RESEARCH ARTICLE

# Mapping of global scientific research in comorbidity and multimorbidity: A cross-sectional analysis

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## Abstract

### Background

The management of comorbidity and multimorbidity poses major challenges to health services around the world. Analysis of scientific research in comorbidity and multimorbidity is limited in the biomedical literature. This study aimed to map global scientific research in comorbidity and multimorbidity to understand the maturity and growth of the area during the past decades.

### Methods and findings

This was a cross-sectional analysis of the Web of Science. Searches were run from inception until November 8, 2016. We included research articles or reviews with no restrictions by language or publication date. Data abstraction was done by one researcher. A process of standardization was conducted by two researchers to unify different terms and grammatical variants and to remove typographical, transcription, and/or indexing errors. All potential discrepancies were resolved via discussion. Descriptive analyses were conducted (including the number of papers, citations, signatures, most prolific authors, countries, journals and keywords). Network analyses of collaborations between countries and co-words were presented. During the period 1970–2016, 85994 papers (64.0% in 2010–2016) were published in 3500 journals. There was wide diversity in the specialty of the journals, with psychiatry (16558 papers; 19.3%), surgery (9570 papers; 11.1%), clinical neurology (9275 papers; 10.8%), and general and internal medicine (7622 papers; 8.9%) the most common. PLOS One (1223 papers; 1.4%), the Journal of Affective Disorders (1154 papers; 1.3%), the Journal of Clinical Psychiatry (727 papers; 0.8%), the Journal of the American Geriatrics Society (634 papers; 0.7%) and Obesity Surgery (588 papers; 0.7%) published the largest number of papers. 168 countries were involved in the production of papers. The global productivity

ranking was headed by the United States (37624 papers), followed by the United Kingdom (7355 papers), Germany (6899 papers) and Canada (5706 papers). Twenty authors who published 100 or more papers were identified; the most prolific authors were affiliated with Harvard Medical School, State University of New York Upstate Medical University, National Taiwan Normal University and China Medical University. The 50 most cited papers ("citation classics" with at least 1000 citations) were published in 20 journals, led by JAMA Psychiatry (11 papers) and JAMA (10 papers). The most cited papers provided contributions focusing on methodological aspects (e.g. Charlson Comorbidity Index, Elixhauser Comorbidity Index, APACHE prognostic system), but also important studies on chronic diseases (e.g. epidemiology of mental disorders and its correlates by the U.S. National Comorbidity Survey, Fried's frailty phenotype or the management of obesity).

## Conclusions

Ours is the first analysis of global scientific research in comorbidity and multimorbidity. Scientific production in the field is increasing worldwide with research leadership of Western countries, most notably, the United States.

## Introduction

Over the last three to four decades, substantial progress has been made toward reducing mortality and extending life expectancy worldwide [1,2]. Although health seems to have improved globally, more people than ever are spending more time with functional health loss and disability [3,4]. In many countries and regions, the management of multiple chronic diseases in a given patient at the same time (the so-called, "comorbidity" or "multimorbidity") poses major challenges to health services [5–9]. People with two or more chronic (physical or mental) diseases are more likely to have poor health outcomes, more complex clinical management and increased healthcare costs [8,9].

Analysis of scientific research in comorbidity and multimorbidity is limited in the biomedical literature [10–16]. For example, Fortin et al. [12] previously investigated the characteristics of the publications on multimorbidity (or comorbidity) and compared the number of publications on it with the number of publications on three common chronic conditions (asthma, hypertension, and diabetes). A restricted search of MEDLINE in 2002 identified 353 papers on multimorbidity and comorbidity for the period 1990–2002. The number and diversity of articles were both insufficient to provide relevant data to inform evidence-based care of people affected by multiple chronic conditions [12].

The scientific landscape has changed considerably in the subsequent years, including the launch of important initiatives for the clinical management of multiple chronic diseases [17–20], but also the proliferation of open-access journals to disseminate research findings [5,7,21–25]. Considering research is needed to increase knowledge in a changing research area, this study aimed to map global scientific research in comorbidity and multimorbidity to understand maturity and growth during the past decades.

## Methods

### Search strategy

We conducted a cross-sectional analysis of the Web of Science, Science Citation Index-Expanded (SCI-E) database, from inception to November 8th 2016. The Web of Science has

been considered the world's leading taxonomic reference for citation analysis and prior to 2004, the only data source on citations available [26]. The search strategy for this study was designed by two senior health information specialists (AA-A, RA-B) and a clinical epidemiologist (FC-L), based on a previously published strategy [13]. The search strategy was constructed by using a combination of the following terms related to comorbidity and multimorbidity (see Box 1 for

### Box 1. Terminology

The terms of "comorbidity" and "multimorbidity" are often used interchangeably. Many possible definitions and interpretations of the concepts of "comorbidity" and "multimorbidity" have been reported in the biomedical literature [9–11]. For example, Valderas and colleagues [9] reviewed the definitions of "comorbidity (and multimorbidity)" and their relationship to related constructs. A brief overview of common terms follows.

**Comorbidity**. A widely accepted definition of "comorbidity" is the occurrence or the existence of any distinct additional medical condition to an index disease [31]. In general, the role of coexisting conditions is of less importance and one does not assume an interaction between the multiple conditions. The nature of the conditions that co-occur have variously included (physical or mental) diseases, disorders, conditions, illnesses, or health problems. Comorbidity was first included as a MeSH term in 1989 [9,10].

**Multimorbidity**. Most authors define "multimorbidity" as the co-occurrence of two or more medical conditions in an individual without any reference to an index disease [6,9–11]. Therefore, in multimorbidity, no index disease is defined and all conditions (or "morbidities") are regarded of equal importance. Multimorbidity constitutes a more generic, patient-centered concept, whereas comorbidity is an index disease-based concept [11]. At present, no MeSH term exists for multimorbidity.

Some authors have introduced other terms to describe the same or closely related concepts. Examples of alternative terms are: "multipathology", "polymorbidity", "polipathology", and "pluripathology" [10,13,51].

**Case example**. Consider a 58-year-old woman with coronary artery disease, hypertension, and major depression. Her mental health professional, focusing on the major depression, would consider her coronary artery disease and hypertension as comorbidities. Her primary care physician might describe her as having multimorbidity, giving equal attention to her coronary artery disease, hypertension and major depression.

terminology): comorbidit* OR co-morbidit* OR multimorbidit* OR multi-morbidit* OR multidisease* OR multi-disease* OR multipatholog* OR multi-patholog* OR polimorbidit* OR poli-morbidit* OR polipatholog* OR poli-patholog* OR pluripatholog* OR pluri-patholog* (full strategy is available in S1 Table). We included two types of papers: research articles or reviews on comorbidity or multimorbidity of any type (physical or mental). Meeting abstracts, proceedings paper (journals, book-based), editorials, book chapters, corrections, retracted publications and other items (e.g. notes, news, etc...) were excluded. No restrictions in languages or publication date were applied to the database search.

## Data extraction

For each included paper, data on the year of publication, the journal title, subject category, keywords, and the authors' names, institutional affiliation(s), and country was downloaded online through the SCI-E from the Web of Science by one researcher (AA-A) in November 2016. A second researcher (FC-L) verified the data to minimize potential information errors. The SCI-E platform is a database that contains all the above information, including the full addresses of all authors of every paper. We also used the SCI-E to determine the extent to which each paper 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). A process of standardization was conducted by two researchers to bring together the different names of an author or country, and keywords. Specifically, one researcher (AA-A) checked the names by which an individual author appeared in two or more different forms (for example, "Ronald C. Kessler" or "Ronald Kessler" or "Ron Kessler"), using coincidence in that author's place(s) of work as the basic criterion for normalization (for example, Harvard University, United States), and a second researcher (FC-L) verified data. We used both "author keywords" and "keyword plus," which are automatically assigned by the Web of Science from the titles of the references of the articles because this approach has proven to be highly effective in representing the conceptual content of articles. 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, "diabetes mellitus" or "diabetes" or "adult diabetes" or "diabetes type 2" or "type 2 juvenile diabetes"). 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 discussion. All these data were entered into a Microsoft Access® (Microsoft, Seattle, WA, United States) database.

## Data analysis

In this paper, we analyzed data including the number of papers, citations, signatures of authors, collaboration index (which is the mean number of author's signatures per paper), countries, journals and keywords. Data were summarized as frequencies and percentages for categorical items. We have presented in tables the most prolific authors and countries (> 100 papers), and the most cited papers (>1000 citations). We have presented network graphs (or diagrams) to represent data visualization of the structure of the most intense scientific collaboration between countries applying a threshold of 50 papers in collaboration. In order to depict the frequency of the most frequently used keywords, a word cloud was created using Wordle (http://www.wordle.net/), which is free-software that generates "word clouds" from text that the user provides and places more emphasis on words that appear with greater frequency in the source text. We identified the most frequently used keywords per journal subject category. We also presented the "co-words network" of keywords representing the co-occurrence phenomenon of highly frequent words in the papers. The co-words network reflects the relation among multiple terms, and so is effective in mapping the associations between keywords in textual data [27]. We used Pajek [28], a software package for large network analysis that is free for non-commercial use, to construct network graphs. PRISMA checklist [29,30] (http://www.prisma-statement.org/) guided the reporting of the present analysis (and is available in S1 Checklist).

## Results

A total of 85994 papers (76350 articles and 9644 reviews) were identified and included in the analyses (Fig 1). Table 1 details the general characteristics of the papers.

## Publication trend

The number of papers increased exponentially over the study period (Fig 2). Approximately two-thirds of the papers have been published since 2010. The first paper was published in 1970 by Prof. Alvan R. Feinstein [31] providing the seminal definition of comorbidity referring to "any distinct clinical entity that has co-existed or that may occur during the clinical course of a patient who has the index disease under study."

## Journals and subject categories

3500 journals published 85994 papers. 596 (17.0%) journals published only one paper, 344 (9.8%) journals published two, 220 (6.3%) journals published three, and 2340 (66.8%) published four or more papers. *PLOS One* (n = 1223; 1.4%) and the *Journal of Affective Disorders* (n = 1154; 1.3%) published the largest number of papers, followed by the *Journal of Clinical Psychiatry* (n = 727; 0.8%), the *Journal of the American Geriatrics Society* (n = 634; 0.7%) and *Obesity Surgery* (n = 588; 0.7%). Most papers were classified in one (n = 50354; 58.6%) or two (n = 52748; 30.7%) journal's subject categories. There was wide diversity in journal's subject categories, with psychiatry, surgery, clinical neurology, and general and internal medicine the most common (Table 1).

## Authors and countries

Most papers were written by 4 or more authors (72.5%; n = 62311) and only 5.5% (n = 4730) of papers were written by one author. The first authors of the papers were based most commonly

Citations retrieved from Web of Science search (n=98238)

Excluded (n=12244):
Meeting abstract (n=5369)
Proceedings paper (n=4312)
Editorial material (n=1527)
Letter (n=686)
Book chapter/review (n=185)
Corrections (n=73)
Other items (n=92)

Total papers included in the analyses (n=85994):
Research article (n=76350)
Review article (n=9644)
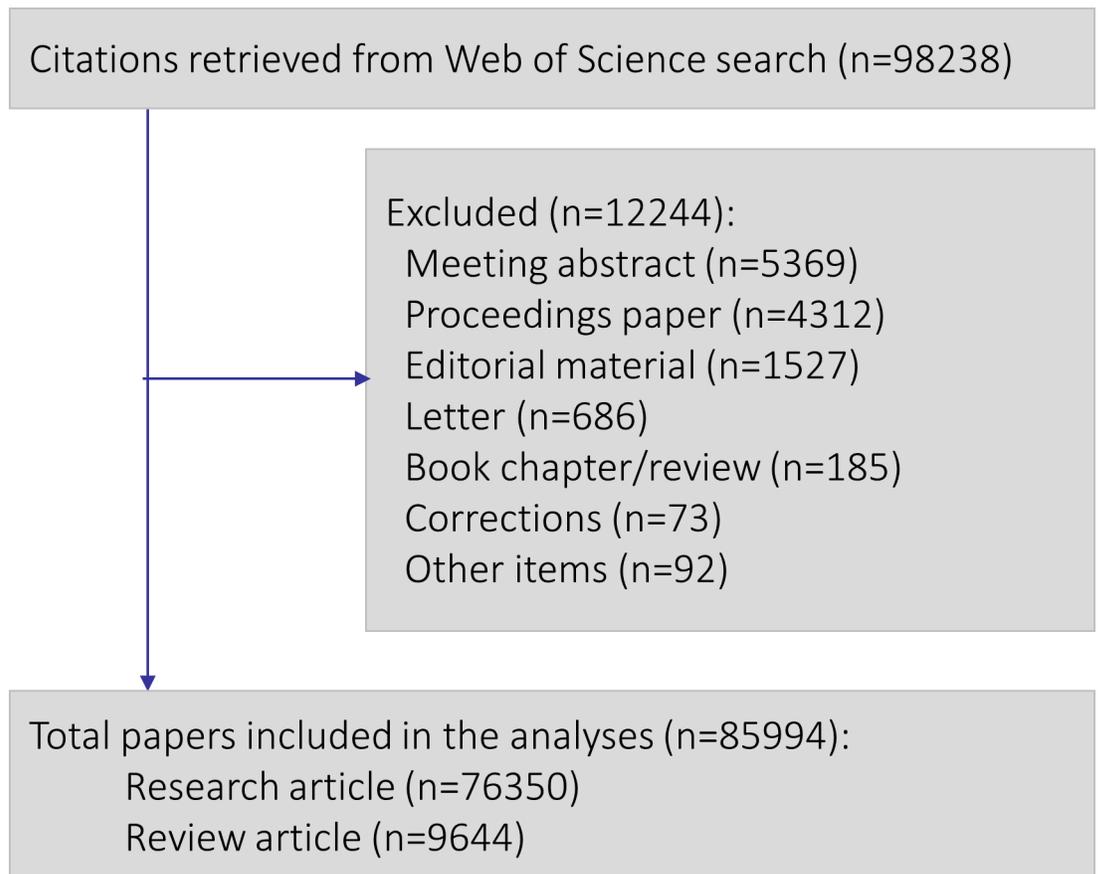
**Fig 1. Selection of papers.** Flowchart.

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**Table 1. General characteristics of the sample of study.**

| Characteristic | Category | Number | Percent |
|---|---|---:|---:|
| Total number of papers | | 85994 | 100.0 |
| Year of publication | | | |
| | 1970–1979 | 3 | 0.0 |
| | 1980–1989 | 52 | 0.1 |
| | 1990–1999 | 4179 | 4.9 |
| | 2000–2009 | 26719 | 31.0 |
| | 2010–2016[a] | 55041 | 64.0 |
| Number of authors | | | |
| | 1 | 4730 | 5.5 |
| | 2–3 | 18953 | 22.0 |
| | 4–6 | 35062 | 40.8 |
| | 7–10 | 20583 | 23.9 |
| | >10 | 6666 | 7.8 |
| Number of subject category[b] | | | |
| | 1 | 50354 | 58.6 |
| | 2 | 52748 | 30.7 |
| | 3 | 7903 | 9.2 |
| | 4 | 1200 | 1.4 |
| | 5 | 163 | 0.2 |
| Main subject category[b] | | | |
| | Psychiatry | 16558 | 19.3 |
| | Surgery | 9570 | 11.1 |
| | Clinical Neurology | 9275 | 10.8 |
| | Medicine, General & Internal | 7622 | 8.9 |
| | Cardiac & Cardiovascular Systems | 5098 | 5.9 |
| Country of first author (top-10) | | | |
| | United States | 33171 | 38.6 |
| | Germany | 5408 | 6.3 |
| | United Kingdom | 4945 | 5.8 |
| | Canada | 4221 | 4.9 |
| | Italy | 4107 | 4.8 |
| | Spain | 3070 | 3.6 |
| | Australia | 2998 | 3.5 |
| | The Netherlands | 2766 | 3.2 |
| | France | 2737 | 3.2 |
| | Taiwan (Republic of China) | 2034 | 2.4 |

[a]November 8th, 2016.
[b]Subject category according to Journal Citation Report.

in North America and Europe; first authors from the United States were responsible for 38.6% (n = 33171) of the papers (Table 1). We identified 20 authors who published 100 or more papers (Table 2). The most prolific authors were Ronald C Kessler with 331 (from Harvard Medical School, United States), Joseph Biederman with 248 (from Harvard Medical School, United States), Stephen V Faraone with 227 (from State University of New York Upstate Medical University, United States), Chia-Hung Kao with 223 (from National Taiwan Normal University, Taiwan) and Cheng-Li Lin with 193 papers (from China Medical University, China).
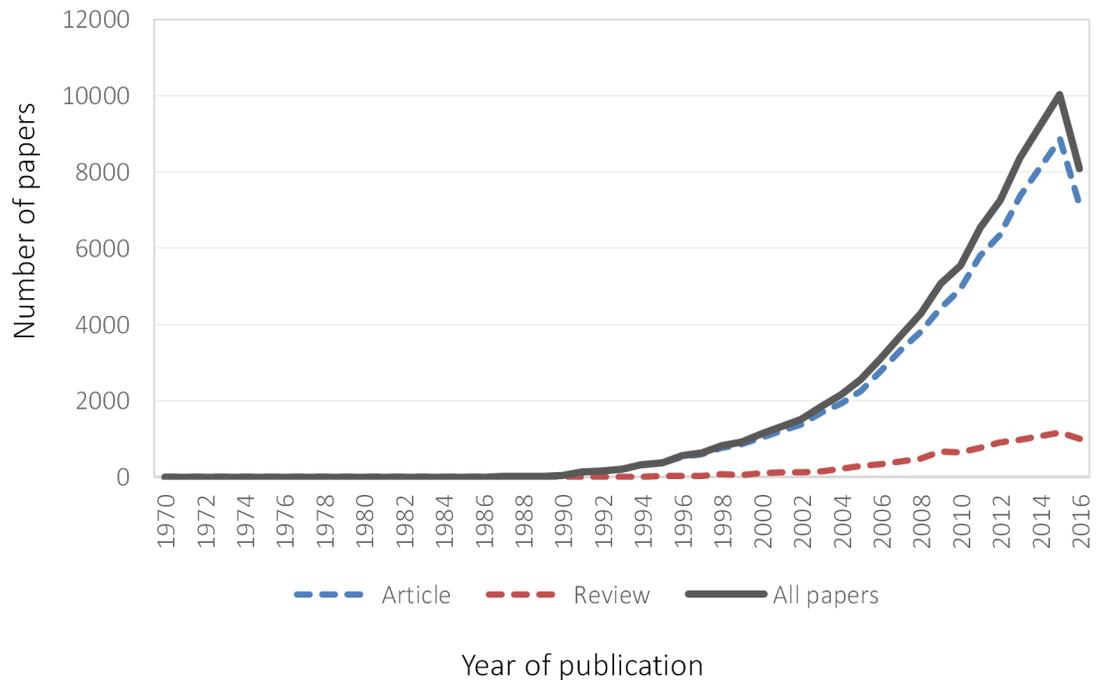
**Fig 2. Number of papers by year of publication.** Note: Data for 2016 up to November 8th.

Overall, 168 countries worldwide were involved in the sample of papers. The productivity ranking for countries with respect to the number of papers (Table 3) was headed by the United States (37624 papers), followed by the United Kingdom (7355 papers), Germany (6899 papers) and Canada (5706 papers). Fig 3 shows a visual representation of the most intense collaborative network between 42 countries (with at least 50 papers in co-authorship), in which we can see the relationships of some countries with respect to others and the position that each occupies in the network.

## Keywords

The most commonly used article/review keywords were "comorbidity" (9223 papers; 10.7%), followed by "depression" (n = 5853; 6.8%), "elderly" (n = 3077; 3.6%) and "mortality" (n = 2806; 3.3%) (Fig 4). The most frequently used keywords in the most common journal subject categories are shown in Table 4. Co-words analysis shows some associations of keywords forming triads (groupings of three terms), such as "comorbidity" and "depression" with either "anxiety/anxiety disorders", "posttraumatic stress disorder", "bipolar disorder", "alcohol dependence", "drug dependence" or "quality of life"; the associations of "diabetes mellitus" with "cardiovascular diseases", "obesity", or "hypertension"; and the association of "depression" with "bipolar disorder" and "suicide" (Fig 5).

## Most cited papers

Overall, included papers received 1.9 million citations, of which 40.9% citations (n = 808817) corresponded to 3596 (4.2%) papers with at least 100 citations. The most cited papers by number of citations ("citation classics" with at least 1000 citations) are listed in Table 5. All the 50 most cited papers were published in English. These most cited articles were published in 20 journals, led by the *Archives of General Psychiatry* (now, renamed *JAMA Psychiatry*) with 11

**Table 2. Most productive authors.**

| Author | Affiliation and country | Total papers | Total citations | Citations per paper | Papers in collaboration | Total signatures | Collaboration index (signatures per paper) |
|---|---|---|---|---|---|---|---|
| Ronald C Kessler | Harvard Medical School, United States | 331 | 81160 | 245.2 | 324 | 3389 | 10.2 |
| Joseph Biederman | Harvard Medical School and Massachusetts General Hospital, United States | 248 | 19964 | 80.5 | 244 | 1685 | 6.8 |
| Stephen V Faraone | State University of New York Upstate Medical University, United States | 227 | 16927 | 74.6 | 226 | 1777 | 7.8 |
| Chia-Hung Kao | National Taiwan Normal University, Taiwan (Republic of China) | 223 | 636 | 2.9 | 223 | 1309 | 5.9 |
| Cheng-Li Lin | China Medical University Hospital, China Medical University, China | 193 | 550 | 2.8 | 193 | 1132 | 5.9 |
| Murray B Stein | University of California, United States | 166 | 10590 | 63.8 | 161 | 1755 | 10.6 |
| Hans-Ulrich Wittchen | Dresden University of Technology, Germany | 162 | 24910 | 153.8 | 158 | 1214 | 7.5 |
| Henrik Toft Sørensen | Aarhus University Hospital, Denmark | 162 | 3299 | 20.4 | 162 | 1022 | 6.3 |
| Kenneth S Kendler | Virginia Commonwealth University, United States | 160 | 19554 | 122.2 | 156 | 1748 | 10.9 |
| Dan J Stein | University of Cape Town, South Africa | 149 | 5773 | 38.7 | 147 | 1937 | 13.0 |
| Kathleen Ries Merikangas | National Institute of Mental Health (NIMH), United States | 137 | 15240 | 111.2 | 132 | 864 | 6.3 |
| Fung-Chang Sung | China Medical University, China | 125 | 977 | 7.8 | 125 | 888 | 7.1 |
| Jitender Sareen | University of Manitoba, Canada | 116 | 4146 | 35.7 | 115 | 617 | 5.3 |
| Ron de Graaf | Netherlands Institute of Mental Health and Addiction (NIMHA), Netherlands | 114 | 8051 | 70.6 | 114 | 1331 | 11.7 |
| Hagop S Akiskal | University of California, United States | 112 | 7029 | 62.8 | 108 | 748 | 6.7 |
| Jordi Alonso | IMIM Hospital del Mar Medical Research Institute, Spain | 111 | 8527 | 76.8 | 111 | 1717 | 15.5 |
| Tzeng-Ji Chen | National Yang-Ming University, Taipei Veterans General Hospital, Taiwan (Republic of China) | 109 | 904 | 8.3 | 109 | 1051 | 9.6 |
| Wayne J Katon | University of Washington, United States | 107 | 9409 | 87.9 | 103 | 738 | 6.9 |
| Josep M Haro | Parc Sanitari Sant Joan de Déu, Spain | 105 | 8410 | 80.1 | 105 | 2712 | 25.8 |
| Luigi Ferrucci | National Institute on Aging (NIA), United States | 104 | 4307 | 41.4 | 104 | 927 | 8.9 |

papers and followed by the *Journal of the American Medical Association* (JAMA) with 8 papers. The list of most cited papers (Table 4) contains contributions dealing with methodological aspects, but also important epidemiological studies on chronic non-communicable diseases, comorbidity and/or multimorbidity. Some of the methodological papers present the most commonly used measures of comorbidities in health services and outcomes research: the "Charlson Comorbidity Index" [32,33] and its various adaptations (papers number-1, number-4, number-17 and number-20 in Table 5) and the "Elixhauser Comorbidity Index" [34] (paper number-10). These comorbidity index measures capture the "comorbidity burden" that

**Table 3. Productivity and patterns of collaboration by 50 top countries.**

| Country | Total papers | Papers per million inhabitants | Total collaborations | Total citations | Citations per paper | Papers in collaboration (distinct country) | Distinct countries of collaboration | Main collaborator (and number of collaborations) |
|---|---|---|---|---|---|---|---|---|
| United States | 37624 | 117.1 | 14296 | 1211072 | 32.2 | 7905 | 146 | Canada (1574) |
| United Kingdom | 7355 | 112.9 | 9301 | 186402 | 25.3 | 3669 | 130 | United States (1336) |
| Germany | 6899 | 84.7 | 7395 | 162829 | 23.6 | 2504 | 126 | United States (999) |
| Canada | 5706 | 159.2 | 4893 | 165784 | 29.1 | 2442 | 118 | United States (1574) |
| Italy | 5373 | 88.4 | 7094 | 120728 | 22.5 | 2093 | 122 | United States (1045) |
| Australia | 3979 | 167.3 | 3809 | 88132 | 22.2 | 1575 | 117 | United States (639) |
| Spain | 3889 | 83.8 | 5391 | 75487 | 19.4 | 1289 | 122 | United States (569) |
| Netherlands | 3885 | 229.4 | 6226 | 110756 | 28.5 | 1786 | 116 | United States (728) |
| France | 3742 | 56.0 | 5747 | 83846 | 22.4 | 1506 | 125 | United States (634) |
| Taiwan/ Republic of China | 2173 | 92.4 | 756 | 23526 | 10.8 | 349 | 95 | United States (218) |
| Sweden | 2066 | 210.8 | 3486 | 53826 | 26.1 | 1167 | 114 | United States (428) |
| Brazil | 1978 | 9.5 | 2356 | 29773 | 15.1 | 658 | 119 | United States (374) |
| Switzerland | 1852 | 223.5 | 3659 | 56315 | 30.4 | 1190 | 118 | Germany (454) |
| China | 1735 | 1.3 | 2458 | 25828 | 14.9 | 693 | 111 | United States (422) |
| Denmark | 1689 | 297.6 | 2498 | 41416 | 24.5 | 798 | 110 | United States (378) |
| Japan | 1576 | 12.4 | 2156 | 29888 | 19.0 | 443 | 109 | United States (313) |
| Belgium | 1264 | 112.0 | 4036 | 36184 | 28.6 | 854 | 96 | Netherlands (405) |
| Turkey | 1203 | 15.3 | 983 | 10626 | 8.8 | 171 | 109 | United States (88) |
| South Korea | 1142 | 22.6 | 925 | 14698 | 12.9 | 288 | 103 | United States (220) |
| Israel | 1087 | 129.7 | 1952 | 26029 | 24.0 | 445 | 108 | United States (310) |
| Norway | 1024 | 197.1 | 1796 | 24185 | 23.6 | 520 | 107 | United States (185) |
| Austria | 1000 | 116.1 | 2577 | 23361 | 23.4 | 597 | 108 | Germany (319) |
| Finland | 923 | 168.4 | 1618 | 24740 | 26.8 | 403 | 110 | United Kingdom (158) |
| Greece | 738 | 68.2 | 1631 | 16008 | 21.7 | 375 | 112 | United States (137) |
| Poland | 664 | 17.5 | 1746 | 10806 | 16.3 | 276 | 83 | United Kingdom (133) |
| India | 652 | 0.5 | 954 | 9278 | 14.2 | 207 | 102 | United States (112) |
| New Zealand | 599 | 130.3 | 1362 | 23448 | 39.2 | 339 | 95 | United States (168) |
| Ireland | 513 | 110.5 | 1094 | 12680 | 24.7 | 276 | 94 | United Kingdom (144) |
| Singapore | 482 | 87.1 | 794 | 9344 | 19.4 | 219 | 108 | United States (111) |
| Mexico | 462 | 3.6 | 1836 | 17048 | 36.9 | 257 | 112 | United States (207) |
| South Africa | 437 | 8.0 | 1462 | 13692 | 31.3 | 316 | 113 | United States (175) |
| Portugal | 412 | 39.8 | 1406 | 8192 | 19.9 | 185 | 108 | United Kingdom (92) |
| Hungary | 295 | 30.0 | 996 | 7159 | 24.3 | 200 | 81 | United States (93) |
| Czech Republic | 272 | 25.8 | 838 | 5653 | 20.8 | 142 | 76 | Italy (53) |
| Iran | 272 | 3.4 | 345 | 3210 | 11.8 | 77 | 105 | United States (31) |
| Russia | 242 | 1.7 | 809 | 6023 | 24.9 | 102 | 111 | United Kingdom (43) |
| Serbia | 230 | 32.4 | 482 | 1904 | 8.3 | 84 | 106 | Italy (30) |
| Argentina | 224 | 5.2 | 834 | 8365 | 37.3 | 115 | 113 | United States (78) |
| Chile | 224 | 12.5 | 416 | 2120 | 9.5 | 105 | 84 | United States (56) |
| Saudi Arabia | 220 | 7.0 | 448 | 4250 | 19.3 | 145 | 95 | United States (63) |
| Romania | 209 | 10.5 | 1273 | 5228 | 25.0 | 119 | 107 | Italy (68) |
| Croatia | 207 | 49.0 | 349 | 2030 | 9.8 | 62 | 70 | Italy (22) |
| Thailand | 184 | 2.7 | 395 | 1767 | 9.6 | 119 | 82 | United States (56) |

(*Continued*)

**Table 3.** (*Continued*)

| Country | Total papers | Papers per million inhabitants | Total collaborations | Total citations | Citations per paper | Papers in collaboration (distinct country) | Distinct countries of collaboration | Main collaborator (and number of collaborations) |
|---|---|---|---|---|---|---|---|---|
| Colombia | 173 | 3.6 | 1316 | 7497 | 43.3 | 120 | 109 | United States (95) |
| Egypt | 165 | 1.8 | 391 | 1792 | 10.9 | 87 | 103 | United States (27) |
| Nigeria | 165 | 0.9 | 767 | 5583 | 33.8 | 70 | 92 | United States (53) |
| Malaysia | 146 | 4.8 | 229 | 1322 | 9.1 | 68 | 83 | Australia (23) |
| Slovenia | 138 | 66.9 | 630 | 2770 | 20.1 | 82 | 78 | Germany (44) |
| Lebanon | 121 | 20.7 | 992 | 6770 | 56.0 | 102 | 98 | United States (81) |
| Pakistan | 118 | 0.6 | 431 | 4854 | 41.1 | 45 | 108 | United States (23) |

top-50 countries with at least 100 papers. Country inhabitants (year 2015) obtained from the World Bank (http://data.worldbank.org/).

exists alongside a primary diagnosis and that may influence outcomes. The list of the most cited paper also reflects major advances in the description of the epidemiology of mental disorders and its correlates by the U.S. National Comorbidity Survey [35–40] (papers number-2, number-3, number-5, number-6, number-7 and number-15, among others in Table 5); the widely-used frailty phenotype framework proposed by Fried et al. [41] (paper number-8 in
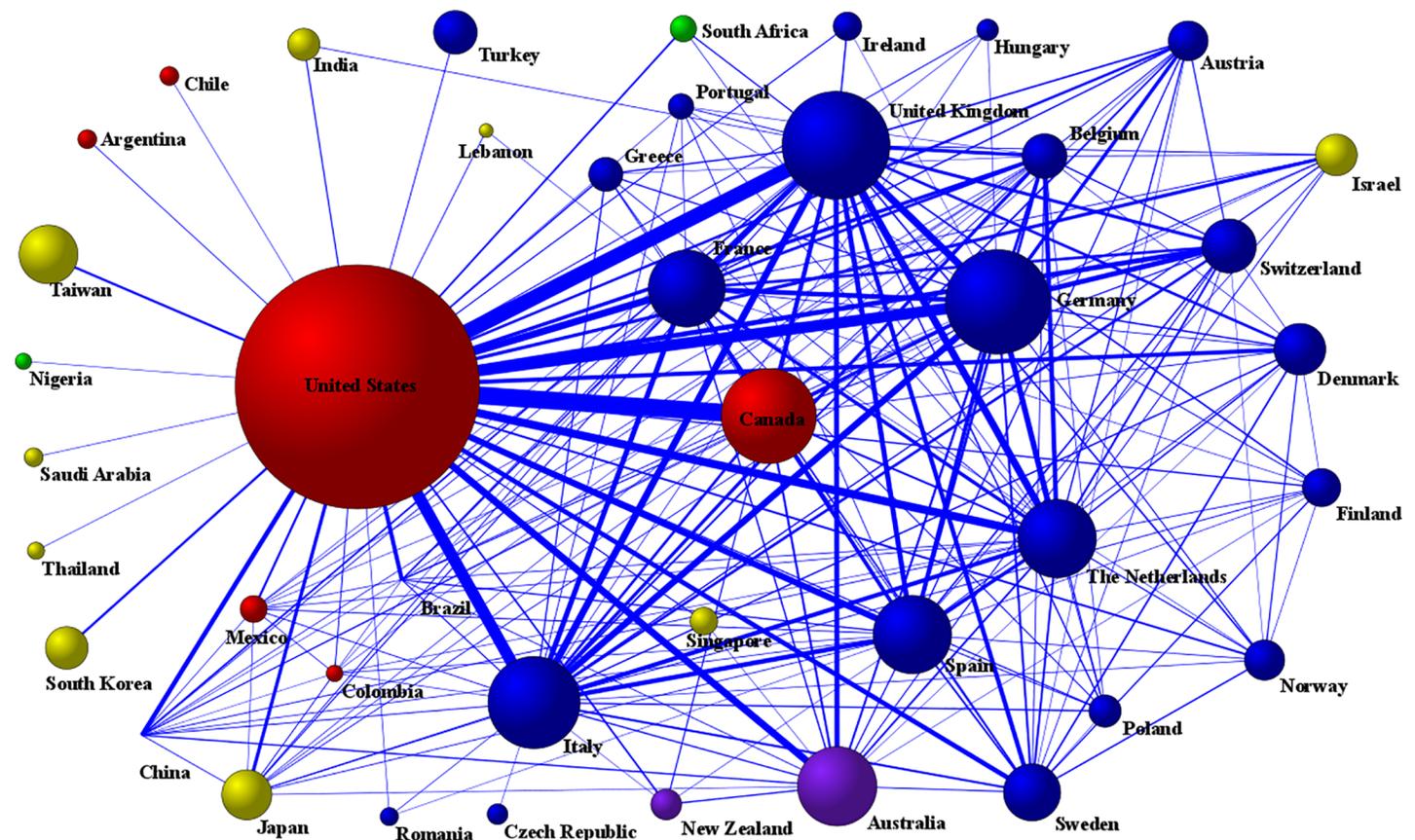


**Fig 3. Global collaborative network between countries.** Note: Most productive cluster of countries applying a threshold of 50 or more papers signed in co-authorship. Node sizes are proportional to the number of papers and line thicknesses are proportional to the number of collaborations. Node colors: America = red; Asia = yellow; Africa = green; Europe = blue; Oceania = purple.

**Fig 4. Word cloud for the frequency of terms.** Note: Most frequently used keywords (at least 500 times).

Table 5)–the concepts of "frailty" and "comorbidity/multimorbidity" are commonly used interchangeably to identify vulnerable older adults [42–44], but there is a growing consensus that these might be distinct clinical entities that are causally related [42,43]; the management of predisposing factors such as obesity and overweight [45–48] (papers number-9, number-12, number-18 and number-33); the importance of hospital volume to operative mortality associated with cardiovascular and cancer procedures [49] (paper number-13 in Table 5); and the development of the widely-used "Acute Physiology and Chronic Health Evaluation (APACHE) prognostic system" [50] (paper number-14 in Table 5) to quantify the severity of illness in the intensive care units.

## Discussion

In this cross-sectional analysis, we analyzed the global scientific research in comorbidity and multimorbidity for the period 1970–2016. We have identified the most productive investigators and countries, most common subjects and keywords, most prolific journals and "citation classics" in comorbidity and multimorbidity based on publications in multiple specialties and disciplines. The most striking results are the increasing number of published articles in recent years, with approximately two-thirds of the papers published since 2010. To the best of our knowledge, this is the first comprehensive global mapping analysis of scientific publications in comorbidity and multimorbidity. This analysis complements and expands the perspective of

**Table 4. Most prolific journals and most commonly used keywords per journal subject category.**

| Journal subject category | Total papers | Journal name | Total papers | | Total papers |
|---|---|---|---|---|---|
| Psychiatry | 16558 | Journal of Affective Disorders | 1154 | Depression | 3290 |
| | | Journal of Clinical Psychiatry | 727 | Bipolar disorder | 1295 |
| | | Psychiatry Research | 528 | Attention deficit hyperactivity disorder | 1083 |
| Surgery | 9570 | Obesity Surgery | 588 | Bariatric surgery | 570 |
| | | Journal of Vascular Surgery | 489 | Morbid obesity | 414 |
| | | Annals of Thoracic Surgery | 338 | Obesity | 356 |
| Clinical Neurology | 9275 | Journal of Affective Disorders | 1154 | Depression | 1568 |
| | | Epilepsy & Behavior | 370 | Bipolar disorder | 727 |
| | | Journal of Nervous and Mental Disease | 365 | Epilepsy | 670 |
| Medicine, General & Internal | 7622 | Medicine | 302 | Primary care | 341 |
| | | Journal of General Internal Medicine | 282 | Depression | 326 |
| | | BMJ Open | 272 | Diabetes mellitus | 318 |
| Cardiac & Cardiovascular Systems | 5098 | Annals of Thoracic Surgery | 338 | Heart failure | 548 |
| | | American Journal of Cardiology | 336 | Mortality | 326 |
| | | International Journal of Cardiology | 269 | Atrial fibrillation | 226 |
| Oncology | 4790 | Cancer | 370 | Elderly | 680 |
| | | Journal of Clinical Oncology | 279 | Breast cancer | 460 |
| | | Annals of Surgical Oncology | 154 | Chemotherapy | 391 |
| Neurosciences | 4698 | Biological Psychiatry | 249 | Depression | 873 |
| | | Encéphale | 244 | Bipolar disorder | 383 |
| | | Bipolar Disorders | 184 | Attention deficit hyperactivity disorder | 311 |
| Pharmacology & Pharmacy | 4223 | Drugs & Aging | 236 | Depression | 380 |
| | | Clinical Therapeutics | 134 | Diabetes mellitus | 173 |
| | | International Journal of Clinical Practice | 125 | Attention deficit hyperactivity disorder | 139 |
| Urology & Nephrology | 4150 | Journal of Urology | 331 | Mortality | 327 |
| | | Nephrology Dialysis Transplantation | 297 | Prostate cancer | 305 |
| | | Urology | 247 | Hemodialysis | 287 |
| Geriatrics & Gerontology | 3399 | Journal of the American Geriatrics Society | 634 | Elderly | 660 |
| | | Drugs & Aging | 236 | Older adults | 435 |
| | | Archives of Gerontology and Geriatrics | 203 | Depression | 278 |
| Public, Environmental & Occupational Health | 3392 | Medical Care | 361 | Depression | 182 |
| | | Journal of Clinical Epidemiology | 220 | Diabetes mellitus | 160 |
| | | BMC Public Health | 220 | Epidemiology | 155 |
| Respiratory System | 3003 | Annals of Thoracic Surgery | 338 | Chronic obstructive pulmonary disease | 622 |
| | | Chest | 282 | Asthma | 160 |
| | | Respiratory Medicine | 185 | Mortality | 155 |
| Health Care Sciences & Services | 2907 | Medical Care | 361 | Quality of life | 188 |
| | | Journal of General Internal Medicine | 282 | Depression | 154 |
| | | BMC Health Services Research | 245 | Diabetes mellitus | 148 |
| Psychology | 2788 | Psychological Medicine | 517 | Depression | 598 |
| | | Depression and Anxiety | 407 | Epidemiology | 166 |

(*Continued*)

**Table 4.** (*Continued*)

| Journal subject category | Total papers | Journal name | Total papers | | Total papers |
|---|---|---|---|---|---|
| | | International Journal of Eating Disorders | 249 | Posttraumatic stress disorder | 144 |
| Pediatrics | 2739 | Journal of the American Academy of Child and Adolescent Psychiatry | 376 | Attention deficit hyperactivity disorder | 330 |
| | | Pediatrics | 167 | Children | 302 |
| | | Journal of Child and Adolescent Psychopharmacology | 103 | Adolescent | 289 |
| Endocrinology & Metabolism | 2517 | Diabetes Care | 185 | Diabetes mellitus | 359 |
| | | Obesity | 137 | Obesity | 239 |
| | | Osteoporosis International | 118 | Depression | 122 |
| Peripheral Vascular Disease | 2446 | Journal of Vascular Surgery | 489 | Hypertension | 190 |
| | | Annals of Vascular Surgery | 193 | Stroke | 159 |
| | | Circulation | 192 | Mortality | 133 |
| Psychology, Clinical | 2429 | Journal of Clinical Psychiatry | 727 | Depression | 374 |
| | | Psychological Medicine | 517 | Anxiety disorders | 130 |
| | | Depression and Anxiety | 407 | Eating disorders | 121 |
| Gastroenterology & Hepatology | 2345 | Journal of Gastrointestinal Surgery | 186 | Colorectal Cancer | 144 |
| | | World Journal of Gastroenterology | 161 | Mortality | 112 |
| | | Diseases of the Colon & Rectum | 127 | Hepatitis C | 105 |
| Orthopedics | 2300 | Spine | 306 | Mortality | 123 |
| | | Clinical Orthopaedics and Related Research | 195 | Risk factors | 96 |
| | | Journal of Bone and Joint Surgery | 164 | Hip fracture | 95 |
| Infectious Diseases | 1792 | Clinical Infectious Diseases | 151 | HIV infection | 398 |
| | | BMC Infectious Diseases | 129 | Mortality | 146 |
| | | Infection Control and Hospital Epidemiology | 90 | Bacteremia | 104 |
| Immunology | 1691 | Clinical Infectious Diseases | 151 | HIV infection | 239 |
| | | Transplantation Proceedings | 134 | Asthma | 136 |
| | | Biology of Blood and Marrow Transplantation | 112 | Influenza | 74 |
| Rheumatology | 1610 | Journal of Rheumatology | 222 | Rheumatoid arthritis | 293 |
| | | Rheumatology | 132 | Osteoarthritis | 91 |
| | | BMC Musculoskeletal Disorders | 122 | Gout | 78 |
| Gerontology | 1597 | Journal of the American Geriatrics Society | 634 | Elderly | 660 |
| | | Journals of Gerontology Series A | 184 | Older adults | 435 |
| | | International Journal of Geriatric Psychiatry | 156 | Depression | 278 |
| Critical Care Medicine | 1589 | Chest | 282 | Mortality | 191 |
| | | Critical Care Medicine | 183 | Intensive care | 156 |
| | | Injury | 123 | Chronic obstructive pulmonary disease | 90 |

previous studies that analyzed some characteristics of articles in comorbidity [10,12], the diversity of terms used in the literature referring to the presence of multiple concurrent diseases [10,12,51], or reviews on the implications and the understanding of research needs and treatment impact [52,53].

In line with previous research in other areas [54–57], the global productivity of scientific papers is dominated by the United States (as a central hub of knowledge), followed by other nodes in Western Europe (such as the United Kingdom, Germany and Italy) and Canada. The large number of publications on comorbidity and multimorbidity from these countries reflects

**Fig 5. Co-words network of the author keywords.** Node sizes are proportional to the number of papers and line thicknesses are proportional to the number of co-occurrences of words. Node colors: blue = words related to general terms; green = words related to diseases/disorders, signs and symptoms; yellow = interventions.

the importance that Western societies devote to research as the basis for socio-economic and technological development, but also reflects the interest in understanding and addressing important challenges of population aging and increased complexity of chronicity. Ageing of the world's population is increasing the number of people living with sequelae of multiple diseases, with an increasing trend in low-income countries [1–4]. As might be expected, the scientific community captured is centered on a nucleus of scientists and researchers from academia, medical and health research centers from North America and Western Europe, but also from Australia and Taiwan (Republic of China). Specifically, the most intense global collaborations took place between authors and institutions from the United States, the United Kingdom and Canada. Perhaps, the very limited participation of low and middle income-based researchers and institutions in research on comorbidity and multimorbidity could warrant further pragmatic action given that the epidemiological transition (e.g. replacement of infectious diseases by chronic diseases) imposes more constraints to deal with the burden of multiple chronic diseases in a poor environment characterized by ill-health systems [3,4,58–60].

Papers on comorbidity and multimorbidity were published most often in journals devoted to neuropsychiatry and neurosciences. Psychiatry has become one of the fastest growing medical disciplines [61]. In fact, the publication activity and interest of comorbidity and multimorbidity in people with mental disorders seems to be increasing [62,63]. Our analysis revealed that nearly 20% of all scientific production was published in journals belonging to psychiatry and mental health. This large relative productivity in psychiatry may be explained by the important role of comorbidity and its implications for theories of etiology, prevention and treatment of mental disorders [63]. Within psychiatry, comorbidity has been traditionally

**Table 5. Most cited papers.**

| Rank | Paper | Total citations | Citations/ year |
|---|---|---|---|
| 1. | Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83. | 15049 | 518.9 |
| 2. | Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51:8–19. | 7752 | 352.4 |
| 3. | Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602. | 5404 | 491.3 |
| 4. | Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:613–9. | 4463 | 186.0 |
| 5. | Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048–60. | 4397 | 209.4 |
| 6. | Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:617–27. | 4180 | 380.0 |
| 7. | Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095–105. | 3476 | 267.4 |
| 8. | Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56. | 3052 | 203.5 |
| 9. | Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37. | 2923 | 243.6 |
| 10. | Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36:8–27. | 2625 | 145.8 |
| 11. | Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990;264:2511–8. | 2462 | 94.7 |
| 12. | Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999;282:1523–9. | 2409 | 141.7 |
| 13. | Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346:1128–37. | 2341 | 167.2 |
| 14. | Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100:1619–36. | 2155 | 86.2 |
| 15. | Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002;32:959–76. | 2064 | 147.4 |
| 16. | Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med. 2004;351:13–22. | 2013 | 167.8 |
| 17. | Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–9. | 1825 | 165.9 |
| 18. | Haslam DW, James WP. Obesity. Lancet. 2005 Oct 1;366(9492):1197–209. | 1787 | 162.5 |
| 19. | DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160:2101–7. | 1525 | 138.6 |
| 20. | Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–51. | 1513 | 68.8 |
| 21. | Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8–160. | 1505 | 188.1 |
| 22. | Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129:674–97. | 1501 | 115.5 |
| 23. | Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092–7. | 1433 | 143.3 |

(*Continued*)

**Table 5.** (*Continued*)

| Rank | Paper | Total citations | Citations/year |
|------|-------|-----------------|----------------|
| 24. | Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003;60:837–44. | 1417 | 109.0 |
| 25. | Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163:28–40. | 1394 | 139.4 |
| 26. | Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65. | 1365 | 455.0 |
| 27. | Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61:348–58. | 1344 | 149.3 |
| 28. | Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163:716–23. | 1336 | 133.6 |
| 29. | Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96. | 1306 | 326.5 |
| 30. | Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull. 2003;129:52–73. | 1282 | 98.6 |
| 31. | Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61:807–16. | 1275 | 106.3 |
| 32. | Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA. 2000;284:2606–10. | 1275 | 79.7 |
| 33. | Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics. 1998;101:518–25. | 1271 | 70.6 |
| 34. | Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, et al. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA. 2004;291:2581–90. | 1265 | 105.4 |
| 35. | Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, Evangelista A, Fattori R, Suzuki T, Oh JK, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA. 2000;283:897–903. | 1200 | 75.0 |
| 36. | Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222:339–50. | 1183 | 56.3 |
| 37. | Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A. 1996;93:3908–13. | 1179 | 59.0 |
| 38. | Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997;54:313–21. | 1142 | 60.1 |
| 39. | Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 1996;276:293–9. | 1133 | 56.7 |
| 40. | Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry. 1999;56:617–26. | 1112 | 65.4 |
| 41. | Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, Howes MJ, Normand SL, Manderscheid RW, Walters EE, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003;60:184–9. | 1108 | 85.2 |
| 42. | Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. Am J Psychiatry. 1994;151:979–86. | 1096 | 49.8 |
| 43. | Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:629–40. | 1093 | 99.4 |
| 44. | Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157:1552–62. | 1089 | 68.1 |
| 45. | Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord. 1993;29:85–96. | 1076 | 46.8 |

(*Continued*)

**Table 5.** (*Continued*)

| Rank | Paper | Total citations | Citations/year |
|---|---|---|---|
| 46. | Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370:851–8. | 1065 | 118.3 |
| 47. | Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993;46:1075–9. | 1061 | 46.1 |
| 48. | Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest. 2004;114:147–52. | 1032 | 86.0 |
| 49 | Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163:2433–45. | 1022 | 78.6 |
| 50. | Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2007;64:830–42. | 1004 | 111.6 |

Most cited (top-50) papers with at least 1000 citations.

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used to refer to the overlap of two or more psychiatric disorders [64]. Similarly, comorbidity (and multimorbidity) between mental disorders and substance use disorders [65–67], cardio-vascular diseases [68–70], cancer [71,72] or other chronic disorders [6,73] has gained prominence within the past few decades.

Our analyses suggest that other medical disciplines with a large number of papers on comorbidity and multimorbidity, including surgery [74,75], clinical neurology [76–78], general and internal medicine [3,4,79,80], cardiology [81] and oncology [82], focus on those conditions with a high global burden of disease. The subject analysis has revealed that the keywords' prioritization in comorbidity and multimorbidity depends on the addressed subject area. For example, "Depression" is the most commonly used keyword in the subject categories of Psychiatry, Clinical Neurology, Neurosciences, Psychology; but also in General and Internal Medicine, Geriatrics and Gerontology, Pharmacology, Endocrinology, Public, Environmental and Occupational Health, and Health Care Sciences and Services. Depression is a common mental disorder that occurs in people of all ages across all world regions and represents a leading cause of disease burden [3,4,78]. Despite existing evidence of the effectiveness of multiple interventions, traditional approaches to the management of the depressive disorders (such as medication alone and brief psychotherapy) have contributed to large treatment gaps [83–86]. In this respect, the complex pathogenesis implicates factors of diverse nature that should be considered in research. For example, integrating the management of depressive disorders with other common mental disorders (e.g. anxiety disorders and bipolar disorder) or other chronic conditions (e.g. cancer, diabetes and diseases of the cardiorespiratory system) through trans-diagnostic interventions [83].

The topic analysis of the most cited papers ("citation classics") allowed us to determine which topics have attracted the most interest in the research on comorbidity and multimorbidity. These include landmark methodological developments in measuring comorbidity (such as Charlson's index, Elixhauser's index and their modifications) [32–34] and descriptive epidemiological studies measuring the burden of comorbidity [35–40], among others. However, important knowledge gaps in comorbidity and multimorbidity remain. The limitations of clinical practice guidelines and treatment for single diseases are well recognized in the biomedical literature, along with the call to make better use of the best evidence base [87,88]. Clinical trials are usually conducted in homogeneous populations, which prevents us from knowing whether treatment effects in people with multiple chronic diseases are equivalent to those in patients with single diseases [89,90]. The evidence base for interventions to improve outcomes for people with multimorbidity therefore remains limited; however, emerging evidence is being

generated to support disease management policies in primary care and community settings [53]. The consideration of people with multimorbidity is essential in future study design and evaluations of health services and technologies. To be of value, it is important that research includes the evaluation of the benefits of multiple approaches for multiple coexisting diseases (e.g. patient-, family- and population-centered), and that generalizability and applicability problems be explicitly addressed [87–91].

There are several limitations to our study. We characterized knowledge structures generated by papers included in the Web of Science database, integrating subject categories of journals, keywords of papers and network analyses. However, these methods represent a scoping approach which could be complemented further by more detailed analyses, for example analyzing the content and reporting quality of papers in evidence syntheses (including systematic reviews of the literature [92]). We only analyzed research articles and review articles. Undoubtedly, there are other important reports (e.g. health policy reports, meeting abstracts and letters/correspondence [93]) that also merit consideration in global debates and discussions in comorbidity and multimorbidity. The validity of keywords mapping and the results of the co-word analyses depend on the definitions of words chosen to conceptualize the papers by the authors or database indexers to categorize papers. The growing interest in comorbidity and multimorbidity by health care providers has resulted in more research on these issues, which may have led to a proliferation of different terms for the same concepts. For example, the traditional (and widely accepted) term "comorbidity" is associated with high volume of papers but may lack specificity, whereas the more recently introduced term of "multimorbidity" is associated with low number of papers (see S1 Table). As Almirall and Fortin stated "[t]he use of clearly defined terms in the literature is recommended until a general consensus on the terminology of multiple coexistent diseases is reached" across multiple disciplines [51]. 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 changes of time (e.g. by means of longitudinal network analyses).

## Conclusion

The global analysis presented in this study provides compelling evidence of the scientific growth of research on comorbidity and multimorbidity. Scientific research in this field is increasingly published in biomedical journals, with research leadership of Western countries, most notably, the United States. This study contributes to a better understanding in this challenging field and identifies the main areas of research, the publication sources chosen for their scientific dissemination and the major scientific leaders. Advances in several subjects and research areas will allow for use of new theories and models to fundamentally changes in the management of people with multiple chronic diseases.

## Supporting information

**S1 Checklist. Reporting checklist.**
(DOCX)

**S1 Table. Search strategy and results.**
(DOCX)

## Acknowledgments

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**Writing – review & editing:** Adolfo Alonso-Arroyo, Matthew J. Page, Brian Hutton, Rafael Tabarés-Seisdedos, Rafael Aleixandre-Benavent.

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