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# Clinical Communications

## Impact of COVID-19 pandemic-associated reduction in respiratory viral infections on childhood asthma onset in Japan

Naomi Matsumoto, MD, PhD[a], Tomoka Kadowaki, MPH[b], Satoe Takanaga, MHIM[b], Masanori Ikeda, MD, PhD[c], and Takashi Yorifuji, MD, PhD[a]

***Clinical Implications***

In the COVID-19 pandemic period, new diagnoses of childhood asthma significantly declined. This trend is reasonably consistent with those reported for respiratory syncytial virus and rhinoviruses, with a particularly large impact on younger children.

The novel coronavirus SARS-CoV-2, which was first reported in December 2019, has caused a worldwide pandemic, leading to interventions limiting the flow of people and promoting hygiene behaviors. These interventions have resulted in marked reductions in respiratory viral infections.[1]

The onset or exacerbation of childhood asthma is strongly associated with the frequency of respiratory viral infections such as rhinovirus and respiratory syncytial virus (RSV) [2]; therefore, a reduction in infections with these viruses may prevent the development of childhood asthma. Fewer emergency departments visits and fewer hospitalizations for asthma (ie, exacerbations) among children were reported worldwide during the first few months after lockdowns in early 2020.[3,4] However, few published studies have investigated how the COVID-19 pandemic and subsequent declines in respiratory viral infections have affected the onset of childhood asthma, and none have examined long-term impacts. We compared the number of newly diagnosed asthma cases among children from January 2017 through May 2021 using a powerful quasiexperimental design (ie, interrupted time series) and a Japanese multicenter electronic medical records (EMR) database. As a control group less susceptible to respiratory viral infections, we compared the number of new diagnoses of atopic dermatitis among children during the same period. We used public infectious disease surveillance data to assess how trends in respiratory viral infections (eg, rhinovirus and RSV) are associated with the onset of childhood asthma.

The monthly number of newly diagnosed cases for each disease was obtained from a large Japanese EMR database (the RWD database) administered by the Health, Clinic, and Education Information Evaluation Institute (Kyoto, Japan), a not-for-profit research service foundation, in cooperation with Real World Data Co, Ltd (Kyoto, Japan), using International Classification of Diseases, 10th Revision codes (asthma: J45; and atopic dermatitis: L20).[5] The RWD is a nationwide database composed of approximately 24.4 million EMR from 225 medical institutions, covering the entire geographic area of Japan. To maintain a constant denominator (ie, number of eligible facilities), we included EMR data from 45 facilities providing complete data from January 2017 through May 2021 to the RWD. For privacy reasons, only the birth year was available in the database. Therefore, to obtain each patient's age, we calculated the age at diagnosis by assuming that all patients were born on January 1 of their birth year. Those aged 15 years or younger at diagnosis, the age range for pediatric consultation in Japan, were included in the analysis. We excluded the category of psychogenic asthma.

Among the various phenomena caused by the COVID-19 pandemic, the decline in respiratory viral infections was the focus of this study. Considering that the Japanese government's request to close elementary and secondary schools took effect on March 2, 2020, we defined the period on and before February 2020 as the pre−COVID-19 period (38 months), and that on and after March 2020 as the COVID-19 pandemic period (15 months).

We used interrupted time series analysis and a self-controlled design to explain the effects of the intervention by accounting for preintervention trends.[6] Segmented Poisson regression models were used, and autocorrelation was addressed using Fourier terms.[7] After applying the models, changes in the number of new diagnoses were visually depicted by comparing the post-intervention trend with a counterfactual scenario in which the intervention would never have occurred. As an objective measure, we also estimated coefficients for the abrupt change in the monthly number of new diagnoses that occurred immediately after intervention (change in level) and the trend change over time in the monthly number of new diagnoses after the intervention compared with before the intervention (change in slope). We also referred to the total number of rhinovirus detections reported in the official Infectious Agents Surveillance Report and the average number of RSV cases reported at approximately 3,000 designated pediatric facilities nationwide.[8]

All analyses were performed using Stata software (version 17, StataCorp LLC, College Station, Texas). This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences approved the study protocol (No. 2107-001).

The number of new diagnoses from January 2017 to May 2021 was 29,845 for asthma and 17,803 for atopic dermatitis. The proportion of children with newly diagnosed asthma in the COVID-19 pandemic period decreased in the age group 0 to 2 years and in Kanto and Kinki, which are densely populated metropolitan areas. These trends were less pronounced for children who received a new diagnosis of atopic dermatitis during the COVID-19 pandemic period (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

The number of patients with new diagnoses of both asthma and atopic dermatitis suggested seasonality, especially asthma, with a marked increase in the number of patients with new diagnoses around October of each year (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The number of new diagnoses decreased after the COVID-19 pandemic started for both diseases, but the decline was particularly pronounced for asthma. In the COVID-19 pandemic period, the monthly number of patients with new diagnosed

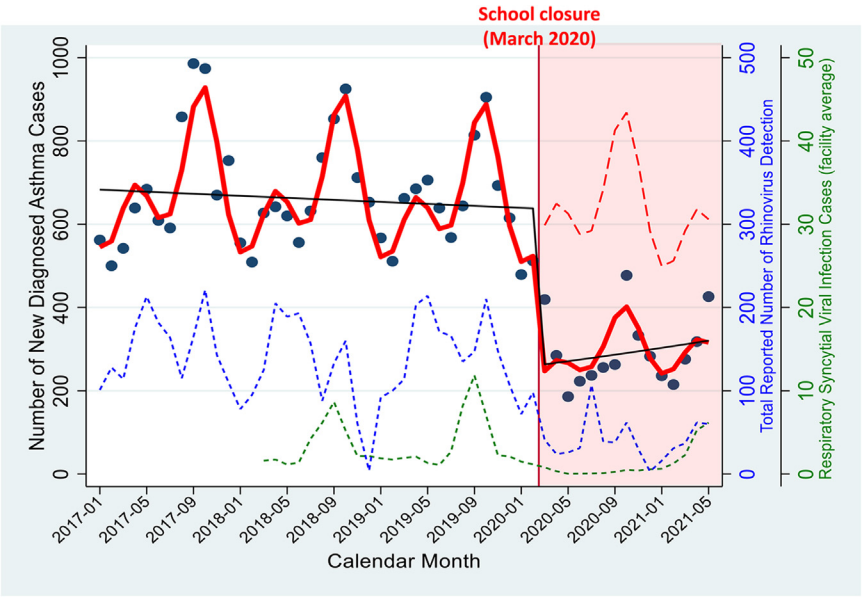


**FIGURE 1.** Monthly reports of newly diagnosed cases (dots) of asthma with trend lines. Solid red line indicates the predicted trend based on seasonally adjusted regression model. Black line shows the de-seasonalized trend. Dashed red line indicates the counterfactual trend assuming no intervention. Dashed blue line shows the total number of rhinovirus detections. Dashed green line shows the average number of respiratory syncytial virus cases per center.

asthma decreased by 59% (change in level, 0.41; 95% CI, 0.34-0.50). The slope then trended slightly upward (change in slope, 1.02; 95% CI, 0.99-1.04); however, the monthly number of patients with new diagnosed asthma remained lower than in the counterfactual hypothetical scenario (red dashed line in Figure 1) in the absence of the pandemic (Table I). Notably, the number of new asthma diagnoses varied relatively consistently with the monthly reported number of RSV cases and the number of rhinovirus detection reported. Conversely, the number of new atopic dermatitis diagnoses decreased by 20% in the COVID-19 pandemic period, which was a smaller change than that for asthma (change in level, 0.80; 95% CI, 0.71-0.90) (Table I and Figure E1). Subgroup analysis by age group also indicated that the number of new asthma diagnoses decreased in the COVID-19 pandemic period, and the peak range associated with seasonality became smaller in younger age groups with a higher risk of respiratory viral infections (Table I).

An EMR database was used in this study. Although the diagnosis of childhood asthma in Japan generally follows the guidelines according to certain standards,[9] diagnostic misclassification may exist. However, because we fixed the denominator (ie, the medical institution providing the data), nondifferential misclassification should not strongly distort the results in pre-post comparisons of the overall number of diagnosed cases. Although viral-induced wheeze is difficult to differentiate from asthma, especially in younger children, a sensitivity analysis excluding asthmatic bronchitis did not change the results. However, the impact on future asthma development in children

**TABLE I.** Monthly number of new asthma and atopic dermatitis diagnoses before and after the start of the COVID-19 pandemic in Japan

| | Monthly new cases | | Coefficient (95% CI) | | |
|---|---|---|---|---|---|
| Variable | Pre COVID-19 period | COVID-19 pandemic period | Baseline incidence rate | Level change* | Slope change† |
| Asthma (all age groups) | 668.74 (133.60) | 295.53 (84.87) | 691.25 (638.81-747.59) | 0.41 (0.34-0.50) | 1.02 (0.99-1.04) |
| 0-2 y | 253.7 (78.4) | 98.5 (37.2) | 242.88 (216.50-272.48) | 0.28 (0.20-0.38) | 1.04 (1.01-1.08) |
| 3-5 y | 203.9 (45.7) | 92.2 (31.1) | 223.29 (203.98-244.44) | 0.45 (0.36-0.56) | 1.025 (0.99-1.05) |
| 6-9 y | 129.9 (22.5) | 62.6 (21.0) | 136.89 (124.89-150.03) | 0.61 (0.49-0.76) | 0.98 (0.95-1.00) |
| 10-15 y | 81.2 (14.1) | 42.2 (9.9) | 84.64 (76.42-93.74) | 0.52 (0.41-0.67) | 1.01 (0.98-1.03) |
| Atopic dermatitis (all age groups) | 353.38 (42.47) | 287.21 (24.47) | 357.37 (337.96-377.89) | 0.80 (0.71-0.90) | 1.00 (0.99-1.02) |
| 0-2 y | 185.2 (23.8) | 161.4 (16.0) | 180.75 (170.61-191.49) | 0.86 (0.76-0.97) | 1.00 (0.99-1.01) |
| 3-5 y | 69.4 (12.5) | 47.9 (7.7) | 75.09 (69.29-81.37) | 0.71 (0.59-0.86) | 1.01 (0.99-1.03) |
| 6-9 y | 54.0 (12.1) | 40.4 (8.5) | 55.06 (48.58-62.42) | 0.71 (0.53-0.94) | 1.01 (0.98-1.04) |
| 10-15 y | 44.9 (8.7) | 37.6 (7.8) | 45.82 (41.02-51.20) | 0.80 (0.63-1.02) | 1.01 (0.99-1.04) |

Data for monthly new cases data are presented as means (SDs) during each period. Pre−COVID-19 period represents January 2017 through February 2020 and COVID-19 pandemic period represents March 2020 through May 2021. Baseline incidence rate, level change, and slope change values are presented with (95% confidence intervals).
*Level change refers to an abrupt level change in pre−COVID-19 versus COVID-19 pandemic periods.
†Slope change refers to slope change over time in pre−COVID-19 versus COVID-19 pandemic periods.

who were less exposed to respiratory infections during childhood should be investigated over the long term. The proportion of telehealth use at the time of new diagnosis of both asthma and atopic dermatitis was negligible in the current data (ie, less than 0.1% before and 0.2% after the start of the pandemic for both diseases). The impact of refraining from in-person medical visits can be accounted for and interpreted by comparing the data on atopic dermatitis. Data on the severity of asthma and changes in air pollution associated with the pandemic were not considered in this study. We used data from Japan; therefore, our findings are not generalizable to other countries.

After the COVID-19 pandemic began, new diagnoses of childhood asthma significantly declined and had not recovered by 15 months later. This trend is reasonably consistent with those reported for RSV and rhinoviruses, with a particularly large impact on younger children. Only a slight decrease was observed in new diagnoses of atopic dermatitis. This study suggested an association between respiratory viral infections and new onset of asthma in children.

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[a]Department of Epidemiology, Faculty of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama, Japan
[b]Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan
[c]Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

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Corresponding author: Naomi Matsumoto, MD, PhD, Department of Epidemiology, Faculty of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, 2-5-1, Shikata-cho, Kita-ku, Okayama-shi, Okayama 700-8558, Japan. E-mail: naomim@okayama-u.ac.jp.

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## ONLINE REPOSITORY

**TABLE E1.** Comparison of baseline characteristics of patients with new diagnosis of asthma and atopic dermatitis before and after the start of the COVID-19 pandemic

| | Asthma | | | Atopic dermatitis | | |
|---|---|---|---|---|---|---|
| Characteristics | Total (n = 29,845) | Pre COVID-19 period (n = 25,412) | COVID-19 pandemic period (n = 4,433) | Total (n = 20,306) | Pre COVID-19 period (n = 16,936) | COVID-19 pandemic period (n = 3,370) |
| Sex | | | | | | |
| Male | 17,217 (57.7%) | 14,555 (57.3%) | 2,662 (60.1%) | 11,857 (58.4%) | 9,792 (57.8%) | 2,065 (61.3%) |
| Female | 12,628 (42.3%) | 10,857 (42.7%) | 1,771 (30.9%) | 8,449 (41.6%) | 7,144 (42.2%) | 1,305 (38.7%) |
| Age group, y | | | | | | |
| 0-2 | 11,120 (37.3%) | 9,642 (37.9%) | 1,478 (33.3%) | 6,379 (31.4%) | 5,406 (31.9%) | 973 (28.9%) |
| 3-5 | 9,132 (30.6%) | 7,749 (30.5%) | 1,383 (31.2%) | 6,160 (30.3%) | 5,123 (30.2%) | 1,037 (30.8%) |
| 6-9 | 5,875 (19.7%) | 4,936 (19.4%) | 939 (21.2%) | 4,598 (22.6%) | 3,806 (22.5%) | 792 (23.5%) |
| 10-15 | 3,718 (12.5%) | 3,085 (12.1%) | 633 (14.3%) | 3,169 (15.6%) | 2,601 (15.4%) | 568 (16.9%) |
| Hokkaido/Tohoku | 5,171 (17.3%) | 4,413 (17.4%) | 758 (17.1%) | 4,137 (20.4%) | 3,478 (20.5%) | 659 (19.6%) |
| Kanto | 2,439 (8.2%) | 2,167 (8.5%) | 272 (6.1%) | 881 (4.3%) | 759 (4.5%) | 122 (3.6%) |
| Chubu | 8,529 (28.6%) | 7,102 (27.9%) | 1,427 (32.2%) | 6,816 (33.6%) | 5,589 (33.0%) | 1,227 (36.4%) |
| Kinki | 10,181 (34.1%) | 8,850 (34.8%) | 1,331 (30.0%) | 6,015 (29.6%) | 5,152 (30.4%) | 863 (25.6%) |
| Chugoku/Shikoku/Kyushu/Okinawa | 3,525 (11.8%) | 2,880 (11.3%) | 645 (14.6%) | 2,457 (12.1%) | 1,958 (11.6%) | 499 (14.8%) |

Data are presented as n (%). Only birth year information was available; therefore, age at the date of diagnosis was calculated by assuming that all patients were born on January 1. The Hokkaido/Tohoku regions are the northernmost area. The Kanto region contains Japan's largest metropolises and is densely populated. The Chubu region is located in the center of Japan. The Kinki region used to be the political center of Japan and contains Japan's third largest metropolis. The Chugoku/Shikoku/Kyushu/Okinawa regions are the southwest area.

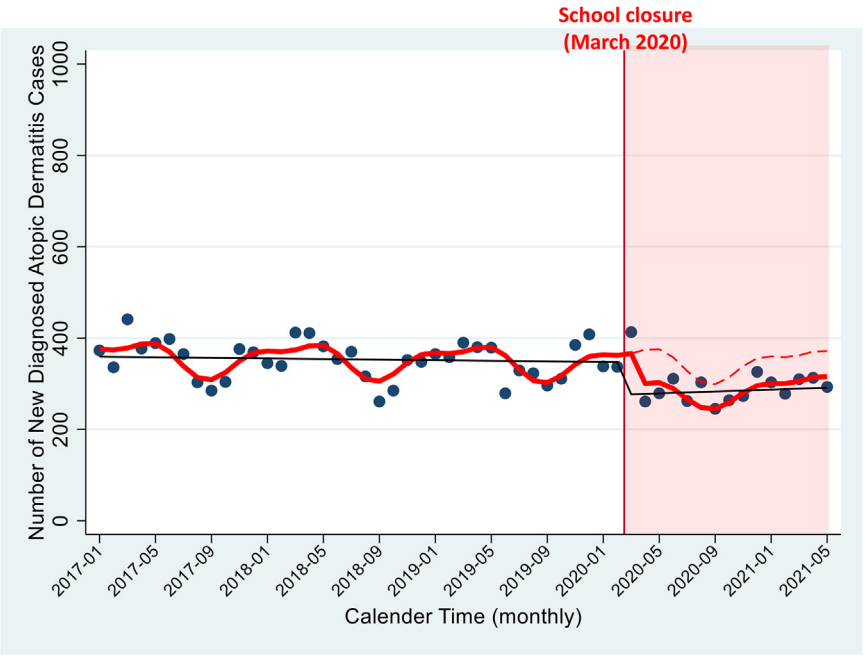


**FIGURE E1.** Monthly reports of newly diagnosed cases (dots) of atopic dermatitis with trend lines. Solid red line indicates predicted trend based on seasonally adjusted regression model. Black line shows de-seasonalized trend. Dashed red line shows counterfactual trend assuming no intervention.