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

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Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease in which immune regulation is disrupted and is 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, a Google Inc. portal, 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 interrogated and the resultant 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, using the "health" category [5]. The cosinor analysis was performed to examine the seasonality. The criterion of significance is set at $p < 0.025$ to control the false discovery rate due to multiple testing. 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 [12]. Cosinor analyses and time series plots were conducted with the use of the "season" package in R version 3.4.4 [12-13].

Our results disclosed a statistically significant seasonal variation in RSV for the term 'lupus' in Ireland and USA (both $p < 0.025$), however, no significant seasonal variations were observed in Australia, Canada, New Zealand and UK (all $p > 0.025$) (**Table 1**). Different seasonal patterns of RSV for 'lupus' in six countries were displayed in **Figure 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 $p < 0.025$), but we did not find any significant seasonal variations in RSV for the term 'rheumatoid arthritis' in Canada and USA (both $p > 0.025$) (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) (**Figure 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

increasingly become a meaningful health resource for both laypeople and health professionals, internet-derived information has been recognized as a surrogate tool for estimating epidemiology and gathering data about patterns of disease [4, 19]. The present study provided additional evidence for seasonality of SLE and RA by applying Google Trends. In fact, data from Internet sources could 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.

Nevertheless, several limitations should be acknowledged. First, Google Trends does not provide the demographic data of the users, therefore, the seasonality cannot be further assessed by stratifying specific subpopulations (e.g., by 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 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.

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

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References

[1] Watad A, Azrielant S, Bragazzi NL, Sharif K, David P, Katz I, et al. Seasonality and autoimmune diseases: The contribution of the four seasons to the mosaic of autoimmunity. J Autoimmun. 2017;82:13-30.

[2] Cutolo M, Villaggio B, Otsa K, Aakre O, Sulli A, Seriolo B. Altered circadian rhythms in rheumatoid arthritis patients play a role in the disease's symptoms. Autoimmun Rev. 2005;4:497-502.

[3] Sabio JM, Vargas-Hitos JA, Martinez-Bordonado J, Navarrete-Navarrete N, Diaz-Chamorro A, Olvera-Porcel C, et al. Association between low 25-hydroxyvitamin D, insulin resistance and arterial stiffness in nondiabetic women with systemic lupus erythematosus. Lupus. 2015;24:155-63.

[4] Cervellin G, Comelli I, Lippi G. Is Google Trends a reliable tool for digital epidemiology? Insights from different clinical settings. J Epidemiol Glob Health. 2017;7:185-9.

[5] Kardes S. Seasonal variation in the internet searches for gout: an ecological study. Clin Rheumatol. 2018.

[6] Yang AC, Huang NE, Peng CK, Tsai SJ. Do seasons have an influence on the incidence of depression? The use of an internet search engine query data as a proxy of human affect. PLoS One. 2010;5:e13728.

[7] Ayers JW, Althouse BM, Allem JP, Rosenquist JN, Ford DE. Seasonality in seeking mental health information on Google. American journal of preventive medicine. 2013;44:520-5.

[8] Ingram DG, Plante DT. Seasonal trends in restless legs symptomatology: evidence from Internet search query data. Sleep medicine. 2013;14:1364-8.

[9] O'Keeffe ST. Summertime blues? A re-examination of the seasonality of web searches for restless legs and leg cramps. Sleep medicine. 2017;37:119-23.

[10] Google Trends help center. https://support.google.com/trends/. Accessed 20 Nov 2018

[11] Google Trends. https://trends.google.com/trends/. Accessed 20 Nov 2018

[12] Barnett AG, Baker P, AJ D. season: Analysing Seasonal Data R Functions. The R Journal. 2018;4:5-10.

[13] R Core Team. R: a language and environment for statistical computing. R Foundation for statistical computing, Vienna. . https://www.R-project.org/2018.

[14] Nuti SV, Wayda B, Ranasinghe I, Wang S, Dreyer RP, Chen SI, et al. The use of google trends in health care research: a systematic review. PLoS One. 2014;9:e109583.

[15] Amital H, Szekanecz Z, Szucs G, Danko K, Nagy E, Csepany T, et al. Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? Ann Rheum Dis. 2010;69:1155-7.

[16] McClain MT, Heinlen LD, Dennis GJ, Roebuck J, Harley JB, James JA. Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry. Nat Med. 2005;11:85-9.

[17] Iikuni N, Nakajima A, Inoue E, Tanaka E, Okamoto H, Hara M, et al. What's in season for rheumatoid arthritis patients? Seasonal fluctuations in disease activity. Rheumatology (Oxford). 2007;46:846-8.

[18] Lin J, Liu J, Davies ML, Chen W. Serum Vitamin D Level and Rheumatoid Arthritis Disease Activity: Review and Meta-Analysis. PLoS One. 2016;11:e0146351.

[19] Radin M, Sciascia S. Infodemiology of systemic lupus erythematous using Google Trends.

Lupus. 2017;26:886-9.

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 $p < 0.025$ to control the false discovery rate due to multiple testing in the cosinor analysis. The cosine *p* value is presented

Figure Legends:

Figure 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