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# Associations between outdoor air pollutants and non-viral asthma exacerbations and airway inflammatory responses in children and adolescents living in urban areas in the USA: a retrospective secondary analysis

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## Associated Data

Supplementary Materials

## Summary

### Background

Asthma prevalence and severity have markedly increased with urbanisation, and children in low-income urban centres have among the greatest asthma morbidity. Outdoor air pollution has been associated with adverse respiratory effects in children with asthma. However, the mechanisms by which air pollution exposure exacerbates asthma, and how these mechanisms compare with exacerbations induced by respiratory viruses, are poorly understood. We aimed to investigate the associations between regional air pollutant concentrations, respiratory illnesses, lung function, and upper airway transcriptional signatures in children with asthma, with particular focus on asthma exacerbations occurring in the absence of respiratory virus.

### Methods

We performed a retrospective analysis of data from the MUPPITS1 cohort and validated our findings in the ICATA cohort. The MUPPITS1 cohort recruited 208 children aged 6–17 years living in urban areas across nine US cities with exacerbation-prone asthma between Oct 7, 2015, and Oct 18, 2016, and monitored them during reported respiratory illnesses. The last MUPPITS1 study visit occurred on Jan 6, 2017. The ICATA cohort recruited 419 participants aged 6–20 years with persistent allergic asthma living in urban sites across eight US cities between Oct 23, 2006, and March 25, 2008, and the last study visit occurred on Dec 30, 2009. We included participants from the MUPPITS1 cohort who reported a respiratory illness at some point during the follow-up and participants from the ICATA cohort who had nasal samples collected during respiratory illness or at a scheduled visit. We used air quality index values and air pollutant concentrations for $PM_{2·5}$, $PM_{10}$, $O_3$, $NO_2$, $SO_2$, CO, and Pb from the US Environmental Protection Agency spanning the years of both cohorts, and matched values and concentrations to each illness for each participant. We investigated the associations between regional air pollutant concentrations and respiratory illnesses and asthma exacerbations, pulmonary function, and upper airway transcriptional signatures by use of a combination of generalised additive models, case crossover analyses, and generalised linear mixed-effects models.

### Findings

Of the 208 participants from the MUPPITS1 cohort and 419 participants from the ICATA cohort, 168 participants in the MUPPITS1 cohort (98 male participants and 70 female participants) and 189 participants in the ICATA cohort (115 male participants and 74 female participants) were included in our analysis. We identified that increased air quality index values, driven predominantly by increased $PM_{2·5}$ and $O_3$ concentrations, were significantly associated with asthma exacerbations and decreases in pulmonary function that occurred in the absence of a provoking viral infection. Moreover, individual pollutants were significantly associated with altered gene expression in coordinated inflammatory pathways, including $PM_{2·5}$ with increased epithelial induction of tissue kallikreins, mucus hypersecretion, and barrier functions and $O_3$ with increased type-2 inflammation.

### Interpretation

Our findings suggest that air pollution is an important independent risk factor for asthma exacerbations in children living in urban areas and is potentially linked to exacerbations through specific inflammatory pathways in the airway. Further investigation of these potential mechanistic pathways could inform asthma prevention and management approaches.

### Funding

National Institutes of Health, National Institute of Allergy and Infectious Diseases.

## Introduction

Outdoor air pollution has been linked to the onset[1–3] and exacerbation[4–7] of asthma, with many pollutants associated with asthma exacerbations, most notably fine particulate matter ($PM_{2·5}$),[8,9] oxidising gases, including $O_3$[10,11] and $NO_2$,[12,13] and reductants, such as $SO_2$.[14] The negative effects of air pollution are likely to be particularly relevant in urban centres, where pollution exposure is high and the prevalence and morbidity of asthma in children is disproportionately high compared with rural and less dense urban areas.[15] However, although physiological effects of air pollutants have been investigated, the molecular mechanisms by which air pollutants trigger asthma exacerbations are poorly understood, especially in susceptible populations, such as children with severe or uncontrolled asthma.[16] Studies of the molecular effects of air pollutants during respiratory illnesses have not been conducted in humans.

We aimed to improve characterisation of the relationship between outdoor air pollution and asthma exacerbations among children living in urban settings by analysing changes in airway physiology and airway gene expression during acute exacerbations and then identifying associations between overall air quality and individual pollutants with distinct gene expression pathways. We performed a secondary analysis of the Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-based Therapy Part 1 (MUPPITS1) cohort,[17] integrating data for air quality to investigate the contribution of air pollution to molecular and physiological mechanisms of exacerbation pathogenesis. We then validated key observations from this cohort in the Inner-City Anti-IgE Therapy for Asthma (ICATA) cohort.[18]

## Methods

### Study design and participants

We performed a retrospective analysis of data from a prospective observational cohort study (MUPPITS1)[17] and validated our findings with data from a randomised, double-blind, placebo-controlled trial in an independent cohort (ICATA).[18]

The MUPPITS1 study was a longitudinal observational study of 208 children with exacerbation-prone asthma in low-income urban centres, who were followed up between 2015 and 2017 for respiratory illnesses. This study has previously been described elsewhere.[17] Briefly, participants were recruited between Oct 7, 2015, and Oct 18, 2016, across hospital clinics in major urban areas in nine US cities. An individual was eligible for enrolment if they were aged 6–17 years; were diagnosed with asthma by a clinician more than 1 year before recruitment; had at least two asthma exacerbations (ie, required systemic corti costeroids or hospital admission, or both) in the year before recruitment; were treated with at least one puff of fluticasone 250 μg twice daily, or its equivalent for children aged 6–11 years, or treated with at least one puff of fluticasone 250 μg plus salmeterol 50 μg twice daily, or its equivalent for children aged 12 years and older; had more than or equal to 150 peripheral blood eosinophils per $mm^3$; did not smoke; and lived in a census tract with a density of more than or equal to 1000 families per square mile and with at least 10% of families with income below the poverty level (based on American Community Survey data[19]). Participants were identified for recruitment through the Registry for Asthma Characterization and Recruitment 2 and site-approved recruitment sources (NCT02513264). Participants were followed up prospectively for up to two respiratory illnesses or approximately 6 months, whichever occurred first. Participants who reported a respiratory illness were asked to return to the clinic twice in the 6-day period after the start of symptoms for collection of nasal samples and pulmonary function testing. Each illness was defined as a viral (V+) or non-viral (V–) event on the basis of virological assessment of the first nasal blow sample by use of the Luminex Respiratory Viral Panel (Luminex, Austin, TX, USA), with (Ex+) or without an asthma exacerbation (Ex–) on the basis of whether the participant was treated with systemic corticosteroids within 10 days following the onset of the respiratory event or not (appendix p 11). The last study visit occurred on Jan 6, 2017.

The ICATA study was a randomised, double-blind, placebo-controlled trial of omalizumab conducted from 2006 to 2009 in 419 inner-city children, adolescents, and young adults (ie, aged 6–20 years) with persistent allergic asthma, as previously described.[18] Briefly, participants were enrolled between Oct 23, 2006, and March 25, 2008, across hospital clinics in major urban areas in eight US cities. An individual was eligible for enrolment if they were aged 6–20 years; were diagnosed with asthma by a clinician more than a year before recruitment or diagnosed with asthma and had symptoms for longer than 1 year; had bodyweight and total serum IgE suitable for omalizumab dosing and a positive skin-prick test to at least one perennial allergen; did not smoke; and lived in a census tract with a density of more than or equal to 1000 families per square mile with and at least 10% of families with income below the poverty level. In an exploratory substudy of 189 of 419 participants in four of eight US cities (ie, New York, NY, Chicago, IL, Dallas, TX, and Cleveland, OH), 100 nasal samples were collected within 7 days of the onset of an asthma exacerbation (ie, required systemic corticosteroids; Ex+) and 165 nasal samples were collected at study week 48 in the absence of an exacerbation. The last study visit occurred on Dec 30, 2009. The nasal samples were used for virological assessment by use of the Eragen Multi-Code Respiratory Virus Panel (Eragen Biosciences, Madison, WI, USA) and defined as V+ or V– (appendix pp 12–13).

In this analysis, we included participants from the MUPPITS1 cohort who reported a respiratory event at some point during the follow-up and participants from the ICATA cohort who had nasal samples collected due to a respiratory event or at a scheduled visit. Sex was self-reported by participants, with the options of male or female.

The MUPPITS1 and ICATA protocols were approved by the Inner-City Asthma Consortium steering committee, protocol review committee, and data safety monitoring board. The MUPPITS1 protocol[20] was reviewed by a single institutional review board, and the ICATA protocol[21] was reviewed by the institutional review boards of all participating institutions. Written informed consent for the MUPPITS1 and ICATA studies was obtained from the parents or legal guardians of all participants and applies to this analysis.

### Procedures

To quantify exposure to air pollution, we downloaded air quality index (AQI) values and individual air pollutant data for $PM_{2·5}$, $PM_{10}$, $O_3$, $NO_2$, $SO_2$, CO, and Pb from the US Environmental Protection Agency (EPA),[22] spanning the years of the studies (2015–17 for MUPPITS1 and 2006–09 for ICATA) and the cities of participant recruitment. The EPA uses set formulas to convert raw measurements of pollutants into a summary AQI (on the basis of the single pollutant with the most hazardous concentration on a given day) for each day and each core-based statistical area (ie, geographical area anchored by an urban centre of at least 10 000 people plus adjacent areas with socioeconomic ties).[23] AQI data were matched to each event for each participant according to the corebased statistical area in which they lived and the date in relation to their reported respiratory illness symptoms. For each pollutant, monitors within each core-based statistical area were subset to include only those in the recruitment census tract, excluding monitors that were in the core-based statistical area but outside of the census tract. For each pollutant, the maximum concentration was then taken for each city census tract and day and similarly matched to each event according to core-based statistical area and date.

In the MUPPITS1 cohort, a subset of respiratory events that were recorded had detailed assessment available, including virological and transcriptomic assessments, pulmonary function tests, and cell differentials, from serial nasal blow and lavage samples collected after the reported onset of respiratory illness symptoms, as previously described.[17] Briefly, viral status was established on the basis of the results of multiplex PCR (Luminex Respiratory Viral Panel, Luminex, Austin, TX, USA) and partial sequencing of nasal blow samples to identify respiratory virus species; cell differentials were determined by cytospin of nasal lavage samples quantify ing neutrophils, lymphocytes, macrophages, eosinophils, respiratory epithelium, and squamous cells; and RNA-sequencing was performed on bulk RNA extracted from nasal lavage cell pellets and is publicly available at Gene Expression Omnibus, accession number GSE115824. RNA-sequencing data were summarised into cell-associated modules of coexpressed genes by use of combined cell association by correlation and weighted gene correlation network analysis[24] and annotated by use of Database for Annotation, Visualization and Integrated Discovery[25] and Search Tool for the Retrieval of Interacting Genes/Proteins;[26] the modules used in this analysis have been previously described.[17] Spirometry and the measurement of fractional exhaled NO (FeNO) were collected according to American Thoracic Society and European Respiratory Society guidelines.[27] In the ICATA cohort, nasal-secretion samples were collected at the onset of an asthma exacerbation or at a routine study visit 48 weeks after study enrolment, and RNA was extracted and analysed for respiratory viruses by the Eragen Multi-Code Respiratory Virus Panel.[18]

### Outcomes

The key outcome was association between AQI values and pollutant concentrations and the respiratory event type. Other outcomes included associations with pulmonary function and nasal module expression values. All outcomes were modelled in relation to the AQI value and concentrations of pollutants.

### Statistical analysis

Differences in AQI and air pollution in MUPPITS1 were assessed by comparing mean values of each metric among specified event groups (ie, among the four event subgroups [V–Ex+, V+Ex+, V–Ex–, and V+Ex–] or between event groups [ie, Ex+ and Ex–]) across timespans before and after the onset of respiratory illness symptoms, designated day 0, and during the onset of asthma exacerbations. In ICATA, differences were compared among groups (V–Ex+, V+Ex+, V– at week 48, and V+ at week 48) relative to the day of nasal sampling, designated day 0. Longitudinal differences among groups were visualised and statistically compared among the groups by generalised additive models,[28–30] including the day relative to respiratory illness symptom onset as the smoothed, continuous variable, and a term for event group. Covariates were added for city of residence or season, where specified. The generalised additive model tested whether the four (or two) groups were different over the entire timespan included in the model. For the four-group comparisons, ANOVA was run to establish whether the four groups were different by use of the Wald test in the generalised additive model, followed by post-hoc pairwise comparisons. The same model syntax and data visualisation were used for both MUPPITS1 and ICATA. Responsible pollutants for AQI values for each day were those defined by the EPA. Case crossover analyses of Ex+ events in MUPPITS1 were performed comparing days –7 to +1 (case) relative to the date of exacerbation onset (designated day 0) to days –16 to –8 (control) or days –37 to –8 (control) as specified. Longitudinal differences were visualised by generalised additive models, and statistical comparisons between time periods were tested by conditional logistic regression,[31] including a covariate for day of the week. Lung function measurements (forced expiratory volume in 1 s as a percentage of predicted [$FEV_1$% predicted] and ratio of forced expiratory volume in 1 s to forced vital capacity [$FEV_1$/FVC]) were compared with AQI values or pollutant concentrations from the same day by use of generalised linear mixed-effects models split by event subgroup with a random effect for participant to account for the correlation between values from the same participants; values collected after the initiation of systemic corticosteroids were excluded for this analysis, and for $FEV_1$/FVC the model also controlled for age and sex. After testing AQI and pollutants, p values were adjusted with the Benjamini-Hochberg method to identify those with a false discovery rate (FDR) of less than 0·05. Module expression was compared with AQI values or pollutant concentrations summed over 3 days (ie, the day of sample collection and the preceding 2 days) by use of a generalised linear mixed-effects model adjusted for cell percentages in the nasal lavage sample and the number of counts in the RNA-sequencing library with a random effect for participant to account for the correlation between values from the same participants; samples collected after the initiation of systemic corticosteroids were excluded for this analysis. Multiple-testing correction for module analysis was performed with the Benjamini-Hochberg method and modules with FDR less than 0·05 were considered significant. Demographic and clinical characteristic variables among event or sample subgroups in each cohort were summarised with median and IQR for continuous variables and count and percentage for categorical variables. Within each cohort, V+ and V– events or samples were compared by use of generalised linear mixed-effect models, assuming a binomial distribution for the categorical variables and ranked continuous variables, and included a random effect for participant to account for the correlation between values from the same participants. In cases where at least one of the categories of a categorical variable was zero, a Fisher's exact test was used instead.

Wherever data were missing they were excluded from the analysis. The number of samples for each analysis are indicated in the figure legends. Every reported respiratory event in MUPPITS1 and every timepoint with a nasal sample in ICATA were included. For all analyses we used R (version 4.1.0) and all figures were constructed with R package ggplot2 (version 3.3.6).

### Role of the funding source

National Institute of Allergy and Infectious Disease project scientists had no role in study design or data analysis but participated collaboratively in the interpretation and writing of the report.

## Results

Of the 208 participants from the MUPPITS1 cohort and 419 participants from the ICATA cohort, 168 participants in the MUPPITS1 cohort (98 male participants and 70 female participants) and 189 participants in the ICATA cohort (115 male participants and 74 female participants) were included in our analysis.

336 respiratory events were recorded in the MUPPITS1 cohort, of which 143 resulted in asthma exacerbations (Ex+) and 193 did not (Ex–). AQI values were significantly higher (ie, indicating worsened air quality) for the Ex+ events compared with Ex– events across the duration of 9 days before the reported start of respiratory symptoms to 9 days after ($p<0·0001$; appendix p 2). Among these events, 154 had detailed assessments during the event and could, therefore, be subdivided into either V+ or V– events. Notably, V– events accounted for 52 (33·8%) of 154 events, and V–Ex+ events accounted for 14 (29·8%) of 47 of Ex+ events (table 1, appendix p 11).

Table 1:

MUPPITS1 demographic and clinical characteristics

| | Ex+ events | | | Ex– events | | |
|---|---|---|---|---|---|---|
| | V+Ex+ (33 [21·4%] of 154 events; 33 participants) | V-Ex+ (14 [9·1%] of 154 events; 12 participants) | p value | V+Ex– (69 [44·8%] of 154 events; 58 participants) | V-Ex– (38 [24·7%] of 154 events; 34 participants) | p value |
| Age at baseline, years | 12 (10 to 14) | 12 (9 to 14) | 0·96 | 9 (8 to 12) | 12 (9 to 13) | 0·028 |
| Sex | .. | | 0.28 | .. | .. | 0·65 |
| Female | 15 (45%) | 9 (64%) | .. | 33 (48%) | 20 (53%) | .. |
| Male | 18 (55%) | 5 (36%) | .. | 36 (52%) | 18 (47%) | .. |
| Site | .. | .. | 014* | .. | .. | 0·69* |
| Boston, MA | 1 (3%) | 4 (29%) | .. | 10 (14%) | 7 (18%) | .. |
| Chicago, IL | 3 (9%) | 0 | .. | 4 (6%) | 1 (3%) | .. |
| Cincinnati, OH | 3 (9%) | 0 | .. | 4 (6%) | 4 (11%) | .. |
| Dallas, TX | 1 (3%) | 0 | .. | 6 (9%) | 3 (8%) | .. |
| Denver, CO | 6 (18%) | 5 (36%) | .. | 8 (12%) | 1 (3%) | .. |
| Detroit, MI | 6 (18%) | 1 (7%) | .. | 8 (12%) | 6 (16%) | .. |

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Data are median (IQR) or n (%) and represent the number of events. Events are the number of unique illness events. Participants are the number of unique participants with illness events. For participants with two respiratory illnesses meeting specified criteria, both illnesses are included in the table. Summaries apply to the first visit during that illness. p values represent the significance of any difference between the proportion of V+Ex+ versus V–Ex+ or V+Ex– versus V–Ex–. All p values are from generalised linear mixed-effect models with a random effect for participant to account for correlation between values from the same participant, except for instances where at least one of the categories of a categorical variable is zero and p values are from a Fisher's exact test. Ex+=exacerbation. Ex–=non-exacerbation. V+Ex+=viral event with exacerbation. V–Ex+=non-viral event with exacerbation. V+Ex–=viral event without exacerbation. V–Ex–=non-viral event without exacerbation. $FEV_1$% predicted=$FEV_1$ as a percentage of predicted. $FEV_1$/FVC=ratio of $FEV_1$ to forced vital capacity. $FEV_1$=forced expiratory volume in 1s. WURSS=Wisconsin Upper Respiratory Symptom Survey for kids—daily symptom report. AUC=area under the curve. NA=not applicable.

*p values are from a Fisher's exact test.

†Urine was not collected for one V–Ex+ event and three V–Ex–events.

‡Seasonal, non-SARS coronaviruses.

AQI values were specifically increased in the V–Ex+ event subgroup, compared with the other three event subgroups across the duration of 9 days before the reported start of respiratory symptoms to 9 days after the start ($p<0·0001$; figure 1A). The AQI values appeared to increase during the period of days around clinical asthma exacerbations in the V–Ex+ group, and exacerbations occurred after several days of mean sustained increase in AQI (figure 1A, 1E; appendix p 3). The other three groups had statistically similar AQI values to one another. V–Ex+ events were thereby largely responsible for the higher AQI values among Ex+ events than among Ex– events (appendix p 2). Similarly, when comparing AQI values over the 9 days before exacerbation onset, V–Ex+ events had sustained higher AQI values than did V+Ex+ events ($p<0·0001$). We performed a case-crossover comparison that also showed significantly higher AQI values in the V–Ex+ event subgroup in the week immediately before exacerbation onset (ie, days –7 to +1) than in the week before this period (ie, days –16 to –8; $p=0·0075$; appendix p 4), or in the 30 days before this period (ie, days –37 to –8; $p=0·016$), which was not true for the V+Ex+ event subgroup.

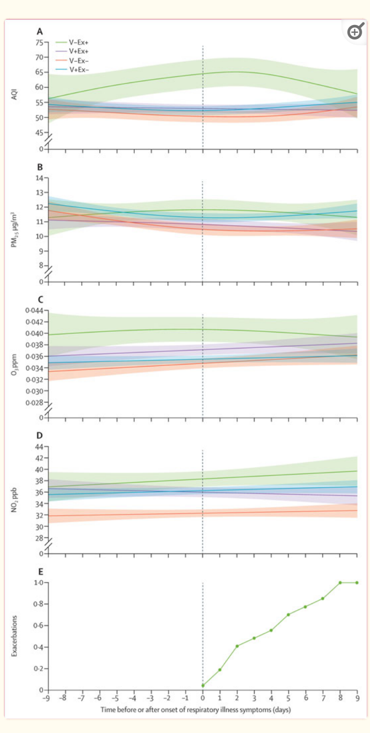


Figure 1:

**AQI values and individual pollutant concentrations over time**

Trend over 9 days before the reported start of respiratory illness symptoms (day 0) to 9 days after in AQI (A), $PM_{2·5}$ concentrations (B), $O_3$ concentrations (C), $NO_2$ concentrations (D), and cumulative incidence of exacerbations in the V–Ex+ subgroup, where 1·0 represents 14 exacerbations (E). Data were plotted using generalised additive model fits showing 95% CIs. There were 14 events in the V–Ex+ group, 33 events in the V+Ex+ group, 38 events in the V–Ex– group, and 69 events in the V+Ex– group. Equivalent plots showing all data points are shown in the appendix (p 3). AQI=air quality index. V–Ex+=non-viral event with exacerbation. V+Ex+=viral event with exacerbation. V–Ex–=non-viral event without exacerbation. V+Ex–=viral event without exacerbation.

The EPA-defined pollutants used to calculate AQI values during V–Ex+ events were $O_3$ (136 [51·1%] of 266 total days analysed), $NO_2$ (47 [17·7%] days), and $PM_{2·5}$ (82 [30·8%] days) but not $PM_{10}$ (1 [0·4%] day), CO (0 days), or $SO_2$ (0 days). Correspondingly, the concentrations of each of these three pollutants were significantly higher in the V–Ex+ group than in the other three groups during this same window of time (figure 1B–1D; appendix p 3; $O_3$ $p<0·0001$, $NO_2$ $p<0·0001$, $PM_{2·5}$ $p=0·0006$). The V+Ex+ group also had modestly higher $O_3$ concentrations than the two Ex– groups ($p=0·0014$; figure 1C; appendix p 3). Case-crossover analyses supported similar trends for these three pollutants (appendix p 4). Mean $PM_{2·5}$ concentrations during the V–Ex+ events on some occasions reached concentrations higher than the EPA primary standards (ie, 12·0 μg/$m^3$ annual mean), but mean $O_3$ and $NO_2$ concentrations did not exceed US National Ambient Air Quality Standards.[32] Similarly, mean AQI assessments did not reach EPA concentrations designated as unhealthy (defined as AQI of 151–200) or unhealthy for sensitive groups (defined as 101–150 for people with heart and lung disease, older adults, children, people with diabetes, and people of lower socioeconomic status) but rather were at concentrations in the moderate category (defined as 51–100 AQI) for several days.[33]

V–Ex+ events were identified in only five of the nine cities with participants in the study. Adjusting the primary model for city showed similar results for AQI (ie, AQI values were higher for the duration of the 9 days before the reported start of respiratory symptoms to 9 days after in the V–Ex+ group), as did a subgroup analysis restricted to individuals living in only those five cities ($p<0·0001$; appendix p 5). V–Ex+ events occurred throughout the year, although were numerically but not significantly more likely than V+Ex+ events to occur in the summer. Adjusting the primary model for season showed similar results for AQI (data not shown; $p<0·0001$). Subsetting by season showed higher AQI associated with V–Ex+ events than with the other types of event both in spring and summer ($p<0·0001$) and autumn and winter ($p=0·0003$), although the magnitude of difference was most pronounced in spring and summer (appendix p 6).

The V–Ex+ event subgroup had physiological airway obstruction, as measured by $FEV_1$% predicted, that was not significantly different to the V+Ex+ subgroup ($p=0·94$) and similar FeNO (table 1; $p=0·66$). There were no significant differences in urine cotinine concentrations, as a measure of tobacco smoke exposure, between groups (table 1). During V–Ex+ events, AQI values showed a significant inverse association with $FEV_1$% predicted (linear mixed effect model parameter estimate [β]=–0·35, FDR=0·014) and $FEV_1$/FVC ratio (β=–0·0028, FDR=0·014; figure 2). No significant inverse association was identified in the other three groups. Among the individual pollutants, $O_3$ was significantly associated with $FEV_1$% predicted (β=–591, FDR=0·052) and $FEV_1$/FVC (β=–6·0, FDR=0·0084) only in the V–Ex+ event subgroup (appendix p 7).

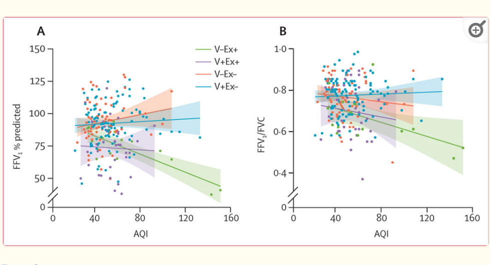


Figure 2:

**Associations of pulmonary functions with AQI values**

Associations of $FEV_1$% predicted (A) and $FEV_1$/FVC ratio (B) with AQI measured on the same day. Regression lines, 95% CIs, and all data points are shown for each group. There were 16 data points for the V–Ex+ group, 36 data points for the V+Ex+ group, 70 data points for the V–Ex– group, and 116 data points for the V+Ex– group. AQI=air quality index. $FEV_1$% predicted=forced expiratory volume in 1 s as a percentage of predicted. $FEV_1$/FVC=ratio of forced expiratory volume in 1 s to forced vital capacity. V–Ex+=non-viral event without exacerbation. V+Ex+=viral event with exacerbation. V–Ex–=non-viral event without exacerbation. V+Ex–=viral event without exacerbation.

Cumulative AQI values over 3 days (ie, the day of sample collection and the preceding 2 days) were significantly associated with expression of upper airway gene expression modules that were previously shown to be increased in expression during incipient asthma exacerbations (12 of 19 modules; FDRs <0·05; table 2).[17] Absolute values of the effect sizes ranged from 0·0015 to 0·0039, where the coefficient represents a change of 0·0015 to 0·0039 in module expression (log2) for a 1 unit increase in AQI over 3 days; expressed differently, this means, for example, a mean 10 unit increase in AQI for 3 days equates to a 3·2–8·5% increase in expression of these modules. A detailed description of these modules was previously published,[17,34] along with their relationships to V–Ex+ and V+Ex+ events[17] and details of their contents and annotation.[35] AQI values were associated with modules that were specifically increased in the V–Ex+ event subgroup but also with core exacerbation modules that were increased in both V+Ex+ and V–Ex+ event subgroups in this population, suggesting a broad effect of air pollution on asthma pathobiological pathways.

Table 2:

Gene expression modules differentially expressed during asthma exacerbations

| | Cell association | Number of genes | AQI FDR | AQI effect size | $PM_{2.5}$ FDR | $PM_{2.5}$ effect size | $O_3$ FDR | $O_3$ effect size |
|---|---|---|---|---|---|---|---|---|
| **V-Ex+ specific modules** | | | | | | | | |
| Keratinisation, epithelial development, cell–cell adhesion, and tight junctions | Epithelium | 1041 | 0·023 | 0·0032 | 0·0060 | 0·0137 | 0·44 | 2·0302 |
| Tissue kallikreins and IL-23–IL-17 axis | None | 143 | 0·074 | 0·0023 | 0·019 | 0·0108 | 0·83 | 0·4875 |
| Squamous epithelium | Epithelium | 56 | 0·0092 | 0·0019 | 0·018 | 0·0057 | 0·44 | 1·0821 |
| **Core modules** | | | | | | | | |
| SMAD3-related cell differentiation | Epithelium | 46 | <0·0001 | 0·0038 | 0·0008 | 0·0115 | 0·42 | 1·7530 |
| Eosinophil | Eosinophil | 69 | 0·0092 | 0·0037 | 0·012 | 0·0116 | 0·10 | 4·0189 |

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Expression of some modules was significantly associated with AQI values, $PM_{2·5}$ concentrations, and $O_3$ concentrations. Module expression was compared with AQI and pollutant values summed over the two preceding days and day of nasal sample collections (V–Ex+ n=17, V+Ex+ n=38, V–Ex– n=72, V+Ex– n=120). Significance was determined by generalised linear mixed effect models with a random effect for participant. Results were considered significant if the FDR was <0·05. AQI=air quality index. FDR=false discovery rate. NS=not significant. NA=not applicable. V–Ex+=non-viral event with exacerbation. V+Ex+=viral event with exacerbation.

*Biology could not be interpreted.

Individual pollutant concentrations were also associated with expression of specific genes. Cytokine/chemokine genes positively associated with bacteria accumulation with airway epithelial cell numbers and epithelial gene pathways. These included three modules enriched in immune, inflammatory, extracellular matrix-binding molecules and IL-23 IL-17 axis (keratinocyte, epithelial development, cell-cell adhesion, and tight junctions), and squamous differentiation (Figure 5, Supplemental Table 5). Gene-level associations between pollutant concentrations were also associated with the epithelial cytokine/chemokine genes IL-1rn/IL-1 and IL-8 (*cxcr2*), CXCL8 (*cxcl8*) and CXCL1 (*cxcl1*) differentiation, extracellular matrix and tissue remodeling, extracellular matrix-binding molecules and IL-23/IL-17 axis, and EGFR signaling and cell-cell adhesion. FDR<0.05, *supporting* p. 29). The directionality of associations was consistent with the IL-23/IL-17 axis, extracellular matrix, and EGFR signaling associations were associated with the epithelial cytokine/chemokine genes and IL-1rn response modules (FDR<0.0007). Absolute values of the effect sizes ranged from 0.08 to 0.25 (median 0.15), and 95% CI of each were cross-positive (p FDR<0.05) for all associations (Figure 5) for a 1 unit increase in $PM_{2.5}$ over 3 days. For example, the coefficient for the tissue response module for a 1 unit increase in $PM_{2.5}$ over 3 days was 0.15 (95% CI: 0.09, 0.21), and a increase in $PM_{2.5}$ of 10 units equates to a 25% increase in tissue response score (*supporting* p. 8). By contrast, O3 concentrations were related specifically to increased expression of the genes IL-1rn/IL-1 and CXCL1 (*cxcl1*) in response to a 1 unit increase in O3 over 3 days (FDR<0.05). A 10 ppb increase in O3 for 3 days equates to a 47.9% increase in module expression (*supporting* p. 8).

We next sought to replicate the finding of increased air pollution concentrations in the 5′-flank of *cxcr2* expression as an independent cohort. The GATA study included children, adolescents, and young adults (n=320, aged 5–20 years) living in urban areas with persistent asthma (Supplemental Table 1). We found that increased exposure to $PM_{2.5}$ was associated with increasing methylation at CpG sites 5′ of *cxcr2* which were strongly associated (FDR<1e-5) and 12 of which were cis-eqtmm (FDR<1e-5). Serving as non-exacerbation comparison timepoints, 141 children had 1 year of follow-up with no exacerbations and 1 exacerbation. The 5′-flank of *cxcr2* and the 5′-flank of *cxcl1* in which were cis-eqtmm (p FDR<0.05) in the GTEx study were strongly associated (p FDR<1e-5). Comparing among these four groups, increased AQ (F1, F2, F3), and F1, relative to no exacerbation observed during the 1 year follow-up (p value=0.0008; *supporting* p. 10). Why, was not significant in this analysis (p=0.09 comparing F1+F2 and F3). Exacerbations were also associated with increased methylation at the 5′-flank of *cxcr2* (*supporting* p. 12). Increased methylation at the 5′-flank of *cxcr2* was associated with increased expression of the gene *CXCR2* and decreased expression of the gene *CXCL1*. Furthermore, our findings suggest that moderate increases in local air pollution relative to a specific GATA study participant parallels adversely affect these susceptible populations. This association suggests either that exposures to mixtures of pollutants were several days or less consistent over a year, or that exposures at the high AQ levels used in the GTEx cohort (Supplemental Figure 1) are not captured by regionally reported AQ values on the basis of GTEx participant residence.

Our study linked individual pollutants to both biological pathways of airway inflammation and epithelial differentiation and specific genes in these pathways. The IL-23/IL-17 axis is a well-characterized biological pathway of airway epithelial cell for both IL-17 and IL-23 receptor, including increases of tissue fibronectin and non-type-2 inflammatory cytokine genes[22] and a large set of functional bronchial epithelial genes, which are unique to IL-17 signaling.[23] The results suggest that increases in $PM_{2.5}$ concentrations trigger many epithelial immune pathways, which are consistent with the known effects of $PM_{2.5}$ on airway cells. Our study also identified pollutants associated with the expression of genes in the EGFR signaling pathway. Furthermore, $PM_{2.5}$ was associated with pathways that are functionally linked to airway remodeling, including EGFR signaling, DNA33 signaling, IL-33 signaling, mucus hypersecretion, and extracellular matrix production. These results are consistent with epidemiologic studies that have linked long-term exposure to ambient $PM_{2.5}$ and asthma incidence,[24] and experimental studies that have shown that exposure to $PM_{2.5}$ and components of these associations was not unique to O3-rich events but congruent in all four groups, suggesting that the effects of $PM_{2.5}$ exposures were present in each respiratory event type but that the degree of response and large magnitude of transcriptional change of these mediators was highest, and potentially most clinically significant, in the AQ group.

We observed that O3, is associated with eosinophilic or type-2 inflammation; it was positively associated with expression of a module containing canonical type-2 cytokines IL-5, IL13, and IL12, among numerous other components of type-2 inflammation, and with a module enriched in genes for IL-1 family cytokines. Our results suggest that exposure to ambient O3 and increasing concentrations of O3 exposure can increase airway eosinophilia and induce airway hyper responsiveness.[25] IL-5 concentrations appeared to be higher for the AQ group than for the other three groups, but the difference was not significant (p=0.09). This pattern may provide a clinical lead to explain the observed increased type-2 inflammation during Y1+Y2- and Y1+ events.[26] Supporting evidence has linked air pollution to airway eosinophilia, and the biological plausibility for O3 to act in this manner.[27] We were unable to measure neutrophil or other pollution data this well, strongly limiting our ability to study the effects of co-pollutants. Our study suggests that increasing O3 exposure can increase eosinophilia in Y1+ events in the spring and summer months relative to Y1+ events, suggesting that seasonal inhaled allergens might also have contributed to Y1+ events. Our study also identified pollutant allergen exposures in this study and were able to adjust only for season and site in our analyses. Our study suggests that O3 and $PM_{2.5}$ exposures may have different mechanisms of effects the potential for related allergens as a contributor under some circumstances. our study. Future studies that can accurately measure acute allergen exposures will be important to confirm our contributions. Our study focused on ambient pollutants with persistent asthma with a type-2 phenotype component (or peripheral blood eosinophilia or IgE). Our study did not include other pollutants such as NO2 or SO2 that have been associated in epidemiologic studies for results would be generalizable to any asthma phenotype. these results are also highly relevant to type-2 low asthma (i.e. often defined as eosinophilia <300 cells/μL). Our study suggests that exposure to $PM_{2.5}$ and O3 may be relevant to a potential combined effect of more than one asthma trigger. Our study suggests that ozone pollution, and other concentrations can act independently or synergise to initiate asthma exacerbations in children with type-2 low asthma. In fact, the effects of pollutants might overlap with the effects of viruses, as the associations between several module expression and pollutants were similar for Y1+ and Y1+Y2- events. Our study suggests that ozone combined increases of $O_3$ and $PM_{2.5}$ in the first 3 days of a cold may increase the risk associated with distinct inflammatory pathways. These pollutants are chemically coupled, so ozone concentrations especially in warm weather[28] and can have additive deleterious effects on the airway. Larger studies will be needed to investigate combined effects among asthma triggers and exacerbations.

## Research in context

### Evidence before this study

Respiratory viral infections are the most common cause of asthma exacerbations in children and adolescents (ages aged <21 years), and human studies of respiratory viruses in vitro have identified many inflammatory pathways mediating their effects. These findings have increasingly led towards targeted therapeutic strategies to prevent exacerbations. Although ambient air pollutants have been associated with viral respiratory infections, the causes and molecular mechanisms of non-viral exacerbations are, in comparison, poorly understood. Over the past several decades, many epidemiologic studies have shown associations between air pollution concentrations and the occurrence of asthma exacerbations. Mechanistic animal, human, and cell culture studies have identified many inflammatory pathways which individual air pollutants can cause through different mechanisms. Studies linking air pollutant exposures to molecular mechanisms in the airways during naturally occurring asthma exacerbations have not been reported. We searched PubMed for articles published in English between Jan 1, 2010, and Oct 1, 2021, using the search terms "asthma", "air pollution", "ozone", "particulate matter", "omics", and "epidemiology" also reviewed all references from in-depth review articles on the topics of environmental exposures, outdoor air pollution, and asthma, published in 2014 and 2019.

### Added value of this study

We identify that air pollution in urban centers, related to increased concentrations of specific air pollutants, significantly contributed to asthma exacerbations in children who are underweight and living in areas with high disease burden. We identify that the effects of pollutants on asthma exacerbations are not uniform, suggesting a promoting respiratory virus. Crucially, we connect individual pollutant associations in airway phenotype and upper airway gene expression during acute exacerbations, identifying associations with decreased lung function and molecular mediator pathways of airway inflammation. We link fine particulate matter ($PM_{2.5}$) exposure to increased expression of many epithelial immune pathways including cytokine and inflammatory cytokines, which are absent in non-exacerbation timepoints, and in airway remodeling pathways. Similarly, we link $O_3$ exposure to type 2 inflammatory signaling pathways and lung function. For the first time, to our knowledge, we identify associations between specific pollutant exposures and airway inflammatory pathways and specific genes in these pathways and mechanisms, contributing to asthma disparities in children living in urban areas.

### Implications of all the available evidence

Regional air pollutants are epidemiologically associated with asthma exacerbations and might response an important role in asthma exacerbations occurring in children occurring independently of respiratory viral infections. Compared with viral exacerbations, non-viral exacerbations associated with air pollution proceed through distinct and overlapping molecular mechanisms and also share some common mechanisms. This study suggests that ozone and $PM_{2.5}$ exposures may have different mechanisms of effects of asthma exacerbation endotypes (an inferior targeted intervention approach) and further the public health argument for policies that reduce outdoor air pollution.

## Supplementary Material

NIHMS

Click here to view.[29] (95.6KB)

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## Footnotes

Declaration of interests

LMM, DEL, PJG, and AT declare no competing interests.

Data sharing

Study design information and data collection for the subjects can be accessed through InnoVeritas (https://www.innoveritas.org) at accession number SDY187. The raw RNA sequencing (fastQ) format data and processed information about all high throughput nucleotide sequencing experiments have been deposited with the US National Center for Biotechnology Information Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) under the accession number GSE151928. The GATA study data, including the DNA methylation data for the pollutants $PM_{2.5}$, $NO_2$, $O_3$, $SO_2$, can be downloaded from the Environmental Protection Agency (https://aqs.epa.gov/aqsweb/documents/data_mart_welcome.html).

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