Seasonal variation in systemic lupus erythematosus and rheumatoid arthritis: An ecological study based on internet searches

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease in which immune regulation is disrupted and characterized by intense inflammation and damage to multiple organs or systems. Rheumatoid arthritis (RA) is another systemic autoimmune disease characterized by chronic synovial joint inflammation that leads to disability and poor quality of life. Although the etiologies and pathogenesis of SLE and RA are not fully understood, it is generally accepted that they are both caused by interactions between genetic and environmental factors. In recent years, emerging studies have demonstrated the potential role of seasonality in the development and disease activity of variety of autoimmune diseases [1–3].

Internet-derived information has been recently recognized as a valuable tool for epidemiological investigation. Google Trends generates data on spatial and temporal patterns according to specified keywords [4–9]. Recently, Google Trends search have become publicly accessible. It represents an unbiased sample of Google search data, which can be extracted from the year of 2004 [5]. In the present study, to derive a more precise estimation on the seasonality of SLE and RA, the Google Trends was searched for the 'lupus' and 'rheumatoid arthritis' within six major English speaking countries.

On November 20 2018, Google Trends was searched and the resulting Comma-Separated Values (CSV) files were exported for the following two query terms, respectively: 'lupus' and 'rheumatoid arthritis' [10,11]. This query was searched within the six major native English-speaking countries (Australia, Canada, Ireland, New Zealand, UK and USA) during the period of January 01 2004 to December 31 2017, under the "health" category [5]. The cosinor analysis was used to examine the seasonality. The criterion of significance was set at $p < .025$ to control the false discovery rate due to multiple testing. Since the data were continuous variables, the Poisson model was used. In order to adjust the unequal number of days in the months, the offset was used in cosinor functions in this study [12]. Cosinor analyses were conducted and time series plots were made with the use of the "season" package in R version 3.4.4 [12,13].

Our results disclosed a seasonal variation in RSV for the term 'lupus' in Ireland and USA (both $p < .025$), however, no significant seasonal variations were observed in Australia, Canada, New Zealand and UK (all $p > .025$) (Table 1). Different seasonal patterns of RSV for 'lupus' in six countries were displayed in Fig. 1. As for the term 'rheumatoid arthritis', there were significant seasonal variations of RSV for 'rheumatoid arthritis' in Australia, Ireland, New Zealand and the UK (all $p < .025$), but we did not find seasonal variations in RSV for the term 'rheumatoid arthritis' in Canada and USA (both $p > .025$) (Table 1). Peaks in the summer months (June/July/August) were found in two southern hemisphere countries (Australia and New Zealand), and peaks in late winter/early spring months (January–April) were observed in four northern hemisphere countries (Ireland, Canada, the UK and USA) (Fig. 1).

Google Trends search volumes are usually increased for conditions with higher social impact, which suggests a higher disease burden during certain periods. Therefore, Google Trends search is gradually gaining much importance in disease surveillance studies [14]. In the present study, Google Trends for 'lupus' presented a specific seasonality in Ireland and USA, but not in Australia, Canada, New Zealand and UK. In terms of 'rheumatoid arthritis', significant seasonal variations were observed in Australia, Ireland, New Zealand and UK, but not in Canada and USA.

Traditional epidemiologic studies have demonstrated the seasonal variation pattern in both SLE and RA presentation, which can be explained by changes in vitamin D, amount of ultraviolet radiation exposure and the appearance of infectious factors [1,15–18]. Recently, Google trends has gradually become a meaningful resource of health related information for both laypeople and health professionals, internet-derived information has been recognized as a auxiliary tool for estimating epidemiology and gathering data about disease patterns [4,19]. The present study provided additional evidence for seasonality of SLE and RA by applying Google Trends. The data from Internet sources may serve as a real-time surveillance tool and an alert for healthcare systems, so as to allocate appropriate resources for specific moments with higher disease burden [5-7].

Nevertheless, several limitations should be acknowledged. First,

Table 1
The seasonal variation in the relative search volume of 'lupus' and 'rheumatoid arthritis'.

Disease	Country	Amplitude	Phase month	Low point month*	P value**
Lupus	Australia	1.27	9.4	3.4	> 0.025
	Canada	1.01	6.3	12.3	> 0.025
	Ireland	1.69	2.5	8.5	< 0.025
	New Zealand	1.71	10.8	4.8	> 0.025
	UK	1.94	5.6	11.6	> 0.025
	USA	2.54	6.1	12.1	< 0.025
Rheumatoid arthritis	Australia	1.88	8.0	2.0	< 0.025
	Canada	0.85	3.1	9.1	> 0.025
	Ireland	2.26	1.5	7.5	< 0.025
	New Zealand	3.5	6.3	12.3	< 0.025
	UK	2.85	3.2	9.2	< 0.025
	USA	0.48	4.0	10.0	> 0.025

Cosinor test was performed to examine the seasonality.

* Numeric values represent 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.

** The threshold of significance is adjusted at $p < .025$ to control the false discovery rate due to multiple testing in the cosinor analysis. The cosine p value is presented.
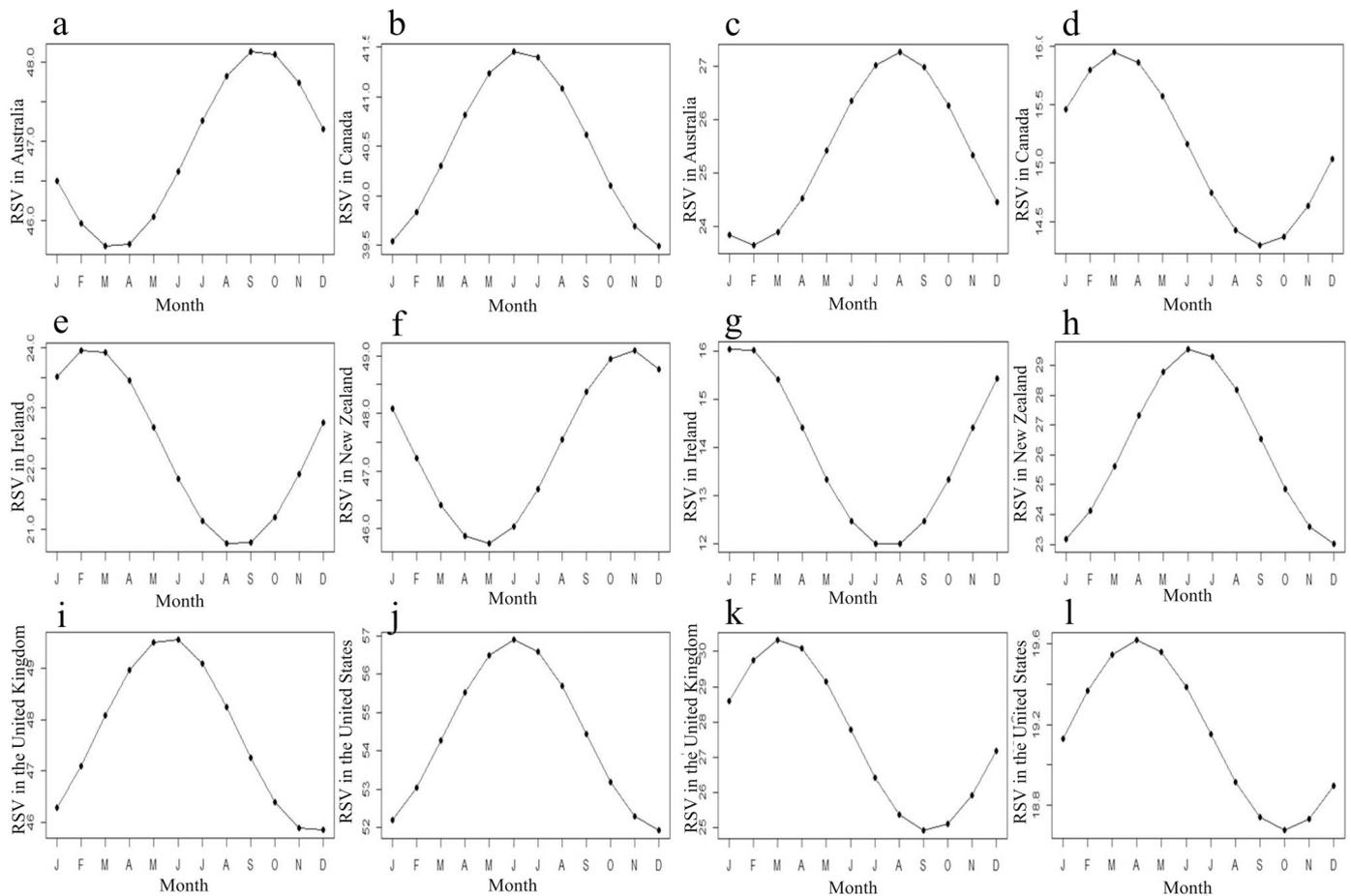
Fig. 1. The plots of cosinor models for the seasonal variation for the RSV of [lupus] and [rheumatoid arthritis].

a Australia [lupus], b Canada [lupus], c Australia [rheumatoid arthritis], d Canada [rheumatoid arthritis], e Ireland [lupus], f New Zealand [lupus], g Ireland [rheumatoid arthritis], h New Zealand [rheumatoid arthritis], i UK [lupus], j USA [lupus], k UK [rheumatoid arthritis], l USA [rheumatoid arthritis].

The months are as follows: January, February, March, April, May, June, July, August, September, October, November, and December.

RSV: relative search volume.

Google Trends does not provide the demographic data of the users, therefore, the seasonality cannot be further assessed by stratifying specific subpopulations (such as different age, gender, etc.). Hence, the findings of this study can only be applied to a general population. Second, there was the possibility that the search volume might be partly from some people other than SLE patients, who are nevertheless interested in this topic. Despite these limitations, our study also have strengths, such as the larger amount of data, the longer period of observation, and the larger geographic areas covered, including countries located above and below the equator [5].

In summary, the present study used internet search query data, provided another line of evidence on seasonal variation in SLE and RA. However, further studies aimed at elucidating the possible mechanisms behind seasonality in these two autoimmune diseases are needed.

Acknowledgement

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Hai-Feng Pan[a,b,1], Peng Wang[c,1], Guo-Cui Wu[d], Yan-Feng Zou[a,b], Zhiwei Xu[e], Dong-Qing Ye[a,b,*], Wenbiao Hu[e,**]

[a] *Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China*

[b] *Anhui Province Key Laboratory of Major Autoimmune Diseases, 81 Meishan Road, Hefei, Anhui, China*

[c] *Center for Genetic Epidemiology and Genomics, School of Public Health, Medical College of Soochow University, 199 Renai Road, Suzhou, Jiangsu, China*

[d] *School of Nursing, Anhui Medical University, 15 Feicui Road, Hefei, Anhui, China.*

[e] *School of Public Health and Social Work, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia*

E-mail addresses: ydq@ahmu.edu.cn (D.-Q. Ye), w2.hu@qut.edu.au (W. Hu).

[*] Correspondence to: D.-Q. Ye, Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China.

[**] Correspondence to: W. Hu, School of Public Health and Social Work, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia.

[1] Hai-Feng Pan and Peng Wang contributed equally to this work and should be considered co-first authors.