reduction in maintenance OCS dosage, improvement in asthma control, and increased lung function following benralizumab treatment. Together these findings suggest that targeting IL-5Rα+ cells decreases EoP cell numbers both systemically and locally within the airways, thereby attenuating potential IL-5–driven eosinophilopoietic processes that may contribute to persistent airway eosinophilia in patients with severe, prednisone-dependent asthma. This contrasts with previous findings that mepolizumab 100 mg (subcutaneous) suppressed blood eosinophils but not sputum eosinophils or EoP cells in some patients and this was associated with more modest clinical outcomes.[2]

Limitations of this study include a small size, although this study design was based on a report that showed that 6 patients per group is adequate to detect a 50% reduction in sputum eosinophil counts.[2,9] In addition, the effect of benralizumab treatment on basophil counts in the airways was not investigated. However, we report a significant reduction in IL-5Rα$^+$ ILC2 cells in the blood and sputum for benralizumab-treated patients. Further studies are underway to investigate the functional relevance of these cells.

In conclusion, our findings indicate that targeting IL-5Rα$^+$ cells interferes with and attenuates IL-5–driven eosinophilopoietic processes that may contribute to persistent airway eosinophilia in patients with severe, prednisone-dependent asthma.

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Age-dependent effect of ambient ozone on emergency asthma hospitalizations in Hong Kong

To the Editor:

There is evidence that short-term air pollution exposure may increase the risk of asthma attacks. However, the association of ambient ozone exposure with the risk of asthma hospitalization has been inconsistent for childhood asthma.[1,2] Ambient ozone may evoke airway inflammation as well as antivirus responses.[3] We hypothesized that the association between ambient ozone exposure and asthma hospitalization is age-dependent because of the differential vulnerability to respiratory virus infections, which are biological triggers of asthma attacks. We conducted a time-series study in Hong Kong to examine the short-term effect of ambient ozone on emergency hospital admissions for asthma in children, adults, and elders, respectively.

We collected air pollution data from Hong Kong Environmental Protection Department, emergency hospital admission data from Hospital Authority, and meteorological data from Hong Kong Observatory for the period 2005 to 2014. Daily emergency hospital admissions for asthma (International Classification of Diseases, Ninth Revision code 493) in young children (≤6 years old), children (<18 years old), adults (18-64 years old), and elders (≥65 years old), respectively, were regressed over daily 24-hour mean concentrations of ozone, other air pollutants, and meteorological measurements including temperature and relative humidity.

TABLE I. Age-stratified percent changes and 95% CIs in asthma emergency hospitalizations with an IQR increase in ozone in different time windows of the lag 0-20 period, based on 2005-2014 data in Hong Kong*

Distributed lags	Asthma in young children (age ≤ 6 y)	Asthma in children (age < 18 y)	Asthma in adults (age 18-64 y)	Asthma in elders (age ≥ 65 y)
Lags 0-6	**−8.6 (−13.4 to −3.4)**	**−6.6 (−10.7 to −2.3)**	**8.5 (4.0 to 13.2)**	**13.2 (8.4 to 18.2)**
Lags 0-2	−2.8 (−0.9 to 1.7)	−2.0 (−4.8 to 0.9)	**5.3 (2.5 to 8.2)**	**7.6 (4.7 to 10.6)**
Lags 3-6	**−6.0 (−8.2 to −3.7)**	**−4.7 (−6.6 to −2.8)**	**3.1 (1.2 to 5.0)**	**5.1 (3.2 to 7.1)**
Lags 7-20	**−21.1 (−26.3 to −15.5)**	**−18.7 (−23.3 to −14.0)**	**−7.0 (−11.7 to −2.0)**	−3.0 (−8.0 to 2.3)
Lags 0-20	**−27.9 (−34.3 to −20.8)**	**−24.1 (−29.8 to −18.0)**	0.9 (−6.1 to 8.4)	**9.7 (2.0 to 18.1)**

Statistically significant risk estimates are in boldface.
*Interquartile range (IQR) for ozone is 31.6 μg/m^3, using 24-h mean concentration as the metric. Risk estimates were derived from Poisson generalized additive distributed lag models, constrained with a second-degree (quadratic) polynomial, while adjusting for time trend and seasonality, weather conditions, day of week, and public holidays.

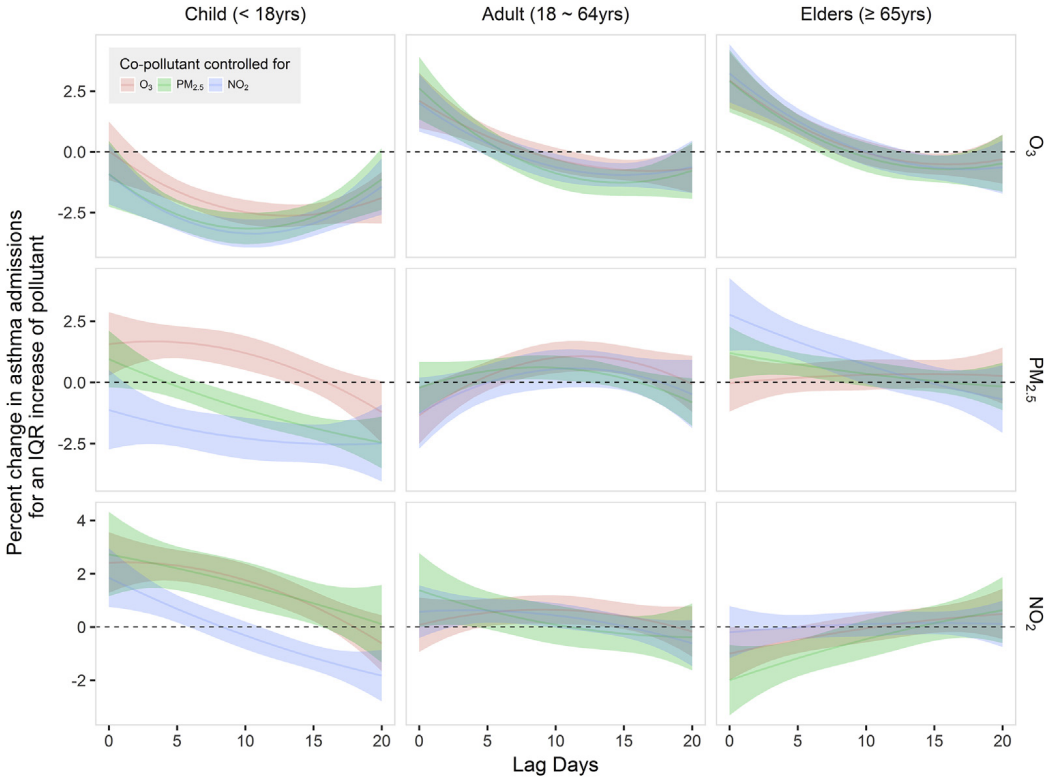

FIG 1. Plots of distributed lag estimates of age-stratified percent changes and 95% CIs in asthma emergency hospitalizations with an IQR increase in air pollutant along the lag 0-20 days, derived from the single- and 2-pollutant regression models of 2005-2014 data in Hong Kong. *IQR*, Interquartile range.

We used generalized additive distributed lag model to examine the association between ozone and asthma.[4] We used the smoothing spline, *s(.)*, with *a priori* model specifications and degree of freedom (*df*) to filter out seasonal patterns and long-term trend in asthma hospitalizations. Time-varying covariates controlled for included daily mean temperature, relative humidity, day of week, and official holidays. We examined the distributed lag effects and cumulative effects of ozone within a period of lag0 to lag20, from the current day to previous 20 days. Sensitivity analyses were conducted by applying different ozone exposure metrics (daytime 8-hour mean and maximum) and adjustment for coexisting pollutants. Stratified analyses by age group, sex, and season were performed. The results were expressed in terms of percentage changes (excess risk) in daily emergency asthma hospitalizations per interquartile range increment in O_3, and 95% CIs. All analyses were conducted using "mgcv" and "dlnm" packages in the statistical environment R 3.3.3 (R Development Core Team, 2016; http://www.r-project.org).

During the study period, there were a total of 62,367 emergency hospital admissions for asthma in Hong Kong, among which 35.1% were children, 32.6% adults, and 32.3% elders. The asthma hospitalization risk associated with ambient ozone varied by age group. An interquartile range increment in O_3 (31.6 μg/m^3) in a previous week (lag0-6) was associated with a 6.6% (95% CI 2.3%-10.7%) decrease in childhood asthma admissions, but 8.5% (95% CI 4.0%-13.2%) and 13.2% (8.4%-18.2%) increases in asthma for adults and elders, respectively (Table I). The prolonged effects of O_3 over lag 7-20 days were also different across age groups. Plots of distributed lag models of O_3 effect on asthma along lag 0-20 days (Fig 1) illustrated the apparently protective effect in

children and adverse effect in adults and the elderly. The risk estimates for ozone were robust to the adjustment of copollutants. After adjustment for ambient ozone, the 2 pollutants $PM_{2.5}$ and NO_2 are associated with higher risks of asthma hospitalizations in children. Sensitivity analyses with different metrics of ozone did not change the risk estimates significantly; the associations did not vary by sex or season; results with the young children group (≤6 years old) were similar to those with children younger than 18 years (see this article's Online Repository at www.jacionline.org). The current study disclosed age-dependent patterns of ozone and asthma relationships in an extended time window of lag0-20 days, which may help explain inconsistent findings of ozone and asthma in the earlier literature.

As a highly reactive gaseous pollutant, ozone exerts both inflammatory and antiviral effects in the respiratory system. The oxygen radicals produced from this exogenous oxidant evoke oxidative stress and airway inflammation, which would directly cause asthma exacerbation. Short-term exposure to ozone may also exacerbate asthma by increasing bronchial allergen responsiveness. On the other hand, ozone was shown to be protective against influenza by reducing influenza disease severity and mitigating acute virus-induced lung injury,[3] which may relate to the ozone-primed immunity via the alarmin IL-33[5,6] against influenza virus infection.[7]

The inflammatory and antivirus effects of ozone may exert opposite effects on asthma hospitalizations, explaining the differential effects of ozone on asthma in different subpopulations. Children are more vulnerable to respiratory infections because of their relatively weak immune system and more social gathering on school days. There are 80% to 85% asthma exacerbations in school-age children in the community associated with viral infection.[8] The inverse correlation between ozone and childhood asthma alludes to the antivirus effect of ozone and viral infections as a mediator for asthma hospitalization. The contribution of viral infection to asthma hospitalization may be larger in children than in adults and the elderly. In the children group, the protective effect of ozone was not observed in the immediate lag 0-2 days (Table I and Fig 1), which may suggest that ozone's inflammatory effect was more immediate whereas its antivirus effects was more delayed.

There is a possibility that the real modifier of the ozone and asthma relationship is asthma phenotype instead of age itself because of the association between clinical phenotypes and age.[9] Furthermore, this study was conducted in Hong Kong, an Asian city with high density of population and higher pollution levels compared with Western countries. Replication of the current study is warranted in other geographical locations.

In conclusion, the reduced risk of asthma hospitalization in children stands in apparent contrast with the elevated risk in adults and the elderly associated with ambient ozone. Age or age-related asthma phenotype may be a modifier of the relationship between ozone and asthma. The differential effects of ozone on asthma reflect the complex roles of ozone in inducing both inflammatory and antiviral responses in different subpopulations.

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ADA2 deficiency: Clonal lymphoproliferation in a subset of patients

To the Editor:

Primary immunodeficiencies (PIDs) encompass heterogeneous monogenic germline disorders, leading to defective development, function, or both of the immune system. The highly varied clinical manifestations along with often narrow initially recognized phenotypes can hamper accurate diagnosis in patients with rare and novel PIDs. At present, whole-exome sequencing (WES) enables the discovery of atypical traits of monogenic syndromes, broadening their phenotypic spectrum. Among reported PIDs, deficiency of adenosine deaminase 2 (DADA2) was originally associated with systemic autoinflammation, polyarteritis nodosa (PAN)–type vasculitis, and mild immunodeficiency.[1,2] Further studies have expanded the clinical phenotypic spectrum of DADA2 to cover common variable immunodeficiency, Blackfan-Diamond anemia, immune dysregulation, and spastic paraplegia.[3-7]

Clinical exome sequencing of 291 unrelated Finnish patients with PIDs identified 4 patients with biallelic loss-of-function variants in *CECR1*, the gene encoding adenosine deaminase 2 (ADA2; Table I). The detailed phenotypes of all patients with DADA2 (see Fig E1 and Tables E1 and E2 in this article's Online

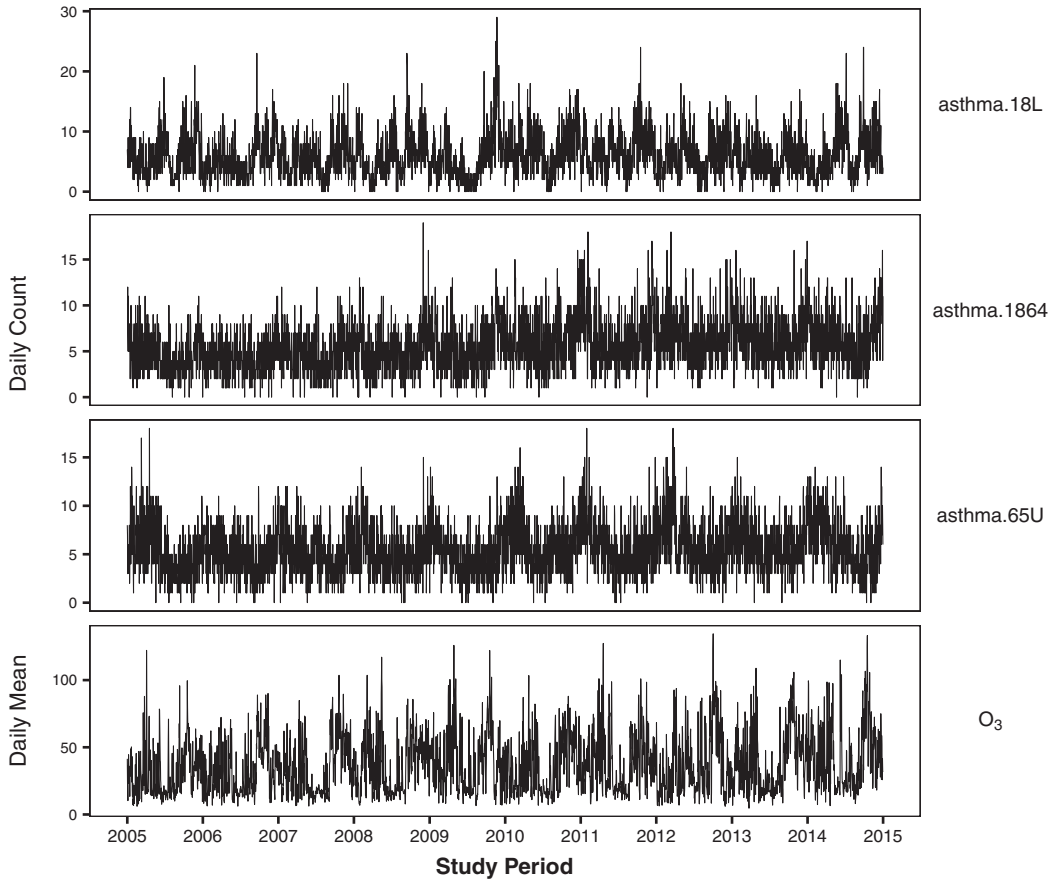

FIG E1. Time-series plots of ambient ozone concentrations ($\mu g/m^3$) and asthma emergency hospitalizations stratified by 3 age groups, from 2005 to 2014 in Hong Kong.

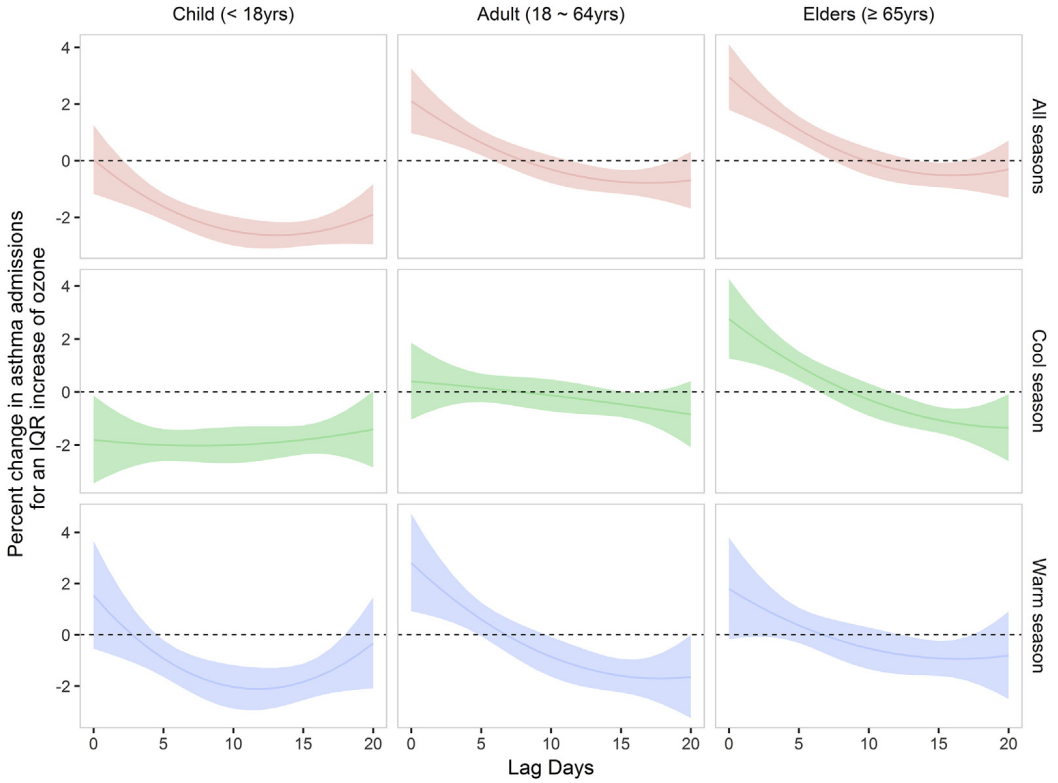

FIG E2. Plots of distributed lag estimates of age- and season-stratified percent changes and 95% CIs in asthma emergency hospitalizations with an IQR increase in ozone along the lag 0-20 days, based on 2005-2014 data in Hong Kong. The general patterns are similar between seasons. *IQR*, Interquartile range.

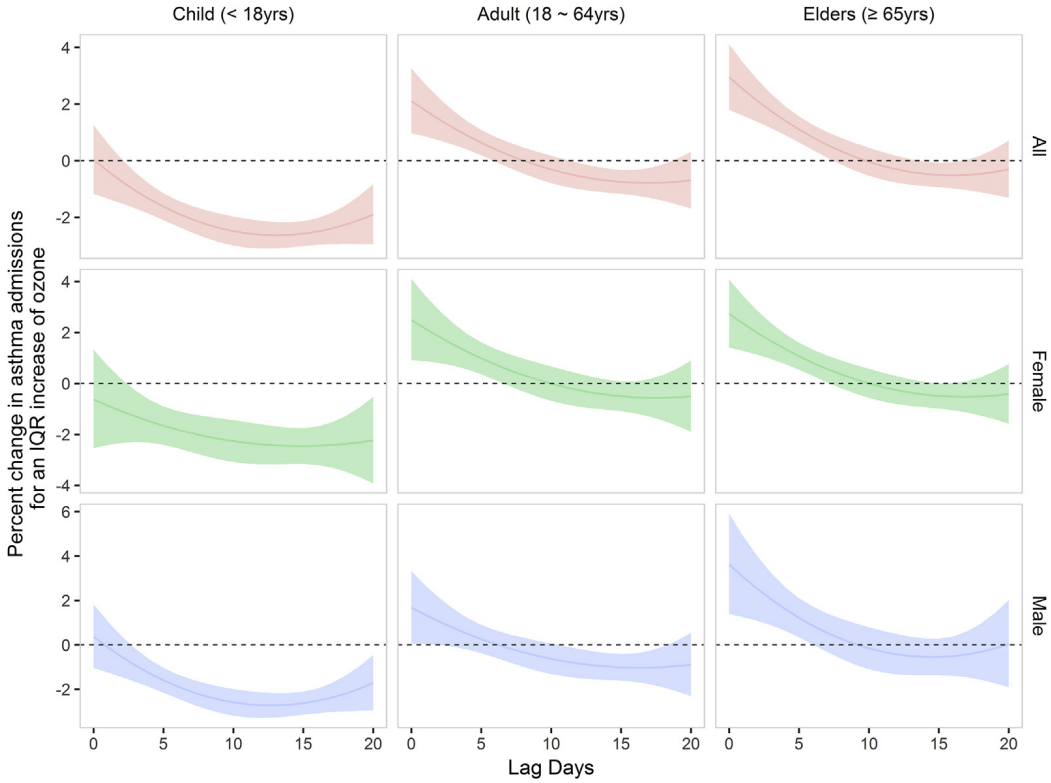

FIG E3. Plots of distributed lag estimates of age- and sex-stratified percent changes and 95% CIs in asthma emergency hospitalizations with an IQR increase in ozone along the lag 0-20 days, based on 2005-2014 data in Hong Kong. The associations did not vary by sex. *IQR*, Interquartile range.

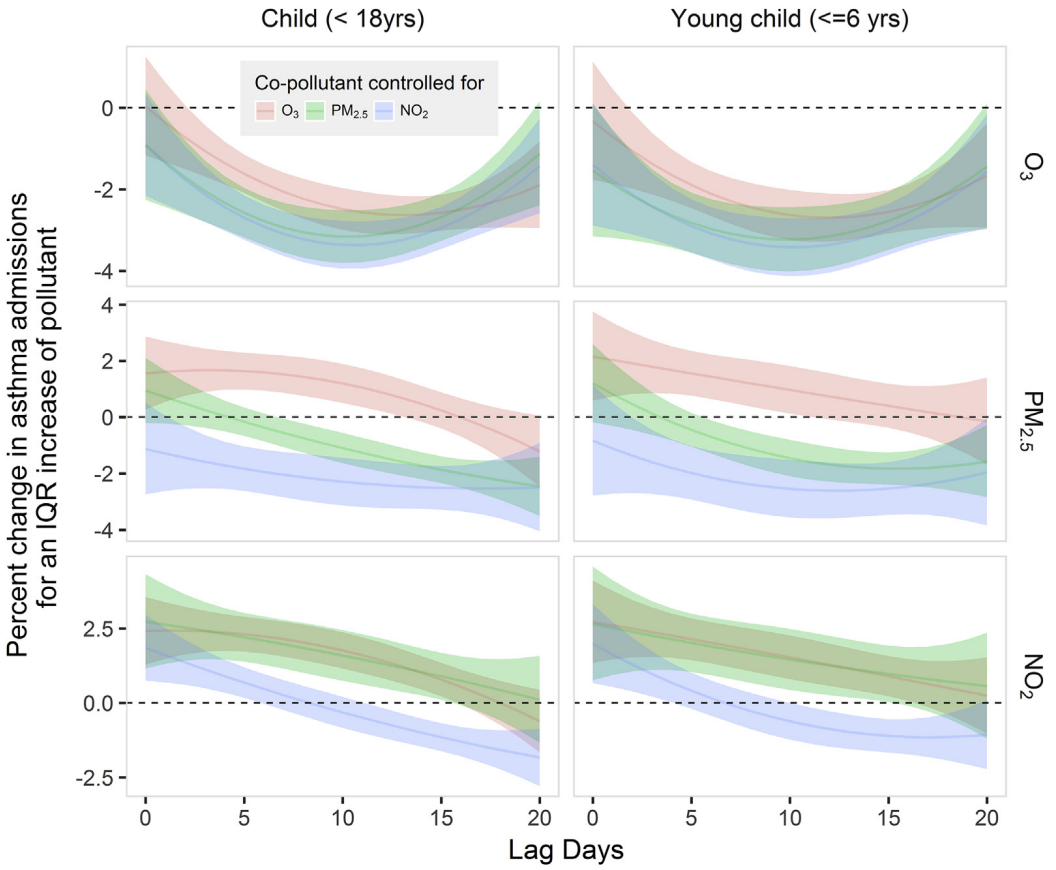

FIG E4. Plots of distributed lag estimates of age-stratified percent changes and 95% CIs in asthma emergency hospitalizations with an IQR increase in air pollutant levels along the lag 0-20 days, derived from the single- and 2-pollutant regression models of 2005-2014 data in Hong Kong. The results with young children 6 years and younger are similar to those with children younger than 18 years. *IQR*, Interquartile range.

TABLE E1. Distribution of emergency hospital admissions for asthma, air pollution concentrations, and meteorological factors in Hong Kong, 2005-2014

Variable	Mean ± SD	Min	25th	50th	75th	Max
Emergency asthma admissions						
Age (y)	17.1 ± 5.8	3	13	17	21	43
Young child (≤6 y)	3.9 ± 2.7	0	2	3	5	22
Child (age < 18 y)	6.0 ± 3.7	0	3	5	8	29
Adult (age 18-64 y)	5.6 ± 2.8	0	4	5	7	19
Elder (age ≥65 y)	5.5 ± 2.7	0	4	5	7	18
Sex						
Female	9.0 ± 3.7	0	6	9	11	22
Male	8.1 ± 3.6	0	6	8	10	26
Season						
Warm	15.5 ± 5.4	3	12	15	19	40
Cool	18.7 ± 5.8	4	14	18	22	43
Air pollution concentrations ($\mu g/m^3$)						
O_3 (24-h mean)	36.7 ± 21.7	4.7	18.5	32.1	50.1	134.4
O_3 (8-h mean)	47.7 ± 30.0	5.2	24.0	40.5	65.8	194.3
$PM_{2.5}$ (24-h mean)	34.5 ± 21.0	4.9	17.7	30.0	46.4	174.5
NO_2 (24-h mean)	55.7 ± 19.2	13	41.7	52.9	66.7	150.5
Weather conditions						
Mean temperature (°C)	23.4 ± 5.2	8.4	19.1	24.6	27.9	31.8
Relative humidity (%)	78.4 ± 10.6	29.0	73.0	79.0	86.0	99.0

25th, 25th percentiles; *Max.*, maximum; *Min.*, minimum.