## REVIEW Open Access



# Schizophrenia and epigenetics: a comprehensive bibliometric analysis

Abd Rahim Nour El Huda<sup>1\*</sup>, Abdull Jalil Mohd Asyraf<sup>1†</sup>, A. Talib Norlelawati<sup>2†</sup>, Mat Rasid Siti Norain<sup>1†</sup>, Wan Salleh Wan Muhamad Salahudin<sup>1†</sup>, Azman Norainin Sofiya<sup>2†</sup> and Norbaiyah Mohamed Bakrim<sup>1†</sup>

#### **Abstract**

**Background and objective(s)** Numerous studies have explored the association between epigenetics and schizophrenia, yielding various findings and reports. Thus, we conducted a bibliometric analysis of the studies that have investigated this association to provide an overview of the evolution of research on this topic and to determine the current status and areas for advancement in this field.

**Methods** We applied several methodologies, such as keyword co-occurrence and co-authorship analysis, to the SCO-PUS database to analyze the most significant authors, institutions, and countries and the most cited publications. Several analytic tools were employed, namely Bibliomagika 2.2 and Bibliomagika 1.5 Split for frequency analysis, VOSviewer for data visualization, and Biblioshiny packages from R software to perform the bibliometric analysis.

**Results** A total of 397 publications were retrieved, and most were published in 2013, revealing an increasing trend over the past decade. The most productive contributors based on the number of published documents were the *Alessandro Guidotti* (24 publications), the *University of Illinois at Chicago* (21 publications), the *United States of America* (159 publications), and the *Journal of Schizophrenia Research* (22 publications). The top keywords were schizophrenia (250 occurrences), DNA methylation (174 occurrences), and epigenetics (121 occurrences).

**Conclusions** The findings shed light on the research trends, country contributions, influential authors, and most active journals on the topic. This information can help researchers identify gaps and future directions in the field and can provide a platform for progressing knowledge in this field.

**Keywords** Schizophrenia, Epigenetics, Bibliometrics, Review, biblioMagika, VOSviewer, Bibliometrix, Biblioshiny, DNA methylation

#### Introduction

Schizophrenia is a severe psychiatric illness that affects approximately one in one hundred people worldwide [4]. It is characterized by a wide range of symptoms that encompasses delusions, hallucinations, social withdrawal, and cognitive difficulties, all of which can result in disability [6]. Early mortality rates are two to three times higher among patients with schizophrenia compared to the general population [14]. The current interventions for schizophrenia are primarily antipsychotic medications, which have significant side effects, including movement disorders, weight gain, and metabolic disturbances [26, 38].



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

<sup>&</sup>lt;sup>†</sup>Abdull Jalil Mohd Asyraf, A. Talib Norlelawati, Mat Rasid Siti Norain, Wan Salleh Wan Muhamad Salahudin, Azman Norainin Sofiya and Norbaiyah Mohamed Bakrim contributed equally to this work.

<sup>\*</sup>Correspondence: Abd Rahim Nour El Huda elhuda@iium.edu.my

<sup>&</sup>lt;sup>1</sup> Department of Basic of Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia, 25200 Kuantan, Malaysia

<sup>&</sup>lt;sup>2</sup> Department of Pathology and Laboratory Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, 25200 Kuantan, Malaysia

Epigenetics refers to the genetic changes associated with the environment that modulate gene expression without changing the nucleotide sequence [3]. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodeling, and noncoding RNA modification [39]. The determination of epigenetic changes in relation to a particular disease or condition is important pharmacologically, as it can result in personalized therapeutic interventions and the potential development of new drug targets [9]. Furthermore, this knowledge has the potential to serve as new diagnostic and therapeutic biomarkers in the management of schizophrenia [10].

A study of the bibliometrics of the available publications regarding any particular topic can help to evaluate the publication trends within a particular time frame [7]. Such a data analysis allows researchers to obtain bibliographic information concerning the authors, institutions, and countries of origin of the publications, in addition to information regarding journals' performance and collaboration patterns among scholars, institutions, and countries [7]. This allows researchers to understand the range of topics of interest and to predict future directions within specific fields.

Several studies have involved bibliometric reviews regarding different aspects of schizophrenia research (Table 1), retrieved from Google Scholar on September 23, 2023 (using allintitle: "bibliometric" and

"schizophrenia"). The most recent publication by Zakaria et al. [42] analyzed trends in genetic studies regarding schizophrenia before and after the genomewide association studies (GWAS) era, using a total of 5615 publications. Based on the authors' keywords, they demonstrated that in the post-GWAS era, there has been a trend toward the application of precision medicine and the interplay between genetic and environmental factors in schizophrenia pathogenesis. This shift would lead to a surge in focusing on the epigenetics of schizophrenia, since epigenetics is one the mechanisms that could explain this relationship. The remaining bibliographic reviews analyzed trends within studies investigating the association of schizophrenia with inflammation, microbiology, oxidative stress, and magnetic resonance imaging findings.

We evaluated the previous literature concerning the epigenetics of schizophrenia using numerous bibliometric analysis methods to generate the distribution patterns of articles within several parameters including the trend of publications, most productive authors, institutions, countries, and journals as well as the characteristics of the article publications. We hoped to gain a deeper understanding of the research's evolution and to assist academicians and researchers in making recommendations for future studies regarding the epigenetics of schizophrenia.

**Table 1** Summary of previous studies

Author	Objective of the study	Data source, retrieval date, and year duration	TDE	
Duan and Zhu [8]	To analyze the use of magnetic resonance imaging (MRI) in schizophrenia	Web of Science (February 9, 2022) (2004–2018)	3596	
Sun et al. [27]	To explore the field of inflammation-related research in schizophrenia	Web of Science (February 19, 2022) (1991–2022)	3596	
Uy and Tantengco [30]	To determine the characteristics and trends of published articles about schizophrenia in Southeast Asia	Scopus (December 12, 2021) (1973–2021)	1068	
Yang et al. [40]	To summarise the association between the gut microbiota and schizophrenia	Web of Science (2013–2022)	162	
Chen et al. [5]	To explore the field of schizophrenia and oxidative stress-related research	Web of Science (1990–2021)	3510	
Şevik and Alkan [23]	To investigate the relationship between schizophrenia and Toxoplasma gondii	Web of Science (May 31, 2022) (1991–2023)	447	
Shekhar [25]	To visualize the trends and themes related to schizophrenia research amidst COVID-19	Scopus (2020–2022)	566	
W. N. A. Zakaria et al. [42]	To analyze genetic studies in schizophrenia in the pre-genome-wide association studies (GWAS) and post-GWAS era	Scopus (March 8, 2021) (1946–2020)	5615	

#### **Materials and methods**

#### Research questions

Clear and concise research questions are necessary to employ the bibliometric analysis methodology. The following research questions are addressed in this study to explore the different trends regarding research productivity, collaboration, and knowledge dissemination in relation to the epigenetics of schizophrenia. The following research questions (RQs) were formulated:

RQ1: What are the research trends and citation patterns in relation to the epigenetics of schizophrenia? RQ 2: Who are the most productive authors, and which institutions drive the advancement of research about the epigenetics of schizophrenia?

RQ 3: Which countries and collaboration networks contributed to the publications regarding the epigenetics of schizophrenia?

RQ 4: What are the most active and influential sources of research publications (i.e., journals) concerning the epigenetics of schizophrenia?

RQ 5: What are the frequent keywords in the existing publications on the epigenetics of schizophrenia?

#### Data search

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, as presented in Fig. 1 [20] to guide our analysis. We extracted data from the Scopus database on the 25th of September in 2023 and confined the search to the publication timeline ranging from the earliest article on epigenetics in schizophrenia research up to August 2023. This study included "articles" and "reviews" when refining document types, and the language was limited to "English."

We performed the search by utilizing specific keywords in the article titles, assuming that all the retrieved articles are related to the topic of the study. Since titles are typically viewed in the initial encounter with the content of an article (R. [41], the title-only search strategy indicates that the retrieved publications are directly related to the subject of interest [16]. The keyword search strings used were as follows: TITLE ( "epigenetic" OR "epigenetics" OR "epigenome" OR "epigenomic" OR "epigenomics" OR "DNA methylation" OR "hypermethylation" OR "hypomethylation" OR "histone modification" OR "non-coding RNA" OR "gene environment interaction" OR "DNA modification" OR "epigenesis" OR "methylation" OR "genome wide methylation" OR "DNA methyltransferase" OR "chromatin remodelling") AND TITLE ( "schizophrenia" OR "antipsychotics" OR "antipsychotic" OR "anti-psychotic" OR "clozapine" OR "risperidone" OR "haloperidol"). A total of 409 journal publications related to the epigenetics of schizophrenia were retrieved from the Scopus database.

#### **Data screening**

To ensure the quality of the bibliometric analysis, we only included journal articles that underwent a peer review process in this study. This was intended to guarantee that the studies were relevant and that they adhered to the standards and were transparent to the readers [17]. Our analysis excluded papers from conference proceedings, books, book chapters, and other forms of publications. The retrieved documents were examined for duplicates, and any irrelevant documents were removed. Based on these criteria, a total of 409 publications in scientific journals were selected. We then removed a further 12 articles (letters to editors and theology articles), resulting in a final total of 397 publications for bibliometric analysis. The selected articles represented a comprehensive overview of epigenetics in schizophrenia research within the Scopus database from 1966 to 2023. The publicationrelated data were exported as comma-separated values (.csv) and format files and saved for further analysis.

#### Data cleaning

Data cleaning and harmonization are critical steps in bibliometric analysis to ensure the accuracy and reliability of the results, due to redundancies in the downloaded raw Scopus data. For example, we identified the keywords and authors' names and affiliations and edited them using various techniques and functions available in the OpenRefine (https://openrefine.org/) clustering tools and biblioMagika® Microsoft Excel filters. These software tools were used to clean and harmonize unstandardized data and essential bibliographic information [2]. biblioMagika®, developed by Ahmi, [1] was employed to conduct extended bibliometric measurements of factors such as total publications (TP), number of contributing authors (NCA), number of cited publications (NCP), total citations (TC), citations per paper (C/P), citations per cited paper (C/CP), citations per author (C/A), citable year, and h-index. The h-index (or Hirsch index) and g-index are metrics that are used to measure the productivity and impact of a researcher's publications. The *h*-index is the highest number of *h*; thus, at least *h* publications in the list have been cited *h* times each [13]. In addition, we identified the missing data facilitated by biblioMagika® and subsequently edited the database manually.

Following the initial data cleaning, we manually checked the screened and edited keywords for accuracy using OpenRefine. Multivalued cells were joined, and the separators initially used during the splitting process

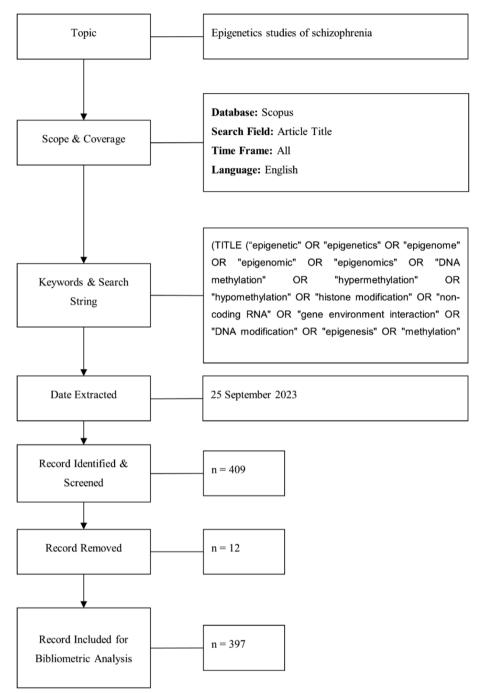


Fig. 1 PRISMA Flow diagram of the search strategy

were re-entered to maintain data consistency. We exported the cleaned and harmonized data to its original format for further analysis. Through the application of these methods, the data analyses became more valid and reliable.

#### **Bibliometric analysis tools**

We employed various tools to conduct a comprehensive bibliometric analysis. We used Bibliometrix (http://www.bibliometrix.org), an R-based package for quantitative bibliometric analysis, along with the web interface

Biblioshiny to analyze the.csv) file. We also used the freely available VOSviewer (http://www.vosviewer.com) software [31] to generate graphical visualizations of the data. Combining these tools and techniques facilitated a thorough and robust examination of studies about the epigenetics of schizophrenia.

#### Results

#### **Publication profiles**

We retrieved a total of 306 original articles and 91 reviews. These articles were published in 165 different journals. Based on the dataset, 2090 authors contributed to the study of epigenetics in schizophrenia, with a total of 3220 author appearances in the articles. There were 16 authors with single-authored papers and an average of eight co-authors per article. Seventeen documents were written by a single author, while the rest had two or more authors. The significant contributions of this area of research are demonstrated by the notably high *h*-index of 63.

#### **Publication trends**

Overall, the annual volume of publications regarding the epigenetics of schizophrenia has expanded over time (Fig. 2). Meanwhile, in terms of citations per year, the number was generally increasing until 2014, when it started to decrease. The yearly output before 2008 remained within single digits. However, the number started to steadily increase from 2009 onwards. Although there were only six publications in 2005, the total number of citations and the average number of citations per paper were remarkably high, at 1186 and 143.86, respectively. The year 2005 also ranks as the second highest for

citations compared to 2014, which had 30 total publications, 1814 total citations, and 60.47 average citations per paper. After 2014, the year with the highest number of publications regarding the epigenetics of schizophrenia was 2021, with a total of 37 articles. This indicates a growing interest in this research area. The bulk of publications were concentrated between 2013 and 2022.

#### Publications by authors and institutions

In total, 2090 authors contributed to this field of research. The top 10 authors included five from the University of Illinois in the USA, three from the University of Toronto in Canada, and one from each of the following institutions: Icahn School of Medicine, New York, USA, and the University of Tokushima, Japan (Table 2). The leading author in this research area was Alessandro Guidotti, with 24 articles. His publications spanned from 2002 to 2022, with an impressive total of 3222 citations. He also obtained 134.25 citations per paper and 140.09 average citations per cited paper, with an h-index of 22. The second most productive author was Dennis R. Grayson (19 articles), with a total of 2843 citations and an h-index of 18. Vincenzo De Luca had 14 articles, and Schahram Akbarian, with 13 articles, achieved h-index values of 5 and 11, respectively, among their 88 and 888 total publications. Meanwhile, Erminio Costa, with 12 articles, holds the fifth spot in the top 10 authors list, accumulating a total of 2158 citations with an h-index of 12.

Table 3 indicates the research productivity at the institutional level. The *University of Illinois* tops the chart, with a total of 31 publications. Its *h*-index of 26 reflects the quality and the high impact of its research output. The high total number of citations (i.e., 3540) further

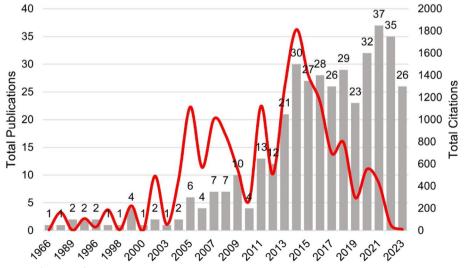


Fig. 2 Total publications and citations by year

**Table 2** Most productive authors

Author's name	Affiliation	Country	TP	NCP	TC	C/P	C/CP	h
Guidotti, A	University of Illinois at Chicago	USA	24	23	3222	134.25	140.09	22
Grayson, D	University of Illinois at Chicago	USA	19	19	2843	149.63	149.63	18
De Luca, V	University of Toronto	Canada	14	11	88	6.29	8.00	5
Akbarian, S	Icahn School of Medicine	USA	13	13	888	68.31	68.31	11
Costa, E	University of Illinois at Chicago	USA	12	12	2158	179.83	179.83	12
Davis, J. M	University of Illinois at Chicago	USA	11	10	1385	125.91	138.50	9
Gerretsen, P	University of Toronto	Canada	11	8	66	6.00	8.25	4
Graff, A	University of Toronto	Canada	11	9	67	6.09	7.44	4
Dong, E	University of Illinois at Chicago	USA	10	10	1035	103.50	103.50	10
Numata, S	University of Tokushima	Japan	9	9	283	31.44	31.44	8

TP Total number of publications, NCP Number of cited publications, TC Total citations, C/P Average citations per publication; C/CP Average citations per cited publication. h h-index: USA the Unites States of America

**Table 3** Most productive institutions with a minimum of five publications

Affiliation	Country	TP	NCP	TC	C/P	C/CP	h
University of Illinois at Chicago	USA	31	30	3540	114.19	118.00	26
Johns Hopkins University	USA	18	18	1414	78.56	78.56	15
University of Toronto	Canada	18	15	436	24.22	29.07	9
Harvard Medical School	USA	13	12	800	61.54	66.67	8
Centre for Addiction and Mental Health Toronto	Canada	12	10	143	11.92	14.30	5
Central South University Hunan	China	12	9	163	13.58	18.11	6
University of California Los Angeles	USA	12	12	1084	90.33	90.33	12
Icahn School of Medicine at Mount Sinai	USA	11	11	336	30.55	30.55	9
Shanghai Jiao Tong University	China	10	7	151	15.10	21.57	5
Boston University	USA	10	9	1005	100.50	111.67	8

TP Total number of publications, NCP Number of cited publications, TC Total citations, C/P Average citations per publication; C/CP Average citations per cited publication; h-index, USA United States of America

reinforces its influence in the research community. *John Hopkins University* and the *University of Toronto*, sharing the same total publication output (18), display varied research impacts. *John Hopkins University* demonstrated a more significant overall research impact, with a higher total number of citations (i.e., 1414), an average citation number per publication of 78.56, and an *h*-index of 15. This data offers a thorough perspective of institutional contributions, providing insightful information for future institutional collaborations.

#### **Publications by countries**

The research productivity of various countries that had produced at least 20 publications is illustrated in Fig. 3. The USA (159) had the highest number of publications, followed by China (72) and Canada (38). The *h*-index of 53 indicates the significant impact and quality of the research contributions. The USA was the most cited country (9692 citations), followed by the UK (1641) and Japan (1403), suggesting their strong influence on the

global scientific community. It is important to note that the high number of research studies concerning the epigenetics of schizophrenia was not limited to Western countries but also extended to Asian nations. China and Japan both exhibited *h*-indices of 19, highlighting their significant research contributions to the field.

The USA dominates in terms of scientific collaborations, collaborating with 29 countries, followed by the UK, with 17 countries. The USA collaborated most closely with China (24 publications), the Netherlands (11 publications), and Germany (9 publications). Meanwhile, the UK worked closely with the Netherlands, with six publications, as well as with Brazil, Germany, Italy, and Spain, with four publications each.

#### **Publications by journals**

The most active journals publishing articles about the epigenetics of schizophrenia from among those that had published a minimum of 10 documents are listed in Table 4. The journal titled *Schizophrenia Research* stood

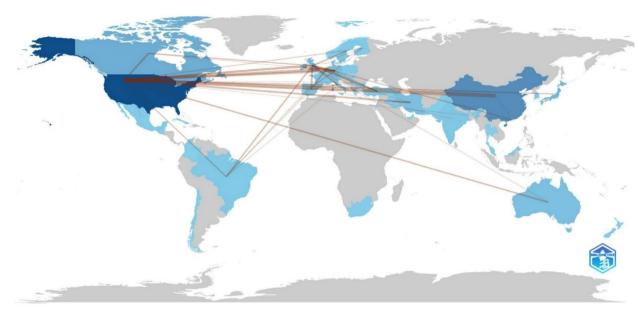


Fig. 3 World map of scientific production. Countries with darker blue shade have a higher number of publications, and the lines show the frequency of collaboration (Biblioshiny)

Table 4 Journals with active publications

Source title	TP	NCP	TC	C/P	C/CP	h
Schizophrenia Research	22	21	1121	50.95	53.38	18
Schizophrenia Bulletin	16	16	1587	99.19	99.19	14
Translational Psychiatry	15	14	551	36.73	39.36	10
Epigenomics	15	15	383	25.53	25.53	10
Psychiatry Research	13	13	130	10.00	10.00	8
Molecular Psychiatry	13	9	807	62.08	89.67	9
Journal of Psychiatric Research	13	13	459	35.31	35.31	10
Frontiers in Psychiatry	10	8	56	5.60	7.00	4

TP Total number of publications, NCP Number of cited publications, TC Total citations, C/P Average citations per publication, C/CP Average citations per cited publication, h h-index

out significantly, with the highest total number of publications of 22 and 1121 total citations, suggesting that it is becoming the primary publication platform for research distribution in this field. The second-highest journal was *Schizophrenia Bulletin*, with 16 publications but a significantly higher total citation count of 1587. Its *h*-index of 18 demonstrated the impact of its influential research, proving it to be a preferred reference source despite having fewer total publications. The *Translational Psychiatry* and *Epigenomics* journals each published 15 articles with noteworthy *h*-indices and *g*-indices of 10 and 15, respectively. While not leading in terms of the number of publications, the *Psychiatry Research* and *Molecular Psychiatry* journals exhibited a remarkable quantity of citations and average citations per paper, underscoring

the strong impact of the papers they published. This valuable information regarding the source titles is crucial for researchers to keep up to date with the latest discoveries and to select the appropriate publication platforms.

#### Top keywords

We performed an analysis of keywords using the cooccurrence of author keywords. Using a minimum number of occurrences of two, 177 out of 482 keywords were identified. Figure 4 presents a network visualization of the keywords in which the circle size represents the frequency of occurrences; the higher the frequency of the keyword, the larger the circle size [12]. The visualization network illustrates 14 clusters, with the largest circle representing the keyword "schizophrenia," indicating

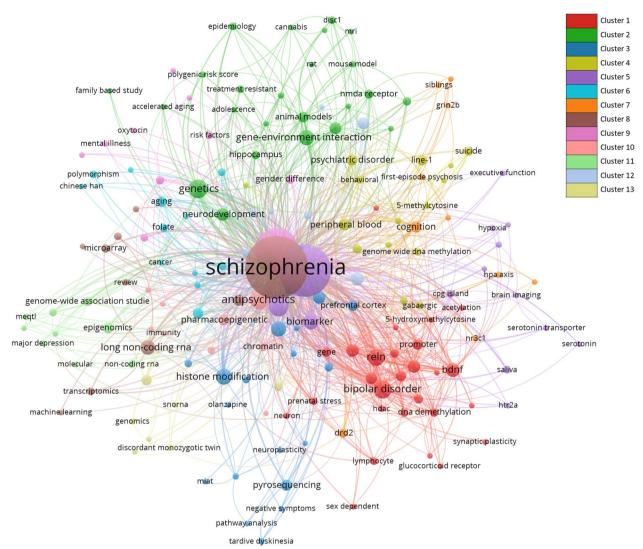


Fig. 4 Network visualization map of the co-occurrence of keywords

frequent occurrences. The keywords were clustered according to the strength of the relationship between each other, and each cluster had one main keyword that became the highlight, indicating that the frequency of the words was high in the publications [22]. "Schizophrenia" dominated in the brown cluster, followed by "DNA methylation" in the purple cluster and "epigenetics" in the pink cluster. The most common keywords were "schizophrenia" (250 occurrences), followed by "DNA methylation" (174 occurrences) and "epigenetics" (121 occurrences). Other keywords, such as "antipsychotics," "brain," "psychosis," "genetics," and "bipolar disorder," had between 20 and 30 occurrences. The wide range of clusters indicates that academic interest in the epigenetics of schizophrenia is highly diverse. Nevertheless, such diversity also suggested that this research field still lacks consistency and clarity.

#### Discussion

In this study, we focused on the evolution of research in the epigenetics of schizophrenia. As demonstrated by Zakaria et al. [42], an increasing number of studies have investigated the genetics of schizophrenia following the introduction of GWAS. Therefore, we undertook this current study to offer a different perspective on the field. We included 397 articles published since the early 1960s, retrieved from the Scopus database, in our bibliometric analysis. Alongside Google Scholar and Web of Science, Scopus is a commonly used scientific publication database. However, it currently offers more comprehensive coverage than Web of Science [28]. Moreover, it has the largest database of abstracts and citations of peer-reviewed literature, with many author and affiliation profiles, in addition to high-quality data and advanced

search and analysis tools [18]. We discussed the bibliometric analysis findings in relation to the five research questions.

Firstly, when examining the research trends pertaining to the epigenetics of schizophrenia and their citation patterns, we found that articles concerning this topic first appeared in 1966 [35] and the number grew slowly for almost the following 40 years. The breakthrough year for this research field was in 2005, with a significant surge of publications, including five original articles [11, 15, 21, 29, 37] and one review article [24]. These articles were eventually cited 1186 times (up to the writing of our study), highlighting their significant contributions. It is also worth noting that three articles [11, 15, 21] focused on investigating the DNA methylation pattern of specific genes using the post-mortem brain tissue of schizophrenia patients, with one of them also performing a comparative analysis of methylation patterns of brain tissue and peripheral blood. The number of published articles grew steadily for the following 20 years, reflecting an increased interest as well as the relevance and importance of epigenetic factors in the pathogenesis of schizophrenia.

Secondly, we investigated who are the most productive authors and which institutions had driven the advancement of this research field. We noted that a total of 2090 authors contributed to the 397 published articles. Only 17 articles were single-authored, while the rest were written in collaboration with other co-authors, frequently in various countries. We also demonstrated that five of the top authors in this research area were from the University of Illinois, which also ranked first on the list of top contributing institutions. Meanwhile, the University of Toronto was ranked third, housing three of the top 20 authors. Although their total publication numbers were high, the total citations were significantly lower compared to some of the authors from the University of Illinois. The high interest in schizophrenia studies at the University of Illinois could have been due to the establishment of the Psychiatric Institute at the university in 1982 [19].

Thirdly, we searched for the most productive countries and studied the collaboration patterns between them. The top five countries were the USA, China, Canada, the UK, and Japan. The USA leads in terms of the total number of published and cited articles. Despite ranking fourth in terms of the number of published articles, the UK was second in terms of total citations. In terms of collaboration, the USA collaborated closely with China, the Netherlands, and Germany, while the UK collaborated closely with several European and South American countries. This result reflects the importance of international collaborations contributing to the high number of citations [34].

Fourthly, we explored questions regarding which journals most actively address this topic. A total of 147 had published articles in this field, but only eight of those had published 10 or more articles. All the journals recently ranked in Q1 except for one (Epigenomics), which ranked in Q2. The results indicated that the manuscripts concerning the epigenetics of schizophrenia were generally accepted by the top-tier journals, reflecting the strong interest in this topic. Notably, the Schizophrenia Bulletin holds the second position in terms of total publications, closely surpassing Schizophrenia Research as the most cited journal within the research area. The high number of citations of this journal might have been contributed by 3 articles within the top 20 highly cited publications which include Van et al. Van Os, Rutten, and Poulton [33] (500 citations), Van Os et al. [32] (197 citations), and Walton et al. [36] (186 citations). This provides valuable information that can guide researchers in research collaboration and selection of publication platforms.

Finally, we examined the keywords used by the authors in these publications. The keywords were grouped into 13 clusters, as generated by the VOSviewer software. To ensure more specific topics from the co-occurrences of the keyword analysis, the major clusters related to the general topics of schizophrenia, DNA methylation, and epigenetics were excluded from the analysis. The key concepts displayed demonstrated the impact of the research area, including antipsychotics, psychosis, the brain, bipolar disorder, genetics, and gene-environment interactions. Based on the analysis, we suggested further exploration of these areas to understand the complex relationships within the keyword co-occurrence clusters. The wide range of clusters demonstrated that academic interest in the epigenetics of schizophrenia is highly diverse. Nevertheless, such diversity reflected that the field of epigenetics of schizophrenia remains unclear and needs more consistent understanding.

Our study had two main limitations. Firstly, we only retrieved publications from a single database, namely SCOPUS. As we are all aware, there is no single optimal database to capture all the available scientific publications regarding a particular topic. Thus, we may have overlooked some research projects and unnecessarily included redundant research despite our efforts to harmonize and clean the data. Using multiple databases enabled the enhanced coverage of articles and offered more data to be analyzed; however, it may have imposed additional complexity in terms of merging the data prior to analysis by the bibliometric software, not to mention the limited bibliometric data provided within some of the database. Secondly, we can only make inferences about the quality of the studies and the networking pattern based on the bibliometrics provided by SCOPUS, such as keywords, citations, and co-occurrences. A thorough dissection of the topic evolution can only be achieved through a systematic literature review.

#### **Conclusions**

This bibliometric analysis is useful for researchers to build a firm foundation to advance their research in epigenetics and schizophrenia. This study serves as a one-stop overview to identify the knowledge gap in this specific area and to further generate novel ideas for future investigations.

#### Acknowledgements

The authors acknowledge the support for publishing this article from the Kulliyyah of Medicine and the Research Management Centre of International Islamic University Malaysia. This work was supported by the Ministry of Higher Education (MOHE), Malaysia, under the Fundamental Research Grant Scheme (FRGS) (Grant no. FRGS/1/2022/SKK05/UIAM/03/1).

#### Authors' contributions

Study concept and design (Nour El Huda), acquisition of data (Nour El Huda, Wan Muhamad Salahudin), analysis and interpretation of data (Norlelawati, Mohd Asyraf, Norainin Sofiya), drafting of the manuscript (Nour El Huda, Siti Norain), critical revision of the manuscript for important intellectual content (Norlelawati, Mohd Asyraf, Mohamed Bakrim), administrative, technical, or material support (Nour El Huda, Wan Muhamad Salahudin). All authors have made a significant contribution to this study and have approved the final manuscript.

#### **Funding**

This publication was aided by workshops attended by the authors, which were funded by the Ministry of Higher Education (MOHE) under the Fundamental Research Grant Scheme (FRGS) (FRGS/1/2022/SKK05/UIAM/03/1). The grant funded the expenses associated with attending the workshops, which provided a collaborative platform for conceptualizing and drafting this manuscript. The funders had no direct role in the intellectual development, composition, or submission of the paper. All final content decisions were made solely by the authors.

#### Availability of data and materials

The datasets supporting the conclusions of this article are included within the article, and the raw files are sourced from Scopus.

#### **Declarations**

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

Received: 11 November 2023 Accepted: 4 December 2023 Published online: 12 December 2023

#### References

- Ahmi, A. (2023a). biblioMagika. Retrieved from https://www.aidi-ahmi. com/index.php/bibliomagika
- Ahmi, A. (2023b). OpenRefine: an approachable tool for cleaning and harmonizing bibliographical data. Paper presented at the AIP Conference Proceedings.

- Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A (2009) An operational definition of epigenetics. Genes Dev 23(7):781–783. https://doi.org/10. 1101/qad.1787609
- Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., . . . Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease Study 2016. Schizophr Bull:44(6):1195–1203. https://doi.org/10.1093/schbul/sby058
- Chen, M.-Y., Zhang, Q., Liu, Y.-F., Zheng, W.-Y., Si, T. L., Su, Z., . . . Xiang, Y.-T. (2023). Schizophrenia and oxidative stress from the perspective of bibliometric analysis. Front Psychiatry, 14;1145409. doi:https://doi.org/10.3389/fpsyt.2023.1145409
- Correll CU, Schooler NR (2020) Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat 16:519–534. https://doi.org/10.2147/NDT.S2256 43
- Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM (2021) How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res 133:285–296. https://doi.org/10.1016/j.jbusres.2021.04.070
- Duan L, Zhu G (2020) Mapping theme trends and knowledge structure of magnetic resonance imaging studies of schizophrenia: a bibliometric analysis from 2004 to 2018. Front Psych 11:27. https://doi.org/10.3389/ fpsyt.2020.00027
- Gavin DP, Sharma RP (2010) Histone modifications, DNA methylation, and schizophrenia. Neurosci Biobehav Rev 34(6):882–888. https://doi.org/10. 1016/j.neubiorev.2009.10.010
- Ghadirivasfi M, Nohesara S, Ahmadkhaniha HR, Eskandari MR, Mostafavi S, Thiagalingam S, Abdolmaleky HM (2011) Hypomethylation of the serotonin receptor type-2A gene (HTR2A) at T102C polymorphic site in DNA derived from the saliva of patients with schizophrenia and bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 156B(5):536–545. https://doi.org/10.1002/ajmg.b.31192
- Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A, Costa E (2005) Reelin promoter hypermethylation in schizophrenia. Proc Natl Acad Sci USA 102(26):9341–9346. https://doi.org/10.1073/pnas.05037 36102
- Guo X (2022) A bibliometric analysis of child language during 1900–2021.
   Front Psychol 13:862042. https://doi.org/10.3389/fpsyg.2022.862042
- Hirsch JE (2005) An index to quantify an individual's scientific research output. Proc Natl Acad Sci 102(46):16569–16572. https://doi.org/10.1073/ pnas.0507655102
- Hjorthoj C, Sturup AE, McGrath JJ, Nordentoft M (2017) Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry 4(4):295–301. https://doi.org/10.1016/ 52215-0366(17)30078-0
- Iwamoto K, Bundo M, Yamada K, Takao H, Iwayama-Shigeno Y, Yoshikawa T, Kato T (2005) DNA methylation status of SOX10 correlates with its downregulation and oligodendrocyte dysfunction in schizophrenia. J Neurosci 25(22):5376–5381. https://doi.org/10.1523/JNEUROSCI.0766-05. 2005
- Jamali HR, Nikzad M (2011) Article title type and its relation with the number of downloads and citations. Scientometrics 88(2):653–661. https://doi.org/10.1007/s11192-011-0412-z
- Köhler, T., González-Morales, M. G., Banks, G. C., O'Boyle, E. H., Allen, J. A., Sinha, R., . . . Gulick, L. M. V. (2020). Supporting robust, rigorous, and reliable reviewing as the cornerstone of our profession: introducing a competency framework for peer review. Industrial Organ Psychol.13(1), 1–27. https://doi.org/10.1017/iop.2019.121
- Magadán-Díaz M, Rivas-García JI (2022) Publishing industry: a bibliometric analysis of the scientific production indexed in Scopus. Publ Res Q 38(4):665–683. https://doi.org/10.1007/s12109-022-09911-3
- Manning, G. E. (1981). History of UIC's Department of Psychiatry. Retrieved from https://www.psych.uic.edu/about-us/history
- Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., ... Group, P.-P (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4(1):1. https://doi.org/10.1186/2046-4053-4-1
- Murphy BC, O'Reilly RL, Singh SM (2005) Site-specific cytosine methylation in S-COMT promoter in 31 brain regions with implications for studies involving schizophrenia. Am J Med Genet B Neuropsychiatr Genet 133B(1):37–42. https://doi.org/10.1002/ajmg.b.30134

- Nadzar N, Bakri A, Ibrahim R (2017) A bibliometric mapping of Malaysian publication using co-word analysis. Int J Adv Soft Comput Appl 9(3):90–113
- Şevik AE, Alkan S (2023) Toxoplasmosis and schizophrenia publication activity in 1991–2023: a Web of Science-based bibliometric analysis. Central Asian J Med Hypotheses Ethics 4(2):100–111. https://doi.org/10. 47316/caimhe.2023.4.2.05
- 24. Sharma RP (2005) Schizophrenia, epigenetics and ligand-activated nuclear receptors: a framework for chromatin therapeutics. Schizophr Res 72(2):79–90. https://doi.org/10.1016/j.schres.2004.03.001
- Shekhar SK (2023) Schizophrenia and COVID-19: A bibliometric analysis
  of trends and themes. Schizophr Res 254:35. https://doi.org/10.1016/j.
  schres.2023.02.013
- Stroup TS, Gray N (2018) Management of common adverse effects of antipsychotic medications. World Psychiatry 17(3):341–356. https://doi. org/10.1002/wps.20567
- Sun, H.-L., Bai, W., Li, X.-H., Huang, H., Cui, X.-L., Cheung, T., . . . Xiang, Y.-T. (2022). Schizophrenia and inflammation research: a bibliometric analysis. Front Immunol. 13; 907851. https://doi.org/10.3389/fimmu.2022.907851
- Thelwall M, Sud P (2022) Scopus 1900–2020: Growth in articles, abstracts, countries, fields, and journals. Quant Sci Stud 3(1):37–50. https://doi.org/ 10.1162/qss\_a\_00177
- 29. Tremolizzo, L., Doueiri, M. S., Dong, E., Grayson, D. R., Davis, J., Pinna, G., . . . Guidotti, A. (2005). Valproate corrects the schizophrenia-like epigenetic behavioral modifications induced by methionine in mice. Biol Psychiatry. 57(5):500–509. https://doi.org/10.1016/j.biopsych.2004.11.046
- Uy MNAR, Tantengco OAG (2022) Landscape, barriers, and facilitators of scientific productivity in schizophrenia research in Southeast Asia: a bibliometric analysis. Ann Med Surg 81:104330. https://doi.org/10.1016/j. amsu.2022.104330
- van Eck NJ, Waltman L (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 84(2):523–538. https://doi.org/10.1007/s11192-009-0146-3
- 32. Van Os, J., Rutten, B. P., Myin-Germeys, I., Delespaul, P., Viechtbauer, W., Van Zelst, C., . . . . Mirjanic, T. (2014). Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophrenia Bull. 40(4):729–736. https://doi.org/10.1093/schbul/sbu069
- Van Os J, Rutten BPF, Poulton R (2008) Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull 34(6):1066–1082. https://doi.org/10.1093/schbul/sbn117
- Velez-Estevez A, García-Sánchez P, Moral-Munoz JA, Cobo MJ (2022) Why do papers from international collaborations get more citations? A bibliometric analysis of Library and Information Science papers. Scientometrics 127(12):7517–7555. https://doi.org/10.1007/s11192-022-04486-4
- Wagner AF, Cirillo VJ, Meisinger MAP, Ormond RE, Kuehl FA, Brink NG (1966) A further study of catecholamine O-methylation in schizophrenia. Nature 211(5049):604–605. https://doi.org/10.1038/211604a0
- 36. Walton, E., Hass, J., Liu, J., Roffman, J. L., Bernardoni, F., Roessner, V., . . . Ehrlich, S. (2016). Correspondence of DNA methylation between blood and brain tissue and its application to schizophrenia research. Schizophrenia Bull. 42(2):406–414. https://doi.org/10.1093/schbul/sbv074
- Wei J, Hemmings GP (2005) Gene, gut and schizophrenia: the meeting point for the gene–environment interaction in developing schizophrenia. Med Hypotheses 64(3):547–552. https://doi.org/10.1016/j.mehy.2004.08. 011
- Chong WX, J., Hsien-Jie Tan, E., Chong, C. E., Ng, Y., & Wijesinghe, R. (2016) Atypical antipsychotics: a review on the prevalence, monitoring, and management of their metabolic and cardiovascular side effects. Ment Health Clin 6(4):178–184. https://doi.org/10.9740/mhc.2016.07.178
- 39. Wu, Y. L., Lin, Z. J., Li, C. C., Lin, X., Shan, S. K., Guo, B., . . . Li, Z. H. (2023). Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduct Target Ther. 8(1):98. https://doi.org/10.1038/s41392-023-01333-7
- 40. Yang C, Lin X, Wang X, Liu H, Huang J, Wang S (2022) The schizophrenia and gut microbiota: a bibliometric and visual analysis. Front Psych 13:1022472. https://doi.org/10.3389/fpsyt.2022.1022472
- Zakaria R, Ahmi A, Ahmad AH, Othman Z (2021) Worldwide melatonin research: a bibliometric analysis of the published literature between 2015 and 2019. Chronobiol Int 38(1):27–37. https://doi.org/10.1080/07420528. 2020.1838534

 Zakaria, W. N. A., Sasongko, T. H., Al-Rahbi, B., Al-Sowayan, N., Ahmad, A. H., Zakaria, R., . . . Othman, Z. (2023). Gene and schizophrenia in the pregenome and postgenome-wide association studies era: a bibliometric analysis and network visualization. Psychiatr Genet, 33(2):37–49. https:// doi.org/10.1097/ypq.000000000000336

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Submit your manuscript to a SpringerOpen journal and benefit from:

- ► Convenient online submission
- ► Rigorous peer review
- ▶ Open access: articles freely available online
- ► High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ▶ springeropen.com