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Estimated time-varying exposures to air emissions from animal feeding operations and childhood asthma

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Abstract

Background/Aim: Industrial-scale animal feeding operations (AFOs) have adverse impacts on regional air quality. Air emissions include endotoxins and other pro-inflammatory components, and exposure may cause airway inflammation and respiratory effects in susceptible individuals residing nearby. We aimed to develop and validate metrics for estimating time-varying exposure to AFO air pollution in surrounding communities and, secondly, to determine whether exposure is associated with health effects in children with asthma.

Methods: We conducted a longitudinal panel study of N=58 children with asthma in an agricultural region of Washington State with a high density of dairy AFOs. Children were followed for up to 26 months with repeated measures of respiratory health (N=2023 interviews; N=3853 lung function measurements); urine was collected in a subcohort (N=16) at biweekly intervals over three months and analyzed for leukotriene E4 (LTE4), a biomarker of systemic inflammation (N=138 measurements). We developed an approach to estimate daily exposure to AFO airborne emissions based on distance to AFOs, AFO size, and daily wind speed and direction, and validated the estimates against direct measurements of ammonia, a chemical marker of AFO emissions, measured biweekly at 18 sites across the region for 14 months. Short-term relationships between AFO pollutant exposure and outcomes were assessed using regression models accounting for within-participant correlation and several potential confounders.

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Results: Estimates of daily AFO air pollution correlated moderately well with outdoor ammonia measurements (N=842; r=0.62). Forced expiratory volume in one second (FEV_1) as percent of predicted was 2.0% (95% CI: 0.5, 3.5) lower with each interquartile increase in previous day exposure, but no associations with asthma symptoms were observed. There was suggestive evidence that LTE4 concentrations were higher following days of elevated exposure to AFO emissions (p=0.07).

Conclusions: A simple metric of time-varying exposure to AFO emissions was correlated with daily outdoor ammonia levels. Children with asthma may be adversely affected by exposure to AFO emissions.

Keywords

air pollution; agriculture; animal feeding operations; industrial food production; dairy farms; pediatric asthma

INTRODUCTION

The rise of industrial-scale agriculture in the United States threatens environmental quality in a number of ways, including pollution of regional airsheds (Aneja et al., 2009). Large-scale facilities where livestock and poultry are raised for food production, called animal feeding operations (AFOs)[1], emit numerous biological and chemical pollutants to the surrounding atmosphere. Previous studies have documented elevated concentrations of hydrogen sulfide (Feilberg et al., 2017 Pavilonis et al., 2013; Thorne et al., 2009;), ammonia (Donham et al., 2006; Schulze et al., 2011; Williams et al., 2009), endotoxins (Dungan et al., 2012; Ko et al., 2010; Williams et al., 2016), bioaerosols (Thorne et al., 2009), odors (Thorne et al., 2009; Wing et al., 2008), and total dust (Purdy et al., 2009; Williams et al., 2009) in the vicinity of AFOs. Many components of AFO emissions are toxic to the respiratory system (Heederik et al., 2007; May et al., 2012). Increased risks of respiratory diseases for AFO workers are well-documented (Arteaga et al., 2015; Donham et al., 1993; Douglas et al., 2018; Reynolds et al., 2013;Von Essen et al., 2010); in contrast, impacts on community health are less certain. Previous epidemiologic studies have described associations between community-level AFO exposures and health effects (Hooiveld et al., 2016; Horton et al., 2009; Kalkowska et al., 2018; Loftus et al., 2015a; Merchant et al., 2015; Mirabelli et al., 2006; Pavilonis et al., 2013; Radon et al., 2007; Rasmussen et al., 2017; Schinasi et al., 2011; Schulze et al. 2011; Sigurdarson et al., 2006; Wing et al., 2013), but most were cross-sectional in design and dependent on time-invariant exposure estimates such as distance to nearest AFO (Kalkowska et al., 2018; Merchant et al., 2015; Mirabelli et al., 2006; Schinasi et al., 2011), count of AFOs within a certain distance (Hooiveld et al., 2016; Pavilonis et al., 2013; Radon et al., 2007) or modeled ambient concentrations of an AFO-related pollutant (Sigurdarson et al., 2006).

[1]**Abbreviations and definitions:** AFARE – Aggravating Factors of Asthma in a Rural Environment; AFO – animal feeding operation; ATS – American Thoracic Society; BMI – body mass index; CI – confidence interval; DNMP – Dairy Nutrient Management Program; FEV_1–forced expiratory volume in 1 second; FEV_1% – forced expiratory volume in 1 second as a percentage of predicted value; GEE – generalized estimating equations; ICC – intraclass correlation coefficient; IQR – interquartile range; LMM – linear mixed models; LOD – limit of detection; LTE4 – leukotriene E4; NH3 – ammonia; PFM – peak flow meter; uLTE4 – urinary leukotriene E4; YVFWC – Yakima Valley Farmworkers Clinic

To date, a small number of longitudinal, repeated measures studies of health effects utilizing time-varying AFO exposures have been conducted (Horton et al., 2009; Loftus et al., 2015a; Schinasi et al., 2011; Wing et al., 2013). This study design, also referred to as a "panel study," is especially well-suited to assess time-varying exposures that result in short-term, reversible health effects. Since each participant is observed repeatedly during periods of varying exposure, within-participant associations between exposure and health can be analyzed and the influence of between-participant confounding is mitigated (Janes et al., 2008). Estimating individual, time-varying exposures in a panel study can be challenging. Personal exposure modeling is often prohibitively expensive and difficult, and there are limited options for estimating individual exposure to airborne emissions from point sources of pollution, like AFOs (Brender et al., 2011; Cordioli et al., 2013; Hoek et al., 2018; Pascal et al., 2013). Relying on simple distance to sources of air pollution as proxy of exposure can lead to substantial exposure measurement error (Hodgson et al., 2007; White et al., 2009).

We previously conducted pediatric asthma panel studies in the Aggravating Factors of Asthma in a Rural Environment (AFARE) study, a community-based participatory research project set in an agricultural region of Washington State. We found that lung function of children with asthma was poorer on days following higher concentrations of outdoor ammonia (Loftus et al., 2015a). Here, we extend this research by first developing and validating a measure of daily exposure to airborne AFO pollutants that accounts for distance to nearby AFOs, AFO size, and wind direction and speed. Secondly, we demonstrate use of this metric and repeat our previous panel study of AFO air pollution exposure and asthma morbidity with a substantially larger sample size. Finally, we evaluate whether modeled AFO emissions are associated with a biomarker of systemic inflammation, urinary leukotriene E4 (uLTE4), measured repeatedly in a subset of the AFARE cohort. uLTE4 is a measure of total body cysteinyl leukotrienes, key mediators in airway inflammation that may play an important role in inflammatory-mediated responses to environmental pollutants (Hoffman et al., 2018).

We hypothesized that children with asthma experience short-term increases in inflammation, more asthma symptoms and poorer lung function following days of elevated exposure to AFO air pollutants.

MATERIALS AND METHODS

The AFARE Study

AFARE was conducted within El Proyecto Bienestar, a community-based participatory research partnership between the University of Washington Pacific Northwest Center for Agricultural Safety and Health; the Yakima Valley Farm Worker Clinics (YVFWC), a network of federally-qualified health clinics serving migrant and seasonal farmworker families as well as other underserved populations in the region; and the Northwest Community Education Center, which provides support and education for the Latino community in the Yakima Valley. Details of AFARE have been described previously (Armstrong et al., 2013; Loftus et al., 2015a; Loftus et al., 2015b); this is a secondary analysis of previously-collected data that expands on previous work by incorporating analysis of a urinary biomarker, described below. The study was conducted from 2010 to

2013 in the Yakima Valley of Washington State, a region spanning from the city of Yakima in the northwest to Prosser in the southeast and roughly 42 miles in length from corner to corner. Approximately 70-80% of the region is used for agriculture, including a high density of animal feeding operations -- predominantly large dairies -- located in the southeastern half of the valley. In 2012 there were 65 dairies in the Lower Yakima Valley licensed through the Washington State Department of Agriculture, housing over 150,000 cows in total (WA State Dept of Agriculture, 2014).

As described previously, AFARE participant recruitment started in August 2010 and spanned one year. Families actively involved in the YVFWC Asthma Program were invited to enroll if children were of school age (6 to 16 years old), had no other serious illnesses and intended to stay in the region during the two-year duration of the study. All research was approved by the University of Washington Institutional Review Board, and consent or assent was obtained from all participants prior to participation. In total, 58 participants were enrolled and 9 (16%) dropped out prior to the end of AFARE data collection in October 2012. Data from participants who left the study were retained in analysis because the choice to end participation was unrelated to health or exposure status (e.g., moved out of region).

Asthma health assessment

Longitudinal asthma health assessments in the AFARE cohort are described in detail in previous papers (Loftus et al., 2015a and 2015b). See Figure 1 for a timeline of health and environmental data collection. Two methods were used to repeatedly assess participants' respiratory health across the study period: 1) biweekly phone surveys regarding child asthma symptoms and medication use and 2) daily home lung function tests.

Biweekly Asthma Symptom Surveys: Approximately every two weeks, phone interviews with either the child or an adult family member were conducted to assess the presence of recent asthma symptoms and medication use. Interviewees were asked five questions about asthma symptoms (shortness of breath, nighttime waking, limitation of activities, wheezing, and morning asthma symptoms) in reference to the week prior. A sixth question pertained to short-acting bronchodilator use over the past week, estimated as average number of "puffs" per day. Our survey is not validated but comprised of questions on asthma symptom occurrence and rescue medication use which are commonly assessed in combination or independently to determine asthma control in clinical practice and in research studies.

In analysis, we analyzed each symptom and medication use separately as a binary value: any reported experience of the symptom (or use of medication) use in the week prior versus no experience of symptom (or use of medication).

Daily home lung function tests: Each child was trained in proper use of a PikoNET PiKo-1 handheld peak flow meter (PFM) with digital memory (nSpire Health, Inc; Longmont, CO) according to American Thoracic Society (ATS) guidelines and instructed to use it every day prior to any short-acting bronchodilator medication. Stored data were downloaded by YVFWC staff at approximately six-week intervals. During a 12-month AFARE follow-up visit, clinical staff observed each child's technique and retrained

participants if necessary. The PFMs produced a value of FEV_1 with each blow, which was converted into the percent of predicted value (FEV_1%) based on standard reference equations (Hankinson et al., 1999). Values of FEV_1% that were implausibly high (above 150%) or low (below 30%) as well as measurements that were flagged by the device as potential errors were omitted from analysis. If multiple FEV_1 values were available on a given day, the highest FEV_1% was chosen to represent daily FEV_1%.

Urinary LTE4 measurements

In the final three months of the AFARE study, we collected urine samples from a subset of the cohort (n=16), chosen based on residential proximity to air monitors. They provided "spot" morning urine samples every six days over 14 weeks. Study field staff picked up the urine samples and kept the samples at 0 degrees C until return to the field office, after which samples were stored at −20 degrees C until time of analysis.

Quantitative analysis of uLTE4 was performed in the UW Department of Environmental and Occupational Health Studies Functional Genomic Lab. First urine samples were purified using Cayman's Cysteinyl Leukotriene Affinity Columns (Item No. 400068 for samples with low volume and Item No. 400069 for samples with higher volume) according to manufacturer's protocol. Then uLTE4 levels of the purified samples were quantified using Leukotriene E4 EIA kit (Cayman Item No. 520411) according to manufacturer's protocol.

Urinary creatinine was analyzed by a modified Jaffe procedure (Beckman Coulter AU System Creatinine [Beckman Coulter Inc.; Brea, CA]). All uLTE4 measurements were adjusted for creatinine and log transformed before statistical analyses.

Ammonia monitoring

Air monitoring was conducted during the second year of the AFARE study. We have described the design, deployment and performance of AFARE air sampling devices elsewhere (Armstrong et al., 2013). In brief, fourteen devices were placed outside the homes of a subset of the AFARE participants selected based on accessibility, security and overall spatial variability across the study region. Four monitors were moved to a new location during the air monitoring period because families changed residences (n=3) or the participant dropped out of the study (n=1), and one monitor was destroyed in a home fire three months prior to the end of the study. As a result, there were 18 monitoring sites during the course of the study. Every six days, devices actively sampled outdoor air for 24 hours using a silica bead sampling tube (SKC Inc; Eighty Four, PA), and flow rates were calibrated once a month. Sampling tubes were transported the University of Washington Environmental Health Laboratory at 0°C, where they were desorbed with deionized water and analyzed for ammonium using ion chromatography. Ammonia masses below the limit of detection (LOD) (either 1 or 0.5 μg, depending on the date of analysis) were replaced by LOD/2 for the calculation of concentration. In sensitivity analyses, we substituted $\mathrm{LOD}/\sqrt{2}$ for values below the LOD and repeated all analyses; all of the results were the same. Average ammonia concentration over the sampling period was calculated as the mass divided by total volume of air sampled over the period. A total of 814 ammonia concentrations were measured during the study period.

Calculation of daily plume exposure (E_{plume})

We developed an approach to estimating daily AFO airborne "plume" exposure at specific locations in the study region based on simple principles of atmospheric plume dispersion from point sources (Curtiss and Rabl, 1996). Four equations were used to calculate daily exposure to AFO plumes at participant locations (Table 1). The first two versions, $E_{plume,1}$ and $E_{plume,2}$, were time-invariant and were calculated based upon characteristics of regional AFOs. $E_{plume,1}$ was calculated using distance to regional AFOs alone, and $E_{plume,2}$ incorporated facility size, a proxy measure for number of animals, in addition to distance. $E_{plume,3}$ and $E_{plume,4}$ were time-dependent quantities calculated with daily resolution based on wind conditions measured at each AFO location during a 24-hour period: $E_{plume,3}$ included a term to account for changing hourly wind directions and the bearing from AFO to participant location, and $E_{plume,4}$ additionally included a term to account for wind speed during the hours when wind was blowing in the direction from AFO to participant location.

To estimate locations and sizes of all AFOs in the study region, we started with the WA State Department of Agriculture database of dairy operations registered through the Dairy Nutrient Management Program (DNMP) in 2012, because the majority of animal operations in the Yakima Valley are dairies. Then we inspected aerial photography images of the entire study region available online via Google Earth for characteristic features of AFOs such as large dirt areas containing cattle, feeding and milking shelters, and animal waste storage ponds. We confirmed or corrected the location of the dairy operations in the region registered with the DNMP (N=65) and, further, identified facilities not in the DNMP database (N=32). We estimated the area of each facility in units of m^2 and approximated the geographic location as the center of the facility. The distance and bearing (360°) from each AFO to every participant location were determined using the "geosphere" package in R (version 2.14.2, The R Foundation for Statistical Computing).

Hourly meteorological conditions (wind speed and direction) at each AFO on every day of the study were obtained from the Washington State University AgWeatherNet database (http://weather.wsu.edu/awn.php [Accessed June 21, 2014]), which maintains historical meteorology data for ten weather stations within the region. For each AFO, the nearest weather station was identified and used as the source of hourly wind measurements. The term in equations for $E_{plume,3}$ and $E_{plume,4}$ pertaining to wind direction, $f(t, s, a)$, was calculated as the proportion of hours when the wind was blowing from the AFO to the participant location based on an eight-point wind rose. Finally, the term describing daily wind speed in $E_{plume,4}$, $u(t, s, a)$, was calculated as the average wind speed only during the hours of the day in which the wind was blowing in the direction from the AFO to participant location. Hourly wind speeds lower than 0.5 m/s were considered to be "calm conditions" and replaced by 0.5 m/s (Hanna et al., 1982).

We utilized $E_{plume,4}$ as our primary exposure metric for all epidemiological analyses. We estimated exposures for each participant's home and school address, and accounted for exposure at both locations by applying simple assumptions about time-activity patterns. For weekends and days outside the regular school year, exposure was assigned based on home location. For weekdays during the school year, a time-weighted average of home- and

school-based values was calculated assuming seven hours spent at school and 17 hours at home.

Statistical analysis

All statistical analyses were performed using Stata 12.0 IC (StataCorp LP; College Station, TX) or R (version 2.14.2, The R Foundation for Statistical Computing). We performed descriptive analyses of all outcomes, exposures and covariates. Relationships between log-transformed ammonia concentrations and E_{plume} estimates were summarized using Pearson correlation coefficients (r). Univariate associations between participant-specific mean uLTE4 concentrations and child characteristics were compared using t-tests with unequal variances with the exception of child age of enrollment, which was compared to participant-specific mean uLTE4 by linear regression with robust standard errors.

Statistical methods for epidemiologic analysis varied by outcome. To models associations between AFO exposure and asthma symptoms and lung function (in separate models), we used linear regression with generalized estimating equations (GEE) and an exchangeable correlation matrix (Diggle et al., 2002). Reported asthma symptoms were based on surveys referring to the week prior to the interview; therefore, we calculated average AFO plume exposure across the seven days prior to the interview date for the primary exposure in analyses of these outcomes. For analyses of daily lung function (FEV_1%), we investigated lagged daily exposures ranging from 0 (same day) to 5 days prior to lung function measurement. Covariates included as potential confounders in analyses of asthma symptoms and lung function were selected *a priori* based on existing scientific evidence of relationships with respiratory health and/or exposure. Our final model included several time-varying factors: temperature, relative humidity (both as cubic splines), elapsed week of study, and seasonality (calendar month). We additionally controlled for participant-specific characteristics likely associated with asthma morbidity: sex, age, atopy, use of inhaled corticosteroids at baseline, BMI at baseline and presence of adult smoker in household.

We also measured associations between estimated AFO exposure and uLTE4. We investigated lagged daily exposure to estimated AFO air pollution ranging from 0 (same day) to 4 days prior to the day of urine collection. We used linear mixed models (LMM) instead of GEE for these analyses because GEE performs best with larger numbers of clusters, and there were only 14 participants in the LTE4 substudy. In addition, we also selected covariates differently due to a much smaller sample size available for LTE4 analyses. For a more parsimonious model, we only included participant characteristics associated with uLTE4 in univariate analyses: child age, use of inhaled corticosteroids at baseline, and atopy status.

In all epidemiologic models, the mean outcome was modeled to be linear in response to the primary exposure of interest, and we present results as effect sizes per interquartile range (IQR) increase in exposure.

RESULTS

Study population and setting

AFARE children ranged in age from 6 to 16 years old at the time of enrollment and were split evenly by gender (Table 2). The majority of participants self-identified as Latino/Hispanic in ethnicity, and half reported that one or more parents were employed in farm work. 24 (41%) children were from families with an annual household income of $15,000 or less. Two thirds (n=38) had been hospitalized for asthma at one point in their lives, and 46 (n=79%) had visited an urgent care clinic or the emergency department for asthma in the 12 months prior to enrollment. The majority of children were taking daily maintenance medications (i.e., “controller” medications) for asthma at baseline, of which the most common was inhaled corticosteroids. 42 (71%) tested positive to at least one aeroallergen in skin prick testing, and 8 (14%) lived with at least one adult smoker. The N=16 children who participated in the urinary LTE4 sub-study were representative of the full cohort (Table 2).

In the AFARE study region there were N=65 dairy operations licensed by the Washington DNMP in 2012, N=5 of which (7.7%) were classified as small, with up to 199 mature animals each; N=16 (25%) as medium, with 200-699 animals; and N=44 (68%) as large, with over 700 animals. Our review of aerial images of the region identified an additional N=32 potential animal facilities. The N=97 total facilities in the region ranged in size from 6500 to 900,000 m^2 in estimated surface area (mean=190,000 m^2).

Longitudinal asthma health

N=2,023 biweekly interviews were conducted over 26 months; the respondent was the child in 35% of the interviews and a parent in 65%. Participant-specific frequencies of report for each symptom were calculated and then averaged to give a mean and standard deviation across the population. Woken by asthma was reported most frequently and shortness of breath was the least frequent symptom, on average (mean of 45% and 19% of surveys, across participants; Table 3). N=3852 lung function measurements were collected, and the participant-average FEV_1 as percent of predicted (FEV_1%) averaged 75% (s.d. = 15%). FEV_1 increased for the cohort across the study period, at an average rate of 0.26 L per year. Participants’ PFM data completeness rates (i.e., percent of days with at least one PFM measurement) ranged from 12 to 80% (mean = 35%). We assessed patterns in PFM missingness and detected no statistically significant relationships between participant-specific completeness rates and symptom reports, average FEV_1%, atopy status, or use of inhaled corticosteroids at baseline. We also found no evidence that the odds of FEV_1 missingness on a specific day of the study was related to average lung function during the same time period (week average FEV_1%). In our previous analyses of lung function data, we imputed missing values and observed no differences in results when analyses were conducted in multiple imputed datasets (Loftus et al., 2015a and 2015b); for the current analysis, we conducted complete case analysis.

Urinary LTE4

Children who participated in the LTE4 substudy (n=16) contributed an average of 9 urine samples each (range = 1 to 15). A total of 138 samples were analyzed for LTE4. The

geometric mean (geometric standard deviation) of creatinine-adjusted uLTE4 concentration was 85 (1.9) pg/mg creatinine. We observed substantial within-participant temporal variability in uLTE4 (Figure A.1). The intraclass correlation coefficient (ICC) of log (adjusted uLTE4) was 0.34, indicating that within participant variability was greater than between participant variability.

In univariate analyses of participant-averaged uLTE4 measurements, uLTE4 was higher for children with atopic asthma ($p = 0.09$) and for children taking inhaled corticosteroids at baseline ($p = 0.028$; Figure 2). Boys had higher uLTE4 than girls, but the difference was small and imprecise. uLTE4 was significantly lower with older age; log (adjusted uTLE4) averaged 0.12 points lower (95% CI: 0.05, 0.19) per each year older.

Estimated AFO air pollution exposure and comparison to outdoor ammonia

All four metrics of plume exposure were moderately-to-highly correlated with directly measured outdoor ammonia concentrations across the region (Figure 3). Ammonia concentrations estimated from ammonia mass below the laboratory LOD are more uncertain than those calculated from higher ammonia masses; these two categories of ammonia concentrations are distinguished in the plots. In general, weaker relationships between ammonia and estimated AFO exposure were observed when ammonia mass was below the LOD. Both time-invariant estimates of exposure ($E_{plume,1}$ and $E_{plume,2}$) displayed a moderate degree of positive correlation with measured ammonia concentrations ($r=0.54$ in both cases).

Adding a variable reflecting wind direction (i.e., the difference between $E_{plume,2}$ and $E_{plume,3}$) increases the correlation to 0.61. That is, accounting for wind direction increased the model R^2 from 0.29 to 0.37, indicating that the wind direction term alone accounts for 8% of the variability in daily ammonia at monitoring sites. Addition of the wind speed term with $E_{plume,4}$ increased correlation from 0.61 to 0.62 (an increase in R^2 from 0.37 to 0.38), a very minor improvement. We examined site-specific relationships between ammonia and $E_{plume,4}$ and observed a consistently positive relationship at all 14 sites (Figure A.2).

Associations between AFO air pollution and asthma health

Analysis of daily FEV_1% and estimated AFO air pollution exposure on various lag days indicated that decrements in lung function occurred following elevated exposures to AFO plumes (Figure 4). Statistically significant decrements were observed one day after exposure: −2.0% (95%CI: −3.5, −0.5) per IQR increase in predicted exposure, while associations with other lag days were smaller in magnitude and null. We observed no associations between reported asthma symptom and medication use and average AFO pollution exposure in the week prior (Table 4).

Associations between AFO air pollution and urinary LTE4

Higher uLTE4 concentrations occurred on days of higher estimated AFO plume exposure, both for the subcohort overall (N=16 children; 134 urine analyses) as well as for most individual participants (Figure 5). In multivariable regression, we found a marginally

significant elevation of uLTE4 associated with same day exposure and nonsignificant elevations of uLTE4 on one or more days after exposure assessment (Table 5).

DISCUSSION

We developed an easy-to-implement approach for modeling spatiotemporal variations in exposure to airborne emissions from AFOs and validated the model against measurements of outdoor ammonia, a chemical marker of AFO-related air pollution, monitored at several sites across the study region over a year (N=814 measurements). This method was then applied to estimate personal daily exposures for a panel study of lung function, asthma symptoms and biological markers of inflammation in children with asthma residing near AFOs. We found that children's lung function was lower in the days following increased exposure to AFO emissions. Note that the effect size was small in magnitude. For comparison, the standard deviation in participant-averaged FEV_1 in this study was 15%, and the ATS classifies a 20% change of FEV_1 as being a mild exacerbation (Reddel et al., 2009). A study of children with asthma in urban Windsor observed a more modest effect size of approximately 0.5% reduction in predicted FEV_1 per interquartile increase in PM2.5 (6 mcg/m3). However, as noted in that study, such modest effects may have public health importance as these ambient exposures are experienced by children across the community. The 2% in FEV_1% associated with an IQR increase in plume exposure we observed is the average difference across the entire cohort and all occurrences of exposure; the decrease in FEV_1 for a specific child on a given day of exposure could be much larger in magnitude. Because child living in close proximity to AFOs may be repeatedly exposed to elevated emissions over time, the impact on asthma health could be substantial.

In general, our findings of increased respiratory morbidity associated with AFO air exposures were in line with findings from our previous, smaller study of lung function and monitored ammonia (Loftus et al., 2015a), as well as those of other recent studies of pediatric asthma in communities impacted by AFO-related pollution (Merchant et al., 2015; Mirabelli et al., 2006; Pavilonis et al., 2013; Radon et al., 2007; Rasmussen et al., 2017). Our finding that systemic inflammation may increase following higher exposures to AFO air pollution are novel, and further strengthens the hypothesis that these exposures contribute to community asthma morbidity. We were not able to conduct statistical tests of mediation or to assess whether uLTE4 predicts asthma symptoms or poorer lung function, however, because timing of biomarker and asthma outcome data did not align well enough.

One contribution of the current work is the development and validation of a simple, time-varying metric of air emissions from point sources for use in epidemiological investigations of short-term health effects. Epidemiological studies of community exposures to air pollution from industrial point sources typically utilize distance to source or number of sources within a circular buffer to estimate exposure (De Sario et al., 2018; Hoek et al. 2018; Pascal et al., 2013). The exposure measurement error introduced by assuming that exposure depends only on distance can bias epidemiological associations. A number of health effects studies have accounted for meteorological factors that affect environmental transport of pollutants emanating from point sources like waste incinerators, refineries, and other industrial facilities (Coudon et al., 2019; Ghannam et al., 2013; Hoek et al., 2018; Micheli et

al., 2014; White et al., 2009; Yu et al., 2005); some have utilized sophisticated dispersion models that additionally incorporate stack height, variations in emissions rate, chemical transformations, and other determinants of pollutant concentration (Ghannam et al., 2013). Most of these modeled long-term exposure and evaluated associations with cancer, birth outcomes and chronic conditions (Brender et al., 2011; Coudon et al., 2019; Coudon et al., 2018; Micheli et al., 2014; Yu et al., 2005;). Few studies of asthma exacerbations or morbidity have utilized time-varying individual exposure to point-source air pollution in a panel or case-crossover study (Lewin et al., 2013; Loyo-Berrios et al., 2007; Smargiassi et al., 2009).

We conducted our modeling approach in stages to evaluate the relative contributions of components of the model. The simplest metric of plume exposure ($E_{plume,1}$), which was calculated solely upon distances to regional AFOs, had a moderate degree of correlation with daily ammonia concentrations (r=0.54). The addition of facility size ($E_{plume,2}$) did not improve correlation with ammonia by a meaningful amount, indicating that the surface area of AFOs in this region might not be an accurate proxy for number of animals, an important determinant of ammonia emissions (Hristov et al., 2011). To address temporal variations in AFO exposure, we incorporated daily wind direction and wind speed. With $E_{plume,3}$ we accounted for changing wind directions at AFO locations; this addition explained an additional 8% of the daily variation in ammonia beyond that of the two simpler, time-invariant metrics of plume exposure. For $E_{plume,4}$ an additional term in the denominator was included to attenuate the estimated exposure with increased wind speeds, because pollutants in plumes should become more dispersed at increased wind speed (Hanna et al., 1982). Counter to our expectations, correlation with $E_{plume,4}$ was not better than with $E_{plume,3}$, reflecting possible increased volatilization rates of ammonia with wind speed (Moore et al., 2014). The relationship between ambient ammonia concentrations and wind speed may be nonmonotonic if faster winds increase the amount of ammonia emitted from an AFO but also decrease the resultant downwind concentrations by dilution. One investigation of swine AFO odor in residential communities found that odor intensity increased at both low speeds and high speeds relative to moderate wind speeds (Wing et al., 2008), implying a nonlinear relationship between wind speed and AFO exposures.

Our findings in this study were similar to those of our earlier smaller longitudinal study of childhood and ambient ammonia (Loftus et al., 2015a). This is not surprising because ammonia is a component of the complex mixture of air pollutants comprising AFO air emissions. From this analysis we are unable to determine whether observed associations with health are due to any specific component of AFO air pollution or a combination of one or more contaminants, many of which have been associated with respiratory effects. The current analysis expands upon the previous one by employing a substantially larger sample size and by focusing on exposure to AFO plumes as a mixture of potential toxicants rather than on a single chemical component. We also report suggestive evidence that increased exposure to AFO air pollution leads to short-term increases uLTE4, a biomarker of short-term immunological changes that increases with asthma exacerbations (Hoffman et al., 2018; Rabinovitch et al., 2012). Urinary LTE_4 is an emerging biomarker of asthma severity and exacerbation, and has been recommended for research on short term asthma morbidity (Hoffman et al., 2018; Rabinovitch et al., 2012). In a separate analysis of the AFARE cohort,

higher LTE4 levels occurred with concurrent elevations in criteria pollutants and pesticides (Benda-Coker et al., 2019). Our current findings provide further evidence of the utility of LTE4 as a sensitive biomarker of asthma morbidity associated with environmental exposures.

Strengths of our study include the panel study design, which mitigates between-participant confounding by leveraging within-participant contrasts in exposure and outcome over time. Another important strength is that we validated our modeled AFO plume exposures with comparisons to ambient concentrations of ammonia, a component of AFO plumes, measured repeatedly at 18 sites across the region. We accounted for exposure at both home and school by modeling exposure at both locations for each child and time-averaging based on school schedules.

There are methodological limitations that should be considered when interpreting our results. The approach to modeling AFO pollution was informed by principles of pollutant dispersion from a point source, but AFOs are area sources rather than true point sources. Violations of this assumption would affect exposure estimates at locations closest to AFOs (Hanna et al., 1982). Another potential limitation is that our calculations of E_{plume} assumed constant pollutant emission rates from each AFO. This is a reasonable assumption considering that most toxic components of AFO plumes are emitted by animal waste, and animals produce waste daily. However, our exposure estimates do not account for the fact that emission rates from individual AFOs can differ substantially by facility-specific characteristics, such as the type and age of animals confined, manure treatment practices, duration of manure storage in waste lagoons, and protein content of animal feed (Hristov et al., 2011). Also, our time-varying exposure estimates did not account for applications of manure slurry or fertilizer to nearby fields, an event likely to significantly increase local concentrations of ammonia, hydrogen sulfide, and other pollutants (Bussink et al., 1998). Our plume modeling did not include occurrence of inversions or other meteorological events that could substantially affect spatial dispersion of AFO emissions, nor did we factor in local topography or nearby buildings. The study region is relatively flat, so regional topography may have had minimal influence on short-range pollutant dispersion, though the mountains that bound the valley could impact long-range dispersion. Further limitations in exposure assessment include crude and unvalidated assumptions about time spent at home versus school in order to calculate time-weighted exposure estimates. In addition, we cannot rule out the possibility that avoidance of intense AFO malodors affected children's behavior and, in turn, outdoor exposures to AFO plumes.

Limitations specific to our epidemiologic analyses include possible outcome misclassification and measurement error. Both reported asthma symptoms and home lung function tests can be inaccurate in pediatric populations (Fritz et al., 1996; Redline et al., 1996). Asthma symptoms were reported by child or parents, and misclassification could vary by reporter. We did not account for time of day of home lung function tests, though diurnal patterns could affect this outcome. Quantification of uLTE4 by immunoassay may overestimate LTE4 concentrations compared to other methods (Armstrong et al., 2009). However, because results of a panel study are driven by within-participant contrasts in exposures, biases due to systematic errors in outcome assessment would be reduced in

comparison to a cross-sectional design. Additionally, children were asked to use peak flow meters on a daily basis, but we had missing FEV_1 data due to imperfect compliance and data loss. As described in our previous analyses of lung function measurements collected in AFARE (Loftus et al., 2015a and 2015b), we assessed likelihood of FEV_1 missingness in association with participant characteristics and did not see evidence of differential missingness; further, re-analysis with multiple imputation of FEV_1 values did not affect results. Because we previously detected no evidence of differential missingness and results were very similar to complete case analyses, we did not conduct multiple imputation for the current work. Finally, it should be noted that despite the large number of repeated measurements collected, the number of children in our cohort was rather small, which may limit generalizability of results to other pediatric populations.

Our findings add to accumulating evidence that exposure to AFO air emissions causes adverse short-term health effects in children with asthma residing nearby (Loftus et al., 2015a; Merchant et al., 2015; Mirabelli et al., 2006; Pavilonis et al., 2013; Radon et al., 2007; Rasmussen et al., 2017) and, further, suggest that health effects may be mediated by increases in inflammation. Emissions from AFOs are a complex mixture of numerous potential respiratory system toxicants. Based on our data collection we cannot identify the toxic agents responsible for adverse effects. AFO emissions are a complex mixture of contaminants with potential respiratory effects, all highly correlated in the exposure scenarios in this study. Ammonia is a respiratory system irritant but evidence linking environmental exposures to asthma exacerbations is scarce; it may serve as a proxy for correlated, established respiratory toxicants, including particulate matter, endotoxins, and hydrogen sulfide. A careful study of emission source contributions would be needed to understand how to mitigate the health effects, if they were confirmed; for example, regulations related to manure management and spraying could reduce community exposures. This research topic is important because pediatric asthma poses a significant public health burden for rural communities in the United States. Families in rural areas tend to be lower in socioeconomic status and have more limited access to quality health care compared to urban and suburban counterparts, increasing risk of respiratory morbidity for children with asthma (Ownby, 2005; Perry et al., 2008; Ungar et al., 2011). Furthermore, environmental pollution associated with industrial agricultural disproportionately impacts lower income and minority populations in the United States (Wing et al., 2000).

CONCLUSIONS

We developed a method for estimating daily exposure to AFO and validated estimates with direct measurements of ammonia, a chemical marker of AFO emissions. We utilized this metric in epidemiologic analyses of short-term changes in asthma outcomes in children with asthma; the results strengthen existing evidence that one or more pollutants emitted by AFOs may compromise community health. These findings motivate further work to identify the most toxic agents in AFO emissions and identify strategies for minimizing exposure, especially for children with asthma and other sensitive individuals.

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APPENDIX A

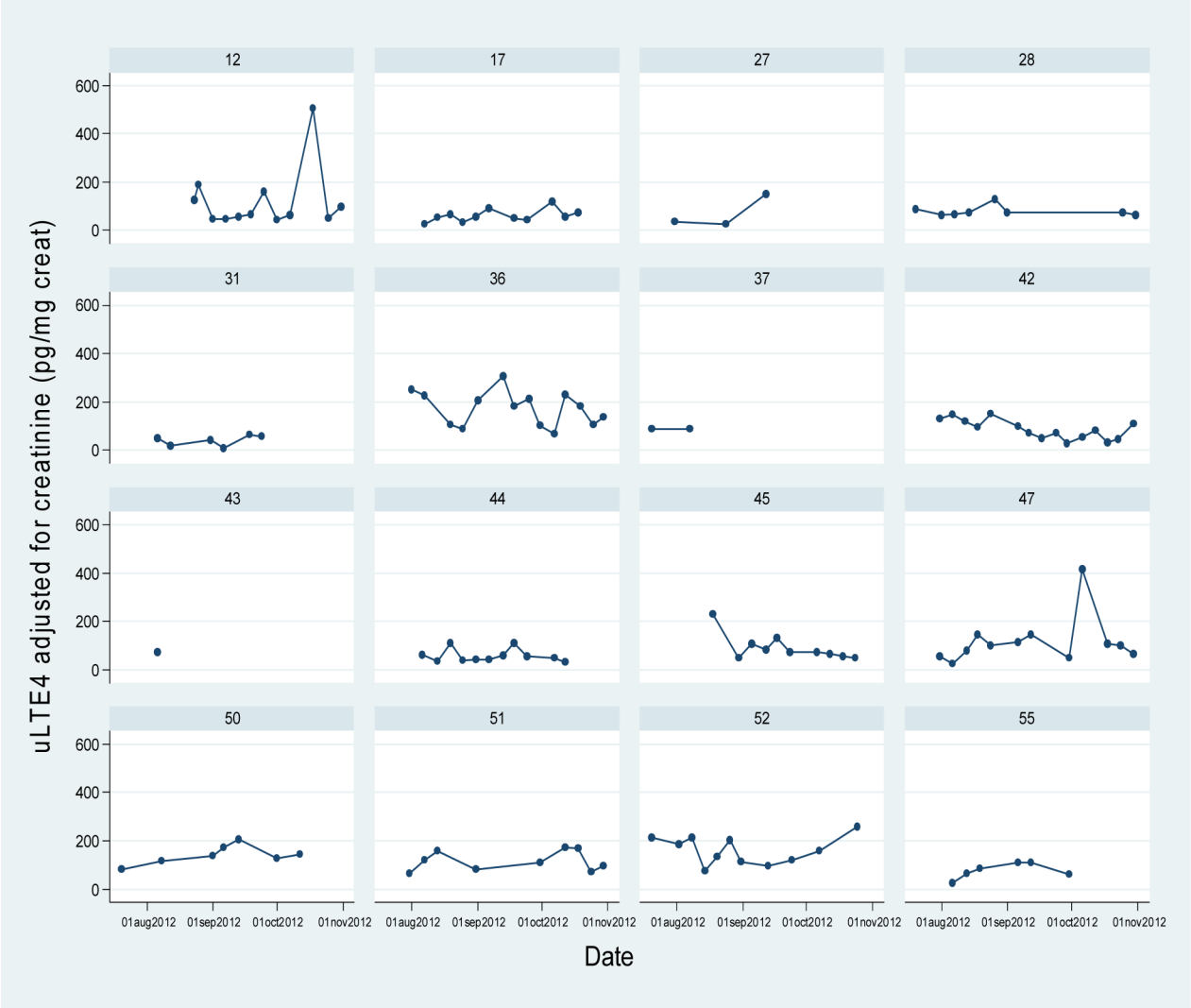

Figure A.1: Repeated measures of urinary LTE4 concentrations for AFARE participants.
Time series plots of uLTE4 (N=16) for all children participating in the LTE4 substudy. uLTE4 concentrations were adjusted for creatinine and log transformed.

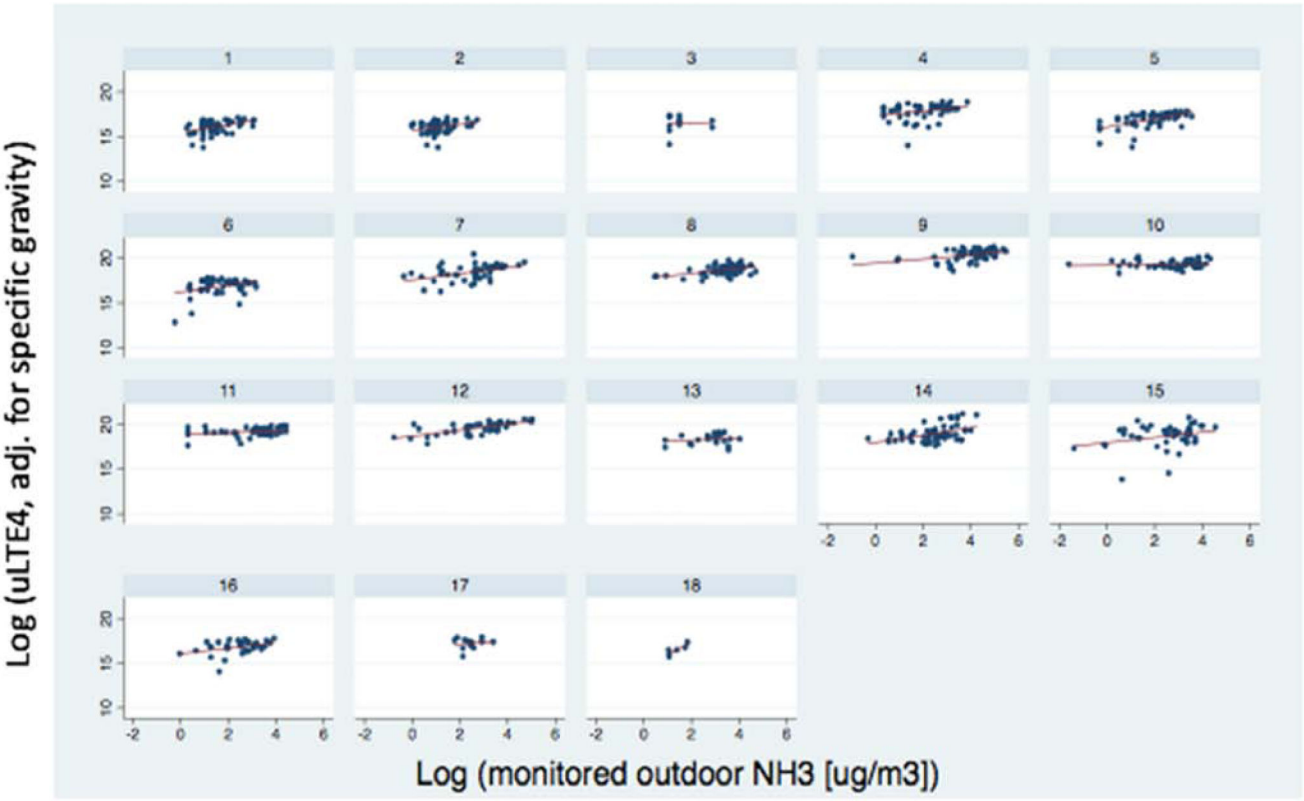

Figure A.2: Site-specific comparisons between outdoor ammonia and estimated ARO-related air pollution exposure.

Outdoor ammonia was measured at 18 sites at six-day intervals over a year (N=834).

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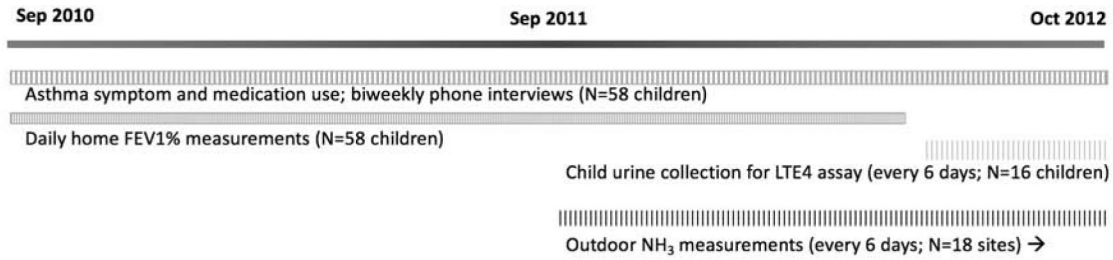

Figure 1: Timeline of health and exposure data collection.

Repeated collection of longitudinal health and exposure data across the span of the AFARE study.

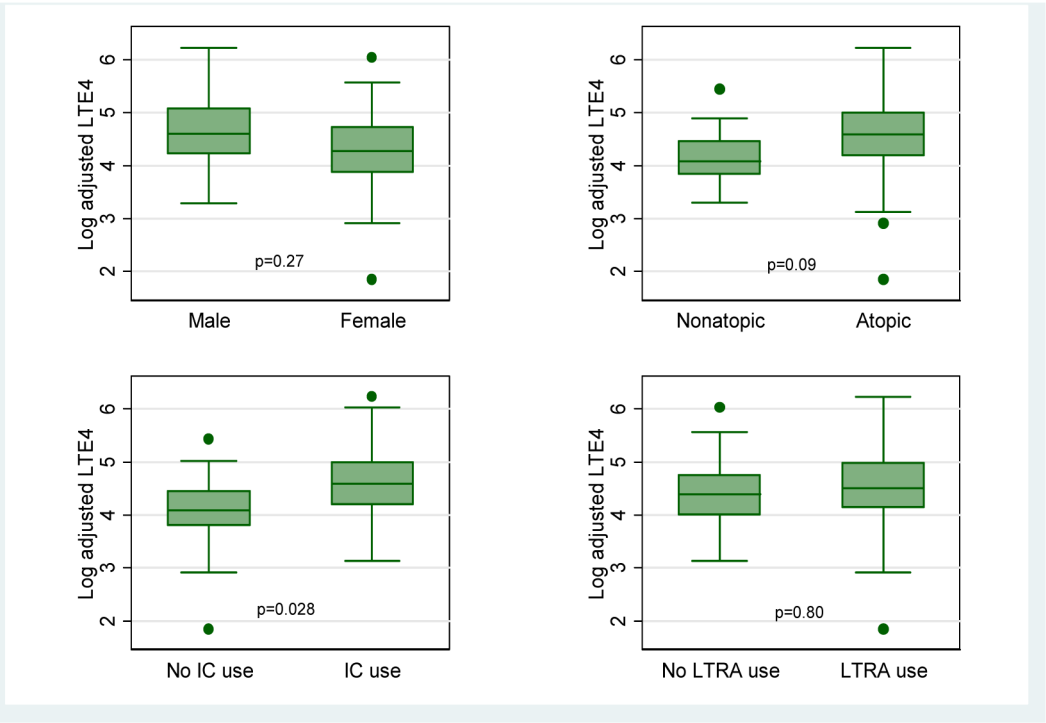

Figure 2: Univariate associations between subject-mean urinary LTE4 and child characteristics.

Average subject-specific mean uLTE4 (N=16) was compared to child characteristics using t-tests with unequal variances. uLTE4 concentrations were adjusted for creatinine and log transformed. Abbreviations: IC = inhaled corticosteroid use reported at baseline; LTRA = leukotriene receptor agonist use reported at baseline; LTE4 = leukotriene E4

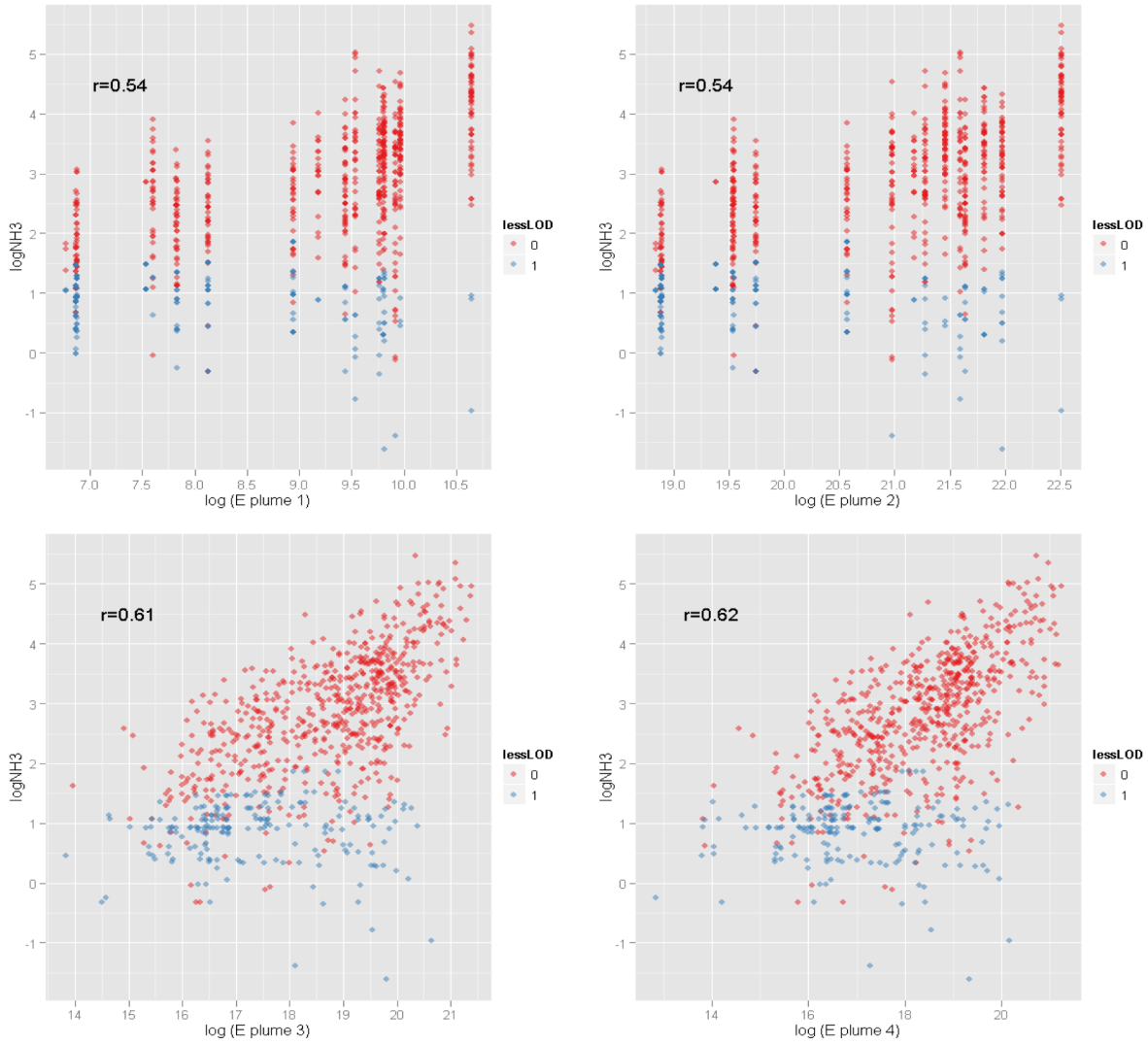

Figure 3: Comparison between outdoor ammonia and estimated ARO-related air pollution exposure at AFARE monitoring sites.

Outdoor ammonia was measured at 18 sites at six-day intervals over a year (N=834). Concentrations estimated from an ammonia mass below the LOD are highlighted in blue.

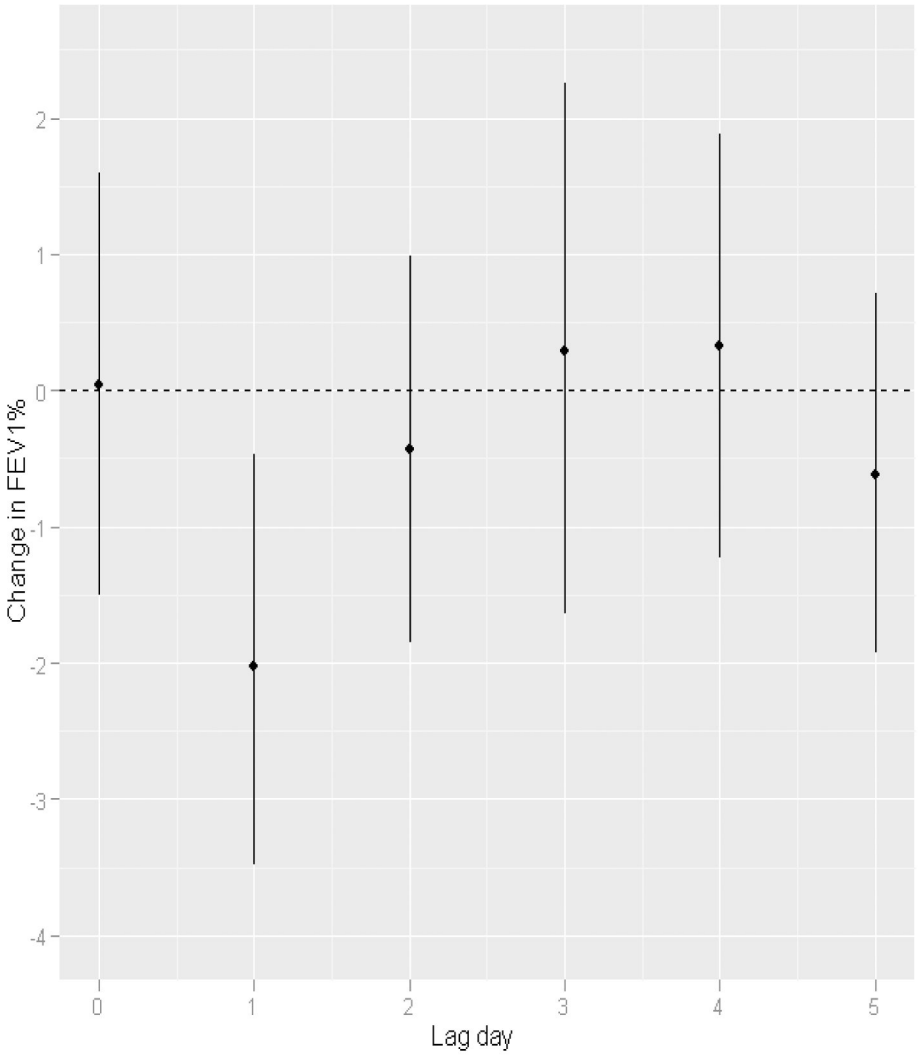

Figure 4: Associations between estimated daily AFO exposure and child lung function (FEV1, % predicted).

Associations between AFO exposure and daily lung function (FEV1, % predicted; N=3853 measurements) were estimated using generalized estimating equations, with adjustment for time-varying factors, each modeled using cubic splines (temperature, relative humidity, elapsed week of study, and seasonality (calendar month)) as well as subject-specific characteristics (sex, age, atopy, use of inhaled corticosteroids at baseline, BMI at baseline and presence of adult smoker in household.) Effect sizes are scaled to an IQR increase in AFO exposure, estimated using E plume 4.

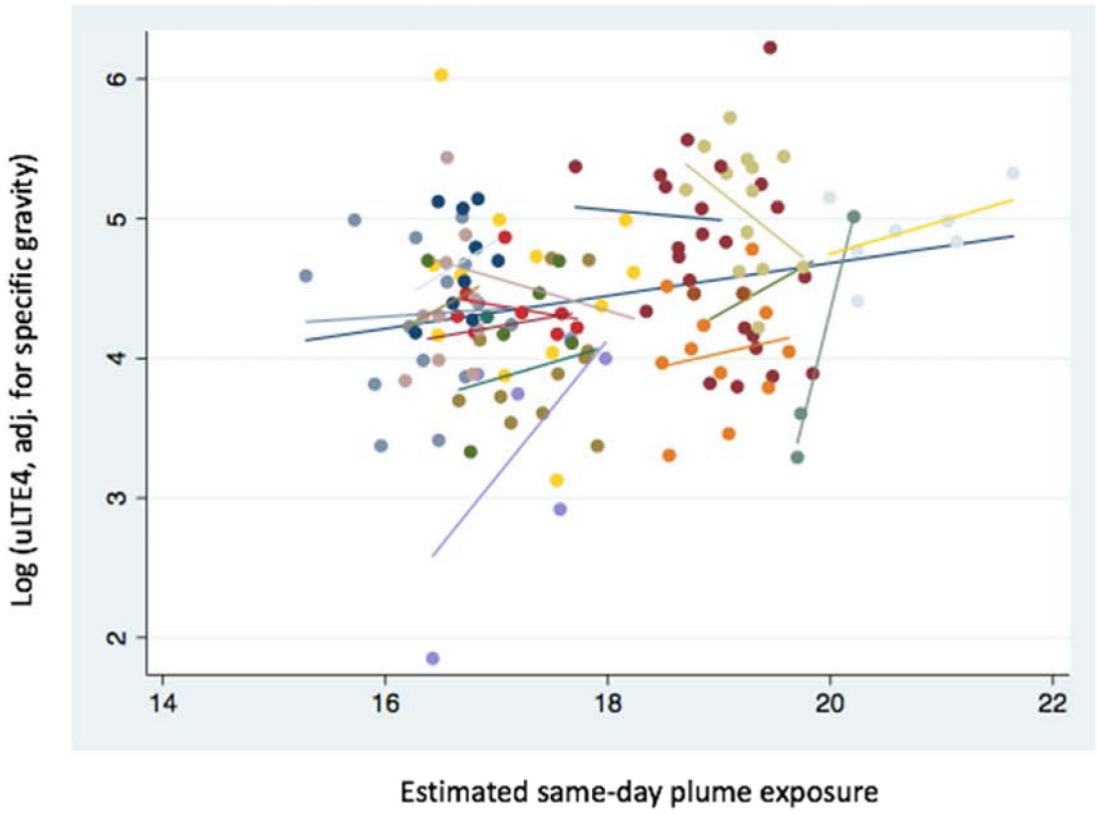

Figure 5: Urinary LTE4 and estimated AFO pollution exposure on the same day.

Participant urinary LTE4 (adjusted for creatinine and log-transformed) and estimated AFO plume exposure on the same day is plotted. Shorter lines show subject-specific slopes and the longer line shows the trend for the entire sample.

Table 1:

Metrics to estimate daily AFO plume exposure

E_{plume}	Formula	Description
1	$E_{plume,1}(s,a) = log\sum_{a=1}^{97} \frac{1}{d_{a,s}^2}$	Exposure depends on proximity to AFOs alone (time invariant)
2	$E_{plume,2}(s,a) = log\sum_{a=1}^{97} \frac{A_a}{d_{a,s}^2}$	Exposure depends on proximity to AFOs and estimated size of facility (time invariant)
3	$E_{plume,3}(t,s,a) = log\sum_{a=1}^{97} \frac{A_a f(t,s,a)}{d_{a,s}^2}$	Exposure depends on distance, size and the percent of time on that day when wind was blowing towards subject location (time varying)
4	$E_{plume,4}(t,s,a) = log\sum_{a=1}^{97} \frac{A_a f(t,s,a)}{d_{a,s}^2 * u(t,s,a)}$	Same as (3) but with an additional term in denominator for average wind speed (time varying)

Abbreviations:

s = subject location (home or school)

a = animal operation (AFO)

t = day of study

A_a = estimated size of AFO facility (in m^2)

$d_{a,s}$ = AFO to subject distance

f (t, s, a) = fraction of hours in day when wind is blowing from AFO to home on 8-point wind rose

u (t, s, a) = average wind speed during the hours when wind is blowing from AFO to home

Table 2:

Characteristics of participants in analytic sample

	All participants (N=58) N (%) or mean +/− s.d.	LTE4 substudy (N=16) N (%) or mean +/− s.d.
Child demographics		
Female	29 (50%)	7 (44%)
Age at baseline (years)	10.4 +/− 2.7	9.7 +/− 2.5
Born outside US	10 (17%)	4 (25%)
Hispanic/Latino ethnicity	54 (93%)	15 (94%)
Household characteristics		
Household income <$15k/year	24 (41%)	8 (50%)
Parent(s) employed as farmworker	29 (50%)	9 (56%)
At least one adult smoker in household	8 (14%)	0 (0%)
Baseline asthma health		
Reported controller medication use		
Inhaled corticosteroids (IC)	41 (71%)	11 (69%)
Leukotriene antagonist (LTRA)	17 (29%)	6 (38%)
Both IC and LTRA	14 (24%)	5 (31%)
Ever hospitalized with asthma	38 (66%)	8 (50%)
Unscheduled visit for asthma in previous 12 months	46 (79%)	14 (88%)
Atopic asthma[a]	42 (71%)	12 (75%)

Abbreviations: s.d., standard deviation; US, United States; ED, emergency department; BMI, body mass index; IC, inhaled corticosteroids; LTRA, leukotriene antagonist.

[a]Indicated by positive skin prick test to at least one of 22 common inhalant allergens.

Table 3:

Summary of participant-specific asthma outcomes[1]

	mean +/− s.d.
Percentage of interviews in which symptom reported in week prior	
Woken by asthma	45 +/− 25%
Limited in daily activities	35 +/− 23%
Shortness of breath	19 +/− 14%
Symptoms in morning	39 +/− 22%
Wheezing	25 +/− 19%
Percentage of interviews in which short-acting medication use reported in week prior	49 +/− 27%
Participant-average FEV_1%	75 +/− 15%

[1] For every outcome, an average value for each participant across all time points was determined. The average and s.d. across all participant-specific means are presented here.

Abbreviations: FEV_1%, forced expiratory volume in 1 second as a percent of predicted value; s.d., standard deviation

Table 4:

Associations between weekly AFO air pollution exposure and reported asthma symptoms and medication use.

Odds ratios for report vs. no report of symptoms or medication use on biweekly surveys (N=2023) were estimated using generalized estimating equations, with adjustment for time-varying factors, each modeled using cubic splines (temperature, relative humidity, elapsed week of study, and seasonality (calendar month)) as well as subject-specific characteristics (sex, age, atopy, use of inhaled corticosteroids at baseline, BMI at baseline and presence of adult smoker in household.) Odds ratios are scaled to an IQR increase in AFO exposure (1.89), estimated using E plume 4, averaged over the week prior.

Reported symptom or medication use in week prior	OR for report vs. no report of symptom	95% CI		p-value
Woken by asthma	0.90	0.75	1.08	0.27
Limited in daily activities	0.93	0.76	1.14	0.29
Shortness of breath	0.93	0.77	1.13	0.48
Symptoms in morning	0.93	0.79	1.12	0.45
Wheezing	0.90	0.75	1.08	0.27
Use of short-acting bronchodilator	1.00	0.78	1.13	0.49

Table 5:

Associations between AFO air pollution exposure at various lag days and urinary LTE4.

Average differences in uLTE4 were calculated for an IQR increase in AFO plume exposure on varying lag days using linear mixed models, adjusted for child age, atopy status, and reported inhaled corticosteroid use at baseline.

Exposure lag	Difference in log pLTE4 (ug/mg creatinine)	95% CI	p-value
0 (same day)	0.17	−0.01, 0.35	0.059
1	0.12	−0.02, 0.26	0.09
2	0.11	−0.07, 0.28	0.23
3	0.13	−0.04, 0.31	0.14