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Polycystic ovary syndrome: analysis of the global research architecture using density equalizing mapping

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KEY MESSAGE

This study provides the first analysis of polycystic ovary syndrome (PCOS) research activities. The scientific architecture differs from other gynaecologic disorders. The top 10 performers in PCOS research include established nations, e.g. the USA and UK, and also a unique set of countries such as Turkey, China and Greece.

A B S T R A C T

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility worldwide. Although the related research output is constantly growing, no detailed global map of the scientific architecture has so far been created encompassing quantitative, qualitative, socioeconomic and gender aspects. We used the NewQIS platform to assess all PCOS-related publications indexed between 1900 and 2014 in the Web of Science, and applied density equalizing mapping projections, scientometric techniques and economic benchmarking procedures. A total of 6261 PCOS-specific publications and 703 international research collaborations were found. The USA was identified as the most active country in total and collaborative research activity. In the socioeconomic analysis, the USA was also ranked first (25.49 PCOS-related publications per gross domestic product [GDP]/capita), followed by the UK, Italy and Greece. When research activity was related to population size, Scandinavian countries and Greece were leading the field. For many highly productive countries, gender analysis revealed a high ratio of female scientists working on PCOS with the exception of Japan. In this study, we have created the first picture of global PCOS research, which largely differs from other gynaecologic conditions and indicates that most related research and collaborations originate from high-income countries.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among females of reproductive age. According to National Institutes of Health criteria, the condition affects between 6% and 10% of women worldwide, with similar prevalences across the globe (Asuncion et al., 2000; Azziz et al., 2004; Mortada and Williams, 2015; Palomba et al., 2015). Stein and Leventhal first recognised PCOS in 1935 (Palomba et al., 2015). It is a complex genetic and heterogeneous condition, which is characterized by androgen excess leading to hyperandrogenism, e.g. hirsutism, ovulatory dysfunction and polycystic ovaries (Khadilkar, 2016; Kollmann et al., 2016; Mortada and Williams, 2015; Palomba et al., 2015; Qi et al., 2016; Zuo et al., 2016). The Rotterdam criteria are a widely used diagnostic tool (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, 2004b). At least two of the following three features are required for diagnosis: chronic oligoovulation or anovulation, clinical, biochemical hyperandrogenism, or both, and polycystic ovaries on ultrasonography (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, 2004b; Mortada and Williams, 2015; Palomba et al., 2015).

Physical and emotional health can be affected by PCOS in a number of ways: the condition is a prevalent cause of subfertility and infertility as a result of anovulation (Goodarzi et al., 2011). Affected women are at risk for type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease and endometrial cancer (Mortada and Williams, 2015; Palomba et al., 2015). Also, the clinical picture of PCOS differs depending on the geographic, socioeconomic and sociocultural background of the patient (Schmid et al., 2004a; Di Fede et al., 2009). For example, high socioeconomic status is associated with increased rates of 'ovulatory PCOS'. This phenotype is defined as hyperandrogenism in concert with regular menstrual cycles. Di Fede et al. (2009) linked this observation to differences in insulin levels and the quantity and distribution of adipose tissue. Also, researchers analysed psychosocial parameters related to infertility in patients with PCOS with different socio-cultural backgrounds (Schmid et al., 2004a, 2004b). In an Austrian study, immigrant Muslim women experienced a very high reproductive pressure and level of suffering from PCOS-related infertility compared with local Austrian women (Schmid et al., 2004b). In this context, Iran is an example of the affect of distinct area-specific, sociocultural issues as a driving force for related research. In the past decade, scientific endeavours related to PCOS were boosted in this nation leading to multiple country-specific studies such as an Iranian version of the modified PCOS health-related quality-of-life questionnaire (Bazarganipour et al., 2012; Khomami et al., 2015; Taghavi et al., 2015).

Although substantial progress has been achieved in investigating the pathogenesis, pathophysiology and related societal aspects of PCOS over the past decades, it is still the most enigmatic, complex and multifaceted disorder in the field of gynaecology. Numerous unresolved issues require investigation (Bachanek et al., 2015; Casarini et al., 2016; Palioura and Diamanti-Kandarakis, 2015; Singh and Singh, 2015). Therefore, multidisciplinary, translational and clinical research is needed to advance the field. Scientometric approaches are helpful in planning research strategies so they meet identified shortcomings and to supply decision makers with information concerning funding strategies. These analytic procedures evaluate the growing body of literature related to a specific field in quantitative and qualitative measures and identify countries and institutions producing scientific work with outstanding relevance to the field. In this context, it is the objective of this study to assess the scientific performance on PCOS. The 'New Quality and Quantity Indices in Science' (NewQIS) platform (Groneberg-Kloft et al., 2009a, 2009b) used here combines scientometric tools and advanced density equalizing mapping procedures (Gastner and Newman, 2004) to assess and depict the global PCOS research architecture as well as to evaluate related scientific productivity in the context of geographical, socioeconomic and gender aspects.

Materials and methods

NewQIS protocol

We used the NewQIS platform to identify PCOS-related research among the extensive amount of biomedical publications in a validated, reliable and standardized way (Groneberg-Kloft et al., 2009a, 2009b). The method encompasses the use of advanced visualization algorithms based on Gastner and Newman's density equalizing calculations and scientometric tools to evaluate PCOS-associated research activity in terms of quantitative and qualitative aspects, geographical and chronological developments, existing research networks and socioeconomic benchmarks (Bruggmann et al., 2016a, 2016b, 2016c, 2016d; Groneberg-Kloft et al., 2009a, 2009b, 2013).

Data source

As previously described (Gerber et al., 2013, 2014; Kusma et al., 2009), the database Web of Science (WoS, Thomson Scientific) was used for data collection. We based this study on this particular resource because WoS provides the unique opportunity to analyse the global publication activity and also allows an in-depth citation analysis. Using this unique feature, we calculated combined semi-qualitative country- and PCOS-specific indices, such as the modified h-indices or average citation rates.

Search strategy

The following search term was used to identify PCOS-related research: TITLE = (PCOS OR polycystic ovar* OR stein-leventhal OR sclerocystic ovar*). We examined the time period from 1900 to 2015; items published in 2016 were excluded from the search as collection of related data, e.g. citations, would not have been completed at the time the study was carried out. The aforementioned search term was entered as described previously (Bruggmann et al., 2016a, 2016b, 2016c, 2016d; Groneberg et al., 2016; Quarcoo et al., 2015; Scutaru et al., 2010). We restricted our investigation to ARTICLES and performed a TITLE in contrast to a TOPIC search to ensure the identification of original research studies only and to minimize the inclusion of unspecific publications compromising the validity of our analysis.

Data analysis and categorization

The exact bibliographic details of all PCOS-related publications were sorted after retrieval of the file metadata and analysed according to numerous criteria (Groneberg et al., 2015; Ohlendorf et al., 2015; Scutaru et al., 2010). These included the following: originating countries, languages, document types, citations, cited references, year published and subject categories for all PCOS-related publications.

From these metadata, PCOS research-specific, country-specific h-indices were constructed. The h-index was developed by Jorge Hirsch in 2005 for the assessment of scientific quality, was applied here to assess country-specific PCOS research and termed modified h-index (Hirsch, 2005; Kusma et al., 2009). We used a regression analysis aiming to explore the chronologic evolution of the total global PCOS research output, and calculated the coefficient of determination (r^2).

Density equalizing mapping procedures

The core feature of the NewQIS programme is to generate world maps representing quantitative and qualitative variables of our analysis by the use of density-equalizing mapping procedures (DEMP) (Groneberg-Kloft et al., 2009). After the transfer of the meta data to excel charts and parameter analysis, PCOS-specific DEMP calculations were constructed referring to algorithms published by Gastner and Newman (Gastner and Newman, 2004). In the present case, the territories of the different PCOS research-publishing countries were separated from each other and resized in proportion to the selected PCOS research-specific criteria, i.e. PCOS-specific country h-indices.

Economic analysis

In order to assess the contributions of highly productive nations in relation to their socioeconomic status, the countries' GDP were related to their PCOS research activities. Economic facts were obtained from the *World Economic Outlook Database* of the International Monetary Fund (2015). Countries were distinguished into high-income, upper and lower middle-income as well as in low-income countries according to the definition of the World Bank (www.data.worldbank.org/country).

Gender analysis

We identified the gender of authors publishing on PCOS through online databases. If first names were not gender-specific or quoted as initials, an additional search was conducted involving websites, corresponding addresses and social networks. To ensure data validity, we applied specific thresholds regarding the number and identifiability of publishing authors affiliated with the countries and subject areas investigated.

Analysis of PCOS research collaborations

To analyse PCOS research collaborations from a global viewpoint, the affiliations of all authors stated on each PCOS article were investigated as previously described for other diseases and chart diagrams were constructed (Bruggmann et al., 2015a, 2015b; Carl et al., 2014; Groneberg et al., 2011).

Results

Density equalizing mapping

Between 1900 and 2015, a total of 6261 publications were identified. The first item on PCOS was published in 1938. From the late 1990s and onwards, more than 100 publications were authored continuously each year. After 2006, we found more than 200 articles per year, and from 2012 onwards more than 400 per year (**Figure 1**). Regression analysis from 1955–2015 indicated a regression quotient of $r^2 = 0.7108$.

In the country-specific analysis, authors from 79 nations participated in PCOS research, with scientists from the USA displaying the highest PCOS publication activity with a total of 1397 PCOS-related articles. They were followed by the UK with 578 publications, Italy (*n* = 519), Turkey (*n* = 510), China (*n* = 455), Greece (*n* = 244), Australia (*n* = 192), Germany (*n* = 185), Iran (*n* = 176), Canada (*n* = 169), the Netherlands (*n* = 151), and Japan (*n* = 150). Accordingly, DEMP analysis demonstrates a distortion of the world map with a focus on Northern America, Europe including Turkey and Asia with China, Japan and Australia (**Figure 1**).

The total citation analysis also revealed a leading position of the USA, with 59,862 citations of PCOS-specific publications. The USA was followed by the UK (24,201 citations), Italy (13,606 citations), Australia (7794 citations), and Turkey (7044 citations) (**Figure 2**). We investigated the PCOS-specific h-index for each country. This parameter again showed a leading position of the USA with an h-index of 119, followed by the UK (84), Italy (55), Australia (43), Canada (42), Greece (42), the Netherlands (39), Germany (39), Turkey (38) and Finland (38).

For the analysis of the citation rate (average citations per PCOS publication), we evaluated only countries in which affiliated authors published a minimum of 30 PCOS-specific articles to ensure validity of our data. The Netherlands was leading the field with 45.67 citations per article, followed by the USA (42.85), the UK (41.87), Australia (40.59), Finland (37.85) and Canada (37.26) (**Figure 2**).

Socioeconomic analysis of PCOS research

Research activities of the leading countries were compared according to established and relevant socioeconomic parameters (**Table 1**). The ratio of the number of PCOS-related articles to the GDP of each country (in 1000 billion US dollars) served as an indicator for total economic strength and the capability of a country to invest in research. This index was defined as the socioeconomic PCOS-Index 1. Among high-income countries, Greece was ranked first with 244 PCOS-related research papers and a calculated socioeconomic PCOS-Index 1 of 1025.21. It was followed by Slovenia (747.32), Finland (387.17) and Israel (371.96). The socioeconomic PCOS-Index 1 of 196.26 was found for the UK, and 80.20 for the USA. In the upper-middle-income country ranking, Serbia was ranked first with a socioeconomic PCOS-Index 1 of 1162.53, followed by Turkey (632.68) and Iran (435.54). Only two lower-middle-income countries were documented among the 40 most productive nations. Here, Egypt had a socioeconomic PCOS-Index 1 of 307.26 and was ranked first followed by India (55.61). No low-income countries published on PCOS.

When the economic strength of a country was analysed by the use of GDP per capita, and these data related to the total number of published articles to evaluate the socioeconomic PCOS-Index 2, high-income countries were leading the field: the USA was ranked first with a socioeconomic PCOS-Index 2 of 25.49, followed by the UK (15.33), Italy (15.04) and Greece (9.46) (**Table 1**).

Country-specific publications on PCOS were related to population size (per 1 million people) to create the socioeconomic PCOS-Index 3. It reflects manpower and the size of the active research community involved in PCOS research. Here, Greece was ranked in first position as the most active high-income country with a socioeconomic PCOS-Index 3 of 22.66, followed by Finland (19.96), Slovenia

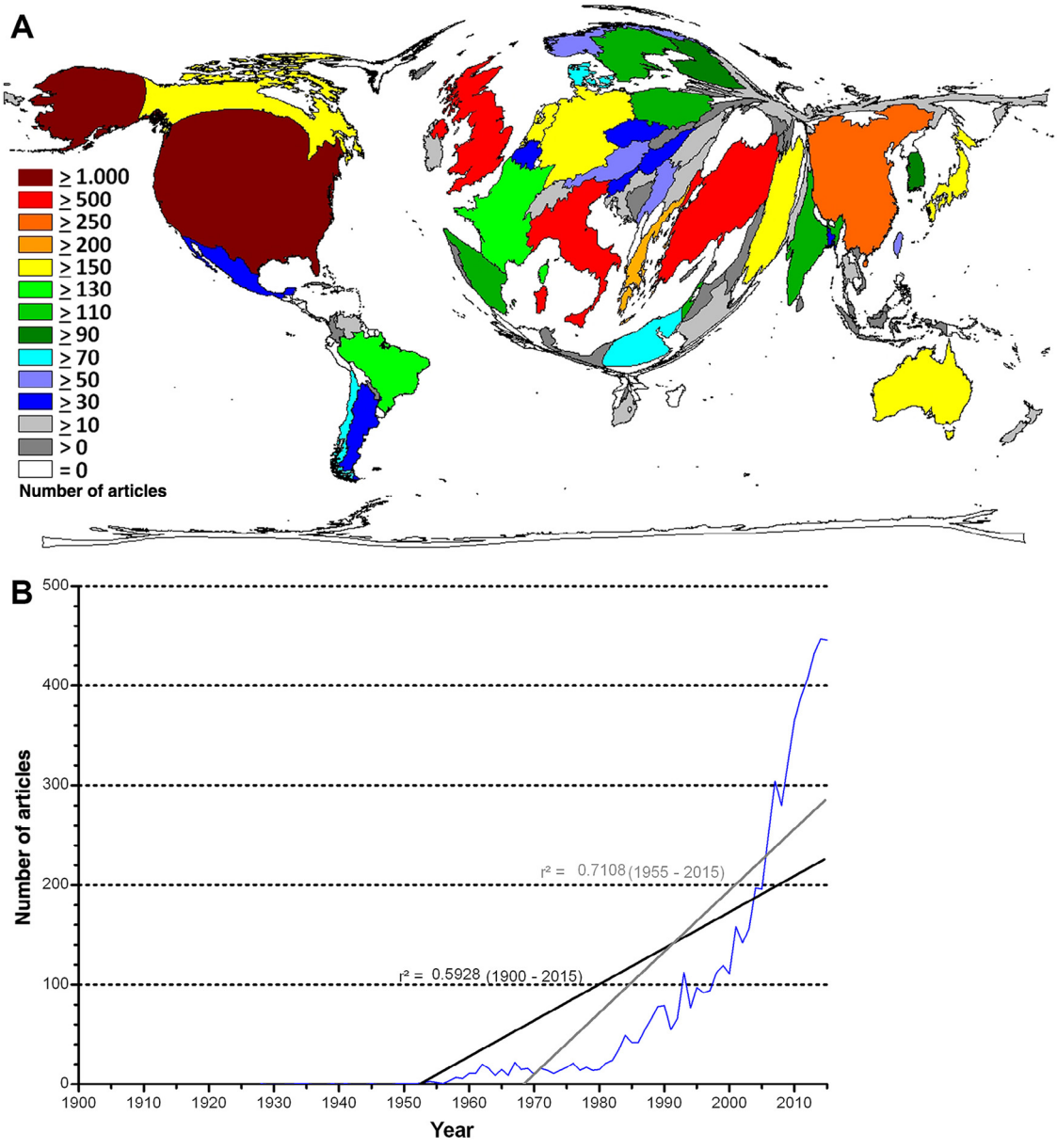

Figure 1 – Research output of articles on polycystic ovary syndrome (PCOS). (A) Density equalizing map of the global PCOS research activity. Colours and territorial sizes indicate numbers of publications on PCOS per country; (B) number of published items per year.

(18.69), Israel (14.45), Denmark (14.03) and Sweden (13.07) (**Figure 3**). In the upper-middle-income country ranking, Serbia was ranked first with a socioeconomic PCOS-Index 3 of 7.08, followed by Turkey (6.25) and Iran (2.18). China had a value of socioeconomic PCOS Index 3 of 0.34 (**Table 1**).

PCOS subject area analysis

We analysed the percentage distribution of the subject areas attributed to PCOS research: the leading subject categories were 'obstetrics and gynaecology', 'endocrinology and metabolism', and 'reproductive biology'. When the chronological evolution of the subject areas was analysed between 1966 and 2015, the percentage of the category 'reproductive biology' increased, particularly after 1990. Also, the field diversified between 2011 and 2015 and a set of quantitatively smaller, other subject areas (e.g. 'nutrition and dietetics' or 'neurosciences and neurology') emerged and totalled more than 15% (**Figure 4**). When the subject area analysis was conducted for the 10 most active countries in PCOS research, the relative contributions of the major three subject areas were approximately constant in all countries. Australia and Canada showed a slightly higher interest in 'reproductive biology' issues compared with Iran or Turkey (**Figure 4**).

International PCOS collaborations

A total of 703 international collaborations were identified that participated in publishing all 6261 PCOS-related articles. The USA was the most active nation, with 307 collaborations, followed by the UK (161 collaborations) and Italy (101 collaborations). Most prolific

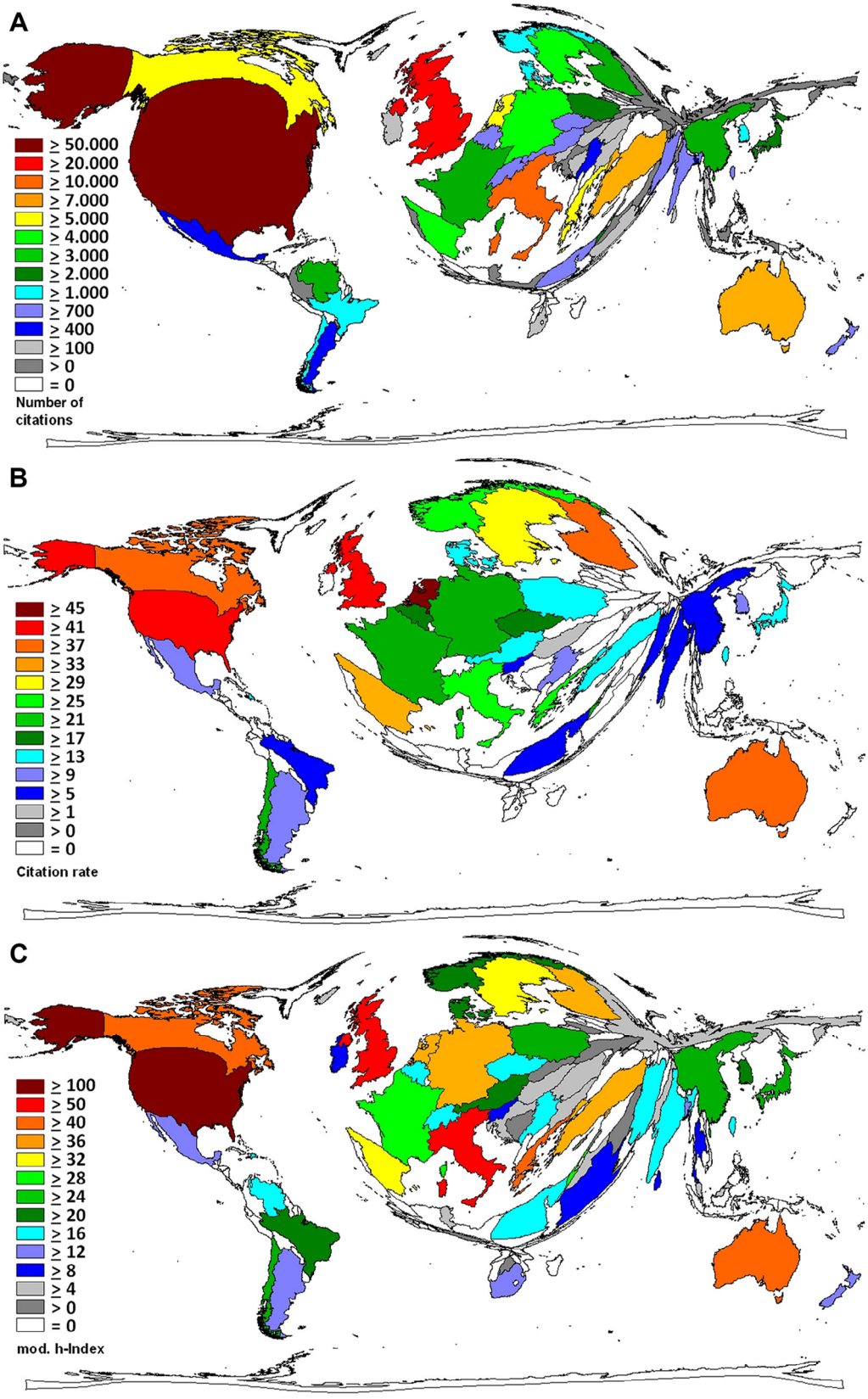

Figure 2 – Density equalizing maps of the global polycystic ovary syndrome (PCOS) research citation parameters. (A) Number of citations per country; (B) citation rates per country (threshold of 30 publications); (C) modified h-indices per country. Colours and territorial sizes indicate the value of the respective parameter.

Table 1 – Socioeconomic analysis of the most active countries researching polycystic ovary syndrome. Sources for GDP (Current Prices in 1000 Billion US Dollars) and gross domestic product per capita (Current Prices in 1000 US Dollars).[a]

Country	Number of PCOS articles	GDP in billions USD	GDP in 1000 billions USD	GDP per Capita	Population, total in millions.	Articles/GDP in 1000 billions USD	Rank 1	Articles / GDP per Capita	Rank 2	Articles/ population in millions.	Rank 3
Serbia	51	43.87	0.04387	12.5	7.2	1162.53	UMI1	4.08	UMI5	7.08	UMI1
Greece	244	238	0.238	25.8	10.77	1025.21	HI1	9.46	HI4	22.66	HI1
Slovenia	37	49.51	0.04951	29.4	1.98	747.32	HI2	1.26	HI24	18.69	HI3
Turkey	510	806.1	0.8061	19.6	81.61	632.68	UMI2	26.02	UMI2	6.25	UMI2
Iran	176	404.1	0.4041	16.5	80.84	435.54	UMI3	10.67	UMI3	2.18	UMI3
Finland	105	271.2	0.2712	40.5	5.26	387.17	HI3	2.59	HI17	19.96	HI2
Israel	113	303.8	0.3038	33.4	7.82	371.96	HI4	3.38	HI13	14.45	HI4
Chile	82	258	0.258	23.2	17.36	317.83	HI5	3.53	HI12	4.72	HI15
Egypt	88	286.4	0.2864	11.1	86.89	307.26	LMI1	7.93	LMI2	1.01	LMI1
Italy	519	2148	2.148	34.5	61.68	241.62	HI6	15.04	HI3	8.41	HI11
Hungary	33	137.1	0.1371	24.3	9.91	240.70	HI7	1.36	HI22	3.33	HI21
Poland	129	546.6	0.5466	24.4	38.34	236.00	HI8	5.29	HI5	3.36	HI19
Denmark	78	340.8	0.3408	44.3	5.56	228.87	HI9	1.76	HI19	14.03	HI5
Sweden	127	570.1	0.5701	44.7	9.72	222.77	HI10	2.84	HI15	13.07	HI6
UK	578	2945	2.945	37.7	63.74	196.26	HI11	15.33	HI2	9.07	HI8
Czech Republic	38	205.7	0.2057	28.4	10.62	184.74	HI12	1.34	HI23	3.58	HI18
Netherlands	151	866.4	0.8664	47.4	16.87	174.28	HI13	3.19	HI14	8.95	HI9
Austria	62	437.1	0.4371	45.4	8.22	141.84	HI14	1.37	HI21	7.54	HI12
New Zealand	28	198.1	0.1981	35	4.4	141.34	HI15	0.80	HI28	6.36	HI13
Australia	192	1444	1.444	46.6	22.5	132.96	HI16	4.12	HI7	8.53	HI10
Norway	63	500.2	0.5002	65.9	5.14	125.95	HI17	0.96	HI27	12.26	HI7
Taiwan	61	529.6	0.5296	43.6	23.35	115.18	HI18	1.40	HI20	2.61	HI22
Romania	22	200	0.2	19.4	21.72	110.00	UMI4	1.13	UMI8	1.01	UMI4
Venezuela	20	205.8	0.2058	17.9	28.86	97.18	HI19	1.12	HI25	0.69	HI30
Canada	169	1789	1.789	44.5	34.83	94.47	HI20	3.80	HI9	4.85	HI14
Spain	119	1407	1.407	33	47.73	84.58	HI21	3.61	HI11	2.49	HI23
USA	1397	17420	17.42	54.8	318.9	80.20	HI22	25.49	HI1	4.38	HI16
Belgium	41	534.7	0.5347	41.7	10.44	76.68	HI23	0.98	HI26	3.93	HI17
Argentina	40	540.2	0.5402	22.1	43.02	74.05	HI24	1.81	HI18	0.93	HI28
South Korea	98	1410	1.41	35.4	49.03	69.50	HI25	2.77	HI16	2.00	HI26
Brazil	146	2353	2.353	15.2	202.6	62.05	UMI5	9.61	UMI4	0.72	UMI5
Thailand	22	373.8	0.3738	14.4	67.74	58.86	UMI6	1.53	UMI7	0.32	UMI7
India	114	2050	2.05	5.8	1236.3	55.61	LMI2	19.66	LMI1	0.09	LMI2
France	147	2847	2.847	40.4	66.25	51.63	HI26	3.64	HI10	2.22	HI25
Germany	185	3860	3.86	44.7	80.99	47.93	HI27	4.14	HI6	2.28	HI24
China	455	10380	10.38	12.9	1355.7	43.83	UMI7	35.27	UMI1	0.34	UMI6
Switzerland	27	712.1	0.7121	55.2	8.06	37.92	HI28	0.49	HI29	3.35	HI20
Japan	150	4616	4.616	37.8	127.1	32.50	HI29	3.97	HI8	1.18	HI27
Saudi Arabia	22	752.5	0.7525	52.8	27.34	29.24	HI30	0.42	HI30	0.80	HI29
Mexico	35	1283	1.283	17.9	120.28	27.28	UMI8	1.96	UMI6	0.29	UMI8

[a] International Monetary Fund.

HI, high-income country; GDP, gross domestic product; UMI, upper-middle-income country; LMI, lower-middle-income country; USD, US dollar.

bilateral collaborations were found between the USA and Italy, the USA and Canada as well as Sweden and China (**Figure 5**).

Gender analysis

In order to analyse gender aspects of the scientific workforce that carried out PCOS research, country-specific and subject area-specific gender ratios were calculated for the most productive countries. In the country-specific analysis (thresholds: 75% gender determination rate of authors, a minimum of 100 authors publishing on PCOS), it was found that the most active country, the USA, had a higher percentage of female scientists compared with male researchers involved in PCOS research (391 females versus 315 males represented by the female to male of 1.24). Also, the female to male ratios in Brazil (1.30) and Iran (1.07) were characterized by a positive female to male ratio that indicated an overrepresentation of female authors in these countries. By contrast, Turkey had a clear dominance of male scientists involved in PCOS research with a female to male ratio of 0.77 (**Figure 6**).

In the subject area-specific gender analysis (thresholds: 50% determination rate, 250 authors), all major subject areas had a dominance of male scientists with the female to male ratio of 0.86 calculated for 'obstetrics and gynecology', 0.91 for 'endocrinology and metabolism', and 0.75 for 'reproductive biology', respectively. Only in the quantitatively small areas of 'paediatrics' and 'nutrition and dietetics', we identified a trend towards female scientists involved in PCOS research with the female to male ratios calculated at 1.29 and 1.26, respectively (**Figure 6**).

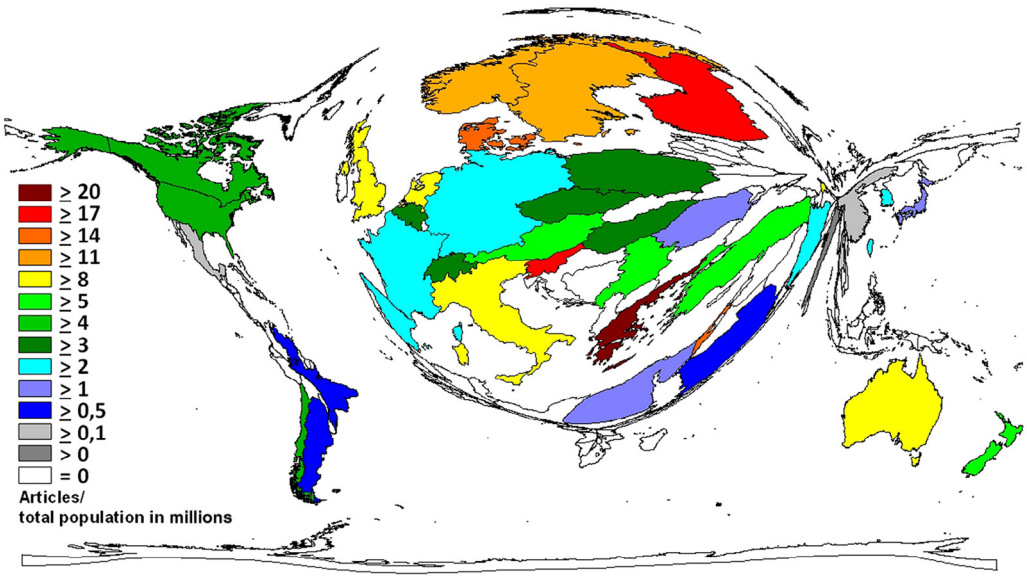

Figure 3 – Density equalizing map of the country-specific articles on polycystic ovary syndrome (PCOS) related to size of population (socioeconomic PCOS index 3). Colours and territorial sizes indicate level of socioeconomic PCOS index 3. Thresholds: more than 20 articles.

Discussion

Stein and Leventhal first described PCOS in 1935, when they reported seven clinical cases with amenorrhoea, hirsutism, obesity and a characteristic polycystic appearance of the ovaries (Ehrmann, 2005). Once underestimated as a condition merely affecting fertility or the physical appearance, PCOS is now recognized as a serious disorder with substantial burden on reproductive, emotional and metabolic health of women around the world. A PCOS-related research output has been constantly growing since 1938, many unsolved questions remain (Abu Hashim, 2016; Facchinetti et al., 2015; Lebbi et al., 2015; Moore and Campbell, 2016). A numerous obstetrical- and gynaecological-related entities have been analyzed in scientometric studies, such as breast cancer (Glynn et al., 2010; Healy et al., 2011), caesarean section (Bruggmann et al., 2015a, 2015b), endometriosis (Bruggmann et al., 2016a, 2016b, 2016c, 2016d) or gestational diabetes (Bruggmann et al., 2016a, 2016b, 2016c, 2016d), but in-depth assessments describing the global scientific landscape of PCOS have so far not been published. Therefore, we conducted the first study on quantitative and semi-qualitative dimensions of PCOS research authored in the past century. The publication output was evaluated regarding chronological and geographical aspects, gender distribution of publishing authors, and in the context of socio-economic indices.

Overall, 6261 PCOS-related research articles were identified. Since 1900, publication output (as represented by published articles) developed in a pattern similar to other areas of biomedical science. We noted only minor scientific activity from 1938 until the 1970s. This period was followed by a moderate increase of yearly publications in the late 1990s when the field's activity started to rocket upwards (over 100 annual publications). Until 2006, research output doubled, and even higher numbers were documented after 2012, with more than 400 articles per year. We attribute the prominent growth in PCOS publication output during the last 25 years to multiple factors: scientific activities around the globe were supported by the ongoing globalization process and the advancing worldwide interconnectedness. The widespread use of the world-wide-web simplified the submission of scientific work for publication and facilitated the exchange of ideas, data and knowledge, fostering collaborations. Also, the increasing research activity in the 1990s and after 2010 may be attributed to a rising number of journals providing platforms for publication and the investigation of relevant groundbreaking concepts in the field. For example, the role of metformin in the treatment of PCOS was introduced in 1994 by Velazquez et al., 1994. In 2011, researchers started to investigate genetic targets related to PCOS in genome-wide association studies (Chen et al., 2011) and established the model of PCOS as a complex genetic trait.

Worldwide, authors affiliated with institutions in 92 countries published research on PCOS. Interestingly, the findings on country-specific publication productivity differed largely from other areas of biomedical sciences. Apart from the dominating role of US-institutions, which is present in almost every area of research (Groneberg-Kloft et al., 2008), a remarkably different set of countries showed an outstanding performance in the field of PCOS research: in our study, Turkey was ranked at fourth position, followed by China and Greece. Iran was identified as the ninth most active player in the PCOS research community. Unexpected results also emerged when socioeconomic indices were assessed. We related PCOS research output to the GDP of investigated countries. Here, Greece ranked first followed by Finland, the Netherlands and Slovenia. These findings were surprising because Scandinavian countries, the USA and the UK are usually prominent in analyses within the framework of socioeconomic variables (Bruggmann et al., 2016a, 2016b, 2016c, 2016d). The country-specific pattern of publication productivity is truly unique to PCOS research, and cannot be found in other studies of important conditions or entities in the field of obstetrics and gynaecology. For example, Glynn et al. (2010) screened publications related to breast cancer, their search covered a period from 1945 until 2008 (Glynn et al., 2010). A total of 180,126 items were identified, and the USA contributed the most. Authors affiliated withUS-institutions issued 77,101

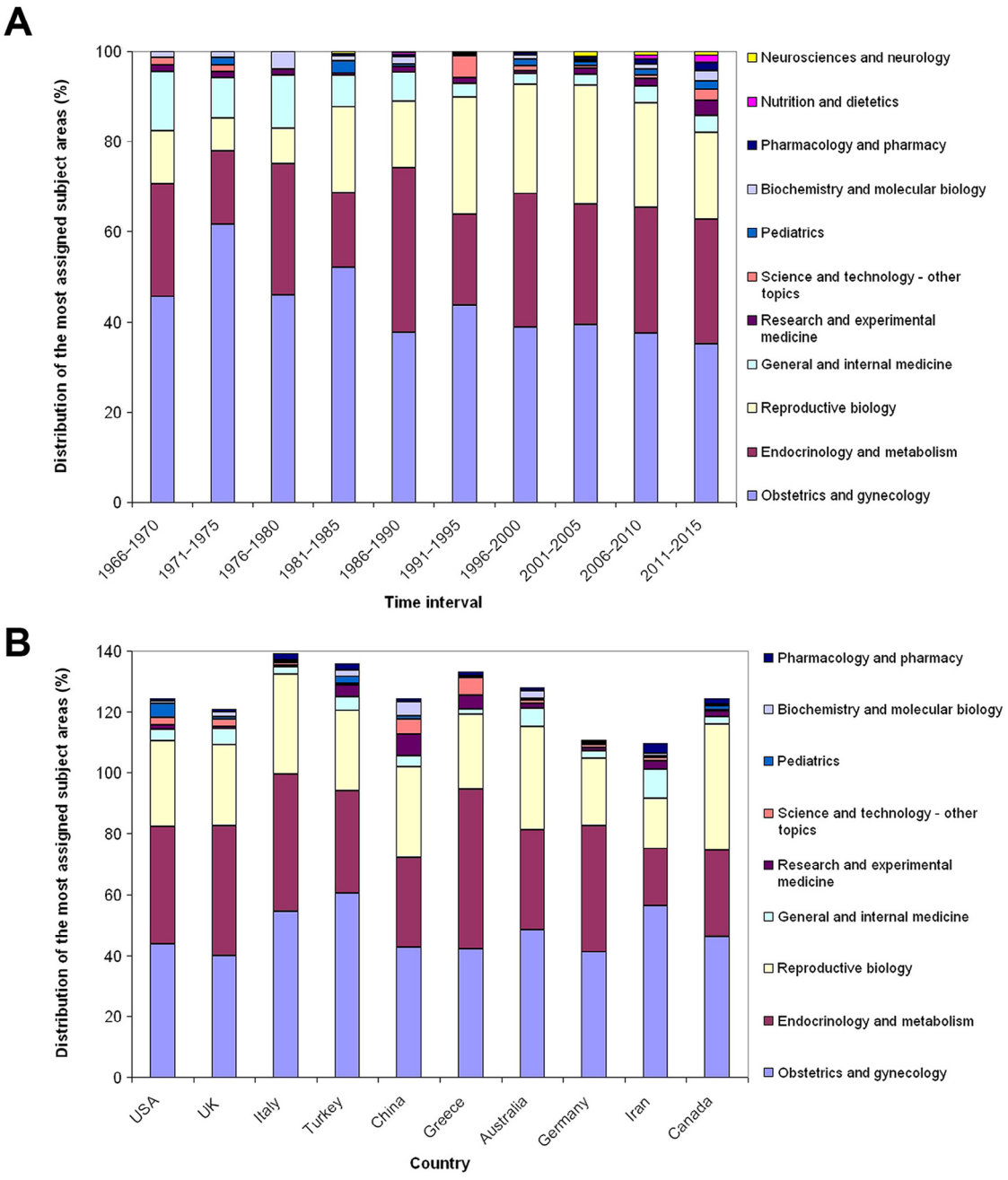

Figure 4 – Subject area analysis of polycystic ovary syndrome (PCOS) research. (A) Relative proportions of subject areas in 5-year intervals between 1965 and 2014; (B) proportions of subject areas in most active countries.

breast cancer-related publications that were cited 2,389,337 times (Glynn et al., 2010). The USA was followed by the UK with 18,357 articles, Germany (n = 12,529), Italy (n = 10,828), Japan (n = 10,109), France (n = 9,412), Canada (n = 9,002), the Netherlands (n = 5594), Australia (n = 4531) and Sweden (n = 4102) in position 10 (Glynn et al., 2010). This picture of global publication activity did not include countries such as Turkey, China, Greece or Iran, which are at the forefront of PCOS research. Again, these countries were also not identified among the major scientific key players in the clinically relevant fields of 'smoking and pregnancy' and 'gestational diabetes' (Bruggmann et al., 2015a, 2015b; Mund et al., 2014).

The unexpected set of highly productive countries within the PCOS research community warrants further discussion, as the results cannot simply be linked to particular high local disease rates: in Turkey and Greece, PCOS prevalences range from 6.10 to 6.77%, which do not differ from global frequencies between 6 and 10% (based on the National Institutes of Health 1990 criteria; Knochenhauer et al., 1998). Hence, we hypothesize that the pronounced positions of Turkey, Greece and Iran on the global map of PCOS research may be attributed to the relatively high infertility rates in these countries. Mascarenhas et al. (2012) estimated prevalences of primary infertility in 190 countries and territories (Mascarenhas et al., 2012). For Iran, Turkey and Greece, the authors found rates of 2.5%, 2.4% and 2.1%, respectively, which were higher than the global average of 1.9% in women aged between 20 and 44 years. Also, Iran and Turkey constitute worldwide centres specialized in fertility treatment (Jalal Abbasi-Shavazi

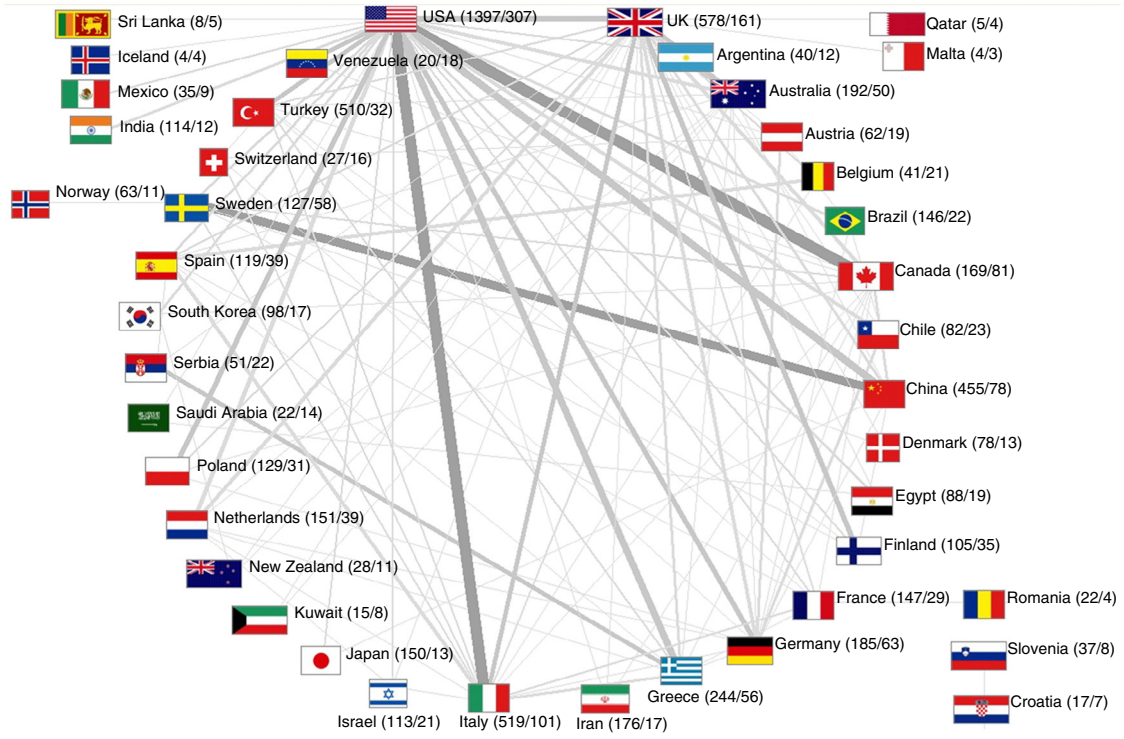

Figure 5 – Collaborations on PCOS research between countries. Greyscale and bar thickness indicate intensity of collaborations. First values in brackets indicate total publication numbers. Second values indicate number of collaborative publications. Threshold: four collaboration articles.

et al., 2008; Sullivan et al., 2013). On the basis of these insights, we hypothesize that, as seen for Iran in the past, sociocultural pressures of reproductive challenges might be linked to an increased public awareness and momentum in these nations to foster research that targets infertility and PCOS specifically.

Gender imbalances are omnipresent in science and persist among scientists in various areas of research. It has been reported that male authors frequently dominate the scientific output in nearly every country, to what extent varies by region (Lariviere et al., 2013). In light of Lariviere's findings, which confirmed a persistent global gender disparity in science, we specifically assessed PCOS research and quantified the number of male and female scientists authoring publications in the field. In most countries such as Turkey, UK or Greece, male authors were clearly overrepresented. A higher number of female compared with male authors, however, was identified in the USA or Brazil. Interestingly, this female-dominated gender distribution was also found in Iran, which illustrates that a country-specific gender dominance is not strictly related to the geographic region but also depends on particular national structures.

We analysed all PCOS-related articles for multi-disciplinary aspects, and our subject area analysis provided detailed insights. Most articles were attributed to 'obstetrics and gynaecology', 'endocrinology and metabolism', and 'reproductive biology', which constituted the leading subject categories. This was not surprising. Regarding the chronological evolution of published articles in a particular subject area, an increase of items attributed to 'reproductive biology' was documented over time and specifically after 1990. This result coincided with the growing popularity of assisted reproductive technologies since the late 1970s, which became a mainstay in the treatment of women with PCOS. Furthermore, a considerable number of articles was also identified in 'general and internal medicine' or 'research and experimental medicine'. We attribute this finding to the multifaceted nature of the disease, which often requires multi-disciplinary care and translational research to optimize patient outcomes. Moreover, the' transatlantic divide' on the diagnostic criteria of PCOS is another frequently discussed topic within the research community. Although we determined the PCOS publication activity in a country-specific manner, we were not able to answer related research questions using the current methodology. Our analysis is based on established NewQIS technologies, which do not provide any tools to identify the use and application of specific diagnostic criteria in the investigated body or literature. Hence, we acknowledge this as a limitation of the study.

Although PCOS is an ancient disorder (Azziz et al., 2011), which has been in the focus of scientists and healthcare providers for a considerable time, more research needs to be conducted. Important topics include the investigation of predisposing factors, the profound in- vitro/in-vivo characterization of altered pathways in steroidogenesis, interplay between hormones, insulin and the ovarian tissue, as well as PCOS phenotypes in adolescent girls or postmenopausal women (Pasquali et al., 2011). Also, in-depth epidemiological assessments are needed as comparisons of worldwide PCOS rates are difficult and related prevalences depend largely upon the criteria used for diagnosis of the condition. Yildiz et al. (2012) assessed 527 women according to National Institutes of Health, Rotterdam and Androgen Excess and PCOS (AE-PCOS) Society criteria, and PCOS rates were documented as 6.1, 19.9 and 15.3%, respectively (Yildiz et al., 2012). Hence, we can assume that a large number of patients in the community remain undiagnosed. As PCOS is associated with a plethora of long-term complications, this finding can be considered as an

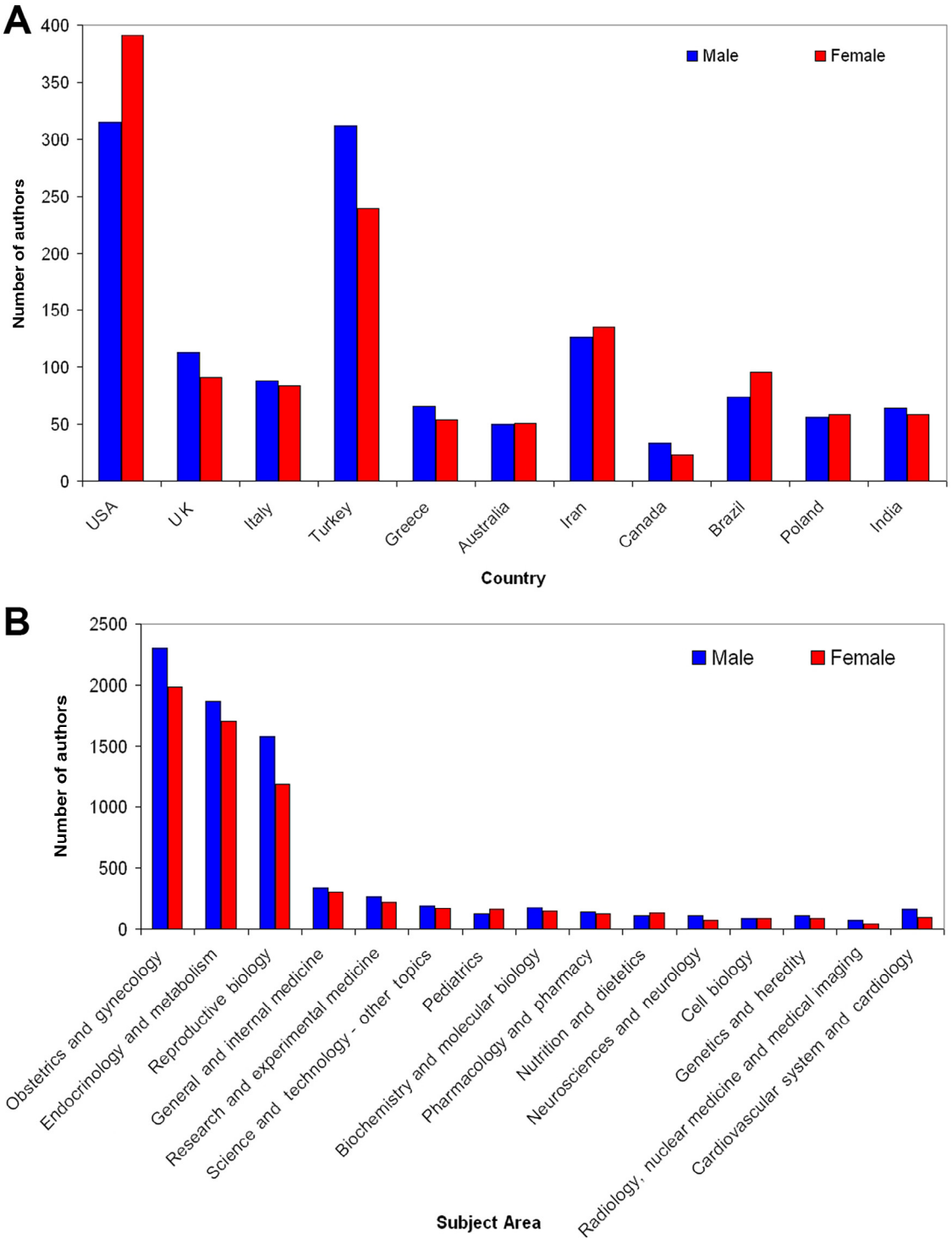

Figure 6 – Gender distribution in polycystic ovary syndrome (PCOS) research. (A) Authors' genders in most active countries. Thresholds: 75% determination rate, 100 authors; (B) authors' genders for subject areas of PCOS research. Thresholds: 50% determination rate, 250 authors.

important and concerning issue that requires further attention from a public health standpoint.

In conclusion, the present study represents the first global assessment of PCOS research activities. We investigated PCOS research activity, including quantitative (overall research output) and semi-qualitative aspects (citation parameters), socioeconomic features and the gender distribution among publishing authors. Using these data, we were able to present the first worldwide picture of PCOS research architecture, which largely differs from other gynaecologic disorders.

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