



Seasonal variation in the internet searches for gout: an ecological study

Sinan Kardeş¹

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Abstract

Introduction/objective While few studies with various types of outcomes and methodology have investigated the seasonality of gout, no internet data has been used in any study. This novel methodology may complement and extend the previous traditional data sources and has increasingly been used in investigating the seasonality of health conditions. Therefore, the objective of this study was to utilize the Google Trends data to test whether there is a seasonal variation in the internet searches for gout on a population basis.

Methods In this observational ecological study, the Google Trends was searched for the [gout] within the USA, the UK, Canada, Ireland, Australia, and New Zealand from January 01, 2004, to December 31, 2017, utilizing the “health” category.

Results The cosinor analyses revealed a statistically significant seasonal variation in relative search volume of the [gout] in the USA, the UK ($p < 0.001$), Canada ($p < 0.001$), Ireland ($p < 0.001$), Australia ($p < 0.001$), and New Zealand ($p < 0.001$), with a peak in the late spring/early summer months and trough in the late fall/early winter months. The peaks in late spring/early summer and troughs in late fall/early winter were out of phase by 6 months in the northern compared to the southern hemisphere countries.

Conclusion Another line of evidence from internet search query data showed a seasonal variation in gout, with a peak in the late spring/early summer months. Further studies aimed at elucidating the possible mechanisms behind seasonality in gout are needed.

Keywords Ecological · Environmental factors · Google trends · Gout · Gouty arthritis · Season · Seasonality

Introduction

Gout is inflammatory arthritis induced by the chronic deposition of monosodium urate crystals, particularly in the cartilage, bone, and periarticular tissues of synovial joints [1, 2]. Its clinical manifestations include intermittent acute attacks of inflammatory arthritis, a chronic arthropathy, and tophaceous deposits in soft tissues or joints [1–7]. A 2010 study on the global burden estimated the global age-standardized prevalence of gout in 2010 of 0.08%, which was higher among men than women [8]. Even though the exact pathogenesis of gout has not been fully elucidated, the considerable evidence

suggests a multifactorial etiology involving a complex interplay between metabolic, genetic, immune, and environmental factors [1–7]. The risk factors that may trigger and/or exacerbate the disease include obesity, diet, infections, hypertension, diuretics, and alcohol [1–7, 9, 10].

Recently, the internet has become a critical source of information for the general population [11]. Keyword-driven internet search engines provide easy and rapid access to online information [11, 12]. The Pew Internet & American Life Project reported that eight out of ten internet users sought health information via the internet [13]. The most common health topic that the internet users searched for was a specific disease, or a medical problem [13]. If collected and archived systematically, the internet search engines data could become one of the greatest dataset ever compiled, having the potential to be an important source of information for healthcare researchers on population-level patterns [14]. Recently, Google search engine searches have become publicly accessible [15]. It represents an unbiased sample of Google engine data, which can be sampled from as far back as 2004 [16]. An increasing number of studies have investigated Google Trends data to test the seasonality of a variety of health conditions,

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✉ Sinan Kardeş
sinan.kardes@istanbul.edu.tr; snmkrds@gmail.com

¹ Department of Medical Ecology and Hydroclimatology, İstanbul Faculty of Medicine, İstanbul University, Çapa, 34093 İstanbul, Turkey

including depression [17], major mental illnesses [18], restless leg syndrome [19, 20], sleep-disordered breathing [21], multiple sclerosis [22], leg cramps [20, 23], brain aneurysms and subarachnoid hemorrhage [24], tinnitus [25], foot and ankle pain [26], ankle swelling [27], vitamin D [28], systemic lupus erythematosus [29], rhinitis [30], tanning using [31], and cellulitis [32].

While few studies with various types of outcomes and methodology (i.e., International Classification of Diseases [ICD] code as a proxy/retrospective study [33, 34], American College of Rheumatology [ACR] criteria/retrospective medical file study [35] or synovial fluid analysis/prospective study [36]) have investigated the seasonality of gout, it has not been studied with the use of the internet data. This novel methodology may complement and extend the previous traditional data sources [11, 12, 14]. Therefore, the objective of this study was to utilize the Google Trends data to test whether there is a seasonal variation in the internet searches for gout.

Methods

This observational, ecological study was conducted in accordance with the Declaration of Helsinki, as well as the Google's terms of service and privacy policy [37]. As highlighted in the previous studies, formal ethics approval was not required [19, 21, 24–27, 31], since this work comprised publicly available anonymous data, and contained no personally identifiable information. In this study, the documentation use followed the recommendations of a recent review addressing Google Trends in healthcare studies [14].

Google trends search and data collection

The Google Trends provides data about the frequency of search terms that people put in the search box when they are looking for information from the Google Search engine [16]. In order to make easier comparisons between the terms, the Google Trends automatically adjusts the results to the time, and location of a search term by dividing each data point by the total searches of the geography, and time period, and then by scaling these resulting numbers based on a given search term's proportion to all searches on a range of 0 to 100 [16]. The higher scores indicate higher relative search volume (RSV) [16]. The data points can be downloaded as Comma-Separated Values (CSV) files [16]. To prevent selection bias, Google Trends eliminates repeated searches from the same person during a short span of time [16].

In June 08, 2018, Google Trends was interrogated and the resultant CSV files were exported for the following query term: [gout]. This query was searched within the USA, the UK, Canada, Ireland, Australia, and New Zealand from

January 01, 2004, to December 31, 2017, utilizing the “health” category. The health category was used, as this study focused and evaluated interest in the field of health. The term gout was chosen because it was reasoned that this term would capture more people with gout who have looked for information via the internet. This assumption was corroborated by the observation that [gout] had a ≈ 25 -fold higher relative search volume than other terms (e.g., gouty). The USA, the UK, Canada, Ireland, Australia, and New Zealand were chosen as majority native English-speaking countries in the northern and southern hemispheres. Including countries from both hemispheres allows for assessing seasonal variations that are expected to be out of phase by about 6 months between these hemispheres, as indicated in earlier investigations [17–32].

The downloaded CSV files provided monthly information and had 168 (12 months per year \times 14 years) data points per search query for each country. The downloaded CSV files are presented in order to provide reproducibility of the study results (Supplementary files 1–6).

Statistical analysis

Similar to previous studies testing the seasonality of health condition utilizing the Google Trends data [19, 21, 25, 28, 31], the cosinor analysis was performed to examine the seasonality. The cosinor analysis and the software utilized to execute it are detailed elsewhere [38, 39]. Briefly, the cosinor analysis is hinged on a sinusoid

$$St = A \cos \left(\frac{2\pi t}{c} - P \right), \quad t = 1, \dots, n,$$

where A denotes the amplitude of the sinusoid and P denotes its phase, c denotes the length of the seasonal cycle (established at 12 for monthly data), t denotes the time of each data point, and n denotes the total number of data points. In this study, $n = 168$, as explained above. The amplitude explains the size of the seasonal changes, and the phase explains where the seasonal peak occurs. The cosinor model fits as part of a generalized linear model; hence, it fits a range of dependent data. The cosinor model is constituted of both sine and cosine terms that together identify the sinusoid. Therefore, it has two p values, one for the sine and one for the cosine. In the cosinor analysis, the threshold of significance is adjusted at $p < 0.025$ to control the false discovery rate due to multiple testing, and then both sine and cosine p values are tested for statistical significance based on the adjusted significance level. One of these two values was presented (i.e., cosine p value), as recommended [38, 39]. Since the data were continuous variables, the Poisson model was used, and to adjust the unequal number of days in the months, the offset was used in cosinor functions in this study. Furthermore, a time series plot was performed to emphasize the consistency in the seasonal

patterns [38, 39]. Cosinor analyses and time series plots were conducted with the use of the “season” package [39] in R version 3.4.4 binary for OS X 10.11 (El Capitan) [40].

Results

The results of the cosinor models are detailed in Table 1, and plots of cosinor models are presented in Fig. 1. The cosinor analyses revealed a statistically significant seasonal variation in relative search volume for the term [gout] in the USA (amplitude [A] = 3.95, phase month [P] = 6.2, low point month [L] = 12.2, $p < 0.001$), the UK ($A = 4.71$, $P = 5.3$, $L = 11.3$, $p < 0.001$), Canada ($A = 4.54$, $P = 5.8$, $L = 11.8$, $p < 0.001$), Ireland ($A = 2.74$, $P = 5.7$, $L = 11.7$, $p < 0.001$), Australia ($A = 7.40$, $P = 12.2$, $L = 6.2$, $p < 0.001$), and New Zealand ($A = 4.23$, $P = 12.2$, $L = 6.2$, $p < 0.001$). Peaks were observed in the late spring/early summer months (May/June for the northern hemisphere countries; December for the southern hemisphere countries) and trough the late fall/early winter months (November/December for the northern hemisphere countries; June for the southern hemisphere countries). The peaks in late spring/early summer and troughs in late fall/early winter were out of phase by 6 months in the northern compared with the southern hemisphere countries (Table 1; Fig. 1).

Visual inspection of time series plots highlighted the consistency in the seasonal pattern that was observed in the cosinor analyses (Fig. 2).

Discussion

This study using the internet data was the first of its kind aimed at examining the seasonality of gout. A statistically

Table 1 The seasonal variation in the relative search volume of the [gout]

Country	Amplitude	Phase month ^a	Low point month ^a	p value ^b
USA	3.95	6.2	12.2	< 0.001
UK	4.71	5.3	11.3	< 0.001
Canada	4.54	5.8	11.8	< 0.001
Ireland	2.74	5.7	11.7	< 0.001
Australia	7.40	12.2	6.2	< 0.001
New Zealand	4.23	12.2	6.2	< 0.001

Cosinor test was used to examine the seasonality

^a Numeric values correspond to months as follows: January = 1, February = 2, March = 3, April = 4, May = 5, June = 6, July = 7, August = 8, September = 9, October = 10, November = 11, and December = 12

^b The threshold of significance is adjusted at $p < 0.025$ to control the false discovery rate due to multiple testing in the cosinor analysis. The cosine p value is presented

significant seasonal variation was detected in the Google searches of gout in the USA, the UK, Canada, Ireland, Australia, and New Zealand, with a peak in the late spring/early summer months, and trough the late fall/early winter months.

As the present study included data from the USA, the UK, Canada, Ireland, Australia, and New Zealand, the study sample provides good representation of both the northern and southern hemispheres. Therefore, the seasonal variations in countries of the northern hemisphere can be compared with southern hemisphere countries, where the meteorological months are reversed. In the comparison of the northern and southern hemisphere countries, it was observed that the pattern of searches on gout was out of phase by 6 months in the northern hemisphere countries compared with the southern hemisphere countries. This finding indicates that the variations were seasonal rather than calendar-driven patterns.

It can be speculated that the observed seasonal variation may simply reflect an increase in internet use in summer months. However, this assumption does not seem to be supported because some previous studies have demonstrated seasonal variation with searches for major mental illnesses [18], sleep-disordered breathing [21], tinnitus [25], and vitamin D [28] peaking in the winter months.

To date, some previous studies with varying study designs have examined the seasonality of gout [33–36]. Elliot et al. retrospectively investigated the general practice network data of England and Wales from 1994 to 2007 for the ICD code of gout [33]. In that study, new gout cases and acute attacks displayed significant seasonality peaking in the summer [33]. In another study with a similar design using ICD code of gout from a nationwide database of the USA, Karmacharya et al. conversely showed seasonality peaking in the fall [34]. In a retrospective medical file study in Italy, the gout attacks were found to be mainly occurred in the summer [35]. The other study in Italy, in which the diagnosis of gout was confirmed by synovial analysis from all suspected cases of crystal arthritis, demonstrated seasonality of acute gout attacks, being more frequent in the spring [36]. A recent meta-analysis evaluating the seasonal and monthly variation of gouty arthritis concludes that acute gouty arthritis seems to develop more frequently in spring by season and between March and July by month in the northern hemisphere [41]. This study provides another line of evidence for a consistent seasonality in gout. Even though direct comparison of the present study with earlier studies is limited by differences in study design, the present results are in accordance with those from most previous studies [33, 35, 36] and meta-analysis [41], by demonstrating the seasonal variation of gout peaking in late spring/early summer.

Several plausible mechanisms might underlie the seasonal variation of gout, and various possible factors might contribute to its seasonal worsening. First, previous studies have

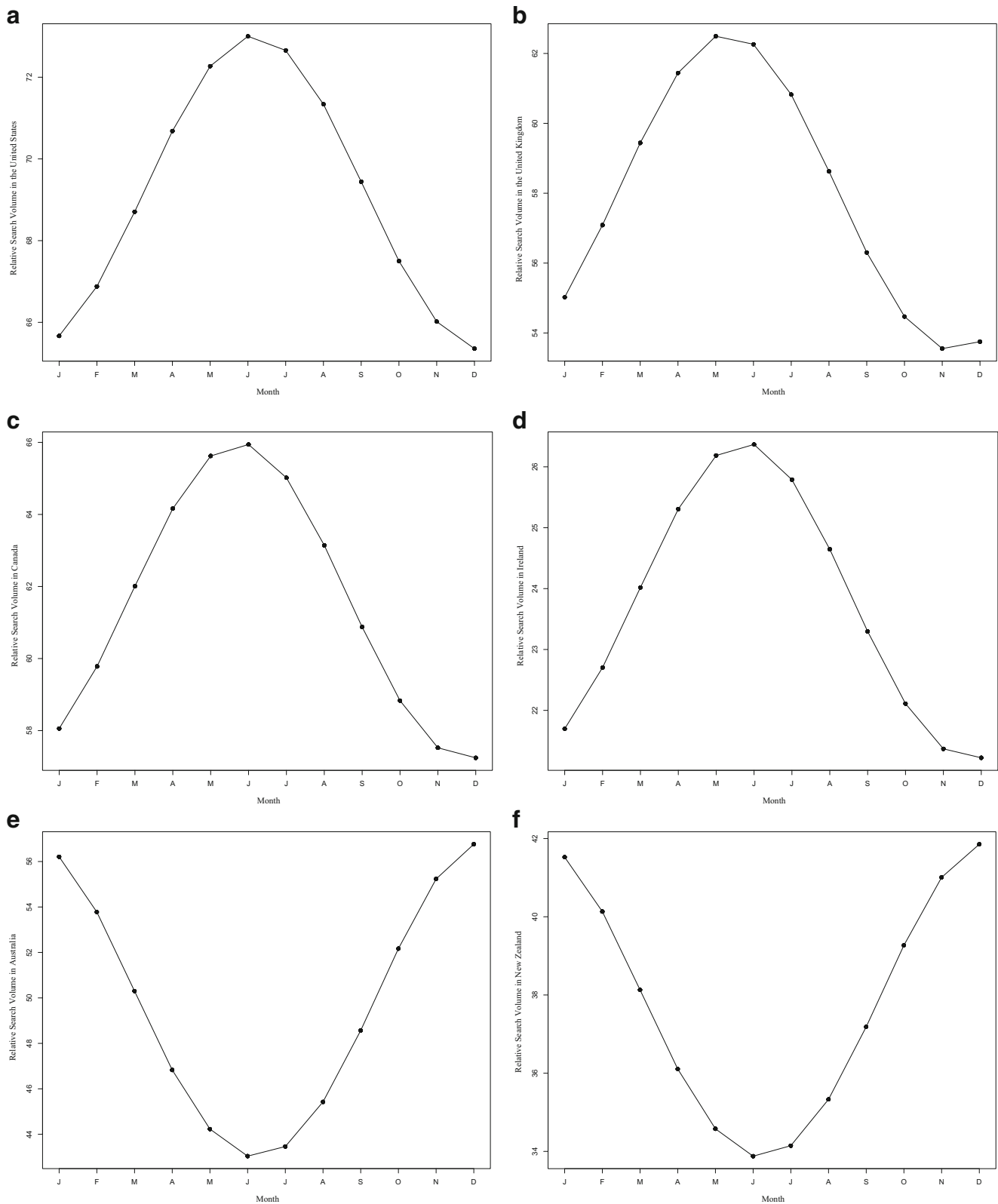


Fig. 1 The plots of cosinor models for the seasonal variation in the relative search volume of [gout] in **a** the USA, **b** the UK, **c** Canada, **d** Ireland, **e** Australia, and **f** New Zealand. The months are as follows:

January, February, March, April, May, June, July, August, September, October, November, and December

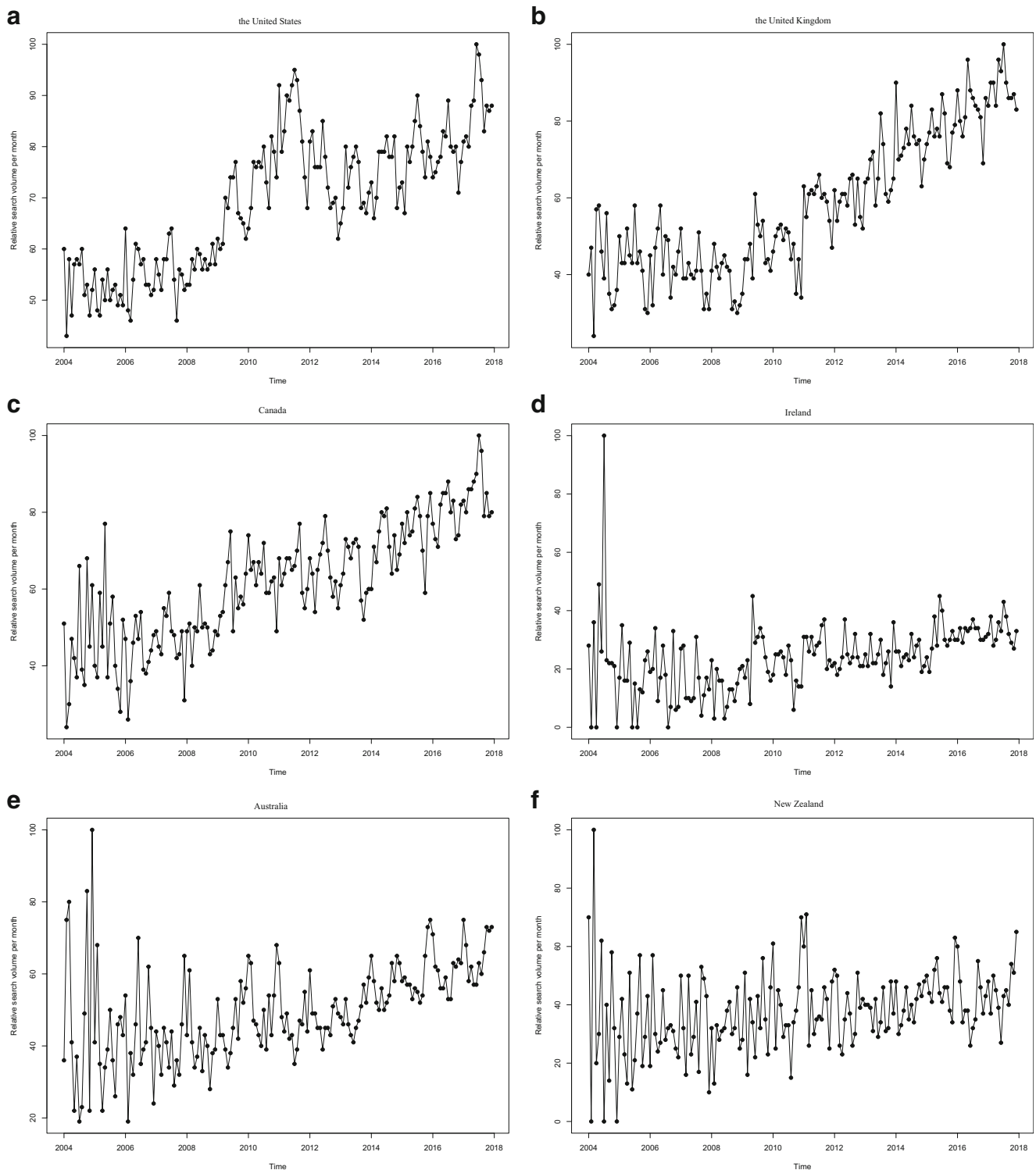


Fig. 2 Time series plots for the relative search volume of [gout] in **a** the USA, **b** the UK, **c** Canada, **d** Ireland, **e** Australia, and **f** New Zealand from January 01, 2004, to December 31, 2017

consistently shown the seasonal fluctuations of serum uric acid levels with the highest concentrations in summer [42–44]. As the uric acid has the main role in the etiology of gout [1–7], the increases in uric acid in summer may trigger a flare in patients with gout. In a related vein, the dehydration

induced by increases in mean temperature between neighboring days has been postulated to precipitate the deposition of monosodium urate crystals and subsequently gout flare-up [41]. Second, the plasma cortisol levels were found to be low in summer compared to the winter in healthy adults

[45]; it is plausible that lower cortisol levels in summer months might contribute to the gout attack [46]. Third, the seasonal elevation of immune functional activity of neutrophils in summer [47] may be a predisposing factor for the gouty attacks [46], since inflammation processes in acute attacks are predominantly mediated by neutrophils [1]. Fourth, the increase in physical activity in the summer months leads to minor joint trauma that accounts for preceding attacks [33, 34]. Fifth, an increase in the intensity of the risk factors (e.g., obesity, diet, infections, and alcohol) for gout during summer might be associated with the observed seasonality of internet searches for gout in the present study. For example, alcohol consumption is higher in spring and summer compared to fall and winter [48, 49].

The strengths of the present study include the large and exhaustive amount of data, the long period of observation, and the large geographic areas covered, including countries that are located above and below the equator. However, this study has some limitations. For example, the Google Trends does not supply the demographic characteristics of the users entering the search query; therefore, the seasonality cannot be assessed by stratifying specific subpopulations (e.g., by age, gender, etc.). Hence, the results of this study can only be applied to a general population. Another limitation of the present study is that the only one search engine was deployed in this study. However, Google search engine is probably representative of all search queries, since it accounts for over 65% of all web search volume worldwide [50]. Despite these limitations, the insights generated from this study would yield important insights into the seasonal variation of gout.

In conclusion, the present study, which used a novel approach of using internet search query data, provided another line of evidence of a seasonal variation in gout, with a peak in the late spring/early summer months. Further studies aimed at elucidating the possible mechanisms behind seasonality in gout are needed.

Compliance with ethical standards

Disclosures None.

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