Mapping theme trends and recognizing hot spots in postmenopausal osteoporosis research: a bibliometric analysis

Siming Zhou[1#], Zhengbo Tao[1#], Yue Zhu[1], Lin Tao[1]

[1]Department of Orthopaedics, First Hospital of China Medical University, Shenyang, Liaoning, China

#These authors contributed equally to this work

Corresponding Author:

Yue Zhu[1], Lin Tao[1]

Shenyang, Liaoning, China

Email address: zhuyuedr@163.com; taolindr@163.com

Abstract

Background: This study aimed to draw a series of scientific maps to quantitatively and qualitatively evaluate hot spots and trends in postmenopausal osteoporosis research using bibliometric analysis.

Methods: Scientific papers published on postmenopausal osteoporosis were extracted from the Web of Science Core Collection and PubMed database. Extracted information was analyzed quantitatively with bibliometric analysis by CiteSpace, the Online Analysis Platform of Literature Metrology and Bibliographic Item Co-Occurrence Matrix Builder (BICOMB). To explore the hot spots in this field, co-word biclustering analysis was conducted by gCLUTO based on the major MeSH terms/MeSH subheading terms-source literatures matrix.

Results: We identified that a total of 5,247 publications related to postmenopausal osteoporosis were published between 2013 and 2017. The overall trend decreased from 1,071 literatures in 2013 to 1,048 literatures in 2017. *Osteoporosis International* is the leading journal in the field of postmenopausal osteoporosis research, both in terms of impact factor score (3.819) and H-index value (157). The United States has retained a top position and has exerted a pivotal influence in this field. The University of California, San Francisco was identified as a leading institution for research collaboration, and Professors Reginster and Kanis have made great achievements in this area. Eight research hot spots were identified.

Conclusions: Our study found that in the past few years, the etiology and drug treatment of postmenopausal osteoporosis have been research hot spots. They provide a basis for the study of the pathogenesis of osteoporosis and guidelines for the drug treatment of osteoporosis.

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Introduction

41 **Introduction**

42 Osteoporosis, described as the microstructural degeneration of bone tissue and low bone mass, is
43 a systemic skeletal disease causing incremental bone fragility and sensitivity to fracture. There is
44 an increasing incidence of osteoporotic fractures at all ages. Women have twice the risk of
45 getting fractures as men, making postmenopausal osteoporosis, which results from estrogen
46 deficiency and leads to an increase in bone turnover, one of the most important types of primary
47 osteoporosis. To repair micro-damage and adapt to mechanical and metabolic needs, bone is
48 being continuously remodeled. The remodeling of bone is performed by two specialized cells:
49 bone-forming osteoblasts and bone-resorbing osteoclasts (Wu et al. 2015). Additionally, the loss
50 of connectivity in trabecular bone, and cortical bone thinning and loss of porosity are affected by
51 an imbalance between bone formation and resorption. The existing treatment of osteoporosis is
52 mainly drug-based. Diphosphonates are given as a first-line treatment, followed by denosumab (a
53 RANKL inhibitor). Teriparatide (a fragment of parathyroid hormone) is the only approved
54 anabolic agent. Estrogen replacement therapy or selective estrogen receptor modulators can be
55 considered in specific conditions (McClung et al. 2005). The prevention of osteoporosis focuses
56 on gaining maximum peak bone mass and minimizing postmenopausal and age-related bone loss
57 through nutrition, maintenance of a normal body mass index, regular physical activity, and the
58 absence of smoking (Oncken et al. 2006). By reducing falls in high-risk populations, fractures,
59 the main complication of osteoporosis, may also be restrained (Schwartz et al. 2005).
60 In recent years, the bibliometric method used most often has been a quantitative analysis,
61 which uses the statistical index to measure the contribution of a subject or scientific publications
62 in an area of research, and shows widely-applied research trends and hot spots. While this
63 method works to a certain extent, different scholars in this field have different results and views,
64 and there is a lack of recent bibliometric research. French bibliometric scientists Callon et al.
65 first presented the co-word analysis in 1986, which was utilized to find information and
66 recognize hot spots in scholarly literature (Hong et al. 2016). To further summarize the focus of
67 the research and structure of the subject by statistical analyses, such as factor analysis, cluster
68 analysis, multivariate analysis or multidimensional scaling analysis, the significant keywords of
69 a theme were categorized. Among these methods, cluster analysis has been widely used to
70 extract a research theme area. Unlike conventional clustering, biclustering permits
71 coinstantaneous cluster rows and columns of matrices, not just the global information, in order to
72 efficiently detect local messages in high-dimensional data. The field of bibliometrics has
73 recommended biclustering analysis in more recent years. Fiannaca et al. revealed miRNA
74 expression profiles in breast cancer using biclustering (Fiannaca et al. 2015), and Li et al. applied
75 biclustering to probe into subject areas and hot spots of research on Internet health information
76 seeking behavior (Zheng et al. 2015). Their research findings suggested that the biclustering
77 method can direct central research focus and the representative literature or research.

78   There have been few bibliometric studies on postmenopausal osteoporosis, and those few
79   paid more attention to studying published information than future research trends (Biglu et al.
80   2014; Pluskiewicz et al. 2018). In this study, an integrated analysis on the external features and
81   content patterns of pertinent literature was performed to clarify the status and progress of
82   postmenopausal osteoporosis research in the past five years. Particularly, co-word biclustering
83   analysis was used to confirm the research hot spots for postmenopausal osteoporosis. We hope
84   that this research will provide some basis for future studies on postmenopausal osteoporosis.
85
86   **Materials & Methods**
87
88   **Data source and search strategy**
89   Literatures were retrieved online through the Social Science Citation Index and the Science
90   Citation Index-Expanded of the Web of Science Core Collection (WoSCC) on September 7,
91   2019. The search strategy was used for the following terms with a timeframe of the January 1,
92   2013 solstice to December 31, 2017: Osteoporosis, Postmenopausal AND Language = English,
93   and only original articles and reviews were included. Related data were extracted and
94   downloaded without the restriction of language from PubMed, developed by the National Center
95   for Biotechnology Information (NCBI) of the National Library of Medicine (NLM), providing
96   free access to MEDLINE, OLDMEDLINE, and other related databases. MeSH (Medical Subject
97   Headings) terms are a series of standardized words that can map the content of literatures.
98   According to the MeSH words used, co-word clustering analysis can be carried out continuously
99   (Li et al. 2015). The search strategy applied was "Osteoporosis, Postmenopausal"[Mesh].
100   Publication date was set from Jan 1st, 2013- Dec 31st, 2017.
101   All of the literature retrieval and download recording were completed in the same day in order to
102   reduce the quantity of citations resulting from frequent database updates.
103
104   **Data collection**
105   Two investigators (Siming Zhou and Zhengbo Tao) independently conducted the primary
106   search by screening the full text, titles and, in some cases, abstracts, of the literatures. The
107   agreement rate between them was 0.90, showing a strong accordance (Landis & Koch 1977).
108   Before reaching an agreement, any differences were discussed. WoSCC data were converted to
109   txt format and imported into CiteSpace V5.5.R1 SE, 64bit (Drexel University, Philadelphia, PA,
110   USA) and the Online Analysis Platform of Literature Metrology (http://bibliometric.com/) for
111   bibliometric analysis. Each downloaded literature was saved from PubMed as a file in XML
112   format and imported into the Bibliographic Item Co-Occurrence Matrix Builder (BICOMB)
113   (developed by Professor Cui from China Medical University and freely available online) (Cui L
114   LW 2008) for hot spot analysis.
115
116   **Analysis methods**

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Bibliometric analysis

119   We tried to create "The WoSCC Literature Analysis Report" to summarize publication
120   characteristics, such as journals, authors, countries, institution condition, number of annual
121   publications, H index, and citation counts. To measure the scientific value of research, we
122   enquired the Journal Citation Reports (JCR) 2018 to obtain the impact factor (IF) and the number
123   of citations, which we regarded as important indicators (Eyre-Walker & Stoletzki 2013). After
124   evaluating these scientific metrics, it was easy to measure different aspects of the publications
125   including their reputation, production and influence. In our study, we used the Literature
126   Metrology online analysis platform to analyze the annual number of publications and
127   country/region growth tendencies. CiteSpace was used for collaboration network analysis to
128   connect journals, authors, institutions and countries. CiteSpace can also use "time slicing", where
129   you could set "years per slice" to 1 and set "top N per slice" to 50, and the top 50 papers in a 1-
130   year slice would be extracted into a single network. According to the aim of our analysis, we
131   selected different node types with the size representing citation counts or the number of
132   publications. (Chen et al. 2010; Chen & Technology 2014).

133

Co-word biclustering analysis of research hotspots

135   BICOMB and Microsoft Excel were utilized to identify the proportion of the frequency
136   permutations of major MeSH terms/MeSH subheading terms in the concerned literature.
137   In this study, the tendencies of the extremely frequent major MeSH terms/MeSH subheading
138   terms were visually stated. Meanwhile, in order to detect the hot spots of postmenopausal
139   osteoporosis research, biclustering of the chosen publications and extremely frequent major
140   MeSH terms/MeSH subheading terms was carried out. Biclustering was applied to show the
141   relationship between source literatures and extremely frequent words, and the relationship among
142   extremely frequent words. From BICOMB, a binary matrix with source literatures as the
143   columns and extremely frequent major MeSH terms/MeSH subheading terms as the rows, was
144   structured for further biclustering by means of the software "gCLUTO", version 1.0 (Graphical
145   CLUstering TOolkit, a graphical front-end for the CLUTO data clustering library, developed by
146   Rasmussen, Newman, and Karypis from the University of Minnesota)(K 2014). Based on the
147   literature, the parameters of biclustering in gCLUTO were set, and were suitable for biclustering
148   analysis. I2 was then selected for criterion function, Cosine was chosen for similarity function,
149   and repeated bisection for clustering method. The biclustering result of the matrix of source
150   literatures showed extremely frequent major MeSH terms/MeSH subheading terms displayed by
151   matrix visualization and mountain visualization. In order to identify the appropriate number of
152   clusters, the biclustering with different numbers of clusters was redirected until the matrix
153   visualization and mountain visualization reached the optimal result. With semantic relationships
154   found between major MeSH terms/MeSH subheading terms and the typical source literatures in
155   clusters, the fundamental structure of our research focus on postmenopausal osteoporosis was
156   mapped and established.

157
158 **Results**
159 **Distribution characteristics of literature**
160
161 **Output of related literature**
162
163 In total, 5,247 literatures comprising 4,466 articles and 781 reviews (Fig.1), were involved in this
164 study based on search strategy and inclusion criteria (Jan. 1st, 2013-Dec. 31st, 2017). The trend
165 in the number of annual publications related to postmenopausal osteoporosis from 2013 to 2017
166 is shown in Fig 2, where you can see the overall trend decreases from 1,071 literatures in 2013 to
167 1,048 literatures in 2017.
168
169 **Distribution characteristics of countries/regions and institutions**
170
171 All of the literatures on postmenopausal osteoporosis contributed by active authors, based on
172 rough statistics, stemmed from at least 81 different countries. The research findings on
173 postmenopausal osteoporosis in different countries or regions are listed in Fig. 3. So far, the
174 United States (1378) has been the largest contributor to postmenopausal osteoporosis research,
175 followed by China (982), Japan (385), England (375), and Italy (352). In regards to the centrality
176 index, although Spain's scientific research output was not very high, it had the largest influence
177 on other countries (centrality=0.14), followed by Australia (0.11) and the United States (0.10)
178 (Table 1). The top 10 related research institutions ordered by the number of published papers
179 included the University of California, San Francisco (131), Columbia University (129), Seoul
180 National University (128), Amgen Inc (126), and Yonsei University (125) (Table 1). The
181 postmenopausal osteoporosis research network map was a low-density map (density=0.0843)
182 (Fig. 4), implying that research groups were relatively dispersed across institutions, and that
183 mutual cooperation still needs to be strengthened. Most centrality indexes were less than 0.15,
184 demonstrating that the influence of most institutions is still at a low level and the amount of
185 cooperation between institutions is inadequate. An analysis of international cooperation is shown
186 in Fig. 5; the most frequent collaboration was between the United States and China, followed by
187 the US and England.
188
189 **Most active journals**
190
191 A total of 1,162 journals have recently emerged in this field. The 10 most active journals
192 published 1,686 publications on postmenopausal osteoporosis, accounting for 32.13% of all
193 5,247 publications. The ranking of the top 10 active journals, which are recognized as the core
194 journals in this field, is shown in Table 2. The top three journals are *Osteoporosis International*,
195 *Bone*, and *Journal of Bone and Mineral Research*, and these three journals make up more than
196 18.27% of the entire indexed literatures in this area. *Journal of Bone and Mineral Research* has
197 the largest IF of 5.711, followed by *Journal of Clinical Endocrinology and Metabolism* (5.605),

198   *Bone* (4.36), *Osteoporosis International* (3.819), and *Maturitas* (3.654). According to the JCR
199   2018 standards, the top 10 most active journals were classified as Q1, sorted by the IF of the JCR
200   category to which they belong.
201
202   **Distribution by author**
203   Of all 19,615 authors included in this subject, the top 10 most productive authors engaged in
204   related research were ranked by the number of published papers. They included Reginster JY,
205   Cooper C, Kanis JA, Lewiecki EM, Rizzoli R, and Eastell R (Table 3). Among them, Reginster
206   JY, from the Department of Public Health, Epidemiology and Health Economics, University of
207   Liège in the Belgium, ranked first with 62 literatures, followed by Cooper C from Nuffield
208   Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford
209   in UK with 51 literatures. These two scholars made great achievements and are authorities in the
210   research of postmenopausal osteoporosis. CiteSpace analyzed the information cited by the
211   authors and co-cited authors, visualizing it in a network (Fig. 6 & 7). Kanis JA, with 1,374 co-
212   citations, ranked first among the top 10 co-cited authors (Table 3), followed by Cummngs SR
213   (991), Black DM (760), and Anonymous (687). These experts conducted a great quantity of
214   research and laid a foundation for the development of the field of postmenopausal osteoporosis.
215   The centrality of the first four authors was more than 0.1, indicating that they had formed an
216   influential core scholar group in the domain of postmenopausal osteoporosis research.
217
218   **Research hot spots of postmenopausal osteoporosis**
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220   In the literature included, 2,439 major MeSH terms/MeSH subheading terms were computed
221   with an accumulated frequency of 9,372 times. After H index standard evaluation, with an
222   appearance of more than 36 times, a major MeSH term/MeSH subheading term was defined as
223   being extremely frequent. Thirty-six extremely frequent major MeSH terms/MeSH subheading
224   terms extracted from the included publications with an accumulated percentage of 38.22%
225   (3582/9372) are displayed in Table 4. Different numbers of clusters were found by biclustering.
226   Mountain visualization and matrix visualization showed the biclustering result of the matrix of
227   source literatures - extremely frequent major MeSH terms/MeSH subheading terms. Mountain
228   visualization and the extremely frequent major MeSH terms/MeSH subheading terms in each
229   cluster classified into eight clusters are illustrated in Fig. 8. The intention of mountain
230   visualization is to visually show the result of biclustering and the essence of high-dimensional
231   datasets. Fig. 8 displays each cluster as a peak in the 3D landform marked with the cluster
232   number (from 0 to 7, a total of eight clusters). The information about the associated cluster was
233   reflected by its location on the plane, altitude, color and volume of its peak. When compared to
234   other peaks, the location on the plane is the most informative attribute of a peak. The relative
235   similarity of clusters is represented by the interval between peaks on the plane. The altitude of a
236   peak is often in direct proportion to the internal similarity of the cluster. The internal standard
237   deviation of objects in each cluster is revealed by the color of each peak. Blue means high
238   deviation, while red means low deviation. Finally, the volume of a peak is in direct proportion to

239   the amount of extremely frequent major MeSH terms/MeSH subheading terms stored within the
240   cluster. Based on the authors' knowledge, a minimum of 30 publications should be contained in
241   each independent cluster and triplet peaks should not appear in the mountain visualization. Fig. 9
242   illustrates the matrix visualization, where the column tags are PMIDs of source literatures, and
243   the row tags are extremely frequent major MeSH terms/MeSH subheading terms, separated on
244   the bottom right of the matrix. The values present in the matrix are graphically represented by
245   colors. The color of each reseau paints the proportional emergence frequency of a major MeSH
246   term/MeSH subheading term in a publication. The cumulatively deeper red indicates greater
247   significance, while the white indicates the significance is closer to none. In Table 5, gCLUTO
248   replumed the rows of the initial matrix so that analogous rows in the same cluster are converged;
249   these clusters are partitioned by black horizontal lines. Thirty-six extremely frequent major
250   MeSH terms/MeSH subheadings terms were clustered into eight clusters in the matrix
251   visualization. The top layered cluster tree describes the relationships among literatures, and the
252   left layered cluster tree demonstrates the relationships among extremely frequent major MeSH
253   terms/MeSH subheading terms. Each cluster also shows which of the major MeSH term/MeSH
254   subheading terms exists in matching literatures. A deeper exploration of the typical literatures in
255   each cluster was conducted to discern between and to outline the themes of each cluster.
256   According to the standards discussed above by the research team, the major MeSH terms/MeSH
257   subheading terms were categorized into eight clusters (Fig. 8). These clusters include:
258   Genetics-related research on bone metabolisms of postmenopausal osteoporosis (Cluster 0),
259   Adverse effects of diphosphonates (Cluster 1),
260   Therapeutic treatment of postmenopausal osteoporosis (Cluster 2),
261   Administration and dosage of Clinical therapy drug——diphosphonates (Cluster 3),
262   Study on epidemiology and etiology of complications of postmenopausal osteoporosis (Cluster
263   4),
264   Physiology and physiopathology of postmenopausal osteoporosis (Cluster 5),
265   Risk factors associated with bone mineral density (BMD) in the diagnosis of postmenopausal
266   osteoporosis (Cluster 6),
267   Clinical drug effects of dietary supplements on postmenopausal osteoporosis (Cluster 7),
268

Discussion

270   According to the statistical and quantitative analysis by the Online Analysis Platform of
271   Literature Metrology, software CiteSpace and BICOMB, the research output on postmenopausal
272   osteoporosis has gradually decreased over the past five years. MeSH terms can represent the
273   content of literatures and a great quantity of MeSH terms can map the current research status and
274   trends of the field. According to a qualitative and co-word biclustering analysis by gCLUTO
275   software, similar MeSH terms can be identified and categorized into clusters. This is how the
276   research hot spots on postmenopausal osteoporosis were generated, making the essential
277   knowledge structure and trends in this field able be examined systematically.

278   Cluster 0 relates to genetic research on bone metabolisms of postmenopausal osteoporosis.
279   Postmenopausal osteoporosis is a common polygenic bone metabolic disease. Genetic factors
280   play an important role in the bone metabolism regulation of postmenopausal osteoporosis. BMD,
281   a crucial risk factor for osteoporosis, is highly genetic with estimates of heritability ranging from
282   0.5 to 0.9. To date, several studies have reported that some functional genes, such as CYP11A1
283   in vitamin D and estrogen hormone-response pathways, the estrogen receptorα (ERα) gene,
284   tumor necrosis factor (TNF)-α gene, and TNFSF11, TNFRSF11A in the RANKL/RANK/OPG
285   pathway, are implied to be associated with BMD in postmenopausal osteoporosis (Tu et al.
286   2015). Exploring different genetic variants underlying the development of osteoporosis would
287   make the early prophylactics of osteoporosis possible, as well as the ability to manage
288   individual-based symptomatic treatment.
289   Cluster 1 relates to adverse effects of diphosphonates. For the treatment of osteoporosis, the
290   most widely used medications are diphosphonates, which are divided into two groups on the
291   basis of their structures. First generation diphosphonates do not contain nitrogen, while new
292   generation diphosphonates have a nitrogen-containing side chain. This structure has a high-
293   affinity for hydroxyapatite at the bone surface, so diphosphonates can preserve for months or
294   even years. After years of evolution, diphosphonates, which include alendronate (ALN),
295   risedronate sodium, ibandronate sodium (IBN) and zoledronic (ZOL), are more durable and
296   stable. The adverse effects of diphosphonates, however, are unavoidable. The first intravenous
297   dose of diphosphonates like IBN and ZOL may trigger an acute-phase response (APR) where
298   after their first diphosphonate infusion, patients have had fevers and pains. Commonly, these
299   symptoms were transient in duration and mild to moderate in intensity, and according to NSAID,
300   the incidence and intensity of such an APR could be efficiently impeded (Ding et al. 2017).
301   Additionally, the atypical femoral fracture (AFF), an unusual atraumatic or minimal-trauma
302   fracture, has also been reported with increasing frequency in long-term diphosphonate users
303   since the first case reports were published in 2005 (Kim et al. 2015). A unique case of AFF after
304   diphosphonate therapy was discovered in 2014, but the patient had a successful recovery through
305   conservative treatment (Pazianas & Smith 2014). To summarize, it is essential to assess the
306   possibility of atypical fractures in osteoporotic patients when they complain about lower
307   extremity pain, and to take into account alternative treatments instead of diphosphonates.
308   Cluster 2 relates to the therapeutic treatment of postmenopausal osteoporosis. Drug therapy
309   for osteoporosis can be divided into antiresorptive agents and anabolic agents. Antiresorptive
310   agents are composed of raloxifene (RAL), diphosphonates, and denosumab. Teriparatide is the
311   only anabolic agent for osteoporosis treatment approved by the Food and Drug Administration.
312   Studies have shown that cortical turnover and cortical bone formation in patients who were either
313   treatment naïve (TN) or had previous ALN therapy increased with 24 months of teriparatide
314   treatment (Ma et al. 2014). In other clinical studies, synergistic effects of combination therapy
315   with an antiresorptive agent and teriparatide have been proposed (Shen et al. 2017). The addition
316   of ALN to ongoing teriparatide treatment, and continuing ALN after teriparatide was stopped
317   may be beneficial for patients in terms of areal and volumetric BMD increase (Muschitz et al.

318   2014). Furthermore, the treatment of combining teriparatide with diphosphonates has shown
319   faster bony unions and highly improved BMD scores (Cho et al. 2017). Although combination
320   therapy has obvious advantages, the best time to start combination therapy should be further
321   studied in order to prevent osteoporotic fractures.
322   Cluster 3 relates to the administration and dosage of diphosphonates. Diphosphonates as an
323   anti-resorptive agent have been accepted for the treatment and prevention of postmenopausal
324   osteoporosis. However, official guidance on the dosage and the length of treatment is lacking,
325   and the curative effect of diphosphonates is not ideal. First, long-term users with 10 dose years or
326   more of a diphosphonates are rare due to periods of low compliance and gaps, with a discrepancy
327   between the length of treatment and doses taken (Abrahamsen 2013). Second, long-term
328   diphosphonate treatment in postmenopausal women does not impair the response to subsequently
329   administered intravenous pamidronate, suggesting that the inadequate response to long-term
330   diphosphonate treatment is not responsible for treatment failure (Yavropoulou et al.
331   2013).What's more, over the past decade, several reports have highlighted the increased risk of
332   AFF in patients treated with long-term diphosphonates. On the basis of this recommendation,
333   patients may be advised to stop taking diphosphonates for a while. Total hip BMD declines
334   significantly within 1 year of discontinuing diphosphonates, particularly in lean patients (Xu et
335   al. 2016). Cluster 1 has narrated the side effects of diphosphonates, and additional studies are
336   needed to identify reasonable treatments using diphosphonates.
337   Cluster 4 relates to the epidemiology and etiology of complications of postmenopausal
338   osteoporosis. The worst complications of postmenopausal osteoporosis are fractures, so the
339   accurate assessment and prediction for the risk of fractures are particularly crucial. DXA had
340   been regarded worldwide as the gold standard for the diagnosis of osteoporosis at the lumbar
341   spine and hip, but BMD reveals only a portion of an individual's fracture risk because of the
342   multi-factor fragility fracture. Additionally, to identify patients with a high risk of fracture, many
343   clinical risk factors must be taken into consideration as well as BMD, increasing the possibility
344   of osteoporotic fractures for high-risky patients. The Fracture Risk Assessment Tool (FRAX),
345   uses nine clinical risk factors to predict an individual 10-year risk of major or hip osteoporotic
346   fractures: age, sex, BMI, prior fragility fracture history, family history of hip fracture, the
347   existence of secondary osteoporosis, exposure to systemic glucocorticoids, current smoking and
348   three or more units of alcohol per day. In addition, the International Osteoporosis Foundation
349   (IOF) One Minute Test, though with the lowest predicting rate when compared to other tested
350   tools, has shown competent prediction precision (Briot et al. 2013; Kharroubi et al. 2017).
351   Moreover, there is an increased risk for hip fracture in postmenopausal women with type 2
352   diabetes (Dytfeld & Michalak 2017). Further etiology studies should be conducted to prevent the
353   occurrence of the complications discussed above.
354   Cluster 5 relates to the physiology and physiopathology of postmenopausal osteoporosis. A
355   strong correlation between BMD scores and the probability of fragility fractures has been well-
356   documented. BMD is affected by multiple factors. Higher BMI scores and moderate levels of
357   physical activity have been found significant in avoiding a decline of BMD (Wee et al. 2013).

358 Life satisfaction and BMD improvement are longitudinally linked with reduced bone loss in
359 postmenopausal women (Rauma et al. 2014).
360   Cluster 6 relates to risk factors associated with BMD in the diagnosis of postmenopausal
361 osteoporosis. With the increasing incidence of postmenopausal osteoporosis, it is important to
362 identify risk factors associated with BMD for the prevention of postmenopausal osteoporosis. As
363 there are many factors causing postmenopausal osteoporosis, it is difficult to accurately pinpoint
364 its risk factors. Exercise is consistently effective in (initially) favorably affecting BMD in early-
365 postmenopausal women without any leveling-off effect after 16 years of exercise (Kemmler et al.
366 2016). Duration of fertility (years of menstruation) longer than 33 years and a BMI greater than
367 32 seem to prevent postmenopausal osteoporosis. Age is also an independent risk factor for
368 postmenopausal osteoporosis (Cavkaytar et al. 2015). When it comes to diagnostic imaging,
369 probabilistic sensitivity analysis, DXA and quantitative CT at 55 years-old with quantitative CT
370 screening every 5 years was the best strategy. Furthermore, a combined assessment of bone
371 strength and BMD is a cost-effective strategy for osteoporosis screening in postmenopausal
372 women and has the potential to prevent a large number of osteoporosis fractures.
373   Cluster 7 relates to the drug effect of alternative therapy— dietary supplements.
374 Pharmacotherapy, diphosphonates for instance, has been widely used to alleviate the risk of
375 fractures and remedy osteoporosis. With low compliance and related adverse effects associated
376 with long-term medication, it is crucial to develop new alternative medicine to treat osteoporosis.
377 Additionally, many people desire alternative and supplemental therapies. A calcium collagen
378 chelate (CC) dietary supplement has shown to be effective in improving BMD and blood
379 biomarkers of bone turnover in osteopenic postmenopausal women (Castelo-Branco 2015; Elam
380 et al. 2015). Context Eucommiae Cortex and Radix Dipsaci, occurring in a ratio of 1:1 in Du-
381 Zhong-Wan (DZW) and Puerarin 600-O-xyloside, also achieved the same effect as above on
382 ovariectomy mice (Li et al. 2016a; Li et al. 2016b). These have provided new ways to treat
383 patients with osteoporosis.
384   Nonetheless, we realize several latent limitations in this study. First, although co-word
385 biclustering, based on extremely frequent MeSH terms, is a highly beneficial way to determine
386 research hot spots in a field, the number of MeSH terms might have some effect on the
387 biclustering analysis results (although the updated emerging themes with low attention may not
388 have been involved). Second, the database updates research continuously, so there may be a
389 discrepancy between bibliometric analysis data and real study conditions, and the number of
390 PMOP papers may grow rapidly with future research breakthroughs.
391
392 **Conclusions**
393
394   Our study found etiology and medication as key points in postmenopausal osteoporosis
395 research. Epidemiology studies developed BMD and FRAX to predict the individual risk of
396 osteoporotic fracture, to summarize high-risk factors associated with PMOP, and to discern
397 between key genes or microenvironmental factors related to PMOP. All these studies laid the

398 foundation of basic research, especially in terms of genetics. Another hot field is drug treatment.
399 After many years of randomized controlled trials (RCT), current anti-osteoclastogenesis drugs
400 and their side effects have been surveyed and evaluated in detail. Teriparatide and some novel
401 medicines with higher efficacy in promoting osteogenesis should be paid more attention from
402 experts and scholars, and dietary supplements would actually be excellent substitutes for drugs
403 because of their accessibility and low toxicity. The aforementioned hot spots might see great
404 scientific breakthroughs in the near future, and our research might reflect a new direction for
405 postmenopausal osteoporosis research.
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Figure 1

Flow chart of literature filtering included in this study.

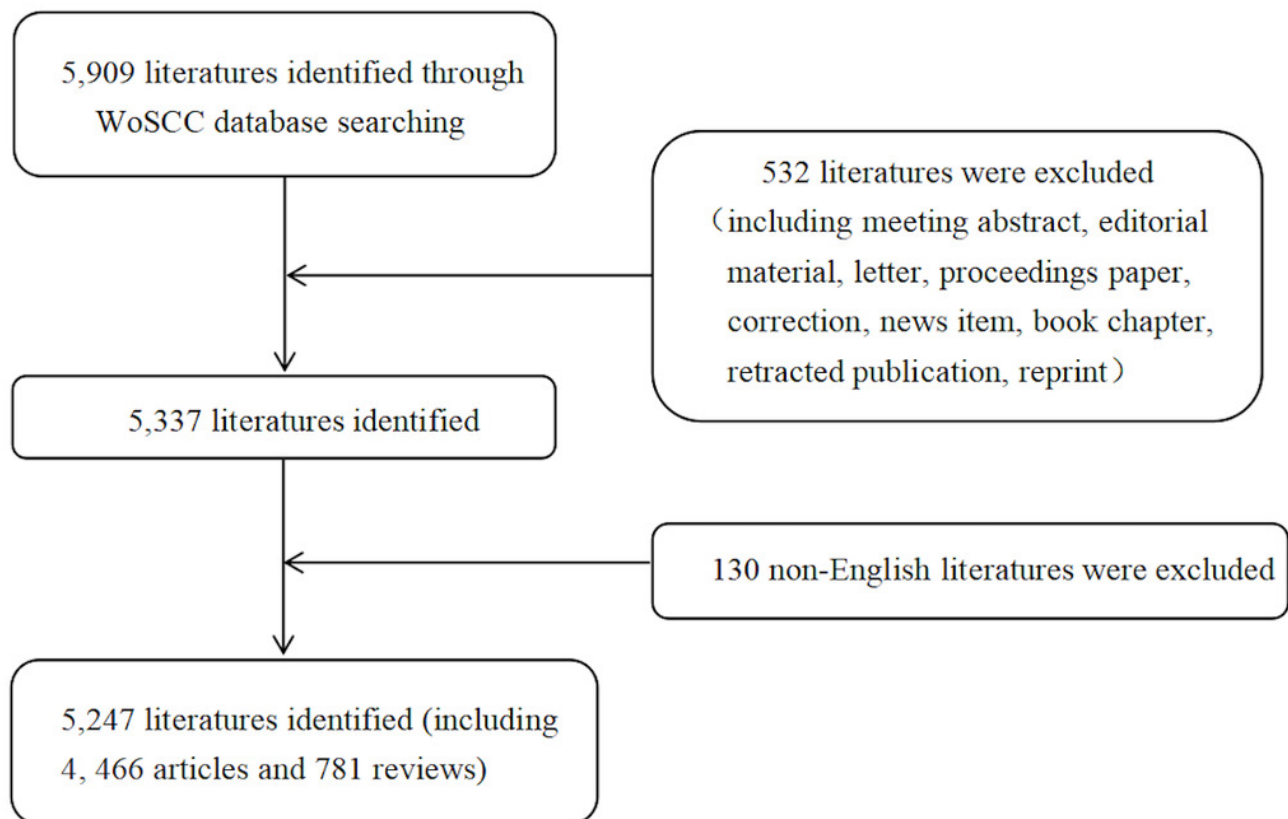



Figure 2

Output of related literature. The number of annual publications in postmenopausal osteoporosis from 2013 to 2017.

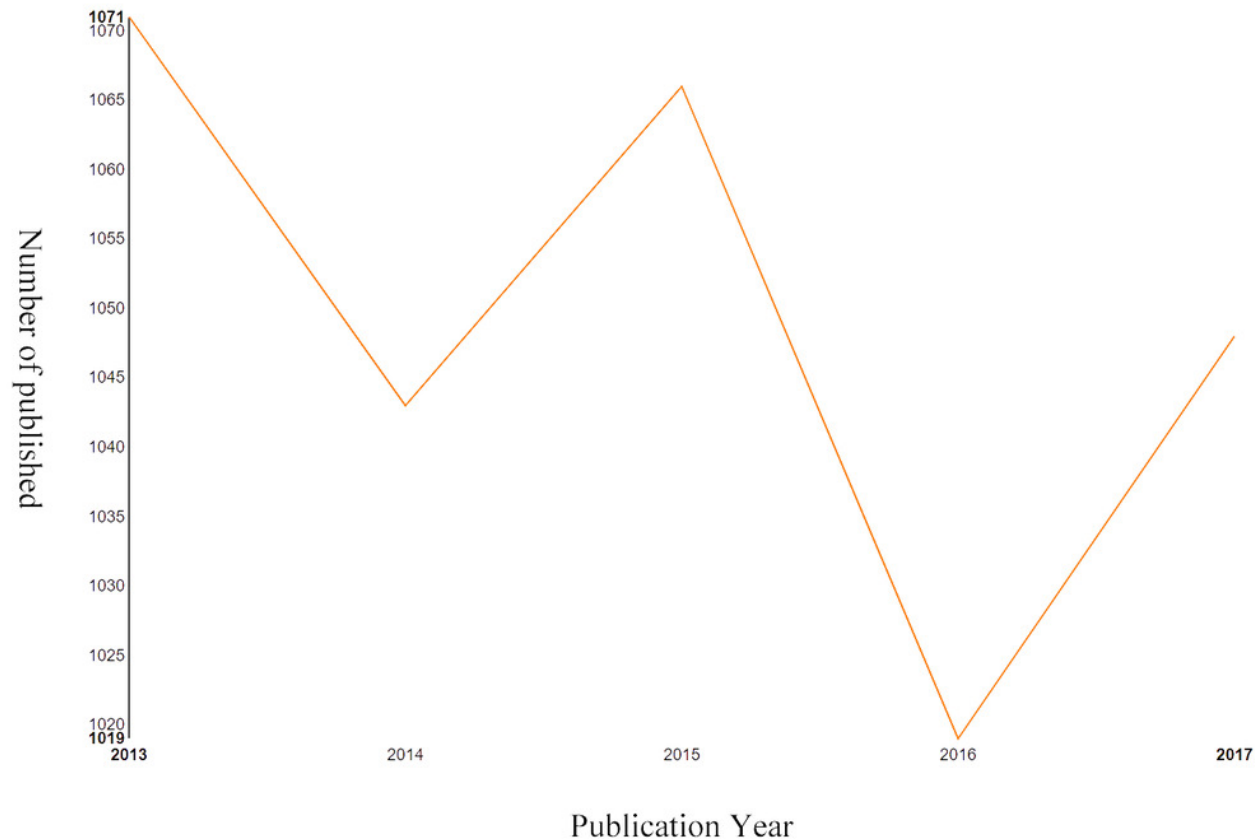



Figure 3

Output of related literature. The growth trends of the top 10 countries/regions in postmenopausal osteoporosis from 2013 to 2017.

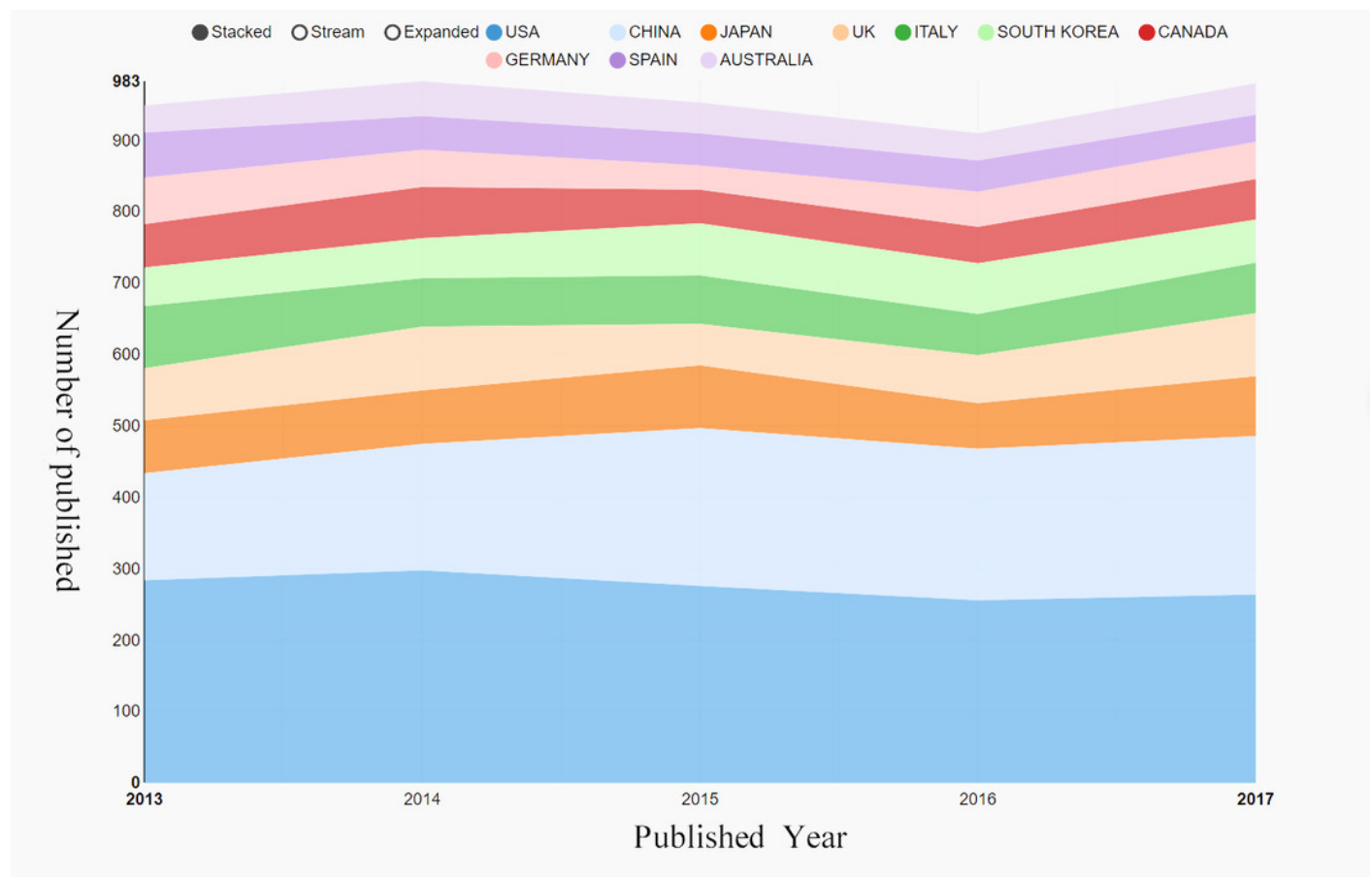



Figure 4

The distribution of countries/regions and institutions. The network map of institutions that involved in postmenopausal osteoporosis research.

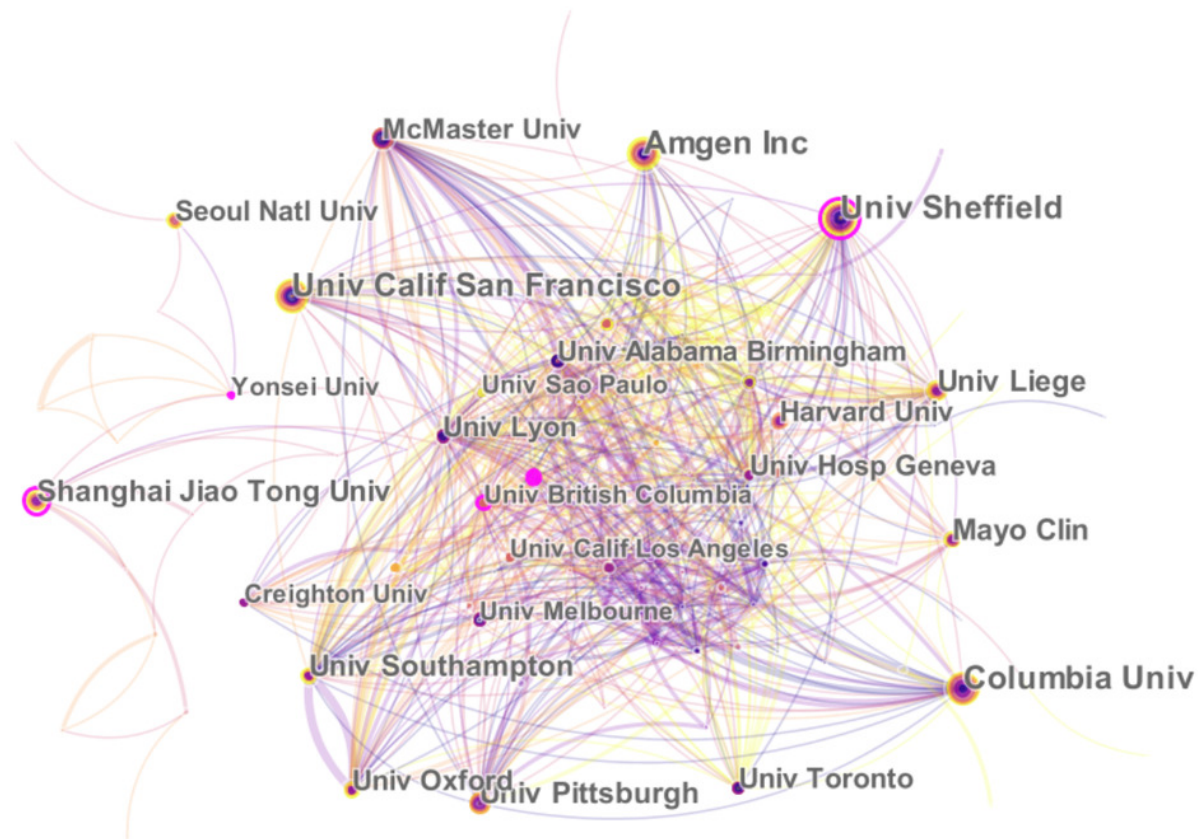



Figure 5

The distribution of countries/regions and institutions. The cooperation of countries/regions that involved in postmenopausal osteoporosis research.

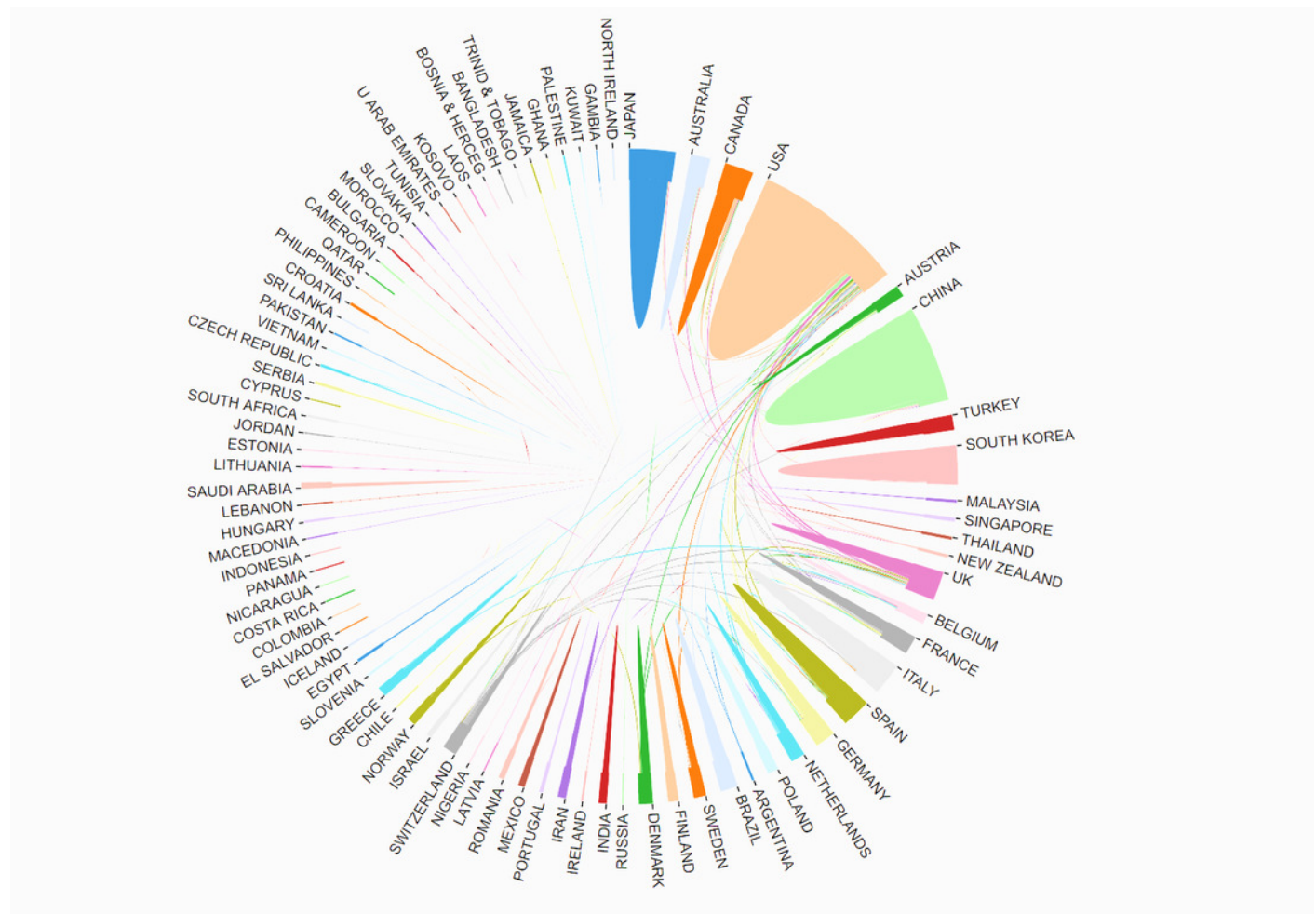



Figure 6

The distribution of authors engaged in postmenopausal osteoporosis research. The network map of productive authors.

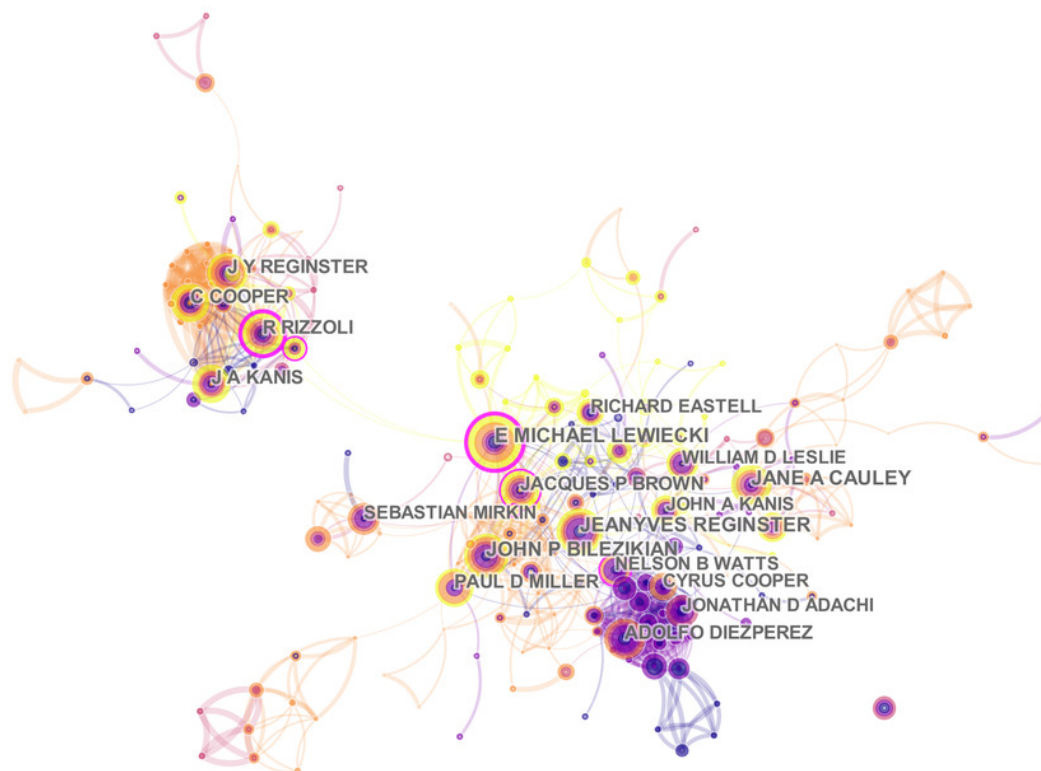



Figure 7

The distribution of authors engaged in postmenopausal osteoporosis research. The network map of co-cited authors.

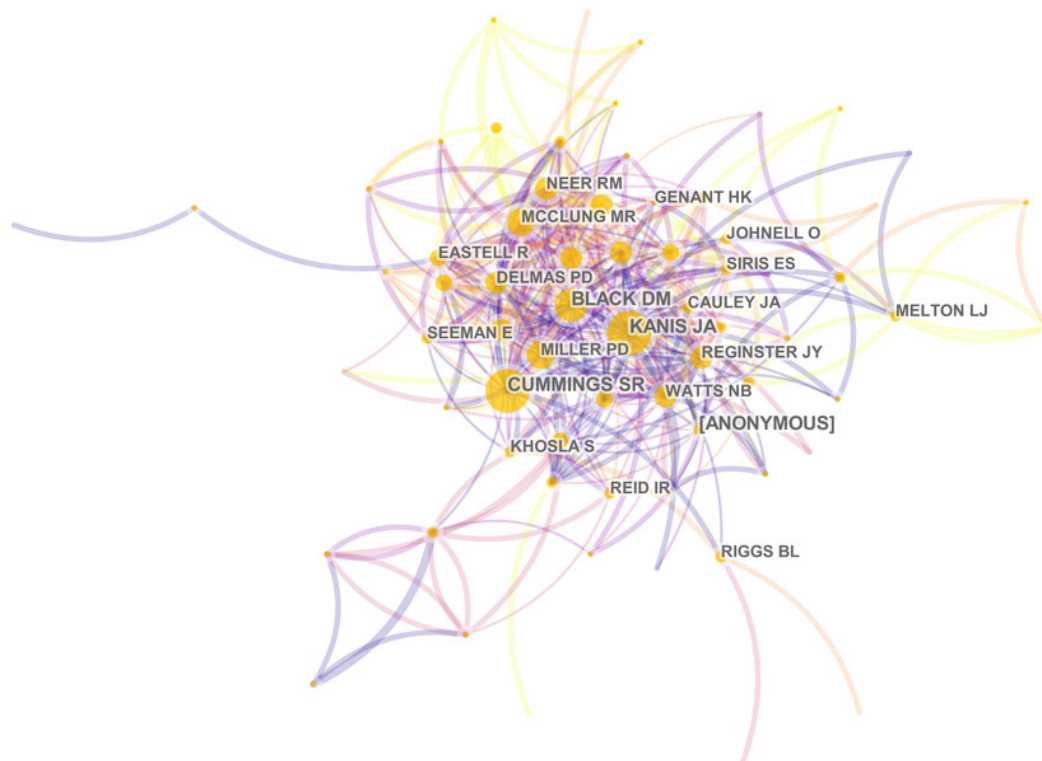



Figure 8

Mountain visualization of biclustering of highly frequent major MeSH terms and articles on postmenopausal osteoporosis

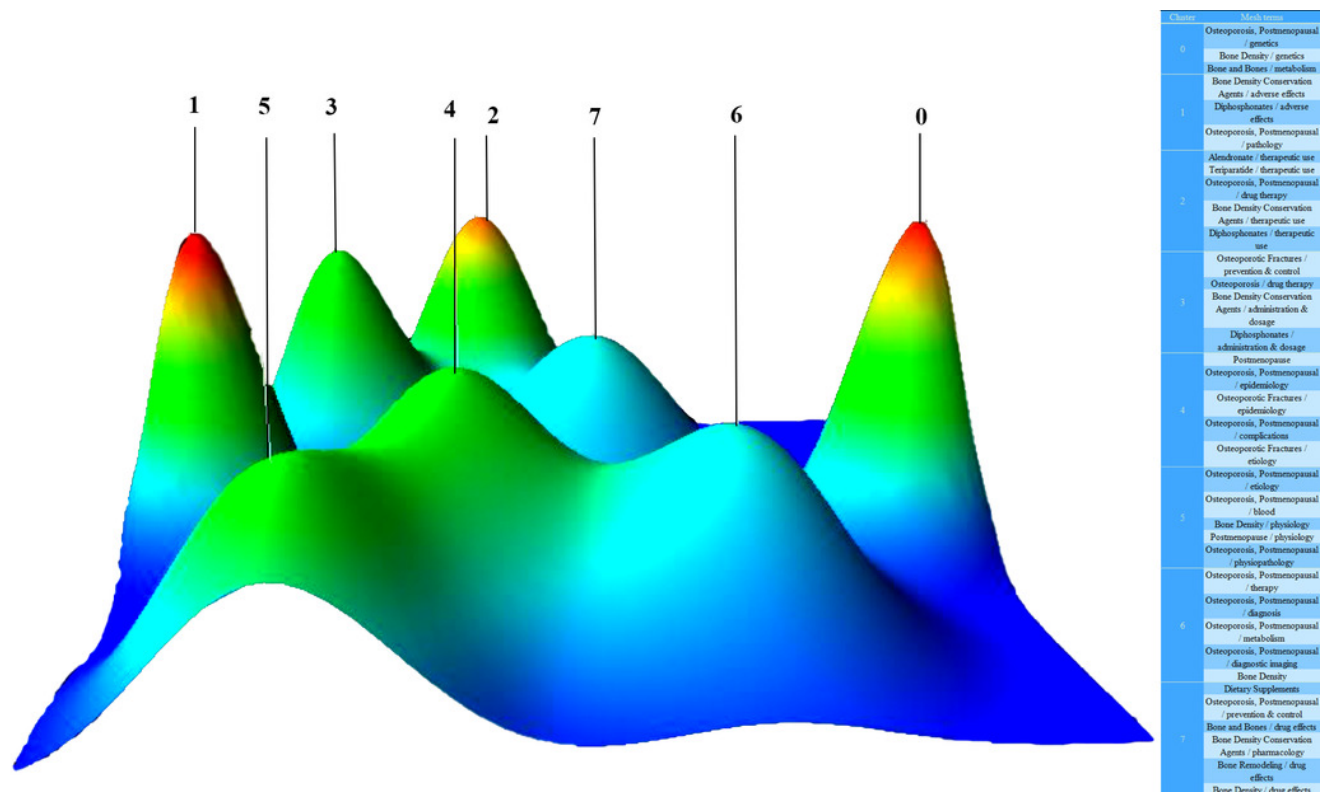
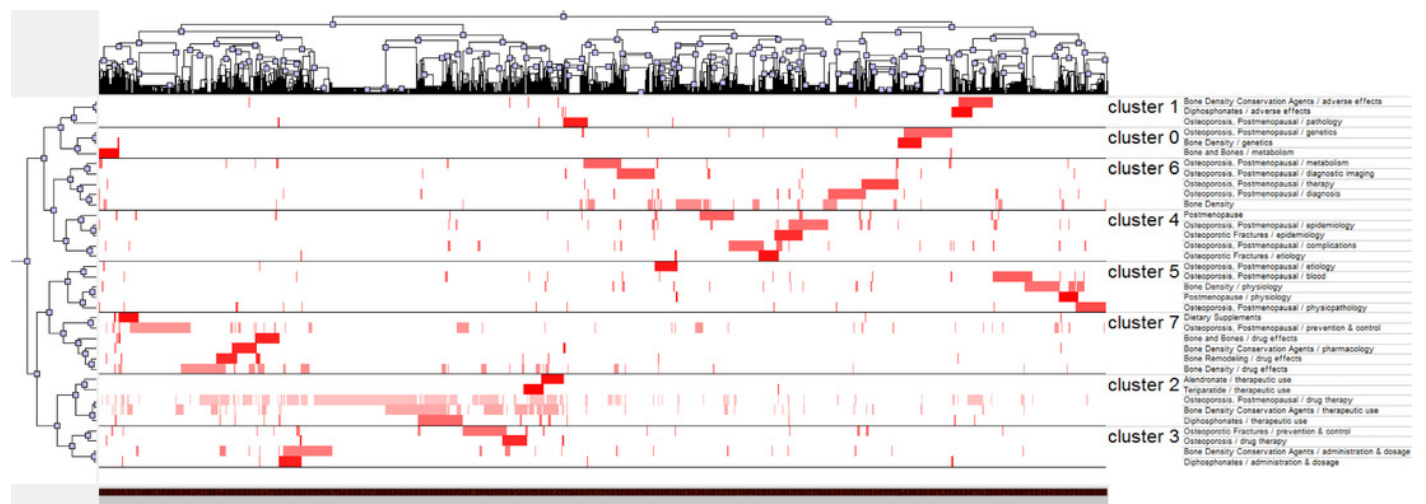



Figure 9

Visualized matrix of biclustering of highly frequent major MeSH terms and PubMed Unique Identifiers (PMIDs) of articles on postmenopausal osteoporosis.

The top 10 countries/regions and institutions contributing to publications in postmenopausal osteoporosis research.

Rank	Country/Region	Article Counts	Centrality	Institutions	Article Counts	Centrality	Total number of citations	Average number of citations	Total number of first authors	Total number of first author citations	Average number of first author citations
1	US	1378	0.10	Univ Calif San Francisco	131	0.08	1133	8.65	30	294	9.8
2	People's Republic of China	982	0.00	Columbia Univ	129	0.04	957	7.42	39	338	8.67
3	Japan	385	0.00	Seoul Natl Univ	128	0.03	203	1.59	35	72	2.06
4	England	375	0.02	Amgen Inc	126	0.05	1087	8.63	18	110	6.11
5	Italy	352	0.01	Yonsei Univ	125	0.15	172	1.38	30	33	1.1
6	South Korea	314	0.00	Mayo Clin	123	0.02	487	3.96	30	92	3.07
7	Canada	288	0.02	Univ Sheffield	115	0.16	1398	12.16	33	170	5.15
8	Germany	252	0.02	Shanghai Jiao Tong Univ	112	0.15	141	1.26	55	74	1.35
9	Spain	237	0.14	Univ Toronto	101	0.02	284	2.81	18	56	3.11
10	Australia	212	0.11	Univ Liege	93	0.02	1145	12.31	28	97	3.46

The top 10 most active journals that published articles in postmenopausal osteoporosis research (sorted by count).

Rank	Journal title	Article Counts	Percentage (N/5,247)	IF(2018)	Quartile in category (2018)	H-index	Total number of citations	Average number of citations
1	OSTEOPOROSIS INTERNATIONAL	497	9.47%	3.819	Q1	157	2175	4.38
2	BONE	238	4.54%	4.36	Q1	183	964	4.05
3	JOURNAL OF BONE AND MINERAL RESEARCH	224	4.27%	5.711	Q1	223	1690	7.54
4	CALCIFIED TISSUE INTERNATIONAL	123	2.34%	3.265	Q1	106	332	2.7
5	JOURNAL OF BONE AND MINERAL METABOLISM	121	2.31%	2.31	Q1	66	218	1.8
6	PLOS ONE	120	2.29%	2.776	Q1	176	179	1.49
7	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	115	2.19%	5.605	Q1	98	778	6.77
8	JOURNAL OF CLINICAL DENSITOMETRY	86	1.64%	2.184	Q1	29	232	2.7
9	MATURITAS	81	1.54%	3.654	Q1	91	291	3.59
10	MENOPAUSE-THE JOURNAL OF THE NORTH AMERICAN MENOPAUSE SOCIETY	81	1.54%	2.942	Q1	93	189	2.33

The top 10 most productive authors and co-cited authors contributed to publications in postmenopausal osteoporosis research.

Rank	Author	Article Counts	Centrality	Total number of citations	Average number of citations	First author counts	First author citation counts	Average first author citation counts	Corresponding author	Corresponding author citation counts	Co-cited author	Citation counts	Centrality
1	Reginster, JY	62	0.01	810	13.06	10	57	5.7	13	75	Kanis JA	1374	0.37
2	Cooper, C	51	0.00	660	12.94	1	13	13	11	75	Cummngs SR	991	0.27
3	Kanis, JA	46	0.02	841	18.28	7	256	36.57	11	279	Black DM	760	0.16
4	Lewiecki, EM	44	0.38	505	11.48	10	45	4.5	19	74	Anonymous	687	0.02
5	Rizzoli, R	42	0.22	456	10.86	10	102	10.2	13	117	Johnell O	534	0.02
6	Eastell, R	39	0.07	280	7.18	5	29	5.8	7	37	Mcclung MR	507	0.08
7	Adachi, JD	38	0.03	181	4.76	1	1	1	1	1	Khosla S	483	0.01
8	Lee, SH	38	0.00	90	2.37	5	8	1.6	7	33	Reginster, JY	449	0.04
9	Brandi, ML	37	0.11	368	9.95	2	3	1.5	11	16	Rjggs BL	438	0.10
10	Miller, PD	36	0.00	306	8.5	9	80	8.89	10	96	Reid IR	428	0.03

Highly frequent major MeSH[1] terms from the included publications on postmenopausal osteoporosis (n=9372).

Rank	Major MeSH terms/ MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
1	Osteoporosis, Postmenopausal / drug therapy	577	6.1566	6.1566
2	Bone Density Conservation Agents / therapeutic use	305	3.2544	9.411
3	Osteoporosis, Postmenopausal / prevention & control	208	2.2194	11.6304
4	Bone Density / drug effects	185	1.974	13.6044
5	Bone Density	172	1.8353	15.4396
6	Bone Density Conservation Agents / administration & dosage	135	1.4405	16.8801
7	Bone Density / physiology	116	1.2377	18.1178
8	Osteoporotic Fractures / prevention & control	113	1.2057	19.3235
9	Osteoporosis, Postmenopausal / epidemiology	110	1.1737	20.4972
10	Osteoporosis, Postmenopausal / complications	104	1.1097	21.6069
11	Diphosphonates / therapeutic use	102	1.0883	22.6953
12	Osteoporosis, Postmenopausal / genetics	96	1.0243	23.7196
13	Osteoporosis, Postmenopausal / diagnosis	94	1.003	24.7226
14	Osteoporosis, Postmenopausal / metabolism	94	1.003	25.7256
15	Postmenopause	92	0.9816	26.7072
16	Osteoporosis, Postmenopausal / blood	91	0.971	27.6782
17	Osteoporosis, Postmenopausal / diagnostic imaging	80	0.8536	28.5318
18	Osteoporosis, Postmenopausal / physiopathology	72	0.7682	29.3
19	Osteoporosis, Postmenopausal / therapy	68	0.7256	30.0256
20	Bone Density Conservation Agents / adverse effects	67	0.7149	30.7405
21	Osteoporotic Fractures / epidemiology	53	0.5655	31.306
22	Bone Remodeling / drug effects	51	0.5442	31.8502
23	Bone Density Conservation Agents / pharmacology	50	0.5335	32.3837
24	Osteoporosis / drug therapy	50	0.5335	32.9172
25	Bone and Bones / drug effects	48	0.5122	33.4294
26	Osteoporosis, Postmenopausal / pathology	47	0.5015	33.9309
27	Diphosphonates / administration & dosage	46	0.4908	34.4217
28	Osteoporosis, Postmenopausal / etiology	43	0.4588	34.8805
29	Bone Density / genetics	43	0.4588	35.3393
30	Osteoporotic Fractures / etiology	41	0.4375	35.7768
31	Dietary Supplements	40	0.4268	36.2036

32	Alendronate / therapeutic use	40	0.4268	36.6304
33	Diphosphonates / adverse effects	39	0.4161	37.0465
34	Postmenopause / physiology	37	0.3948	37.4413
35	Bone and Bones / metabolism	37	0.3948	37.8361
36	Teriparatide / therapeutic use	36	0.3841	38.2202

Highly frequent major MeSH a terms-source articles matrix (localized).

No.	Major MeSH terms / MeSH subheadings	Pubmed Unique Identifiers of source articles				
☐	☐	21631599	22057139	22302614	...	29782125
1	Osteoporosis, Postmenopausal / drug therapy	0	0	0	...	0
2	Bone Density Conservation Agents / therapeutic use	0	0	0	...	0
3	Osteoporosis, Postmenopausal / prevention & control	1	0	1	...	0
4	Bone Density / drug effects	0	0	1	...	0
...	...	...	...	...	...	...
35	Bone and Bones / metabolism	0	0	0	...	0
36	Teriparatide / therapeutic use	0	0	0	...	0