RESEARCH ARTICLE

Chronic lifestyle diseases display seasonal sensitive comorbid trend in human population evidence from Google Trends

Jai Chand Patel, Pankaj Khurana, Yogendra Kumar Sharma, Bhuvnesh Kumar, Sugadev Ragumani

Defence Institute of Physiology and Allied Sciences, Defence Research and Development Organization, Timarpur, Delhi, India

* ragusugadev@gmail.com

Abstract

Seasonal and human physiological changes are important factors in the development of many diseases. But, the study of genuine seasonal impact on these diseases is difficult to measure due to many other environment and lifestyle factors which directly affect these diseases. However, several clinical studies have been conducted in different parts of the world, and it has clearly indicated that certain groups of population are highly subjected to seasonal changes, and their maladaptation can possibly lead to several disorders/diseases. Thus, it is crucial to study the significant seasonal sensitive diseases spread across the human population. To narrow down these disorders/diseases, the study hypothesized that high altitude (HA) associated diseases and disorders are of the strong variants of seasonal physiologic changes. It is because, HA is the only geographical condition for which humans can develop very efficient physiological adaptation mechanism called acclimatization. To study this hypothesis, PubMed was used to collect the HA associated symptoms and disorders. Disease Ontology based semantic similarity network (DSN) and disease-drug networks were constructed to narrow down the benchmark diseases and disorders of HA. The DSN which was further subjected to different community structure analysis uncovered the highly associated or possible comorbid diseases of HA. The predicted 12 lifestyle diseases were assumed to be “seasonal (sensitive) comorbid lifestyle diseases (SCLD)”. A time series analyses on Google Search data of the world from 2004–2016 was conducted to investigate whether the 12 lifestyle diseases have seasonal patterns. Because, the trends were sensitive to the term used as benchmark; the temporal relationships among the 12 disease search volumes and their temporal sequences similarity by dynamic time warping analyses was used to predict the comorbid diseases. Among the 12 lifestyle diseases, the study provides an indirect evidence in the existence of severe seasonal comorbidity among hypertension, obesity, asthma and fibrosis diseases, which is widespread in the world population. Thus, the present study has successfully addressed this issue by predicting the SCLD, and indirectly verified them among the world population using Google Search Trend. Furthermore, based on the SCLD seasonal trend, the study also classified them as severe, moderate, and mild. Interestingly, seasonal trends of the severe seasonal comorbid diseases displayed an inverse pattern between USA (Northern hemisphere) and New Zealand.
Introduction

Seasonal changes in the environment have huge impact in all species and their adaptation is critical for their survival [1,2]. Indeed, several clinical studies have been conducted in different parts of the world, clearly indicating that certain groups of population are highly subjected to seasonal triggering, and their maladaptation can possibly lead them to several seasonal sensitive disorders/diseases [3–7]. Even though seasonal variations affect the entire human physiological systems, the cardio-vascular systems, cardio-respiratory systems, and circadian rhythms are most sensitive to these seasonal changes. In recent days, there is an impressive pattern of seasonal rhythm in hospitalizations of patients with cardio-vascular and cardio-respiratory diseases or disorders, with a notable increase in winter [8–11].

However, the study of genuine seasonal impact on these diseases is highly complex to decipher due to two main reasons: (i) apart from seasonal changes, a number of other environment and lifestyle factors which directly affect these diseases onset and severity needs to be controlled, such as air pollution, geographic location, ethnicity, physical exercise, social interactions and so on [7,12–19]. For example, the seasonal pattern in the incidence of asthma attacks onset and severity was highly influenced by several environment and lifestyle factors [20–23]; (ii) this severity was further enhanced and was proportional to the number of co-occurrence of diseases (comorbid diseases). For example, asthma is highly comorbid with many other diseases such as cardio cerebrovascular diseases, obesity, hypertension, diabetes, psychiatric conditions, neurological disorders, gut and urinary disorders, cancer, respiratory problems, and so on [24]. Among these, identifying the most significant seasonally comorbid diseases of asthma is crucial. Lack of reports on these seasonal linkages restricts the implementation of human seasonal adaptation in clinical environment.

High altitude (HA) elevations are ranging from 3,000 to 5,000 meters and the partial oxygen pressure is only about 70% of the value at sea-level [25]. Firstly, in HA, humans undergo significant physiological changes, mainly in cardio respiratory and cerebral functions, leading to the temporary physiological human adaptation called acclimatization [26]. HA disorders encompass the pulmonary and cerebral syndromes that occur in non-acclimatized individuals shortly after rapid ascent to HA [27]. The maladapted human population develop several HA disorders like acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), and high altitude cerebral edema (HACE). Many seasonal symptoms and disorders act as the predisposing factors of HA disorders. For example, patients with asthma, obesity, and hypertension were more prone to develop AMS [28–30]. The present study tried to address both the limiting factors using the high altitude linked diseases and disorders.

The internet is now an important source of health information for millions of people worldwide, which makes google search queries a valuable source of information for the collection health trends [31]. In recent years, “Google Trends” (GT) is gaining momentum to assess seasonal changes in diseases because it offers search information about a disease for long period of Jan 2004 to the present week. For example, the seasonality in Cold Flu, Influenza, Urinary Tract Infection, Ankle swelling, and Vitamin D were accurately estimated using Google
Trends [32–35]. Furthermore, GT provides the total volumes for requested diseases terms, normalized in a way that countries of different size can be compared [31]. Importantly, GT was used to study the precise interaction of search terms effect using combined diseases terms (https://support.google.com/trends/answer/4359550?hl=en-GB&ref_topic=4365530). The present study utilized GT to estimate the seasonality in the diseases as well as to measure the comorbid associations among them.

The current study had the following research objectives: (1) to decipher the genuine seasonal diseases using the HA related diseases and disorders from the literature mining; (ii) to conduct disease ontology based semantic similarity network and community detection approach to find the most likely seasonal comorbid diseases; (iii) to evaluate seasonal comorbid diseases, the GT search terms volume of the respective diseases were subjected to rigorous time series analysis. The main outcome of the analysis includes: (a) reveals that a considerable number of human populations is severely subjected to annual seasonal variations; (b) highlights of observed high seasonal rhythm among hypertension, obesity, asthma, and fibrosis diseases are widely spread among the human population. To our knowledge, this is the first study of its kind to examine the possibility of existence of seasonal association in comorbid lifestyle diseases in human population.

Materials and methods

Data mining

The aim of this study is to contribute a novel association generation among high altitude related diseases/disorders, symptoms, drugs, and medicines. Fig 1 illustrates various steps involved in the data collection and analysis. The first step in the study was to retrieve all relevant papers related to the topic of interest, i.e., high altitude. Abstracts that contain the most important and concise diseases/disorders and symptoms linked to high altitude were then chosen to be examined. Although the full-text analysis is more informative, the abstract based disease terms analysis has added advantages. Mainly, the analysis is more informative and concise. Also, it is faster to compute with reduced noise level. Keeping in view, a PubMed medical subject headings (MeSH) terms query was used to collect all possible high-altitude related abstracts. PubMed was queried for four types of key terms related to high altitude including: “High altitude disease”, “High altitude disorder”, “High altitude medicine” and “High altitude drug”. PubMed abstracts related to human studies were extracted by using the search filter option “Human”. The total number of Pubmed Identification numbers (PMIDs) retrieved from the four key terms was 6159 as on Jan 2017. The redundant PMIDs were reduced resulting in 3513 unique PMIDs. The abstracts of these unique PMIDs were fetched using "PubMed-Wordcloud" of R console [36]. Overall, 2976 abstracts were ready for knowledge discovery.

Entity selection and extraction

The next step is to extract the entities such as diseases/disorders, symptoms, drugs and medicines associated with high altitude. The association of the entities with high altitude means any loose relation that covers biological, biomedical or health related interest. To study the association, an online application programming interface (API) called BioMedical Concept Annotation System (BeCAS) was adopted [37]. This API is widely used to identify biomedical concepts in text [38–40]. BeCAS employs a standard pipeline that consists of sentence boundary detection, tokenization, lemmatization, part of speech tagging, and chunking and abbreviation disambiguation. 2976 abstracts were supplied as input to BeCAS. Among the 11 default entities of BeCAS, the term fetching for diseases and disorders entities was carried out. GDep, a dependency parser with the option of domain adaptation using unlabeled data of the target...
domain, was used to achieve most of the pre-processing steps in BeCAS. For entity recognition, BeCAS uses UMLS extended with a series of more specialized dictionaries such as the Joint chemical dictionary (Jochem).

Benchmark high altitude diseases/disorders
First, the high altitude related chemicals and their target diseases/disorders were used to generate a bipartite network. The known associations between chemicals (or equivalently, drugs) and disorders or its descendants were collected from Comparative Toxicogenomics Database (CTD) in Feb 2017 [41]. In this study, the researchers mainly extracted curated associations of chemical-diseases from CTD to ensure the strong association between chemicals (or equivalently, drugs) and disorders or its descendants. The size of the nodes is based on the frequency of the diseases that were occurring in the resulting dataset composed of the 2976 abstracts. The Gephi open source graph visualization software tool is used to develop a graphic representation
of the extracted interaction network [42]. Analysis of the generated network was carried out by Cytoscape network analyser [43]. Diseases that missed their links with drugs/chemicals were left out from their disease module. Drug-disease network property and node size (frequency in literature) were used to narrow down the significant high altitude diseases/disorders and chemicals/drugs.

**Clustering disease-disease networks**

The disease-disease association among the benchmark high altitude diseases/disorders was depicted in the form of network. The association was established using the DOSE package for R based on computing semantic similarities among Disease Ontology (DO) terms associated with every disease pair [44]. The DO score in correlation matrix ranged between 0–1. Various types of cut-off techniques such as clustering based, score based, percentage based, etc., were employed. In the execution, the threshold value as topmost three edge score (even after transposition of matrix) arising from a single node was used. The clustered disease modules were constructed using fast greedy, edge betweenness, spin glass and walk trap based clustering methods [45–48]. These different disease network modules were superimposed with each other to identify the overlapped cluster disease modules. The DO score-based disease mapping was carried out to detect disease outliers.

**Google trend data collection**

Fig 2 shows the various steps in the analysis of GT. GT is used to study the temporal trends in web search using monthly and weekly Relative Search Volume (RSV). In the query, “all categories” and “all types of web search” were used, which are the default setting of GT. We searched “worldwide”, using the default settings, for the time period of Jan 2004 to Dec 2016. The rationale behind the selection of default option was to include wide variety of web resources such as image, you tube, news and Google shopping in the GT web search. The “worldwide” search option allowed us to collect RSV from almost 250 political regions, including sovereign as well as dominion states with most of them (162 countries) in the northern hemisphere (NH), covering almost 90% of our human population. RSV is calculated based on how often search terms entered in Google relative to the total search volume in a specific region. These RSV were also collected with and without a reference disease such as obesity in our case. The rationale behind the selection of obesity as the reference disease will be explained in the discussion section under the sub heading “Widespread seasonal comorbid rhythm in the severe SCLD”. The search volume of the term was normalized by dividing an unrelated common web search query. This normalization process of GT was compensated for population sizes, increased sensitivity in detection, and allowed the direct comparison of the search volume from countries/cities and different diseases. The RSV scaled between 0 and 100, with 100 being the highest search proportion per week. GT uses internet protocol (IP) addresses from server logs to assign the origin of web search queries. The monthly and weekly RSV for 12 diseases was downloaded in " .csv format with and without reference diseases for the period of 2004 to 2016 across the world. It should be noted that the relative medical terminologies, similar medical conditions and related search strings excluded in the GT search. In our opinion, such a comprehensive analysis is beyond the scope of the current study. Our GT search terms were limited to English speaking population, because this population is widely spread in world. Furthermore, two English speaking countries, United States of America (USA) and New Zealand (NZL) were geographically selected above 23.5˚N and below 23.5˚S to represent Northern and Southern hemispheres (SH) seasonal changes respectively. In both the countries, RSV of the four severe
seasonal comorbid diseases namely Asthma, Hypertension, Obesity and Fibrosis were collected with obesity as the reference for the period from January 2004 to December 2016.

**Time series analysis**

Data processing and statistical analysis were carried out using Trend package of R [49]. Time series related figures were produced using the TSA package [50]. The seasonal data component decomposition of each search term time series was carried out by local regression (LOESS) [51]. The Mann-Kendall and seasonal Mann-Kendall trend tests were used to detect overall trends significantly larger than the variance in the data for each search term (α = 0.05). To determine the significant seasonal components, an exponential smoothing state space model with Box-Cox transformation, trend, and seasonal components (TBATS) were fitted to the data using forecast package [52]. The shape based distance matrix analysis was carried out to check out the distance based on coefficient-normalized cross-correlation which reflects a time series clustering with dynamic time warping optimization [53]. This algorithm first calculates the Z-score to normalize the matrix, and forms a cross-series correlation [54]. After getting final correlation matrix, hierarchical clustering (using pvclust) was used to obtain possible groups [55]. Further, autocorrelation was observed in the disease group showing strong seasonality. Autocorrelation gives an idea about the cyclic pattern present in the data. Fast Fourier Transform (FFT) based periodograms were produced to identify key seasonal cycles in the data from 2004 and 2016 [50]. The breaking down moving average (BMA) with window size of 6 months for the periods October to March and April to September were calculated.

**Results**

**High altitude disease-drug network**

We developed a systems approach to infer benchmark diseases/disorders of high altitude to investigate their seasonality. As mentioned earlier, we have collected comprehensive list of high altitude related disorders/disease and drugs from PubMed. After excluding duplicate medical terms, they were annotated using the most commonly used Medical Subject Headings (MeSH). From 2976 high altitude related abstracts, 1710 diseases and 865 drugs were extracted using the text analytics method BeCAS. In search of closely connected high altitude diseases, the clinically reported drug-disease pairs associations were obtained from CTD [41]. After excluding duplicate drug-disease pairs and unlinked pairs, a high altitude related drug-disease bipartite network with six drugs/chemicals and 73 diseases connected by 95 edges was built (Fig 3A). The node size of each disease term in the network corresponds to its frequency of occurrence in the high altitude related abstracts. The network showed large node size for edema, hypertension, asthma, fatigue, apnea, and obesity diseases/disorders. The outlier plot further showed these six diseases have the high term frequency than the rest of the 67 diseases. Interestingly, edema, hypertension, asthma, fatigue, apnea, and obesity have the high term frequencies (>90 percentile) and node sizes and were termed as key bottleneck diseases of high altitude (Fig 3B).
High altitude associated diseases community structure analysis

To generate a high altitude disease network in which diseases that have similar signs and symptoms were clustered together. Firstly, we generated the disease similarity network (DSN) based on semantic similarities scores among DO terms associated with every disease pair. We computed the pairwise disease-disease semantic similarity matrix from the 73 high altitude related diseases. Among 73 diseases, only 41 diseases (including the six key bottleneck diseases) have disease pair similarity scores with other diseases. The weighted average disease similarity scores were used to generate the DSN. The DSN consisted of 41 nodes and 820 edges (after removing duplicates and self-loop edges) as shown in Fig 4. The DSN network was further subjected to most widely used community detection algorithms, namely- fast greedy (FG), edge betweenness (EB), spin glass (SG) and walk trap (WT) available in the “igraph” package [56]. Each algorithm clustered the DSN into four major disease communities or sub networks (Fig 5). The sub networks identified from the four algorithms were overlapped to uncover the highly associated or possible comorbid diseases. The bottleneck disease associated community clusters were chosen for detailed analysis. Interestingly, in these community clusters, hypertension formed intra-community interactions with hyperglycemia, hyperhomocysteinemia, hypercholesterolemia, and acidosis, whereas obesity formed intra-community interactions with fibrosis and esophagitis. Overall, these six bottleneck diseases and their six community disease pairs formed a core DSN (Fig 6). The core DSN (12 diseases) possessed almost 60% of the similarity score of DSN (41 diseases).

Monthly google seasonal trend analysis

Using obesity as the benchmark keyword, the month wise varying RSV for the 12 diseases (including obesity) were analyzed for seasonal trend in the 2004–2016 period. All the six bottleneck diseases showed high RSV. Except fibrosis, the remaining five community diseases with low RSV were excluded from the trend analysis (Fig 7). The seasonal Mann–Kendall and Mann–Kendall showed positive seasonal trend for asthma, hypertension, obesity, fibrosis,
apnea, and fatigue whereas edema showed no seasonal trend (Table 1). The seasonal Mann-Kendall and Mann-Kendall of the month wise RSV of the seven diseases without benchmark keyword also showed similar trends (Table 2). Based on their trend P-values, the seven diseases were clustered into two groups (1 and 2) (Fig 8A, Table 1). The strong seasonal trend in the group 1 diseases was exhibited by TBATS and LOESS analysis (Figs 9 and 10). The auto correlation analysis also revealed the presence of six months periodicity in the group 1 diseases (Fig

---

**Fig 4.** Disease ontology (DO) based semantic similarity disease network (DSN) of high altitude. The disease (red colour square shape) pairs showing the >90 percentile (outliers) literature frequency were used in the construction. The average degree (number of links with other diseases) of all diseases in the disease network is 0.1418 (marked as gray lines). The edge thickness represents the SS score between two diseases. Note that the bottleneck diseases of high altitude in the network are in square shapes rather than circle otherwise.

[https://doi.org/10.1371/journal.pone.0207359.g004](https://doi.org/10.1371/journal.pone.0207359.g004)
In this direction, we further calculated the optimal shape alignments among the seven diseases RSV using dynamic time warping method. Importantly, the clustering of the...

Fig 5. The DSN subjected to the four community detection algorithms based on the (a) edge betweenness (EB), (b) fast greedy (FG), (c) spin glass (SG) and (d) walk trap (WT) available in the “igraph” package. Here, we clearly see that among the six bottleneck diseases (square shape edges) only hypertension community (green colour) and obesity community (magenta colour) are tightly maintained by the four community detection algorithms (encircled). Please note that in all the community detection algorithms, the hypertension community associated diseases (acidosis, hypocholesterolemia, hyperhomocysteinemia, and hyperglycemra) formed a major community cluster. Similarly, the obesity community diseases (esophagitis and fibrosis) formed a short community cluster. Whereas, other bottleneck diseases not able to maintain a separate community cluster. Moreover, the overall inter community cluster interactions (red colour edges) are more than intra community cluster interactions (gray colour edges). Visualization of the network was done using cytoscape (Shannon et al., 2003).

https://doi.org/10.1371/journal.pone.0207359.g005

Fig 6. The left-hand side is the DSN of high altitude marked with six bottleneck diseases (square, red colour) and six community diseases (square, green colour). The overall semantic similarity (SS) average score of the DSN is 0.14188. The right-hand side is core DSN network of 12 diseases (six bottleneck and six community diseases). The overall semantic similarity score of the core DSN is 0.19624 and named as “highly comorbid diseases of high altitude”.

https://doi.org/10.1371/journal.pone.0207359.g006
shape extraction matrix again divided the seven diseases into two groups (1 and 2) (Fig 8B). All these results strongly suggested that group 1 diseases maintain widely spread seasonal comorbid trend.

Using obesity as the benchmark keyword, the month wise varying RSV from USA and NZL for group 1 diseases (including obesity) were analyzed for seasonal trends in the 2004–2016 period. The seasonal Mann-Kendall and auto correlation analysis of month wise RSV from both the countries revealed positive seasonal trends and 6 months periodicity respectively in most of the group 1 diseases (Table 3). The BMA of the group 1 diseases from the same periods were combined for USA and NZL separately. The BMA scores revealed that at any point of time USA and NZL have completely opposite search trends for group 1 diseases (Fig 12).

### Weekly google seasonal trend analysis

The RSV seasonal trends of the query diseases may vary depending upon the selection time interval. To avoid this, weekly RSV of the group 1 diseases were collected for the 2004–2016 period without any benchmark diseases. Furthermore, the group 1 diseases were subjected to Mann-Kendall and seasonal Mann-Kendall analysis. Both the analysis

### Table 1. Widespread monthly RSV of GT time series seasonal analysis of the core DSN diseases (Jan 2004 to Dec 2016) with obesity as the reference term. (Complete raw data is given in S1 Table).

| Seasonal Comorbid Lifestyle diseases (SCLD) of core DSN | Average RSV | Mann-Kendall Trend Test | Seasonal Mann-Kendall Trend Test | Seasonal Decomposition | Autocorrelation | Periodicity |
|--------------------------------------------------------|-------------|-------------------------|----------------------------------|------------------------|-----------------|------------|
|                                                        | p-value  | tau | z | S | varS | p-value | z | S | varS | TBATS | LOESS |            |
| Asthma                                                 | 49.55     | <0.0001 | -0.44 | -8.02 | 5274 | 431995 | <0.0001 | -8.32 | -465 | 3108 | Yes | Yes | Yes | 6 months |
| Obesity                                                | 43.01     | <0.0001 | -0.7 | -12.81 | 8440 | 433651 | <0.0001 | -16.16 | -917 | 3215 | Yes | Yes | Yes | 6 months |
| Hypertension                                           | 35        | <0.0001 | -0.63 | -11.4 | 7500 | 432005 | <0.0001 | -13.71 | -767 | 3122 | Yes | Yes | Yes | 6 months |
| Fibrosis                                               | 27.22     | <0.0001 | -0.54 | -9.71 | 6383 | 431473 | <0.0001 | -11.98 | -669 | 3108 | Yes | Yes | Yes | 6 months |
| Fatigue                                                | 43.61     | 0.0018 | 0.17 | 3.11 | 2050 | 431349 | <0.0001 | 4.05 | 229 | 3168 | Yes | Yes | Yes | 6 months |
| Edema                                                  | 24.29     | 0.1896 | -0.07 | -1.31 | 855 | 423864 | 0.2632 | -1.19 | -62 | 3072 | Yes | Yes | Yes | 6 months |
| Apnea                                                  | 22.71     | 0.0036 | -0.17 | -2.91 | -1888 | 420193 | 0.0265 | -2.22 | -123 | 3024 | Yes | Yes | Yes | 6 months |
| Acidity                                                | 7.07      | 0.73 | - | - | - | - | - | - | - | - | - | - | - | - |
| Hyperglycemia                                          | 3.35      | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Esophagitis                                            | 2.56      | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hypercholesterolemia                                   | 1.1       | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Hyperhomocysteinemia                                   | 0         | - | - | - | - | - | - | - | - | - | - | - | - | - |

https://doi.org/10.1371/journal.pone.0207359.t001
showed strong seasonal trends in the group 1 diseases, also supported by LOESS seasonal decomposition analysis (Table 4). Further, seasonal decomposition analysis by TBATS revealed high seasonal trend in obesity even in the noisy weekly RSV of the four diseases. The optimal shape alignments were also achieved among the group 1 diseases weekly RSV (S4 Table). All these results again strongly suggested that group 1 diseases maintain widespread seasonal comorbid trend.

**Discussion**

A fundamental question in biology and medicine is to what degree the seasonality is related to the manifestation of human disorders, a hypothesis that we aimed to test in the present work. We find: (i) HA diseases and disorders with similar signs and symptoms reduced into the core DSN (12 diseases); (ii) RSV time series analysis revealed that most of the core DSN diseases

| Seasonal Comorbid Lifestyle diseases (SCLD) of core DSN | Average RSV | Mann-Kendall Trend Test | Seasonal Mann-Kendall Trend Test |
|--------------------------------------------------------|-------------|-------------------------|---------------------------------|
|                                                        | p-value     | tau z S varS            | p-value z S varS                |
| Asthma                                                 | 59.09       | <0.0001 -0.48 -8.68 -5658 424575 | <0.0001 -8.98 -505 3149 |
| Obesity                                                | 41.71       | <0.0001 -0.71 -12.95 -8446 425435 | <0.0001 -15.97 -906 3212 |
| Hypertension                                           | 57.56       | <0.0001 -0.64 -11.69 -7620 424882 | <0.0001 -13.43 -758 3178 |
| Fibrosis                                               | 53.76       | <0.0001 -0.53 -9.74 -6348 424934 | <0.0001 -11.52 -650 3173 |
| Fatigue                                                | 72.01       | 0.0010 0.18 3.29 2144 424894 | <0.0001 4.13 234 3183 |
| Edema                                                  | 76.26       | 0.2155 -0.07 -1.24 -808 424478 | 0.3453 -0.94 -54 3154 |
| Apnea                                                  | 67.82       | 0.0121 -0.14 -2.51 -1633 423451 | 0.0881 -1.71 -97 3168 |
| Acidosis                                               | 73.31       | <0.0001 -0.22 -3.96 -2580 424853 | <0.0001 -5.6 -315 3154 |
| Hyperglycemia                                          | 73.01       | 0.0124 0.14 2.5 1632 425133 | <0.0001 3.83 217 3175 |
| Esophagitis                                            | 62.1        | 0.0184 -0.13 -2.36 -1537 424163 | 0.0231 -2.27 -129 3176 |
| Hypercholesterolemia                                   | 12.42       | <0.0001 -0.21 -3.9 -2531 421592 | 0.0006 -3.41 -192 3137 |
| Hyperhomocysteinemia                                   | 35.2        | <0.0001 -0.46 -8.49 -5535 425072 | <0.0001 -8.54 -484 3196 |

**Fig 8.** Widespread seasonal sensitive comorbid diseases. (a) Seasonal Mann-Kendall p-values of seasonal sensitive life style diseases represented as heat map for the entire period (Jan 2004 to Dec 2016). The hierarchical clustering clearly divided them into diseases with (red box) and without (blue box) season trend. (b) Shape based distance matrix scores among the major highly comorbid diseases of high altitude represented as heat map for the entire period (Jan 2004 to Dec 2016). The hierarchical clustering clearly divided them into diseases with (red box) and without (blue box) seasonal pattern matching. Please note that the four diseases (obesity, asthma, hypertension, and fibrosis) in the red boxes have similar seasonal trends and seasonal patterns named as “Group 1” diseases (S1 Table).
(except edema) have significant seasonal trends; (iii) Among the core DSN diseases, the public interest in asthma, hypertension, obesity, and fibrosis diseases exhibit strong global seasonal comorbid trend in human population. The merits of each findings, limitations, and implications are discussed below.

Seasonal (sensitive) comorbid lifestyle diseases (SCLD) network

The DSN is derived from many clinical and systemic studies of major HA disorders and diseases. The core DSN renders a dense network of highly similar signs and symptoms reveal their strong comorbid association. Several clinical evidences support the strong comorbid
association of the core DSN (Fig 13). The core DSN is exploited further to study their shared underlying disease etiologies. There are several clinical evidences that support that the major common etiology of core DSN is seasons along with lifestyle factors such as biological clock, inadequate exercise, and bad diet, which further contribute to their disease progression and activation (Table 5). Based on these findings, we named the “core DSN” as “seasonal (sensitive) comorbid lifestyle diseases (SCLD) network”.

One of the key objectives in the identification of comorbid diseases is to find a common pathological process of significant clinical importance [57]. Interestingly, the major common pathological process of SCLD flares turned out to be the onset of hypoxic state during their pathophysiological process. For example, asthma [58,59], fibrosis [60], apnea [61–63], edema [64–66] and obesity [67,68] create endogenous hypoxic state in lungs, which leads to the disruption of energy supply functions and plastic processes. This lung hypoxic environment increases pulmonary hypertension [69–71] in turn leads to fatigue [72–74], respiratory acidosis [75] and lethal esophagitis [76] in certain maladapted population. Unlike, to our knowledge, none of the clinical studies addressed the onset of hypoxic state in hypercholesterolemia.
[77–79], hyperhomocysteinemia [80–83], and hyperglycemia [84–86] patients disease progression. Surprisingly, all the three disorders impair endothelium-dependent vasodilatation by reducing the key hypoxia responsive molecule nitric oxide (NO) production [87]. Overall, the onset of hypoxic state during the disease progression appears to be shared by SCLD. This predicted common pathological process is of clinical importance in the sense that inhaled NO is proposed as a long-term therapy or used as a rescue therapy to some of the SCLD patients [88–91]. Furthermore, individual genetic makeup is one of the major factors that determines an individual’s susceptibility to seasonal changes by invoking complex patho-physiological pathways [92,93].

### Classification of SCLD with benchmark

Several studies have successfully correlated the Google RSV with disease prevalence and their seasonal trend with diseases progression [94,95]. For the first time, a benchmark disease such as obesity based RSV is used to classify the SCLD into severe, moderate, and mild categories. First, based on high RSV, the present study classifies hypertension, obesity, asthma, and fibrosis diseases as the most severe widespread seasonally associated SCLD. In other words, their high RSV indicators a majority of the human population is more severely subject to

**Table 4. Widespread weekly time series seasonal analysis of life style diseases (Jan 2004 to Dec 2016).**  (Complete raw data is given in S4 Table).

| Severe Comorbid Diseases | Average RSV | p-value | tau | z   | S     | varS  | p-value | z   | S     | varS  | TBATS | LOESS |
|--------------------------|-------------|---------|-----|-----|-------|-------|---------|-----|-------|-------|-------|-------|
| Asthma                   | 84.72       | <0.0001 | 0.13| 4.89| 28621 | 34351640| <0.0001 | 10.79| 1262 | 13665 | No    | Yes   |
| Obesity                  | 74.86       | 0.0002  | 0.09| 3.61| 21225 | 34382780| <0.0001 | 12.2 | 1426 | 13688 | Yes   | Yes   |
| Hypertension             | 85.21       | <0.0001 | 0.16| 6.15| 36025 | 34355190| <0.0001 | 14.13| 1652 | 13655 | No    | Yes   |
| Fibrosis                 | 68.48       | <0.0001 | -0.11| -4.24| -24854| 34381480| 0.004 | -2.88| -339 | 13808 | No    | Yes   |

https://doi.org/10.1371/journal.pone.0207359.t004

https://doi.org/10.1371/journal.pone.0207359.g012
seasonal changes in these diseases. Their RSV pattern shape alignments further indicates their strong widespread high bi-seasonal comorbid in the human population. These disease’s high seasonal severity and comorbidity is becoming a major health issue in most of the countries around the world [96]. Second, based on the moderate RSV, the present study classifies edema, apnea, acidosis and fatigue as the moderate SCLD diseases. Several clinical studies indicate the presence of bi and quarterly seasonal variations in them [97–99]. Even though they have the moderate average RSV widespread, in certain countries, the average RSV of the disease terms edema (South America, Italy, Spain, Indonesia, and Lithuania), and apnea (Venezuela, Italy, Spain, and Turkey) is more than the severe SCLD. This may be due to the influence of the language bias in these disease search term RSV. Finally, the present study classifies hypercholesterolemia, hyperglycemia, hyperhomocysteinemia, and esophagitis as mild SCLD diseases/disorders with bi and quarterly seasonal variations. The results, also supported by several clinical studies, demonstrate the seasonal variation of lipid and glycemic levels in blood and serum from the hypercholesterolemia and hyperglycemia patients respectively [100–102].
Although we classify hyperhomocysteinemia as mild SCLD, the evidence of its seasonal variation of blood homocysteine level remains controversial [103]. In tune, the weekly RSV analysis of hyperhomocysteinemia shows no seasonal trend. In USA, a mild but consistent seasonal variation in the diagnosis of esophagitis was observed, which corroborates with the present study [104]. Interestingly, the bi-annual peaks (six months periodicity) in most of the diseases occur in the late winters (October through December) and falls (March through April) (Fig 7). This observation is also of significant clinical importance, especially for the chronic disease asthma. The annual exacerbations rate of asthma follows these two peaks, one in October through December, and the other from March through April and is a well reported global phenomenon [105–108]. Several potentially important SCLD disease risk factors such as seasonal variations in the serum level of insulin, cholesterol, and glucose which also tend to follow the same trend [109].

### Widespread seasonal comorbid rhythm in the severe SCLD

Apart from RSV and high significant seasonal trend, even from the noisy weekly data, we consider obesity as our benchmark disease to predict the comorbidity based on multiple factors. Worldwide obesity (higher BMI values) has nearly doubled since 1980, and current estimates indicate that >1.4 billion adults are overweight or obese [110]. Whilst, there is considerable evidence that obesity is strongly associated with seasonality [111]. In correlation, our study finds the highly significant widespread seasonal trend in the public interest on obesity for the period 2004–2016. However, in modern society, especially those who access internet, are mostly used to living in artificial lighting, heating and air-conditioning systems that considerably reduce the exposure of individuals to seasonal (day and light exposure) and environmental changes [112]. Probably, studies also claimed that the extensive use of these artificial aids may develop mismatch between the season and the body clock that may promote obesity [113,114]. Importantly, being overweight or obese leads to higher prevalence of risk association with chronic diseases such as systemic and pulmonary hypertension, chronic kidney diseases, stroke, obstructive sleep apnea, gastroesophageal reflux disease, type 2 diabetes, osteoarthritis etc. [115]. The risk association of these diseases at any given level of obesity varies with ethnicity. For example, Asians have been shown to have a higher absolute risk of

| Diseases/Symptoms | Seasonal (PMID) | Lifestyle (PMID) |
|-------------------|-----------------|------------------|
| Edema             | 11420189 (44)   | 5695605 (6)      |
| Hypertension      | 8301109 (50), 22688260 (27), 7074993 (23), 15331861 (8), 20859042 (6) | 28775806 (1) |
| Asthma            | 10899242 (22), 26922932 (4) | 22555908 (3), 27238186 (1), 29221919 |
| Fatigue           | 8064638 (1), 26846791 | 18562170 (15), 11858191 (10), 19812026 (7), 20886027 (3), 17660146 (3) |
| Apnea             | 22700779 (6) | 24082315 (27), 28833858 |
| Obesity           | 16154393 (13) | 22591544 (20), 26911589 (5) |
| Fibrosis          | 18689582 (11) | 29045951, 28452727, 29479443 |
| Acidosis          | 26265754 | 22935845 (12), 22853725 (5) |
| Hyperglycemia     | 28173630 | 15589017 (14), 18301331 (11) |
| Hypercholesterolemia | 15111372 (44), 3315294 (14), 1482576 (4) | 16144549 (11) |
| Hyperhomocysteinemia | 9550566 (7) | 11447048 (19), 15739593 (2) |
| Esophagitis       | 26059636 (4), 26235409 (2) | 19360912 (23), 22554226 (16) |

https://doi.org/10.1371/journal.pone.0207359.t005

| Table 5. List of clinical studies (PMIDs) reported the seasonal and life style factors impact on etiology of the core DSN. Please note that this list is not exhaustive and only includes some of the frequently cited reference PMIDs. The citation numbers of each PMIDs as on June 2018 from PubMed is given in the bracket. |
|---|---|---|
| Diseases/Symptoms | Seasonal (PMID) | Lifestyle (PMID) |
| Edema             | 11420189 (44) | 5695605 (6) |
| Hypertension      | 8301109 (50), 22688260 (27), 7074993 (23), 15331861 (8), 20859042 (6) | 28775806 (1) |
| Asthma            | 10899242 (22), 26922932 (4) | 22555908 (3), 27238186 (1), 29221919 |
| Fatigue           | 8064638 (1), 26846791 | 18562170 (15), 11858191 (10), 19812026 (7), 20886027 (3), 17660146 (3) |
| Apnea             | 22700779 (6) | 24082315 (27), 28833858 |
| Obesity           | 16154393 (13) | 22591544 (20), 26911589 (5) |
| Fibrosis          | 18689582 (11) | 29045951, 28452727, 29479443 |
| Acidosis          | 26265754 | 22935845 (12), 22853725 (5) |
| Hyperglycemia     | 28173630 | 15589017 (14), 18301331 (11) |
| Hypercholesterolemia | 15111372 (44), 3315294 (14), 1482576 (4) | 16144549 (11) |
| Hyperhomocysteinemia | 9550566 (7) | 11447048 (19), 15739593 (2) |
| Esophagitis       | 26059636 (4), 26235409 (2) | 19360912 (23), 22554226 (16) |

https://doi.org/10.1371/journal.pone.0207359.t005
diabetes and hypertension and African Americans to have a lower risk of cardiovascular disease than other groups [116]. Similarly, the prevalence of obesity risk associated diseases varies according to geographical location of the country. For example, the relative risk of death associated with diabetes in Mexico far exceeds that in the United States and Europe [117]. Significantly, first time, our study has shown that public interest in major chronic lifestyle diseases such as obesity, asthma, hypertension, and fibrosis follow a similar strong seasonal pattern or seasonal rhythm which is independent of ethnicity and most likely dependent on seasons. For example, October is commonly associated with the season of autumn in USA and with spring in NZL. In October, our study showed the SCLD search patterns of USA and NZL follow totally opposite seasonal trends and supported by clinical studies [118–122]. In this electronic search study, trends of internet user interest on these SCLD determined for 250 regions from seven continents, suggesting that this is a global phenomenon. This predicted pattern of increase in the prevalence of seasonal comorbid association among asthma, hypertension and obesity is highly supported by clinical evidences [123–125]. Even though fibrotic diseases strongly associate with season, their seasonal comorbid association with obesity, hypertension, and asthma is poorly evaluated [10,126,127]. Further studies in this direction could help healthcare providers to design season based strategies for the better management and prevention or efficacy of treatment start at different months of the year to control the seasonal flare.

Limitations

This study has several limitations in the text mining as well as electronic search (GT) that need to be considered while interpreting the results. In text mining, the coverage of diseases and symptoms are limited to the abstracts of “PUBMED”, the search terms “high altitude disease”, “high altitude disorder”, “high altitude medicine”, and “High altitude drug” and the search period (Jan 2004–Jan 2017) [128]. In addition, the DO semantic similarity between DSN diseases should be available in the DOSE package [44]. These limits variety of other diseases, and their interactions could be left out in the DSN probably of decisive importance for the generality of results. In the electronic search, our search study revealed the seasonal trends of public interest in the 12 DSN diseases, but not the seasonal trend of the 12 diseases itself. Furthermore, the individual performing the search is not necessarily suffering from the diseases. To validate our predictions, they should be correlated with clinical data. Meanwhile, the demographic characteristics were not available for the users who were performing the search. Besides the GT ability to cover a large geographical area (250 regions from seven continents), 90% of human population living in the northern hemisphere dominate the worldwide RSV seasonal patterns. Moreover, efforts were not made in our study to give special attention to the remaining 10% of human population living in southern hemisphere seasonal changes. In addition, the seasonal patterns were not studied using any language other than English and with a search engine other than Google. Finally, important covariates other than 12 diseases terms affect the development of these 12 diseases or search behaviors could not be assessed.

Conclusions

Despite several limitations, there are several strengths in this study. Majority of the human population adapts well to these seasonal changes. But significant world human population maladaptive to seasonal changes, and render their body highly susceptible to one or other kind of disorders [129,130]. Less progress is made to classify this highly seasonal sensitive population from the normal population. This is mainly due to the challenge in prioritizing seasonal sensitive diseases from the environmental sensitive diseases and lifestyle diseases. In this direction, the present study has successfully addressed this issue by predicting the SCLD, and
indirectly verified them in the world population using Google Search Trends. Furthermore, based on the SCLD seasonal public interest trend, the study also classified them as severe, moderate and mild. To our knowledge, for first time, these results provide a basis to predict and classify seasonal sensitive population. The study also necessitates the need to study these categories of seasonal sensitive population separately, because they are genetically susceptible host for the SCLD flares. The dense semantic similar diseases network of SCLD further reflects the most possible comorbid seasonal sensitive diseases. Further, knowledge in the so called “seasonal sensitive populations” physiological and molecular response to seasonal triggers such as winter, summer, spring, and autumn become crucial to modulate disease incidence, disease course, or clinical prevention.

Supporting information

S1 Table. Worldwide monthly RSV raw data for the period Jan 2004 to Dec 2016 with obesity as the reference term and shape distance matrix for this period.

S2 Table. Worldwide monthly RSV raw data for the period Jan 2004 to Dec 2016 without reference term.

S3 Table. Monthly RSV of USA (NH) and NZL (SH) for obesity, hypertension, obesity and fibrosis diseases (Jan 2004 to Dec 2016) with obesity as the reference term. The combined RSV for the Group 1 diseases, the season wise window size of six months period and BMA for Group 1 diseases were displayed for both USA (Red) and NZL (Blue).

S4 Table. Worldwide weekly RSV raw data for the period Jan 2004 to Dec 2016 without reference term and shape distance matrix for this period.

S5 Table. The complete reference of the labelled PMIDs of the Fig 13.

Author Contributions

Conceptualization: Jai Chand Patel, Sugadev Ragumani.
Data curation: Jai Chand Patel.
Formal analysis: Jai Chand Patel.
Funding acquisition: Sugadev Ragumani.
Investigation: Jai Chand Patel, Sugadev Ragumani.
Methodology: Jai Chand Patel.
Project administration: Sugadev Ragumani.
Resources: Bhuvnesh Kumar, Sugadev Ragumani.
Software: Jai Chand Patel.
Supervision: Pankaj Khurana, Yogendra Kumar Sharma, Sugadev Ragumani.
Validation: Jai Chand Patel, Sugadev Ragumani.
Visualization: Jai Chand Patel.
Writing – original draft: Sugadev Ragumani.
Writing – review & editing: Bhuvnesh Kumar, Sugadev Ragumani.

References

1. Acevedo-Whitehouse K, Duffus AL (2009) Effects of environmental change on wildlife health. Philos Trans R Soc Lond B Biol Sci 364: 3429–3438. https://doi.org/10.1098/rstb.2009.0128 PMID: 19833653

2. Milligan SR, Holt WV, Lloyd R (2009) Impacts of climate change and environmental factors on reproduction and development in wildlife. Philos Trans R Soc Lond B Biol Sci 364: 3313–3319. https://doi.org/10.1098/rstb.2009.0175 PMID: 19833643

3. Sipila JO, Ruuskanen JO, Kauko T, Rautava P, Kyto V (2017) Seasonality of stroke in Finland. Ann Med 49: 310–318. https://doi.org/10.1080/07853890.2016.1254350 PMID: 27786555

4. Han MH, Yi HJ, Kim YS, Kim YS (2015) Effect of seasonal and monthly variation in weather and air pollution factors on stroke incidence in Seoul, Korea. Stroke 46: 927–935. https://doi.org/10.1161/STROKEAHA.114.007950 PMID: 25669311

5. Lontchi-Yiagou E, Tsalefac M, Tapinme LM, Noubiap JJ, Balti EV, Nguewa JL et al. (2016) Seasonality in diabetes in Yaounde, Cameroon: a relation with precipitation and temperature. BMC Public Health 16: 470. https://doi.org/10.1186/s12889-016-3090-1 PMID: 27266270

6. Moltchanova EV, Schreier N, Lammi N, Karvonnen M (2009) Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. Diabet Med 26: 673–678. https://doi.org/10.1111/j.1464-5491.2009.02743.x PMID: 19573115

7. McNally RJ, James PW, Ducker S, James OF (2011) Seasonal variation in the patient diagnosis of primary biliary cirrhosis: further evidence for an environmental component to etiology. Hepatology 54: 2099–2103. https://doi.org/10.1002/hep.24597 PMID: 21826693

8. Fares A (2013) Winter cardiovascular diseases phenomenon. N Am J Med Sci 5: 266–279. https://doi.org/10.4103/1947-2714.110430 PMID: 23724401

9. Barne C, Alexis NE, Bernstein JA, Cohn JR, Demain JG, Horner E et al. (2013) Climate change and our environment: the effect on respiratory and allergic disease. J Allergy Clin Immunol Pract 1: 137–141. https://doi.org/10.1016/j.jaip.2012.07.002 PMID: 23687635

10. Bhatia S, Bhatia S, Mears J, Dibu G, Deshmukh A (2017) Seasonal Periodicity of Ischemic Heart Disease and Heart Failure. Heart Fail Clin 13: 681–689. https://doi.org/10.1016/j.hfc.2017.05.004 PMID: 28865777

11. Bahonar A, Khosravi A, Khovash V, Maracy M, Saadatnia M (2017) Seasonal and Monthly variation in stroke and its subtypes-10 Year Hospital-Based Study. Mater Sociomed 29: 119–123. https://doi.org/10.5455/msm.2017.29.119-123 PMID: 28883775

12. Bernard SM, Samet JM, Grampsch A, Ebi KL, Romieu I (2001) The potential impacts of climate variability and change on air pollution-related health effects in the United States. Environ Health Perspect 109 Suppl 2: 199–209.

13. Guarnieri M, Balmes JR (2014) Outdoor air pollution and asthma. Lancet 383: 1581–1592. https://doi.org/10.1016/S0140-6736(14)60617-6 PMID: 24792855

14. Gabb G, Arnolda L (2017) Geographic location as a modifiable cardiac risk factor. CMAJ 189: E482–E483. https://doi.org/10.1503/cmaj.170116 PMID: 28385892

15. Wang L, Southerland J, Wang K, Bailey BA, Alamian A, Stevens MA et al. (2017) Ethnic Differences in Risk Factors for Obesity among Adults in California, the United States. J Obes 2017: 2427483. https://doi.org/10.1155/2017/2427483 PMID: 28352473

16. Shirota EJ, Lee IM (2010) Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 122: 743–752. https://doi.org/10.1161/CIRCULATIONAHA.109.194721 PMID: 20713909

17. Barone Gibbs B, Petree Gabriel K, Carnethon MR, Gary-Webb T, Jakicic JM, Rana JS, et al. (2017) Sedentary Time, Physical Activity, and Adiposity: Cross-sectional and Longitudinal Associations in CARDIA. Am J Prev Med 53: 764–771. https://doi.org/10.1016/j.amepre.2017.07.009 PMID: 29032856

18. Rozanski A (2014) Behavioral cardiology: current advances and future directions. J Am Coll Cardiol 64: 100–110. https://doi.org/10.1016/j.jacc.2014.03.047 PMID: 24998134
19. Olsson T, Barcellos LF, Alfredsson L (2017) Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 13: 25–36. https://doi.org/10.1038/nrneuro.2016.187 PMID: 27934854

20. Sears MR (1997) Epidemiology of childhood asthma. Lancet 350: 1015–1020. https://doi.org/10.1016/S0140-6736(97)01468-2 PMID: 9329526

21. Khot A, Burn R, Evans N, Lenney C, Lenney W (1984) Seasonal variation and time trends in childhood asthma in England and Wales 1975–81. Br Med J (Clin Res Ed) 289: 235–237.

22. Garcia-Marcos L, Carvajal Uruena I, Escrivano Montaner A, Fernandez Benitez M, Garcia de la Rubia S, Tauler Toro E, et al. (2007) Seasons and other factors affecting the quality of life of asthmatic children. J Investig Allerg Clin Immunol 17: 249–256. PMID: 17694697

23. Subbarao P, Mandalhe PJ, Sears MR (2009) Asthma: epidemiology, etiology and risk factors. CMAJ 181: E181–190. https://doi.org/10.1503/cmaj.080612 PMID: 19752106

24. Su X, Ren Y, Li M, Zhao X, Kong L, Kang J (2016) Prevalence of Comorbidities in Asthma and Non-asthma Patients: A Meta-analysis. Medicine (Baltimore) 95: e3459.

25. Peacock AJ (1998) ABC of oxygen: oxygen at high altitude. BMJ 317: 1063–1066. PMID: 9774298

26. Subudhi AW, Bourdillon N, Bucher J, Davis C, Elliott JE, Eutermoster M, et al. (2014) AltitudeOmics: the integrative physiology of human acclimatization to hypobaric hypoxia and its retention upon reascent. PLoS One 9: e92191. https://doi.org/10.1371/journal.pone.0092191 PMID: 24689407

27. Gallagher SA, Hackett PH (2004) High-altitude illness. Emerg Med Clin North Am 22: 329–355, viii. https://doi.org/10.1016/j.emc.2004.02.001 PMID: 15163571

28. Seys SF, Daenen M, Dilissen E, Van Thienen R, Bullens DM, Hespel P, et al. (2013) Effects of high altitude and cold air exposure on airway inflammation in patients with asthma. Thorax 68: 906–913. https://doi.org/10.1136/thoraxjnl-2013-203280 PMID: 23821393

29. Yang B, Sun ZJ, Cao F, Zhao H, Li CW, Zhang J (2015) Obesity is a risk factor for acute mountain sickness: a prospective study in Tibet railway construction workers on Tibetan plateau. Eur Rev Med Pharmacol Sci 19: 119–122. PMID: 25635984

30. Gilbert-Kawai E, Martin D, Grocott M, Levett D (2016) High altitude-related hypertensive crisis and acute kidney injury in an asymptomatic healthy individual. Extreme Physiol Med 5: 10. https://doi.org/10.1186/s13728-016-0051-3 PMID: 27051893

31. Hesse BW, Nelson DE, Kreps GL, Croyle RT, Arora NK, Rimer BK, et al. (2005) Trust and sources of health information: the impact of the Internet and its implications for health care providers: findings from the first Health Information National Trends Survey. Arch Intern Med 165: 2618–2624. https://doi.org/10.1001/archinte.165.22.2618 PMID: 16344419

32. Shiffman S, Battista DR, Kelly JP, Malone MK, Weinstein RB, Kaufman DW (2018) Prevalence of exceeding maximum daily dose of paracetamol, and seasonal variations in cold-flu season. Br J Clin Pharmacol 84: 1250–1257. https://doi.org/10.1111/bcp.13551 PMID: 29516533

33. Lotto M, Ayala Aguirre PE, Rios D, Andrade Moreira Machado MA, Pereira Cruvinel AF, Cruvinel (2017) Analysis of the interests of Google users on toothache information. PLoS One 12: e0186059. https://doi.org/10.1371/journal.pone.0186059 PMID: 29049315

34. Moon RJ, Curtis EM, Davies JH, Cooper C, Harvey NC (2017) Seasonal variation in Internet searches for vitamin D. Arch Osteoporos 12: 28. https://doi.org/10.1007/s11657-017-0322-7 PMID: 28285938

35. Rossignol L, Pelat C, Lambert B, Flahault A, Chartier-Kastler E, Hanslik T (2013) A method to assess seasonality of urinary tract infections based on medication sales and google trends. PLoS One 8: e76020. https://doi.org/10.1371/journal.pone.0076020 PMID: 24204587

36. FY F (2017) PubMedWordcloud: ‘Pubmed’ Word Clouds. R package version 0.3.4.

37. Nunes T, Campos D, Matos S, Oliveira JL (2013) BeCAS: biomedical concept recognition services and visualization. Bioinformatics 29: 1915–1916. https://doi.org/10.1093/bioinformatics/btt317 PMID: 23736528

38. Jonquet C, Shah NH, Musen MA (2009) The open biomedical annotator. Summit Transl Bioinform 2009: 56–60. PMID: 21347171

39. Shah NH, Bhatia N, Jonquet C, Rubin D, Chiang AP, Musen MA (2009) Comparison of concept recognizers for building the Open Biomedical Annotator. BMC Bioinformatics 10 Suppl 9: S14.

40. Campos D, Matos S, Oliveira JL (2013) A modular framework for biomedical concept recognition. BMC Bioinformatics 14: 281. https://doi.org/10.1186/1471-2105-14-281 PMID: 24063607

41. Davis AP, Grondin CJ, Johnson RJ, Sciacr D, King BL, McMorrone R, et al. (2017) The Comparative Toxicogenomics Database: update 2017. Nucleic Acids Res 45: D972–D978. https://doi.org/10.1093/nar/gkw838 PMID: 27651457
42. Bastian M. HS, Jacomy M. (2009) Gephi: an open source software for exploring and manipulating networks. International AAAI Conference on Weblogs and Social Media.

43. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13: 2498–2504. https://doi.org/10.1101/gr.1239303 PMID: 14597658

44. Yu G, Wang LG, Yan GR, He QY (2015) DOSE: an R/Bioconductor package for disease ontology semantic and enrichment analysis. Bioinformatics 31: 608–609. https://doi.org/10.1093/bioinformatics/btu684 PMID: 25677125

45. Girvan M, Newman ME (2002) Community structure in social and biological networks. Proc Natl Acad Sci U S A 99: 7821–7826. https://doi.org/10.1073/pnas.122653799 PMID: 12060727

46. Reichardt J, Bornholdt S (2006) Statistical mechanics of community detection. Phys Rev E Stat Nonlin Soft Matter Phys 74: 016110. https://doi.org/10.1103/PhysRevE.74.016110 PMID: 16907154

47. Clauset A, Newman ME, Moore C (2004) Finding community structure in large networks. Phys Rev E Stat Nonlin Soft Matter Phys 70: 066111. https://doi.org/10.1103/PhysRevE.70.066111 PMID: 15697438

48. ML PP (2006) Computing communities in large networks using random walks. Journal of Graph Algorithms and Applications 10: 191–218.

49. T P (2016) trend: Non-Parametric Trend Tests and Change-Point Detection. R package version 0.2.0.

50. BR K-SC (2012) TSA: Time Series Analysis. R package version 1.01.

51. Robert B. Cleveland JEM, and Irma Terpenning (1990) STL: A Seasonal-Trend Decomposition Procedure Based on Loess. Journal of official statistics 6.

52. YK RJH (2008) Automatic Time Series Forecasting: the forecast Package for R. Journal of Statistical Software 27.

53. A S-E (2017) dtwclust: Time Series Clustering Along with Optimizations for the Dynamic Time Warping Distance.

54. T G (2009) Computing and Visualizing Dynamic Time Warping Alignments in R: The dtw Package. Journal of Statistical Software 31.

55. Ryota Suzuki HS (2006) Pvclust: an R package for assessing the uncertainty in hierarchical clustering. Bioinformatics.

56. NT CG (2006) The igraph software package for complex network research. InterJournal Complex Systems 1695.

57. Torrens M, Martin-Santos R, Samet S (2006) Importance of clinical diagnoses for comorbidity studies in substance use disorders. Neurotox Res 10: 253–261. PMID: 17197374

58. Lowhagen O (2012) Diagnosis of asthma—a new approach. Allergy 67: 713–717. https://doi.org/10.1111/j.1398-9995.2012.02821.x PMID: 22571439

59. Ritz T, Rosenfield D, Dewilde S, Steptoe A (2010) Daily mood, shortness of breath, and lung function in asthma: concurrent and prospective associations. J Psychosom Res 69: 341–351. https://doi.org/10.1016/j.jpsych res.2010.05.004 PMID: 20946535

60. Todd NW, Luzina IG, Atamas SP (2012) Molecular and cellular mechanisms of pulmonary fibrosis. Fibrogenesis Tissue Repair 5: 11. https://doi.org/10.1186/1755-1536-5-11 PMID: 22824096

61. Stein MB, Millar TW, Larsen DK, Kryger MH (1995) Irregular breathing during sleep in patients with panic disorder. Am J Psychiatry 152: 1168–1173. https://doi.org/10.1176/ajp.152.8.1168 PMID: 7625465

62. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328: 1230–1235. https://doi.org/10.1056/NEJM199304293281704 PMID: 8484434

63. Jordan AS, White DP, Lo YL, Wellman A, Eckert DJ, Yim-Yeh S et al. (2009) Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 32: 361–368. PMID: 19294956

64. Trayes KP, Studdiford JS, Pickle S, Tully AS (2013) Edema: diagnosis and management. Am Fam Physician 88: 102–110. PMID: 23939641

65. Marmor MF (1999) Mechanisms of fluid accumulation in retinal edema. Doc Ophthalmol 97: 239–249. PMID: 10896337

66. Wrig H (2011) Pathophysiology of tissue fluid accumulation in inflammation. J Physiol 589: 2945–2953. https://doi.org/10.1113/jphysiol.2011.206136 PMID: 21486781

67. Foti DP, Brunetti A (2017) Editorial: "Linking Hypoxia to Obesity". Front Endocrinol (Lausanne) 8: 34.
68. Norouzirad R, Gonzalez-Muniesa P, Ghasemi A (2017) Hypoxia in Obesity and Diabetes: Potential Therapeutic Effects of Hyperoxia and Nitrate. Oxid Med Cell Longev 2017: 5350267. https://doi.org/10.1155/2017/5350267 PMID: 28607631

69. Wedgwood S, Lakshminrusimha S, Schumacker PT, Steinhorn RH (2015) Hypoxia inducible factor signaling and experimental persistent pulmonary hypertension of the newborn. Front Pharmacol 6: 47. https://doi.org/10.3389/fphar.2015.00047 PMID: 25814954

70. Bosc LV, Resta T, Walker B, Kanagy NL (2010) Mechanisms of intermittent hypoxia induced hypertension. J Cell Mol Med 14: 3–17. https://doi.org/10.1111/j.1582-4934.2009.00929.x PMID: 19818095

71. Calbet JA (2003) Chronic hypoxia increases blood pressure and noradrenaline spillover in healthy humans. J Physiol 551: 379–386. https://doi.org/10.1113/jphysiol.2003.045112 PMID: 12844510

72. Harbison JA, Walsh S, Kenny RA (2009) Hypertension and daytime hypotension found on ambulatory blood pressure is associated with fatigue following stroke and TIA. QJM 102: 109–115. https://doi.org/10.1093/qjmed/hcn146 PMID: 19033353

73. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM et al. (1987) Primary pulmonary hypertension. A national prospective study. Ann Intern Med 107: 216–223. PMID: 3605900

74. Weinstein AA, Chin LM, Keyser RE, Kennedy M, Nathan SD, Woolstenhulme JG et al. (2013) Effect of aerobic exercise training on fatigue and physical activity in patients with pulmonary arterial hypertension. Respir Med 107: 778–784. https://doi.org/10.1016/j.rmed.2013.02.006 PMID: 23478192

75. Daum S (1972) [Pulmonary hypertension in acute respiratory acidosis]. Med Welt 23: 1012–1013. PMID: 5077662

76. Gudlaugsdottir S, Verschueren W, Dees J, Stijnen T, Wilson J (2002) Hypertension is frequent in patients with reflux esophagitis or Barrett's esophagus but not in those with non-ulcer dyspepsia. Eur J Intern Med 13: 369. PMID: 12225781

77. Ivanovic B, Tadic M (2015) Hypercholesterolemia and Hypertension: Two Sides of the Same Coin. Am J Cardiovasc Drugs 15: 403–414. https://doi.org/10.1007/s40256-015-0128-1 PMID: 26062915

78. Tunon J, Martin-Ventura JL, Blanco-Colo LM, Tarin N, Egido J (2007) Common pathways of hypercholesterolemia and hypertension leading to atherothrombosis: the need for a global approach in the management of cardiovascular risk factors. Vasc Health Risk Manag 3: 521–526. PMID: 17969382

79. Rodriguez-Porcel M, Lerman A, Herrmann J, Schwartz RS, Sawamura T, Condorelli M et al. (2003) Hypertension exacerbates the effect of hypercholesterolemia on the myocardial microvasculature. Cardiovasc Res 58: 213–221. PMID: 12667964

80. Baszczuk A, Kopczynski Z, Thielemann A (2014) [Endothelial dysfunction in patients with primary hypertension and hyperhomocysteinemia]. Postepy Hig Med Dosw (Online) 68: 91–100.

81. Wang B, Lin L, Zhao C (2016) Related factors of serum uric acid in patients with primary hypertension and hyperhomocysteinemia. Clin Exp Hypertens 38: 312–316. https://doi.org/10.1080/10641963.2015.1107088 PMID: 27028598

82. Mazza A, Crippini S, Schiavon L, Zuin M, Balbi G et al. (2014) Hyperhomocysteinemia is an independent predictor of sub-clinical carotid vascular damage in subjects with grade-1 hypertension. Endocrine 46: 340–346. https://doi.org/10.1007/s12020-013-0063-3 PMID: 24197804

83. Sowmya S, Swathi Y, Yeo AL, Shoon ML, Moore PK, Bhatia M et al. (2010) Hydrogen sulfide: regulatory role on blood pressure in hyperhomocysteinemia. Vascul Pharmacol 53: 138–143. https://doi.org/10.1016/j.vph.2010.05.004 PMID: 20685250

84. Cryer MJ, Horani T, DiPette DJ (2016) Diabetes and Hypertension: A Comparative Review of Current Guidelines. J Clin Hypertens (Greenwich) 18: 95–100.

85. Araki S, Maegawa H (2015) [Hypertension and diabetes mellitus]. Nihon Rinsho 73: 1885–1890. PMID: 26619663

86. Scheen AJ, Philips JC, Krzesinski JM (2012) [Hypertension and diabetes: about a common but complex association]. Rev Med Liege 67: 133–138. PMID: 2261829

87. Umbrello M, Dyson A, Feelisch M, Singer M (2013) The key role of nitric oxide in hypoxia: hypoxic vasodilatation and energy supply-demand matching. Antioxid Redox Signal 19: 1690–1710. https://doi.org/10.1089/ars.2012.4979 PMID: 23311950

88. Sansbury BE, Hill BG (2014) Regulation of obesity and insulin resistance by nitric oxide. Free Radic Biol Med 73: 383–399. https://doi.org/10.1016/j.freeradbiomed.2014.05.016 PMID: 24878261

89. Taylor DR (2006) Nitric oxide as a clinical guide for asthma management. J Allergy Clin Immunol 117: 259–262. https://doi.org/10.1016/j.jaci.2005.11.010 PMID: 16461124
91. Journois D, Pouard P, Mauriat P, Malhere T, Vouhe P, Safran D et al. (1994) Inhaled nitric oxide as a therapy for pulmonary hypertension after operations for congenital heart defects. J Thorac Cardiovasc Surg 107: 1129–1135. PMID: 8159035

92. Wu X, Lu Y, Zhou S, Chen L, Xu B (2016) Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environ Int 86: 14–23. https://doi.org/10.1016/j.envint.2015.09.007 PMID: 26479830

93. Ferrari U, Enner T, Wanka ER, Bergemann C, Meyer-Arnke J, Hildenbrand B et al. (2012) Influence of air pressure, humidity, solar radiation, temperature, and wind speed on ambulatory visits due to chronic obstructive pulmonary disease in Bavaria, Germany. Int J Biometeorol 56: 137–143. https://doi.org/10.1007/s00484-012-0405-x PMID: 21301889

94. Nuti SV, Wayda B, Ransinghe I, Wang S, Dreyer RP, Chen SI et al. (2014) The use of google trends in health care research: a systematic review. PLoS One 9: e109583. https://doi.org/10.1371/journal.pone.0109583 PMID: 25337815

95. Cervellin G, Comelli I, Lippi G (2017) Is Google Trends a reliable tool for digital epidemiology? Insights from different clinical settings. J Epidemiol Glob Health 7: 185–189. https://doi.org/10.1016/j.jegh.2017.06.001 PMID: 28756828

96. Burstein R, Fleming T, Haagsma J, Salomon JA, Vos T, Murray CJ (2015) Estimating distributions of health state severity for the global burden of disease study. Popul Health Metr 13: 31. https://doi.org/10.1186/s12963-015-0064-y PMID: 26582970

97. Liu F, Allan GM, Korownyk C, Kolber M, Flook N, Sternberg H et al. (2016) Seasonality of Ankle Swelling: Population Symptom Reporting Using Google Trends. Ann Fam Med 14: 356–358. https://doi.org/10.1370/afm.1953 PMID: 23597817

98. Telfer S, Woodburn J (2015) Let me Google that for you: a time series analysis of seasonality in internet search trends for terms related to foot and ankle pain. J Foot Ankle Res 8: 27. https://doi.org/10.1186/s13047-015-0074-9 PMID: 26146521

99. Ayers JW, Althouse BM, Allem JP, Rosenquist JN, Ford DE (2013) Seasonality in seeking mental health information on Google. Am J Prev Med 44: 520–525. https://doi.org/10.1016/j.amepre.2013.01.012 PMID: 23959781

100. Ryu OH, Lee S, Yoo HJ, Choi MG (2014) Seasonal variations in glycemic control of type 2 diabetes in Korean women. J Endocrinol Invest 37: 575–581. https://doi.org/10.1007/s40618-014-0080-y PMID: 24789539

101. Kershenbaum A, Kershenbaum A, Tarabeia J, Stein N, Lavi I, Rennert G (2011) Unraveling seasonality in population averages: an examination of seasonal variation in glucose levels in diabetes patients using a large population-based data set. Chronobiol Int 28: 352–360. https://doi.org/10.3109/07420582.2011.560315 PMID: 21539427

102. Sasaki J, Kumagae G, Sata T, Ikeda M, Tsutsumi S, Arakawa K (1983) Seasonal variation of serum high density lipoprotein cholesterol levels in men. Atherosclerosis 48: 167–172. PMID: 6615581

103. McKinley MC, Strain JJ, McPartlin J, Scott JM, McNulty H (2001) Plasma homocysteine is not subject to seasonal variation. Clin Chem 47: 1430–1436. PMID: 11468233

104. Jansen ET, Shah ND, Hoffman K, Sonnenberg A, Genta RM, Dellon ES (2015) Seasonal variation in detection of oesophageal eosinophilia and eosinophilic oesophagitis. Aliment Pharmacol Ther 42: 461–469. https://doi.org/10.1111/apt.13273 PMID: 26059636

105. Yeh KW, Fang W, Huang JL (2008) Increasing the hospitalization of asthma in children not in adults—from a national survey in Taiwan 1996–2002. Pediatr Allergy Immunol 19: 13–19. https://doi.org/10.1111/j.1399-3038.2007.00598.x PMID: 18199087

106. Isezuo SA (2003) Seasonal variation in hospitalisation for hypertension-related morbidity in Sokoto, north-western Nigeria. Int J Circumpolar Health 62: 397–409. PMID: 14964766

107. Larsen K, Zhu J, Feldman LY, Simatovic J, Dell S, Gershon AS et al. (2016) The Annual September Peak in Asthma Exacerbation Rates. Still a Reality? Ann Am Thorac Soc 13: 231–239. https://doi.org/10.1513/AnnalsATS.201508-545OC PMID: 26636481

108. Cronise RJ, Sinclair DA, Bremer AA (2014) The “metabolic winter” hypothesis: a cause of the current epidemics of obesity and cardiometabolic disease. Metab Syndr Relat Disord 12: 355–361. https://doi.org/10.1089/met.2014.0027 PMID: 24918620

109. Larsen TS, Lagercrantz H, Riemersma RA, Blix AS (1985) Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. Acta Physiol Scand 124: 53–59. https://doi.org/10.1111/j.1748-1716.1985.tb07631.x PMID: 3893041

110. (2015) Obesity and Overweight Fact Sheet No. 311. WHO.
111. Kobayashi M, Kobayashi M (2006) The relationship between obesity and seasonal variation in body weight among elementary school children in Tokyo. Econ Hum Biol 4: 253–261. https://doi.org/10.1016/j.ehb.2005.08.002 PMID: 16154393

112. Isen A, Rossin-Slater M, Walker R (2017) Relationship between season of birth, temperature exposure, and later life wellbeing. Proc Natl Acad Sci U S A 114: 13447–13452. https://doi.org/10.1073/pnas.1702436114 PMID: 29036545

113. Johnson F, Mavrogiani A, Ucci M, Vidal-Puig A, Wardle J (2011) Could increased time spent in a thermal comfort zone contribute to population increases in obesity? Obes Rev 12: 543–551. https://doi.org/10.1111/j.1467-789X.2010.00851.x PMID: 21261804

114. Wyse CA, Selman C, Page MM, Coogan AN, Hazlerigg DG (2011) Circadian desynchrony and metabolic dysfunction: did light pollution make us fat? Med Hypotheses 77: 1139–1144. https://doi.org/10.1016/j.mehy.2011.09.023 PMID: 21983352

115. Heymsfield SB, Wadden TA (2017) Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med 376: 254–266. https://doi.org/10.1056/NEJMra1514009 PMID: 28099824

116. Karter AJ, Schillinger D, Adams AS, Moffet HH, Liu J, Adler NE et al. (2013) Elevated rates of diabetes in Pacific Islanders and Asian subgroups: The Diabetes Study of Northern California (DISTANCE). Diabetes Care 36: 574–579. https://doi.org/10.2337/dc12-0722 PMID: 23069837

117. Alegre-Diaz J, Herrington W, Lopez-Cervantes M, Gnatiuc L, Ramirez R, Hill M et al. (2016) Diabetes and Cause-Specific Mortality in Mexico City. N Engl J Med 375: 1961–1971. https://doi.org/10.1056/NEJMoa1603568 PMID: 27959614

118. Weiss KB (1990) Seasonal trends in US asthma hospitalizations and mortality. JAMA 263: 2323–2328. PMID: 2325233

119. Shrestha P, Poudel DR, Dhitial R, Karmacharya P (2018) Seasonal and regional variation of asthma-related hospitalizations and mortality among adults in the United States. Ann Allergy Asthma Immunol 121: 368–369. https://doi.org/10.1016/j.anai.2018.06.032 PMID: 29981441

120. Turi KN, Gebretsadik T, Lee RL, Hartert TV, Evans AM, Stone C et al. (2018) Seasonal patterns of Asthma medication fills among diverse populations of the United States. J Asthma 55: 764–770. https://doi.org/10.1080/02770903.2017.1362426 PMID: 28881155

121. Kimbell-Dunn M, Pearce N, Beasley R (2000) Seasonal variation in asthma hospitalizations and death rates in New Zealand. Respirioplogy 5: 241–246. PMID: 11022986

122. Deshmukh A, Pant S, Kumar G, Murugiah K, Mehta J (2012) Seasonal variation in hypertensive emergency hospitalization. J Clin Hypertens (Greenwich) 14: 269–270.

123. Schatz M, Zeiger RS, Zhang F, Chen W, Yang SJ, Camargo CA Jr (2013) Overweight/obesity and risk of seasonal asthma exacerbations. J Allergy Clin Immunol Pract 1: 618–622. https://doi.org/10.1016/j.jaip.2013.07.009 PMID: 24565709

124. Kotchen TA (2010) Obesity-related hypertension: epidemiology, pathophysiology, and clinical management. Am J Hypertens 23: 1170–1178. https://doi.org/10.1038/ajh.2010.172 PMID: 20706196

125. Modesti PA, Morabito M, Massetti L, Rapi S, Oriandini S, Mancia G et al. (2013) Seasonal blood pressure changes: an independent relationship with temperature and daylight hours. Hypertension 61: 908–914. https://doi.org/10.1161/HYPERTENSIONAHA.111.00315 PMID: 23381792

126. Kim SW, Myong JP, Yoon HK, Koo JW, Kwon SS, Kim YH et al. (2017) Health care burden and medical resource utilisation of idiopathic pulmonary fibrosis in Korea. Int J Tuberc Lung Dis 21: 230–235. https://doi.org/10.5588/ijtld.16.0402 PMID: 28234090

127. Muir LA, Neely CK, Meyer KA, Baker NA, Brosius AM, Washabaugh AR et al. (2016) Adipose tissue fibrosis, hypertrophy, and hyperplasia: Correlations with diabetes in human obesity. Obesity (Silver Spring) 24: 597–605.

128. Westergaard D, Staerfeldt HH, Tonsberg C, Jensen LJ, Brunak S (2018) A comprehensive and quantitative comparison of text-mining in 15 million full-text articles versus their corresponding abstracts. PLoS Comput Biol 14: e1005962. https://doi.org/10.1371/journal.pcbi.1005962 PMID: 29447159

129. Au WW (2001) Life style factors and acquired susceptibility to environmental disease. Int J Hyg Environ Health 204: 17–22. https://doi.org/10.1078/1438-4639-00067 PMID: 11725340

130. Burgner D, Jamieson SE, Blackwell JM (2006) Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis 6: 653–663. https://doi.org/10.1016/S1473-3099(06)70601-6 PMID: 17008174