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Seasonal manifestations of sickle cell disease activity

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To the Editor:

Sickle cell disease (SCD) is a β -globin disorder characterized by recurrent vaso-occlusive episodes, driven by hemoglobin S polymerization and neutrophil recruitment, and influenced by environmental factors^{1,2}. Whether the cold weather is associated to acute pain episodes has been controversial, likely due to the small number of patients in each series and methodology that relied on analyses of hospital admissions^{2–8}. In the digital age, the first line of defense for most patients is the search engine of their smartphones or computers. A search engine gathers data from millions of users around the world and thus may represent a powerful tool to estimate disease activity. For example, Google web search queries have been reported to detect influenza epidemics⁹. Here, we have used the *Google Trends* tool (<https://trends.google.com>) to investigate whether there is a seasonal change in SCD manifestations.

Google Trends displays the relative search interest in a given region and time period. We examined the trend for ‘sickle cell disease’ in the United States from January 2004 to August 2018, and found robust oscillations in the queries with yearly troughs during the summer months (June to August) and yearly peaks during the winter months (November to April; Fig. 1a and f). The same oscillation patterns exist in cold states (e.g. Indiana and New York; Extended Data Fig. 1a and b) or warmer states of the US (Texas and Georgia; Extended Data Fig. 1c and d). In addition, similar oscillations are observed in other countries of the Northern Hemisphere with a SCD population such as the United Kingdom or Canada (Extended Data Fig. 2a and b). To distinguish between seasonal variations and other factors, we examined the trend in countries of the southern hemisphere where the seasons are inverted relative to the US. We found that the oscillations in queries were inverted in Brazil as the peaks were observed in June and August (winter) while the lowest average indexes were in December and January (summer) (Fig. 1b and g). In addition, similar inverted oscillations were observed in Chile, Argentina or Australia (Extended Data Fig. 2c–e). By contrast, we did not observe significant oscillations in tropical countries of Africa without a cold season such as Ghana and Nigeria (Fig. 1c and Extended Data Fig. 2f).

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Data availability: All data supporting this article are available from the corresponding author upon request.

Code availability: All custom codes used in this article are available from the corresponding author upon request.

A search for several other non-seasonal chronic diseases (e.g. ‘*prostate cancer*’, ‘*myeloma*’, ‘*dementia*’ or ‘*cirrhosis*’ did not reveal any seasonal variations (Extended Data Fig. 3a–d), indicating that the oscillations in queries were not due to a seasonal change in the users’ habits. Queries are likely elicited by the presence of SCD patients since searches in countries without SCD patient populations (e.g. Russia or South Korea) did not gather enough data to generate a graph (data not shown).

To confirm further the periodicity of disease manifestations, we evaluated the profiles of well-established seasonal diseases. For example, the trend for ‘*bronchiolitis*’ showed a strong periodicity with peaks during the winter months in the US whereas the trend profile was also inverted in Brazil (Fig. 1d,e, h and i). Similar results were obtained with ‘*influenza*’, although in this case, the profiles were punctuated by high-amplitude peaks corresponding to well-documented outbreaks (Extended Data Fig. 3e–g). Taken together, these results taking input from numerous users in the world strongly support the notion that sickle cell disease activity has seasonal manifestations in temperate countries. In addition to the temperature variations, the climatic influence likely involves other factors such as humidity and the occurrence of viral infections which can be associated with vaso-occlusive manifestations, and may also be mitigated by access to health care. More practically, as new drugs are under evaluation to prevent SCD pain episodes and diminish disease activity, the time of enrollment in multicenter clinical trials should be monitored to avoid a seasonal-time bias, particularly if enrollment was shorter or longer than a full year, as it was the case for the recent phase 3 trial of L-glutamine which was conducted over 48 weeks¹⁰. A seasonal-time bias could influence the major conclusions of SCD clinical trials if the time of enrollment between treated and placebo-controlled groups was imbalanced.

Extended Data

Extended Data Fig. 1: Trends for sickle cell disease in different states of the US.

a-d, Trends of search indexes from January 2004 to August 2018 for '*sickle cell disease*' (under disorder) in Indiana (**a**) ($P < 0.001$), New York (**b**) ($P < 0.001$), Texas (**c**) ($P < 0.001$), and Georgia (**d**) ($P < 0.01$). Search index was plotted in the red tracings. The vertical dotted blue lines mark the beginning of each year. Cosinor analysis was performed using R Packages. The black lines correspond to the fitted cosine curves.

Extended Data Fig. 2: Trends for sickle cell disease in different countries.

a-g, Trends of search indexes from January 2004 to August 2018 for '*sickle cell disease*' (under disorder) in United Kingdoms (**a**) ($P < 0.0001$), Canada (**b**) ($P < 0.0001$), Chile (**c**) ($P < 0.0001$), Argentina (**d**) ($P < 0.01$), Australia (**e**) ($P < 0.01$), and Nigeria (**f**) ($P = 0.58$). Search index was plotted in the red tracings. The vertical dotted blue lines mark the beginning of each year. Cosinor analysis was performed using R Packages. The black lines correspond to the fitted cosine curves.

Extended Data Fig. 3: Trends for prostate cancer, myeloma, dementia, cirrhosis and influenza. Trends of search indexes from January 2004 to August 2018 for ‘prostate cancer’ (under disease) in the United States (a) ($P = 0.6$), ‘myeloma’ (under term) in the United States (b) ($P = 0.5$), ‘dementia’ (under disease) in the United States (c) ($P = 0.99$), ‘cirrhosis’ (under disease) in the United States (d) ($P = 0.34$), ‘influenza’ (under disease) in the United States (e) ($P < 0.00001$), ‘influenza’ (under disease) in Brazil (f) ($P < 0.01$), and ‘influenza’ (under disease) in Australia (g) ($P < 0.00001$). Search index was plotted in the red tracings. Note the high amplitude peaks in influenza tracings correspond to pandemic episodes (e.g. H1N1

swine flu pandemic in spring 2009). The vertical dotted blue lines mark the beginning of each year. Cosinor analysis was performed using R Packages. The black lines correspond to the fitted.

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Fig. 1: Google Trends reveals seasonal interest in sickle cell disease.

a-d, Trends of search indexes and fitted cosine curves from January 2004 to August 2018: for ‘*sickle cell disease*’ (under disorder) in the United States (**a**) ($P < 0.00001$) and Brazil (**b**) ($P < 0.01$), for ‘*sickle cell disease*’ (under disorder) in Ghana (**c**) ($P = 0.38$), for ‘*bronchiolitis*’ (under topic) in the United States (**d**) ($P < 0.00001$) and Brazil (**e**) ($P < 0.00001$). Search index is the relative search volume normalized to the highest one within a given time period and region. Relative interest was plotted in the red tracings. The vertical dotted blue lines mark the beginning of each year. Cosinor analysis was performed using R

Packages. The black lines correspond to the fitted cosine curves. **f-i**, Average monthly search indexes from January 2004 to August 2018 for ‘*sickle cell disease*’ (under disorder) in the United States (**f**) and Brazil (**g**), and ‘*bronchiolitis*’ (under topic) in the United States (**h**) and Brazil (**i**).