Ambient Ammonia Exposures in an Agricultural Community and Pediatric Asthma Morbidity

Christine Loftus,[a] *Michael Yost,*[b] *Paul Sampson,*[c] *Elizabeth Torres,*[d] *Griselda Arias,*[e] *Victoria Breckwich Vasquez,*[f] *Kris Hartin,*[b] *Jenna Armstrong,*[b] *Maria Tchong-French,*[b] *Sverre Vedal,*[b] *Parveen Bhatti,*[a] *and Catherine Karr*[a,b,g]

Background: Large-scale animal feeding operations compromise regional air quality in the rural US through emission of pollutants, such as ammonia gas. Exposure to airborne pollution from animal feeding operations may cause pediatric asthma exacerbations in surrounding communities.

Objectives: To describe spatial and temporal patterns in ambient ammonia concentrations in an agricultural region, and to investigate associations between short-term fluctuations in ammonia and subsequent changes in respiratory health in children with asthma.

Methods: For 13 months in the Yakima Valley of Washington State, 14 monitors sampled ammonia in outdoor air for 24-hour periods every 6 days. School-age children with asthma (n = 51) were followed for two health outcomes: biweekly reports of asthma symptoms and quick relief medication usage, and daily measurements of forced expiratory volume in 1 second. We assessed associations between each outcome and ammonia using generalized estimating equations.

Results: Twenty-four-hour ammonia concentrations varied from 0.2 to 238.1 μg/m^3 during the study period and displayed a strong correlation with proximity to animal feeding operations. The percentage of forced expiratory volume in 1 second was 3.8% lower (95% confidence interval = 0.2, 7.3) per interquartile increase in 1-day lagged ammonia concentration and 3.0% lower (95% confidence interval = 0.5, 5.8) for 2-day lagged concentration. We observed no associations between self-reported asthma symptoms or medication usage and estimated ammonia exposure.

Conclusions: Ammonia concentrations were elevated in this community and strongly predicted by proximity to animal feeding operations. Ammonia's association with acute lung function decrements in children with asthma in the surrounding community may be causal or, alternatively, ammonia may be a marker for other pollutants from animal feeding operations associated with respiratory effects.

(*Epidemiology* 2015;26: 794–801)

In recent decades, the industrialization of commercial agriculture has affected environmental quality in the rural US, in part due to the rise of large-scale facilities for confinement of livestock and poultry, termed animal feeding operations.[1] The largest such operations house over a hundred thousand animals in a relatively small area free of vegetation, and substantial amounts of animal manure are generated continuously on site. Liquid and solid animal wastes combine to form a slurry that is commonly stored at animal feeding operation sites in waste lagoons and may eventually be applied to adjacent growing fields as fertilizer. During manure storage as well as application to farmlands, a variety of chemical and biologic pollutants are released to the atmosphere, and resultant impacts on regional air quality have been observed.[1–5]

Several components of emissions from animal feeding operations may cause or exacerbate respiratory disease for nearby residents, including ammonia gas. Ammonia is water soluble and dissolves in the mucosa of the upper respiratory system upon inhalation, causing eye, nose, and throat irritation,[6] a suggested trigger for lower respiratory tract dysfunction, including bronchospasm.[7] In addition, ammonia may penetrate to the lower respiratory tract after absorption to particulate matter.[8] Animal studies show that ammonia causes epithelial damage and impairment of the lung's mucociliary clearance mechanism, potentially leading to increased susceptibility to inhaled particles and infectious organisms.[6] Elevated ambient ammonia can affect the health and well-being of nearby residents according to nontoxicological mechanisms as well. Ammonia has a strong, unpleasant odor that contributes to the overall malodor in vicinity of animal feeding operations, often intense enough to register community complaints.[9,10] Malodor can lead to feelings of unease, stress,

Submitted 30 May 2014; accepted 15 July 2015.

From the [a]Department of Epidemiology, University of Washington, Seattle, WA; [b]Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, WA; [c]Department of Statistics, College of Arts and Sciences, University of Washington, Seattle, WA; [d]Northwest Communities Education Center, Radio KDNA, Granger, WA; [e]Yakima Valley Farm Workers Clinic, Yakima, WA; [f]Pacific Northwest Agricultural Safety and Health Center, School of Public Health, University of Washington, Seattle, WA; and [g]Department of Pediatrics, School of Medicine, University of Washington, Seattle, WA.

The authors report no conflicts of interest.

Supported with Grant Number 5R21ES17906-2 from the National Institute of Environmental Health Sciences (NIEHS). C.L. was supported by training Grant Number HD052462-01 from the National Institutes of Health.

Correspondence: Catherine Karr, Department of Epidemiology, 4245 Roosevelt Way NE, Seattle, WA 98105. E-mail: ckarr@uw.edu.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 1044-3983/15/2606-0794
DOI: 10.1097/EDE.0000000000000368

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

and agitation in exposed individuals and may cause subsequent respiratory effects at concentrations below established toxicity thresholds.[11]

Previous epidemiologic investigations of community-level exposures to animal feeding operations and respiratory health are limited to cross-sectional studies,[12–17] with the exception of one longitudinal, repeated measures study of healthy adults living near swine feeding operations.[18,19] Although some cross-sectional studies have included pediatric subjects, none involved repeated measures of respiratory health for assessment of time-varying asthma health and none included direct measurements of ambient ammonia in the community.[12–14,17] Here, we describe results of a longitudinal study of pediatric asthma exacerbations using health and environmental data collected from the Aggravating Factors of Asthma in a Rural Environment (AFARE) project set in the Yakima Valley, an agricultural region of Washington State characterized by a high density of large dairy operations.

The primary objectives of our investigation were to describe spatial and temporal patterns in community-level ammonia concentrations in the Yakima Valley, and to estimate associations between time-varying ammonia concentrations outside subjects' homes and short-term fluctuations in asthma health, measured as daily lung function and biweekly reports of symptom and medication use. In all cases, our analyses are focused on ambient concentrations of a single contaminant, ammonia; however, any observed associations may be due to ammonia itself or to one or more components of animal feeding operation airborne emissions, for which ammonia is a marker.

METHODS

Study Setting

AFARE was conducted within El Proyecto Bienestar (EPB), a community-based participatory research partnership seeking to protect the health of agricultural workers and their families in the Yakima Valley. Project partners include the University of Washington Pacific Northwest Center for Agricultural Safety and Health; Yakima Valley Farm Workers Clinic (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 Communities Education Center, which includes Radio KDNA, a Spanish language public radio station that provides support and education for the Latino community in the Yakima Valley. There is a high density of large-scale agricultural operations in the region including many dairy feeding operations, largely concentrated in the southern half of the valley.

Study Subjects

Beginning in August 2010, AFARE subjects were recruited from the YVFWC Asthma Program.[20] Inclusion criteria included being of school age and having no serious illnesses other than asthma. A total of 59 children were enrolled in the AFARE study; however, for the analyses described here, we consider only the 51 children who participated for at least 3 months during the period of air monitoring (September 2011 to October 2012). At enrollment all subjects underwent skin prick testing to 22 common and locally relevant inhalant allergens to assess atopy (grass mix, Johnson grass, wheat, kochia, Russian thistle, cockroach, pigweed, mite mix, oak, cottonwood, alfalfa, cat, alder, sagebrush, horse, Western juniper, dog, mixed mold, mouse, Western ragweed, smut mix, and cow). Families also completed a health history survey to describe clinical features of past and present asthma health. Research activities were approved by the University of Washington Institutional Review Board, and informed consent was obtained from all children before participation. Research materials for all stages of the AFARE study, from recruitment through data collection, were available in both Spanish and English.

Identification of Animal Feeding Operations

We used the WA State Department of Agriculture database of dairy operations registered in 2012 through the Dairy Nutrient Management Program to identify animal feeding operations in the region. We systematically inspected aerial photography images of the entire study region available online via Google Maps and Google Earth for characteristics of animal feeding operations, such as large dirt areas containing cattle, feeding and milking shelters, and animal waste storage ponds to confirm—and when necessary, correct—the location of the 67 dairy operations registered with the Dairy Nutrient Management Program. We also identified additional nondairy operations, including heifer, beef, and poultry operations not included in the WA State Department of Agriculture database. The area of all land that appeared to be part of each operation was estimated in units of m^2 and the geographic location was approximated as the center of the facility.

Outcome Variables

Biweekly Asthma Symptom Survey

At approximately 2-week intervals, phone interviews with either the child or an adult family member were conducted. Interviewees were asked to recall the 1-week period before the interview date in their responses. The interview included five questions about asthma symptoms (nighttime waking, shortness of breath, limitation of activities, wheezing, and morning asthma symptoms). A sixth question ascertained short-acting bronchodilator frequency of use as average number of "puffs" per day.

Daily Home Lung Function Tests

At the time of enrollment, each child received a PikoNET PiKo-1 handheld peak flow meter with digital memory (nSpire Health, Inc; Longmont, CO) and was instructed in proper use of the device according to guidelines of the American Thoracic Society. Children were asked to use the peak flow meter

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

twice daily, in the morning and evening, every day of the study and to withhold use of short-acting bronchodilator medication in the period prior. At approximately 6-week intervals, a staff member from the YVFWC Asthma Program visited participants and uploaded peak flow meter measurements from the participant's device. During a 12-month AFARE follow-up visit with the research team at clinics and immediately before the start of ammonia monitoring, each subject's technique and ability to produce an error-free measurement was observed, and subjects were retrained in peak flow meter use if necessary. Forced expiratory volume in 1 second (FEV1) measurements from the peak flow meter were converted into percent of predicted values (FEV1%) based on standard reference equations.[21] Values of FEV1% 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. FEV1 measurements were not available for all subjects on every day enrolled in the study on account of several factors, including imperfect compliance as well as technical problems with the equipment used to upload peak flow meter data during home visits. To the best of our knowledge, loss of data in the field due to technical difficulties was completely random to health and exposure status of subjects.

Ammonia Measurements and Meteorology

We have described the design, deployment, and performance of the air sampling device previously.[22] Fourteen devices were placed outside the homes of a subset of the AFARE participants that were selected based on property accessibility and security as well as consideration of overall spatial variability across the study region. Four monitors were moved during the air monitoring period because study subjects changed residences (n = 3) or the family dropped out of the study (n = 1), and one monitor was destroyed in a home fire 3 months before the end of the study and was not replaced. The monitoring device was constructed to collect multiple air samples simultaneously for analysis of multiple contaminants for 24-hour periods at 6-day intervals, including ammonia, $PM_{2.5}$, total dust, and various pesticide compounds. Only ammonia concentrations are discussed in this report due to lack of sample analysis data for other contaminants. Devices actively sampled outdoor air for ammonia using a silica bead sampling tube (SKC Inc; Eighty Four, PA) with flow rates ranging from 0.10 to 0.32 L/minute according to the Occupational Safety and Health Administration method ID-188. Flow rates of sampling pumps were calibrated once a month and were adjusted to meet the intended flow rate range when necessary. Sampling tubes were transported to the University of Washington Environmental Health Laboratory at 0°C, where they were desorbed with deionized water and analyzed for ammonium ion using ion chromatography. Ammonia masses below the limit of detection (either 1 or 0.5 μg, depending on the date of analysis) were approximated as (limit of detection)/2.

Two local weather stations central to the study region provided data on 24-hour average temperature, relative humidity and precipitation (Washington State University AgWeatherNet stations at Toppenish and Snipes).

Statistical Analysis

We assessed relationships between ammonia concentrations and animal feeding operation (AFO) proximity using four metrics calculated relative to each monitor location: distance to nearest animal feeding operation, count of operations within a 5 km buffer, count of operations within a 10 km buffer, and a weighted sum of regional operations calculated according to Equation 1:

$$\text{AFO proximity} = \sum_{\text{All AFOs}} \frac{\log(\text{area})}{\text{distance}} \quad (1)$$

We calculated Pearson correlation coefficients (r) to assess pairwise correlations between each of the four estimates of animal feeding operation exposure and median ammonia measured at the 18 monitoring sites.

We modeled associations between time-varying ammonia exposure and each of the outcome measures separately using generalized estimating equations (GEEs) with an exchangeable correlation matrix.[23] For analyses of FEV1%, lagged relationships ranging from 0 (same day) to 5 days were investigated. We estimated ammonia exposure at homes without monitors using the ammonia concentrations measured at nearest neighbor monitors. In contrast, we did not attempt to extrapolate ammonia measurements to days without readings, because the temporal variability in measured ammonia did not appear to vary in a predictable manner. Instead, only the available ammonia measurements and FEV1 readings corresponding to specific lag relationships (i.e., same day, lag 1, lag 2, etc.) were analyzed even though this greatly reduced the amount of data available for analysis.

For the six outcomes derived from biweekly interviews about asthma symptoms and medication usage, responses to each of the six questions were dichotomized as no symptom/medication use versus any symptom/medication use reported. The odds ratio for report of each symptom or medication use was estimated using GEE in association with the weekly average ammonia concentrations. Weekly average ammonia concentrations were estimated by identifying all ammonia measurements made at the five nearest neighbor monitors for a subject's home between 8 days and 1 day before the interview date and averaging these measurements by the inverse square distance between home and monitor site. (Inverse distance weighting was not possible for FEV1 analysis because there was a 1 day difference in sampling dates for monitors in the northern vs. southern half of the study region.) In all epidemiologic models, the mean outcome was modeled to be linear in response to the primary exposure of interest, and we presented the final results as effect sizes per interquartile range increases. In sensitivity analysis, the main analyses were

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

repeated after restriction to children living within the median distance to the nearest air monitor (1.0 km).

Covariates included in models as potential confounders were selected a priori based on existing evidence of relationships between the covariate and both respiratory health and exposure: temperature and relative humidity (averaged over the week prior for outcomes related to reported asthma symptoms) as well as two variables related to temporal trends, days elapsed in study and seasonality, represented by cubic splines. Also included were subject-specific characteristics potentially associated with asthma: sex, age, atopy, use of inhaled corticosteroids at baseline, body mass index at baseline, and the presence of adult smoker in household.

Model diagnostics were performed to determine whether the central assumptions of GEE were violated. Specifically, plots of residuals versus the linear predictor were inspected, and the possibility of influential subjects was explored using the "leave one out" method. These analyses did not indicate the presence of any issues related to model assumptions. Analyses were repeated using linear mixed models, and in all cases produced similar results to those obtained with GEE.

All analyses were performed using Stata 12.0 IC (StataCorp LP; College Station, TX), with the exception of distance and nearest neighbor determinations, which were conducted using R (version 2.14.2, The R Foundation for Statistical Computing).

RESULTS

Cohort Characteristics

Of the 51 children enrolled in AFARE in the second year, many were from low-income families with one or more adults employed as a farm worker, and self-identified as Hispanic/Latino (Table 1). The average age at enrollment was 10.3 years. Most of the children were taking controller medications at the time of enrollment (i.e., inhaled corticosteroids and/or leukotriene antagonists), and 38 subjects (74%) were identified to be atopic on the basis of skin prick testing performed at baseline. Only seven children (14%) lived with at least one adult smoker. Based on a clinical exam performed at baseline, nearly half of the subjects (49%) were classified as overweight, defined as body mass index-for-age above the 85th percentile.

Longitudinal Health Data

In the period during which residential air monitors collected samples for ammonia analysis, subjects completed an average of 20 interviews each. Each individual symptom was reported to have occurred in fewer than 50% of the interviews. An average of 87 FEV1 measurements was collected for each child. The average completion rate, calculated from the number of days on which FEV1 readings were available relative to the period of study enrollment for each subject, was estimated to be 30%. This value does not reflect true compliance rates, however, as it was substantially reduced by time periods during which data was lost due to technical difficulties. We thoroughly explored whether the probability of missingness in a given week was associated with each subject's asthma health during a particular week or over the entire study period (assessed with results from symptom interviews), lung function before and following periods of missing data, and exposure status, and found no relationships (data not shown.)

FEV1 increased for the cohort across the study period on average, with the population-average lung function growth estimated to be 0.26 L per year (SD = 0.37 L). Across the overall study period, the average FEV1% was 81% (SD = 17%).

TABLE 1. Characteristics of AFARE Children (n = 51)

	N (%)
Demographics	
Female	25 (49%)
Household income ≤$15 k/year[a]	20 (39%)
Born outside US	10 (20%)
Hispanic/Latino ethnicity	47 (92%)
Parent(s) employed as farm worker	23 (45%)
Asthma and general health at baseline	
Medication use at baseline	
IC only	22 (43%)
LTRA only	2 (4%)
Both IC and LTRA	14 (27%)
Ever hospitalized with asthma	34 (67%)
Unscheduled visit for asthma to urgent care or ED in 12 months before enrollment	39 (76%)
Atopic[b]	38 (74%)
At least one adult smoker in household	7 (14%)
BMI for age >85th percentile	25 (49%)

[a]Two subjects did not respond.
[b]Indicated by positive skin prick test to at least one of 22 common inhalant allergens.
AFARE indicates aggravating factors of asthma in a rural environment; BMI, body mass index; ED, emergency department; IC, inhaled corticosteroids; LTRA, leukotriene antagonist.

Community Ammonia Concentrations

There were 18 locations where monitoring was conducted throughout the Yakima Valley region (Figure 1). For AFARE subjects without monitors placed at their homes, the distance from subject home to the nearest AFARE monitor ranged from 0.01 to 9 km. Twenty-four-hour ammonia concentrations varied from 0.2 to 238.1 μg/m^3 during the study period and the median ammonia measured at each site ranged from 2.9 to 72.7 μg/m^3, with higher concentrations observed in the southern region of the study area (Figure 2). Concentrations at each site exhibited a high degree of temporal variability on short time scales (i.e., days to weeks). Ammonia concentrations were weakly and negatively correlated with both daily wind speed ($r = -0.29$) and direction (defined as degrees on a 360° wind rose; $r = -0.22$), weakly correlated with relative humidity ($r = 0.17$) but not correlated with temperature or precipitation ($r < 0.05$). Some evidence for seasonal patterns in

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

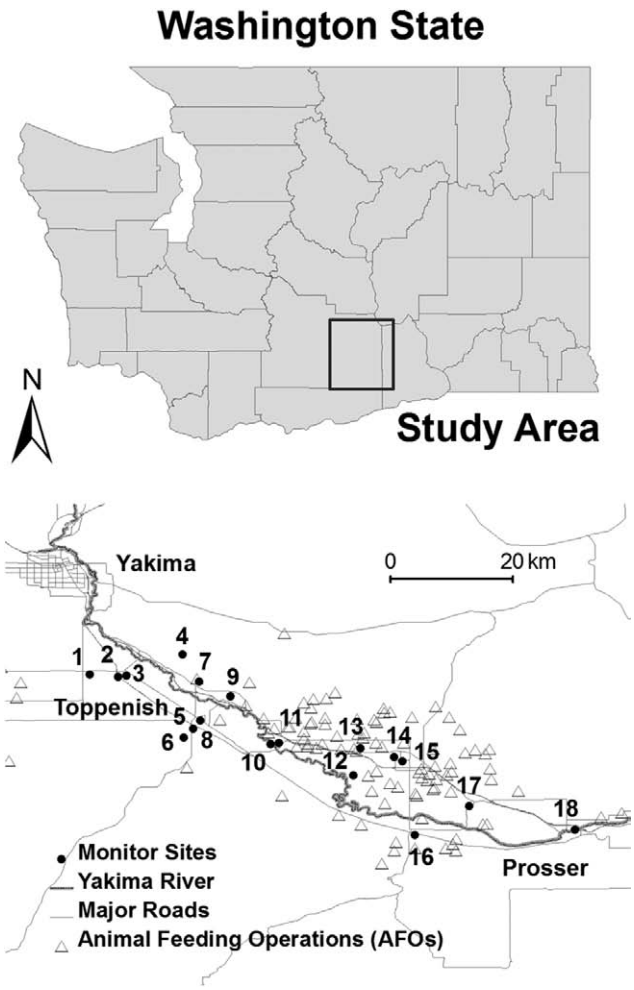

FIGURE 1. Map of study region, including 18 monitoring locations and 97 animal feeding operations (AFOs). Locations of monitors are jittered in random directions and distances (up to 1 km) to protect subject identities.

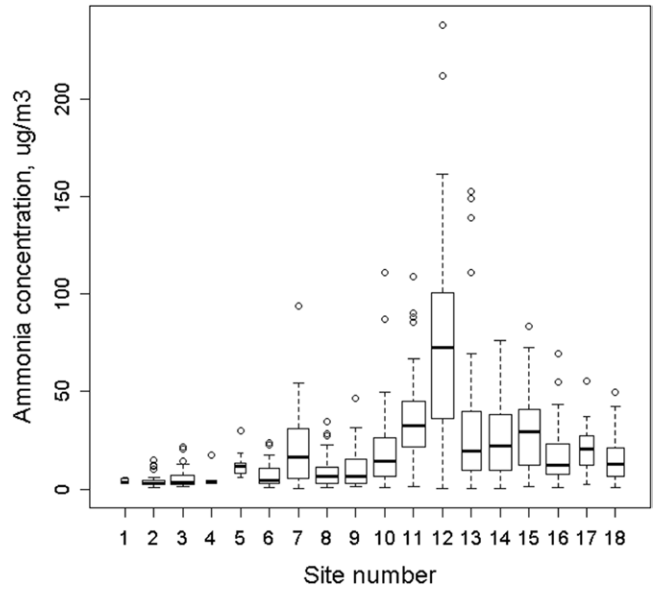

FIGURE 2. Twenty-four-hour average ammonia concentrations (n = 814) measured at 6-day intervals over a 14-month sampling period. Monitoring sites are numbered east to west across the study area. The width of each box is inversely proportional to the number of measurements made at that site.

TABLE 2. Twenty-four-hour Average NH_3 Concentrations by Season

Season	Median NH_3 (μg/m^3)	IQR
Dec–Feb	17.2	3.8, 40.8
March–May	11.6	3.5, 22.1
June–Aug	11.8	3.5, 27.8
Sept–Nov	12.9	4.3, 31.2

IQR indicates interquartile range; NH_3, ammonia.

ammonia concentrations was observed, with slightly elevated concentrations measured during the winter months (Table 2).

Our scan of aerial images of the region identified 97 likely animal feeding operation sites, ranging in size from 6,500 to 900,000 m^2 in estimated surface area (mean area = 190,000 m^2). Median ammonia measured at each monitoring site exhibited a correlation with each measure of animal feeding operation proximity (Table 3). Distance to the nearest facility explained the smallest amount of variability in site median ammonia (R^2 = 0.56), while the sum of inverse distances accounted for 78% of the variability in ammonia. Each of the four metrics of proximity to animal feeding operations displayed a high degree of pairwise correlation.

Ammonia Exposure and Asthma Morbidity

We found no relationship between reported asthma symptoms or medication usage and the weekly ammonia exposure estimated for the week before the interview date (Table 4). Expanding the exposure window to include 2 and 4 weeks before the interview data had no meaningful effect on the results.

Ammonia exposure was associated with FEV1% at various lag intervals, with FEV1% being lower following days of elevated ammonia (Figure 3). FEV1% was decreased by 3.8% (96% confidence interval [CI] = 0.2, 7.3) per interquartile range increase in ammonia 1 day following ammonia measurement and decreased by 3.0% (96% CI = 0.5, 5.8) 2 days later. When we restricted analyses to children living within 1.0 km of an air monitor (n = 23), associations were larger in magnitude (i.e., more negative) but generally less precise. FEV1% decreased 6.3% (95% CI = 2.3%, 10%) 2 days after exposure, for example, for the subset of children living near monitors.

DISCUSSION

Our results provide unique insight into population-level ammonia exposures occurring in an agricultural community and potential effects on the respiratory health of children with asthma. We found that ambient ammonia concentrations were

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 3. Median NH_3 and Metrics of Animal Feeding Operation Proximity: Correlation Matrix

	Log (Median NH_3 [μg/m^3])	Distance to Nearest AFO (km)	# AFOs < 5 km	# AFOs < 10 km	Σ Log(Area)/Distance for All AFOs in Region (Equation 1)
Log (median NH_3 [μg/m^3])	1.00				
Distance to nearest AFO (km)	−0.75	1.00			
# AFOs < 5 km	0.84	−0.64	1.00		
# AFOs < 10 km	0.80	−0.64	0.97	1.00	
Σ log(area)/distance for all AFOs in region	0.88	−0.73	0.98	0.97	1.00

NH_3 indicates ammonia; AFO, animal feeding operation.

TABLE 4. Odds of Specific Asthma Symptoms Associated with Estimated Weekly Ammonia

Symptom or Medication Use	OR (95% CI)[a]
Limitation of activities	1.1 (0.79, 1.4)
Wheezing	0.99 (0.77, 1.3)
Nighttime waking	0.92 (0.76, 1.3)
Shortness of breath	1.1 (0.86, 1.3)
Symptoms worse in morning	0.88 (0.75, 1.0)
Use of short-acting "relief" medication	0.97 (0.82, 1.2)

[a]OR is the odds ratio for report of any symptom/medication use in week prior associated with an IQR increase in weekly ammonia (18 μg/m^3).
IQR indicates interquartile increase; OR, odds ratio.

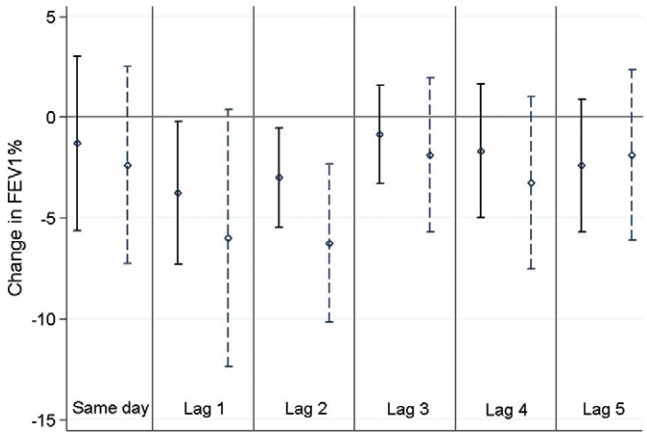

FIGURE 3. Associations between FEV1% and ammonia (NH_3) concentrations measured at the nearest neighbor monitors. For each lag relationship, results for the entire cohort (*solid line*) as well as those obtained after restriction to subjects living within 1 km of the nearest monitor (*dashed line*) are displayed. Point estimates and 95% CI represent changes associated with an IQR increase in 24-hour average ammonia (25 μg/m^3). FEV1% indicates forced expiratory volume in 1 second as percent of predicted; IQR, interquartile range; BMI, body mass index.

elevated in the southern half of the Yakima Valley where most animal feeding operations were located. At the monitoring site with the highest density of surrounding feeding operation, the 75th percentile of 24-hour ammonia concentrations was 101 μg/m^3; this can be compared with the EPA reference concentration for chronic inhalation exposure of 100 μg/m^3. The annual average ammonia concentrations in our study region was 19 μg/m^3, comparable with concentrations reported by some investigators in similar study regions.[4,16,24,25]

Our findings indicate that geographic differences in ammonia concentrations were explained in large part by proximity to animal operations, with 77% of the between site variability in time-averaged ammonia concentrations explained by a distance- and size-weighted measure of proximity (Equation 1). This is not surprising given that the majority of anthropogenic ammonia emissions worldwide are attributable to animal production facilities, which release ammonia during the production and handling of animal manure, as well as during application of liquid and solid wastes to nearby fields.[1] We found that ambient concentrations were slightly higher in winter months, the time of year when fertilization occurs in this region, even though ammonia emission rates from animal feeding operations generally increase at higher temperatures.[26] We observed a high degree of temporal variability in ammonia concentrations with 6-day sampling intervals, a feature that is important to consider in design of epidemiologic studies to estimate associations between ambient ammonia exposure and short-term health effects.

We found no evidence that increased ammonia exposure was linked to worsened asthma health as measured by self-reported symptoms and medication usage. In contrast, we found associations between a measure of lung function, FEV1%, and estimated ammonia exposure at subjects' homes. Effect sizes were largest in magnitude and most precise in relation to ammonia measured 1 and 2 days before lung function measurements, supporting our hypothesis that short-term respiratory effects would occur. In sensitivity analysis, we restricted analysis to children who lived within 1 km of the nearest air monitor to address the hypothesis that nondifferential error increases with distance from the nearest monitoring site. As predicted, this restriction resulted in larger estimates of effect. Nondifferential exposure measurement error

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

associated with using measurements made at distant monitors is likely to bias measured associations with health toward the null and/or increase the imprecision of results.

Our findings may reflect a true causal relationship between ammonia exposure and decreased lung function, although further studies are necessary to infer causality. One previous study of pediatric respiratory health and ambient ammonia took place in a region with a high density of fertilizer production plants, where mean ambient ammonia concentrations ranged from 54 to 113 μg/m^3, exceeding most exposure levels experienced by our cohort.[27] No differences were found in FEV1 of children living in high ammonia communities when compared with children in a "control" neighborhood with no known ammonia sources. However, lung function was assessed only twice for the cohort, and the concentrations of ammonia in the control area were elevated as well, ranging from 30 to 63 μg/m^3. We have found no other published studies of population-level exposures to ambient ammonia and pediatric respiratory health or examining effects on a vulnerable subgroup, such as children with asthma. A cross-sectional study of healthy adults residing near biodegradable waste sites did report a relationship between modeled exposure to ambient ammonia and increased frequency of self-reported respiratory and sensory effects, including coughing.[28]

Ammonia may serve as a marker for the complex airborne emissions from animal feeding operations, and the observed decreases in lung function may have resulted from exposure to one or more co-pollutants with established respiratory system toxicity, such as endotoxin, particulate matter, or hydrogen sulfide.[29–31] Occupational studies of animal feeding operation workers have established a strong link between respiratory disease and exposure to air pollutants from these operations.[32–34] Regardless of whether the decreases in lung function reported here were caused by exposure to ammonia or to one or more of other the toxicants emitted from animal feeding operations, our findings add to the existing body of evidence for a causal relationship between community-level animal feeding operation exposure and respiratory disease.[35–37] Previous investigations have described relationships between prevalence of childhood asthma, either lifetime or current, and exposures to animal feeding operations.[12–14,17] However, all previous epidemiologic studies involving pediatric subjects have been cross-sectional in design.

To the best of our knowledge, we have conducted the first longitudinal, repeated measures study of community-level ammonia exposures and respiratory health, as well as the first study of this design to address exposures to animal feeding operations in relation to pediatric health. A longitudinal repeated measures study is the ideal design to investigate exposures and outcomes that vary in time, and the within-subject comparisons help mitigate the influence of between-subject confounding. This is important in the context of proximity to animal feeding operations and asthma morbidity because residence on or near a farm raising animals may be associated with subject characteristics related to risk of respiratory disease, such as socioeconomic status, atopy, and early-life exposures to a farming environment.[38,39]

Despite these strengths, we acknowledge several limitations. As mentioned previously, it is uncertain whether the relationships with lung function are due to ammonia or other components of animal feeding operation emissions. Second, our exposure assessment was based solely on children's residences; we did not collect information about time-activity patterns. It is possible that children were less likely to play outdoors on days of higher ammonia exposures, but we are unable to account for such avoidance behavior in our analyses. In addition, our weekly estimates of ammonia exposure assigned to each symptom survey were based on only one, and sometimes two, measurement(s) of ammonia made at some time in the week before the interview. Because ammonia concentrations vary substantially on a time scale of days in this study region, this method is likely influenced by a large degree of nondifferential measurement error. This nondifferential error may have masked any true relationships between asthma symptoms and ammonia exposure by biasing results toward the null and/or increasing the standard errors association with effect estimates. Another important limitation of our analysis of symptoms and medication use is that outcome variables were dichotomized in analysis, and therefore analysis may be underpowered to detect any true associations in comparison to analyses of continuous outcome measures, such as lung function. Finally, substantial outcome misclassification likely results from the fact that symptoms and medication use were reported by subjects and caregivers, and therefore influenced by subjective perceptions. Our statistical approach, focused on within-subject rather than between-subject differences in reported symptoms and medication, use may have helped reduce the influence of this misclassifications.

Limitations of our analysis of FEV1% and ammonia include potential bias on account of missing FEV1 data. Results of GEE in analysis of correlated data is susceptible to bias when missingness mechanisms are not missing completely at random.[23] Linear mixed models are more robust to such a bias, and in sensitivity analysis, we found that results of either modeling technique to be similar.

In conclusion, we present preliminary evidence that children living near dairy operations in rural Washington State are exposed to elevated levels of ammonia likely attributable to air pollution from animal feeding operations. We found that exposure to elevated ammonia or any of numerous co-pollutants correlated with ammonia concentrations may be associated with lung function decrements in the following days for children with asthma. These potential health effects are important to consider in an environmental justice framework, as populations living near animal feeding operations in the US are more likely to be low income and belong to racial/ethnic minority groups.[38] Further research into impacts of emissions from animal feeding operations on regional air quality and community health is warranted.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

ACKNOWLEDGMENTS

We are grateful for the participation of research subjects and their families, and for the work of Ginger Ellingson, project coordinator. Two companies (ALK and Lincoln Diagnostics) donated supplies for skin prick testing.

REFERENCES

1. Aneja VP, Schlesinger WH, Erisman JW. Effects of agriculture upon the air quality and climate: research, policy, and regulations. *Environ Sci Technol*. 2009;43:4234–4240.
2. National Research Council (U.S.). *Air emissions from animal feeding operations: Current knowledge, future needs*. Washington, DC: National Academies Press; 2003.
3. Thorne PS, Ansley AC, Perry SS. Concentrations of bioaerosols, odors, and hydrogen sulfide inside and downwind from two types of swine livestock operations. *J Occup Environ Hyg*. 2009;6:211–220.
4. Williams DL, Breysse PN, McCormack MC, Diette GB, McKenzie S, Geyh AS. Airborne cow allergen, ammonia and particulate matter at homes vary with distance to industrial scale dairy operations: an exposure assessment. *Environ Health*. 2011;10:72.
5. Dungan RS, Leytem AB. Ambient endotoxin concentrations and assessment of offsite transport at open-lot and open-freestall dairies. *J Environ Qual*. 2012;41:1702–1702.
6. Roney, N. Toxicological Profile for Ammonia. Atlanta, GA: Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry; 2004.
7. Shusterman D. The effects of air pollutants and irritants on the upper airway. *Proc Am Thorac Soc*. 2011;8:101–105.
8. Donham KJ, Cumro D, Reynolds S. Synergistic effects of dust and ammonia on the occupational health effects of poultry production workers. *J Agromed*. 2002;8:57–76.
9. Morrow SM, O'Quin J, Hoet AE, Wilkins JR III, DeGraves F, Smith KA. Complaints associated with animal feeding facilities as reported to Ohio local health departments, 2006-2008. *J Environ Health*. 2013;75:8–13.
10. Fry JP, Laestadius LI, Grechis C, Nachman KE, Neff RA. Investigating the role of state permitting and agriculture agencies in addressing public health concerns related to industrial food animal production. *PLoS One*. 2014;9:e89870.
11. Shusterman D. Odor-associated health complaints: competing explanatory models. *Chem Senses*. 2001;26:339–343.
12. Merchant JA, Naleway AL, Svendsen ER, et al. Asthma and farm exposures in a cohort of rural Iowa children. *Environ Health Perspect*. 2005;113:350–356.
13. Mirabelli MC, Wing S, Marshall SW, Wilcosky TC. Asthma symptoms among adolescents who attend public schools that are located near confined swine feeding operations. *Pediatrics*. 2006;118:e66–e75.
14. Sigurdarson ST, Kline JN. School proximity to concentrated animal feeding operations and prevalence of asthma in students. *Chest*. 2006;129:1486–1491.
15. Radon K, Schulze A, Ehrenstein V, van Strien RT, Praml G, Nowak D. Environmental exposure to confined animal feeding operations and respiratory health of neighboring residents. *Epidemiology*. 2007;18:300–308.
16. Schulze A, Römmelt H, Ehrenstein V, et al. Effects on pulmonary health of neighboring residents of concentrated animal feeding operations: exposure assessed using optimized estimation technique. *Arch Environ Occup Health*. 2011;66:146–154.
17. Pavilonis BT, Sanderson WT, Merchant JA. Relative exposure to swine animal feeding operations and childhood asthma prevalence in an agricultural cohort. *Environ Res*. 2013;122:74–80.
18. Schinasi L, Horton RA, Guidry VT, Wing S, Marshall SW, Morland KB. Air pollution, lung function, and physical symptoms in communities near concentrated Swine feeding operations. *Epidemiology*. 2011;22:208–215.
19. Merchant JA. Advancing industrial livestock production: health effects research and sustainability. *Epidemiology*. 2011;22:216–218.
20. Postma JM, Smalley K, Ybarra V, Kieckhefer G. The feasibility and acceptability of a home-visitation, asthma education program in a rural, Latino/a population. *J Asthma*. 2011;48:139–146.
21. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159:179–187.
22. Armstrong JL, Fitzpatrick CF, Loftus CT, Yost MG, Tchong-French M, Karr CJ. Development of a unique multi-contaminant air sampling device for a childhood asthma cohort in an agricultural environment. *Environ Sci Process Impacts*. 2013;15:1760–1767.
23. Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*. Oxford: Oxford University Press; 2002.
24. Donham KJ, Lee JA, Thu K, Reynolds SJ. Assessment of air quality at neighbor residences in the vicinity of swine production facilities. *J Agromed*. 2006;11:15–24.
25. Buijsman E, Maas HFM, Asman WAH. Anthropogenic NH3 emissions in Europe. *Atmos Environ*. 1987;21:1009–1022.
26. Hristov AN, Hanigan M, Cole A, et al. Review: ammonia emissions from dairy farms and beef feedlots. *Can J Anim Sci*. 2011;91:1–35.
27. Gomzi M, Sarić M. Respiratory impairment among children living in the vicinity of a fertilizer plant. *Int Arch Occup Environ Health*. 1997;70:314–320.
28. Blanes-Vidal V, Bælum J, Schwartz J, Løfstrøm P, Christensen LP. Respiratory and sensory irritation symptoms among residents exposed to low-to-moderate air pollution from biodegradable wastes. *J Expo Sci Environ Epidemiol*. 2014;24:388–397.
29. Schwartz DA, Thorne PS, Jagielo PJ, White GE, Bleuer SA, Frees KL. Endotoxin responsiveness and grain dust-induced inflammation in the lower respiratory tract. *Am J Physiol*. 1994;267:L609–L617.
30. Campagna D, Kathman SJ, Pierson R, et al. Ambient hydrogen sulfide, total reduced sulfur, and hospital visits for respiratory diseases in northeast Nebraska, 1998-2000. *J Expo Anal Environ Epidemiol*. 2004;14:180–187.
31. Heederik D, Sigsgaard T, Thorne PS, et al. Health effects of airborne exposures from concentrated animal feeding operations. *Environ Health Perspect*. 2007;115:298–302.
32. Reynolds SJ, Donham KJ, Whitten P, Merchant JA, Burmeister LF, Popendorf WJ. Longitudinal evaluation of dose-response relationships for environmental exposures and pulmonary function in swine production workers. *Am J Ind Med*. 1996;29:33–40.
33. Shenker M, Christiani D, Cormier Y, et al. Respiratory health hazards in agriculture. *Am J Respir Crit Care Med Suppl*. 1998;158:S1–S76.
34. Von Essen S, Moore G, Gibbs S, Larson KL. Respiratory issues in beef and pork production: recommendations from an expert panel. *J Agromed*. 2010;15:216–225.
35. Iowa State University and The University of Iowa 2002. Iowa Concentrated Animal Feeding Operations Air Quality Study. Iowa City, IA: The University of Iowa College of Public Health. Available at: https://www.public-health.uiowa.edu/ehsrc/CAFOstudy.htm. Accessed May 23, 2014.
36. O'Connor AM, Auvermann B, Bickett-Weddle D, et al. The association between proximity to animal feeding operations and community health: a systematic review. *PLoS One*. 2010;5:e9530.
37. May S, Romberger DJ, Poole JA. Respiratory health effects of large animal farming environments. *J Toxicol Environ Health B Crit Rev*. 2012;15:524–541.
38. Wing S, Cole D, Grant G. Environmental injustice in North Carolina's hog industry. *Environ Health Perspect*. 2000;108:225–231.
39. von Mutius E, Radon K. Living on a farm: impact on asthma induction and clinical course. *Immunol Allergy Clin North Am*. 2008;28:631–647.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.