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**New Insights from Age-dependent Variations in Kawasaki Disease Incidence in Japan**

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**Keywords**

Kawasaki Disease, Japan, seasonal cycle, age dependence, spatiotemporal analysis, pediatrics

**Key Points**

**Question:** Does the epidemiologic Kawasaki Disease (KD) record in Japan yield new clues regarding the mechanism of disease transmission when stratified by age?

**Findings:** In this case series study, KD incidence in Japan differed by age group and region across Japan, including the rate of increase over the past three decades, the seasonal cycle, and the correlation of the seasonal cycle between prefectures.

**Meaning:** Distinct seasonality and differences in correlations between prefectures of the seasonal cycle of KD incidence across age groups suggest different age-related mechanisms of exposure that must be accounted for in any explanation of KD etiology.

## Abstract

**Importance:** The etiology of Kawasaki disease (KD) remains elusive with immunologic and epidemiologic data suggesting different triggers in genetically susceptible hosts. KD remains the most common cause of acquired heart disease in children and Japan is the country of highest incidence with increasing numbers of cases each year despite a falling birth rate.

**Objective:** Determine if an analysis of the epidemiologic KD record in Japan stratified by age and prefecture (sub-region) might yield new clues regarding mechanisms of exposure to the etiologic agent(s) of KD.

**Design:** Case series analysis of a data set of KD patients with detailed information on location and age at onset created through nationwide questionnaire surveys of hospitals in Japan, with some analyses using the full record (1970-2020) and some using a subset of years (1988-2019).

**Setting:** Hospitals caring for children with KD throughout Japan.

**Participants:** Children hospitalized in Japan for KD from 1970-2020

**Exposure:** Children with KD.

**Main Outcome(s) and Measure(s):** The KD dataset was analyzed by patient age with investigations of seasonal cycles, interannual variations, and correlations across regions.

**Results:** In this case series study of 422,528 patients (58% male, 42% female), infants, toddlers, and children ≥ 3 years exhibited different rates of increase in incidence, different seasonality, and different degrees of coherence of seasonality across prefectures. Although the incidence of KD among infants remained relatively stable over the past 30 years, the incidence rate for children ≥ 3 years increased more than five-fold. The older children saw a 22% reduction in incidence rate in 2016-2017 not seen in the younger children. Incidence among infants had a summer maximum but children older than 2 years had a winter peak and an autumn nadir. The seasonal cycle for toddlers changed dramatically beginning in the early 2010s. Across Japan, the seasonal cycle of KD incidence of older children exhibited correlations between prefectures ranging between 0.35 and 0.78, while that of infants was much less, ranging from 0.02 to 0.43.

**Conclusions and Relevance:** In this case series study, distinct temporal signatures and the changing degree of the spatial consistency of KD incidence across age groups suggested different age-related mechanisms of exposure. Marked changes in these patterns with age were consistent with social factors modulating exposure to the etiologic agent(s) of KD. However, the pronounced rise in KD incidence in children $\geq 3$ years coupled with the remarkable correlation across prefectures in KD incidence suggested that the intensity of an environmental exposure that triggers KD in this age group has increased over time.

## Introduction

Despite five decades of research, the etiology of Kawasaki disease (KD), the leading cause of acquired heart disease in children, remains a mystery. Tomisaku Kawasaki first described the condition in a landmark publication reporting 50 children with fever, rash, mucocutaneous findings, and lymphadenopathy.(1) Without treatment, the acute phase of the illness can last for weeks and then resolves spontaneously. However, 25% of untreated children will develop aneurysms of the coronary arteries that may lead to myocardial infarction and death.(2) Treatment with intravenous immunoglobulin within days after the onset of fever reduces the risk of cardiac complications.(3) However, identification of the triggers for KD would be transformative for patient care and would surely lead to improved diagnostics and more specific treatments.

Most authorities believe that KD was a new pediatric disease that emerged in Japan following World War II. Patients meeting the clinical case definition were rare in the 1950s.(4) Nationwide epidemics in 1979, 1982, and 1986 were consistent with new widespread exposure in a highly susceptible population.(5) Subsequent research has revealed an important role for genetic variants that influence susceptibility to KD.(6) Japan remains the country of highest incidence, although cases are now diagnosed worldwide.(7) While the etiology remains unknown, a complex interplay of host genetics and environmental factors is suspected.

The epidemiology team at Jichi University has meticulously curated a nationwide survey of KD in Japan since 1970, which has fueled decades of research on KD. Basic features of KD epidemiology in Japan that have been gleaned from this source include: incidence with a male: female ratio of 1.5:1, 85% of patients younger than 5 years, an increase in the total number of cases in Japan over time, peak incidence at age 9 months, and a low recurrence rate of 3-4%.(8-10) ~~*and 15*~~ Further analyses using the database have identified an overall seasonal structure of KD incidence and spatiotemporal clustering, with similar characteristics noted in North America, the UK, and Western Europe.(11, 12) A previous analysis of 127,398 Japanese KD patients explored age-related differences in KD incidence and seasonality.(13) Here we add to this literature by conducting an analysis over a longer time period at higher spatial and temporal resolution, enabling a more robust study of age-dependent seasonality and changes in seasonality over decades, as well as spatial coherence of KD incidence.

## Methods

We hypothesized that different age groups of KD patients would exhibit differences in KD incidence, seasonal patterns, and spatiotemporal correlations in seasonality across Japan's 47 prefectures (sub-regions). To test these hypotheses, we utilized data compiled from 26 nationwide surveys of KD patients in Japan, which provided the date of birth, date of onset, and home prefecture of 422,528 patients between 1970 and 2020. Starting in 1970, the survey was conducted every two years by questionnaires sent to pediatricians at hospitals with >100 beds, and at specialized pediatric hospitals. The response rate was over 70% for the last two decades and the majority of non-responding hospitals had either few or no KD cases (https://www.jichi.ac.jp/dph/inprogress/kawasaki/). The diagnosis of cases was based on the guidelines created by the Japan Kawasaki Disease Research Committee. The survey was approved by the Bioethical Committee for Epidemiologic Research, Jichi Medical University, Japan.(14) Using these data, a 50-year time series of KD incidence rate was computed by counting the number of patients on each date of onset in the record and smoothing that count with a 365-day running mean (the value of each day was averaged with the 182 previous days and 182 following days). We used a 365-day running mean to smooth the data to remove the seasonal cycle from the result. The incidence rate was computed relative to the population of 0–14 year-olds from the e-Stat Portal Site of the Government Statistics of Japan (https://www.e-stat.go.jp/en). The time series values were then normalized by dividing the incidence rates in each of six age brackets (less than 6 months, 6-15 months, 15-24 months, 24-36 months, 36-60 months, and 60 months and older) by the average number of patients in that age bracket between 1987 and 1992, when the total annual number of KD patients in Japan was relatively constant (**Figure 1**). The result is the KD incidence rate for each age bracket relative to the incidence rate from 1987 to 1992. For each age bracket, we performed 2-tailed t-tests to evaluate a) the recent average incidence rates compared to those within the stable 1987-1992 post-epidemic period, and b) the 2016-2017 low period incidence rate to the average rates of the peaks on either side, wherein *P*-values < 0.05 were considered significant.

We further analyzed the data in terms of the seasonal cycle using a subset of the Japanese nationwide surveys (1988-2019). The 1979, 1982 and 1986 KD epidemics and the COVID-19 pandemic greatly altered the incidence and seasonality of KD.(15, 16) ~~and 17~~ Consequently, the record beginning in 1988 and ending in 2019 was employed to avoid the influence of the KD epidemics and COVID-19 pandemic. For this analysis we computed the seasonal cycle of KD incidence rate based on a time series smoothed with a 31-day running mean by averaging the number of KD onsets for each day of the year between 1988 and 2019. We used a 31-day running mean to remove the day-to-day variation in the record. Unique seasonal cycles were computed for four different age groups and Japan's 47 prefectures. Age groups were characterized as follows: less than 6-months, called infants (9% of 1988-2019 patients); 6 to 24-months, called toddlers (41%); 24 to 36 months, called 2-year-olds (17%); and 36 months and older, called ≥ 3 years (33%). The toddler group combined two age groups from **Figure 1** based on the similar incidence patterns of those age groups, and likewise the ≥ 3 years was a combination of two groups from **Figure 1**. In an analysis of changes in seasonal cycles over 1988-2019, the incidence rates were normalized by dividing by the average incidence rate for relevant subsets of years. To test for significant differences between seasonal cycles we used a random sampling approach, as described in the supplemental material.

A third analysis was performed to investigate the similarities of seasonal cycles between Japan's 47 prefectures. A seasonal cycle for each prefecture was computed as above and Pearson correlations of the seasonal cycles were computed between each pair of prefectures to investigate coherence of KD incidence across regions. The resulting 46 correlations for each prefecture were then averaged to give a single value for each prefecture. These pair-wise correlations above 0.59 were significant at 95%.

All computations were performed in MATLAB version R2023a. The study was reviewed and approved by the Institutional Review Board of the University of California San Diego (UCSD # 170045) who provided a waiver of consent as no protected health information was collected or disclosed for the performance of this study.

**Results**

In this case series study of 422,528 patients (58% male, 42% female, median age 24 months), time series of KD incidence rates for six age groups show that the well-known increase in KD cases in Japan over time was evident in each of the age groups to varying extents (**Figure 1**). However, the increase in normalized incidence rates differed between age groups, particularly between the infants and the children ≥ 3 years. Following the major KD epidemics in 1979, 1982 and 1986, each age group experienced a period of nearly steady KD incidence until the late 1990s. Thereafter, from 2000 through 2019, cases rose rapidly. For the infants, from the base period in 1987-1992 to the peak years 2011-2016, KD incidence increased by a factor of 2 (*P*-value $< 0.0005$). In contrast, KD incidence for the children ≥ 3 increased much more, by a factor of over 5 between the base period (1987-1992) and the peak years for older children in 2014-2019 (*P*-value $< 0.0005$). In the later years of this long-term increase, KD incidence in children 24 months and older had two marked shorter period declines. The first was a dip in cases in 2016 and 2017. For the children 24 months and older the dip highlighted in the center gray box in **Figure 1** (January 2016 through June 2017) was a reduction of 21% (*P*-value $< 0.005$) compared to the peaks on either side (October 2014 through June 2015 and July 2018 through March 2019). Notably, the reduction for the 6-to-24-month children was much smaller (7% reduction for 15 to 24-month children, 8% reduction for 6 to15-month children, both with *P*-value $< 0.05$) and there was no significant reduction for infants. The second decline was a sharp drop in cases in 2020 that coincided with the COVID-19 pandemic.(15).

We analyzed the seasonal cycles of KD incidence in each age bracket using a subset of the Japanese nationwide survey (1988-2019, which avoided the KD epidemics and COVID-19 pandemic) with 323,531 patients (58% male, 42% female, median age 24 months). These long-term averages (**Figure 2)** showed different seasonal cycles of KD incidence rates for each age group. Infants, who experienced a lower overall incidence than other age groups, nonetheless had a discernable peak in July and August that rose approximately 20% (p-value < 0.05, based on 2-tailed t-test) over other months. In contrast, toddlers (6-24 months) experienced a seasonal peak in December and January, with relatively constant numbers from March through October. Two-year-olds had a similar winter peak as toddlers but exhibited a pronounced decrease in October. Children ≥ 3 years showed the most complex seasonal cycle. The pattern was similar to 2-year-olds with a winter peak and an autumn nadir, but also included secondary peaks in April and June. The typical school calendar shown by the shaded boxes in **Figure 2h** highlights that the number of KD cases of children ≥ 3 years fell at the beginning of each school session and then rose after about 5 weeks of school attendance.

Looking beyond the long-term 1988-2019 averages shown in **Figure 2a-d**, there were noticeable shifts and distortions of the overall seasonal cycle over time, shown by seasonal cycles of normalized KD incidence for successive 4-year periods (**Figure 2e-h**). Most of the larger differences were outside of the 95$^{th}$ or 99$^{th}$ percentile of statistical odds of random occurrence, as shown in the supplementary material (**eFigure 2**). Infants, who exhibited the least amount of change over time (**Figure 2e**), had a summer peak that consistently occurred from the early 1990s until 2015. In 2016-2019, the summer peak disappeared. Incidence patterns among toddlers changed the most (**Figure 2f**). Toddlers experienced a January peak and October nadir in the

1990s until the early 2000s, but their seasonal cycle shifted in 2012- 2015 such that October was no longer a low point, and during 2016-2019, October became the peak in the seasonal cycle.

Two-year-olds (**Figure 2g**) had a consistent January peak and October nadir until 2015. However, like the toddlers, the October low disappeared during 2016-2019. In comparison to toddlers, the structure of the seasonal cycle of children ≥ 3 years (**Figure 2h**) was quite consistent through the entire period. The October nadir occurred throughout the period, as did the January peak, although it was lower in the 1990s compared to the 2000s. Secondary features of KD incidence in children ≥ 3 years were also surprisingly consistent: peaks in April, June and September occur across the decades.

To assess whether the seasonal cycle varied spatially across Japan, the data record was disaggregated into prefectures and the seasonal cycle for each prefecture was correlated with that of every other prefecture (**Figure 3**, average, and **eFigure 3**, heatmap of unaveraged values). The standard deviation of the seasonal cycle between prefectures is shown in gray in **Figure 2a-d**. For infants, the seasonal cycles of different prefectures showed essentially no correlation with other prefectures (**Figure 3a**). The seasonal cycles for toddlers and two-year-olds (**Figures 3b and 3c**) exhibited higher correlations, with a few prefectures having average correlations that rise above the 95% significance level. The lowest correlations for toddlers and two-year-olds occurred in prefectures on the southern island of Kyushu. The seasonal cycles for children ≥ 3 years (**Figure 3d**) exhibited the greatest spatial coherence, with over 80% of prefectures pairs having average correlations above the 95% significance level. Correlations were particularly high for prefectures in the central portion of Japan (e.g., Honshu), with Kanagawa prefecture outside

Tokyo (prefecture number 14), exhibiting the highest average correlation of 0.78. Although the age groups had different sample sizes, the large difference between the weak correlation of the infants and the strong correlation of children ≥ 3, that are generally consistent across prefectures, reduces concerns about spurious correlations due to small sample size.

There was additional time-varying structure underlying these prefecture-level associations, such that in earlier years the correlations across prefectures for toddlers was higher than that for children ≥ 3 years, as shown in the supplementary material (**eFigure 4**).

## <u>Discussion</u>

Although previous studies have described overall KD incidence in Japan, a sharper and more complex picture appeared when KD incidence was assessed by age groups. A series of age-related patterns add new insights into the epidemiology of KD in Japan and are thus important clues to understanding its etiology. Hypotheses regarding KD etiology must explain 1) the distinctly different epidemiology between infants and older children, 2) the changing seasonal cycle for toddlers, 3) a complex seasonal cycle for children ≥ 3 years with secondary peaks in the spring that strongly aligned across prefectures, and 4) the five-fold increase in incidence rates for older children since 1990. These findings argue both for social factors modulating exposure as well as large scale environmental exposures that are increasing over time.

Looking at infants, we found KD incidence increased little over 1987-2019 and the seasonal cycle, with a summer peak, showed essentially no coherence across prefectures. It is possible that this distinct difference from the epidemiology of older children was due in part to the tendency of infants to be in the home. A previous analysis of birth order of KD patients 6-18 months of age in Japan identified having an older sibling as a risk factor for developing KD.(17) This association was less pronounced if the younger child was in day care. These observations suggest the importance of social factors on KD exposure, potentially by allowing the transmission of an agent to the younger child by an older sibling or by exposing the younger child to agents out of the home more often.

Toddlers exhibited a large change in their seasonal cycle in the mid-2010s, which again suggested potential social or behavioral drivers of exposure changes. Around that same time, the Japanese government launched a number of initiatives to provide increased day care options for toddlers. Most notably, The Comprehensive Support System for Children and Childcare (CSSCC) was launched in April 2015, which aimed to expand child intake capacity for children under age 3 (details shown in **eFigure5**). While this change in day care use does not completely explain the timing or the change in the seasonal cycle, it is plausible that this change in behavior contributed to the change in seasonal cycle. The change in the nationally averaged seasonal cycle was also accompanied by a decrease in correlation of the seasonal cycle between prefectures. Spatial correlations demonstrated that these seasonal changes in toddler incidence in Kyushu differed from those in other regions in Japan, suggesting that the drivers of these seasonal changes may have differed across regions.

The seasonal cycle of children ≥ 3 years consistently exhibited minor peaks in April and June, in addition to having a winter peak and autumn nadir. The nadirs preceding the secondary peaks each occurred about five weeks after the start of a school session and there was a relative peak at the start of each school session. While it is unclear why KD incidence would fall for the first five weeks of a school session, the consistent pattern suggests that levels of exposure to KD agent(s) differ according to the times when children are in or out of school. Ae and colleagues also saw evidence for a connection between school attendance and KD incidence in Japan based on the influence of the COVID-19 special mitigation measures.(18) The connection to the school calendar and the drop in cases during the special mitigation measures were both consistent with person-to-person spread of an infectious aerosol that triggers KD.

While other KD epidemiologic characteristics suggest social or behavioral factors modulated KD exposure by person-to-person spread or other mechanisms, the large increase in KD incidence since 1990 and the strong coherence of the seasonal cycle of KD incidence in children ≥ 3 years across most of Japan suggest waves of concurrent environmental exposures whose intensity is increasing over time and is affecting the older children disproportionately. The biologic plausibility of these two apparently competing mechanisms of transmission deserves consideration. One possibility is that an aerosol carried by regional scale winds can carry an infectious agent that can also be transmitted from person to person with only genetically susceptible individuals manifesting KD. Infants might be exposed in the home environment through contact with older siblings. Alternatively, there could be more than one etiology for KD with infants and older children responding to different triggers.

**Limitations**

We recognize limitations of the analysis presented here. Japan is the country of highest KD incidence, and the meticulous curation of their dataset ensures that these data accurately reflect the epidemiology of KD in Japan. However, because there is no standard test to diagnose KD, the dataset relies on the clinical diagnosis by experienced physicians and there could exist errors in both under and over-diagnosis of KD. In addition, it is unknown if findings discussed herein also apply to other countries.

## Conclusions

In this case series study of the historical record of KD in Japan, distinct patterns of KD incidence were revealed when separated into age groups which suggested differences in exposures that varied by age group. First, the differences in seasonal cycles and the different rates of increase over the observational record between age groups suggested exposure was modulated by social practices, including day-care availability and school vacation schedules. Second, the remarkable increase and spatial coherence of KD incidence in children $\geq 3$ years suggested that environmental factors are involved that lead to increased exposure to a KD trigger. The summary of these characteristics, along with the characteristics of previous studies are listed in **eTable 1**. Theories regarding KD etiology must account for the contrasting KD temporal and spatial patterns associated with different age groups in Japan.

**Data availability statement**
The Japanese database is maintained at Jichi University in Japan and interested parties should contact Dr. Yosikazu Nakamura.

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~~**Figure 1**: Normalized Time Series of KD Incidence Rate by Age Group~~

**Figure 1**: Time series of KD incidence rate for each age group, normalized by dividing by the average number of cases in 1987-1992 for each age bracket, based on daily smoothed data. The incidence rate is computed relative to the population of 0- to 14-year-olds for each year. The inset shows the number of patients in each age bracket for the 1970-2020 record. The three shaded areas in 2014 to 2019 indicate the dip in cases (middle shaded area) and the peaks on either side, as referred to in the text. For comparison, the time series that is not normalized by the 1987-1992 base period is shown in the supplement (**eFigure** 1).

~~**Figure 2**: Seasonal Cycle of KD Incidence Rate for Four Age Groups~~

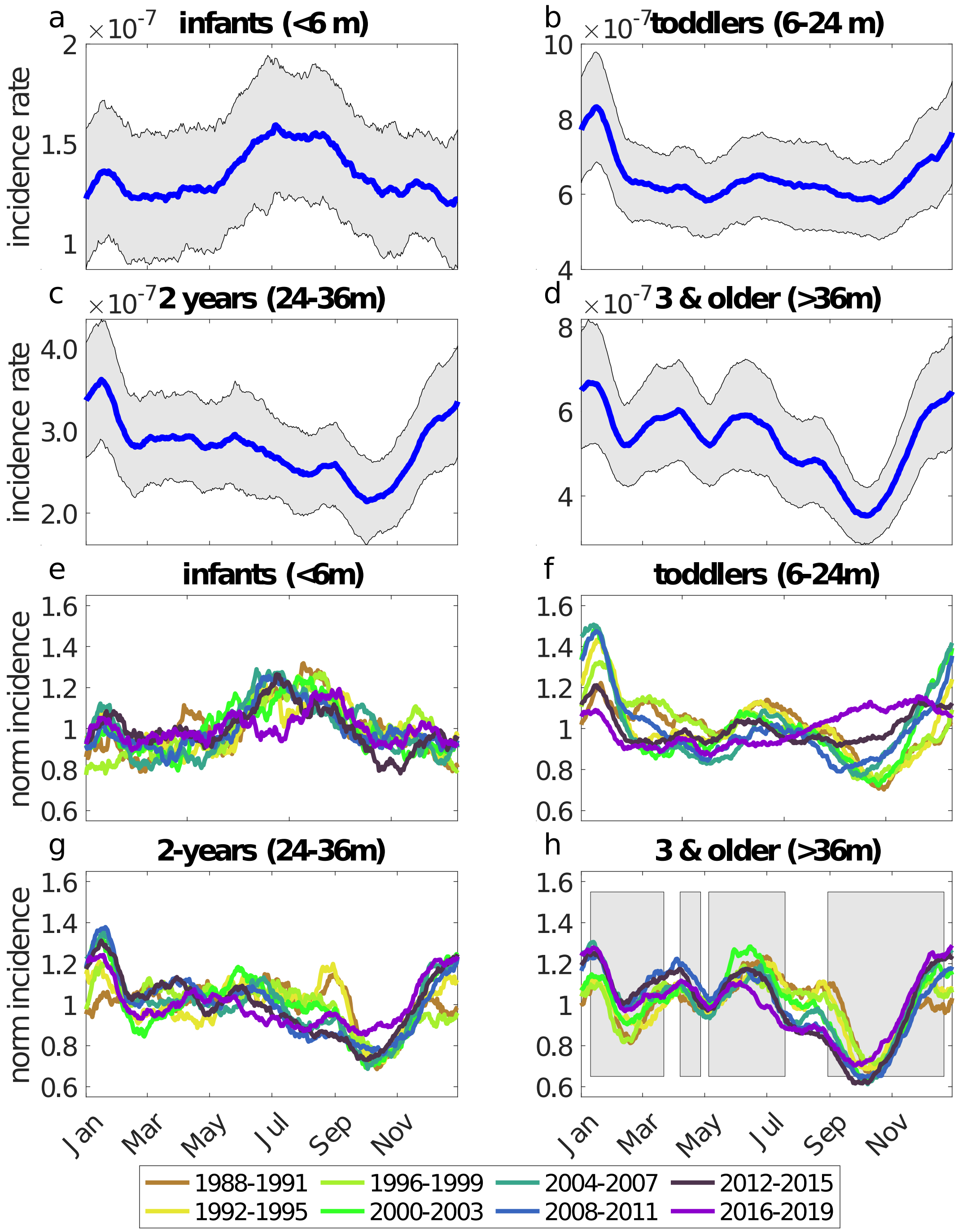


**Figure 2**: Seasonal cycle of daily KD incidence rate for four age groups averaged over 1988-2019 (a-d) and averaged over successive 4-year periods (e-h). Panels e-h were normalized by the average incidence rate for the relevant subsets of years. Vertical axis differs for each panel in a-

d. Shading in a-d shows the standard deviation of the seasonal cycle between prefectures, with one standard deviation above the mean and one below. Shaded boxes on (h) delineate the typical periods during which school is in session. Note that not all children between 36 months and 72 months attend preschool, which has this school schedule. Children in day care or at home do not have this schedule.

**Figure 3**. ~~Correlations of KD Seasonal Cycles between Prefectures~~

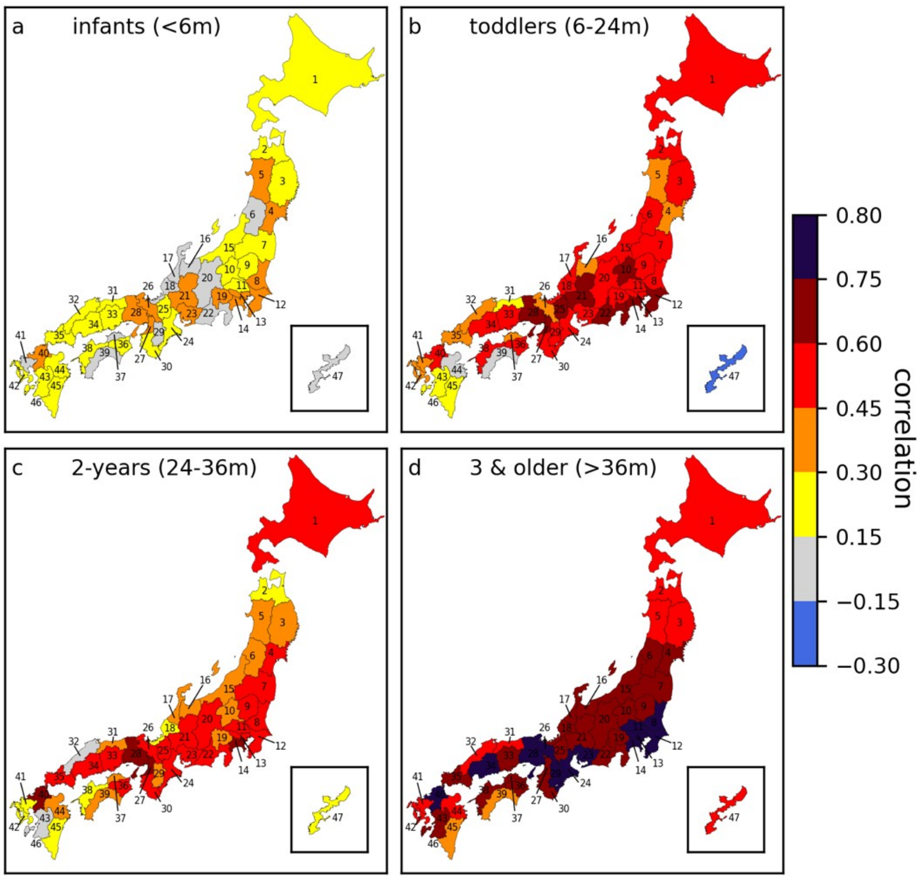


**Figure 3**. Average correlations of KD seasonal cycles (1988-2019) between prefectures for 4 age groups. Correlations greater than 0.59 are significant at 95%. The southern island of Okinawa is shown in the inset.