REVIEW ARTICLE

A Scientometrics Analysis and Visualization of Depressive Disorder

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Abstract: Multiple studies on the pathomechanisms of depressive disorder and antidepressants have been reported. However, literature involving scientometric analysis of depressive disorder is sparse. Here, we use scientometric analysis and a historical review to highlight recent research on depression. We use the former to examine research on depressive disorders from 1998 to 2018. The latter is used to identify the most frequent keywords in keyword analysis, as well as explore hotspots and depression trends. Scientometric analysis uncovered field distribution, knowledge structure, research topic evolution, and topics emergence as main explorations in depressive disorder. Induction factor, comorbidity, pathogenesis, therapy and animal models of depression help illustrate occurrence, development and treatment of depressive disorder. Scientometric analysis found 231,270 research papers on depression, a 4-fold increase over the last 20 years. These findings offer a vigorous roadmap for further studies in this field.

Keywords: Scientometrics analysis, visualization, depressive disorder, citespace, VOSviewer.

1. INTRODUCTION

Depressive disorder is a primary public health challenge that appears at all ages. This chronic disorder substantially weakens patients' psychosocial and occupational function, affecting patients' feelings, as well as their perception of themselves and the world around them [1]. Recent years have seen growing research interest in depressive disorder, as evidenced by the high number of research and review articles on this topic. For example, systematic review and meta--analysis of longitudinal studies on overweight, obesity, and depression, found a reciprocal link between depression and obesity, and that obesity may enhance the risk of depression [2]. A patient-level meta-analysis of antidepressant effects on depression severity found that while the benefits of antidepressants relative to placebo may be minimal or nonexistent in patients with mild or moderate symptoms, the opposite was true in cases of very severe depression [3]. However, comprehensive reviews on depression are lacking. There are some scientometric articles on depression, including center of epidemiological studies of depression scale [4], biological treatments for major depressive disorder [5], and artificial intelligence application in the management of depressive disorders [6]. While these studies offer preliminary insight into the field of depression, a more comprehensive scientometric analysis of depression is not available in literature.

In this article, scientometric analysis is mainly reflected in bibliometric and manual analysis. Bibliometric analysis is an emerging tool for quickly exploring structures and trends of a subject or domain *via* statistical methods and visualization. This approach identifies relevant nodes and extracts useful information from large volumes of information [7, 8]. Bibliometric software, including CiteSpace [9], VOSviewer [10], bibExcel [11], Science of Science (SCI2) [12] and HistCite [13] have been used in scientometric analysis. Of these, CiteSpace and VOSviewer are the most popular. CiteSpace is a freely available Java application that can visualize and analyze scientific literature trends and patterns. CiteSpace was designed by Professor Chaomei Chen for progressive knowledge domain visualization and identification of critical points in the development of a field, especially intellectual turning points and pivotal points [14]. VOSviewer was created by Centre for Science and Technology Studies, Leiden University and is used to visualize science mapping. VOSviewer is freely available and has been used to visualize bibliometric maps [15].

Despite methodological limitations, scientometrics is useful for evaluating scientific research in a given subject or field [16]. Relative to descriptive literature reviews (conventional reviews), systematic reviews like scientometrics have advantages that can quickly identify critical issues in the field of interest and guide future research. For example, a bibliometric analysis of research on the topic "cancer rehabilitation", led to the conclusions that National Cancer Institute was the most prominent funder, and that cognitive and behavioral therapies, as well as psychological interventions were major topics, followed by depression and exercise therapy [17]. Bibliometric analysis of global research on PD-1 and PD-L1 in cancer concluded that, after 2014, PD-1 and PD-L1 studies rose significantly, most publications came from USA, and future research should develop new topics,

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like boosting anti-cancer therapeutic strategies [18]. Bibliometric analysis of traditional Chinese medicine formula (TCMF) concluded the most journal, disease types, the hottest category and keywords of TCMF [19]. Bibliometric analysis of journal trends, such as Sustainability offered new directions for the development of periodicals [20]. Thus, bibliometric analysis of depressive disorder may uncover valuable insights. Generally, science mapping can effectively demonstrate bibliometric visualization, illuminating the discipline's current situation and development trends [21].

Here, we sought to put forward a scientometric method for depressive disorder and suggested future research directions [21]. Statistical results of keyword analysis were analyzed and summarized by manual classification, which included induction factor, comorbidity, pathogenesis, therapy and animal models of depression. Combining scientometric analysis and historical review will uncover critical evidence and highlight emerging depressive disorder trends.

2. DATA AND METHODS

Citation data used in bibliometric research was downloaded from science citation index expanded (SCI-E) database on Web of Science (WOS). Relative to general databases like Scopus, Derwent, China national knowledge infrastructure (CNKI) and Chinese social sciences citation index (CSSCI), WOS includes more scientific publications and provides overall data sources for bibliometric software. Thus, WOS is the database most frequently used for bibliometric research [22-24]. The scientometric research process is shown in (Fig. **1**). WOS's core collection database as of July 22, 2019 was used for this bibliometric analysis. We took "depression" or "depressive disorder" as topical retrieval terms and time span limited to 1998-2018. The literature data used in this study were downloaded from WOS. CiteSpace was initially used for bibliometric analysis, including country, institute, keyword, category, reference, and cited journal. Parameter settings included the time slicing (1998-2018), node types, and selection criteria (top 50 levels of the most cited or occurring items) from each slice. VOSviewer was used to optimize and supplement the unaesthetic map. Impact factor (IF) and H-index were added to the table for a comprehensive, scientometric, results analysis.

3. RESULTS AND DISCUSSION

231,270 articles related to "depressive disorder" or "depression" were identified. Based on the search results for depressive disorder or depression in WOS, publication growth on this topic can be divided into 2 stages, a slow phase from 1998-2003 and a rapid growth phase from 2004-2018 (Fig. **2**). Rapid growth in depression research may be explained by 2 factors. First, depression affects >320 million people worldwide [25, 26], and has been associated with increased cancer risk and shortened survival [27]. The big data research and development initiative [28], and the precision medicine initiative [29], launched by the Obama administration in 2012 and 2015, respectively, may also contribute to

the increased rate of depression research. From 1998-2018, the average annual publication was 11,012, a very high publication rate. For bibliometric analysis on the topic of depression, the more the data, the more reliable the results.
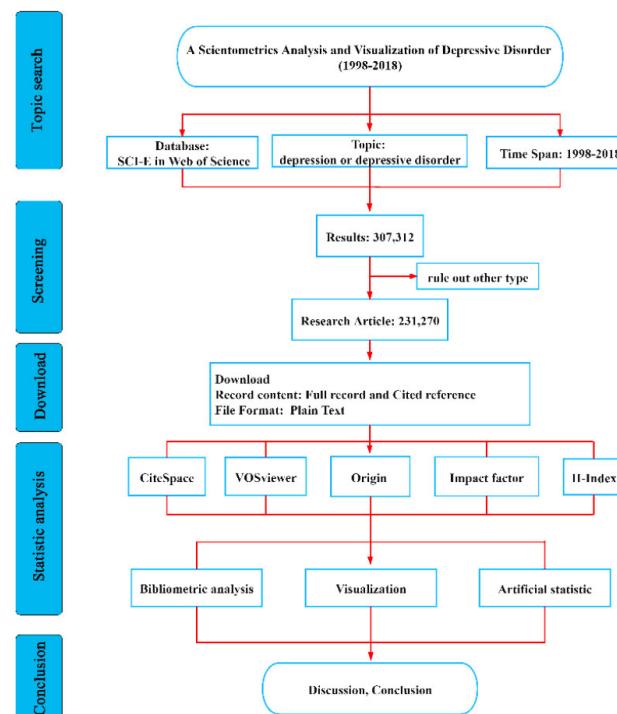

Fig. (1). Flow chart of scientometric analysis. SCI-E = Science citation index expand; WOS = Web of science; IF = impact factor; H index = high citation index. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).
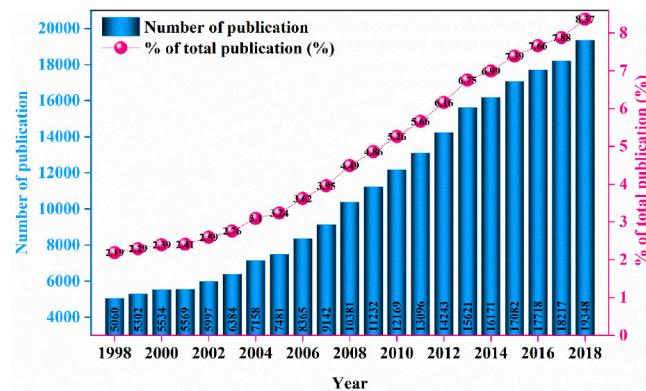

Fig. (2). Annual publications between 1998-2018. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.1. Cooperation Map of Country/region and Institute

Citespace offers 3 levels of scientific cooperation network analysis: microcosmic author cooperation network, mesoscopic institutional cooperation network, and macroscopi-

cal national cooperation network. In the cooperative network obtained *via* CiteSpace, node size represents the number of publications published by an author, institution, or country/region [30, 31]. It is observed that the US ranks first and has >80,000 publications (36.082% of the total) (Fig. **3A**), (Fig. **3C**). The US is followed by England, Germany, China, Canada, Australia, Netherlands, Italy, and Japan, with >100,000 publications (48.762% of the total). For depression research, there is close cooperation between countries, highlighting depression as a global challenge. Developed countries have a greater share of total publications, which may be explained by objective and subjective factors. Objectively, developed countries dedicate more funding to scientific research. Subjectively, common chronic pain con-

ditions related to depression are more prevalent in developed countries. Making it a problem in need of urgent solutions [32]. From an institutional perspective, the US has 7 institutes in the top-10, with Harvard University (4773) ranking first (Fig. **3B**, **3D**) The ranking of the US country/region first reflects its stronger scientific prowess. This analysis also ranked University of Toronto (3192) (Canada) and Kings College London (3181) (England) in the top 10. Citation frequency bursts indicate that a paper is highly cited in a certain period. Vrije University (Amsterdam), University of Texas, and Harvard medical school are speculated to have made novel discoveries in depression research. The H-index and global rank (Fig. **3C**, **3D**) are trustworthy indicators aimed at measuring an individual's scientific achievements
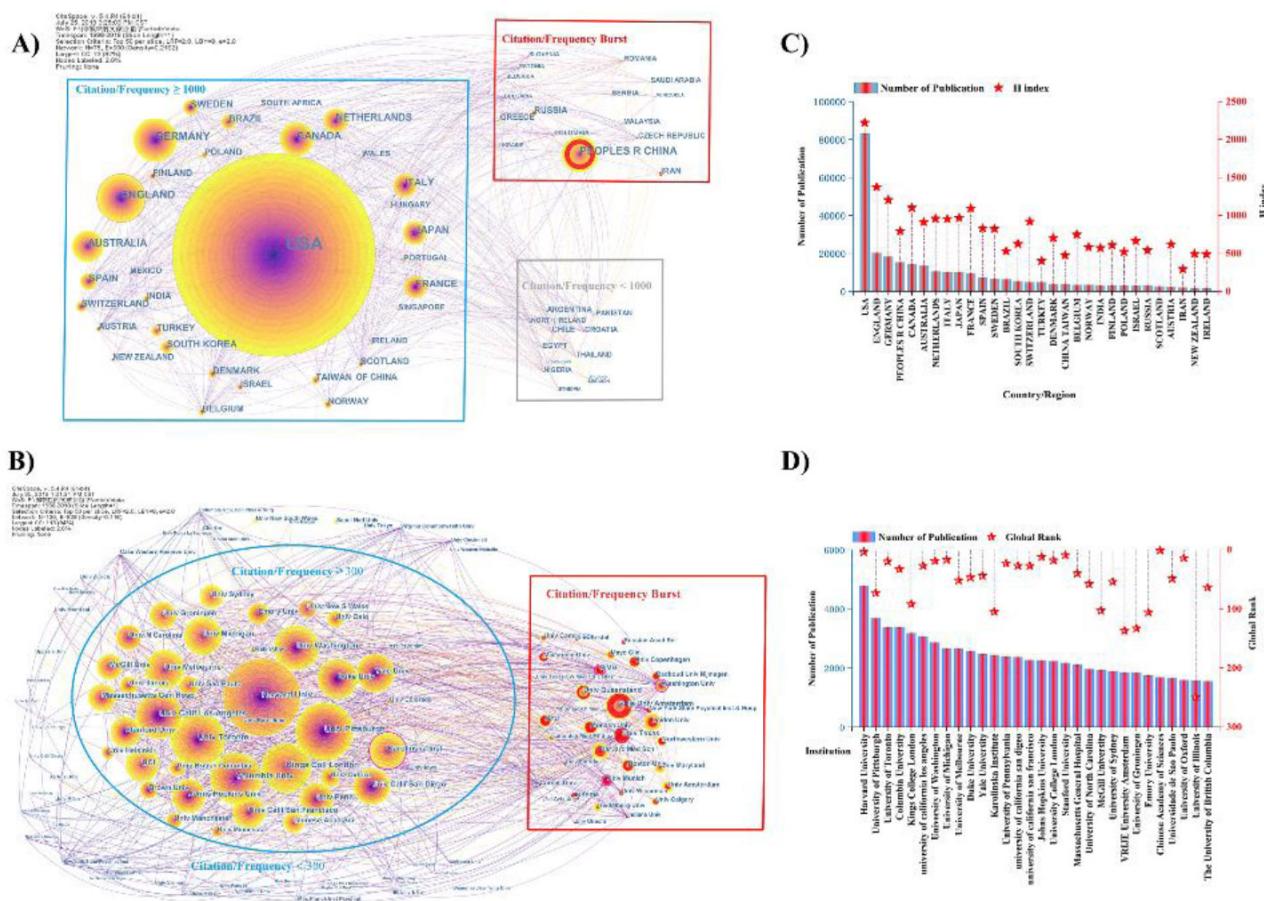
Fig. (3). Cooperation map of country/region and institute. **A)** Country/region co-occurrence network. 75 nodes and 600 connection lines emerged. Node and line size represent the number of publications from a country/region and the cooperative relationship in the country/region, respectively. Red nodes indicate that publications of the country/region have a citation or frequency burst. Connecting lines of different colors represent different years. Blue rectangles show a citation/frequency of >1000 for a country/region. Gray rectangles indicate citation/frequency of <1000 for a country/region. Red rectangles indicate a burst in the citation/frequency of country/region. **B)** Number of publications and H-Index scores for countries/regions. **C)** Institute co-occurrence network. 120 nodes and 828 connection lines emerged. Node size and lines represent the number of publications from institutes and their cooperative relationship, respectively. Red nodes indicate a citation or frequency burst in publications of the institutes. Connecting lines of different color represent different years. Blue ellipses show that the citation/frequency of institute is >300. The outside of the blue ellipses indicates that the citation/frequency of the institute is <300. Red rectangles indicate burst in the citation/frequency of the institute. **D)** Number of publications and global institutional rank. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

or influence [33] and to offer a reliable metric for a scientist's academic evaluation [34]. H-index (high citations index) shows an individual's citation rate. For example, a researcher's H-index shows that they have at most H papers cited at least H times [35]. By combining countries with institutes, the US has a H-index of 2222 and is home to several world-famous institutions. Relative to other countries/regions, it has an obvious advantage and makes outstanding contributions to depression research. England (1373), Germany (1203) and China (794) also make prominent contributions to depression research.
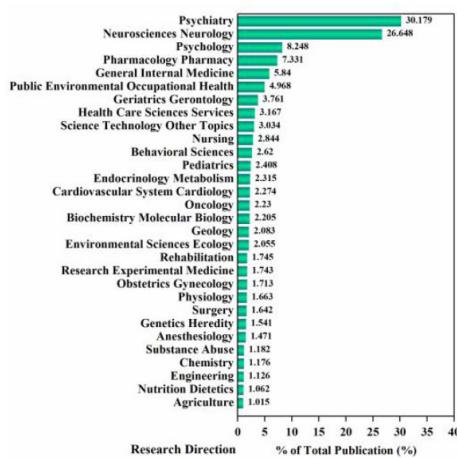

Fig. (4). Category exploration map. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

56.827% of the total publications regard psychiatry and neurosciences (Fig. **4**). Psychiatric disorders account for 22.8% of the disease burden worldwide [36]. Depression, a major cause of disability, has considerably surged since 1990, mostly driven by population growth and aging [26, 37]. Depression is treated using physiologic and psychologic means. Thus, there are a higher number of publications on psychiatry and neurosciences, followed by pharmacological pharmacy, due to the need for antidepressants. For instance, given that oral antidepressants have poor bioavailability, nanoparticles given *via* nose-to-brain delivery have emerged as novel promising candidates for evaluation of the antidepressant activity of original drugs [38]. Psychology accounts for 8.248% of total publications, suggesting that psychological therapies, including psychological consultation, are therapeutic effects against depression [39]. There are numerous categories, including public environmental occupational health, health care sciences services, nursing, environmental sciences ecology, physiology, surgery, nutrition dietetics, and agriculture, indicating that depression is a major disorder, often accompanying other diseases. For instance, there is post-stroke depression [40], and postpartum depression [41]. These results highlight the complexity of depression, and indicate that depression treatment should have broad and multi- factorial considerations.

3.2. Journal and Co-cited Journal

Table (**1**) presents the top 30 journals in the field of depression. Journal of affective disorders (6058, 2.619%) ranks first, followed by PLOS One (4060, 1.756%) and psychiatry research (2930, 1.267%). Of the top 10 journals, 5 are from the US, 3 from England, and 2 from Netherlands. The number of publications in the top 20 is >1000. Among the top 30, there are 7 journals with impact factors >5 that include Journal of neuroscience (6.074), psychological medicine (5.641), biological psychiatry (11.501), American journal of psychiatry (13.655), neuropsychopharmacology (7.16), British journal of psychiatry (7.233), Journal of the American Academy of child and adolescent psychiatry (6.391). Journal of nervous and mental disease (1.859) has the lowest impact factor among the top 30 journals Table (**2**). Based on the cited number of publications, archives of general psychiatry (71,718) ranked first, followed by American journal of psychiatry (70,801), journal of affective disorders (52,623), biological psychiatry (51,404), and British journal of psychiatry (51,126). There are 7 Journals with impact factors >10, including American journal of psychiatry (13.655), biological psychiatry (11.501), JAMA (51.273), Lancet (59.102), Science (41.037), Nature (43.07), NEJM (70.67), British medical journal (27.604), Neuron (14.403), and molecular psychiatry (11.973). Many publications on depression are published in low impact factor journals, suggesting that researchers demand further research in this field. Research on depression includes studies on novel preparations [42], and exploration of pathological mechanisms [43-45]. Compared with journal analysis, the co-cited top journal has a surge, demonstrating that the study of this journal is closer to basics or has a stronger theory.

3.3. Co-cited Reference

Co-cited reference means that one or more references have been co-cited in one or more publications. The top 30 co-cited references regarding depression research are presented in Table (**3**). One reference is co-cited over 1000 times, eighteen references are co-cited between 500 and 1000 times, and others are co-cited between 300 and 500 times. Topics covered by highly co-cited papers include survey [46], meta-analysis [47], epidemiology [48], moderation by gene polymorphisms, such as serotonin transporter [49], inflammation pathophysiology [50-52], use of depression scale [53], antidepressants, such as citalopram [54], and reviews neurotrophic models of stress-related mood disorders [55]. 19 papers were in top journals (IF >10) of the top 30: Science (4), Lancet (3), JAMA (3), Biological psychiatry (3), Neuron (2), Nature (1), American journal of psychiatry (1), PLOS medicine (1), and Trends in immunology (1). The co-cited reference timeline view is shown in (Fig. **5**). The reference network map has 402 nodes and 1604 links. All references form 10 clusters and there is active co-citation between references, including the serotonin transporter (#2) and serotonin transporter gene (#8) clusters, suggesting that the serotonin transporter is critical for regulating serotonin function in the brain [56]. Because serotonin regulates excitatory and inhibitory neurotransmitters, its transporters are used as indexes in depression studies [57-59].

Table 1. The top 30 journals related to depression research.

Ranking	Number of Publication	% of Total Publication	Journal			
			Name	Country / Region	Impact Factor (2018)	H-Index (2018)
1	6058	2.619	Journal of Affective Disorders	Netherlands	4.084	165
2	4060	1.756	PLOS One	USA	2.776	268
3	2930	1.267	Psychiatry Research	Netherlands	2.208	118
4	1777	0.768	Journal of Clinical Psychiatry	USA	4.023	189
5	1722	0.745	Journal of Neuroscience	USA	6.074	422
6	1691	0.731	Psychological Medicine	England	5.641	188
7	1587	0.686	Biological Psychiatry	USA	11.501	290
8	1502	0.649	BMC Psychiatry	England	2.666	79
9	1441	0.623	Journal of Psychiatric Research	England	3.917	123
10	1342	0.58	International Journal of Geriatric Psychiatry	USA	3.141	116
11	1339	0.579	Journal of Psychosomatic Research	Netherlands	2.722	141
12	1197	0.518	Depression and Anxiety	USA	4.935	110
13	1171	0.506	American Journal of Psychiatry	USA	13.655	325
14	1127	0.487	Comprehensive Psychiatry	England	2.586	94
15	1119	0.484	Psycho neuroendocrinology	England	4.013	155
16	1061	0.459	Neuroscience Letters	Netherlands	2.173	155
17	1058	0.457	Neuropsychopharmacology	England	7.16	204
18	1034	0.447	Journal of Nervous and Mental Disease	USA	1.859	113
19	1010	0.437	American Journal of Geriatric Psychiatry	USA	3.488	108
20	1010	0.437	Neuroscience	England	3.244	204
21	995	0.43	Psychosomatic Medicine	USA	3.937	171
22	965	0.417	Behavioural Brain Research	Netherlands	2.77	154
23	963	0.416	Psychopharmacology	Germany	3.424	181
24	943	0.408	British Journal of Psychiatry	England	7.233	209
25	938	0.406	Acta Psychiatrica Scandinavica	England	4.694	132
26	929	0.402	Psycho-Oncology	USA	3.43	123
27	914	0.395	Brain Research	Netherlands	2.929	188
28	884	0.382	General Hospital Psychiatry	Netherlands	3.22	94
29	825	0.357	Journal of The American Academy of Child and Adolescent Psychiatry	Netherlands	6.391	222
30	819	0.354	BMJ Open	England	2.376	69

Table 2. The top 30 co-cited journals related to depression research.

Rank	Cited Number	Journal			
		Name	Country/Region	Impact Factor (2018)	H index (2018)
1	71718	Archives of General Psychiatry	USA	/	/
2	70801	American Journal of Psychiatry	USA	13.655	325
3	52623	Journal of Affective Disorders	Netherlands	4.084	165
4	51404	Biological Psychiatry	USA	11.501	290
5	51126	British Journal of Psychiatry	England	7.233	209
6	47113	Jama-Journal of The American Medical Association	USA	51.273	622
7	43381	Psychological Medicine	England	5.641	188
8	40554	Journal of Clinical Psychiatry	USA	4.023	189
9	40328	Lancet	England	59.102	700
10	38753	Acta Psychiatrica Scandinavica	England	4.694	132
11	36545	Science	USA	41.037	1058

Rank	Cited Number	Journal			
		Name	Country/Region	Impact Factor (2018)	H index (2018)
12	36321	Proceedings of The National Academy of Sciences of The United States of America	USA	9.58	699
13	32946	Journal of Neuroscience	USA	6.074	422
14	32807	Nature	England	43.07	1096
15	30766	New England Journal of Medicine	USA	70.67	933
16	29052	Psychiatry Research	Netherlands	2.208	118
17	27297	PLOS One	USA	2.776	268
18	26371	Journal of Psychosomatic Research	England	2.722	141
19	26027	Neuropsychopharmacology	England	7.16	204
20	25219	Psychosomatic Medicine	USA	3.937	171
21	24788	Brain Research	Netherlands	2.929	188
22	22634	Neurology	USA	8.689	331
23	21937	Journal of Neurology Neurosurgery and Psychiatry	England	8.272	188
24	21698	Journal of Consulting and Clinical Psychology	USA	4.358	218
25	21123	British Medical Journal	England	27.604	392
26	20212	Psychopharmacology	Germany	3.424	181
27	20164	Neuroscience	Netherlands	3.244	204
28	18959	Neuron	USA	14.403	430
29	18946	Archives of Internal Medicine	USA	/	/
30	17068	Molecular Psychiatry	England	11.973	196

"/": The magazine is not included in the latest SCI-E database, so the impact factor and H-index are missing.

Table 3. The top 30 cited articles related to depression research.

Rank	Cited Number	The Title of Article	Year	Journal			
				Name	Country	Impact Factor (2018)	H-Index (2018)
1	1111	Lifetime prevalence and age-of-onset distributions ' of DSM-IV disorders in the national comorbidity survey replication	2005	Archives of general psychiatry	USA	/	/
2	950	A Meta-Analysis of Cytokines in Major Depression	2010	Biological psychiatry	Netherlands	11.501	290
3	927	The epidemiology of major depressive disorder - Results from the National Comorbidity Survey Replication (NCS -R).	2003	JAMA-Journal of The American Medical Association	USA	51.273	622
4	869	Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene	2003	Science	USA	41.037	1058
5	815	Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication	2005	Archives of general psychiatry	USA	/	/
6	788	From inflammation to sickness and depression: when the immune system subjugates the brain	2008	Nature reviews Neuroscience	England	33	375
7	699	Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression	2009	Biological psychiatry	Netherlands	11.501	290
8	672	The validity of the Hospital Anxiety and Depression Scale An updated literature review	2002	Journal of psychosomatic research	Netherlands	2.722	141
9	666	Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice	2006	Science	USA	41.037	1058
10	636	Overweight, Obesity, and Depression A Systematic Review and Meta-analysis of Longitudinal Studies	2010	Archives of general psychiatry	USA	/	/
11	586	A neurotrophic model for stress-related mood disorders	2006	Biological psychiatry	Netherlands	11.501	290
12	561	Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis	2009	Psychosomatic medicine	USA	3.937	171
13	546	mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists	2010	Science	USA	41.037	1058

14	517	Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report	2006	American Journal of Psychiatry	USA	13.655	325
15	512	The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review	2010	General hospital psychiatry	Netherlands	3.22	94
16	511	Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants	2003	Science	USA	41.037	1058
17	510	Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010	2013	PLOS medicine	USA	11.048	197
18	504	Depression, chronic diseases, and decrements in health: results from the World Health Surveys	2007	The Lancet	England	59.102	700
19	500	Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010	2013	The Lancet	ENGLAND	59.102	700
20	493	The molecular neurobiology of depression	2008	Nature	ENGLAND	43.07	1096
21	444	The PHQ-9 - Validity of a brief depression severity measure	2001	Journal of general internal medicine	Germany	4.606	161
22	442	Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression	2008	Brain structure and function	Germany	3.622	82
23	414	Cytokines sing the blues: inflammation and the pathogenesis of depression	2006	Trends in immunology	Netherlands	13	209
24	411	Neurobiology of Depression	2002	Neuron	USA	14.403	430
25	405	The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI)	2004	International journal of methods in psychiatric research	USA	2.276	66
26	396	Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models	2008	Behavior research methods	Germany	3.579	114
27	395	Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study	2012	The Lancet	ENGLAND	59.102	700
28	385	Deep brain stimulation for treatment-resistant depression	2005	Neuron	USA	14.403	430
29	345	Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial	2002	JAMA-Journal of The American Medical Association	USA	51.273	622
30	344	Antidepressant drug effects and depression severity: a patient-level meta-analysis	2010	JAMA-Journal of The American Medical Association	USA	51.273	622

3.4. Keywords Analysis

According to bibliometrics theory, keywords indicate hotspots and trends in a research field [60]. Keyword analysis also provided a typical overview of study trends that stood for the journal, as they reflect the focus of an article or an author [61]. Based on (Fig. **6A**), the biggest node is depression, which is same as research topic. This includes 3 main aspects: basic scientific research, social science research and clinical study, that exhibit a complex relationship. (Fig. **6B**). shows that the group on depression mainly includes women, children, adolescent, and adult, suggesting that these groups are at high risk of depression. These keywords also show that depression has far-ranging distribution in all ages.

3.5. Keywords with Citation Bursts

Keywords with citation bursts indicate that keywords have higher citations in a given period, which can test whether a field of research is hot or not over a given period

[62], as well as highlight emerging topics. Through the observation of keywords such as rat (strength, 949.2387; time span, 1998-2009), serotonin (739.1515, 1998-2008), fluoxetine (596.0059, 1998-2005), hippocampus (473.3706, 1998-2004), rat brain (316.2198, 1998-2002), and receptor (257.5575, 1998-2001) (Fig. **7**), it is inferred that animal experiments, particularly hippocampus studies in rat brain, such as brain-derived neurotrophic factor (BDNF) studies [63], was a hotspot in the first ten years. Keywords like United States (64.6058, 2010-2012) indicated that the US is one of the most studied countries with regards to depression, which is consistent with results from country, institute, and journal analysis.

4. MAJOR FINDING

Based on keyword analysis, we summarized the top 15 keywords for each classification in (Fig. **8**) so as to systematically understand depression and inform future research direction.
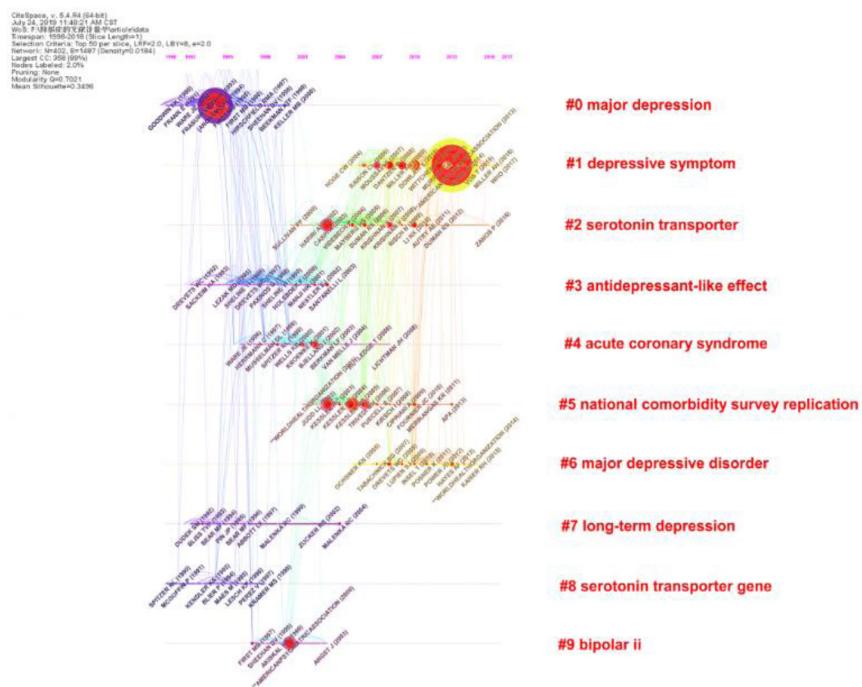
Fig. (5). Reference timeline view. Node size and color represents total number of citations and a single time slice, respectively. Lines of different colors show that the two articles were co-cited in an article. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).
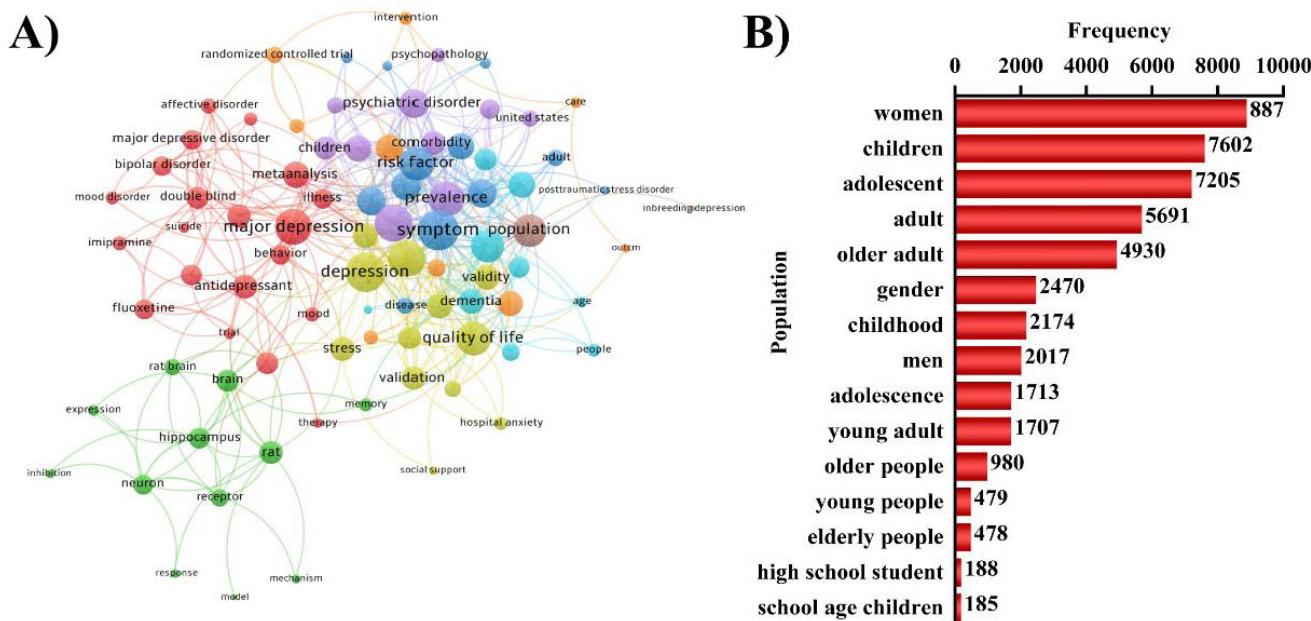
Fig. (6). Keywords map. (**A**) Keywords co-occurrence network. Node size and color represents the number of keywords and cluster. Lines of different colors show that the 2 keywords appear in an article. (**B**) Population distribution. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Top 30 References with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1998 - 2018
rat	1998	945.3343	1998	2009	
efficacy	1998	751.583	1998	2010	
serotonin	1998	737.4327	1998	2008	
follow up	1998	609.0293	1998	2012	
community	1998	608.6092	1999	2007	
fluoxetine	1998	595.1077	1998	2005	
people	1998	590.6451	2015	2018	
illness	1998	544.9579	1998	2005	
intervention	1998	518.841	2013	2018	
disability	1998	474.2686	1998	2009	
hippocampus	1998	472.831	1998	2004	
diagnosis	1998	463.8467	1998	2004	
affective disorder	1998	343.0245	1998	2002	
expression	1998	334.5361	1998	2003	
rat brain	1998	325.9826	1998	2002	
posttraumatic stress disorder	1998	322.0643	2013	2018	
mood	1998	287.3839	1998	2002	
receptor	1998	257.4141	1998	2001	
neuron	1998	243.6808	1998	2001	
older adult	1998	241.7968	2014	2018	
mood disorder	1998	238.3337	2009	2010	
double blind	1998	231.0473	1999	2009	
memory	1998	126.3324	2000	2001	
response	1998	121.416	1998	1999	
imipramine	1998	113.3699	1998	1999	
therapy	1998	84.7193	2012	2013	
psychiatric disorder	1998	79.0618	2007	2012	
united states	1998	64.4141	2010	2012	
major depression	1998	56.6875	2001	2003	
brain	1998	4.8269	1998	1999	

Fig. (7). Top 30 keywords with strongest citation bursts. Blue bars and red bars mean that some keywords are cited frequently in a certain period. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.1. Induction Factor of Depression

The major causes of depressive disorder include long-term, chronic, and low-intensity stress. It is thought that depression is induced by various biological factors, including psychosocial factors, genetic factors, and pathogenic factors [64]. The top 15 keywords related to the induction factor are shown in (Fig. **8A**).

Physical illness usually accompanies biological abnormalities, such as metabolic abnormalities of neurotransmitters. The lack of neurotransmitters in the central nervous system directly affects brain function and may induce depression [65]. Physical illnesses also affect neuroimmune and neuroendocrine processes, causing emotional disorders. Many physical diseases can cause brain chemical imbalance, which may trigger or accompany depression [66], which has 6 main types; endocrine diseases such as hyperthyroidism or hypothyroidism [67]; metabolic diseases such as diabetes [68]; infectious diseases such as AIDS, encephalitis, pneumonia, and hepatitis [69]; internal organ diseases such as pulmonary encephalopathy, hepatic encephalopathy, coronary atherosclerotic heart disease, heart failure, and renal failure [70]; organic brain diseases such as traumatic brain injury, stroke [71], Alzheimer's disease [72], Parkinson's disease [73]; obesity [74], sexual dysfunction [75], cancer [76], disability [77], systemic lupus erythematosus, rheumatoid arthritis, autism, as well as malnutrition and eating disorders. Side

effects of drugs such as opioids and substance abuse may also induce depression [78].

Survival pressures and competition greatly increase depression incidence. Various social stresses may cause feelings of frustration and helplessness [79], contributing to depression. Such life stresses include childhood trauma, divorce, loss of love, pregnancy, postpartum stress, abortion and economic burden [80]. Natural and social factors, such as earthquakes, accidents, rape, robbery, and catastrophic emergencies [81, 82] contribute to depressive disorder.

Multiple studies show that stressful life events are correlated with depression. If there were stressful life events, the incidence of depression is high. However, not all people facing the same life pressures get depression, suggesting that psychological factors are involved [83]. Individuals with different psychological qualities have different tolerances to external stimuli. Individuals who suffered from childhood trauma are more likely to suffer depression. Also, negative life events such as disability and postpartum stress may cause different degrees of psychological trauma. Depression may also be influenced by genetic factors. People from families with depression histories tend to have the same disease more often than those without family depression history [84].

4.2. Disease Type Accompanying Depression

Studies on mental disorder comorbidity have increased in recent years. For example, depression is often accompanied by various disorders, including nervous system disorders, cardiovascular diseases, and cancer (Fig. **8B**). Depression comorbidities aggravate negative emotions, greatly reduce the quality of life, and also increase difficulty in disease treatment.

Comorbid depression is very common in nervous system diseases, especially schizophrenia, one of the most serious mental disorders. Depression worsens schizophrenia and increases the risk of suicide [85]. A systematic review and meta-analysis showed that antidepressants may relieve depression with schizophrenia [86]. Bipolar disorder is a combination of mania and depression, characterized by manic and depressive phases of varying recurrence rates and episode duration [87, 88]. Relative to depression, bipolar patients have longer durations of depressive symptoms. Most people who have experienced trauma exhibit post-traumatic stress disorder (PTSD) symptoms, partly resulting from depression complications [89]. PTSD and depression patients are harder to treat, and suffer severer mental and physical trauma. Chronic acquired progressive mental retardation syndromes, including dementia, are characterized by a slow decline in intelligence and varying degrees of personality change. Although cognitive impairment and social dysfunction are the core symptoms of dementia, depression is also common in dementia and may increase patient mortality and burden to caregivers [90].

Alzheimer's disease is a progressive neurodegenerative disease with hidden onset, and is accompanied by symptoms like the decline in cognitive function, behavioral disorders,

and a decline in living ability [91]. Studies indicate that depression is one of the most common symbiotic mental disorders in Alzheimer's disease. These patients suffer losses in quality of life and cognitive ability, significantly increasing morbidity and mortality [92].

Parkinson's disease, a neurodegenerative disease common in middle-aged and elderly people, is characterized by symptoms like static tremor, ankylosis, and bradykinesia [93]. Up to 35% of Parkinson's patients have depression

symptoms [94]. Depression in Parkinson's disease accelerates the loss of patients' cognitive abilities, lowering quality of life [95].

Stroke survivors often suffer from psychological distress and neuropsychiatric disorders. A third of stroke survivors experience depression, anxiety or apathy, the most common neuropsychiatric sequela. Post-stroke depression affects about 33% of stroke survivors.
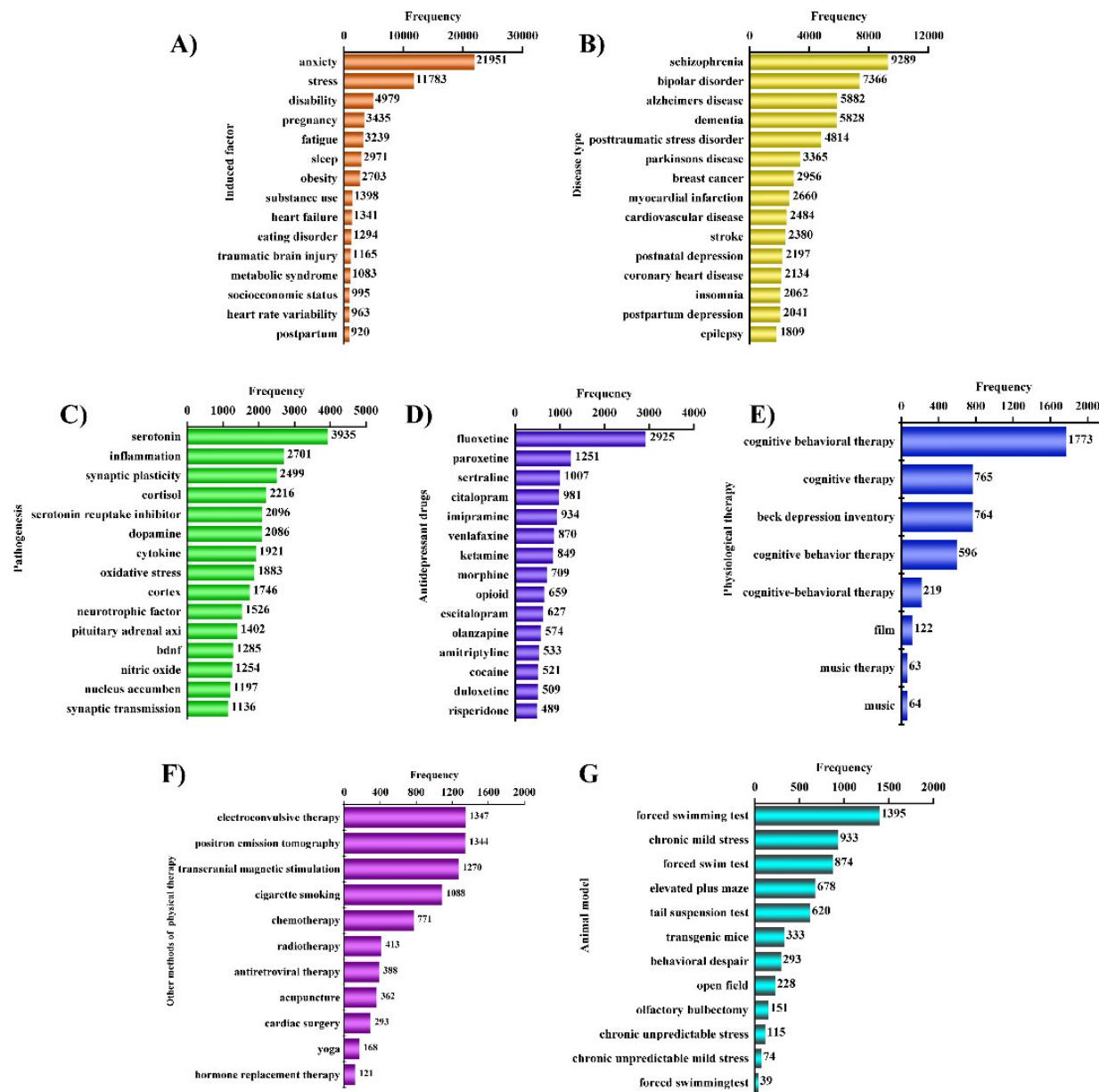
Fig. (8). Manual analysis results. (**A**) Induction factor. (**B**) Disease type. (**C**) Disease mechanism. (**D**) Antidepressant drugs. (**E**) Physiological therapy. (**F**) Other antidepressive ways. (**G**) Animal models. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Depressive seizures in epilepsy are the most common co-morbidities. One to sixty-two percent of epilepsy patients suffer depression. Epilepsy patients have higher depression and suicide rates relative to healthy people. Depression is often seen as a response to epilepsy stigma and associated poor quality of life [96].

Migraine, characterized by recurrent pulsatile headaches, is a common psychosomatic disease associated with psychosocial factors. Patients with migraine are 2.2 to 4 more likely to suffer from depression relative to those without [97]. Headache is a depression predisposing factor and depressive symptoms are indicators of increased headache and disability [98]. The degree of headache positively correlates with depression severity.

Postpartum depression is a subtype of depression that typically occurs within 4 weeks of delivery and is accompanied by puerperal mental illness, including postpartum restlessness and postpartum psychosis [99]. Patients with postpartum depression experience persistent depression, insomnia, excessive sleep, fatigue, low self-evaluation, low confidence, and suicidal thoughts.

Obsessive-compulsive disorder (OCD) is a common psychological condition affecting 1-3% of the general population [100] and is characterized by obsessive-compulsive concepts and behavior, conscious self-compulsion, and self-anti-obsessive-compulsive coexistence. A multinational study found that people with OCD are at higher risk of severe depression relative to the general population [101]. Depression makes the treatment of OCD more difficult.

Depression also raises the risk of cardiovascular disorders, which are the leading cause of death [102]. Acute myocardial infarction is the main cause of cardiovascular disease, and depression patients are at greater risk of cardiovascular diseases, including myocardial infarction. Depression adversely affects cardiovascular disease prognosis and has been shown to be an independent risk factor for death from arrhythmia and heart failure [103]. Coronary heart disease (CHD) and mental illness are the main causes of global morbidity and mortality. Decades of research suggest that the 2 might lead to each other but the nature of these links are unclear [104].

Depression is the most common psychiatric problem in cancer patients. Because symptoms range from sadness to severe emotional disorders, the study of depression has always been a challenge. When patients suffer from repeated life threats, cancer treatment, and fatigue, it is often difficult to assess emotional changes. Depression highly correlates with oropharyngeal, pancreatic, breast [105], ovarian [106], prostate [107] and lung cancer. It is reported that patients with other cancers, such as colon cancer, gynecological cancer and lymphoma, have lower depression rates, and that depression in cancer patients occurs throughout the course of the disease [108].

Other diseases, including rheumatoid arthritis, a major cause of disability worldwide, are associated with depression [109]. A systematic review and meta-analysis of the strength of association between rheumatoid arthritis and depression found that depression is more common in patients with rheumatoid arthritis relative to healthy individuals. This difference was not due to the sociodemographic differences between the population but the degree of pain experienced [110].

Insomnia is also an important diagnostic criterion for depression. About 90% of depression patients have insomnia symptoms [111] and 30% of insomnia patients have varying mental disorders [112]. Depression has been reported as a potential cause of insomnia, the most common clinical complaint and consistent biological change in depression patients. The relationship between mood and glycemic control suggests that diabetes may double the risk of comorbid depression. Clinically, depression is very common in type I and type 2 diabetes and has a significant impact on the course and outcome of this disease. Patients with diabetes mellitus experience greater difficulty in glycemia control and greater complications, including microvascular and macrovascular complications [113]. Therefore, the combination of conventional antidepressants with hypoglycemics may be effective, but such treatment should be individualized. Glycemia control may also help improve mood and well-being [114].

Depression is also very common in HIV/AIDS patients. The prevalence of depression in HIV+ patients ranges from 18-81%. Depression might alter lymphocyte function in HIV patients and reduce activity of natural killer cells, thereby increasing mortality in these patients. Depression treatment can improve the quality of life for HIV-positive patients [115].

Depression is considered a predisposing factor for irritable bowel syndrome (IBS), an intestinal dysfunction caused by structural and biochemical abnormalities in the gastrointestinal tract. IBS is associated with a high prevalence of mental illness. Thus, the level of anxiety and depression in IBS patients is significantly higher than in healthy people. Thus, IBS patients should be actively monitored and treated for anxiety and depression symptoms, because psychological factors influence symptom severity, persistence, decision to seek treatment, and treatment responses [116].

4.3. Pathogenesis of Depression

The etiology of depression is unclear and its pathogenesis is complicated. Several hypotheses have been proposed to explain its pathogenesis. Bibliometric analysis results shown in (Fig. **8C**) revealed that monoamine transmitters and receptors, glutamate and its receptors, neuroendocrine systems, neuropeptides, neurotrophic factors, hormones and inflammatory response doctrines play a role in the pathogenesis of depression.

It was earlier proposed that depression is caused by insufficient levels of noradrenaline in the central nervous system, particularly in the brain [117]. Hypersensitivity of presynaptic membrane α_2 receptor reduces the release of noradrenaline [118], which eventually affect brain functions, increase

the compensatory sensitivity of noradrenaline β-receptor leading to the development of depression [119]. Serotonin is also a major factor the contributes to depression. Clinical studies have demonstrated that cell-mediated immune activation increases indoleamine-2, 3-dioxygenase (IDO) activity in serum. This, in turn, can accelerate the breakdown of the tryptophan kynurenine pathway, reduce the metabolism of serotonin, and decrease the level of serotonin between synapses. These processes contribute to the pathogenesis of depression [59]. Other monoamine neurotransmitters such as dopamine potently alter the neural encoding of depressive behavior in the downstream nucleus accumbens of experimental animals which exhibit depressive symptoms [120].

Evidence collected over the past decade supports the role of the excitatory amino acid (EAA) neurotransmitter glutamate, and its receptors in depressive disorder and antidepressant activity [121]. Studies have shown that increased glutamate in the frontal lobe may induce depression, mainly through the ionotropic glutamate receptor NMDA receptors [122]. Antidepressants modulate the release or uptake of glutamate through binding to NMDA receptors and outcompeting the binding of NMDA receptor ligands [123-125]. Chronic unpredictable stress process may reduce expression of glutamate receptor in the medial prefrontal cortex, increase nitric oxide synthase (NOS) expression and excessive NO production by causing over-activation of hippocampal NMDA receptors. This may induce depression [126].

Depression may also be caused by various pathogenic processes such as hypothalamic-pituitary-adrenalin (HPA) axis dysregulation that includes corticotropin-releasing hormone, peripheral adrenocorticotropic hormone, and glucocorticoids levels. Stress signals are transmitted to the hypothalamus and to the cerebral cortex, which then elevate serum glucocorticoid (GC) levels as a result of enhanced HPA axis [127]. Overexcitation of HPA axis impairs hypothalamic-pituitary-thyroid (HTP) axis function. This explains the recurrence rate of depression in patients with hyperthyroidism is higher than in those with non-thyroid function. Dysregulation of HPA axis affects the hippocampal glutamate and NMDA receptors and glucocorticoid receptors, which mediate the close association of depression with HPA axis [128].

Depression is associated with the function of neuropeptides and neurotrophic factors, substance P antagonists (S-PA) and substance P (SP). These factors regulate the secretion of serotonin in the dorsal raphe nucleus by altering the functional activities of the habenular nucleus, causing antidepressant effects [129]. Animal models show that neuroplastic markers brain-derived neurotrophic factor (BDNF) modify the structure and function of the hippocampus. Long-term use of antidepressant therapy promotes synthesis and signaling pathways of BDNF. In mouse with BDNF knocked-out, decreased hippocampal dentate gyrus neurons regeneration was observed, indicating that neurotrophic factors affect depression [130-132].

Changes in hormone levels have been shown to influence the development of depression. Activation of paraven-

tricular nucleus neurons affects the corticotropin-releasing hormone (CRH), the key regulator of the HPA axis *via* the hypothalamic paraventricular nucleus (PVN). Elevated CRH increases Crhr1, estrogen receptor alpha (Esr-α), vasopressin receptor (Avpr1a) and glucocorticoid receptor gene expression leading to the development of depression in response to stress [133]. Increased estrogen levels have been implicated in the occurrence of depression. A survey study demonstrated that more women develop depression, twice the number of men, such as postpartum and menopausal mood disorders [134]. In addition, abnormal glucocorticoid levels have been linked to depression. Genetic variations of the glucocorticoid receptor gene (Nuclear Receptor Subfamily 3, Group C, Member 1; NR3C1) affects the development of depression. Polymorphisms in the 5' region of the NR3C1 gene may play a role in the genetic vulnerability for major depressive disorder [135].

Inflammatory cytokines regulate not only inflammatory responses but also neurogenesis and neuroprotection [136]. High levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) lead to chronic neuroinflammation and eventually depression. In addition, inflammatory cytokines trigger peripheral immune activation, and this in turn causes neuroendocrine and immune system dysfunction that lead to depression. Multiple inflammatory-cytokines and oxygen radicals have been found in patients with depression as well as animal models of depression [137].

4.4. Antidepressant Therapy

Currently, depression is treated with drugs which improve depression by regulating neurotransmitter and hormone levels in the brain. Common antidepressants include traditional tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) as well as reversible inhibitors of monoamine oxidase-A (RIMAs). The top 15 antidepressant medicines are showed in (Fig. **8D**).

Clomipramine, one of the TCAs, has been widely used in Europe [138]. TCAs exert antidepressant and anxiolytic effects by restraining norepinephrine and serotonin reuptake in the central nervous system, which may also improve the compliance of patients when toxic reactions are produced. Amitriptyline is another drug used to treat depression [139]. It improves the emotional state of depressed patients, therapy anxiety or agitated depression.

SSRIs are also mainstream antidepressants used in clinical practice. They include fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram, known as the five golden flowers of new antidepressants. Fluoxetine elevates serotoninergic neurotransmission by restraining neuronal reuptake of serotonin [140]. However, fluoxetine alone has a slow effect, and its early effect on the 5-HT2 receptor also causes anxiety and uneasiness in patients. Some atypical antipsychotics such as olanzapine reduce the discharge of dopaminergic neurons in the inter-brain limbic system. They can con-

trol the affinity of dopamine, block central 5-HT2A and 5-HT2C receptors to lower symptoms of depression. Moreover, olanzapine may be applied to alleviate bipolar disorder after using serotonin reuptake inhibitors, placating the sentiment of patients [141]. A combination of olanzapine and fluoxetine has shown benefits in bipolar depression [142]. Paroxetine is a widely prescribed and reliable antidepressant [143], which effectively inhibits the uptake of serotonin. Sertraline is used as the first SSRIs to limit *in vivo* ingestion of dopamine by reducing the liveness of the presynaptic terminal [144]. Fluvoxamine increases the concentration of serotonin in the synapse and fortifies the effects of serotonin on nerve conduction, thereby exerts antidepressant and anxiolytic effects [145]. Citalopram plays a feeble role in the regulation of norepinephrine, epinephrine receptors, dopamine, histamine, muscarine, and benzodiazepines in depressive disorder [146, 147]. It is highly selective for serotonin receptor, hence can treat depression by decreasing serotonin levels.

As one representative drug of SNRIs and an emblematic phenylethylamine derivative, venlafaxine exerts antidepressant effects. Venlafaxine differs from general antidepressants. It relieves depression symptoms by increasing the concentration of norepinephrine and serotonin, slightly inhibiting dopamine uptake, and decreasing the number of adrenaline receptors [148].

Mirtazapine, as a member of NaSSAs, is generally used to treat depression [149]. It is however, associated with side-effects such as sexual dysfunction, nausea, and anorexia. Mirtazapine can block 5-HT2 and 5-HT3 receptors to improve 5-HT1-mediated serotonin neurotransmission, thereby mitigating depression and anxiety.

Moclobemide is a newly developed reversible MAO-A subtype inhibitor and the key metabolic enzyme of norepinephrine, dopamine and serotonin. It reduces the degradation of central monoamine mediators. The broad-spectrum antidepressant effect of moclobemide may heal endogenous and exogenous depression, there improve the sleep quality of patients. Compared to other antidepressants, moclobemide does not cause significant hepatotoxicity or adverse effects in cardiovascular tissues. It is therefore a safe medicine, especially on the autonomic nervous system [150].

The currently used first- and second-generation antidepressants are not sufficiently effective. For instance, agomelatine and bupropion have a selective action on melatonin receptors and dopamine receptors making them ineffective antidepressants. Agomelatine is a melatonin agonist and selective serotonin antagonist [151]. It is suitable for severe depression complicated with insomnia. Bupropion controls depression by inhibiting noradrenaline and dopamine secretion [152]. Given the side effects of bupropion, it is generally contraindicated in patients with epilepsy.

In addition to antidepressants, other interventions have been developed to be used as adjuncts to drug therapy, some of them are shown in (Fig. **8E**). It has been reported that patients put on cognitive behavioral-therapy regained confidence [153]. Cognitive-behavioral therapy is not different from second-generation antidepressants. On the basis of medication, cognitive therapy, an effective auxiliary tool, improved the condition of depression and reduced the recurrence rate [154]. Electroconvulsive therapy is another effective intervention applied in most psychiatric diseases, but it cannot be used more than thrice a week because of its side effects like headaches and nausea [155]. Therefore, electroconvulsive therapy is often used as second-line therapy [156].

In addition to conventional treatments, acupuncture has been proposed as a complementary therapy. The data shown in (Fig. **8F**). Indicates that it improves depression in a number of clinical trials [157]. There is evidence that acupuncture regulates hormones such as norepinephrine, dopamine, endorphins and affects the endocrine system and the nervous system thereby modulates depression symptoms [158]. Therapies combining acupuncture and other treatment are more effective than single therapies [159]. In addition, music therapy, yoga, and meditation are used to manage emotions and alleviate anxiety and passivity symptoms [160]. Music therapy improves patients' condition and enhances their conversational and social skills. Aerobic exercise, such as yoga can make depressive patients relax and improve depression symptoms [161]. Yoga reduces the harmful side effects of drugs and can be combined with drugs to improve the treatment of depression [162].

4.5. Animal Models of Depression

(Fig. **8G**). shows the four animal models related to depression, namely, behavioral despair in mice, chronic unpredictable mild model (CUMS), transgenic mice and olfactory bulbectomy. Behavioral despair in mice is used to screen the efficacy of antidepressants [163], including forced swimming (FST), tail suspension test (TST), open field test (OFT). The latter three models are used for pharmacology studies to explore the pathomechanisms of depression [164, 165]. These animal models of depression provide an important tool to develop more effective antidepressants.

5. LIMITATIONS AND ADVANTAGE

The data of this study are from SCI-E database in WOS. Although there are several databases, SCI-E provides the highest quality research findings of depression making it ideal for bibliometric analysis [166]. For author analysis of this literature, bibliometric software cannot distinguish the abbreviation of the author in the current and so it has no appearance for avoiding false conclusions in this paper. Although we only used the SCI-E database, this platform contains a large amount data to study the theme of depression. Therefore, the results obtained here are highly credible. Compared to other bibliometric analyses, the results of journals analysis were contained in this paper and they provided the selection of a journal for the submission of the article. Moreover, the data presented here reveal the trends in depression research to guide other researchers in the field of depression.

CONCLUSION

In this paper, scientometrics is used to analyze literature in the SCI-E database. Our results reveal research hotspots, key research directions, productive countries and institutions focusing on depression in the past 20 years. Research publications on depression vary across regions. The first reason is that people's lives have been under great pressure in recent years. The second reason is that various factors can lead to the occurrence of depression. Hence there are more and more studies in the field of depression. In conclusion, it is found the most productive country, institute, category, journal, the most cited journal, reference and keywords through the statistical analysis of scientometrics. In addition, the traditional review concludes induction factor, comorbidity, pathogenesis, therapy and animal models of depression in the current by the most frequent keywords of keyword analysis. These not only show the current research hotspots but also reveals grey areas for further research.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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