Increased Kawasaki Disease Incidence Associated With Higher Precipitation and Lower Temperatures, Japan, 1991–2004

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Background: Kawasaki disease (KD) is an acute febrile vasculitis, which primarily affects children. The etiology of KD is unknown; while certain characteristics of the disease suggest an infectious origin, genetic or environmental factors may also be important. Seasonal patterns of KD incidence are well documented, but it is unclear whether these patterns are caused by changes in climate or by other unknown seasonal effects.

Methods: The relationship between KD incidence and deviations from expected temperature and precipitation were analyzed using KD incidence data from Japanese nationwide epidemiologic surveys (1991–2004) and climate data from 136 weather stations of the Japan Meteorological Agency. Seven separate Poisson-distributed generalized linear regression models were run to examine the effects of temperature and precipitation on KD incidence in the same month as KD onset and the previous 1, 2, 3, 4, 5 and 6 months, controlling for geography as well as seasonal and long-term trends in KD incidence.

Results: KD incidence was negatively associated with temperature in the previous 2, 3, 4 and 5 months and positively associated with precipitation in the previous 1 and 2 months. The model that best predicted variations in KD incidence used climate data from the previous 2 months. An increase in total monthly precipitation by 100 mm was associated with increased KD incidence (rate ratio [RR] 1.012, 95% confidence interval [CI]: 1.005–1.019), and an increase of monthly mean temperature by 1°C was associated with decreased KD incidence (RR 0.984, 95% CI: 0.978–0.990).

Conclusions: KD incidence was significantly affected by temperature and precipitation in previous months independent of other unknown seasonal factors. Climate data from the previous 2 months best predicted the variations in KD incidence. Although fairly minor, the effect of temperature and precipitation independent of season may provide additional clues to the etiology of KD.

Key Words: Kawasaki disease, climate, temperature, precipitation

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Kawasaki disease (KD) is an acute febrile vasculitis, which primarily affects children. This disease was first described in Japan by Dr. Tomisaku Kawasaki in 1967[1] and since has been reported in over 60 countries worldwide.[2] KD has been reported in males and females of all races spanning from neonates to adults,[3–5] but males, children below 5 years of age and children of Asian descent, are at increased risk of KD.[6] Currently, there is no diagnostic test for KD and treatment options are limited due to an incomplete understanding of disease etiopathogenesis.

While much remains unknown about the etiology of KD, certain characteristics of the disease suggest a possible infectious origin.[7–9] These characteristics include the clinical similarity to other infections such as rashes or fever illnesses, the self-limited nature of the disease, age distribution of those affected and the relative rarity of cases in the first 6 months. Geographic and temporal clustering of cases[10,11] and occurrences of past epidemics[12,13] have been observed for KD.

The seasonality of KD also supports the theory of infectious etiology. Many studies have observed seasonal patterns of KD incidence starting with Dr. Kawasaki in 1967.[1] Although seasonality is well documented worldwide, peak seasons often differ between countries.[14–19] In addition, previous studies have noted that KD incidence is correlated with temperature and precipitation. Two studies conducted in the United States have found KD incidence to be negatively correlated with average ambient temperature but positively correlated with average precipitation although one of these studies measured only snowfall, not all precipitation.[20,21] An 18-year study in Chicago found that during one unseasonably warm winter, mean time between KD hospital admissions was shorter, which would not be expected if temperature was negatively correlated with KD incidence. However, the explanatory power of a single data point from a small-scale study (~40 KD cases were recorded per year) is limited. This study also found no association between precipitation and KD incidence.[22] Similarly, Chang[23] also found no association between temperature, precipitation and KD incidence in their California study.

Temperature and precipitation can affect incidence for assorted infectious diseases by mechanisms such as influencing environmental survival of pathogens or the abundance of vectors.[24] Regarding KD, the more pertinent issue may be whether temperature and precipitation are directly affecting incidence, or if they are simply correlates of other seasonally dependent variables. Notably, there exists evidence that noninfectious diseases such as coronary heart disease,[25] type 1 diabetes[26] or assorted rheumatic diseases[27] may display seasonal fluctuations. Proposed mechanisms for seasonality of noninfectious diseases tend to lean toward seasonal changes in human behavior (e.g., exercise levels, diet, indoor crowding) or human physiology (immune competence, hormone levels).[25,28]

To determine if temperature and precipitation (as opposed to other seasonal factors) actually have an effect on KD incidence, it is necessary to control for overall seasonality. This study (1) examines whether temperature and precipitation have an effect on KD incidence independent of time of year, (2) determines the time frame in which these factors have the greatest/most pronounced effect and (3) quantifies the effect for the best fit model.

METHODS

Data Sources and Case Selection

Data from the 12th through 18th Japanese biannual nationwide epidemiologic surveys were used, consisting of information on KD incidence from 1991 to 2004. These surveys measure KD

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incidence by sending questionnaires to all pediatric departments in hospitals with at least 100 beds or hospitals specializing in pediatrics with less than 100 beds. Questionnaires collect demographic and clinical information for physician-diagnosed KD patients, including sex, date of birth, date of hospitalization and discharge, illness day of hospitalization and geographic area of residence. The geographic units used for this study were the 47 prefectures of Japan. Response rate to surveys varied by prefecture: between 40% and 93% of hospitals in a given prefecture responded to each survey. To correct for missing data due to hospital nonresponse, we used the commonly used method of calculating adjusted KD rates through dividing recorded cases by prefecture response rate.[29–31] All rates are presented as KD cases per 100,000 children less than 5 years old.

Climate data were collected from the Japan Meteorological Agency for 155 weather stations across Japan. After excluding 19 weather stations on outlying minor islands, data from 136 weather stations were used for this study. Monthly mean air temperature (°C) and total monthly precipitation (mm) by prefecture were calculated by averaging data from all included weather stations within each prefecture. Climate for Okinawa prefecture was based on 2 weather stations on Okinawa Island (Fig. 1).

Data Analysis

Determining the Best Fit Model

To determine the effects of temperature and precipitation simultaneously on the number of KD cases, 7 separate Poisson-distributed generalized linear regression models were run. These models determined whether temperature and precipitation in the same month as KD onset and in the previous 1, 2, 3, 4, 5 or 6 months predicted monthly KD incidence in each prefecture. All models included prefecture, year (categorical) and month (categorical) to control for effects of geography, increasing annual KD incidence, and normal seasonal patterns. To determine which climate time frame best explained KD incidence, all models were compared using the Akaike Information Criterion (AIC) and the model with the lowest AIC score was selected as the best fit model.

Importantly, temperature and precipitation are heavily dependent on month of year. Because month, year and prefecture are included in the models, the explanatory variables are not temperature and precipitation per se, but rather the deviations of temperature and precipitation from the expected values for a given month of year in each prefecture. Monthly mean temperatures by prefecture ranged between −6.7 and 30.3°C (interquartile range: 7.9–22.0°C), while deviation from expected temperature ranged between −3.9 and 3.5°C (interquartile range: −0.6 to 0.7°C). Monthly mean precipitation by prefecture ranged between 0 and 1126.3 mm (interquartile range: 69.5–186.2 mm), while deviation from expected precipitation ranged between −394.9 and 750.2 mm (interquartile range: −43.7 to 33.6 mm). For ease of communication, we defined the measure of effect as the rate ratio (RR) per increase of 1°C or 100 mm precipitation.

FIGURE 1. The 47 prefectures of Japan, with the 136 weather stations used for this study (black circles) and the 19 excluded weather stations on minor outlying islands (gray circles).

Using KD cases adjusted for hospital response rate assumes that nonresponding hospitals are similar to hospitals that respond to the KD surveys, which may not be accurate. As a sensitivity analysis, we ran the same models to predict unadjusted (recorded) KD cases.

We also conducted testing to see if the effect of deviations in precipitation and temperature varied by season. We ran additional models, which included the same predictor variables along with interaction terms for season with precipitation and season with temperature (season was defined by month of climate measurement as December–February for winter, March–May for spring, June–August for summer and September–November for autumn).

RESULTS

There were 99,580 recorded KD cases in Japan from 1991 to 2004. Of those, 203 cases had unknown prefecture of residence or were of foreign residence, leaving 99,377 cases available for analysis. Annual rates of KD increased from 89.5 cases per 100,000 children under 5 per year in 1991 to 174.3 cases per 100,000 children under 5 per year in 2004 (Fig. 2). Nationwide hospital response rates remained relatively stable between surveys, ranging from a low of 65.5% to a high of 70.1%. Adjusting for hospital response rate, there were an estimated 146,722 KD cases during this time period. The adjusted KD incidence increased from 130.2 cases per 100,000 children under 5 per year in 1991 to 249.1 cases per 100,000 children under 5 per year in 2004. There was marked seasonality in KD incidence, with a peak of 223.9 adjusted KD cases per 100,000 children under 5 per year during January, a secondary peak of 192.4 cases per 100,000 children under 5 per year during June, and lower incidence during the spring and autumn with a low of 133.2 cases per 100,000 children under 5 per year during October.

The 7 regression analyses showed that KD incidence was negatively associated with temperature in the previous 2, 3, 4 and 5 months. KD incidence was positively associated with precipitation in the previous 1 and 2 months (Fig. 3). KD incidence was most strongly associated with temperature and precipitation 2 months prior (AIC = 49077.36). Under this model, an increase of monthly mean temperature by 1°C was associated with decreased KD incidence (RR 0.984, 95% confidence interval [CI]: 0.978–0.990) and an increase in total monthly precipitation by 100 mm was associated with increased KD incidence (RR 1.012, 95% CI: 1.005–1.019).

For the sensitivity analysis using unadjusted (recorded) KD rates, the results were similar: for temperature and precipitation 2 months prior, an increase of monthly mean temperature by 1°C was associated with decreased KD incidence (RR 0.984, 95% CI: 0.977–0.991) and an increase in total monthly precipitation by 100 mm was associated with increased KD incidence (RR 1.011, 95% CI: 1.003–1.019).

For models assessing if effects of temperature and precipitation varied by season, there were statistically significant interaction terms for season with precipitation ($P < 0.0001$) and temperature ($P = 0.0002$). Specifically, rates of KD 2 months later were significantly increased following increased precipitation during the

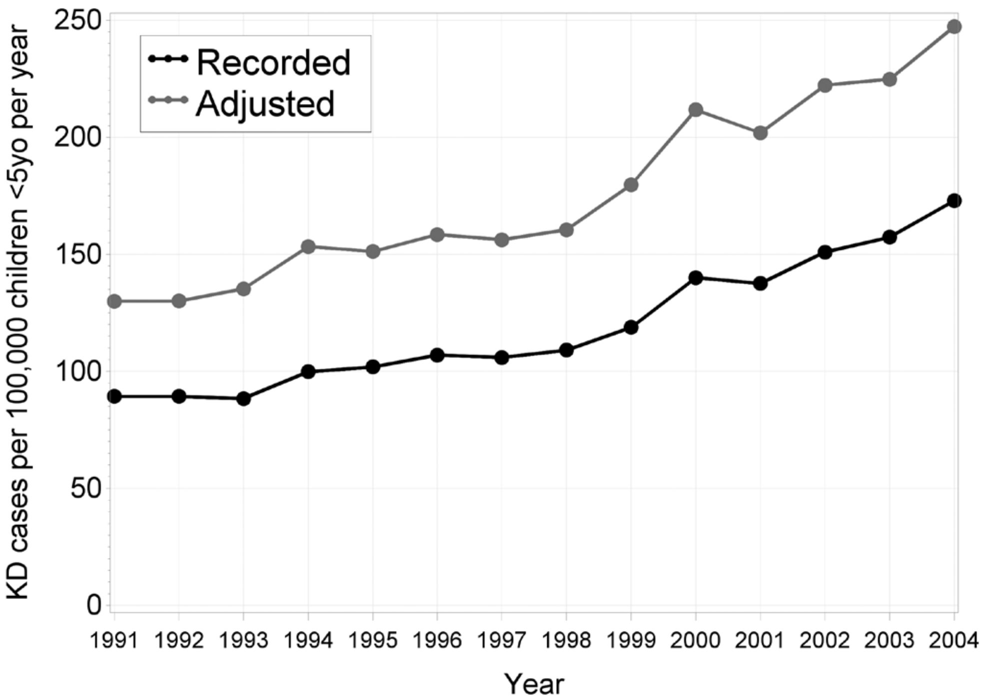

FIGURE 2. Annual rates for recorded and adjusted KD cases per 100,000 children under 5 years old in Japan, 1991–2004, for all cases with known prefecture of residence.

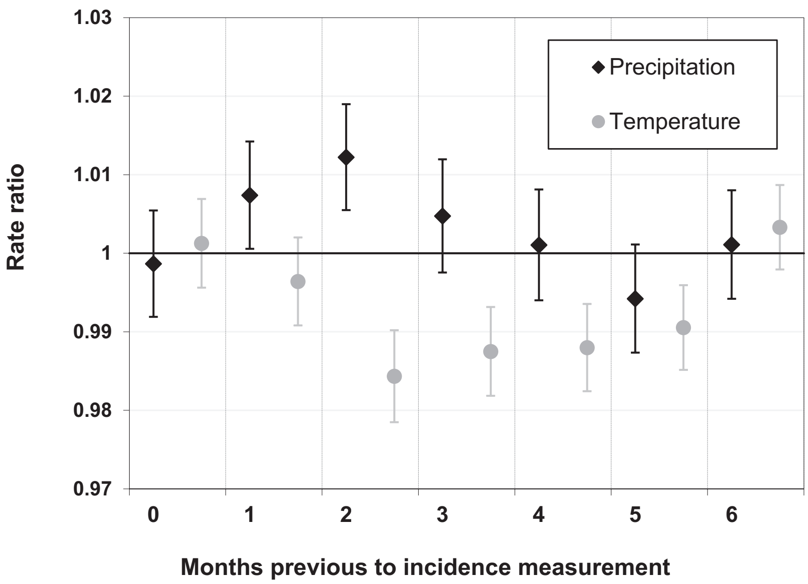

FIGURE 3. Effect of climate in previous months on KD incidence in Japanese prefectures, controlling for geography, seasonality and year 1991–2004. RRs and 95% CIs per 100 mm deviation from expected monthly total precipitation are in black; RRs and 95% CIs per 1°C deviation from expected monthly mean temperature are in gray.

summer (RR 1.021, 95% CI: 1.009–1.032) and autumn (RR 1.014, 95% CI: 1.004–1.025) (Fig. 4). Rates of KD 2 months later were significantly decreased following higher temperatures in the winter (RR 0.983, 95% CI: 0.977–0.989) and spring (RR 0.989, 95% CI: 0.978–1.000).

DISCUSSION

This retrospective study shows that KD incidence is significantly affected by climate deviations in the previous 1–5 months independent of other unknown seasonal factors. Climate data from 2 months prior best predicted the variations in KD incidence. Under this model, mean monthly air temperature was negatively associated and mean monthly precipitation was positively associated with KD incidence.

Because RRs per 100 mm precipitation or 1°C deviation were between 0.98 and 1.02, the estimated effects of temperature and precipitation deviations on KD incidence initially appear to be fairly minor. However, during this time period, there were an average of ~900 estimated KD cases per month, meaning a month where nationwide temperatures averaged 1°C lower than expected would result in an estimated 13.7 additional cases 2 months later, while a month where precipitation totals averaged 100 mm more than expected would result in an estimated 10.7 additional KD cases

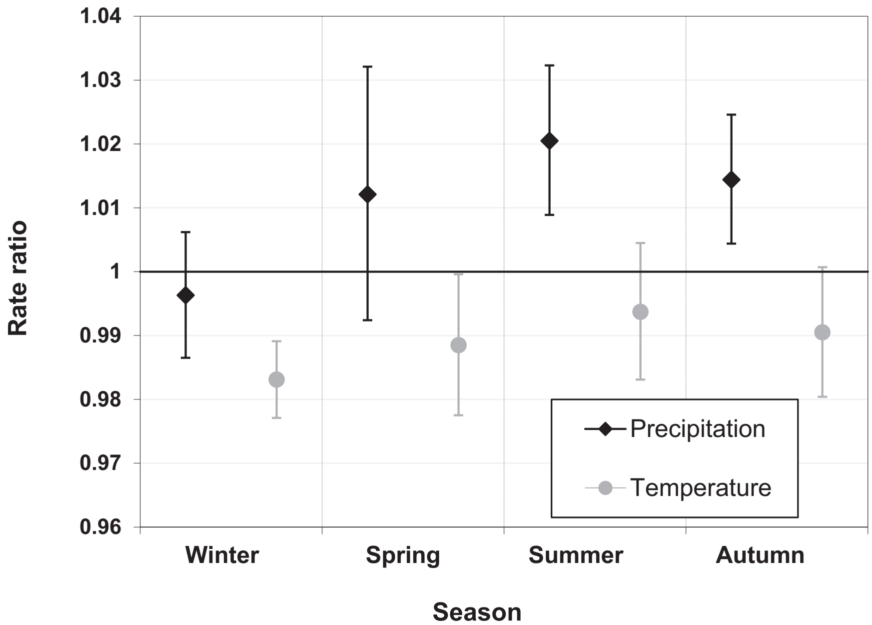

FIGURE 4. Effect of seasonal climate deviations on KD rates 2 months later. RRs and 95% CIs per 100 mm deviation from expected monthly total precipitation are in black; RRs and 95% CIs per 1°C deviation from expected monthly mean temperature are in gray. Seasons reflect period of climate measurement: winter, December–February; spring, March–May; summer, June–August; autumn, September–November.

2 months later. In addition, these results may only capture part of the effect of climate on KD seasonality because seasonal changes in temperature and precipitation are much greater than monthly deviations from expected. Even if the effects of temperature and precipitation independent of seasonality are quite small, the overall impact of temperature and precipitation on KD incidence might be more substantial.

While some studies found associations between temperature and/or precipitation and KD incidence of a similar magnitude and direction,[20,21] others failed to find any relationship between the climate variables and KD.[23,32] Of four published studies that examine the effects of temperature and precipitation separately, one study accounted for an incubation period but examined climate only 2 weeks before the outcome, a relatively narrow window.[32] The other 3 studies calculated correlations of climate and KD incidence within the same timeframe.

We assessed if effects of temperature and precipitation on KD incidence varied by season, and found that KD incidence was most increased after particularly cold winters and rainy summers. KD in Japan is seasonally bimodal with peaks in January and June, and the temporally distinct effects of temperature and precipitation could suggest multiple causal pathways to KD.

This study showed that temperature and precipitation were associated with KD incidence independent of any unidentified seasonal confounding, but much remains to be known about the mechanisms for these effects. For example, temperature and precipitation may affect the survival and transmissibility of hypothetical infectious agents or possible vectors in the environment. Alternately, indirect effects of climate such as through modifications of human behavior (e.g., more people staying inside during cold or wet conditions) may lead to a higher disease incidence. Considering the variation of seasonal trends across countries, additional analyses are necessary to determine whether these results hold true in other regions around the world.[33]

Measuring exposure and outcome variables by month is a limitation of this study because this time period may not capture exact patterns in weather and KD incidence. For example, particularly cold or rainy weather or a cluster of KD cases may start at the end of 1 month and continue into another month. Other possibilities should be explored when looking at units of analysis for weather patterns. The analysis of a large nationwide survey with many years of data revealed significant associations between KD incidence and temperature and precipitation while controlling for seasonality. Future studies could further examine the types of disease processes that could be affected by weather conditions up to 2 months before clinical illness onset.

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