Global mapping of randomised trials related articles published in high-impact factor medical journals: a cross-sectional analysis

Ferrán Catalá-López (ferran_catala@hotmail.com)
National School of Public Health, Institute of Health Carlos III https://orcid.org/0000-0002-3833-9312
Rafael Aleixandre-Benavent
Consejo Superior de Investigaciones Cientificas
Lisa Caulley
University of Ottawa
Brian Hutton
Ottawa Hospital Research Institute
Rafael Tabarés-Seisdedos
Universitat de Valencia
David Moher
Ottawa Hospital Research Institute
Adolfo Alonso-Arroyo
Universitat de Valencia

Research

Keywords: Evidence based medicine; Randomized controlled trial; Scientific collaboration.

Posted Date: July 26th, 2019

DOI: https://doi.org/10.21203/rs.2.11988/v1

Version of Record: A version of this preprint was published on January 7th, 2020. See the published version at https://doi.org/10.1186/s13063-019-3944-9.

Abstract

Background Randomised controlled trials (RCTs) provide the most reliable information to inform clinical practice and patient care. We aimed to map the global clinical research publication activity through RCTs related articles in high-impact factor medical journals over the past five decades. Methods Cross-sectional analysis of articles published in the highest ranked medical journals with an impact factor > 10 (according to Journal Citation Reports published in 2017). We searched PubMed/MEDLINE (from inception to December 31, 2017) for all RCTs related articles (e.g. primary RCTs, secondary analyses and methodology papers) published in high-impact factor medical journals. For each included article, raw metadata were abstracted from the Web of Science. A process of standardization was conducted to unify different terms and grammatical variants and to remove typographical, transcription, and/or indexing errors. Descriptive analyses were conducted (including the number of articles, citations, most prolific authors, countries, journals, funding sources and keywords). Network analyses of collaborations between countries and co-words were presented. Results We included 39305 articles (period 1965-2017) published in forty journals. The Lancet (n=3593; 9.1%), the Journal of Clinical Oncology (n=3343; 8.5%), and The New England Journal of Medicine (n=3275 articles; 8.3%) published the largest number of RCTs. 154 countries were involved in the production of articles. The global productivity ranking was led by the United States (n=18393 articles), followed by the United Kingdom (n=8028 articles), Canada (n=4548 articles) and Germany (n=4415 articles). Seventeen authors who published 100 or more articles were identified; the most prolific authors were affiliated with Duke University (United States), Harvard University (United States), and McMaster University (Canada). Main funding institutions were the National Institutes of Health (United States), Hoffmann-La Roche (Switzerland), Pfizer (United States), Merck Sharp & Dohme (United States) and Novartis (Switzerland). The 100 most cited RCTs were published in 9 journals, led by The New England Journal of Medicine (n=78 articles), The Lancet (n=9 articles) and JAMA (n=7 articles). These landmark contributions focused on novel methodological approaches (e.g. "Bland-Altman method") and trials on the management of chronic conditions (e.g. diabetes control, hormone replacement therapy in postmenopausal women, multiple therapies for diverse cancers, cardiovascular therapies such as lipid-lowering statins, antihypertensive medications, antiplatelet and antithrombotic therapy). Conclusions Our analysis identified authors, countries, funding institutions, landmark contributions and high-impact factor medical journals publishing RCTs. Over the last 50 years, publication production in leading medical journals has increased with research leadership of Western countries, but with very limited representation from low and middle-income countries.

Background

Randomised controlled trials (RCTs) are considered one of the simplest and most powerful tools for assessing the safety and effectiveness of treatment interventions [1-3]. When appropriately designed, conducted and reported, RCTs can produce an immediate impact on clinical practice and patient care [4].

The evolution of RCTs has been an enduring and continuing process [5-15]. Since the 1970s, the publication landscape for RCTs has exhibited an exponential growth. For example, a 1965-2001 bibliometric analysis of the literature identified 369 articles published in 1970 compared to 11159 published in 2000 [5]. The development of clinical trial registries (such as clinicaltrials.gov) [9,10], the exponential increase in journals publishing trial protocols, results and secondary studies, and growing support for data-sharing policies [11,12] have created an open research environment of transparency and accountability. Furthermore, the publication of reporting guidelines (such as CONSORT and SPIRIT) [4,13-15] have served to facilitate the transition between research and reporting to ensure standardisation and ease of readability.

RCTs published in major medical journals are highly cited and have an instrumental role in clinical practice [5,16,17]. Previous studies have focused on the quality of reporting of methods and results of RCTs [18-22], and publication practices [23-28] in selected samples of articles published in high impact factor (IF) medical journals. However, to the best of our knowledge, there have been no mapping studies of major medical journals investigating the most common subjects, most productive scientists and countries, most prolific journals and "citation classics" across multiple specialties.

The objective of this study was to describe and characterise the global clinical research publication activity through RCTs articles published in high IF medical journals during the past decades.

Methods

Eligibility criteria

This cross-sectional analysis investigated RCTs related articles (that is, primary RCTs, secondary analyses and methodology papers using clinical data) published in major medical journals. We excluded narrative reviews, systematic reviews, meta-analyses, pool-analyses, letters and newspaper articles. All RCT related articles indexed in PubMed/MEDLINE had to be published in one of the major medical journals with an IF exceeding 10 (2016 IF according to the Journal Citation Reports [JCR] published in June 2017). These medical journals were chosen as they were determined to publish clinical research with scientific merit and clinical relevance (see BOX for a list of included medical journals).

Search

On March 22, 2018 we systematically searched MEDLINE through PubMed (National Library of Medicine, Bethesda, MD, United States) for all RCTs related articles published in high IF medical journals (from inception to December 31, 2017). A senior information specialist (AA-A) and a clinical epidemiologist (FC-

L) designed an electronic literature search using a validated research methodology filter for RCTs (with 97% specificity and 93% sensitivity) [29]. The search was peer reviewed by members of the study team, including a second (senior) information specialist (RA-B). The full search strategy is provided in Additional file 1. On May 7, 2018 we searched the Web of Science (WoS) (Clarivate Analytics, Philadelphia, PA, United States) by using PubMed IDs (PMIDs) from the PubMed/MEDLINE searches. Merging MEDLINE with other citation indices such as the WoS combines the advantages of MEDLINE (e.g. Medical Subject Headings [MeSH], a comprehensive controlled vocabulary for indexing journal articles) with the relational capabilities and data of the WoS [30].

Data extraction and normalisation

For each included article, raw (meta)data on the journal and article titles, subject category, the year of publication, keywords, and the authors' names, institutional affiliation(s), funding source, and country was downloaded online through the WoS by one researcher (A-AA). We also used the WoS to determine the extent to which each article had been cited in the scientific peer-review literature using the "times cited" number (that is, the number of times a publication has been cited by other publications). Two researchers (FC-L, RA-B) verified independently the data to minimise potential information errors. A process of normalisation was conducted by two researchers to bring together the different names of an author or country, and keywords (further details are available in Additional file 2). Specifically, one researcher (AA-A) checked the names by which an individual author appeared in two or more different forms (for example, "John McMurray "or "John J. McMurray" or "John J.V. McMurray") using coincidence in that author's place(s) of work as the basic criterion for normalisation (for example, University of Glasgow, Scotland, United Kingdom) [31], and a second researcher (FC-L or RA-B) verified data. A threshold of 30 articles was applied to review 200 names by which an individual author appeared in two or more different forms.

We extracted both "author keywords" and "keyword plus," which are automatically assigned by the WoS from the titles of the references of the articles, as topical (also called textural, linguistic, or sematic) data [32]. To ensure consistency in the data, one researcher (RA-B) corrected keywords unifying grammatical variants and using only one keyword developed names of the same concept (for example, "randomized trial" or "randomized clinical trial" or "randomized controlled trial" or "randomised controlled trial"). In addition, the same researcher (RA-B) removed typographical, transcription and/or indexing errors, and a second researcher (FC-L) verified data. All potential discrepancies were resolved via consensus amongst these investigators. All these data were collected and entered into a Microsoft Access® (Microsoft, Seattle, WA, United States) database between May 7, 2018 and January 9, 2019.

Data analysis

We analysed data including the number of articles, citations, signatures (or total number of authors included in all the articles of each author), collaboration index (that is the mean number of author's signatures per article), countries, journals and keywords. Data were summarised as frequencies and percentages for categorical items. The most prolific authors (> 100 articles), countries (> 100 articles), funding institutions (> 100 articles), and the most cited papers ("top-100 citation classics") were identified. Network plots were generated for intense scientific collaboration between countries (applying a threshold of 100 articles in collaboration).

We conducted exploratory analyses of topical data using a set of unique keywords or and their frequencies to examine the topic coverage, major topics ("word clouds" of keywords) and their interrelations ("co-words networks") in RCT articles. The main goal in topical analyses are to understand the topical distribution of a dataset – what topics are covered and how much of each topic is covered in a scientific discipline [32]. The most frequently used keywords were identified for most prolific journals (with at least 1000 articles). Based on most frequently used keywords (with at least 500 articles), a word cloud was created from text that the user provides and places more emphasis on words that appear with greater frequency in the source text. A "co-words network" was created to illustrate the co-occurrence of highly frequent words in the articles (applying a threshold of 100 articles in collaboration). The network analysis was carried with the use of PAJEK (University of Ljubljana, Slovenia) [33], a software package for large network analysis that is free for non-commercial use, to construct network graphs. PRISMA checklist [34] (http://www.prisma-statement.org/) guided the reporting of the present analysis (and is available in Additional file 3).

Results

There were 39329 records identified by the PubMed/MEDLINE search (Fig 1). A total of 39305 articles met the study inclusion criteria (Additional file 4), after 24 records were excluded (Additional file 5). Table 1 details the general characteristics of the articles.

Publication trend

The number of articles increased exponentially over the 1965-2017 period (Fig 2). Approximately 60% (n=23635) of the articles have been published since 2000.

Journals and subject category

Forty journals published 39305 articles and 23.8% of them (n=9355) were published by four journals with an IF > 30. *The Lancet* (9.1%; n=3593), the *Journal of Clinical Oncology* (8.5%; n = 3343), and *The New England Journal of Medicine* (8.3%; n=3275) published the largest number of articles, followed by *The BMJ* (6.4%; n=2516) and *Circulation* (5.9%; n=2331). Most articles were classified in "medicine, general &

internal" (30.7%; n=13688), "cardiac & cardiovascular systems" (13.1%; n=5828), or "oncology" (12.9%; n=5760) according to the WoS journal categorisations (Table 1).

Authors, institutions and countries

Most articles (62.3%; n=24496) were written by 7 or more authors and only 11.4% (n=4469) of articles were written by 3 or less authors. The first authors of the articles were based most commonly in North America and Western Europe; first authors from the United States were responsible for 36.9% (n=14508) of the articles (Table 1). We identified 17 authors who published 100 or more articles (Table 2). All the most productive authors were male. The most prolific authors were Robert M Califf with 239 articles (from Duke University, United States), Eugene Braunwald with 218 (from Harvard University, United States), Salim Yusuf with 217 (from McMaster University, Canada), Eric J Topol with 212 (from Scripps Translational Science Institute, United States), Harvey D White with 186 (from University of Auckland, New Zealand), Lars Wallentin with 144 (Uppsala University, Sweden), and Christopher B Granger with 140 (from Duke University, United States).

Overall, 154 countries worldwide contributed to the analysed articles. The publication productivity ranking for countries (Table 3) was led by the United States (n=18393 articles with 3.4 million citations), followed by the United Kingdom (n=8028 articles with 1.3 million citations), Canada (n=4548 articles with 1.0 million citations) and Germany (n=4415 articles with 0.9 million citations). There were 37 countries with at least 100 articles in co-authorship. Fig 3 shows a visual representation of the most intense collaborative network between these 37 countries, in which we can see the relationships of some countries with respect to others and the position that each occupies in the network.

Funding source

16485 articles (41.9%) reported sources of funding. The 40 most frequent funding institutions (with 100 or more articles) are listed in Table 4. The main funders were the National Institutes of Health (NIH) with 7422 articles, Hoffmann-La Roche (n=1188), Pfizer (n=1139), Merck Sharp & Dohme (n=1097) and Novartis (n=1052).

Most cited articles

Overall, included articles received 5.9 million citations, of which 83.1% citations (n=4950604) corresponded to 15142 (38.5%) articles with more than 100 citations. There were 641 (1.63%) articles with more than 1000 citations that accumulated 20.7% of the total citations (n=1234462). The most cited articles by number of citations ("100 citation classics") are listed in Table 5. All of the most cited papers were published in English. These most cited articles were published in 9 journals, led by *The New England Journal of Medicine* with 78 articles, followed by *The Lancet* (n=9) and *JAMA* (n=7). The list of most cited papers contained innovative research methodologies. For example, the most cited article was a method paper published in *The Lancet* ("Bland-Altman method") [35]. This seminal paper changed how method comparison studies are performed in clinical research. The list of the most cited papers also reflected important studies examining the health effects of pharmacological interventions on patients with chronic diseases. Common themes in major advances in health interventions included diabetes control [36-41]; the effects of hormone replacement therapy in postmenopausal women [42,43]; therapies for diverse cancers such as glioblastoma, colorectal cancer, breast cancer, melanoma and hepatocellular carcinoma [44-50]; important interventional studies in the field of clinical cardiology such as lipid-lowering statin therapy trials, antihypertensive trials, and antiplatelet and/or antithrombotic trials [51-63].

Common keywords

The most commonly used article keywords were "clinical trial" (16.1%; n=6332 papers), followed by "therapy" (10.8%; n=4267), "randomised controlled trial" (6.6%; n=2587), "chemotherapy" (5.6%; n=2224), "risk" (5.1%; n=2026), "efficacy" (4.9%; n=1933), and "double-blind" (4.9%; n=1929). The most frequently used keywords in the most prolific journals are shown in Table 6. In addition, exploratory analyses of word clouds and networks based on keywords (co-words) showed a broad range of topics covered (see Additional file 6).

Discussion

In this cross-sectional analysis, we presented a global mapping of RCTs related articles published in high IF medical journals for the period 1965–2017. We identified the most prolific scientists, institutions and countries, most common subjects and topics, "citation classics" and most prolific high IF medical journals from multiple specialties over the last 50 years.

In general, we found a strong clustering of articles published in British and American medical journals (*The Lancet, Journal of Clinical Oncology, The New England Journal of Medicine, The BMJ*, *Circulation, JAMA, JACC*, and *Diabetes Care* accounted for 53% of RCTs related articles). Many of these journals have been developed by active medical associations, both nationally and internationally. We hypothesize that different publishing patterns between journals may potentially reflect editorial policies and/or preferences, with some general medicine journals (such as *The Lancet and The New England Journal of Medicine*) and specialty journals (such as *Journal of Clinical Oncology* and *Circulation*), being more interested in and/or promoting the publication of RCTs. In contrast, a substantial amount of these articles are behind publication paywalls (very few of the medical journals in our study sample are Open Access) and thus, research results may not be accessible to a large fraction of the scientific community and society as a whole, including clinicians (and patients) who may want them to help inform their clinical practice.

The results of this study highlight the expanding collaborative networks between countries in multiple regions, revealing a discernable scientific community, with the most productive countries having an important number of collaborations. Publication activity efforts were global during the study period, with articles from scientists and institutions in more than 150 different countries. However, the scientific community is centered on a nucleus of scientists from Western countries – the most intense global collaborations took place between the United States, United Kingdom and Canada. The presence and influence these countries have on biomedical research [64-66] may be due to their large multi-stakeholder research partnerships, greater financial investment in clinical research, and high population of active scientists and research centers compared to other countries.

Publication activity worldwide shows that low and middle-income countries have low levels of articles in high IF medical journals. Difficulties in healthcare, education and research systems, information access and communication, language barriers, economic and institutional instability, all represent challenges (and clear disadvantages) for productivity in low and middle-income regions. In addition, restrictions and difficulties in conducting clinical research in resource-poor situations result in the exclusion of many of these countries from planning, conduct and publication of RCTs [67-69]. As might be expected, our results support previous findings that low and middle-income countries [31,70,71] had minimal contributions in articles published in major medical journals. For example, a previous study [70] showed that most of the authors of original papers published in five high impact general medical journals (including *The New England Journal of Medicine*, *The Lancet*, *JAMA, The BMJ* and *Annals of Internal Medicine*) were more frequently affiliated with institutions in the same country as the journal. To address some of these problems, scientists, institutions and funders should promote collaborations (beyond historical, cultural and political factors) to share knowledge, expertise and innovative methodologies for clinical research. This may involve partnerships with Western countries to support capacity and resource development and research training.

RCTs related articles were published most often in high IF medical journals devoted to general and internal medicine, cardiology and oncology (nearly 57% of all articles). Similarly, the lists of the most cited articles identified topics which reflect major advances in the management of chronic conditions (such diabetes, cardiovascular disorders and cancer). The large relative productivity in general internal medicine, cardiology and oncology may be explained by the important role of randomised evidence to novel treatments and preventive strategies for these chronic diseases. In line with previous research [72-75], most of these highly-cited RCTs addressed interventions for burdensome conditions that are health priorities in Western countries [76,77]. Funding of (international, collaborative) RCTs may come from varying sources including commercial and non-commercial sponsors. However, previous analyses of

RCTs related articles published in high IF journals have suggested study sponsors may influence how RCTs are designed, conducted and reported, sometimes serving financial rather public interests [78]. Given that research funding is often restricted, it is the responsibility of scientific community to use the resources available most efficiently when exploring research priorities to afford research users and population health needs [76,77,79,80].

Our findings suggest that women are vastly underrepresented in the group of most prolific scientists publishing in high-impact medical journals. This is in direct contrast to recent studies that have identified a gender gap in research publications [81-84]. For example, a previous study [84] showed that women in first authorship positions increased from 27% in 1994 to 37% in 2014 in leading medical journals (including *Annals of Internal Medicine*, *JAMA Internal Medicine*, *The BMJ*, *JAMA*, *The Lancet*, and *The New England Journal of Medicine*), but progress has plateaued or declined since 2009. There is an urgent need to investigate the underlying causes of the potential gender gap in order to help to identify publication practices and strategies to increase women's influence [82,84].

There are several limitations to our study. First, we characterised knowledge structures generated by articles published in major medical journals included in the WoS database. Although the publication production analysed has been drawn from an exhaustive analysis of the biomedical literature, it is possible that the search missed some relevant articles (and journals). Some reports may be published in journals without being indexed as RCTs, making them difficult to identify. Second, as in many bibliometric analyses, the importance of normalising the different names of an author, country, and funding sources is fundamental to avoiding potential errors. We conducted a careful manual validation of the references and textual data to avoid typographical, transcription and/or indexing errors. However, we recognize this procedure does not assure complete certainty. Third, the affiliation addresses of authors do not necessarily reflect the country where the research was conducted, nor the research funding source. Fourth, topical analysis extracting a set of unique keywords, word profiles and co-words may indicate intellectual organization in publication production, albeit with inherent limitations [85,86]. Fifth, use of citation analysis carries with some problems [87-91]. There is a potential length time-effect bias which puts more recent articles at a disadvantage. In addition, the biomedical literature is rich in barriers and motivations for publication and citation preferences [87], including self-citation (bias towards one’s own work) [88], language bias (bias towards publishing and citing English articles), omission bias (bias purposely not citing competitors), and selective reporting and publication bias (bias withholding “negative” results from publication and citation) [89-92]. In addition, citations are also treated as equal regardless of whether a research is being cited for its positive contribution to the field, but also for being criticized. Finally, our methods represent only a mapping approach which could be complemented further by more detailed analyses, for example examining the content, the reporting and reproducible research practices through research of research (“meta-research”) studies [92-95].

Conclusion

The global analysis presented in this study provides evidence of the scientific growth of RCTs related articles published in high IF medical journals. Over the last 50 years, publication activity in leading medical journals has increased with leadership of Western countries (most notably, the United States), but with very limited representation from low and middle-income countries. Our analysis contributes to a better conceptualization and understanding of RCTs articles and identified the main areas of research, the most influential publication sources chosen for their scientific dissemination and the major scientific leaders. Given the dynamic nature of the field, it will be interesting to see whether the growth trend remains in the coming years, and how the characteristics of the field change over time.

Declarations

Ethics approval and consent to participate

This study outlines a cross-sectional analysis of secondary data and hence does not require ethical approval or consent to participate.

Consent to publish

Not applicable.

Availability of data and materials

With the publication of this manuscript, the full dataset will be freely available online in the Open Science Framework (https://osf.io/r2vw5/), a secure online repository for research data.

Competing interests

The authors declare that they have no competing interests to declare.

Funding

FC-L and RT-S are supported by the Institute of Health Carlos III/CIBERSAM. BH is supported by a New Investigator Award from the Canadian Institutes of Health Research and the Drug Safety and Effectiveness Network. DM is supported by a University Research Chair, University of Ottawa. The funders were not involved in the design of the study or decision to submit the manuscript for publication, nor they were involved in aspect of the study conduct. The views expressed in this manuscript are those of the authors and may not be understood or quoted as being made on behalf of, or reflection the position of, the funder(s) or any institution.

Author's contributions

FC-L, RA-B, RT-S and AA-A contributed to conceptualizing and designing the study. FC-L and AA-A supervised the study. AA-A curated data. AA-A and FC-L performed data analysis and visualizations. FC-L, RA-B, LC, BH, RT-S, DM, and AA-A interpreted the study findings. FC-L drafted the first version of the manuscript. RA-B, LC, BH, RT-S, DM, and AA-A commented for important intellectual content and made major revisions. All authors read and approved the final version of the manuscript. All authors meet the ICMJE criteria for authorship. FC-L and AA-A accept full responsibility for the finished manuscript and controlled the decision to publish.

Declaration of transparency

FC-L affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Schulz KF, Grimes DA. The Lancet Handbook of essential concepts in clinical research. London: Elsevier Ltd.; 2006. 2. Gabriel SE, Normand SL. Getting the methods right–the foundation of patient-centered outcomes research. N Engl J Med. 2012;367(9):787-90. 3. Jadad AR. Randomised controlled trials: A user's guide. London: BMJ Books; 1998. 4. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996;276(8):637-9. 5. Tsay MY, Yang YH. Bibliometric analysis of the literature of randomized controlled trials. J Med Libr Assoc. 2005;93(4):450-8. 6. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med. 1984;3(4):409-22. 7. Roundtable on Value and Science-Driven Health Care, Forum on Drug Discovery, Development, and Translation, Board on Health Sciences Policy, Institute of Medicine. Large Simple Trials and Knowledge Generation in a Learning Health System: Workshop Summary. Washington (DC): National Academies Press; 2013. 8. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312(7023):71-2. 9. Zarin DA, Tse T, Williams RJ, Carr S. Trial Reporting in ClinicalTrials.gov - The Final Rule. N Engl J Med. 2016;375(20):1998-2004. 10. Zarin DA, Tse T, Ide NC. Trial Registration at ClinicalTrials.gov between May and October 2005. N Engl J Med. 2005;353(26):2779-87. 11. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, et al. Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors. PLoS Med. 2016;13(1):e1001950. 12. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in The BMJ and PLOS Medicine. BMJ. 2018;360:k400. 13. Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-91. 14. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials. 2010;11:32. 15. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7. 16. Thelwall M, Kousha K. Are citations from clinical trials evidence of higher impact research? An analysis of ClinicalTrials.gov. Scientometrics. 2016;109(2):1341-1351. 17. Brueton VC, Vale CL, Choodari-Oskooei B, Jinks R, Tierney JF.

Measuring the impact of methodological research: a framework and methods to identify evidence of impact. Trials. 2014;15:464. 18. Hays M, Andrews M, Wilson R, Callender D, O'Malley PG, Douglas K. Reporting quality of randomised controlled trial abstracts among high-impact general medical journals: a review and analysis. BMJ Open. 2016;6(7):e011082. 19. Ghimire S, Kyung E, Kang W, Kim E. Assessment of adherence to the CONSORT statement for quality of reports on randomized controlled trial abstracts from four high-impact general medical journals. Trials. 2012;13:77. 20. Charles P, Giraudeau B, Dechartres A, Baron G, Ravaud P. Reporting of sample size calculation in randomised controlled trials: review. BMJ. 2009;338:b1732. 21. Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JP. Reporting and interpretation of SF-36 outcomes in randomised trials: systematic review. BMJ. 2009;338:a3006. 22. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med. 2009;169(19):1756-61. 23. Ebrahim S, Montoya L, Kamal El Din M, Sohani ZN, Agarwal A, Bance S, Saquib J, Saquib N, Ioannidis JP. Randomized trials are frequently fragmented in multiple secondary publications. J Clin Epidemiol. 2016;79:130-139. 24. Alsheikh-Ali AA, Qureshi W, Al-Mallah MH, Ioannidis JP. Public availability of published research data in high-impact journals. PLoS One. 2011;6(9):e24357. 25. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA. 2009;302(9):977-84. 26. Trikalinos NA, Evangelou E, Ioannidis JP. Falsified papers in high-impact journals were slow to retract and indistinguishable from nonfraudulent papers. J Clin Epidemiol. 2008;61(5):464-70. 27. Siontis KC, Evangelou E, Ioannidis JP. Magnitude of effects in clinical trials published in high-impact general medical journals. Int J Epidemiol. 2011;40(5):1280-91. 28. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. JAMA. 2005;294(2):218-28. 29. Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR; Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ. 2005;330(7501):1179. 30. Sugimoto CR, Larivière V. Measuring research: what everyone needs to know®. Oxford: Oxford University Press; 2018. 31. Catalá-López F, Alonso-Arroyo A, Hutton B, Aleixandre-Benavent R, Moher D. Global collaborative networks on meta-analyses of randomized trials published in high impact factor medical journals: a social network analysis. BMC Med. 2014;12:15. 32. Börner K, Polley DE. Visual insights: a practical guide to making sense of data. Cambridge, Massachusetts: MIT Press; 2014. 33. Batagelj V, Mrvar A. Pajek 1.28. Program for large network analysis. Ljubljana: University of Ljubljana; 2010. 34. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. 35. Bland JM. Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10. 36. Diabetes Control and Complications Trial Research Group. Nathan DM. Genuth S. Lachin J. Cleary P. Crofford O. Davis M. Rand L. Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86. 37. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53. 38. Knowler WC. Barrett-Connor E. Fowler SE. Hamman RF. Lachin JM. Walker EA. Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403. 39. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343-50. 40. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854-65. PubMed PMID: 9742977. 41. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59. 42. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33. 43. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605-13. 44. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96. 45. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42. 46. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92. 47. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-88. 48. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23. 49. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16. 50. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90. doi: 10.1056/NEJMoa0708857. 51. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Thorgeirsson G, Pyorala K, Miettinen T, Wilhelmsen L, Olsson AG, Wedel H, Kristianson K, Thomsen H, Nordero E, Thosen B, Lyngborg K. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9. 52. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301-7. 53. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001-9. 54. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22. 55. Heart Outcomes Prevention Evaluation Study Investigators. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145-53. 56. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. 57. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH; The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med. 1992;327(10):669-77. 58. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9. 59. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456-62. 60. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581-7. 61. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51. 62. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502. 63. CAPRIE Steering Committee, Gent M, Beaumont D, Blanchard J, Bousser MG, Coffman J, Easton JD, Hampton JR, Harker LA, Janzon L, Kusmierek JJ, Panak E, Roberts RS, Shannon JS, Sicurella J, Tognoni G, Topol EJ, Verstraet M, Warlow C, Cairns JA, Chesebro

JH, von der Lippe G, Ross Russell RW, Wolf PA, Boissel JP, Friedman L, Fuster V, Harrison MG, Pocock S, et al. A randomised. blinded. trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348(9038):1329-39. 64. Røttingen JA, Regmi S, Eide M, Young AJ, Viergever RF, Ardal C, Guzman J, Edwards D, Matlin SA, Terry RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382(9900):1286-307. 65. Moses H 3rd, Matheson DH, Cairns-Smith S, George BP, Palisch C, Dorsey ER. The anatomy of medical research: US and international comparisons. JAMA. 2015;313(2):174-89. 66. Sussex J, Feng Y, Mestre-Ferrandiz J, Pistollato M, Hafner M, Burridge P, Grant J. Quantifying the economic impact of government and charity funding of medical research on private research and development funding in the United Kingdom. BMC Med. 2016;14:32. 67. Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. N Engl J Med. 2001;345(2):139-42. 68. Berkley JA. Randomised trials in developing countries. Arch Dis Child. 2014;99(7):607-8. 69. Knepper TC, McLeod HL. When will clinical trials finally reflect diversity? Nature. 2018;557(7704):157-159. 70. Sumathipala A, Siribaddana S, Patel V. Under-representation of developing countries in the research literature: ethical issues arising from a survey of five leading medical journals. BMC Med Ethics. 2004;5:E5. 71. Uthman OA, Okwundu CI, Wiysonge CS, Young T, Clarke A. Citation classics in systematic reviews and meta-analyses: who wrote the top 100 most cited articles? PLoS One. 2013;8(10):e78517. 72. Atal I, Trinquart L, Ravaud P, Porcher R. A mapping of 115,000 randomized trials revealed a mismatch between research effort and health needs in non-high-income regions. J Clin Epidemiol. 2018;98:123-132. 73. Emdin CA, Odutayo A, Hsiao AJ, Shakir M, Hopewell S, Rahimi K, Altman DG. Association between randomised trial evidence and global burden of disease: cross sectional study (Epidemiological Study of Randomized Trials–ESORT). BMJ. 2015;350:h117. 74. Catalá-López F, García-Altés A, Alvarez-Martín E, Gènova-Maleras R, Morant-Ginestar C. Does the development of new medicinal products in the European Union address global and regional health concerns? Popul Health Metr. 2010;8:34. 75. Isaakidis P, Swingler GH, Pienaar E, Volmink J, Ioannidis JP. Relation between burden of disease and randomised evidence in sub-Saharan Africa: survey ofresearch. BMJ. 2002;324(7339):702. 76. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789-1858. 77. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1859-1922. 78. Rasmussen K, Bero L, Redberg R, Gøtzsche PC, Lundh A. Collaboration between academics and industry in clinical trials: cross sectional study of publications and survey of lead academic authors. BMJ. 2018;363:k3654. 79. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gülmezoglu AM, Howells DW, Ioannidis JP, Oliver S. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65. 80. Moher D, Glasziou P, Chalmers I, Nasser M, Bossuyt PM, Korevaar DA, Graham ID, Ravaud P, Boutron I. Increasing value and reducing waste in biomedical research: who's listening? Lancet. 2016;387(10027):1573-86. 81. van den Besselaar P, Sandström U. Vicious circles of gender bias, lower positions, and lower performance: Gender differences in scholarly productivity and impact. PLoS One. 2017;12(8):e0183301. 82. Lundine J, Bourgeault IL, Clark J, Heidari S, Balabanova D. The gendered system of academic publishing. Lancet. 2018;391(10132):1754-1756. 83. Lundine J, Bourgeault IL, Clark J, Heidari S, Balabanova D. Gender bias in academia. Lancet. 2019 Feb 23;393(10173):741-743. 84. Filardo G, da Graca B, Sass DM, Pollock BD, Smith EB, Martinez MA. Trends and comparison of female first authorship in high impact medical journals: observational study (1994-2014). BMJ. 2016;352:i847. 85. Leydesdorff L. Words and co-words as indicators of intellectual organization. Research Policy. 1989;18(4):209-223. 86. Leydesdorff L. Why words and co-words cannot map the development of the sciences. J Am Soc Inf Sci. 1997;48(5):418-427. 87. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. BMJ. 2009;339:b2680. 88. Mishra S, Fegley BD, Diesner J, Torvik VI. Self-citation is the hallmark of productive authors, of any gender. PLoS One. 2018;13(9):e0195773. 89. Dwan K, Gamble C, Williamson PR, Kirkham JJ; Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PLoS One. 2013;8(7):e66844. 90. Phillips AT, Desai NR, Krumholz HM, Zou CX, Miller JE, Ross JS. Association of the FDA Amendment Act with trial registration, publication, and outcome reporting. Trials. 2017;18(1):333. 91. Goldacre B, Drysdale H, Dale A, Milosevic I, Slade E, Hartley P, Marston C, Powell-Smith A, Heneghan C, Mahtani KR. COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time. Trials. 2019;20(1):118. 92. Dechartres A, Bond EG, Scheer J, Riveros C, Atal I, Ravaud P. Reporting of statistically significant results at ClinicalTrials.gov for completed superiority randomized controlled trials. BMC Med. 2016;14(1):192. 93. Dechartres A, Trinquart L, Atal I, Moher D, Dickersin K, Boutron I, Perrodeau E, Altman DG, Ravaud P. Evolution of poor reporting and inadequate methods over time in 20 920 randomised controlled trials included in Cochrane reviews: research on research study. BMJ. 2017;357:j2490. 94. Wallach JD, Boyack KW, Ioannidis JPA. Reproducible research practices, transparency, and open access data in the biomedical literature, 2015-2017. PLoS Biol. 2018;16(11):e2006930. 95. Ioannidis JP, Fanelli D, Dunne DD, Goodman SN. Meta-research: Evaluation and Improvement of Research Methods and Practices. PLoS Biol. 2015;13(10):e1002264.

Additional Files

Additional file 1: Full strategy in PubMed/MEDLINE (.docx)

Additional file 2: Data extraction and normalisation processes (.docx)

Additional file 3: Reporting checklist (.docx)

Additional file 4: List of PMID for included articles (.docx)

Additional file 5: List of excluded articles (.docx)

Additional file 6. Exploratory analysis of topical data (.docx)

Figures

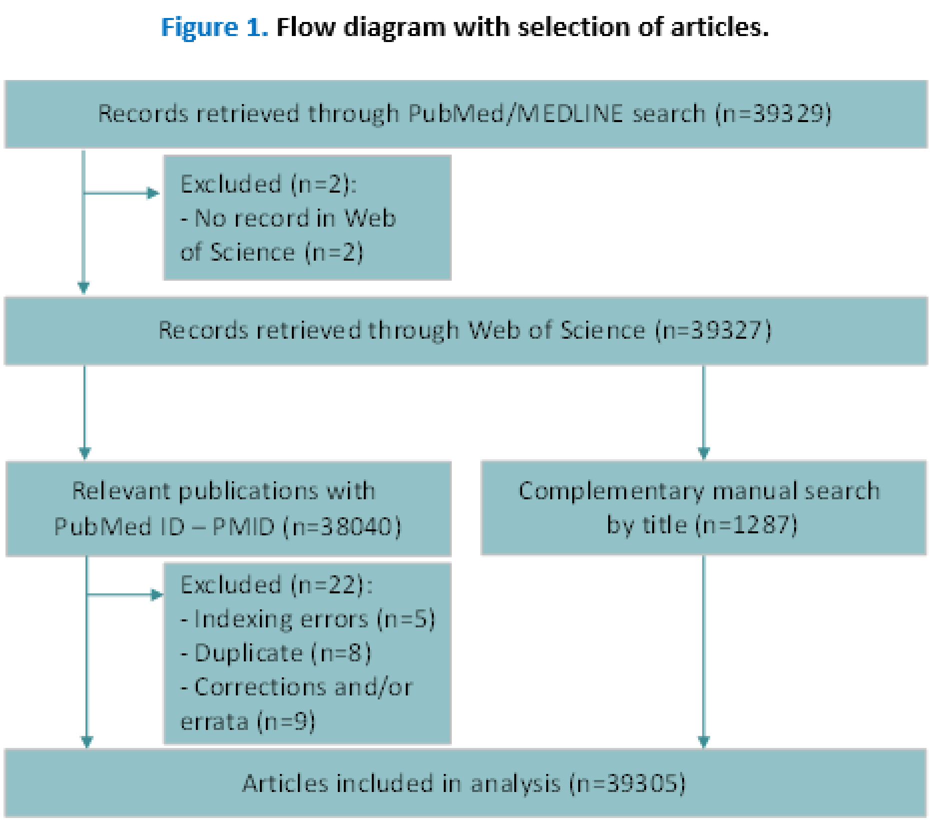


Figure 1

Flow diagram with selection of articles.

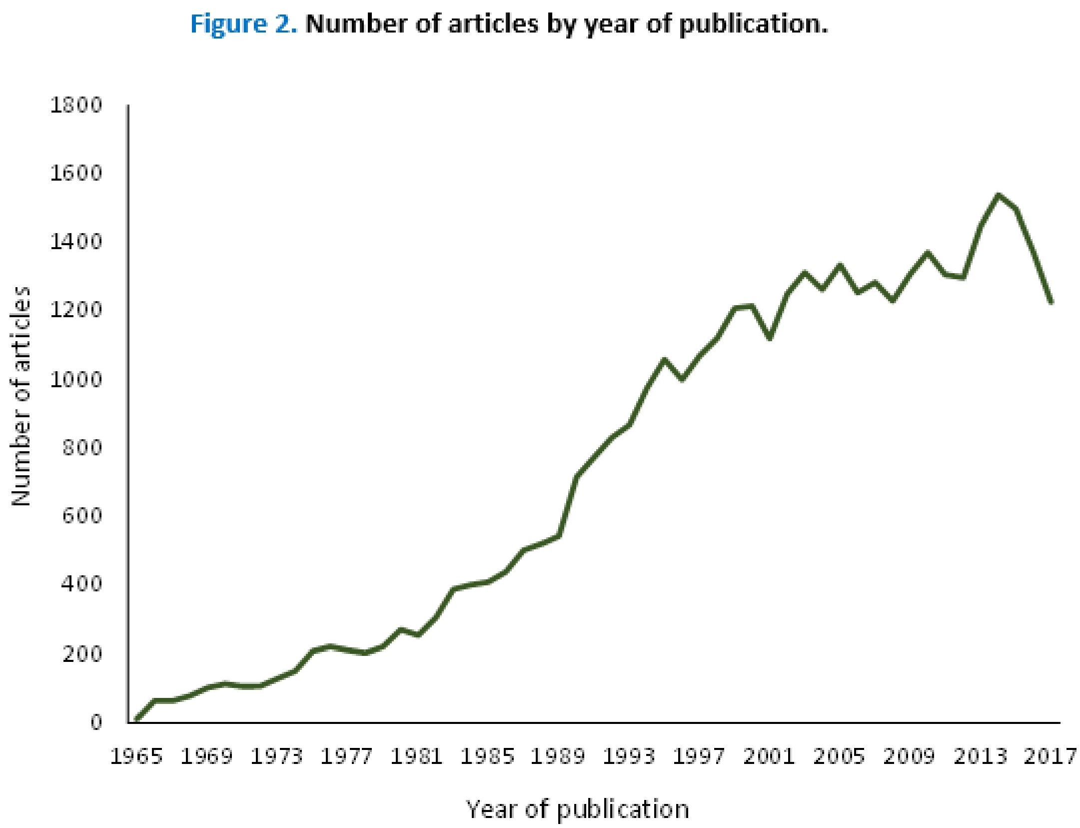
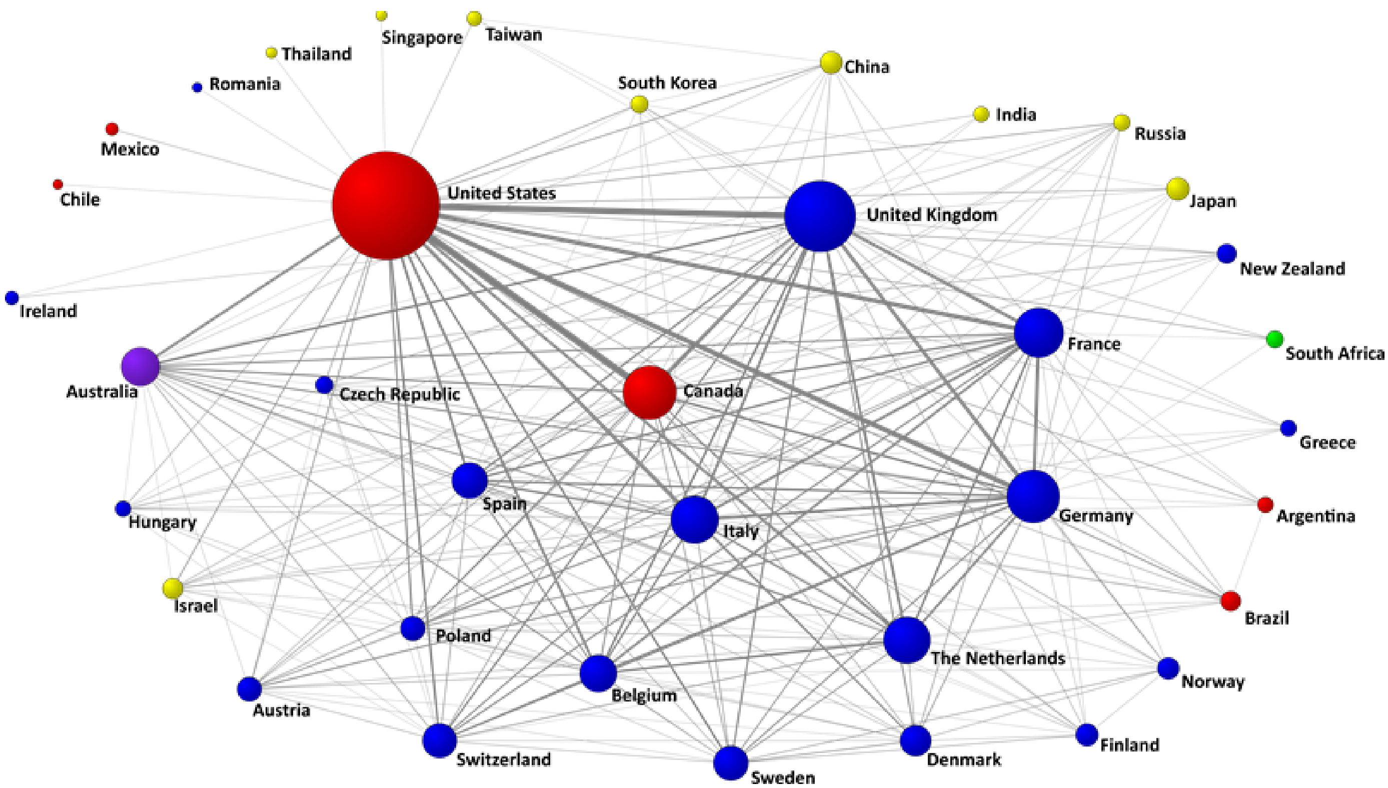


Figure 2

Number of articles by year of publication.

Figure 3. Global collaborative network between countries.



Note: Most productive cluster of countries applying a threshold of 100 or more papers signed in co-authorship. Node sizes are proportional to the number of papers and line thicknesses are proportional to the number of collaborations. Node colors: America = red; Asia = yellow; Africa = green; Europe = blue; Oceania = purple.

Figure 3

Global collaborative network between countries.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.pdf
- supplement2.pdf
- supplement3.pdf
- supplement4.pdf
- supplement5.jpg
- supplement6.pdf
- supplement7.pdf
- supplement8.pdf
- supplement9.pdf