Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Human Health in the Face of Climate Change*

Revisiting the role of environmental and climate factors on the epidemiology of Kawasaki disease

Xavier Rodó,[1,2] Joan Ballester,[1] Roger Curcoll,[1] Joseph Boyard-Micheau,[1] Sílvia Borràs,[1] and Josep-Anton Morguí[1]

[1]Institut Català de Ciències del Clima (IC3) and [2]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Address for correspondence: Xavier Rodó, ICREA, Passeig Lluís Companys 23, 08010 Barcelona, Spain, and Institut Català de Ciències del Clima (IC3), Carrer Doctor Trueta 203, 08005 Barcelona, Catalonia, Spain. xavier.rodo@ic3.cat

Can environmental factors, such as air-transported preformed toxins, be of key relevance to the health outcomes of poorly understood human ailments (e.g., rheumatic diseases such as vasculitides, some inflammatory diseases, or even severe childhood acquired heart diseases)? Can the physical, chemical, or biological features of air masses be linked to the emergence of diseases such as Kawasaki disease (KD), Henoch–Schönlein purpura, Takayasu's aortitis, and ANCA-associated vasculitis? These diseases surprisingly share some common epidemiological features. For example, they tend to appear as clusters of cases grouped geographically and temporarily progress in nonrandom sequences that repeat every year in a similar way. They also show concurrent trend changes within regions in countries and among different world regions. In this paper, we revisit transdisciplinary research on the role of environmental and climate factors in the epidemiology of KD as a paradigmatic example of this group of diseases. Early-warning systems based on environmental alerts, if successful, could be implemented as a way to better inform patients who are predisposed to, or at risk for, developing KD. Further research on the etiology of KD could facilitate the development of vaccines and specific medical therapies.

Keywords: environmental toxins; vasculitides; Kawasaki disease; epidemiology; wind

Research on the potential link between environmental factors and vasculitides

Links between environmental factors and medical conditions have long been suspected, including with respect to cardiovascular diseases. For instance, primary systemic vasculitis and childhood vasculitis are also under similar scrutiny as being associated with environmental factors (e.g., Wegener granulomatosis, polyangiitis, Churg–Strauss syndrome, antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis,[1] sarcoidosis;[2] see Ref. 3 for a general review on pediatric vasculitides). A common trait of these diseases is inflammation of blood vessels of different sizes in the human body. Vasculitides of small vessels develop in anti-glomerular basement membrane (anti-GBM) disease and Henoch–Schönlein purpura (HSP), whereas the same condition develops in large vessels for Takayasu arteritis and giant cell arteritis (GCA). HSP and Kawasaki disease (KD) are the most common vasculitides accounting for 49% and 23%, respectively, of all childhood vasculitis.[3] There are also a few studies on the environmental links to the occurrence of severe cardiovascular diseases, such as ST-segment elevation myocardial infarction (STEMI)[4,5] and acute aortic dissection (AAD).[6] STEMI and AAD share similar tissue inflammation outcomes, and much controversy emerged when these studies suggested a potential influence of different weather conditions (e.g., associated to the physics or the chemical characteristics of air masses). Previous studies have unsuccessfully attempted to relate single weather parameters (e.g., temperature, pressure) to AAD,[7–9] but more recently, complex biometeorological weather analysis showed that it was plausible that distinct weather conditions might have significant influences on the occurrence of type A AAD.[10] Whether it is the physical or chemical properties of air masses that are associated with disease, the high occurrences of clusters of cases in cardiology

doi: 10.1111/nyas.13201

emergency wards appearing at certain times of the year, all showing artery inflammation, raise concerns; however, the topic remains largely unaddressed.

Studies published in the last decade have pointed to environmental processes and/or infectious agents, pollutants, or organic toxins to explain the incidence of some of the human diseases for which the etiology is still unknown. More specifically, studies have pointed to environmental pollutants such as chemical byproducts from nearby industries or urban centers, as well as organic debris and by-products from large agricultural harvests (potentially also from massive application of herbicides, fungicides, and/or fertilizers in dense agricultural regions). These factors have been statistically implicated or are suspected to be modulators or triggers for at least a portion of the recent increase in the levels of chronic disease incidence in many regions.[11,12] The same applies for some ailments with unknown etiologies, for example, primary systemic vasculitis and its alleged links to environmental risk factors associated with farming practices in the United Kingdom.[1] Although statistics might sometimes provide hints on the environmental links, a more mechanistic explanation of the different processes involved is always deemed necessary and should be pursued at least at the level of populations. There have been similar attempts to find environmental links as etiological sources for ailments related to medium-to-large vessel arteritis, such as GCA. Several studies have indeed associated GCA with varicella zoster virus, although many others tested negative for the same agent and results therefore remain inconclusive.[13] Interestingly, sarcoidosis—a multisystem disease of unknown etiology—clearly displays a marked seasonality in both the Northern and Southern Hemispheres in those symptomatic patients diagnosed with Löfgren's syndrome. Seasonal clustering of cases strongly suggests a common environmental trigger in the etiology of sarcoidosis,[2,14] although, to date, subsequent studies have been unable to clarify the nature of the alleged links. One clear example of the link between environmental factors and disease lies in the discovery of the role of *Streptococcus pyogenes* as the primary cause of rheumatic fever.[15]

KD, a self-limited inflammatory process affecting medium-sized arteries, including the coronary arteries, is now the leading cause of acquired heart disease in children in developed countries, second only to rheumatic fever worldwide.[16,17] It is potentially life threatening, depending on the extent of cardiac involvement. The diagnosis of KD is based on clinical criteria that include fever, exanthema, conjunctival injection, changes in the extremities, erythema of the oral mucosa and lips, and cervical lymphadenopathy. Prognosis depends on the extent of cardiac involvement; coronary aneurysms develop in 20–25% of untreated patients and may lead to myocardial infarction and sudden death.[18] Furthermore, KD causes inflammation of the arterial wall that compromises the structural integrity, which leads to aneurysm formation. The major sequelae of aneurysms, even at an adult age and if previously unnoticed, include thrombosis, scarring with stenosis, myocardial ischemia, myocardial infarction, and death.[19] Epidemiologic studies suggest that, by 2030, one in every 1600 adults in the United States will have suffered from KD.[20] In Japan, the country of highest incidence (240/100,000 children $<$ 5 years; one in every 150 children affected), there are more than 12,000–15,000 new cases each year and rates continue to rise.[21] Although KD is more prevalent in Asian countries, especially in Japan, it has a universal distribution and can be manifested in children of any ethnicity. In the United States,[22] KD has a global hospitalization rate of 17.1 per 100,000 children under 5 years of age, with higher incidence among Americans of Asian and Pacific Island descent (32.5/100,000 children under 5 years of age). In Europe, some studies have reported KD incidences that range from 4.9 per 100,000 children under 5 years in Denmark[23] to 9 per 100,000 children in France.[24] In Spain, epidemiological studies showed a KD incidence of 15.1/100,000 children under 5 years of age.[25] The present review addresses how rheumatic diseases are emerging as one area where environmental factors are thought to be playing a determinant, although presently overlooked, role in their epidemiology.

Is KD an infectious disease? Lessons from KD epidemiology

The etiology of KD is still unknown, although clinical, laboratory, and epidemiological features of the disease have long suggested an infectious origin or trigger. Under certain situations, intracytoplasmic inclusion bodies have been identified in acute KD tissues, consistent with aggregates of viral proteins

and RNA.[26] Concomitant coinfection with other pathogens that are not considered to have a primary role in KD etiology should not be disregarded. Some case reports have reported on different potential causative agents, such as *Mycoplasma pneumoniae*, *Staphylococcus aureus*, rotaviruses, and pertussis, although none of them could be later confirmed.[27–29] A genetic basis leading to increased susceptibility has also been explored and proposed by many studies and is an active area of research.[30] Other studies have suggested that abnormal levels of mercury and cadmium found in the blood of KD children in some regions of the world confer an increased risk to suffer from the disease.[31] However, results are inconclusive at this stage and exposure to any drug or a response to a superantigen has not been shown.

One common feature evident in KD children is activation of the immune system, and the concentrations of many proinflammatory cytokines and chemokines are being studied in patients with KD, which could lead to improved anti-inflammatory therapies in the future.[32] These inflammatory processes could be produced only in response to either intrinsically autoimmune reactions or extrinsically inhaled particles, or as a result of infections. A recent study postulated that KD is similar to other pediatric viral infections and suggested a long-term persistence in the host, as for *Exanthema subitum*.[33] However, this assumption would imply long incubation times and lifelong persistence and, therefore, a large pool of asymptomatic infections, which has been disregarded on the basis of detailed studies of KD population epidemiology in Japanese prefectures.[34]

In the present study, person-to-person spread of an infection was examined to determine if such an etiological agent could fit the observed data. A simple susceptible–exposed–infected–recovered (SEIR) population disease model was built (Fig. S1, online only). Children younger than 6 months were considered to not be susceptible because of protection from maternal antibodies.[35] The results showed that not even an extremely, rapidly replicating infectious disease could propagate as quickly as is seen in observations for diseases with idealized incubation times as short as 2 hours. Given that time for admission in hospitals would also be needed for case recognition, these times would be around 10 times shorter than the fastest respiratory viruses known to date (e.g., influenza B and rhinovirus[36,37]). No known infectious agent would therefore be able to produce synchronous (same day) infections over distances between cities in the Greater Tokyo Area on the basis of secondary infections only (see Fig. S7 in Ref. 34). Conversely, more than 5 days and 1% of asymptomatic individuals in the population would be needed for an infectious agent—with even such a short incubation time and with the current city populations in the Greater Tokyo Area—to spread over the distance between any two cities using secondary infections. Therefore, the possibility that a known infectious agent is responsible for these dynamics is not supported by epidemiological data. Alternative views suggest that an immediate response takes place within 24 h (perhaps after inhalation of an environmental trigger) and leads to an idiosyncratic immune reaction in genetically susceptible children.

The wind connection and the use of local statistics

Rodó *et al.*[38] postulated that the trigger for KD could be a windborne environmental trigger transported over vast distances. This study was based on the detailed epidemiological analysis of the Japanese KD dataset, the country with the highest KD incidence and the best records for the disease worldwide (Fig. 1).[17] A series of studies analyzed the three major KD epidemics in Japan (Fig. 1A), the major nonepidemic interannual fluctuations of KD cases in Japan and San Diego, and the seasonal variation of KD in Japan (Fig. 1C), Hawaii, and San Diego, as a way to test a potential atmospheric connection through the North Pacific. All revealed a consistent pattern where KD cases were clearly linked to the same synoptic weather conditions developing over Japan and Northeast China. Advection of air from large-scale wind currents originating in Central Asia can be associated with KD in Japan and later traverse the North Pacific through an atmospheric duct to potentially also influence the incidence of KD on the U.S. West Coast.[38,39] Therefore, monitoring of regional seasonal-to-interannual atmospheric processes (e.g., wind patterns in Fig. 1A and C and sea-level pressures), but also the state of the ocean and atmosphere in surrounding regions, can be used to derive both short-term monthly forecasts and long-term predictions to alert healthcare professionals during periods of increased regional KD activity.[39] A set of analyses performed on a number of more conventional climate drivers all tested

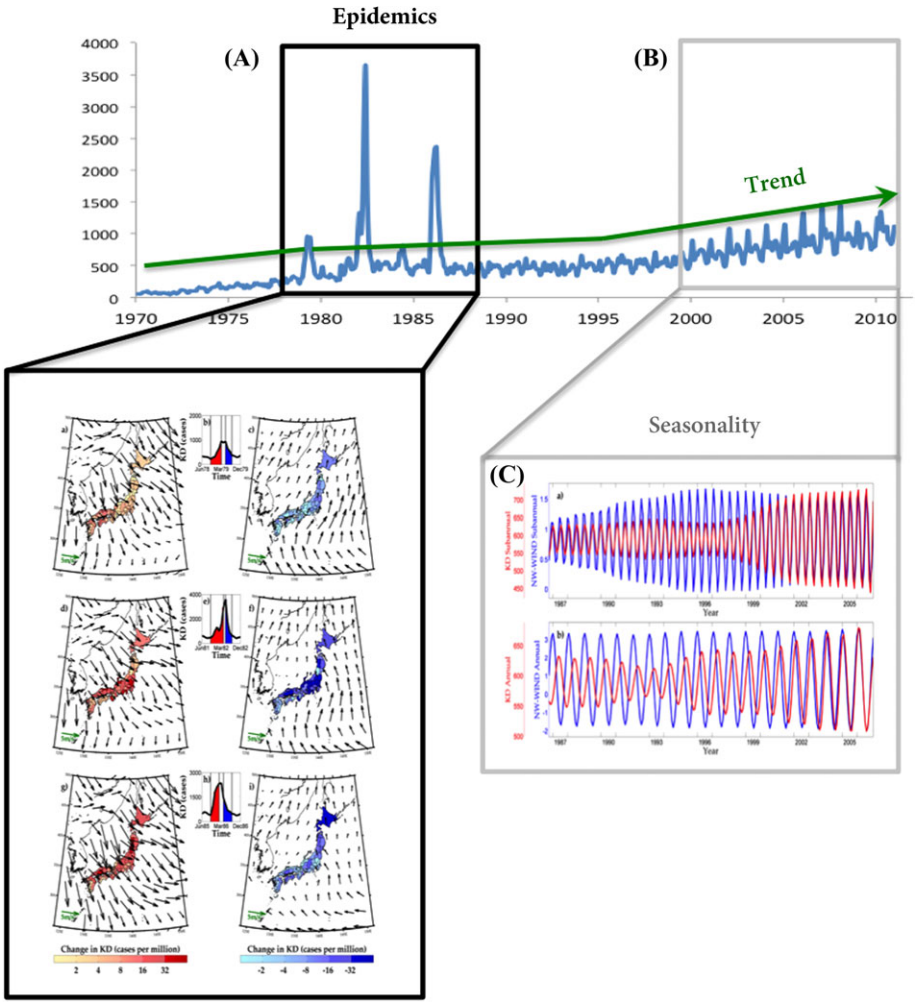

Figure 1. Monthly evolution of the composite series of Kawasaki disease clinical cases for all of Japan between 1970 and 2011. Note three interesting features of this time series, namely (A) the three large epidemics, (B) the decadal changes in trends in the 1980s and mainly after the year 2000, and (C) the amplification of seasonal fluctuations toward the present. (A) Time-averaged sea-level pressure (hPa) and surface winds (m/s) before and after March/May 1979 (a–c), May 1982 (d–f), and March 1986 (g–i) epidemics, respectively. Monthly atmospheric variables were averaged for the subsequent summer (June–July–August– (JJA) 1979 in a, JJA 1982 in d, and JJA 1986 in g), when winds from the south typically blow across Japan, and for the rising phase of the epidemics, from September to the last month before the peak (September 1978–March 1979 in Aa, September 1981–April 1982 in Ad, and September 1985–February 1986 in Ag), when winds blew from the northwest. Red/blue colored areas depict increases/decreases in KD incidence (per million inhabitants) by prefecture between the preceding September and the KD peak (April 1979 minus September 1978 in a, May 1982 minus September 1981 in d, and March 1986 minus September 1985 in g). (C) Coherence in subseasonal winds developing over Japan and the variability in KD incidence at the same timescale (a) and for the annual components (b). Wind intensity (blue) and KD (red) are composited for all prefectures in Japan. Partly adapted from Ref. 38.

negative, consistent with previous studies (namely, minimum and maximum temperatures, precipitation and moisture, atmospheric pollutants measured in urban stations, and diverse pollen species).

Signal-decomposition techniques aimed at uncovering discrete temporal or spatial processes need to be applied when dealing with processes that occur only for limited durations in time or that are very localized in space.[40,41] This is the case when a relation to meteorological factors exists, such as for wind intensity and direction that usually display much less persistent patterns than precipitation or

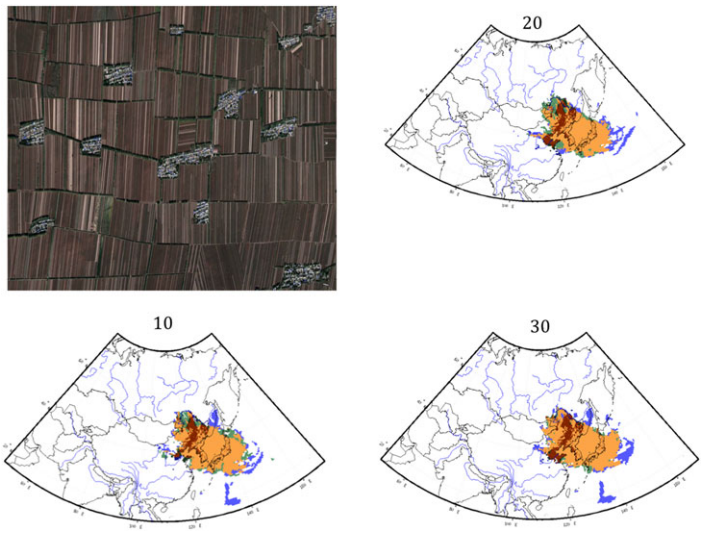

Figure 2. **Maximum residence times (TR) for the air arriving at Tokyo. Colors indicate TR for days with a rising KD incidence (percentile 95, green) and days of maximum KD incidence (percentile 99.9, violet), whereas brown areas depict common areas. Dark brown dots denote cropland dominance (over 50% in coverage). Numbers denote days before the peak in KD incidence for each of the three epidemics (1979, 1982, and 1986). Inset shows the typical aerial view of the agricultural fields over the center of the dark brown areas.**

temperatures. The need to go beyond basic statistics has traditionally precluded work on wind covariates to be more commonplace in epidemiological studies, despite the obvious interest for respiratory diseases. Also, working with nonlinear and nonstationary processes, as for KD time series in Japan that display stark differences in disease incidences through time, is not trivial (e.g., compare values in the large epidemics to those in the mid-1990s and to the recent amplified seasonal occurrences; Fig. 1). In epidemiological studies where disease incidence is low, signal-to-noise ratios need to be maximized whenever possible, so that relevant pieces of information are not unintentionally disregarded. Constraining the interval of time to analyze so that stationarity assumptions might still be kept is a feasible option and can be facilitated by techniques such as recurrence plots, orthogonal wavelet analysis, and scale-dependent correlation analysis.[40,42–44] Otherwise, information at the level of epidemics is normally regarded as outliers and is often left out of analyses because of a violation of statistical requirements for parametric techniques. Such homogeneity assumptions to be complied by customary statistical approaches may eventually lead to important sources of epidemiological information being ignored.

As an example, Figure 2 shows the persistence in the wind source for air masses arriving at Tokyo when the maximum incidence of cases in history was recorded for Japan. More than 40,000 simulations were performed to discern between days of low and high KD incidence, with the help of a Lagrangian backtrajectory model (Flexpart v.9.02[45]). Several KD situations were included (days within the three large epidemics, days at epidemic maxima, days with KD incidence above 95% and 99% percentiles in interepidemic intervals, and days with a low or minimal incidence in KD; Fig. 2), and the resulting provenance and residence times of areas over land or sea immediately before arriving at different locations around the Japanese archipelago were retrieved. The analysis had to be performed with data collected daily, as winds change quickly beyond a few weeks (contrary to more persistent atmospheric processes, such as temperatures, atmospheric pressures, or geopotential heights). Figure 2 shows land regions swept by wind currents and are composited for the three large epidemics (1979, 1982, and 1986), with the numbers indicating days before the maximum occurrence of cases, namely for incidences at the peak of the three epidemics, highlighting that even as far as 30 days before the peak in KD, stability in wind conditions persists and strong winds

emanating from a region in Northeast China arrived at Tokyo loaded with particles. The middle inset in Figure 2 presents an aerial photograph of this region, characterized by intensive cereal croplands. Cold strong winds in winter uplift the large amount of particulate matter, which is transported in a few hours to the Japanese archipelago. Recently, this new hypothesis raising the possibility of an increased exposure to an extrinsic causative agent, presumably an environmental toxin stemming from intensive cereal croplands, is opening new research avenues to approach the epidemiology of KD.[34,38]

In the search for an etiologic agent

While the biochemical basis of KD is unclear, the evidence to date suggests—albeit inconclusively—an interplay between a microbial infection and a genetic predisposition in the development of the disease. Although it is clear that identification of inflammatory, proteomic, and genetic biomarkers may assist in earlier and more effective diagnosis and treatment, the isolation of such biomarkers has not been conclusively addressed. It has been suggested that a review of observational studies and clinical trials in the search for biomarkers might be used to establish a gold-standard test for KD diagnosis.[46] As there are no specific laboratory tests used to diagnose KD, options for the search for biomarkers have been diverse. For instance, certain abnormalities coincide with various stages in the development of the disease. Acute-phase reactants (i.e., erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and α-1 antitrypsin levels) are almost universally elevated during the first stages of the disease. For instance, ESR $\geq$ 40 mm/h, leukocyte count $\geq 16 \times 10^9$/L, and increased white blood cell count are together suggestive of the presence of KD. Among proteomic biomarkers, elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and differing levels of several other proteomic biomarkers, such as inducible nitric oxide synthase in monocytes and neutrophils, have been observed in KD patients. Genetic polymorphisms of six human leukocyte antigen class I genes have also been linked with the disease, alongside the MICA alleles A4 and A5.1. The results suggest that NT-proBNP is currently a very promising biomarker. CXCL10/IP-10 has also been suggested to be a biomarker and mediator for KD.[47]

In addition, there are two urine proteins that hold promise as biomarkers of KD: meprin A and filamin C, which are considered to be diagnostically superior to ESR or CRP. Investigators identified more than 190 proteins that were present only in children with KD, including the proteins associated with endothelial and myocardial cell injury (filamin C) and immune regulators (meprin A). Elevated macrophage migration factor and interleukin-6 may be useful markers in the acute stages of KD. In complete blood counts, mild-to-moderate normochromic anemia has been observed in the acute stage, and thrombocytosis is the outstanding marker during the subacute stage. Another study[48] sought to develop a panel of biomarkers that could distinguish between acute KD patients and febrile controls with sufficient accuracy to be clinically useful (81–96% of KD patients were accurately diagnosed in a series of three independent cohorts).

An experimental atmospheric survey performed during high KD incidence and with the air provenance from the Chinese region (Fig. 2) found abundant fungal material in the tropospheric samples and could amplify a fragment that mapped to 11 different *Candida* spp.[34] *Aspergillus* genus was largely dominant in surface samples (Fig. S1B, online only). Whereas several fungi and bacteria have been isolated from air samples at high altitudes in the troposphere in the past, the diversity found above the boundary layer has always been low. The large number of *Candida* spp. isolated within particulate material aloft came as a surprise, since it had not been reported in previous surveys of microbes collected from filtered samples from aircraft campaigns over Asia, the Mediterranean, the Northwest Coast of the United States, or the Caribbean.[49,50] Variability in the size and amount of particulate material in air samples arriving at Tokyo rapidly changes depending on the origin of air masses (Fig. S1A, online only). Results of 18s rRNA amplification from Rodó *et al.*[34] showed distinct dominance of species during high KD incidence between samples collected above the boundary layer and the surface (Fig. S1B, online only).

Fungi bear an incredible degree of adaptability and survival capacity in adverse environments and kill more people than malaria and tuberculosis worldwide. They also destroy about one-third of all arable food crops. Although there are high numbers of fungal species on earth, only around a few

hundred species cause disease, and of them, only a few cause disease specifically in humans.[51] More specifically, only five fungal species are a threat to human health (causing infections such as candidiasis, aspergillosis, cryptococcal disease, histoplasmosis, and pneumocystis). While most fungal infections are trivial, serious invasive diseases do affect 2.5 million people each year worldwide. While invasive fungi are difficult to treat, prompt treatment remains crucial for successful patient outcomes.[52] The main limitation still lies in the time-consuming process needed to accurately determine the specific fungal species responsible. In this respect, diagnostic errors can be fatal in nosocomial infections. With regard to a potential link to KD, fungal infection was disregarded on the basis of results from the SEIR model. The results indicated that the disease was not an infection but an immediate reaction to the inhalation of airborne particles. A reaction to fungal toxins or to any other atmospheric constituent was therefore hypothesized to be responsible for the inflammatory process leading to KD.[34]

Most fungi live for the most part in soil and dead matter and as symbionts of other organisms. Fungal infections are increasingly becoming a global concern, and, in most cases, rapid diagnosis and treatment are critical.[53] *Candida*, for instance, is a genus of yeasts and a commensal human colonizer of almost all mucosal surfaces.[54] There are more than 50 species identified, of which *Candida albicans* is the most invasive species associated with opportunistic oral and genital infections, despite having a commensal relationship with humans.[55] Interestingly, *C. albicans* was not isolated from the atmospheric filtered samples at the times of high KD incidence. *Candida* is known to be ubiquitous worldwide, easily colonizing many soils and agricultural environments. *Candida* spp. has been suggested to be a/the potential etiological agent for KD, as *Candida* mouse models developed for cell wall extracts reproduced the symptoms of the disease, in a way similar to those experienced by affected children[56] (the same occurred for a *Lactobacillus* model[57]). In agriculture, it is well known that fungal infestation can lead to massive economic loss and can compromise global food security. If management of large farms does not properly control the fate and accidental release of organic debris, or if the use of pesticides and/or fertilizers or the production of dangerous by-products can easily be incorporated into the atmosphere by strong winds, the effects on human health can be severe and remain largely unknown. For instance, fungi can produce volatile organic compounds (VOCs), which are chemicals with low molecular weights that easily evaporate into the air. Whereas they mainly come from industrial processes, VOCs can also be produced normally by microorganisms, such as fungi and bacteria. The greatest occurrence of microbial VOC (MVOC) production for fungi seems to coincide with spore formation and mycotoxin production, as observed in species of *Aspergillus* and *Penicillium*. However, mycotoxins differ from MVOCs in that they are relatively large molecules that are, in principle, not volatile, and are not easily uplifted unless very energetic winds develop.[58] Consequently, they are usually not airborne unless attached to a particle through aerosolization and, as a result, significant exposure to particles larger than 10 μm through inhalation is unusual. However, risk of exposure to fungal spores and toxins through inhalation may be larger in children who do not have a mature immune system. The amount of mycotoxins contained in fungal spores is normally low; only one nanogram of mycotoxin is sufficient to cause adverse health effects in adults and even less is sufficient for children. Many mycotoxins are secondary metabolites of fungi, meaning that they are not required for growth, and are produced under suboptimal conditions for fungi, such as when nutrients are limited and environmental conditions are unfavorable. Fungi such as *Fusarium tricintum* produce significant amounts of toxin when temperatures are lower than 15 °C and release very little when it is warmer. Other factors affecting the amount of mycotoxins produced are the scarcity of nutrient sources, competition with other organisms, relative humidity, growth rate, and fungal maturity.[59] In the case of KD patients, the role of fungal antigens as an alternative to fungal mycotoxins deserves further investigation (Burns, personal communication, 2016).

Seasonality of KD in Japan

In an attempt to further validate the wind hypothesis, other studies have further analyzed the seasonal variation of winds and KD at the level of prefectures in Japan and in other world sites where the disease is currently present.[38,60,61] KD has been described in a total of 60 countries,[62] in which aggregated country

datasets integrated in the Kawasaki Disease Consortium Database, covering more than 39 locations in 25 countries spanning the two hemispheres, were analyzed for seasonality (see global seasonality map in Ref. 61). The results showed that the strongest seasonality components were in the mid-latitudes of the two hemispheres, although apparent variability at these timescales might also be present for other regions (tropics) where winds are not so seasonal. The lack of accurate long-term records prevented further definite conclusions to be drawn from these regions; however, there is a possibility that seasonality arises not only from winds but also from cropland variability. In Japan, the spatial and temporal distribution of seasonal changes in both KD and wind intensity highlights a clear coherence as described in previous studies.[38] Figure 1C shows the main subannual variability components for both winds and KD averaged over Japan. A clear peak in winter emerges as the dominant window for KD variability at the annual scale, together with a secondary maximum around early summer. Wind intensity shows similar dynamics in those regions with largest incidences and North to South of the country (e.g., Sapporo, Tokyo, Yokohama, Osaka, Kobe), as well as for all of Japan (not shown).

KD is not a disease of mandatory notification, and therefore, unified and cross-validated registries are lacking. Notwithstanding this, there are international efforts by the medical community to build an international registry database in the near future, and other independent efforts are also underway, namely by the U.S. Centers for Disease Control and Prevention through the Kids' Inpatient Database (http://hcup-us.ahrq.gov/kidoverview.jsp) and by the University of California, San Diego (see Table I and Fig. 1 in Ref. 59 for a list of hospitals, main contributors, cities, period of records, and total cases). Some national ministries also provide partial information on KD prevalence or/and incidence, for example, the Ontario Ministry of Health Hospital Directory[63] and the Japanese Ministry of Health and Welfare (http://www.mhlw.go.jp). To date, however, KD historical datasets are not yet openly and easily available for research purposes or accessible to the general public. Despite the current lack of a successful international registry, unified criteria are already in place that are followed by all hospitals worldwide and can facilitate future construction of such a registry. The criteria are set by the Research Committee of Kawasaki Disease sponsored by the Ministry of Health and Welfare of the Japanese Government and demands for the recording of demographic and clinical data from all patients, regardless of age, who were discharged with a diagnosis (most responsible diagnosis or secondary diagnosis) of KD (International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) as code 446.1, or alternately by the Tenth Revision (ICD-10) as code M30.3) for each calendar year. This information is requested and recorded everywhere on standardized case report forms.

The distribution of intra-annual variation in KD in Japan and that of wind components, together with year-to-year differences in seasonal intensities, need to be further studied in order to highlight geographical differences that might shed light on crucial (but still unknown) aspects of KD epidemiology. However, the possibility that concurrent changes in the types of crops and the introduction/intensification of certain cereal species in other seasons cannot be disregarded as contributing to the recent magnification of the seasonal cycle in KD across Japan (e.g., through rising amounts of maize harvested, introduction and alternation of harvests in the form of two crop seasons, or even through concurrent increases in the area devoted to other crops).

What do KD trends in Japan indicate?

One striking feature of KD epidemiology in Japan is the decadal changes in the trends of the disease (Fig. 1B). The steeper trend after the last few large nationwide epidemics in 1986 and after 2000 is concomitant with a more pronounced seasonality and the shift toward winter dominance in the occurrence of new cases. The age distribution of KD cases shows a shift toward younger ages in epidemic years. Despite the rising trend clearly evident after 1987, the continuous drop in the population between the ages of 0 and 4 years can only explain part of this change.[64] A clear explanation is therefore still lacking, and current incidences are already higher now than they were in the 1979 epidemics.[62] A number of studies have long suggested that the increased incidence in Japan is related to specific genetic risk factors, although an increasing trend is also reported in many other places around the world (e.g., Indonesia, France, many U.S. cities, China). Similarly, an increase in the identification of KD cases that do not involve at least four KD

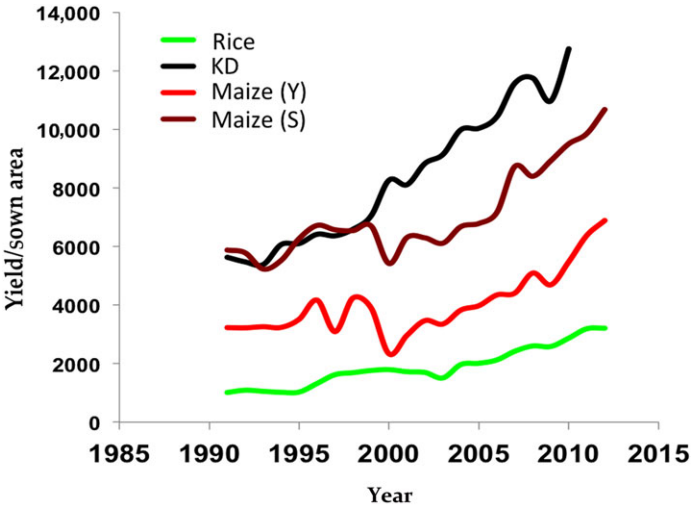

Figure 3. Year-to-year changes in yield and sown area for maize and rice in Northeast China and KD in Japan for the interval after the big 1986 KD epidemics.

clinical signs (unilateral lymphadenopathy, nonexudative conjunctivitis, polymorphous exanthema, oral mucosa changes, and edema/peeling of extremities) in addition to fever (incomplete KD) has already been reported in North America.[18,65,66] This finding may indicate an increasing index of suspicion for KD, as well as an increasing surveillance of KD. With regard to the wind connection theory, three possibilities arise that may account for the trend. Whether the source region producing the etiological agent has changed, the wind connecting the source and the recipient population in Japan and the United States has intensified accordingly in the last decades. The latter hypothesis has not been disregarded, but it has little credit because of the long time needed for such changes to operate in a population in comparison to the fast and pronounced changes seen in both trend and seasonality of cases. When wind intensification was investigated, no clear sign was found over the source region and/or Japan in a study of changes in either the zonal and/or meridional wind components and despite the marked global warming signature in temperatures in Central Asia.[38,39,67] However, a temporal shift in the orientation of mean maximum winds around the peak in the KD season, and possibly of the wind component over the center of the source region, might instead account for the clear phase locking in both winds and KD at this time scale. The role that both the long-term decrease of Siberian High pressure and the rise in Siberian High temperatures in late fall and winter and their effects on regional winds will have to be further studied in the context of KD.[67]

There is an alternative explanation of the decadal changes occurring in the source region where winds uplift debris from terrestrial sources. The study of the evolution in both harvests and cropland area devoted to cereals such as maize, dominant in Northeast China (a region known to be the breadbasket of China), shows a clear rising trend concomitant to that of KD. Interannual variability also appears to mimic changes in the disease incidence at this temporal scale (Fig. 3). In addition, other crops with a minor presence in the region do not display such a pattern of long-term variability (e.g., rice and/or wheat). Indeed, year-to-year variability in rice mimics, to a certain extent, the variability of maize and KD incidence, indicating a regional synchronization factor potentially associated with changes in climate variability over the region in those years. This complex behavior of agricultural fields and the potential link to KD deserve further investigation.

Toward prediction of KD with the use of climatic covariates

Periods of higher-than-normal KD cases in Japan preferentially occur under either El Niño Modoki or La Niña conditions, while in San Diego they take place during the mature phase of El Niño or La

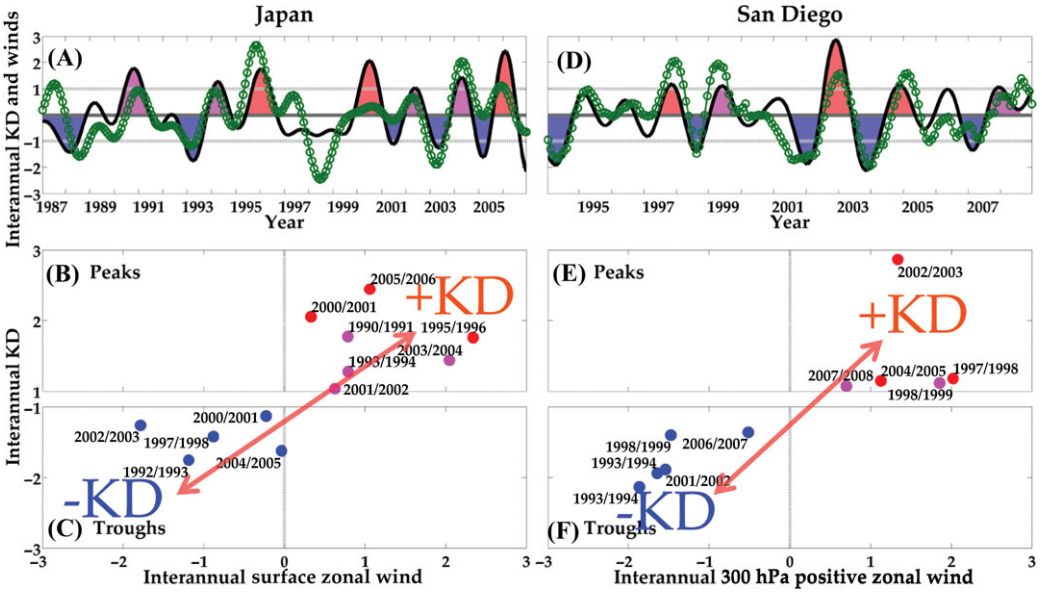

Figure 4. Relationship between atmospheric winds and KD in Japan (A–C) and San Diego (D–F). Green curves in panels A and D depict the standardized (unitless) interannual component of surface zonal wind in Japan (130–135E, 40N) and 300 hPa positive zonal wind in the Central North Pacific (170–150W, 10–45N), respectively. The positive zonal wind for a given month and region is here defined as the spatial average of only those grid points with positive interannual zonal wind anomalies (i.e., interannual easterly anomalies are excluded from the spatial average). Black lines in panels A and D correspond to the standardized (unitless) interannual component of monthly KD in Japan and San Diego, respectively. Note that correlations for time series in panels A and D are 0.61 and 0.76 ($P < 0.001$), respectively. Peaks (red and pink) and troughs (blue) reaching the 1 standard deviation level are shaded. Peaks are grouped into two classes in order to separate among the different typologies of ocean–atmosphere patterns described in the text. The correspondence between the standardized (unitless) interannual component of monthly KD with (B,C) surface zonal wind in Japan (130–135E, 40N) and (E,F) 300 hPa positive zonal wind in the Central North Pacific (170–150W, 10–45N) is shown for the peaks (B,E) and troughs (C,F).

Niña events.[39] Given that El Niño Southern Oscillation (ENSO) offers a degree of predictability at lead times of 6 months, these modulations suggest that seasonal predictions of KD could be used to alert clinicians of periods of increased disease activity. The reconstructed interannual component of monthly KD time series (black lines in Fig. 4A and D; also see Ballester *et al.*[39]) allows a classification of KD peaks and troughs reaching the 1 standard deviation criterion (red, pink, and blue events in Fig. 4A and D). Given the impact of sea surface temperature anomalies on the tropospheric circulation in subtropical and extratropical latitudes, the redistribution of equatorial surface temperatures in the Pacific Ocean, and thus the phase of ENSO variability, can be used as the criterion for classifying the different typologies of KD peaks in Japan and San Diego. Equatorial warm anomalies during the mature phase of El Niño (La Niña) events, including those considered as El Niño Modoki,[68] are generally found to the east (west) of longitude 155E.[69] Peaks in KD occurrence clustered into two basic types (red and pink events in Fig. 4A and D) as a function of the zonal range of anomalous equatorial warming. This way, they provided a comprehensive and precise characterization of the different ocean–atmosphere interactions and of the tropospheric teleconnections involved in the exacerbation of the disease. As a general rule of thumb, years with increased KD in Japan (+KD) are associated with enhanced local low-troposphere westerly winds driven by a low-pressure anomalous area centered to the north of Japan. The former corresponds to the westerly shift of the climatological Aleutian low. Thus, even if each typology of peak is associated with a distinct ENSO-related ocean–atmosphere signature, increased average westerly wind anomalies are found for all of them (Fig. 4D and E), with anomalies of opposite sign for those years located in troughs (Fig. 4D and F). Although the

strengthening of zonal winds is the main common feature of all of the periods with higher-than-normal KD in Japan and San Diego, interevent variability suggests that other processes may interfere with the tropical–extratropical interplay, such as extratropical variability modes, planetary waves, nonlinear feedbacks, or stochastic noise.[70] For example, periods of higher-than-normal KD in Japan are always associated with an enhancement of westerly winds in the lower troposphere, which makes the development of a future prediction system a feasible opportunity.[39] It is clear though that additional environmental and demographic factors might, in turn, help to better explain the generally larger magnitude of KD anomalies for certain types of KD years.

Discussion and conclusions

Recent studies reinforce the idea that KD, a cardiovascular disease that affects children worldwide, may be triggered by an environmental aerosolized particle, a preformed fungal toxin, and elicit an idiosyncratic immune response in genetically susceptible children. It has also been shown that KD is not caused by an infectious agent, using mathematical models of the disease. Laboratory KD mouse models for *Candida* spp. have also been developed in the past, and, despite being commensal to humans, *Candida* has been detected in the stools of children with KD. In tropospheric air samples collected during high KD incidence in Japan, genetic material found in filters could be amplified and a fragment reconstructed to potentially match 11 different *Candida* species. All of these results would be consistent with the presence of an external environmental trigger for KD.

The adult human body is made up of approximately 10 trillion (10^{14}) cells, of which only 10% are human cells. Instead, the vast majority of our cell composition is microbial (including 100 trillion bacteria), inhabiting our bodies in communities known as microbiomes. Disruptions in these delicate ecosystems have been linked to diseases including obesity, diabetes, inflammatory bowel disease, rheumatoid arthritis (RA), and multiple sclerosis. Many studies have also demonstrated the presence of both bacteria and viruses within diseased blood vessels,[71] and recent reports have been published about the potential role of microbes in nonatherosclerotic aortic aneurysms[72] and vasculitis-like GCA.[73] Exploring the possible role of the microbiome (also the referred to as the extrinsic microbiome) and the exposome in KD patients therefore becomes meaningful in the search for whether correlations with regional differences in incidence and prevalence in KD can be further obtained. Along these lines, the new idea of dysbiosis as the cause for certain rheumatic and inflammatory diseases, for example, RA—not only through ingestion but also inhalation of certain particles containing microbial toxins that might alter the human microbiome homeostasis and lead to health imbalances—is gaining credit for explanations of some of the autoimmune diseases. In the case of RA, for instance, it has become clear that genetic factors alone cannot explain differences in incidence. There may be subsequent activation of the cascade of processes involving proinflammatory cells that are linked to diseases such as KD and similar vasculitides. This situation makes the gene–environment concept with regard to the development of disease emerge as a very attractive and plausible hypothesis.[74] In the future, biomarkers for the different *Candida* spp., as well as for other potential precursory agents for KD, need to be tested on KD patients. Responses should be sought in the form of an elicited immune response similar to that of KD.

Two independent approaches have identified regulation of immune activation as the critical factor in determining susceptibility to, and severity of, KD in children. First, a genetic association study identified a polymorphism in several genes that is responsible for regulating immune activation and is associated with susceptibility to, and increased severity of, KD.[75] A second independent approach using an animal model of KD also identified regulation of immune activation as the critical determinant of coronary disease. In this respect, new approaches to test the role of danger signals in regulating immune activation in KD that can be found in windborne aerosols will be uniquely positioned to address critical questions on the pathogenesis of KD and their direct role in conferring risk and determining coronary outcome in children with KD.

Viability of human pathogens in tropospheric wind aerosols has not been tested, but new studies are appearing that point to a much easier capacity for survival of those microbes (e.g., embedded into the protective inorganic/organic particulate matter fraction). The example of *Aspergillus sydowii*

traveling on Saharan dust across the Atlantic and causing disease in coral in the Caribbean demonstrates that long-range transport of viable organisms does occur,[76] but the scope of organisms that can survive these conditions is largely unknown. Generation of cDNA from aerosol samples that can be amplified for embedded bacteria, fungi, and viruses might soon be customary and proceed using broadly cross-hybridizing primers. The last generation of portable laser fluorimetry devices is additionally proving successful in detecting distinctive bacterial and fungal signatures.[77] Similarly, surface-enhanced Raman spectroscopy with species-specific encoded nanoparticles can be a promising avenue to follow, as it has already been proven successful in detecting nosocomial infections in hospital wards.[78] The mortality rate associated with fungi, including *Candida* spp., is increasing worldwide. Most of these fungi are commensals and become opportunistic pathogens upon immunosuppression. Hence, an understanding of the molecular interactions of the host–pathogen interfaces and the fragile equilibria maintained by humans as hosts and their commensal flora is needed for helping to prevent disease in the more susceptible, predisposed fractions of the population, particularly children. Thus, in a stepwise manner, future research should necessarily seek to integrate approaches ranging from environmental and atmospheric sciences to the development of new organism-detection methodologies. The use of large clinical cohorts that are already established can be useful in integrating new knowledge and in testing new hypotheses. Mouse models and immunoassays on KD tissues can be very informative, if performed in conjunction with the results arising from epidemiological studies having a closer look at regional-to-local climate and atmospheric circulation patterns. This way, understanding of the environmental triggers of KD could be improved. The use of a backtrajectory model the type Flexpart v. 9.02[46] can effectively aid in tracing provenance of air masses, if highly detailed information is available (e.g., at the daily resolution of KD incidence records). Future attempts should seek to reproduce all situations from the 47 prefectures in Japan and the same should be repeated in all world sites where the disease is present in sufficient numbers. Determining the characteristics of the source region (and its changes over the last years to decades) that might substantiate the alleged link is a logical next step. Satellite imagery might be helpful in searching how changes in land-use cover, particularly with regard to cropland vegetation changes, might be related to the etiological source of the KD agent. In this regard, future research should also seek to further explore the nature of the vegetative cycle of crops in that region in Northeast China to assess whether coherent dynamical associations exist. The use and tracking of fertilizer and/or pesticide byproducts needs to also be addressed preferentially at the source region itself through close collaboration with local scientists and agencies. In addition to applying this new knowledge to improve the lives of children with KD and to develop new therapies, current research shows that similar approaches can be applied for other rheumatic diseases as well and even for AAD and STEMI patients.

Acknowledgments

We would like to thank Sahar Sodoudi for her assessment on the relation of AADs to different types of weather conditions. Special thanks to Jane Burns from the University of California, San Diego for useful discussions and the revision and editing of this manuscript. Thanks also for useful discussions to Ian Lipkin and Brent Williams from Columbia University; to Hiroshi Tanimoto from NIES/Tsukuba; to Atsushi Matsuki from Kanazawa University; and to Manel Rubio, Juliana Bordignon, and Joan Torres from the Bellvitge Hospital. All authors wish to thank the Daniel Bravo Foundation for financial support received through an award to X. Rodó. J. Ballester gratefully acknowledges funding from the European Commission through a Marie Curie International Outgoing Fellowship (Project MEMENTO from the FP7-PEOPLE-2011-IOF Call) and from the European Commission and the Catalan Government through a Marie Curie Beatriu de Pinós Fellowship (Project 00068 from the BP-DGR-2014-B Call).

Supporting Information

Additional supporting information may be found in the online version of this article.

Figure S1. (A) Particle size distribution to test for the performance of a new laser fluorescence prototype. (B) Differences in the distribution of fungi obtained from surface and flight filters by ITS1–ITS4 region and 18s rRNA gene PCR.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Lane, S.E., R.A. Watts, G. Bentham, *et al.* 2003. Are environmental factors important in primary systemic vasculitis? A case–control study. *Arthritis Rheum.* **48:** 814–823.
2. Demirkok, S.S., M. Basaranoglu, E. Dervis, *et al.* 2006. Analysis of 87 patients with Löfgren's syndrome and the pattern of seasonality of subacute sarcoidosis. *Respirology* **11:** 456–461.
3. Weiss, P. 2012. Pediatric vasculitis. *Pediatr. Clin. North Am.* **59:** 407–423.
4. Green, A. 2002. Spatial clustering and temporal trends in coronary heart disease. *Heart Drug* **2:** 49–50.
5. Samet, J.M., F. Dominici, F.C. Curriero, *et al.* 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N. Engl. J. Med.* **343:** 1742–1749.
6. Taheri Shahraiyni, H., S. Sodoudi & U. Cubasch. 2016. Weather conditions and their effect on the increase of the risk of aortic dissection events in Berlin. *Int. J. Biometeorol.* **60:** 1303–1305.
7. Mehta, R.H., T. Suzuki, P.G. Hagan, *et al.* 2002. Predicting death in patients with acute type a aortic dissection. *Circulation* **15:** 200–206.
8. Verberkmoes, N., M. Hamad, H. ter Woorst, *et al.* 2012. Impact of temperature and atmospheric pressure on the incidence of major acute cardiovascular events. *Neth. Heart J.* **20:** 193–196.
9. Benouaich, V. *et al.* 2010. Impact of meteorological conditions on the occurrence of acute type A aortic dissections. *Interact. Cardiovasc. Thorac. Surg.* **10:** 403–406.
10. Schuld, J., O. Kollmar, S. Schuld, *et al.* 2013. Impact of meteorological conditions on abdominal aortic aneurysm rupture: evaluation of an 18-year period and review of the literature. *Vasc. Endovasc. Surg.* **47:** 524–531.
11. Garry, V.F., J.T. Kelly, J.M. Sprafka, *et al.* 1994. Survey of health and use characterization of pesticide appliers in Minnesota. *Arch. Environ. Health* **49:** 337–343.
12. Schreinemachers, D.M. & A.J. Ghio. 2016. Effects of environmental pollutants on cellular iron homeostasis and ultimate links to human disease. *Environ. Health Insights* **10:** 35–43.
13. Gilden, D., T. White & N. Khemeleva. 2015. Prevalence and distribution of VZV in temporal arteritis of patients with giant cell arteritis. *Neurology* **84:** 1948–1955.
14. Wilsher, M.L. 1998. Seasonal clustering of sarcoidosis presenting with erythema nodosum. *Eur. Respir. J.* **12:** 1197–1199.
15. Veasy, L.G., S.E. Wiedmeier & G.S. Orsmond. 1987. Resurgence of acute rheumatic fever in the intermountain area of the United States. *N. Engl. J. Med.* **316:** 421–427.
16. Kawasaki, T., F. Kosaki, S. Okawa, *et al.* 1974. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* **54:** 271–276.
17. Nakamura, Y., E. Aso, M. Yashiro, *et al.* 2013. Mortality among Japanese with a history of Kawasaki disease: results at the end of 2009. *J. Epidemiol.* **23:** 429–434.
18. Newburger, J.W., M. Takahashi, M.A. Gerber, *et al.* 2004. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* **110:** 2747–2771.
19. Gordon, J., A. Kahn & J.C. Burns. 2009. When children with Kawasaki disease grow up: myocardial and vascular complications in adulthood. *J. Am. Coll. Cardiol.* **54:** 1911–1920.
20. Huang, S.K., M.T. Lin, H.C. Chen, *et al.* 2013. Epidemiology of Kawasaki disease: prevalence from national database and future trends projection by system dynamics modeling. *J. Pediatr.* **163:** 126–131.
21. Nakamura, Y., M. Yashiro, R. Uehara, *et al.* 2012. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. *J. Epidemiol.* **22:** 216–221.
22. Callinan, L.S., F. Tabnak, R.C. Holman, *et al.* 2012. Kawasaki syndrome and factors associated with coronary artery abnormalities in California. *Pediatr. Infect. Dis. J.* **31:** 894–898.
23. Fischer, T.K., R.C. Holman, K.L. Yorita, *et al.* 2007. Kawasaki syndrome in Denmark. *Pediatr. Infect. Dis. J.* **26:** 411–415.
24. Heuclin, T., F. Dubos, V. Hue, *et al.* 2009. Increased detection rate of Kawasaki disease using new diagnostic algorithm, including early use of echocardiography. *J. Pediatr.* **155:** 695–699.
25. Sanchez-Manubens, J., J. Anton, F. Prada, *et al.* 2014. Incidence and clinical features of Kawasaki disease in Catalonia (Spain). *Pediatr. Rheumatol. Online J.* **12:** 123.
26. Rowley, A.H. 2011. Kawasaki disease: novel insights into etiology and genetic susceptibility. *Annu. Rev. Med.* **62:** 69–77.
27. Uehara, R. & E.D. Belay. 2012. Epidemiology of Kawasaki disease in Asia, Europe and the United States. *J. Epidemiol.* **22:** 79–85.
28. Principi, N., D. Rigante & S. Esposito. 2013. The role of infection in Kawasaki syndrome. *J. Infect.* **67:** 1–10.
29. Brusadelli, T., S. Antoniazzi, M. Pozzi, *et al.* 2014. Kawasaki disease and pertussis epidemics. *Epidemiology* **25:** 310–311.
30. Onouchi, Y. 2012. Genetics of Kawasaki disease: what we know and don't know. *Circ. J.* **76:** 1581–1586.
31. Yeter, D., M. Portman, M. Aschner, *et al.* 2016. Ethnic Kawasaki disease risk associated with blood mercury and cadmium in U.S. children. *Int. J. Environ. Res. Pub. Health* **13**. doi: 103390/ijerph13010101.
32. Shimizu, C., S. Jain, S. Davila, *et al.* 2011. Transforming growth factor-β signaling pathway in patients with Kawasaki disease. *Circ. Cardiovasc. Genet.* **4:** 16–25.
33. Nagao, Y., C. Urabe, H. Nakamura & N. Hatano. 2016. Predicting the characteristics of the aetiological agent for Kawasaki disease from other pediatric infectious diseases in Japan. *Epidemiol. Infect.* **144:** 478–492.
34. Rodó, X., R. Curcoll, M. Robinson, *et al.* 2014. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. *Proc. Natl. Acad. Sci. U.S.A.* **111:** 7952–7955.
35. Nomura, Y., M. Yoshinaga, K. Masuda, *et al.* 2002. Maternal antibody against toxic shock syndrome toxin-1 may

protect infants younger than 6 months of age from developing Kawasaki syndrome. *J. Infect. Dis.* **185:** 1677–1680.
36. Lessler, J., N.G. Reich, R. Brookmeyer, *et al.* 2009. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect. Dis.* **9:** 291–300.
37. Reich, N.G., T.M. Perl, D.A. Cummings & J. Lessler. 2011. Visualizing clinical evidence: citation networks for the incubation periods of respiratory viral infections. *PLoS One* **6:** e19496.
38. Rodó, X., J. Ballester, D. Cayan, *et al.* 2011. Association of Kawasaki disease with tropospheric wind patterns. *Sci. Rep.* **1:** 152.
39. Ballester, J., J. Burns, D. Cayan, *et al.* 2013. Kawasaki disease and El Niño-Southern Oscillation. *Geophys. Res. Lett.* **40:** 2284–2289.
40. Rodó, X. 2001. Reversal of three global atmospheric fields linking changes in SST anomalies in the Pacific, Atlantic and Indian oceans at tropical latitudes and mid-latitudes. *Clim. Dyn.* **18:** 203–217.
41. Ballester, J., R. Lowe, P.J. Diggle & X. Rodó. 2016. Seasonal forecasting and health impact models: challenges and opportunities. *Ann. N.Y. Acad. Sci.* **1382:** 8–20.
42. Eckmann, J.P., S.O. Kamphorst & D. Ruelle. 1987. Recurrence plots of dynamical systems. *Europhys. Lett.* **5:** 973–977.
43. Marwan, N., M.C. Romano, M. Thiel & J. Kurths. 2007. Recurrence plots for the analysis of complex systems. *Phys. Rep.* **438:** 237.
44. Rodríguez-Arias, M.A. & X. Rodó. 2004. A primer on the study of transitory dynamics in ecological series using the scale-dependent correlation analysis. *Oecologia* **138:** 485–504.
45. Stohl, A., M. Hittenberger, & G. Wotawa. 1998. Validation of the Lagrangian particle dispersion model FLEXPART against large scale tracer experiment data. *Atmos. Environ.* **32:** 4245–4264.
46. Parthasarathy, P., A. Agarwal, K. Chawla, *et al.* 2015. Upcoming biomarkers for the diagnosis of Kawasaki disease: a review. *Clin. Biochem.* **48:** 1188–1194.
47. Ko, T.M., H.C. Kuo & J.S. Chang. 2015. CXCL10/IP-10 is a biomarker and mediator for Kawasaki disease. *Circ. Res.* **116:** 876–83
48. Tremoulet, A.H., J. Dutkowski, Y. Sato, *et al.* 2015. Novel data-mining approach identifies biomarkers for diagnosis of Kawasaki disease. *Pediatr. Res.* **78:** 547–553.
49. Griffin, D.W., N. Kubilay, M. Kocak, *et al.* 2007. Airborne desert dust and aeromicrobiology over the Turkish Mediterranean coastline. *Atmos. Environ.* **41:** 4050–4062.
50. Kakikawa, M., F. Kobayayshi, T. Maki, *et al.* 2008. Dustborne microorganisms in the atmosphere over an Asian dust source region, Dunhuang. *Air Qual. Atmos. Health* **1:** 195–202.
51. Drgona, L., A. Khachatryan, J. Stephens, *et al.* 2014. Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of *Aspergillus* and *Candida* species. *Eur. J. Clin. Microbiol. Infect. Dis.* **33:** 7–21.
52. Burge, H.A. 1996. Health effects of biological contaminants. In *Indoor Air and Human Health.* R.B. Gammage & B.A. Berven, Eds.: 171–178. Boca Raton: CRC Press/Lewis Publishers.
53. Davies, S.F. 1988. Diagnosis of pulmonary fungal infections. *Semin. Respir. Infect.* **3:** 162–171.
54. Manolakaki, D., G. Velmahos, T. Kourkoumpetis, *et al.* 2010. *Candida* infection and colonization among trauma patients. *Virulence* **1:** 367–375.
55. Pfaller, M. & D.J. Diekema. 2007. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin. Microb. Rev.* **20:** 133–163.
56. Ohno, N. 2004. Murine model of Kawasaki disease induced by manno-protein–beta-glucan complex, CAWS, obtained from *Candida albicans. Jpn. J. Infect. Dis.* **57:** S9–S10.
57. Lehman, T.J., R. Warren, D. Gietl, *et al.* 1988. Variable expression of *Lactobacillus casei* cell wall-induced coronary arteritis: an animal model of Kawasaki's disease in selected inbred mouse strains. *Clin. Immunol. Immunopathol.* **48:** 108–118.
58. Walinder, R., L. Ernstgard, G. Johanson, *et al.* 2005. Acute effects of a fungal volatile compound. *Environ. Health Perspect.* **113:** 1775–1778.
59. Khun, D.M. & M.A. Ghannoum. 2003. Indoor mold, toxigenic fungi, and *Stachybotyrs chartarum*: infectious disease perspective. *Clin. Microbiol. Rev.* **1:** 144–172.
60. Burns, J.C., D.R. Cayan, G. Tong, *et al.* 2005. Seasonality and temporal clustering of Kawasaki syndrome. *Epidemiology* **16:** 220–225.
61. Burns, J.C., L. Herzog, O. Fabri, *et al.* 2013. Seasonality of Kawasaki disease: a global perspective. *PLoS One* **8:** e74529.
62. Nakamura, Y. & H. Yanagawa. 2004. The worldwide epidemiology of Kawasaki disease. *Prog. Pediatr. Cardiol.* **19:** 99–108.
63. Lin, Y., C. Manlhiot, J. Ching, *et al.* 2010. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. *Pediatr. Int.* **52:** 699–706.
64. Nagao, Y. 2013. Decreasing fertility rate correlates with the chronological increase and geographical variation in incidence of Kawasaki disease in Japan. *PLoS One* **8:** e67934.
65. Minich, L.L., L.A. Sleeper, A.M. Atz, *et al.* 2007. Delayed diagnosis of Kawasaki disease: what are the risk factors? *Pediatrics* **120:** e1434–e1440.
66. Witt, M.T., L.L. Minich, J.F. Bohnsack & P.C. Young. 1999. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. *Pediatrics* **104:** e10.
67. Kim, D., H. Byun & Y. Lee. 2005. The long-term changes of Siberian High and winter climate over the Northern Hemisphere. *J. Korean Meteorol. Soc.* **41:** 275–283.
68. Takahashi, K., A. Montecinos, K. Goubanova & B. Dewitte. 2011. ENSO regimes: reinterpreting the canonical and Modoki El Niño. *Geophys. Res. Lett.* **38:** L10704.
69. Kug, J.S., F.F. Jin & S.I. An. 2009. Two types of El Niño events: cold tongue El Niño and warm pool El Niño. *J. Climate* **22**. doi: 10.1175/2008JCLI2624.1.
70. Trenberth, K.E. 1997. Short-term climate variations: recent accomplishments and issues for future progress. *Bull. Am. Meteorol. Soc.* **78:** 1081–1096.
71. Clifford, A. & G.S. Hoffman. 2015. Evidence for a vascular microbiome and its role in vessel health and disease. *Curr. Opin. Rheumatol.* **27:** 397–405.

72. Marques da Silva, R., D.A. Caugant, E.R. Eribe, *et al.* 2006. Bacterial diversity in aortic aneurysms determined by 16S ribosomal RNA gene analysis. *J. Vasc. Surg.* **44:** 1055–1060.
73. Bhatt, A., V. Manzo, C. Pedamallu, *et al.* 2014. In search of a candidate pathogen for giant cell arteritis: sequencing-based characterization of the giant cell arteritis microbiome. *Arthritis Rheum.* **66:** 1939–1944.
74. Round, J.L. & S.K. Mazmanian. 2009. The gut microbiota shapes intestinal immune responses during health and disease. *Nat. Rev. Immunol.* **9:** 313–323.
75. Onouchi, Y., T. Gunji, J.C. Burns & C. Shimizu. 2008. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nat. Genet.* **40:** 35–42.
76. Prospero, J.M., E. Blades, G. Mathison & R. Naidu. 2005. Interhemispheric transport of viable fungi and bacteria from Africa to the Caribbean with soil dust. *Aerobiologia* **21:** 1–19.
77. Pan, Y.L. 2015. Detection and characterization of biological and other organic-carbon aerosol particles in atmosphere using fluorescence. *J. Quant. Spectrosc. Radiat. Transf.* **150:** 12–35.
78. Guerrini, L., E. Pazos, C. Penas, *et al.* 2013. Highly sensitive SERS quantification of the oncogenic protein c-jun in cellular extracts. *J. Am. Chem. Soc.* **135:** 10314–10317.