of unfolded protein response in NTDs has received attention, and the knowledge framework and clinical applications in this field have rapidly developed. Research on the mechanisms underlying oxidative stress is also progressing, but at a somewhat modest pace. Since "policy acid" and "expression" are popular issues in both current and upcoming study in this field, researchers have concentrated on the relationship between neural tube abnormalities and these two factors in recent years.

Literature Emergence

Figure 12 listed the top 10 most cited references. The top three references with the strongest explosive citations are Occupational stress-induced JNK1/2 activation triggers, which lead to diabetic embryopathy, Material objectivity, Gestational diamonds, central nervous system birth defects, and Prediction objectivity as a risk factor for congenital structural abnormalities. The double map overlay of journals represents the distribution of academic journal topics

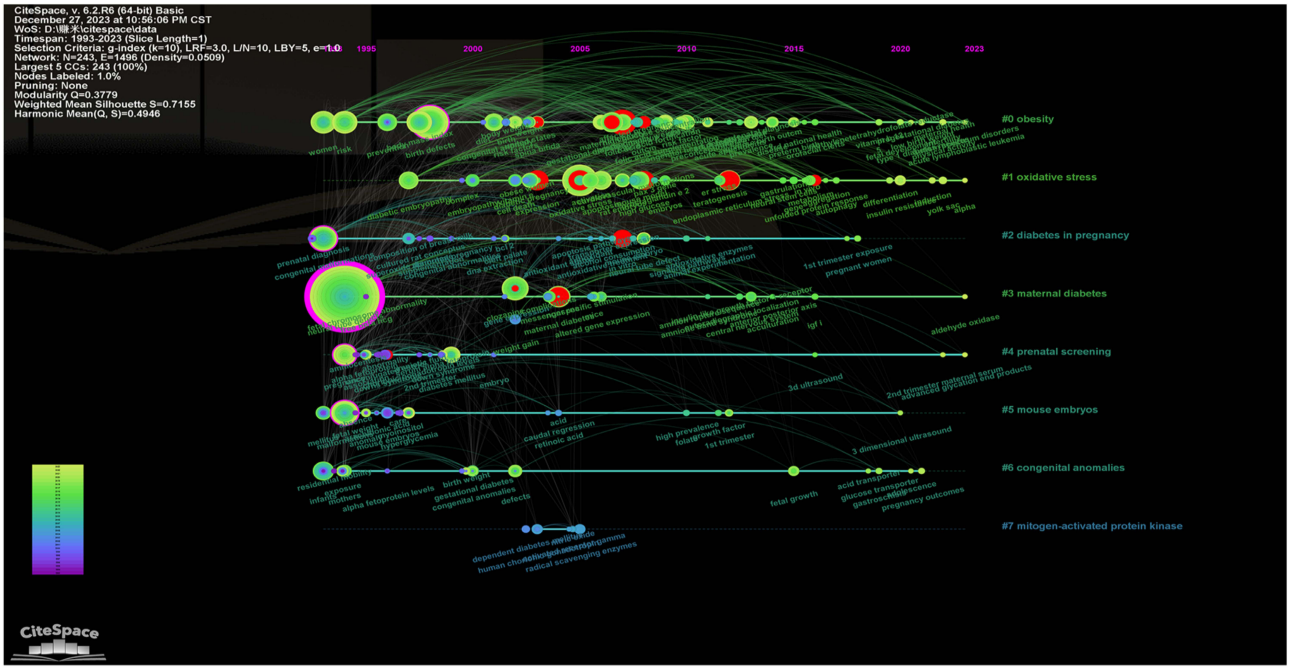

Figure 10 A timeline map of important keyword clustering from 1993 to 2023.

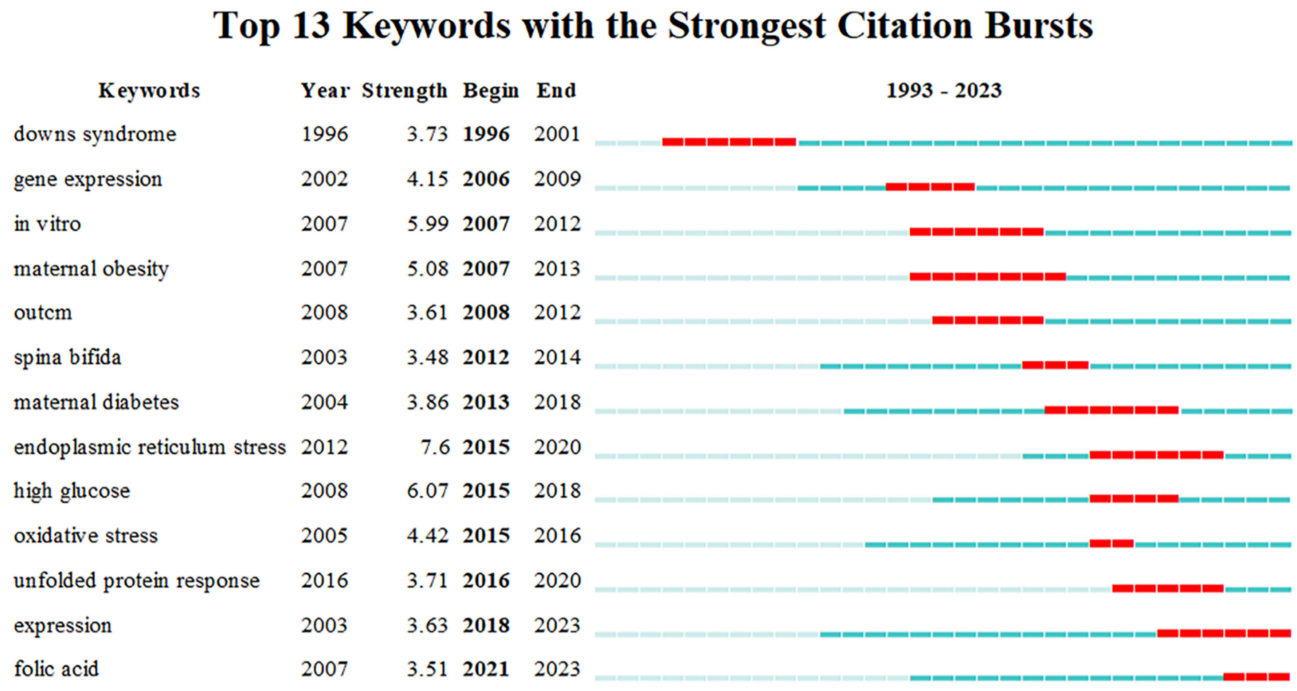

Figure 11 Top 13 keywords with the strongest citation bursts.

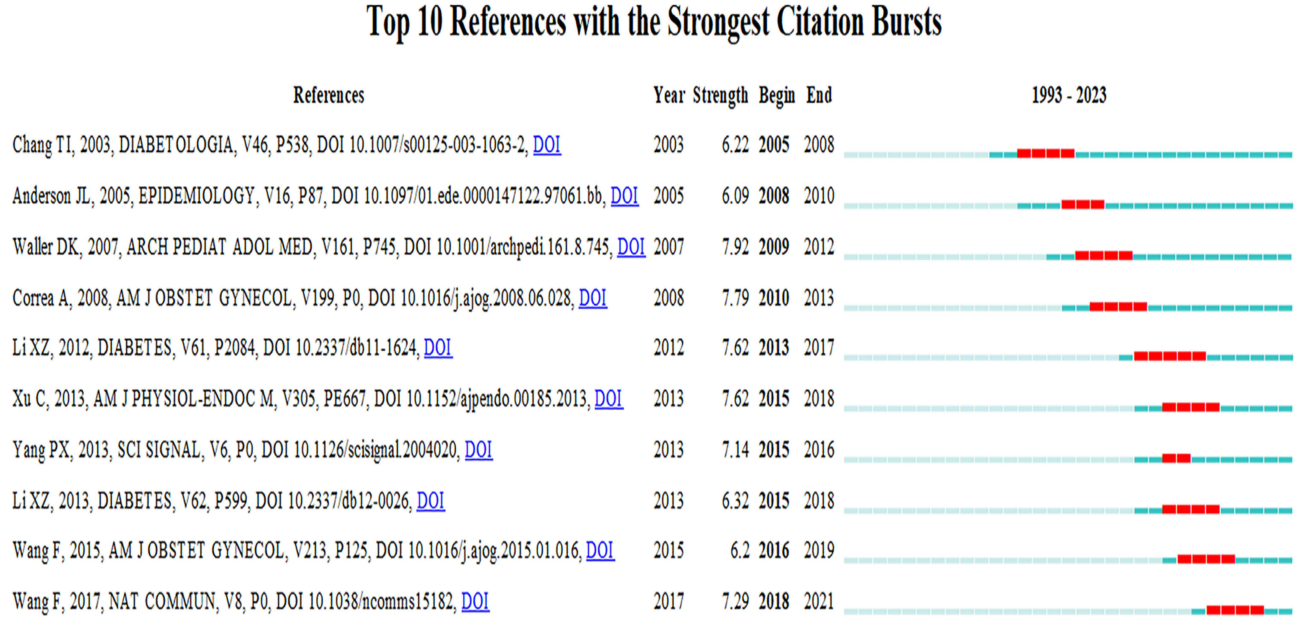

Figure 12 Top 10 references with the strongest citation bursts.

(Figure 13). On the double graph overlay results of journals, each journal is represented by a node, with points distributed on the left representing cited literature and points distributed on the right representing cited literature. Each arc represents a citation instance of a study, and the color of the citation link distinguishes different sources. After double graph superposition and journal clustering, it can be found that the cited journals are mainly distributed under the corresponding disciplinary themes of clinical research, molecular, biology, and immunology, while the cited literature disciplines are concentrated in the fields of health, drug development, molecular, biology, and genetics.

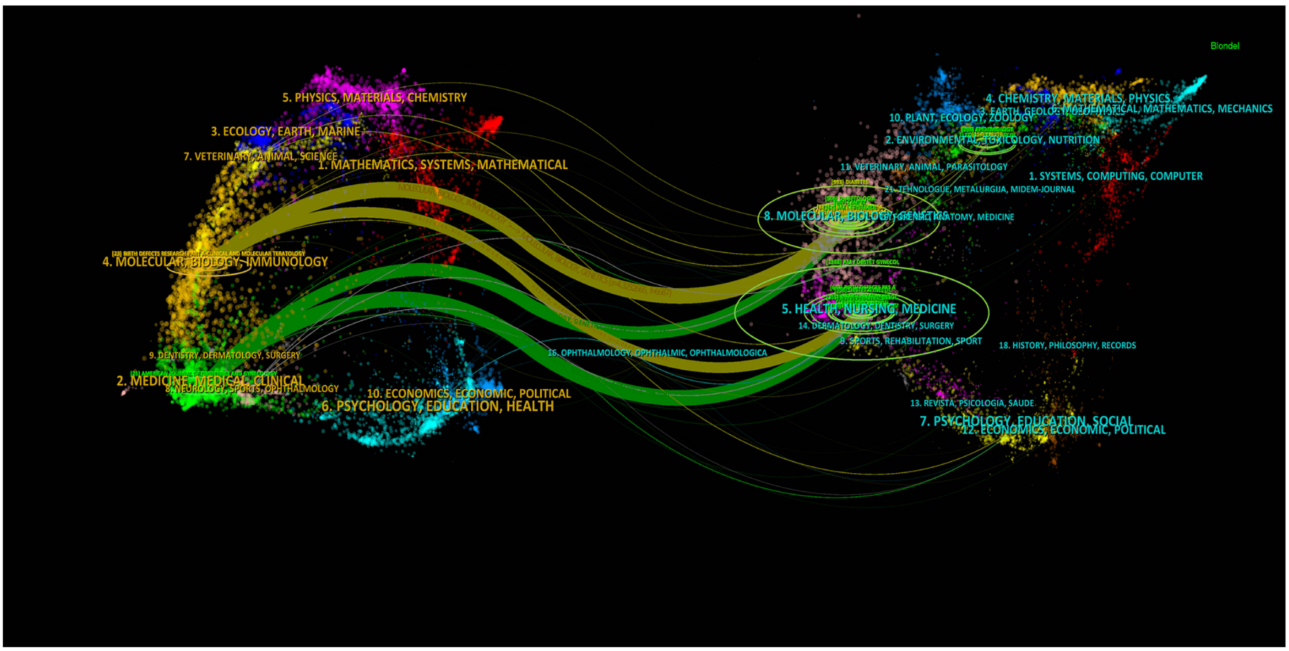

Figure 13 Dual-map overlay of journals related to maternal diabetes and neural tube defects.

Theme Strategic Analysis

The thematic strategic coordinate map, based on co-words and clustering, describes the development of research topics within a specific research field and the mutual influence between topics. As shown in Fig As shown in Figure 14, the strategic map represents the development status of the research topic during this period from two dimensions: centrality and density. There are four clusters visible in the figure The clusters located in the upper right quadrant include oxidative stress, expression, apoptosis, endoscopic stress, high glucose, and in vitro. They have received high attention and are important and well-developed topics in recent years (core research field). The cluster located in the upper left quadrant is

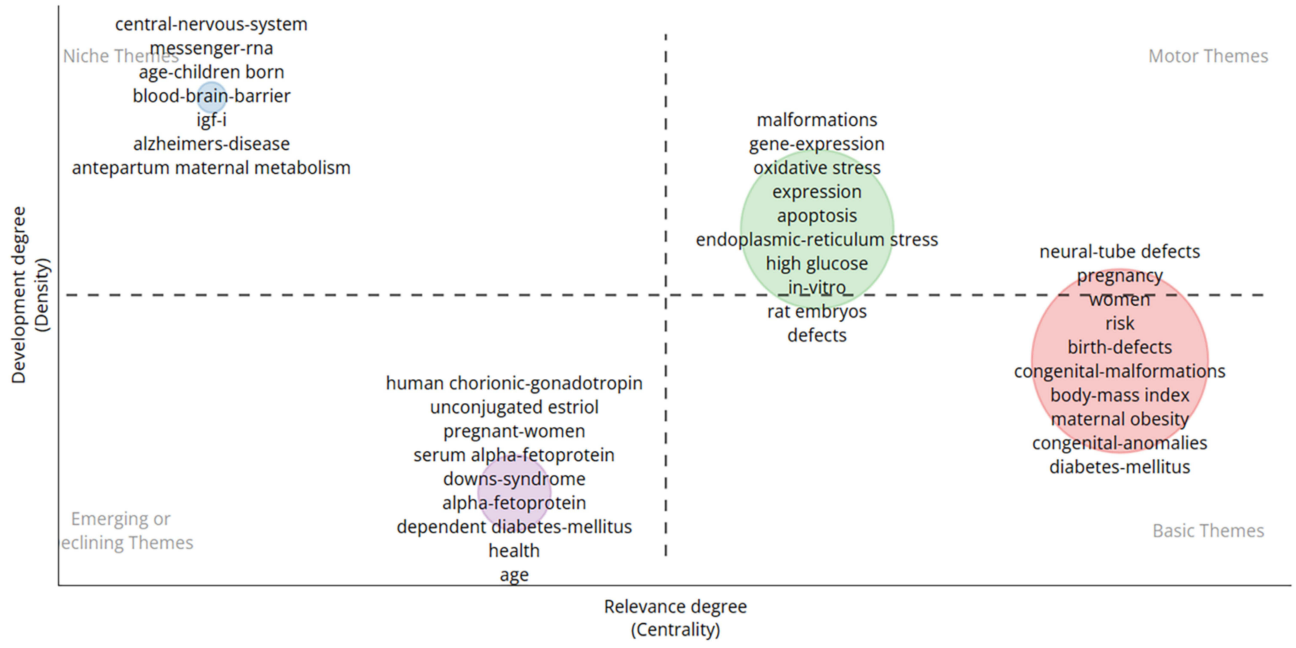

Figure 14 Strategy map. The clustering in the upper right quadrant is the core research area.

called the blood-brain barrier, which is a well-developed but relatively isolated topic and a new research hotspot in recent years. However, the level of attention is weak and may become the core content of research (potential research field).

Discussion

General Information About This Study

We used bibliometric methods and bibliometric software for the first time to comprehensively analyze the research overview of maternal diabetes and NTDs over the past 30 years, focusing on the current research status, summarizing the main research trends, and predicting future research hot spots and frontiers. The results indicated that the quantity of publications in this sector has fluctuated slightly over the past 30 years, but the overall trend is rising. Researchers' attention has been drawn to the establishment of neural tube abnormalities caused by maternal diabetes, as seen by the sharp increase in publications.

First, we examined the contributions of the state, institutions, journals, and authors in the study of the relationship between maternal diabetes and NTDs. The United States, Canada, and China were the key nations in this field of study, specifically the United States, which had a much higher quantity of publications, citations, and H-index than other countries, making it one of the leading countries in this research field. The majority of the top 10 institutions, authors, and journals in terms of publication quantity were from the United States, demonstrating the nation's rapid progress in the sector and proving to have the most reputable research journals, professional researchers, and institutions in the world. Chinese researchers and institutions ought to accumulate more experience in this subject and produce more high-quality articles, as evidenced by a comparatively small amount of publications, research institutions, and author impact in China as compared to the United States. Our research revealed that there were still disparities in this field's advancement on a national and regional level. Only China is a developing nation among the top five research-producing nations; the majority of research was conducted in industrialized nations like the US, Canada, and the UK. Therefore, there should be more exchange and collaboration between nations.

In addition, the most published articles and the greatest author influence in its field belonged to the esteemed American researcher REECE E.A. He was unswervingly committed to revealing the complex relationship between maternal diabetes and NTDs and had made indelible contributions to the creation of tactics to stop and cure this severe sickness caused by structural birth defects. The most compelling reference is that proapoptotic signaling and apoptosis that result in diabetic embryopathy are triggered by oxidative stress-induced JNK1/2 activation. This study proves that hyperglycemia-induced oxidative stress activates apoptotic JNK1/2 signal transduction and triggers neural tube cell apoptosis, indicating that targeted deletion of the JNK1 gene can improve diabetes-induced NTD.[2]

Keyword clustering and emergence analysis reflect the core theme and main content of current research and are hot topics in current and future research. An increasing amount of data highlights the connection between neural tube malformations and maternal diabetes, which is crucial to understanding the etiology of NTDs. At the same time, the exploration of the mechanism is the first step to reveal the potential therapeutic target of neural tube abnormalities caused by maternal diabetes, which is of great significance for guiding clinical practice and taking effective preventive measures.

Research Status

Early embryonic development is known as "neurogenesis", a process in which growing neuroepithelial cells fold into neural tubes, the rudimentary form of the central nervous system (CNS).[3] The failure of neural tube closure will lead to NTD (NTD), which is a serious structural birth defect, and will affect the mortality and incidence rate of offspring. It is the second largest birth defect after congenital heart disease.[4] The global prevalence of NTDs ranges from 0.5 ‰ to 10 ‰, with 300000 to 500000 new cases occurring globally each year.[5] Nongenetic causes are the primary cause of most human NTDs. The primary and increasingly common nongenetic cause causing NTDs is maternal diabetes.[6] Maternal diabetes can trigger a variety of cell stress responses and subsequent abnormal signal transduction pathways, such as mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress, leading to gene imbalance in the affected organs of developing embryos and increased programmed cell death (apoptosis) in neural folds, and inducing the formation of NTD.[7–9] Using bibliometric analysis, we examined the primary mechanisms behind neural tube abnormalities caused by maternal diabetes.

Endoplasmic Reticulum Stress

The primary job of the endoplasmic reticulum is to modify and appropriately fold newly synthesized proteins into dimensional structures after translation. Because hyperglycemia impairs the endoplasmic reticulum's (ER) ability to function, aberrant protein folding and misfolded proteins remain in the ER.[10] The accumulation of misfolded proteins can trigger unfolded protein response (UPR) and endoplasmic reticulum stress.[12] Maternal diabetes-induced ER stress activates CHOP (C/EBP homologous protein), PERK (protein kinase RNA like ER kinase), and eIF2 α (Eukaryotic initiation factor 2α). The signal cascade reaction to regulate protein quality control and cell activity increased CHOP expression, which has a significant part in the route that promotes apoptosis execution by inhibiting C/EBP β Transcriptional activity to inhibit peroxisome proliferator activated receptors- γ Co activation factor-1 α (PGC-1α).[13] The expression of mitochondrial DNA induces mitochondrial dysfunction and ultimately leads to NTD.[14] Treatment with 4-phenylbutyric acid, an endoplasmic reticulum stress inhibitor, can considerably lessen the development of NTD and eradicate the high glucose-induced endoplasmic reticulum stress in cultured embryos at the neurogenesis stage, bolstering the theory that the development of maternal diabetes-induced NTD is caused by endoplasmic reticulum stress.[15]

Mitochondrial Disorder

Aberrant mitochondrial architecture is one of the main signs of mitochondrial malfunction. Mitochondria exposed to maternal diabetes embryonic neuroepithelial cells show structural abnormalities, including crest disorder or destruction, reduced matrix electron density, and mitochondrial swelling with complete loss of crest, which is related to diabetes embryopathy. Maternal diabetes can activate apoptosis-promoting Bcl-2 family members (including Bax, Puma, Bak, and Bim), leading to mitochondrial dysfunction.[9,16] Mitochondrial dysfunction can enhance the production of ROS.[11] Nitric oxide (NO) synthase 2 (NOS2) and reactive oxygen species (ROS) both produce more NO when blood sugar levels are high. ROS is a chemically reactive molecule containing oxygen and a natural byproduct of aerobic respiration and substrate oxidation. It is essential to maintaining homeostasis and cellular signaling, typically present at low levels in cells.[11] NO is a key signaling molecule involved in many processes, regulating cell survival, apoptosis, and differentiation. An appropriate intracellular concentration of nitric oxide has a significant impact on the early development of the embryo, which is a prerequisite for normal embryonic development. The imbalance of nitric oxide concentration is related to abnormal embryonic outcomes. When NO production increases, nitrite, oxidative stress, and endoplasmic reticulum (ER) stress conditions are generated in the embryo, triggering neural folds to undergo programmed cell death, also known as apoptosis, causing NTDs (NTD) in embryos.[17]

Autophagy

An internal metabolic process called autophagy eliminates damaged organelles and abnormal protein aggregates, thereby maintaining cellular homeostasis. Damage to autophagy causes an imbalance within the cell, which in turn triggers cell death. Protein kinase C (PKC) mediates cell stress response and can eliminate maternal diabetes-induced embryonic organelle stress in the stage of neurogenesis.[18] It is a negative regulator of autophagy and mediates maternal diabetes's inhibition of autophagy.[19] One factor that promotes autophagy is PGC-1α, that regulates mitochondrial function and cell vitality, and is abundant in the central nervous system. By boosting mitochondrial proliferation, DNA maintenance, oxidative phosphorylation, and reactive oxygen species (ROS), it promotes mitochondrial biogenesis and function. Overexpression in neuroepithelial cells eliminates autophagy damage induced by maternal diabetes and solves cell homeostasis imbalance by avoiding ER stress and mitochondrial malfunction, Overexpression inhibits cell apoptosis and ultimately reduces the formation of NTD.[20] Wang et al used PKC-α knockout mice to test the function of this gene activation in NTD induced by diabetes. They found that the deletion of PRKCA can inhibit mitochondrial translocation of Bak, Bax, Puma, and Bim, members of the Bcl-2 family that promote apoptosis induced by maternal diabetes, alleviate organelle stress, restore cell homeostasis and prevent cell apoptosis, improve the formation of NTD. They also clarified the role of two negative autophagy regulators in maternal diabetes and established a framework for possible therapeutic intervention to treat NTDs caused by diabetes in mothers by either increasing PGC-1α activity or targeting PKCα.[19]

Oxidative Stress

Oxidative stress is the core mechanism of inducing diabetes embryopathy. Evidence from clinical and experimental studies shows that maternal diabetes induces oxidative stress by increasing the production of ROS and reducing the activity of cellular antioxidant defense enzymes.[21] NTD is created when aberrant cells in embryonic neural tubes die as a result of oxidative stress activating a set of pro-apoptotic kinase signal intermediates. There is proof that transcriptional pathways used by mothers with diabetes contribute to autophagy impairment. By altering the expression of the autophagy gene, Forkhead box O3a (FoxO3a) mediates the suppression of autophagy caused by high glucose in vitro and maternal diabetes. FoxO3a knockout mice were used to generate neural-specific dominant negative (DN) FoxO3a transgenic mouse lines lacking chromatin remodeling domains (TADs). FoxO3a deletion or DN FoxO3a overexpression eliminated the inhibition of maternal diabetes on the expression of autophagy-related genes (Atgs) and autophagy, thereby improving the apoptosis of neuroepithelial cells and NTDs induced by diabetes.[22]

Superoxide dismutase (SOD) enzyme is responsible for most of the ability of cells to clear and reduce cellular ROS levels. SOD1 is mainly located in the cytosol, but also in the nucleus, lysosome, and peroxisome. Overexpression of SOD1 reduces oxidative stress and eliminates diabetes-induced PKCα activation and superoxide production blocked endoplasmic reticulum stress and reduces the incidence of NTDs.[10] Quercetin 3-glucoside (Q3G) can inhibit NOS2 and increase the expression of SOD1, enhance the antioxidant capacity of cells, improve intracellular stress, regulate gene expression, and reduce embryonic abnormalities in diabetes pregnancy.[23] Only the mitochondrial matrix contains SOD2. Overexpression of SOD 2 reverses mitochondrial dysfunction induced by maternal diabetes by inhibiting the production of mitochondrial ROS and oxidative stress, activation of Bcl-2 members, ER stress, and caspase cleavage to reduce apoptosis of neuroepithelial cells and improve the incidence rate of NTD in developing embryos.[11]

Roles of Folic Acid

Water-soluble vitamin B, folic acid, is a vital element for mammalian cell viability. It cannot be synthesized in the body and must be obtained from exogenous sources, such as fruits and green leafy vegetables. Folic acid enters cells through folate receptor I or reduced folate carriers for nucleotide biosynthesis, methylation reactions, and oxidative stress. When a shortage in folate impairs cells' ability to operate normally biologically, it can lead to oxidative stress, affect the integrity of mitochondrial DNA, and impair genomic stability.[24] Pathological studies have found that inadequate folate in early stages of development of an embryo can lead to disruption of the fibroblast growth factor (FGF) pathway and result in NTDs.[25] In the meantime, under low folate conditions, inhibition of H3K79 (histone H3 lysine 79) demethylation is connected to the development of NTDs.[26] Zhang et al discovered that pregnant women with NTDs had considerably lower serum folate concentrations than the control group, and insufficient folate intake (less than 7.01 nmol/L in serum) increased the risk of NTDs.[27] Supplementing with folic acid (0.4mg/d) during pregnancy can reduce the incidence of NTDs.[28] Therefore, folic acid is effective in preventing NTDs.

High Glucose

High glucose can also inhibit the differentiation of neural cells. Oxidative stress and ER stress may be the reasons why high glucose inhibits the differentiation of neural stem cells. High glucose induces severe ER stress and sustained UPR through oxidative stress, leading to the occurrence of HDT.[29] In addition, a study showed that high glucose treatment significantly reduced the expression of neuronal and glial cell markers, while enhancing the autophagy activity mediated by peroxisome proliferator activated receptor gamma (PPAR gamma). Changing PPAR gamma activity affects the differentiation of neural stem cells exposed to HG, so high glucose may inhibit the differentiation of neural stem cells by enhancing PPAR gamma mediated autophagy activity.[30] Another study shows that high glucose will increase miR-200c in neural stem cells, which will lead to cell aging and DNA damage in neural stem cells, thus causing maternal diabetes to induce HDT.[31]

Prospects

The swift advancement of high-throughput sequencing technologies, like genomics and space transcriptomics, A substantial amount of studies have been carried out on maternal diabetes and NTDs. By researching the etiology of

neural tube abnormalities brought on by diabetes in mothers, we will find new key targets. At the same time, future research needs to further explore the relationship between maternal diabetes and the occurrence, development, and treatment of NTDs, and explore new treatment strategies.

Limitations

Based on the bibliometric method, this study visualized the study of maternal diabetes-induced NTDs to understand the trends and hot spots in this field. Nonetheless, significant limitations exist in the study. Firstly, because of the shortcomings of the scientific econometric software that is now in use, there may be a possibility that relevant literature has not been included. In the future, We will try to analyze data from more databases. Secondly, since English literature serves as the primary source for our research, some excellent works written in other languages may be overlooked. We hope to provide detailed explanations of these restrictions in the future.

Conclusion

Maternal blood glucose control during pregnancy is of great significance in preventing NTD. By improving folate metabolism, reducing oxidative stress, regulating cell apoptosis, and ensuring angiogenesis and nutrient supply, the risk of NTD can be effectively reduced. Future research should focus on the damage pathways of oxidative stress at the cellular level, as well as the intrinsic relationship between endoplasmic reticulum stress, blood glucose control, and NTD pathogenesis, in order to provide a basis for relevant treatment strategies. In addition, when using bibliometric analysis in this study, there are limitations in the scope of the database and language bias, which affect the comprehensiveness and universality of the research. In the future, it is necessary to integrate multiple sources of databases and multilingual literature. In conclusion, pregnant women who are at risk of diabetes or have been diagnosed need to strictly control their blood sugar, which is of great significance in reducing the incidence of NTD and improving the quality of the birth population. In the future, more comprehensive data should be combined to conduct in-depth research on the relationship between blood glucose control and the pathogenesis of NTD, in order to provide more precise strategies for clinical intervention.

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Disclosure

The authors report no conflicts of interest in this work.

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