

Med. Pharm. J. Review article

Sex hormones and the immune system: a bibliometric analysis

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DOI: [10.55940/medphar202495](https://doi.org/10.55940/medphar202495)

Submitted: 25-July -2024

Accepted: 12- Sep -2024

Published: 15-Oct-2024

Abstract

Background: Sex hormones are considered to have complex impacts on immune responses, and there has been a notable increase in interest regarding their role in the immune system over the past ten years.

Objective: This descriptive bibliometric analysis provides insights into publication trends related to sex hormones and the immune system.

Methods: Utilizing the Scopus database, the analysis highlights the most prolific authors, countries, institutions, journals, and keywords associated with this field of research.

Results: For the years 2000 to 2023, 928 articles were analyzed, revealing a significant upward trend in annual publications concerning sex hormones and immune functions. The United States accounted for the largest share, with 331 articles published, the most productive authors were Boyd, R.L. and Chaves-Pozo, E. with 6 articles for each, Inserm University shared the most published articles (14 articles), and Plos One journal had the largest number of publications (17 articles).

Conclusion: Sex hormones play complex roles in affecting the immune system, and this bibliometric analysis concentrated on the significant interest that has appeared in the research community concerning these roles.

KEYWORDS: Sex hormones, Immune system, Immune response, Bibliometric analysis

INTRODUCTION

Hormones are chemical messengers secreted by several glands, organs, or tissues to coordinate different body functions and control hundreds of physiological processes. Hormones can be divided into several types according to their structure. Steroid hormones are derived from cholesterol. It regulates metabolism, inflammation, immune responses, and the balance of salt and water in the body. Steroid hormones are classified as corticosteroids and sex steroids. Corticosteroids are made by the adrenal cortex and are secreted as glucocorticoids and mineralocorticoids. Glucocorticoids, such as cortisol, have anti-inflammatory and antiallergic effects. Mineralocorticoids, such as aldosterone, regulate water and salt balance in the body [1].

Sex steroids are mostly made by the gonads and secreted as androgens, estrogen, and progesterone. Androgens are male-sex hormones like testosterone that have anabolic effects. Estrogens and progesterone are female sex hormones. Estradiol is the most potent form of estrogen. Less testosterone is secreted in females, and a lesser amount of estrogen is secreted in males by the adrenal gland [2, 3].

Sex hormones and the immune system are linked in a complex manner. Estrogen may have an immunoenhancing effect, while progesterone and testosterone may have an immunosuppressive effect. Therefore, progesterone helps to maintain pregnancy by preventing rejection of the developing fetus, while testosterone may regulate certain immune responses,

helping to suppress inflammation. Fluctuations in estrogen levels during pregnancy and during the menstrual cycle may lead to varying incidences and severities of autoimmune diseases in females, while testosterone may play a role in providing some protection against autoimmune diseases. This might explain the lower incidence of certain autoimmune conditions in males [4-6].

Interest in how sex hormones influence the immune system has grown significantly in the past ten years. This rise in interest is likely due to advancements in endocrinology, allowing researchers to explore the connection between sex hormones and immune function [7], differences in disease susceptibility, such as autoimmune diseases and infectious diseases, depending on sex differences [8], and trials of hormones and hormone replacement therapies for treating several conditions, such as autoimmune diseases, cancer, and infectious diseases [9].

MATERIALS AND METHODS

This study utilized a descriptive bibliometric analysis [10] to create a scientific map of publications on sex hormones and the immune system. Analysis was conducted using the VOSviewer software program.

Data collection

The Scopus database served as the data source, with data extracted on March 1, 2024. The search was conducted using the following criteria: TITLE-ABS-KEY (sex AND hormones AND immune AND

system) AND PUBYEAR > 1999 AND PUBYEAR < 2024 AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (DOCTYPE, "ar"))

The search focused on publications from 2000 to 2023, excluding those from 1999 and 2024. Only articles published in English were considered. The final dataset was then downloaded and analyzed. A descriptive bibliometric analysis was conducted to examine the scientific landscape of sex hormones and their link to the immune system from 2000 to 2023.

Statistical analysis

This analysis covered trends in annual publications, key researchers, relevant journals, contributing countries, and patterns of co-authorship. The data were analyzed using the Scopus database and VOSviewer.

RESULTS

The initial search generated 2767 publications. After limiting the results to the years 2000-2023, it included 2268 papers. English-language papers were 2170. This search was restricted to 928 articles.

Increasing trend in annual publications

From 2000 to 2023, the Scopus database yielded 928 articles examining the relationship between sex hormones and the immune system. The annual publication numbers are as follows: 2000 (n = 25), 2001 (n = 17), 2002 (n = 37), 2003 (n =19), 2004 (n = 21), 2005 (n = 22), 2006 (n = 24), 2007 (n = 31), 2008 (n = 28), 2009 (n =27), 2010 (n = 36), 2011 (n = 55), 2012 (n = 28), 2013 (n = 33), 2014 (n = 44), 2015 (n =41), 2016 (n = 49), 2017 (n = 37), 2018 (n = 44), 2019 (n = 58), 2020 (n = 67), 2021 (n = 72), 2022 (n = 49), and 2023 (n = 64). The peak year for publications was 2021, with a total of 72 articles (Figure 1).

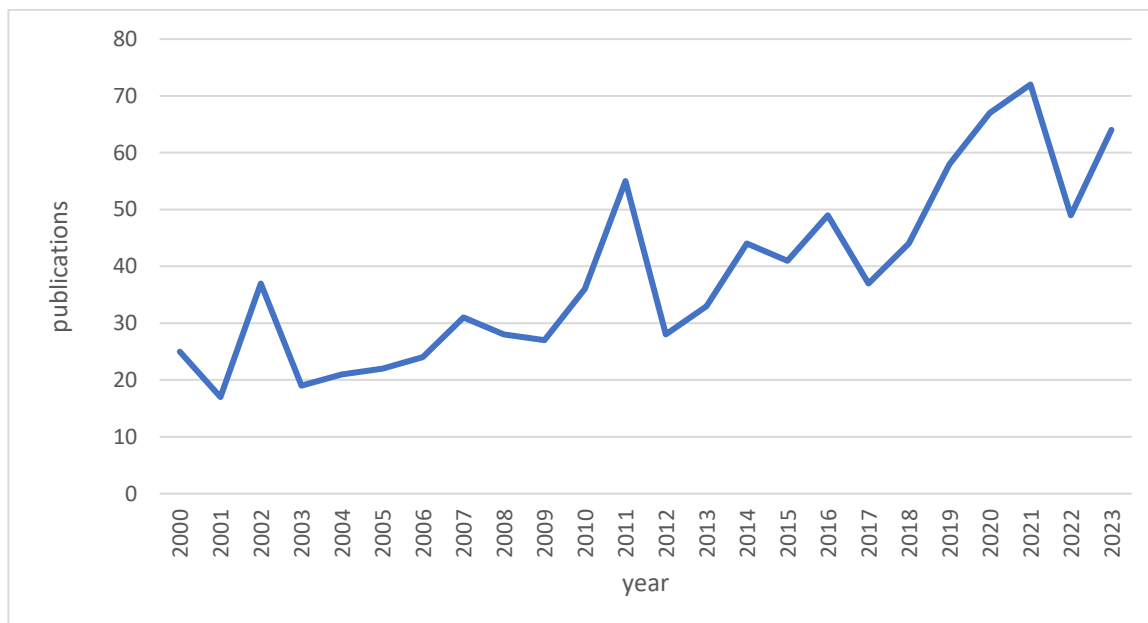


Figure 1. Annual publications on sex hormones and immune system

Countries

The total number of countries identified by the Scopus analysis tool that shared publications on sex hormones and the immune system was 75 (Table S1). The United States led with the highest number of publications at 331 articles, with the

United Kingdom contributing 82 articles, China (64 articles), Italy (64 articles), Germany (63 articles), Canada (57 articles), Spain (48 articles), France (46 articles), Australia (43 articles), and the Netherlands (30 articles) (Figure 2).

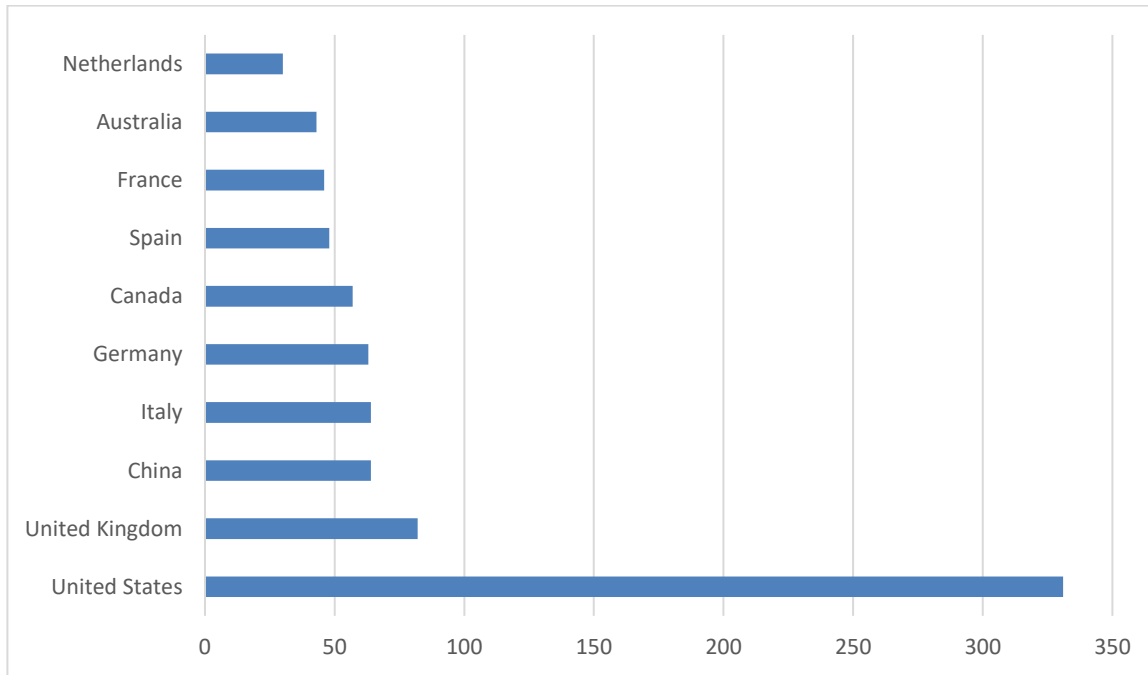


Figure 2. Top 10 countries published on sex hormones and immune system

The density map of countries involved in co-authorship highlights the leading nations in this field. The intensity of the

yellow color indicates the volume of publications (Figure 3).

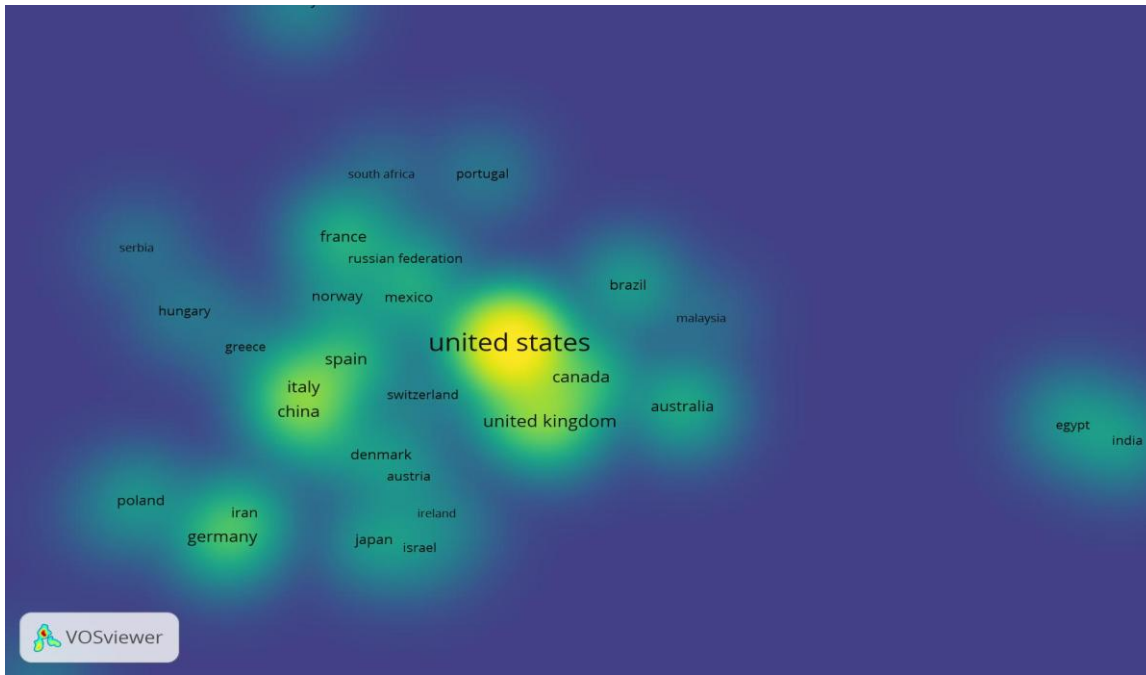


Figure 3. Density map illustrating countries involved in co-authorship

Country Co-authorship

The VOSviewer network visualization map illustrates international collaboration among countries in sharing publications authored by individuals from different nations. There are 41 countries counted in co-authorship across 8 clusters. Every cluster is represented by a specific color on the map, indicating that most collaborations occur within the same cluster, although interactions with countries from other clusters are also present (Figure 4).

- Cluster 1: 9 countries (Austria, Belgium, Denmark, Ireland, Israel, Japan, the Netherlands, Sweden, and Taiwan)
- Cluster 2: 8 countries (France, Greece, Hungary, Italy, Portugal, Serbia, Spain, and Turkey)

- Cluster 3: 7 countries (Argentina, Finland, Mexico, Norway, the Russian Federation, South Africa, and Switzerland)
- Cluster 4: 5 countries (Egypt, India, Saudi Arabia, South Korea, and Thailand)
- Cluster 5: 5 countries (China, Iran, Poland, Slovakia, and the United States)
- Cluster 6: 4 countries (Australia, Brazil, Malaysia, and the United Kingdom)
- Cluster 7: 2 countries (Bulgaria and Germany)
- Cluster 8: 1 country (Canada)

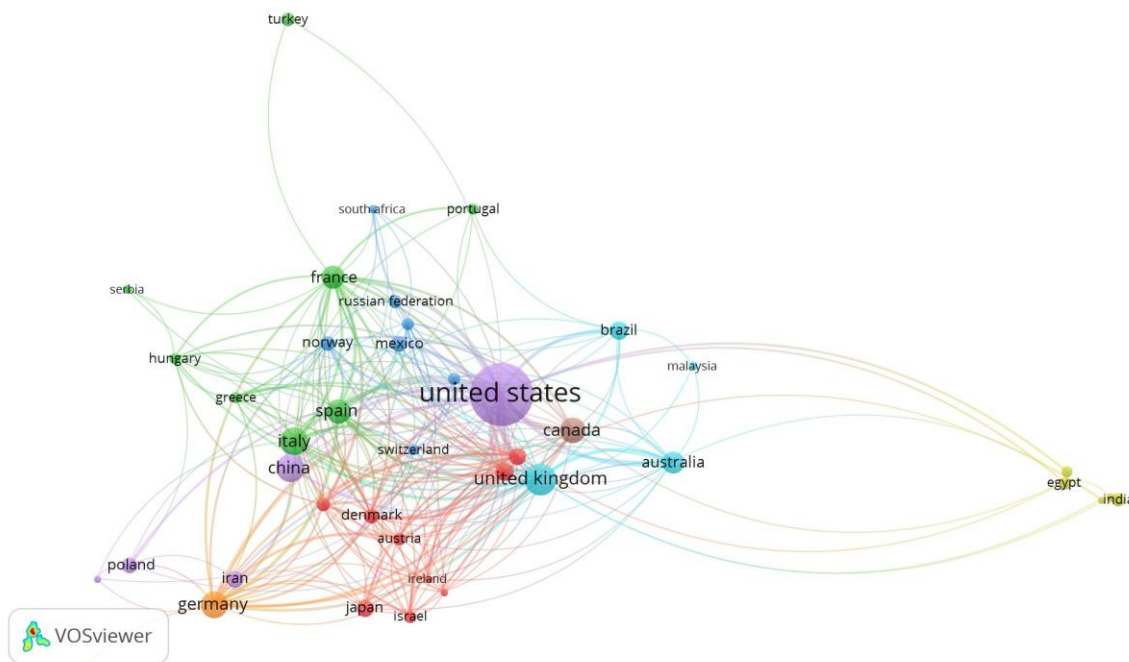


Figure 4. Map of country co-authorship

To shed light on this co-authorship, a quick search was performed for the most highly cited articles from the top 10 countries, focusing on the educational institutions of the first authors. These findings were surprising. The most cited article was shared among the United Kingdom, Italy, and the Netherlands, with the first author affiliated with Inc., Naples, United States. Another highly cited article was common to Germany and

Spain, with the first author from the University of Oslo, Oslo, Norway. In Canada, the highest-cited article's first author was affiliated with the Johns Hopkins Bloomberg School of Public Health, Baltimore, United States. Additionally, the first author of the highest-cited article in Australia was associated with Nippon Medical School, Tokyo, Japan (Table 1).

Table 1: Institution of the first author of the most highly cited article in top 10 countries

NO.	Country	Most cited article for human	Affiliation of the first author
1	United States	Obesity is associated with macrophage accumulation in adipose tissue	Columbia University Irving Medical Center, New York, United States
2	United Kingdom	Current Knowledge of Buprenorphine and Its Unique Pharmacological Profile	Inc, Naples, United States
3	China	Endocrine-Disrupting Effects of Pesticides through Interference with Human Glucocorticoid Receptor	Hangzhou Normal University, Hangzhou, China

4	Italy	Current Knowledge of Buprenorphine and Its Unique Pharmacological Profile	Inc, Naples, United States
5	Germany	Sex and gender issues in multiple sclerosis	Universitetet i Oslo, Oslo, Norway
6	Canada	Sex-based differences in immune function and responses to vaccination	Johns Hopkins Bloomberg School of Public Health, Baltimore, United States
7	Spain	Sex and gender issues in multiple sclerosis	Universitetet i Oslo, Oslo, Norway
8	France	The pathology of dry eye	Quinze-Vingts National Ophthalmology Hospital, France
9	Australia	Interferon- γ and lipopolysaccharide potentiate monocyte tissue factor induction by C-reactive protein: Relationship with age, sex, and hormone replacement treatment	Nippon Medical School, Tokyo, Japan
10	Netherlands	Current Knowledge of Buprenorphine and Its Unique Pharmacological Profile	Inc, Naples, United States

Authors

The total number of authors identified by the Scopus analysis tool who shared publications on sex hormones and the immune system was 159 (Table S2). The authors of the highest publications were

Boyd, R.L. and Chaves-Pozo, E. (6 articles), then Chaudry, I.H., Chidgey, A.P., Cutolo, M., Kaushic, C., Meseguer, J., Morales-Montor, J., Mulero, V. (5 articles), and Bland, K.I. (4 articles) (Figure 5).

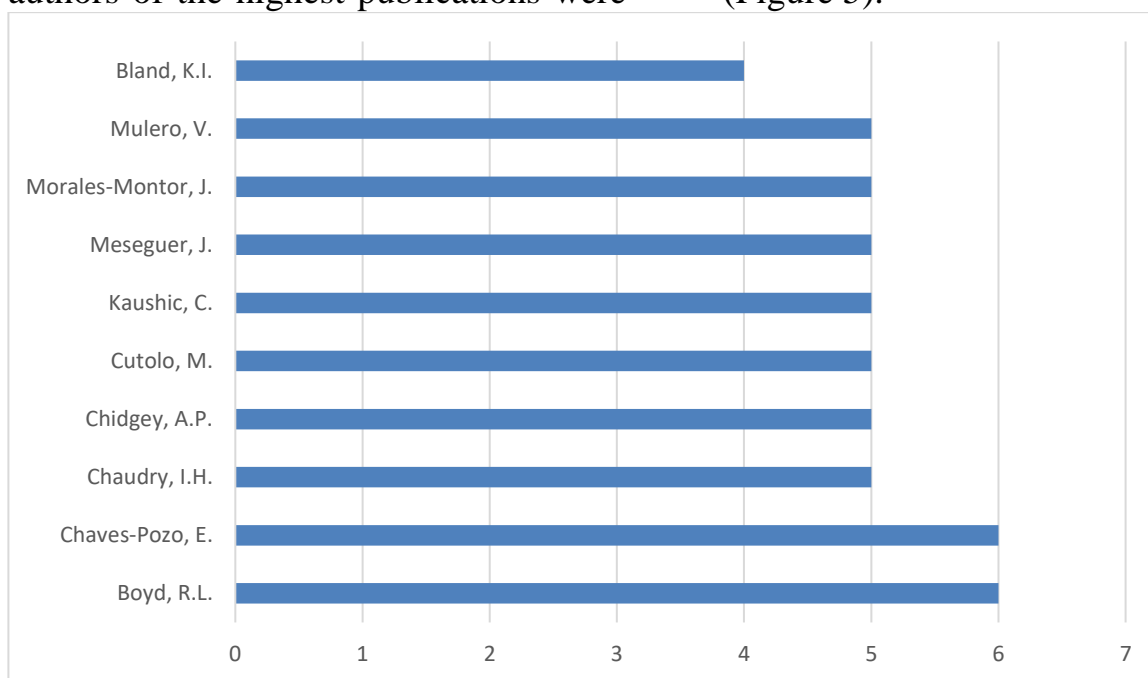


Figure 5. Top 10 authors in publications on sex hormones and immune system

Affiliation

The total number of affiliations identified by the Scopus analysis tool that shared publications on sex hormones and the immune system was 160 (Table S3). Inserm University led in the number of published articles with 14 contributions, followed closely by Universidade de São Paulo, and the University of Toronto,

each with 12 articles. The University of Illinois Urbana-Champaign, Karolinska Institutet, and Monash University published 11 articles. Additionally, the University of Sheffield, Harvard Medical School, National Institutes of Health (NIH), and CNRS Centre National de la Recherche Scientifique each contributed 10 articles (Figure 6).

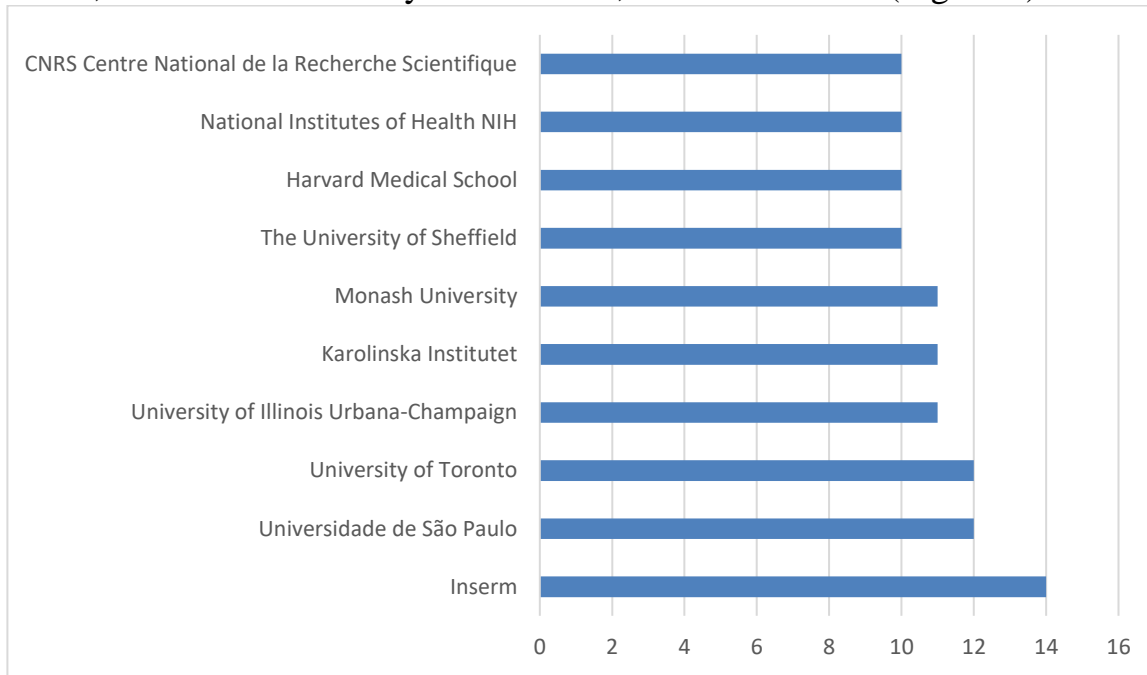


Figure 6. Top 10 affiliations published on sex hormones and immune system Journals

The net number of journals identified by the Scopus analysis tool that shared publications on sex hormones and the immune system was 160 (Table S4). Plos One had the highest number of publications (17 articles), General And Comparative Endocrinology (14 articles), Brain Behavior And Immunity, and Frontiers In Immunology (13 articles), American Journal Of Reproductive

Immunology (12 articles), Frontiers In Endocrinology, and Psychoneuroendocrinology (11 articles), Hormones And Behavior, and Proceedings Of The National Academy Of Sciences Of The United States Of America (10 articles), and International Journal Of Molecular Sciences (8 articles) (Figure 7).

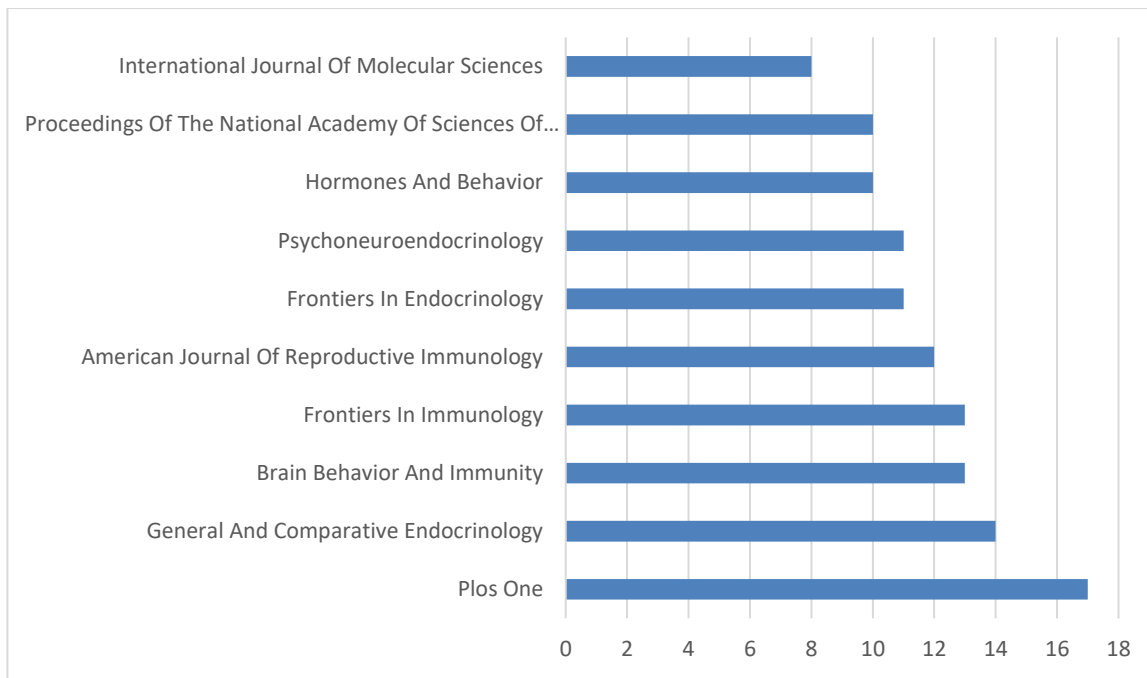


Figure 7. Top 10 journals published on sex hormones and immune system

For more scope on the top 10 journals sharing publications concerning sex hormones and the immune system, the leading publisher is Elsevier, which publishes 4 of the top 10 journals. The most highly cited article appeared in Brain Behavior and Immunity journal,

with 404 citations and a highest cite score of 24.3. The International Journal of Molecular Sciences achieved the largest total citations, while Plos One recorded the highest number of total publications (Table 2).

Table 2. Top 10 journals

Journal	Total publications	Total citation	Cite score	The most cited article	Times cited	Publisher
Plos One	63236	377961	6.0	Lactobacillus rhamnosus Accelerates Zebrafish Backbone Calcification and Gonadal Differentiation through Effects on the GnRH and IGF Systems	103	Public Library of Science
General And Comparative Endocrinology	744	4590	6.2	Differential in vitro suppressive effects of steroids on leukocyte phagocytosis in two teleosts, tilapia and common carp	105	Elsevier
Brain Behavior And Immunity	1193	29043	24.3	The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X	404	Elsevier
Frontiers In Immunology	19982	188368	9.4	Sex hormones determine immune response	338	Frontiers Media SA

American Journal Of Reproductive Immunology	454	2868	6.3	Impact of female sex hormones on the maturation and function of human dendritic cells	72	Wiley-Blackwell
Frontiers In Endocrinology	39090	6996	5.6	Do the interactions between glucocorticoids and sex hormones regulate the development of the metabolic syndrome?	37	Frontiers Media SA
Psychoneuroendocrinology	1195	10014	8.4	Stress hormones in health and illness: The roles of work and gender	343	Elsevier
Hormones And Behavior	546	3362	6.2	An alternate pathway for androgen regulation of brain function: Activation of estrogen receptor beta by the metabolite of dihydrotestosterone, 5 α -androstane-3 β ,17 β -diol	173	Elsevier
Proceedings Of The National Academy Of Sciences Of The United States Of America	14386	276478	19.2	Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation	287	National Academy of Sciences
International Journal Of Molecular Sciences	45382	452748	7.8	Sex-dependent effects of perinatal inflammation on the brain: Implication for neuro-psychiatric disorders	51	Multidisciplinary Digital Publishing Institute (MDPI)

Keywords

The most mentioned keywords appeared in the included articles: sex hormone (305 times), immune system (290 times), immune response (190 times), testosterone (194 times), immunology (174 times), estrogen (148 times), inflammation (139 times), T lymphocyte (75 times), immunomodulation (65

times), hormone action (57 times), hormones (63 times), hormone (67 times), estrogens (58 times), immunity (60 times), multiple sclerosis (43 times), androgen receptor (43 times), estrogen receptors (43 times), and sex hormones (41 times) (Table 3).

Table 3. Common keywords used and their occurrence

keyword	Number of their occurrence
Sex hormone	305
Immune system	290
Immune response	190
testosterone	194

immunology	174
estrogen	148
inflammation	139
T lymphocyte	75
immunomodulation	65
Hormone action	57
hormones	63
hormone	67
estrogens	58
immunity	60
Multiple sclerosis	43
Androgen receptor	43
Estrogen receptor	43
Sex hormones	41

Figure 8 shows the most common keywords. The words appeared in the

same color, forming a net, and appeared together in the included articles.

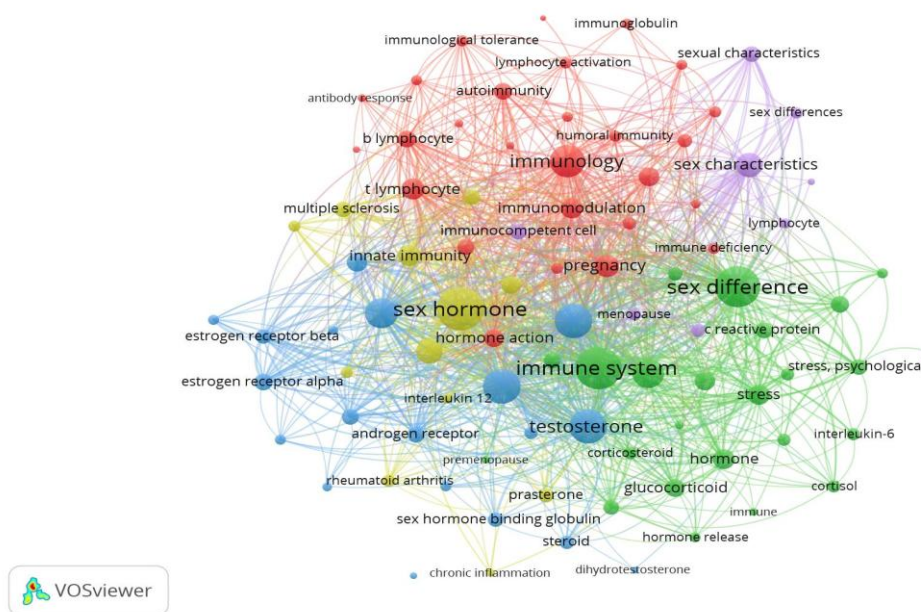


Figure 8. Most common keywords

DISCUSSION

A total of 928 articles were included. The data were restricted to the years from 2000 to 2023.

This review highlighted a rising trend in publications, with the leading contributors being the United States, the United Kingdom, and China. Plos One journal had the highest output of articles on this subject. Inserm University shared

the most published articles. The highest number of publications were by Boyd, R.L. and Chaves-Pozo, E. The most frequently mentioned keywords are sex hormone, immune system, immune response, testosterone, immunology, estrogen, and inflammation.

Sex hormones play complex roles in affecting the immune system. Fighting against infectious diseases is one of the

goals of the immune system. In recent years, numerous studies and reviews have focused on the COVID-19 pandemic from different perspectives. A study by Jienan Gu et al [11] founded that females exhibited distinct autoimmune responses post-COVID-19 infection compared to males, and one of the suggested mechanisms was that estrogen promotes vigorous humoral immunity compared to testosterone. Another study [12] showed that progesterone modulates the maternal immune system to prevent fetal rejection. A study concerning multiple sclerosis [13] indicated it is a chronic autoimmune disease that occurs more frequently in females. Female sex hormones play complex and diverse roles in the development of multiple sclerosis and its episodes. It differs according to the change in hormone concentration during pregnancy and the menstrual cycle. A study discussing sex hormones and vaccination [14] revealed that females exhibit an exaggerated immune response, increased antibody production, and more adverse effects from many types of vaccination than males. Therefore, measures need to be taken to decrease female adverse effects and increase male responses to vaccination. Another study [15] showed that certain female sex hormones, like human chorionic gonadotropin, are secreted during pregnancy and modulate dendritic cell activity to maintain pregnancy and protect the fetus.

Sex hormones may affect mucosal immunity differently. Mucosal immunity refers to special immune responses that occur at mucosal surfaces such as ocular surfaces and the nasal mucosa. Female sex hormones induce IgE sensitization, while testosterone decreases IgE

sensitization. IgE is responsible for many allergic symptoms, such as allergic asthma and allergic rhinitis [16]. The eye is also considered a target organ for sex hormones, and disturbance of normal regulatory mechanisms may lead to inflammation [17]. Fibromyalgia is often predominant in females. A theory in a study by Meester I et al may conclude that various immunology biomarkers are altered by female sex hormones [18]. This bibliometric analysis offers a comprehensive overview of global research findings on sex hormones and the immune system.

ACKNOWLEDGMENTS

Nil

Conflict of interest

None

Funding

None

Supplementary materials

10.5281/zenodo.13918065

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How to cite this article:

Heba Ramadan. Sex hormones and the immune system: a bibliometric analysis. *Med. Pharm. J.* 2024; 3(3): 106-118.

DOI: [10.55940/medphar202495](https://doi.org/10.55940/medphar202495)

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