Short-Term Weather Variability in Chicago and Hospitalizations for Kawasaki Disease

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Background: Kawasaki disease exhibits a distinct seasonality, and short-term changes in weather may affect its occurrence.

Methods: To investigate the effects of weather variability on the occurrence of this syndrome, we conducted a time-between-events analysis of consecutive admissions for Kawasaki disease to a large pediatric hospital in Chicago. We used gamma regression to model the times between admissions. This is a novel application of gamma regression to model the time between admissions as a function of subject-specific covariates.

Results: We recorded 723 admissions in the 18-year (1986–2003) study period, of which 700 had complete data for analysis. Admissions for Kawasaki disease in Chicago were seasonal: The mean time between admissions was 34% shorter (relative time = 0.66, 95% confidence interval 0.54–0.81) from January–March than from July–September. In 1998, we recorded a larger number of admissions for Kawasaki disease (n = 65) than in other years (mean n = 37). January–March months of 1998 were warmer by a mean of 3°C (1.5°C–4.4°C) and the mean time between admissions was 48% shorter (relative time = 0.52, 0.36–0.75) than in equivalent periods of other study years.

Conclusions: Our findings show that atypical changes in weather affect the occurrence of Kawasaki disease and are compatible with a link to an infectious trigger. The analysis of interevent times using gamma regression is an alternative to Poisson regression in modeling a time series of sparse daily counts.

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Kawasaki disease is an acute systemic vasculitis of small-to-medium sized vessels in children, characterized by fever, skin rash, conjunctival injection, mucosal inflammation, erythema and swelling of the hands and feet, and cervical adenopathy. If untreated, the disease may lead to serious cardiovascular complications including coronary artery aneurysms, myocardial infarction, and valvular heart disease.[1] Kawasaki disease is a common cause of heart disease in children and has replaced rheumatic heart disease as the leading cause of childhood-acquired heart disease in the developed world.[2]

The epidemiology of Kawasaki disease exhibits 3 distinctive characteristics. One is seasonality. Tomisaku Kawasaki was the first to recognize this syndrome in 1967 and the first to describe its seasonality.[3] Several investigators have since described seasonal patterns of the disease, which seem to vary by geographic region.[4–11] Reports in the United States have consistently shown that Kawasaki disease admissions peak in the winter or early spring.[11–14] A second distinctive characteristic is that Kawasaki disease has caused epidemics among Japanese children similar to epidemics of many classic infectious diseases. This phenomenon has led scientists to speculate that an infectious agent may be the cause. Although no specific infectious organism has been confirmed, Rowley et al[15,16] have found that Kawasaki disease synthetic antibodies detect antigen in ciliated bronchial epithelium of patients in the acute phase of Kawasaki disease. Their findings point strongly to a respiratory virus as the etiologic agent.

Finally, there is evidence that children who develop Kawasaki disease are genetically susceptible. Children with siblings or parents who have had Kawasaki disease have a greater risk of developing Kawasaki disease.[17,18] Recently, genetic polymorphisms have been linked either to a greater risk of developing this disease[18] or to a more complicated disease course.[19]

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Unusual weather patterns affect the occurrence of many infectious diseases.[20] Seasonal variation in ambient temperature is likely to play an important role in the occurrence of viral infections in children. We, therefore, conjectured that if a viral infection were a trigger for Kawasaki disease, weather variability could affect the occurrence of Kawasaki disease. Chicago experienced an episode of unseasonably high ambient temperature from January to March 1998.[21] To investigate our hypothesis, we analyzed the time between consecutive admissions of children with Kawasaki disease to a large pediatric hospital in Chicago between 1986 and 2003. The primary goal of this study was to determine whether the mean number of days between consecutive hospital admissions for Kawasaki disease in the unseasonably warm months of 1998 was different from the mean time between admissions in the remaining periods from 1986–2003. A shorter mean time between admissions for Kawasaki disease over a time period corresponds to a larger number of admissions during that period.

Our analytical approach includes a novel application of gamma regression to model the time between consecutive admissions for Kawasaki disease as a function of subject-specific covariates and day-specific weather covariates. We compare this approach to a more conventional analysis that uses Poisson regression with overdispersion to model the daily numbers of admissions.

METHODS

We reviewed retrospectively records of patients with Kawasaki disease between 1986 and 2003 at Children's Memorial Hospital. Children's Memorial Hospital is a 250-bed facility with 94,000 emergency medicine visits, 9000 hospital admissions, and 330,000 outpatient visits yearly. In 2004, we identified all children diagnosed with Kawasaki disease and treated at Children's Memorial Hospital from a database maintained by physicians in the Division of Pediatric Infectious Diseases.

We reviewed all available outpatient clinic charts and inpatient medical records for each case. Collected data included age at presentation, sex, race, date of diagnosis, duration of illness at the time of diagnosis, clinical presentation, date the child received therapy, duration of therapy, choice of therapy, and home address. We included children if they had at least 5 days of fever with at least 4 of the 5 standard clinical criteria for Kawasaki disease and no alternative diagnosis. If there was no alternative diagnosis, we also included children who had coronary artery abnormalities after prolonged fever but not at least 4 other clinical manifestations of Kawasaki disease. Incomplete records were excluded (see Results section). We counted patients only once during data collection, excluding subsequent hospital admissions for children who required more than 1 hospital admission for management of Kawasaki disease. The International Research Institute for Climate and Society of Columbia University provided meteorologic data for this analysis, including daily data for average ambient temperature and precipitation.

Biostatistical Analysis

The outcome for our analysis was the time between consecutive admissions for Kawasaki disease. We calculated time between admissions in days. There were 45 instances of 2 admissions in the same day. For these instances, the time between admissions is an artificial 0 because the 2 admissions are not exactly simultaneous. To avoid artificial 0 outcomes when fitting a gamma regression model, we separated these 0s with 0.5 days.

We used gamma regression to model the number of days between consecutive admissions.[22] We defined trimester-specific indicators to model the seasonal pattern of Kawasaki disease. Trimester indicators included in the model were January–March, April–June, and October–December, with July–September as the baseline. Trimester-specific parameters modeled their corresponding effects. We modeled the number of days between consecutive admissions with the following covariates: trimester indicators, an indicator for the year 1998, interaction terms between the indicators for trimesters and 1998, age (AGE), sex (SEX), and calendar time (t). We included calendar time in the model to account for a secular trend in the time between admissions. We indexed the times between consecutive admissions, $Y_j = t_j - t_{j-1}$, with $j = 2, \ldots, 700$. There were 699 interevent times ($Y_2, \ldots, Y_{700}$) for the 700 children with complete data. We used a log-linear link with gamma errors to model the mean. The variance for times between admissions was smaller in 1998 than in other years. Therefore, our model estimated a variance parameter for 1998 and a separate variance parameter for other years. We fitted the model with restricted maximum likelihood.[23] The form of the model was as follows:

$$Y_j \sim \text{Gamma}(\mu_j, \sigma_j^2)$$

$$\text{E}[Y_j] = \mu_j$$

$$\text{var}(Y_j) = \sigma_j^2$$

$$\begin{aligned}\log(\mu_j) = {} & \beta_1 + \beta_2 \text{I}_{\text{JFM}}(t_j) + \beta_3 \text{I}_{\text{AMJ}}(t_j) + \beta_4 \text{I}_{\text{OND}}(t_j) \\ & + \beta_5 \text{I}_{1998}(t_j) + \beta_6 \text{I}_{\text{JFM}}(t_j)\text{I}_{1998}(t_j) + \beta_7 \text{I}_{\text{AMJ}}(t_j)\text{I}_{1998}(t_j) \\ & + \beta_8 \text{I}_{\text{OND}}(t_j)\text{I}_{1998}(t_j) + \beta_9 \text{AGE}_j + \beta_{10} \text{SEX}_j + t_j\end{aligned}$$

$$\log(\sigma_j^2) = \gamma_1 + \gamma_2 \text{I}_{1998}(t_j).$$

In a separate analysis, we used a gamma regression model to study the interaction effects between daily average ambient temperature and the year 1998 on the time between

admissions for Kawasaki disease, after controlling for the effects of daily precipitation. Higher daily average ambient temperatures (T) were associated with longer times between admissions for Kawasaki disease; however, 5 outlying data points significantly altered this relationship. Three of these data points corresponded to admissions during years other than 1998 (−12°C vs. 52 days, −12.5°C vs. 19 days, and −12.2°C vs. 32 days), and 2 corresponded to admissions during 1998 (−13.9°C vs. 19 days and −10.6°C vs. 12 days). These outliers represented less than 1% of the dataset, and were excluded from our regression analysis. We included daily average ambient temperature in degrees Celsius as a continuous variable, and daily precipitation in tenths of millimeters as a categoric variable with the following strata: 0 (I_0), 1–9 (I_{1-9}), 10–49, 50–99 (I_{50-99}), and 100 (I_{100}) of precipitation or greater. The stratum 10–49 in tenths of millimeters was the reference category. In this model, we estimated a variance parameter for 1998 and a variance parameter for other years. We were unable to assess adequately interaction effects between precipitation and the period corresponding to the year 1998 because there were only 17 data points with precipitation values greater than 0 in 1998. The form of this model was as follows:

$$Y_j \sim \text{Gamma}(\mu_j, \sigma_j^2)$$

$$\text{E}[Y_j] = \mu_j$$

$$\text{var}(Y_j) = \sigma_j^2$$

$$\log(\mu_j) = \alpha_1 + \alpha_2 T(t_j) + \alpha_3 I_{1998}(t_j) + \alpha_4 T(t_j) I_{1998}(t_j) + \alpha_5 I_0(t_j) + \alpha_6 I_{1-9}(t_j) + \alpha_7 I_{50-99}(t_j) + \alpha_8 I_{100}(t_j) + \alpha_9 t_j$$

$$\log(\sigma_j^2) = \lambda_1 + \lambda_2 I_{1998}(t_j).$$

We also conducted a Poisson regression analysis of the times series of daily admissions for Kawasaki disease to compare it with our approach. In this model, the outcome was the number of daily counts (Y_t) and the covariates were trimester indicators, an indicator for the year 1998, interaction terms between trimesters and 1998, and a smooth function of calendar time. There were a total of 6574 days ($t = 1, \ldots, 6574$), with 0–2 counts for a total of 700 admissions. We used a log link to model the mean and allowed the variance to vary from the mean according to an estimated overdispersion parameter. We included a natural cubic spline, s(t), with 3 internal knots as a predictor to account for any additional serial autocorrelation. The form of the model was as follows:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$\text{E}[Y_t] = \mu_t$$

$$\text{var}(Y_t) = \phi\mu_t$$

$$\log(\mu_t) = \beta_1 + \beta_2 I_{\text{JFM}}(t) + \beta_3 I_{\text{AMJ}}(t) + \beta_4 I_{\text{OND}}(t) + \beta_5 I_{1998}(t) + \beta_6 I_{\text{JFM}}(t) I_{1998}(t) + \beta_7 I_{\text{AMJ}}(t) I_{1998}(t) + \beta_8 I_{\text{OND}}(t) I_{1998}(t) + s(t).$$

We conducted all analyses in R (The R Project for Statistical Computing, www.r-project.org). We obtained the algorithm for a gamma regression model with structured dispersion ("remlscoregamma" function in the "statmod" package) from STATLIB (lib.stat.cmu.edu/R/CRAN).

RESULTS

We identified 723 admissions for Kawasaki disease between 1986 and 2003 (18-year period). Of these, 700 admissions (97%) had complete information available for analysis. Of 700 admissions, 646 (92%) were residents of

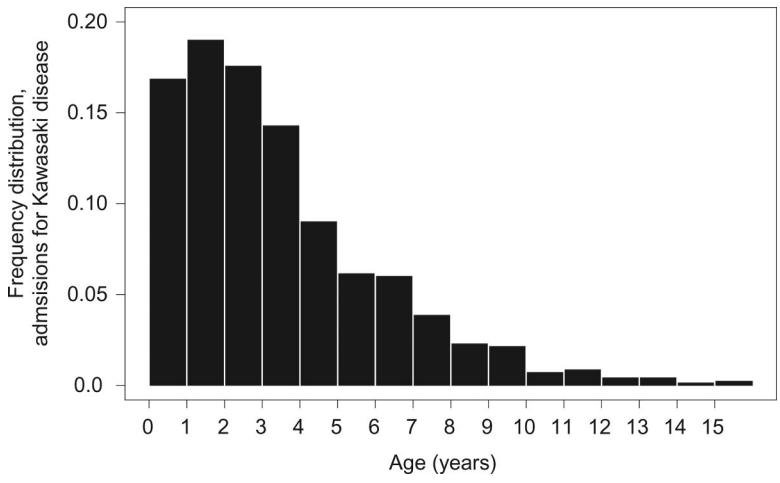

FIGURE 1. Age distribution (in years) of admissions for Kawasaki disease to a large pediatric hospital in Chicago, 1986–2003.

Illinois. The mean age of admission for Kawasaki disease was 3.5 years, with a range of 1.5 months–15.6 years (Fig. 1). Of 700, 163 (23%) were 5 years of age or older. The number of boys (418) admitted were 1.5 times the number of girls (282). Of 700, 370 (53%) of the study children were white, 17% (118 of 700) were Hispanic, 16% were black (110 of 700), and 14% (102 of 700) were of other races or ethnicities.

We show the series of interevent times (top panel), daily average ambient temperature (middle panel), and daily precipitation for Chicago between 1986 and 2003 (bottom panel) in Figure 2. Vertical segments (top panel of Fig. 2) represent admissions for Kawasaki disease and the distance between consecutive vertical bars represents the time between admissions. A shorter time between admissions corresponds to a larger number of admissions for Kawasaki disease during a given period. In exploratory analysis, we found that the mean time between admissions for Kawasaki disease was shorter in winter than summer. The mean time between admissions appeared shorter in 1998 than in other years. Mean time between admissions for Kawasaki disease was 5.7 days in 1998 (standard deviation 4.9 days) and 9.8 days in other years (standard deviation 10.4 days). Admissions for Kawasaki disease peaked more often during the cooler months of January–March (12 years) than during other trimesters (6 years) (Fig. 3).

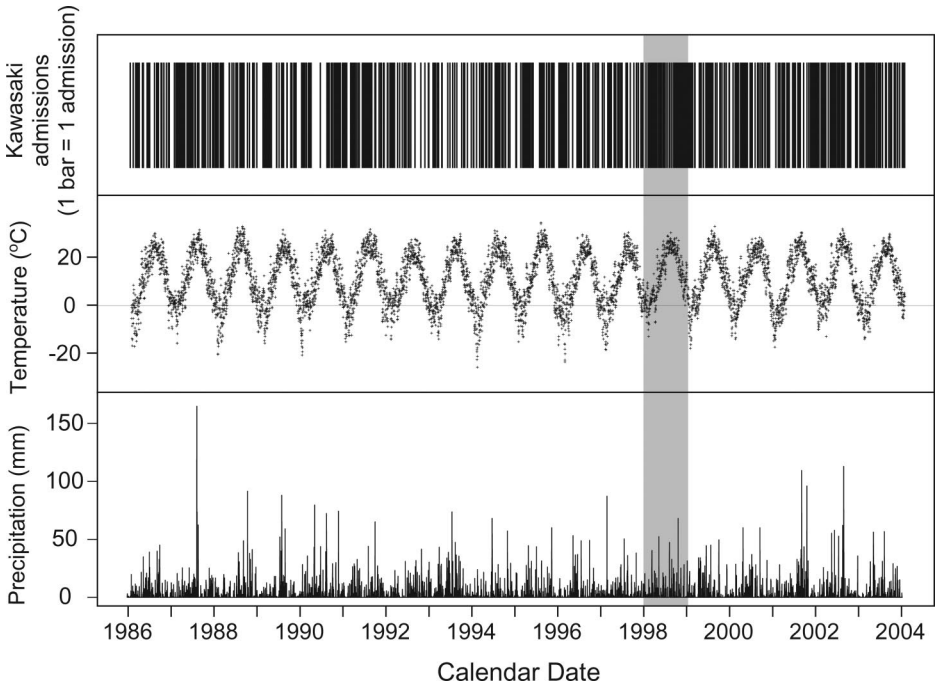

FIGURE 2. Time series of days between admissions for Kawasaki disease, daily average ambient temperature (degrees Celsius), and daily precipitation (millimeters) in Chicago, 1986–2003.

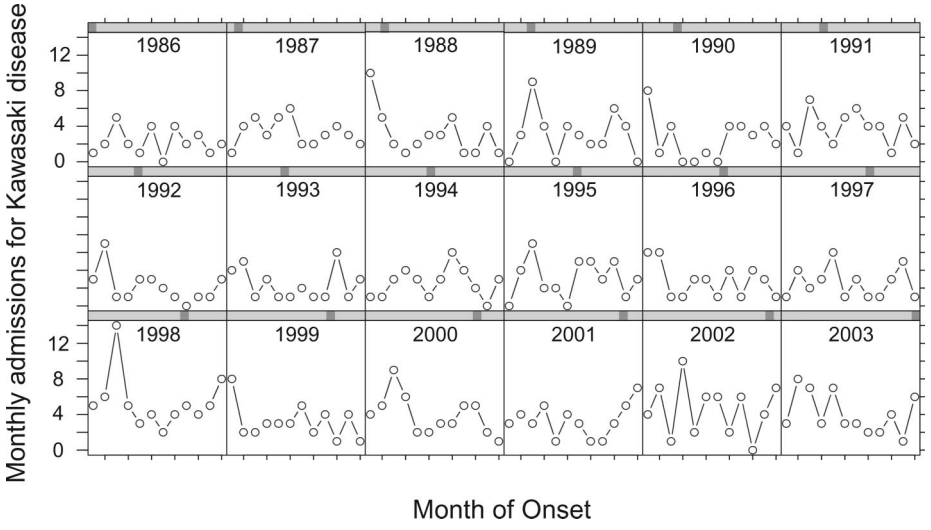

FIGURE 3. Monthly admissions for Kawasaki disease to a large pediatric hospital in Chicago, 1986–2003.

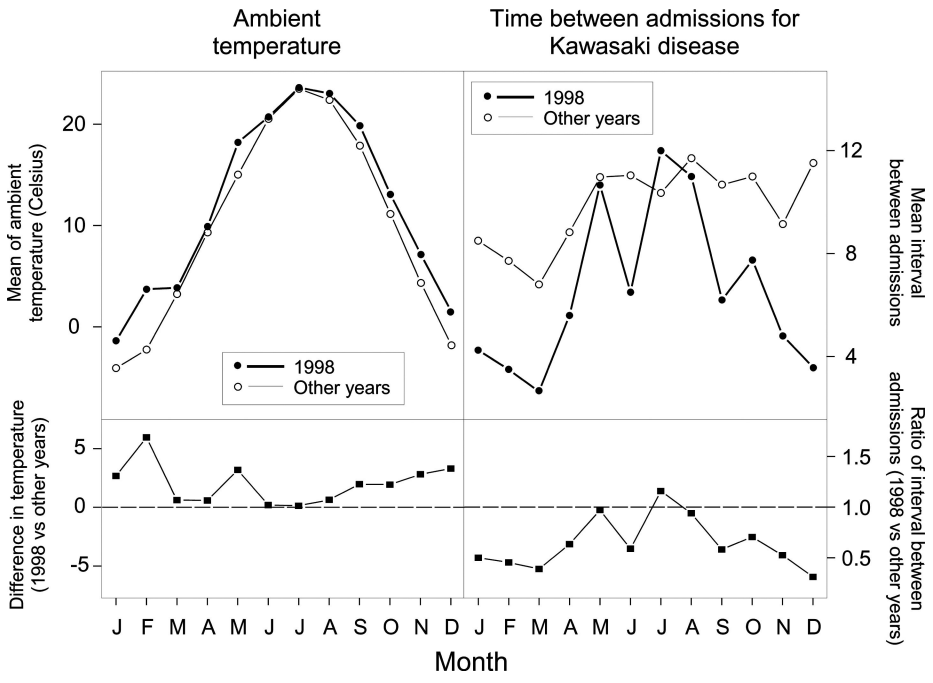

FIGURE 4. Monthly mean of daily average ambient temperature (Celsius) and the mean time between consecutive admissions for Kawasaki disease in Chicago, 1986–2003.

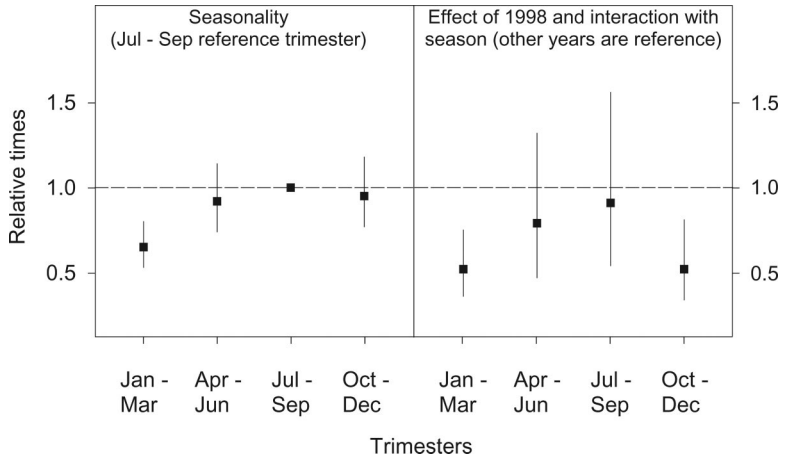

FIGURE 5. Seasonality of hospital admissions for Kawasaki disease and the interaction effects between seasonality and 1998 data for the number of days between consecutive admissions for Kawasaki disease in Chicago, 1986–2003. Associated 95% confidence intervals are represented with vertical lines.

The daily average ambient temperature from January–March 1998 was 3°C warmer [95% confidence interval (CI) = 1.5–4.4°C] than the daily average ambient temperature from January–March of other years (Fig. 4). The most unseasonably warm month was February 1998, with a daily average ambient temperature 6.2°C (4.3–8.0°C) warmer than the daily ambient temperature in February of other years. Precipitation was also greater from January–March 1998 (eFigure, http://links.lww.com/A717), with an additional 0.9 mm (95% CI = −0.1–1.9 mm) of precipitation per day over the average daily precipitation from January–March of other years.

Admissions for Kawasaki disease in Chicago were seasonal (Fig. 5). Adjusted for age, sex, and calendar time, the mean time between admissions for Kawasaki disease in January–March was 34% shorter [relative time (RT) = 0.66; 0.54–0.81] than in July–September. The year 1998 exhibited a larger-than-expected number of admissions for Kawasaki disease, with 65 admissions compared with an average of 37 per year in other years. Adjusted for quarterly differences, age, sex, and calendar time, the mean time between admissions for Kawasaki disease was 36% shorter (RT = 0.64; 95% CI = 0.51–0.80) in 1998 than in other years. When stratified by trimester and adjusted for age, sex, and calendar time, the mean time between admissions in January–March 1998 was 48% shorter (0.52; 0.36–0.75) than in January–March of other years. The observed and fitted values of the time between admissions over calendar time are shown in (eFigure 2, http://links.lww.com/A718).

We compared results obtained with a gamma regression model for the times between admissions to the results obtained with a Poisson regression model for the daily number of admissions (Table 1). We used July–September as the

TABLE 1. Estimates for Expected Daily Counts Stratified by Trimester and Year Obtained From a Poisson Regression Analysis of Daily Counts, and Expected Time Between Admissions Stratified by Trimester and Year Obtained From a Gamma Regression With Structured Dispersion of the Time Between Consecutive Admissions

	Gamma Regression (n = 699)		Poisson Regression (n = 6574)	
	Expected Time Between Admissions (d)	Relative Times (95%CI)	Expected Rate (Cases/d)	Relative Risk (95%CI)
January–March 1998	5.5	0.52 (0.36–0.75)	0.23	2.15 (1.38–3.36)
January–March other years	10.6	1.0 (ref)	0.11	1.0 (ref)
April–June 1998	11.3	0.80 (0.48–1.33)	0.11	1.38 (0.75–2.56)
April–June other years	14.2	1.0 (ref)	0.08	1.0 (ref)
July–September 1998	13.9	0.91 (0.54–1.56)	0.10	1.29 (0.68–2.45)
July–September other years	15.3	1.0 (ref)	0.07	1.0 (ref)
October–December 1998	8.0	0.52 (0.34–0.81)	0.15	1.94 (1.14–3.31)
October–December other years	15.4	1.0 (ref)	0.08	1.0 (ref)

baseline trimester. Note that in the gamma regression model, the mean time between admissions in July–September of years other than 1998 was 15.3 days. The reciprocal of this mean is equivalent to the daily rate of events. Therefore, the mean time between admissions in July–September of years other than 1998 was 1/15.3 or 0.07 cases/day, which was equivalent to the expected rate estimated from the Poisson regression model. We present the parameters from which we derived the expected values in an Appendix (eAppendix, http://links.lww.com/A719).

The time between consecutive admissions for Kawasaki disease increased with daily average ambient temperature (Fig. 6). In 1998, the mean time between admissions decreased more per degree Celsius of decrease in daily average ambient temperature than in other years, after adjusting for the effects of precipitation. In effect, the mean time between admissions in 1998 decreased multiplicatively by a factor of 1.04 (95% CI = 1.02–1.06) for each degree (1°C) decrease in daily average ambient temperature. In years other than 1998, the mean time between admissions decreased multiplicatively a factor of 1.01 (95% CI = 1.00–1.02; P = 0.04) for each degree decrease in daily average ambient temperature. We show the observed and fitted values of the number of days between consecutive admissions as a function of daily ambient temperature in Figure 6. Precipitation did not seem to affect the mean time between admissions for Kawasaki disease in Chicago.

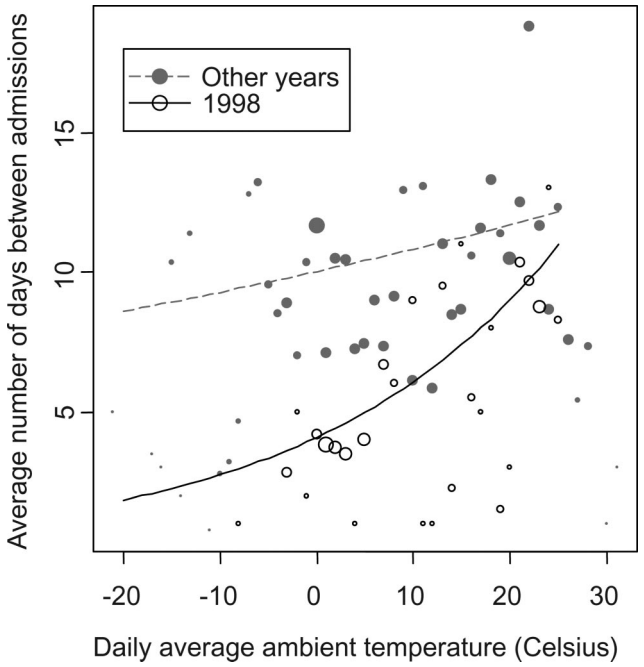

FIGURE 6. Scatter plot of daily average ambient temperature (Celsius) versus the mean number of days between consecutive admissions for Kawasaki disease in Chicago; 1986–2003. The size of the circles is proportional to the number of data points for each exact value of daily average ambient temperature. Five outlying data points altered the relationship between ambient temperature and the time between admissions for Kawasaki disease. Three of these data points corresponded to admissions during years other than 1998 (−12°C vs. 52 days, −12.5°C vs. 19 days, and −12.2°C vs. 32 days), and 2 corresponded to admissions during 1998 (−13.9°C vs.19 days and −10.6°C vs. 12 days).

DISCUSSION

In this extended (1986–2003) retrospective time-between-events analysis of consecutive admissions for Kawasaki disease, the unseasonable warming in 1998 was associated with a shorter mean time between admissions than in other years. Our analysis suggests that short-term variations in meteorologic conditions affect the occurrence of Kawasaki disease.

The seasonality of Kawasaki disease is well recognized,[4–14] although its seasonal peak seems to vary by region and possibly by country within region. The mean time between admissions for Kawasaki disease was shorter (ie, a larger number of admissions) during January–March than during other trimesters. In Chicago, the period from January–

March is the coldest trimester. The finding that Kawasaki disease is more common between January and March is consistent with other studies in the United States[11–14] and in Ireland.[9] Some Asian countries, however, exhibit a different seasonal pattern. For example, studies in China and South Korea report a larger incidence of Kawasaki disease in the late spring and summer months.[4,5,7,10] In Japan, the incidence of Kawasaki disease seems to peak twice yearly, in January and in July.[6] The variability in peak incidence of Kawasaki disease by country suggests that the specific etiologic agent of Kawasaki disease described by Rowley et al,[15,16] may have epidemiologic characteristics that vary by area of the world. Alternatively, Kawasaki disease may be caused by different infectious agents in different regions.

Published information on the relationship between weather variability and Kawasaki disease is limited. Although multiple studies report on the seasonality of Kawasaki disease, we identified only 2 that examined the association between weather and seasonality of Kawasaki disease hospitalizations.[6,24] In a study[24] conducted in San Diego, California, the incidence of Kawasaki disease was negatively associated with average monthly temperature (correlation coefficient of −0.47) and positively associated with average monthly precipitation (correlation coefficient of 0.52). Our study extends the current knowledge of the relationship between weather variability and Kawasaki disease and confirms an inverse relationship between daily average ambient temperature and the number of admissions for Kawasaki disease in a locale with more extreme temperature fluctuations than San Diego. We did not find evidence of a relationship between precipitation and the rate of admissions. The relationship between precipitation and the occurrence of Kawasaki disease, however, seems to be complex, and further studies are needed to elucidate this association.

Our study also revealed an effect of atypical weather on the occurrence of Kawasaki disease. That is, the effect of the increase in average ambient temperature on the mean time between admissions in 1998 was beyond what one would expect from seasonal variation alone. We found that the unseasonably warm winter months of 1998 were associated with a shorter mean time between admissions, rather than a longer mean time as we would have expected. There are 2 possible explanations. First, there may have been an increased opportunity for exposure to an infectious agent because of warmer weather conditions. Second, there was possibly an optimal daily average ambient temperature for transmission of an infectious agent. Although our analysis controls for the potentially confounding effects of age and sex, we were not able to control for environmental exposures other than seasonality or ambient temperature. Previous investigations have linked Kawasaki disease to environmental exposures such as freshly cleaned carpets, humidifier use, and residence near a body of water, although none of these findings has been consistently replicated.[25]

We present a novel application of gamma regression to model the number of days between consecutive admissions as a function of subject-specific and day-specific weather covariates. Classic time-series methods assume that the data follow a normal distribution.[26] In our case, the numbers of daily admissions for Kawasaki disease were not normally distributed. Common manipulations to normalize data include transformations; however, this strategy was not helpful in our analysis because the numbers of daily admissions were very small. Poisson regression with overdispersion is increasingly used in environmental epidemiology to analyze the number of counts as a function of multiple predictors.[27–30] These methods use smooth functions of time to account for autocorrelation and fluctuations in counts that may potentially confound estimates. Although it is common practice to aggregate cases over specific time intervals to obtain a time series of counts, this approach can also be used with daily counts[31] even when counts are sparse. The use of aggregate counts can limit the ability to model the outcome in terms of covariates; however, a Poisson time-series can accommodate these data while preserving the subject-specific covariates if the days on which 2 events fell are separated by 1 day. We instead chose to use gamma regression to model the number of days between consecutive admissions for Kawasaki disease. Our approach was readily applicable with standard statistical software and it provided flexibility to incorporate subject-specific covariates and day-specific weather covariates in both the mean and the variance. In our analysis, the use of the gamma distribution was particularly helpful in modeling the positively valued times between consecutive admissions for Kawasaki disease. Gamma regression has been commonly used to model duration data[22] such as duration of unemployment, time between trades, and duration of diarrheal disease, and it is widely applied in survival analysis. Our proposed approach performed equally well as a Poisson regression model with overdispersion to detect differences in Kawasaki disease admissions between 1998 and other years. Our counting process formulation is a more general form of a model for counts, and one can obtain the expected rate from the expected interevent times. Therefore, the analysis of interevent times using gamma regression complements the important analysis based on counts, and it may be a particularly useful alternative when daily counts are sparse.

In summary, Kawasaki disease is an acute vasculitis that seems to be influenced by a combination of environmental and genetic factors. In our study, the occurrence of Kawasaki disease was not only seasonal but was also affected by short-term weather variability observed in 1998. The results of this study lend further support to a link with a specific infectious trigger.

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