Living near concentrated animal feeding operations (CAFOs) and respiratory and allergic disease: Results from the Survey of the Health of Wisconsin 2008-2017

By

Amy Ann Schultz

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This dissertation is approved by the following members of the Final Oral Committee

Kristen Malecki, PhD, MPH, Assistant Professor, Population Health Sciences
Paul Peppard, PhD, Associate Professor, Population Health Sciences
Ronald Gangnon, MD, PhD, Associate Professor, Population Health Sciences
Rebecca Larson, PhD, Associate Professor, Biological Systems Engineering
James Gern, MD, Associate Professor, Pediatric Medicine

Table of Contents

List of Figures

List of Tables

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Abstract

Background: Over the last several decades, large livestock industrial farms, also known as concentrated animal feeding operations (CAFOs), have increasingly replaced small farms. The change in agricultural practices from smaller farms to large-scale farming operations has increased both the quantity and concentration of airborne particulates associated with livestock farming. Multiple sources, including particulate matter from the increased volume of vehicle traffic, manure, and dust from animal housing facilities, all contribute to changes in air quality. The public health implications of this large shift in agricultural practice, while more efficient for meat production, may have unintended public health risks. It has been well documented that workers of CAFOs, including veterinarians, have excessive respiratory symptoms. However, few studies have investigated whether individuals living in close proximity to CAFOs are also at increased risk for respiratory ailments.

Objective: This study investigates the association between residential proximity to CAFOs and allergies, asthma, and lung function among adults and children cross-sectionally. Additionally, a relative exposure metric is used to estimate the additive exposure from CAFO air emissions near children's home and school, taking into account CAFO size, distance, wind direction and wind speed.

Methods: This study uses data from the Survey of Health of Wisconsin, a unique statewide health survey which gathers both objective and subjective health data. Multivariate logistic and linear regression are used to analyze all relationships. Restricted cubic splines are used to account for nonlinear relationships in regression models.

Results: This study found a higher prevalence of wheezing, asthma, asthma medication use, and asthma attacks among both children and adults living in close proximity to a CAFO. Evidence from this study suggests that CAFOs may be an important source of air pollution which may affect the respiratory health of both adults and children who live and attend school near CAFOs.

Conclusion: These findings support the need for future research which refines the measurement of exposure to CAFO air emissions and considers collection of antibiotic and microbiome data from both the facility and nearby residents themselves. Findings from this study, in addition to prior and future studies, are important to strengthen our understanding of how exposure to livestock my affect respiratory health. While this study does not provide conclusive evidence by which to drive policy changes, it begins to build the foundation of research necessary to inform future decision-making around CAFOs and their potential effects on public health.

Chapter 1. Introduction

1.1 Overview

The U.S. Department of Agriculture (USDA) and the U.S. Environmental Protection Agency (EPA) estimates show a greater than fivefold increase in the number of concentrated animal feeding operations (CAFOs) from 1982 to 2012.[1,2] A farm where a 100 head of cattle graze grassy pastures and provide natural fertilization has transformed into a CAFO of 700+ head of cattle, confined in close quarters for 45 days or more with no access to vegetation, and where manure is stored in large lagoons, basins or pits for later application onto crop fields.[3] The change in normative agricultural practices has increased both the quantity and concentration of airborne particulates associated with farming. More than 400 compounds have been found in emissions from CAFO facilities, including non-biological aerosols such as volatile organic compounds (VOCs) from animal feed, skin cells, hair, and dried manure, as well as biological aerosols including endotoxins, bacteria, and fungi from liquid manure.[4]

Studies show that several agents, such as ammonia and endotoxins, can be absorbed by dust particles and stay airborne for long periods and travel great distances.[5,6] Most primary research studies on potential adverse respiratory health effects from CAFOs come from occupational settings.[7,8] Farmers and farm workers of CAFOs are at an increased risk of chronic bronchitis, asthma, bronchial hyper responsiveness, sensitization against farm specific allergens, and inflammation of the upper and lower respiratory tract.[7,8] However, few primary research studies have investigated whether these adverse health effects spill over into the communities of individuals living near CAFOs. Additional research is needed, as results thus far have been mixed.

There have been more than a handful of cross sectional studies assessing residential proximity to large livestock farms and respiratory and allergic health outcomes among adults. However, the majority of studies have been in Europe.[9–14] Large livestock farms in the European studies are often smaller than the CAFOs seen in the United States, as defined by the U.S. EPA.[9–11] Furthermore, these studies have commented on the lack of generalizability to the United States due to differences in geographic locations of industrial livestock farms in relation to residences and regulation in place.[9,12,13] Only a couple cross-sectional studies among adults have been conducted in the United States, in North Carolina and Pennsylvania,[15,16] as well as six longitudinal studies among a panel of volunteers in North Carolina living near swine CAFO. [17–22]

All of the longitudinal studies have been short-term, aiming to assess acute effects. Five of the six studies take place over 2 weeks, where participants answer questions and complete exams twice a day for 14 days.[18–22] The sixth study consists of two 1-hr sessions where participants are exposed to hog CAFO emissions in an air chamber.[17] All six studies are in the same region in North Carolina, and four of the studies are from the same 101 adult volunteers, from 16 neighborhoods within 1.5 miles from a hog CAFO.[17–22] CAFOs in North Carolina tend to be predominately in low-income, minority communities, whereas that has not been seen in other states like Washington and Iowa.[23] Furthermore, only a couple of these studies have specifically looked at respiratory and allergy outcomes beyond just self-reported symptoms.[17,22] Two studies used objectively based exam measurements of lung function and IgE from skin prick tests.[17,18,24]

To-date, no studies have investigated the relationship between residential proximity to CAFOs and respiratory health in the upper Midwest. It is important that this research extend into different regions in the US. Agricultural practices, Right to Farm laws, livestock siting laws, and settlement, placement and zoning of CAFOs vary by state in the US. Additionally, the majority of studies among adults have included a mix of different types of livestock CAFOs or AFOs.[9–11,13,14,16,25] Different types and concentrations of airborne microorganisms have been identified outside of swine, poultry, cattle, and dairy facilities, [26–28] suggesting that different animal CAFOs may present different allergic, asthmatic, and respiratory responses in nearby residents. More research is needed concerning health risks posed by living in close proximity to CAFOs, especially in new areas in the US where management practices and regulations can vary.

There have been just as many studies assessing residential (or school) proximity to large livestock farms among children, as there have been among adults. However, unlike the adult studies which primarily occur in Europe, most of the studies on children are in the United States, in North Carolina, Iowa, and Washington.[29–34] Yet, even so, many of them investigate children living near AFOs (smaller in size than CAFOs), most of them swine AFOs.[9,11,30,33] Only one study to date has looked at children living near dairy AFOs and respiratory health outcomes, and that study was conducted on a small sample size (n=51) in a specific valley in Washington State.[32] In fact, all studies to date, which assess residential proximity to large livestock farms and respiratory health among children, have been within a specific county or among a small community in Iowa, Washington, and Germany.

Only two studies have investigated school proximity (instead of residential proximity) to CAFOs and respiratory health, one at a state-wide level in North Carolina,[35] and one in Iowa, among two schools (one near a CAFO and not one not near a CAFO).[31] Furthermore, studies to-date have relied on questionnaire data by the child or adult.[30,31,33,35] Only two studies have exam data on children (IgE and lung function).[32,36] While three studies have used asthma and allergy ascertainment using electronic medical records, they combined their study sample and results among children and adults, making it difficult to tease out differences by age.[9,11,16] Additional research is needed among children, particularly ones which attempt to refine the measures of exposure and expands into different populations beyond the few study samples investigated thus far.

Most studies have relied on distance as a proxy measure of exposure to CAFO air emissions. Wilson and Serre (2007) measured weekly average concentrations of ammonia at varying distances from hog CAFOs in North Carolina and found distance to one or more CAFOs to be the single best predictor of ammonia concentrations.[37] The number of animal units, temperature, wind speed and direction were also important predictors of ammonia, but to a lesser degree. More recent studies are finding concentrations of endotoxin, PM, and antibiotics to be orders of magnitude higher downwind from CAFOs when compared to upwind concentrations.[26,38–43]

Wind speed and direction have also been found to affect concentrations of particulates and the rise of plumes downwind from livestock facilities. Wind speeds of < 9 miles per hour have been found to be when concentrations of particulates were most elevated near the site.[44] Higher wind speed is when dispersion to background levels tends to occur at nearer distances to the source.[44] A recent study found indoor and outdoor settled dust concentrations of Bos d2 and endotoxin were highest in homes closet to a dairy CAFO, with a decreasing concentration gradient extending out to 3 miles from a CAFO.[45] Dispersion modeling of H2S from a hog CAFO also found a non-linear decay as distance from the source increased.[46] However, only three studies among children have used an estimate of exposure which incorporates size of the farm (a proxy measure of the quantity of air emissions), wind direction, and wind speed into their model, the rest relied on only distance.[30,32,35] Furthermore, while both school proximity and residential proximity to a CAFO have been found to be associated with pediatric asthma and respiratory symptoms, none have attempted to estimate a cumulative exposure which includes exposure to CAFOs both while at school and home.

The overarching goal of this dissertation is to gain a better understanding of whether living in proximity to CAFOs pose a potential risk of asthmatic, allergic, and respiratory health effects among nearby community residents. This study is unique in that it will use the Survey of the Health of Wisconsin (SHOW), a data infrastructure that includes health data collected from across the state. The sampling, recruitment, and data collection of SHOW reduces the chance of over-reporting and selection bias. This would be the first study in the state to investigate the association between residential and school proximity to CAFOs and respiratory health. Prior rural asthma studies have focused on exposure to farms of a smaller scale. Wisconsin is unique in that it has fewer CAFOs than North Carolina and Iowa, where much of the U.S-based research has been done. It is also a state that has over 90% dairy CAFOs,[47] whereas prior studies have included mostly swine CAFOs. The SHOW data enables this study to look at both adults and children. The SHOW data also provides the ability to estimate a more complete exposure metric by having both school and residential proximity to CAFOs for children and adolescents.

1.2 Literature Review

1.2.1 Concentrated Animal Feeding Operations (CAFOs)

1.2.1.a. Definition of a CAFO

The United States Environmental Protection Agency (EPA) defines an animal feeding operation (AFO) as a facility that (1) confines animals for more than 45 days in any 12-month period and (2) animals do not have access to crops, vegetation or forage growth in the normal growing season.[48] The EPA considers an AFO to be a Concentrated Animal Feeding Operation (CAFO) if it meets certain size thresholds. The EPA has delineated three categories of CAFOs, ordered in terms of capacity: large, medium and small. The categorization of CAFOs affects whether a facility is subject to regulation under the Clean Water Act (CWA).[49] The CWA prohibits anyone from discharging pollutants from a point source into a water of the Unites States unless they have a National Pollutant Discharge Elimination System Permit (NPDES), which contains limits on discharges and requires monitoring and reporting in order to protect water quality and public health.[49]

Any AFO that meets the regulatory definition of a CAFO is considered a point source and is subject to regulation under the CWA. AFOs that have 1000 or more animal units are considered to be a large CAFO (1000+ cattle, 700+ dairy cows, 2,500+ swine, 55,000+ turkeys). Medium CAFOs (300-999 cattle, 200-699 dairy cows, 750-2,499 swine, 16,500-54,999 turkeys) are additionally regulated under the CWA if the facility not only meets size requirements but has a manmade ditch or pipe that carries manure or wastewater to surface water or if the animal come into contact with surface water that passes through the area where they're confined.[48] Small CAFOs are not considered a CAFO by regulatory definition, but are designated a CAFO under NPDES based on a case-by-case basis determined by whether it discharges pollutants into waterways of the United States through a man-made conveyance such as a road, ditch or pipe. See Table A1. for categorical CAFO definitions.[48] In most states the EPA has delegated regulatory authority of NPDES to state agencies. In Wisconsin, the Wisconsin Department of Natural Resources (WDNR) regulates CAFOs under the CWA through the Wisconsin Pollutant Discharge Elimination System (WPDES) permitting program.[47]

History of CAFOs

Innovations in technology of the late 19th and early 20th Centuries, combined with a global demand to feed an increasing population, resulted in a systemic national effort to produce the highest output of all agricultural products at the lowest cost. This was achieved by relying on economies of scale, modern machinery, biotechnology and global trade.[50] As a result, the latter half of the 20th Century experienced the industrialization of livestock farming.[50] Large livestock industrial farms, also known as factory farms or concentrated animal feeding operations (CAFOs) and large monocrop farms started to replace small farms by the 1980s and increasingly so throughout the 1990s and 2000s.[51,52]

The shift from small-scale farming to industrial farming changed normative agricultural practices, thereby increasing the quantity and concentration of externalities associated with farming (odor, manure runoff, chemical drift, and groundwater contamination).[51,52] Industrial farm facilities house significantly more animals in smaller quarters, resulting in an increased concentration of livestock and volume of manure than traditional farming which poses significant manure storage and disposal issues.[8] In fact, the U.S. EPA estimates America's livestock create three times more fecal waste than the human population.[2] However, unlike human waste which goes through advanced treatment and processing, animal waste goes largely untreated.[53]

Contaminants from the animal wastes can pollutant both the air and nearby surface- and groundwater through pathways such as manure lagoon leakage, manure lagoon overflow from major precipitation events, runoff or atmospheric uptake from application on crop fields, or atmospheric deposition from manure lagoons followed by dry or wet weather event.[53] The presence of livestock waste contaminants, including nitrates, bacteria, pathogens, veterinary pharmaceuticals, heavy metals, and naturally excreted hormones, have been documented in both surface water and groundwater supplies in agricultural areas within the United States, resulting in contaminated private well drinking water among residents living near CAFOs.[53]

1.2.1.b. CAFO-related Air Emissions

Animal waste (in pits, lagoons, and spread on crop fields), animal feed, the animals themselves and the vehicle traffic (often on gravel roads) release toxic and malodorous gases, vapors and particulates such as ammonia, hydrogen sulfide, volatile organic contaminants, particulate matter, pathogens and allergens into the air.[32,54–56] In fact, agriculture is Wisconsin's primary source of fine particulate matter, defined as having an aerodynamic diameter of 2.5 µm or less (PM2.5), and course particulate matter, defined as being 2.5 to 10 micrograms per cubic meter in size (PM10).[57] Agriculture, including livestock, crops and livestock dust, and fertilizer application, account for 38% of all PM2.5 emission in Wisconsin and 54.8% of all PM10 emissions in Wisconsin (See Figure A1.).[57] Ammonia is a precursor of PM2.5 and is the primary contribution to PM2.5 emissions from CAFOs. Ammonia (NH3) is formed by microbial decomposition of undigested organic nitrogen compounds in animal manure.[58] Once emitted, the NH3 can be converted rapidly to ammonium (NH4+) aerosol by reactions with acidic species (e.g., HNO3 [nitric acid] and H2SO4 [sulfuric acid]) found in ambient aerosols.[58]

Particulate matter (both PM2.5 and PM10) from CAFOs is also comprised of organic material such as fecal matter, feed materials, pollen, bacteria, endotoxins, fungi and viruses, skin and hair cells, and the products of microbial action on urine and feces.[59] Sources of PM include manure storage (both wet and dry), manure transportation and spreading of manure on crop fields, animal feed, animal dander, bedding materials, unpaved roads and surfaces.[60] Key variables affecting emissions of PM10 include the amount of mechanical and animal activity on the dirt of manure surface, the water content of the surface, and the fraction of the surface material in the size range.[59] Endotoxins, which are produced by Gram-negative bacteria, also contribute significantly to CAFO particulate matter.[60] Endotoxins are lipopolysaccharides that are products of the bacterial cell walls of gram-negative bacteria and are present in CAFO dusts.[60]

While the complete list of gases and vapors emitted from CAFOs is long, the other most commonly found gases along with ammonia, are hydrogen sulfide and methane. Hydrogen sulfide (H2S) is a gas arising from storage, handling and decomposition of animal waste from CAFOs.[61] H2S is produced by anaerobic bacterial decomposition of protein and other sulfur containing organic matter.[61] It is heavier than air and can accumulate in manure pits, holding tanks and other low areas in a livestock facility.[61] While the concentration of H2S found in closed animal facilities is not usually harmful, (<10 ppm), the release of this gas from manure slurry agitation may produce concentrations up to 1,000 ppm or higher.[62] Methane is produced by the microbial degradation of organic matter under anaerobic conditions.[63] The primary source of methane in agriculture is from the digestive processes of ruminant animals and the storage, treatment and handling of manure.[58] However, methane emissions from CAFOs do not pose a health threat to surrounding communities.[63]

Pathogens are biological agents that occur naturally and can cause disease.[64] Some microorganisms found in bioaerosols emanating from CAFOs are pathogenic in themselves and some can serve as vehicles for other pathogens.[64] Pathogens at CAFOs can be spread from animal to animal, from human to human, and from direct contact between human and production animal.[26,64]

Manure is the greatest source of pathogenic contamination and has the potential to enter air, surface water, or groundwater sources if not properly managed.[55,65] It has been well documented that the air within CAFOs is highly contaminated with bacteria, yeasts, and molds.[42] Common pathogens found near dairy CAFOs are Staphylococcus, Pseudomonas, Streptococcus, Cryptosporidium parvum, Escherichia coli 0157:H7, Giardia, Listeria monocytogenes.[24,40,62]

Steroid and antibiotic use is correlated with herd size on livestock farms. As the quantity and concentration of livestock increase, so does the use of antibiotics and steroids.[66–68] Concerns over the spread of antibiotics and antibiotic resistance genes from CAFOs into the environmental and humans continue to rise as these substances have been found in water, air and dust measured outside of CAFO facilities, as well as in food products from treated livestock.[69,70] Up to 80% of antibiotics that are consumed by cattle are not metabolized and can get transported via air particulates.[71] A recent study found monensin in 100% of samples up- and downwind of cattle feed yards, with a mean downwind concentration of 1,800 ng/g PM.[71] Tylosin was measured in 80% of samples downwind of feed yards, and the three tetracyclines were present together in 60% of downwind samples, with oxytetracycline detected individually in all downwind samples.[71] A similar study identified five veterinary antibiotics down and upwind from 10 beef cattle feed yards, ranging from 0.5 to 4.6 ug/g of PM.[70] Additionally, androgen-mediated transcriptional activation induced by exposure to extracts from PM collected downwind of CAFO livestock feed yards was significantly higher than upwind.[72]

Volatile organic contaminants (VOCs) and volatile fatty acids (VFAs) emitted from CAFOs constitute a mixture of chemicals comprised of various acids, esters, alcohols, aldehydes, ketones, halogenates, amines, and hydrocarbons.[73] Researchers have suggested that between 100 to 400 different VOCs/VFAs are generated depending on the type of animals and the practices found at each concentrated animal feeding operation.[4]

1.2.1.c. CAFOs in Wisconsin

Wisconsin has not been an exception to the industrialization of farming. The number of Wisconsin farms has decreased steadily from a peak of 200,000 in 1935 to fewer than 70,000 today.[74] While at the same time, the size of farms has increased from 117 acres in 1935 to more than 200 acres today.[74] The same trends are seen when specifically looking at dairy farms in the state, where the total number of dairy farms continues to decline while the number of cows is stable or increasing.[75] From 2007 to 2012, the number of herds with 50 to 99 cows declined by 1,919, while the number of herds with 200 to 499 cows increased from 750 to 815.[75] CAFOs began to emerge in Wisconsin in the 1980s. In 1982, Wisconsin had fewer than 14 CAFOs and today it has more than 250 CAFO.[47] Figure 1 shows the increase in CAFOs in Wisconsin from 1985 to 2014 according to the Wisconsin Pollutant Discharge Elimination System Permit program.[47] Figure 1 also visually displays that over 90% of the CAFOs in Wisconsin are dairy CAFOs, second only to California in terms of the number of dairy CAFOs the state has.

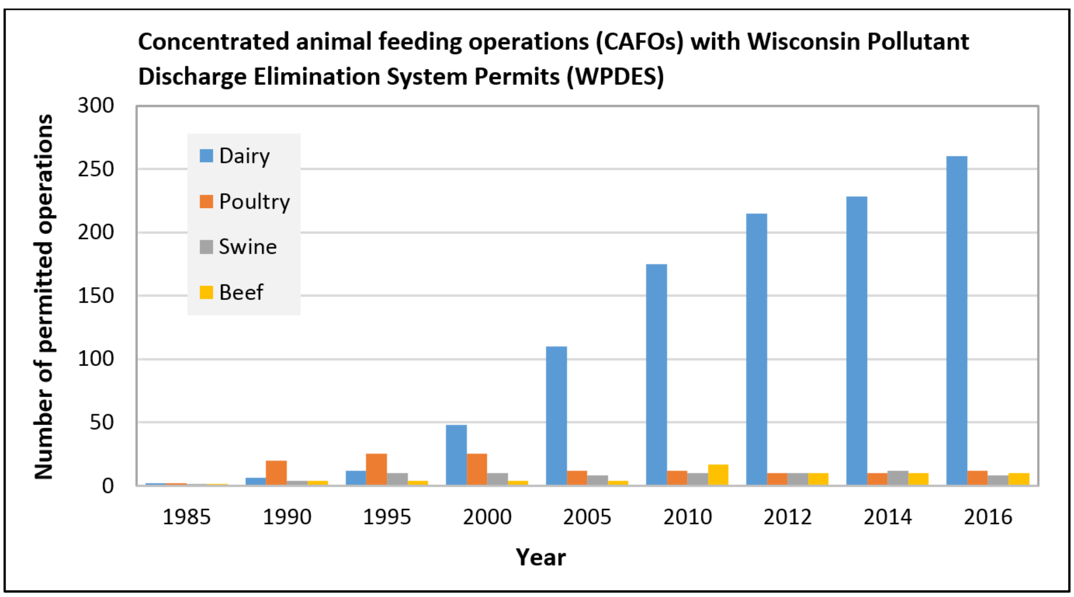


Figure 1. Wisconsin Department of Natural Resources estimation of the number of CAFOs in the state by required Wisconsin Pollutant Discharge Elimination System permits.[47]

Additionally, Wisconsin is second only to California in terms of total dairy animal units and milk produced, and continues to lead the country in cheese production.[74] University of Wisconsin-Madison economists estimate that CAFOs in Wisconsin accounted for 40% of state milk production in 2013 compared to 22% in 2007, and the percent of production from CAFOs continues to grow.[76] Wisconsin's dairy farms are an enormous benefit to the state economy, generating 43.4 Billion each year for the state's economy.[77] This is more than the combined value of citrus to Florida, potatoes to Idaho, apples to Washington and raisins to California.[78] Figures A2 and A3 show the improved efficiency in production over the last several decades, which has resulted in fewer, but larger farms.[78] A survey among farmers in Wisconsin in 2008 from the UW found 74% of farmers said efficiencies in production, which included the ability to increase their herd, afforded them more time with family, less stress, and improved quality of life.[79]

Yet while CAFOs have increased efficiencies in livestock production, there has also been increasing conflict between CAFOs and neighboring communities. According to the Midwest Environmental Advocates, the leading nonprofit environmental law center who has handled and filed many of the complaints and lawsuit claims pertaining to nuisances from agricultural uses in the state, there has been increasing conflict as seen by the number of cases associated with externalities form CAFOs. A few individual private nuisance lawsuits have been claimed and proven successful, such as when the Treml family filed a lawsuit after becoming seriously ill when their private well became contaminated a few days after Stahl Farms had spread tens of thousands of gallons of animal waste on nearby fields. However, the family only won and received settlement after they intervened when Wisconsin Department of Justice filed a lawsuit against Stahl Farms in Kewaunee County Circuit Court for violating the terms of its water pollution discharge permit and discharging manure into School Creek (*State of Wisconsin vs. Glen Stahl*, 2007). Due to the difficulty of filing a private nuisance claim under Wisconsin's Right to Farm law, residents affected by CAFO nuisances often must come together to form organizations and coalitions in order to make an effort in proving a "threat to public health and safety" and disperse any litigation costs endured if a lawsuit fails.

One such recent case involved People Empowered Protect the Land (PEPL), a grassroots grouped formed by neighbors of Rosendale Dairy, an industrial dairy that milks 8,300 head of dairy cows in Fond du Lac County. PERL formed out of concern the dairy was producing air pollution, groundwater pollution and excessive withdrawals, and truck traffic which was affecting their air quality and drinking water.[80] While the Midwest Environmental Advocates were able to file a case claiming the dairy's pollution discharge permit did not comply with water quality standards, the case settled with only a change to the permit and not the outcome PERL was hoping for – a change to future farming practices governed by a change in law. The community of Saratoga also recently was able to stall a proposed CAFO due to violations of Siting Law.[81,82]

According to the Department of Health Services, coliform bacteria could be present in as many as 169,000 of Wisconsin's private wells.[83] While the DNR recommends private well water testing, they estimate only 10 percent of the private well owners test their well water.[84,85] In a series of studies viruses in Wisconsin groundwater were identified as most certainly from fecal matter from agricultural sources.[83] Studies headed by Mark Borchardt with the USDA recently confirmed most nitrate and coliform in Kewaunee County wells was from animal waste, a county with one of the highest concentrations of CAFOs in the state.[86,87] Manure irrigation, odors, and air pollution have become a concern as well. A recent local media article highlighted a landowner whose rural home became surrounded by manure irrigation systems and as a result of the externalities, was ultimately forced out of his home.[88] The landowner claimed the liquid manure spray drifted onto the property from the Central Sands Dairy across the road, and the ammonia smell was so bad it hurt to breathe.[88] Residents near CAFOs not only potentially face increased health concerns, but a recent study from the Wisconsin Department of Revenue reported that homes near large dairy operations have been selling for as much as 13% below their assessed value in Kewaunee county, due to the CAFO.[89]

1.2.1.d. Regulation of CAFOs

Unlike other industries, agricultural operations have traditionally been exempt from numerous federal environmental laws.[90] Both state and federal governments have focused on regulating more visible polluters such as factories, waste treatment plants, and motor vehicles than on smaller and more dispersed sources such as farms.[65] CAFOs are open-air systems, which makes monitoring and measuring actual releases of pollutants into the environment extremely difficult.[91] This is further complicated by the numerous biological processes from livestock production which are more complex than those from industrial sources.[92]

Clean Water Act (CAA)

CAFO regulation has primarily focused on protecting the environment from contaminants being released into waterways of the US.[65] CAFOs require a NPDES permit, but because regulatory power is delegated from EPA to state agencies (in most states it is the Department of Natural Resources) there is a varying degree of compliance, regulation and oversight.[93] Some states regulate in accordance of the bare minimum set by the CWA.[93] Others implement stricter regulations, like Iowa, which requires all AFOs, of smaller sizes to apply.[94] Furthermore, states have varying resources which have left some scrambling to keep up with monitoring CAFOs.[95] A survey study published in 2013, interviewed state agencies in the US that regulated CAFOs and found many state agencies were unable to adequately address health concerns and meet regulatory requirements due to limited budgets, staff size, and political factors.[96] In Wisconsin, one-third of CAFOs were estimated to be operating under expired permits in 2017 due to limited resources in the DNR to keep up.[97]

Clean Air Act (CAA), CERCLA, EPCRA

Current federal environmental laws are not well suited to regulate air emissions from agricultural activities. The Clean Air Act (CAA) focuses on controlling major sources that emit more than threshold quantities of regulated pollutants.[65,98] However, CAFOs are not covered under CAA because air emission quantities are either not the category of pollutant covered or do not emit enough to trigger permitting requirements.[99] However, CAFOs have been regulated under two provisions of federal law: sections of Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Emergency Planning and Community Right-to-Know Act (EPCRA).[100,101] Both of these laws require reporting whenever a certain quantity of a hazardous substance is released into the environment.[101] CAFOs release large quantities of substances the EPA has classified as hazardous - ammonia and hydrogen sulfide.[100] These are reportable substances under both CERCLA and EPCRA and if the reportable quantity of 100 pounds per day is reached of either substance, CAFOs were historically required by law to report under both CERCLA and EPCRA, or are at risk of facing civil suits and penalty fees.[100]

However, reporting under CERCLA and EPCRA has changed over the last decade. The poultry industry petitioned the EPA in 2005 to create an exemption for agricultural operations from the reporting requirements under EPCRA and CERCLA.[102] They claimed these releases of ammonia and hydrogen sulfide posed "little or no risk to public health, while reporting imposes an undue burden on the regulated community and government responders."[103] In response to this petition, the EPA released a proposal in December 2007 to exempt CAFOs from reporting under both statutes.[103] The EPA, supported by the agriculture industry and government responders, reasoned that CERCLA and EPCRA's "reports are unnecessary because, in most cases, a federal response is impractical and unlikely."[104]

However the response to the petition received a large number of comments from people demanding information regarding releases from large CAFOs.[104] So the EPA amended the proposed rule and only exempt reporting under CERCLA and certain livestock facilities under EPCRA.[104] The Final Rule became effective in 2009.[104] It was immediately challenged by environmental groups known collectively as the Waterkeeper Alliance which challenged that neither CERCLA nor EPCRA permitted the EPA to grant reporting exemptions to the EPA.[92] The courts determined the Final Rule of was not justified as a reasonable interpretation of any statutory or implementation of a deminimus exemption.[92] The Waterkeeper Alliance decision was released in April 2017 and granted the EPA motion to stay until May 1, 2018 in order to develop documents to help CAFOs comply with new reporting requirements under CERCLA.[105,106] However, on March 23, 2018, President Trump signed the Omnibus Bill and tucked within the massive appropriations bill is Title XI, called the "Fair Agricultural Reporting Method Act" or "FARM Act" which amends section Section 103€ of CERCLA to no longer apply to air emissions from animal waste at any farm.[107]

Right to Farm law

Historically, if a large CAFO produced excessive odors or noises, a neighbor could bring a private nuisance claim against the CAFO to stop the problem. Nuisance is a civil rather than criminal wrongdoing which alleges that another's practices unreasonably interfere with a person's private or public rights. Wisconsin law, like most states, recognizes two types of nuisance: 1) public nuisance is defined as "an unreasonable interference with a right common to the general public;"[108] and 2) private nuisance is defined as ―the invasion of another's interest in the private use and enjoyment of land.[109] Generally, the state employs the public nuisance doctrine while citizens file private nuisance claims.

An individual can sue a neighboring property owner if odor, noise, excessive light interferes with the individual's use and enjoyment of their property. The State may bring a public nuisance claim against things like prostitution houses, illegal gaming facilities, or stream polluters. Wisconsin law makes it very difficult to prove a nuisance against an agricultural producer unless you can establish that the alleged nuisance presents a substantial threat to public health or safety.[110] It virtually eliminates citizens' right to bring nuisance claims against CAFOs even if the nuisance came to them. For example, if a neighboring small family farm that grows corps and has a couple of cows becomes a large concentrated animal feeding operation with thousands of cows, it is still considered a preexisting agricultural practice shielded by Wisconsin's Right to Farm law.[110]

The Right to Farm statute also states that if no nuisance is found, the plaintiff must pay all the defendant's litigation expenses.[111] As a result, neighbors may be reluctant to bring actions against farmers because if no nuisance is found, they will have to pay all of the farmer's legal fees. Right to farm laws emerged in the 1980s in response to urban encroachment on rural farming lands and were a way to protect farmers from litigations from urbanities not able to adapt to rural smells, dust, and noise.[112] While some states have changed their right to farm laws to exclude protection of CAFOs, Wisconsin's right to farm law has been amended over the last couple decade in favor of more protection for farmers, regardless or type or size.[113]

Livestock Siting Law

Lastly, CAFOs are regulated under Livestock Siting Law. Wisconsin's Livestock facility siting and expansion law required Wisconsin Department of Agriculture, Trade, and Commerce Protection (DATCP) to create rules setting standards for new and expanding livestock facilities.[114] The livestock siting law streamlines local approvals and standards for farm permits.[114–116] Local towns and counties are not required to regulate the siting of new or expanding livestock facilities.[114] However, if local political divisions choose to require livestock farms to apply for a license or conditional use permit, those local communities must have a common application and approval process.[115] The state standards in the siting rules regulate (1) the location of livestock facilities (setbacks), (2) odor emissions, (3) nutrients management, (4) manure waste storage facilities and (5) runoff management.

Though the livestock siting law was intended to provide consistency in livestock siting rules, local communities have to approve plans that may not be enough to protect local needs. Communities which have zoning designating where livestock farms can be and where they cannot have been able to using Siting Law to protect the people and environment from externalities CAFOs pose.[117] Individuals and communities do have the ability to appeal local siting decisions. Some of which have been proven to be successful in Wisconsin.[118,119] Communities without zoning and those which do not regulate under the livestock siting law leave communities and individuals with few options to combat nuisance and potential threats to their health from CAFOs.

1.2.2 Asthma and Allergies

1.2.2.a. Air Pollution as a Risk Factor for Allergies and Asthma

The prevalence of allergies and asthma has increased around the world in recent decades.[120] Due to the relatively short period in time this increase in allergy and asthma prevalence has occurred, genetic variance or changes are unlikely to be the only explanation.[121] Exposure to environmental pollutants or microorganisms especially in air (both indoors and outdoors) has in fact been identified as a main driver of many common respiratory ailments, including allergies and chemical sensitivities.[122] As discussed above, current evidence suggests the development and phenotypic expression of atopic diseases (i.e., allergic rhinitis (hay fever), allergic conjunctivitis, allergic asthma, etc.) most likely depends on a complex interaction between genetic factors, environmental exposure to allergens and microbes, and non-specific adjuvant factors such as tobacco smoke, air pollution, and infections.[123,124]

The idea that outdoor air pollution can cause exacerbations of pre-existing asthma is supported by an evidence base that has been accumulating for several decades, with several studies suggesting a contribution to new-onset asthma as well, both in children and adults.[125] At high concentrations, such as those noted in megacities in India and China, air pollutants may have direct irritant and inflammatory effects on airway neuroreceptors and epithelium, but such levels of exposure rarely occur in North America or Europe.[125] At the lower concentrations that are more typical in high-income countries, other mechanisms are likely at play. Specific pollutants can induce airway inflammation (eg,ozone, nitrogen dioxide, and PM2.5[126] and airway hyper-responsiveness (ozone and nitrogen dioxide)[127] two characteristic features of asthma. In addition, oxidative stress (a feature of severe asthma) has been associated with pollutant exposures (ozone, nitrogen dioxide, and PM2.5).[128,129] Therefore, exposure to these pollutants is unsurprisingly associated with exacerbations and possibly even the onset of asthma.

Size of the particulate matter (PM) affects the depth of penetration in the respiratory tract and the potential health outcomes associated with the particulate matter. PM is categorized on the basis of its aerodynamic diameter, with implications for its typical site of deposition when inhaled. Coarse PM, with an aerodynamic diameter of 2.5–10 μm, deposits mainly in the head and large conducting airways.[130] Fine PM or PM2.5 deposits throughout the respiratory tract, particularly in small airways and alveoli. Ultrafine PM (<0・1 μm) deposits in the alveoli.[130] PM10 includes the coarse, fine, and ultrafine fractions. The composition and size distribution of PM varies according to the source, whether it is natural or anthropogenic, and whether it is derived from combustion or not.[130] Transition metals, polycyclic aromatic hydrocarbons, and environmentally persistent free radicals are constituents of PM of special interest because of their potential to cause oxidative stress and many of the phenotypic changes associated with asthma.[130] Additionally, PM frequently contains various immunogenic substances, such as fungal spores and pollen, which have been independently associated with exacerbation of asthma symptoms.[131,132]

The mechanisms by which pollutants induce these effects are not completely clear. A framework for how air pollution might contribute to the development and exacerbation of asthma proposed by the UK's Committee on the Medical Effects of Air Pollutants identified four main mechanisms: oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses, and enhancement of respiratory sensitization to aeroallergens (Figure

A4).[133] Variation in the genes that regulate these mechanisms could confer increased susceptibility to development of new-onset asthma or exacerbations of existing disease with exposure to air pollution.[125]

Studies to date, which have assessed sources of air pollution rather than ambient measures of air pollution, have primarily focused on urban areas.[127,129,134,135] Traffic-related air pollution (TRAP) exposure has been given a lot of attention in the last several decades as a driver of asthma and allergy in urban areas.[133,136–138] While many studies have identified residential proximity to traffic or industries to be associated with increased prevalence of allergies and asthma,[125,139,140] few studies have focused on the rural environment and residential proximity to CAFOs, which can also emit high levels of fine particulate matter, gases and vapors.

1.2.2.b. Farm Exposure and the Hygiene Hypothesis

In 1989, Strachan first coined the term the "hygiene hypothesis" after discovering children who grew up with a high number of siblings had a lower risk of hay fever, allergies, and eczema when compared with children with few to no siblings.[141] Strachan suggested, "allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings or acquired prenatally from a mother infected by contact with her older children."[141,142] Several similar observational studies followed, with results supporting the hygiene hypothesis; early-life day-care attendance, common viral infections of childhood, and farming were among other exposures discovered to be associated with the hygiene hypothesis and their protective effect against allergies.[143–147] However, throughout the 1990s and early 2000s, the hygiene hypothesis started to receive criticism as studies began to reveal conflicting results and the prevalence of atopic diseases, including allergies, eczema and asthma, continued to rise.[148–150]

Since the 1990s epidemiologists and immunologists have been addressing the rise in atopic diseases with a plethora of studies.[124,150,151] These studies led to the most recent idea that the rise of atopic diseases may be a result of Western lifestyle influences on the microbiome.[150,152] Studies revealed allergies are 20 times more common in Westernized countries when compared with countries of low average incomes.[148,150] The Western lifestyle - characterized by low physical activity, high amount of time spent indoors, and a poor diet rich in saturated fats and carbohydrate sweeteners – can lead to a reduction in microbial diversity.[150] Changes in the living environment, diet, lifestyle and weight heavily influence the composition and diversity of the microbiome in the gut and skin.[124] Therefore, research studies have supported a shift in theory, away from the hygiene hypothesis (or lack of immune stimulation by infectious agents) to immune modulation by nonpathogenic microbial experience.[153] It is now believed that the increase in allergic diseases is at least partly due to the loss of symbiotic relationships with parasites and bacteria that were once beneficial to our evolution.[154]

Numerous studies have shown that young children at risk of developing allergies have gut microbiome dysbiosis, where particular strains are lacking (Lachnospira, Veillonella, Fecalibacterium and Rothia) while others, such as Clostridia species, are overrepresented.[155] Changes in the microbiome of the gut, skin and nose have been associated with eczema, asthma and food allergy.[150] A common finding is that not a single microbe is missing, but the overall degree of microbiome diversity is reduced among those with asthmatic and allergic symptoms and aliments.[156] For example, several studies have found children with pets to have a decreased risk of allergies and asthma when compared to children raised without pets.[157–159] Complementary findings show households with dogs have rich diverse house dust microbiomes with an abundance of Firmicutes and Bacteroides phyla when compared with households without dogs or other outdoor pets.[157,160,161] In addition, it has been shown that mice exposed to such dust from homes with dogs have alterations in their gut flora composition, as well as fewer allergic reactions.[162]

The biodiversity hypothesis helps to explain conflicting research results concerning the protective versus deleterious effects of farm animal exposure. The most comprehensive studies dedicated to disentangling the various factors of the protection against allergy provided by farming, such as ALEX, GABRIEL Advanced Surveys, and PASTURE, have been performed in European regions where dairy production is the main activity and where farming is not industrialized;[163–165] rather in mid-mountain-altitude and among small cheese farms in areas like the Alps.[28,166] Similar protective effects from farming exposure have been documented in the U.S. as well. For example, a study among a large rural cohort of children aged 5-17 in Wisconsin (MESA), found those born on dairy farms had significant decreased risk of developing common childhood allergic and infectious conditions when compared to rural children who did not grow up on farms.[167] However, studies which have since been conducted among farm workers exposed to large-scale livestock farming on CAFOs, or among children and adults living on or near large-scale CAFOs are finding exposure to farming to be potentially harmful and positively associated with allergies, asthma, and respiratory problems.[9,168] In a recent study comparing Amish with Hutterite farming populations in the United States, farm exposure was found to protect Amish children six times more efficiently against asthma and atopy than it did Hutterite children.[169] The authors found this was likely due to the Hutterites having adopted large-scale industrial farming practices, whereas the Amish still live on traditional farms.[169]

While the exact reason for the discrepancy in results is not well understood, higher levels of microbial diversity on a small, more traditional farm when compared to large-scale industrial farm is thought to play a major role.[150,170] In the ALEX and GABRIEL studies, the overall farm effect has been explained by specific and diverse exposure to types of livestock, crops, straw, fodder storage, manure, and unpasteurized milk.[124,170] However, the industrialization of farming is thought to have decreased the microbial diversity and increased the abundance of specific bacterial genera which may induce inflammatory response.[171–173] Sequencing of 16SrRNA components of aerosols at varying distances from dairy CAFOs in Colorado revealed a microbiome derived predominantly from animal sources with bacterial genera dominate by Staphylococcus, Streptococcus, Haemphilus and Pseudomonas, all of which have pro-inflammatory and pathogenic capacity in humans.[174] In fact, a recent study which collected nasopharynx (NP) viral and bacterial communities from infants in their first year and documented acute respiratory infections, found Moraxella, Streptococcus, and Haemphilus to be significantly more dominant in those with Acute Respiratory Infection (ARI) compared with healthy NP samples.[175]

Dairy cattle are principal reservoirs of reservoirs of Staphylococcus, an opportunistic pathogen among humans that can rapidly evolve toward an antibiotic-resistant phenotype.[174] Antibiotic useage and resistance is a well-known disruptor of asymptomatic colonization patterns and can result in reduced microbial diversity.[175] This has also been cited as a potential contributing factor as to why large-scale commercial livestock farms may have deleterious effects on allergic disease outcomes.[70,71,176,177] As livestock farms grow in quantity and concentration, so does the risk of disease and antibiotic usage.[66–68] In fact, high concentrations of several veterinary antibiotics have been found in airborne PM downwind and upwind of cattle CAFOs, where microbial communities of PM downwind were enriched with ruminant-associated taxa and were distinct when compared to upwind PM.[70,71] Furthermore, gene encoding resistance to tetracycline antibiotics were significantly more abundant in PM collected downwind.[70]

Research comparing microbial diversity found on different types and sizes of farms is scare. However some supporting evidence suggesting the antibiotics may play a role in decreased microbial diversity and increased risk of allergic disease come from a rural pediatric asthma study in Iowa, where asthma prevalence was found to be higher among children growing up on swine farms that use antibiotics in the feed.[33] The latest research is discovering is that microbial diversity is likely an underlying factor explaining the prior differences seen in urban versus rural settings, where rural subjects were likely exposed to more microbial diversity than urban subjects.[124,178,179] However, microbial diversity is associated with allergic diseases regardless of exposure to farming and urbanicity. A study among school-aged rural children found the reduced Alpha and beta diversity of nasal microbiota among those with asthma.[171] The association was in both farm-raised and nonfarm-raised children.[171] An inner city urban asthma study also found microbial diversity to have an effect on asthma and allergy prevalence in urban settings.[180]

1.2.2.c. The Role of Genetics and Family History with Allergies and Asthma

The German Multicentre Allergy Study was the first longitudinal birth cohort to examine multimorbidity of asthma, allergic rhinitis, and eczema up to 20 years of age and to provide sex-specific and family history-specific prevalence data.[181] They found having parents with allergies is not only a strong predictor of developing any allergy, but it strongly increases the risk of developing allergic multimorbidity.[181] At 20 years of age, participants with allergic parents developed coexisting allergies three times more often than those with non-allergic parents.[181] In adulthood, the prevalence of allergic multimorbidity seemed similar in both sexes, whereas single allergic diseases were slightly more common in women than men. Asthma occurred more frequently with coexisting allergic rhinitis and/or eczema than as a single entity from pre-puberty to adulthood.[181] A meta-analysis screened the medical literature from 1966 to 2009 to compare the effect of maternal asthma versus paternal asthma on offspring asthma susceptibility and made similar conclusions.[182] Aggregating data from 33 studies, the odds ratio for asthma in children of asthmatic mothers compared with non-asthmatic mothers was significantly increased at 3.04 (95% confidence interval: 2.59–3.56).[182] The corresponding odds ratio for asthma in children of asthmatic fathers was increased at 2.44 (2.14–2.79). When comparing the odds ratios, maternal asthma conferred greater risk of disease than did paternal asthma (3.04 vs. 2.44, $p = 0.037$).[182]

The first study to identify the heritability of allergy found that 48.4% of a group of 621 sensitized individuals had a family history of sensitization to common environmental allergens, compared with only 14.5% of the control group of 76 non-sensitized individuals.[183] A few years later, the term atopy was first coined, to mean inherited hypersensitivity.[184] More recent studies in twins provide further evidence for allergy heritability, due to the higher levels of concordance for allergic phenotypes in monozygotic, compared with dizygotic twins, where atopy heritability is estimated between 50% and 84%.[185,186] Heritability estimates for allergic disease vary, but have been described as high as 95% for asthma, 91% for Allergic Rhinitis and 84% for Allergic Dermintitis.[187] The apparent heritability of asthma and/or allergies has led to increased interest in using Genome-Wide Association Studies (GWAS) to identify any common gene variants that may help to explain allergic diseases.[184] The first GWAS for asthma was completed in 2007 by Moffatt and colleagues, a discovery cohort of 994 patients with childhood onset asthma and 1243 nonasthma controls identified significant association to a locus on chromosome 17q21.[188] Subsequent GWAS in asthma have now identified more than 15 susceptibility loci with confidence in the Caucasian population. Overall, the susceptibility genes identified to date using GWAS are consistent with the hypothesis that asthma is caused by epithelial barrier/function abnormalities and altered innate and adaptive immune responses. It was reported by the GABRIEL consortium that ~49% of the lifetime risk of asthma could be explained by the one of the identified loci.[184] In contrast to asthma, there are limited data for GWA approaches in allergic rhinitis in the Caucasian population with only one study published to date that identified genome-wide significant association.[189] See Figure A5 which suggests that allergic diseases and traits share a large number of genetic susceptibility loci.[184]

While there is evidence for a genetic susceptibility to acquiring allergies or asthma, it does not explain the entire picture. The literature suggests allergic diseases have an environmental contribution and likely develop from a combination of a gene-environment interaction. Several studies even suggest the environmental contribution to be quite strong with evidence of a negligible role for genetic transmission.[190–192] A large Nuclear-Family cohort study demonstrated that family members are at increased risk of allergies of the esophagus and airways compared to the general population, but that the inheritance is complex and not Mendelian.[193] The Nuclear-Family–based design yielded an inflated heritability estimate.[193] Twins heritability estimates suggested that familial clustering is due in large part to common, or shared, family environment rather than genetics.[193] Similar conclusions have been from other familial studies where shared environmental factors such as diet, antibiotic use, birth weight, breast-feeding history, pet/animal exposure, and social economic status explained the heritability estimates.[194,195]

Additional supporting evidence of the role the environment plays in contracting allergic disease was found in a meta-analysis on allergic disease prevalence among immigrants, and another studies comparing biological offspring to adoptees. A systematic review on asthma and allergies and immigration status found the prevalence of asthma to be higher in second generation than first generation immigrants.[195] Asthma and allergic diseases increased steadily as length in host country increased. These findings were consistent across study populations, host countries, and children as well as adults, suggesting a changing environment as the primary driver behind the change in prevalence of asthma and allergies.[195] A recent study which included approximately 2000 adoptees and large numbers of similar biological families found the relative importance of genetic transmission differed by socioeconomic status (SES).[196] In high SES families, parent–child asthma associations are approximately 75% weaker among adoptees than biological children, suggesting a dominant role for genetic transmission.[196] In lower SES families, parent–child asthma associations are virtually identical across biological and adoptive children, suggesting a negligible role for genetic transmission.[196]

The role the environment versus genes play will need more epigenetic research as it is likely a complex relationship, dependent on the types on environmental exposures, the doses of exposures, and the timing of exposure. However, one thing that is well supported in the literature, is that it is evident environmental exposures such as dander, pollen, dust and other particulates and aerosols can trigger and exacerbate symptoms among those more susceptible to allergic disease symptoms.

1.2.3 CAFOs and respiratory health – epidemiological evidence

1.2.3.a. Respiratory and Allergic Disease Among Farmworkers

The first research study which investigated the occupational health and safety among workers in confined livestock operations began in 1977.[197] After the first study, several studies followed, with the focus of research on respiratory health among swine confinement workers.[198,199] This research collectively found chronic inhalation of air in animal confinement facilities resulted in workers having an increased risk of developing respiratory diseases, such as asthma, rhinosinusitis, hypersensitivity pneumonitis, organic dust toxic syndrome, chronic bronchitis.[200–203] Livestock workers also have a higher risk of developing chronic bronchitis and COPD when compared to crop farm workers.[203] Chronic exposure to air emissions from swine facilities has been associated with a decrease in inflammation responses by respiratory and immune cells of humans, mice and pigs in vitro[204–207] and in vivo, a condition called chronic inflammation adaptive response.[200,204]

While earlier research on organic dust exposures and lung disease and aliments among farm workers is still highly relevant today, many of those studies were among more traditional style farms or farms of a smaller size than seen today. [199,208] The scale of production has increased, and new technologies and changing work practices have altered exposure patterns in modern dairies.[208]A recent systematic review highlighted updated knowledge, specifically in regards to occupational exposure and respiratory outcomes among workers on dairy CAFOs.[208] Several researchers have confirmed an increased prevalence of self-reported adult onset asthma among US dairy workers compared with rural controls.[209,210] Futhermore, while there has been a decrease in the incidence of farmer's lung (hypersensitivity pneumonitois - HP) due to changes in farming practices, a low prevalence continues to be associated with dairy farming.[211] In fact, proportionate mortality ratios for HP were reported as being highest for worked in livestock, and Wisconsin counties with the highest prevalence also had a higher proportion of dairy operation workers.[211]

Lung function decline has also been documented in two large cohorts in France and Sweden, as well as in the U.S. among farm workers[212,213] Mild acute airway obstruction has been found to be associated with work in large California dairies, with both baseline and cross-shift reductions in FEV1 and FVC.[214] Reductions in lung function were similarly seen in a cross-sectional study in Colorado and Nebraska (n=174), where personal work shift exposures to inhalable dust, endotoxin, and 3-hydroxy fatty acid, post-work shift nasal inflammatory markers, and pulmonary function tests were measured and collected.[215,216]

1.2.3.b. Residential Proximity to CAFOs and Respiratory & Allergic Disease Among Adults

The majority of cross-sectional epidemiologic studies investigating the relationship between residential proximity to CAFOs and respiratory and allergic health among adults come from Europe (Netherlands, Germany, and Greece).[9–14] The studies out of the Netherlands found mostly null, and some inverse, relationships between residential proximity to large livestock farms and asthma and allergies.[9–11] All three studies used the International Classification of Primary Care (ICPC) codes from Electronic Medical Records (EMR) to ascertain asthma and allergy outcomes.[9–11] Two studies out of Germany and one in Greece, found mixed results.[13,14,25] Radon et al. (2007) found decreased lung function and a higher prevalence of wheezing without a cold among those living near more than 12 animal houses when compared those living near less than 5 in Germany.[12] However, null associations were found when Radon et al. (2007) looked at self-reported asthma and allergies, and Immunoglobulin E (IgE) sensitization to common allergens.[12] Additionally, the prevalence of self-reported asthma symptoms and nasal allergies increased with self-reported odor annoyance.[12] Schulze et al (2011) conducted a study among a subset of the same cohort as Radon et al (2007) in Germany.[13] Schulze et al. (2011) found positive associations between ammonia levels measured from air samplers near homes with self-reported wheezing, allergic rhinitis, sensitization to ubiquitous allergens, and a decrease in lung function; although only the objective measures of lung function and allergic sensitization were statistically significant.[13] In Greece, Michalopoulos et al. (2016) also found positive associations with physician diagnosed asthma, allergic rhinitis, wheezing, night time awakenings, and night/day time coughing without a cold. However, only wheezing and awakenings, and coughing was statistically significant.[14]

Contrary to the mixed results seen in the European studies, the two studies in the United States both found positive associations with residential proximity to CAFOs and asthma symptoms, wheezing, and asthma exacerbations.[15,16] Wing and Wolf (2000) found residents living near a hog CAFO in North Carolina experienced more occurrences of headaches, runny nose, sore throat, excessive coughing, diarrhea and burning eyes, and reported decreased quality of life, when compared with residents of a community not living near any CAFOs. Rasmussen at el. (2017) found asthma oral corticosteroid (OCS) medication orders, asthma-related hospitalizations, and asthma-related emergency room encounters were all higher among those living within 3 miles of a CAFO when compared to those living farther from a CAFO, although ER encounters was not statistically significant. The discrepancy in results across all these studies is likely due to a combination of factors including differences in study design, study samples, and measurements of the exposure and outcomes.

Exposure assessment varies greatly across studies and is likely a contributing factor for differences in results. Among the six studies in Europe, only two from the Netherlands provided detailed data about the size and types of livestock farms in their studies, and neither study included CAFOs that met the size threshold for a large size CAFO as defined by the EPA.[9,11] Both studies defined CAFOs using size thresholds similar to what would be considered a medium or small CAFO in the U.S., a size that is typically not regulated unless "a manmade ditch or pipe that carries manure or wastewater to surface water or if the animal come into contact with surface water that passes through the area where they're confined." [9,11,48] The remaining four studies in Europe did not provide any information about the size of livestock farms in their study, even though all referred to them as "CAFOs."[10,12–14] In fact, Radon et al. (2007) included all animal houses, regardless of type and size, as they were unable to obtain more detailed information for confidentiality reasons. These studies have increased potential for misclassification of the exposure, which can lead to underestimation of the effects. This may partially explain why associations among these studies are null or weak, when compared to the U.S. studies, where CAFOs were defined using U.S. EPAs definition of a large CAFO. In fact, Wing and Wolf (2000) found statistically positive associations among those living near a very large hog CAFO (6,000 hogs), when compared to those not living near a CAFO. Yet, they found null associations when comparing those living near two dairy AFOs (small CAFO size, similar to the size seen in European studies) with those not living near any CAFOs or AFOs. Similarly, Rassmusen et al (2016) found positive associations with asthma morbidity when comparing those living within 3 miles of CAFO to those living further than 3 miles from a CAFO in Pennsylvania. Furthermore, all European studies include a mixture of CAFO types in their studies, some pig, cattle, dairy cow, turkey, and goat livestock farms are included in all studies, and only one study attempts to assess associations stratified by type of CAFO.[9–14] In the United States studies, the Pennsylvania study includes dairy, veal, and swine CAFOs,[16] whereas the North Carolina study looks at 1 swine CAFO and 2 non-CAFO sized dairy AFOs.[15]

All studies used some degree of a proxy measure for measuring the exposure to CAFO air emissions, but the measurements have varied. Most studies relied on a measure of distance from the residence to the nearest farm. Studies in the Netherlands and Germany use 500m (0.31 miles) and 1000m (0.62 miles) cut points,[10,11,13] whereas Greece and the U.S. tend to use cut points of 1.5, 2, or 3 miles.[14–16] Difference in distances used likely has to do with the differences in the size of the CAFOs and how close nearby residences realistically are living in relation to the nearest CAFOs or non-CAFO livestock farms. A few studies have also looked at the number of farms within 500m or 1000m from the residence,[10,11,13] or have used air samplers and interpolated measures of ammonia[13] and fine particulate matter[11] to each residence. Self-reported odor annoyance has also been used as a measure of exposure to nearby CAFO air emissions.[12] Unfortunately, the more accurate assessments of exposure are not used within the same studies that have detailed CAFO data. For example, Hooiveld et al. (2016) provided detailed definitions of the size and type of CAFOs used in the study, but allowed no measure of variability in the exposure with each participant. Exposure was determined at the zip code level, and participants either lived in a low density CAFO zip code, or high density CAFO zip code.[9]

Ascertainment of asthma, allergies and respiratory health, as well as the generalizability of the study samples, varied as well. The three studies from the Netherlands relied on ICPC codes to determine asthma and allergy outcomes among their study sample.[9–11] The remaining three European studies rely on self-reported questionnaire data, with the two German studies also collecting exam data on IgE and lung function.[12–14] In the U.S. Wing and Wolf (2000) relied on self-reported symptoms only, while Rasmussen et al. (2017) used ICD-9 codes to assess asthma exacerbations among asthmatics based on hospital visits. While study samples derived from EMR records in the Netherlands may be a fine representation of the general population, they often do not capture the general population in the United States. Rasmussen et al. (2016) study did not include those who have asthma and/or allergies but have not sought medical care due to limited access to health care, whether it be a lack of insurance, anti-trust of the medical field, or far distance to care. Furthermore, the North Carolina study was in a small community, and includes only 101 volunteers, primarily of minority and low-income status.[15] In fact, except for the EMR studies, studies have relied on convenience samples, rather than population-based study samples.

Longitudinal evidence

Seven longitudinal studies exist which examine associations between residential proximity to a CAFO and respiratory or allergic health effects.[17–22,217] However, six of the seven are all in North

Carolina,[17–22] and five of those six are among the exact same non-smoking adult volunteers (n=101).[18–22] These five published papers relied on the same study, and only vary in terms of which exposures and outcomes they report on.[18–22] Exposures include air measurements (H2S, PM2.5, PM10, ammonia, endotoxin VOCs,) and self-reported malodor.[18–22] Outcomes include self-reported questionnaire-based quality of life measures, stress, physical symptoms, mood, attention, and exam-based measures of IgE, lung function and blood pressure (BP).[18–22] All exposures and outcomes were captured from the same 14-day long study, where participants had to live within one and a half miles of a hog operation, and were asked to sit outside, twice daily for two weeks, and record the odor, along with physical symptoms.[18–22] The study found an increase in self-reported odor was associated with higher levels of PM10 and H2S, and an increase of reporting a change in daily activities, difficulty breathing, eye and respiratory symptoms, and measured BP.[20–22] Self-reported stress was also associated with BP, but PM10 levels were not associated with BP.[18,19] Endotoxin was associated with sore throat, chest tightness, and nausea.[22] This study was also conducted in a disproportionately low-income area, with the potential for unmeasured confounding.[19] While efforts were made to introduce the study as a respiratory health study among rural residents, the authors reported that many residents already had negative feelings and connotations towards hog farms in the area, which may have produced over-reporting of odor and symptoms. [18–22]

The one other study from North Carolina was conducted at the University's field laboratory swine house.[17] Here, 48 healthy adult volunteers were subjected to two 1-hour sessions in a dust chamber; 1 hour of exposure to diluted swine air and 1 hour of exposure to clean air.[17] Aerial emissions from swine house dust were diluted to a level that could occur at varying distances downwind from a hog CAFO both within and beyond the property line (H2S, ammonia, total suspended particulates, endotoxin).[17] Physical symptoms, mood attention, and lung function were measured immediately after each 1-hour session.[17] No difference was detected between the two sessions in regards to physical symptoms, including lung function, mood and attention. However, when comparing the swine air session to the clean air session, participants were 4.1 times more likely to have headaches, 6.1 times more likely to report eye irritation, and 7.8 times more likely to report naseau.[17]

1.2.3.c. Residential and School Proximity to CAFOs and Respiratory and Allergic Disease Among Children

While many adult studies found null or inverse results, the studies among children have found primarily positive associations, albeit some weak, when looking at residential or school proximity to CAFOs and respiratory health. Unlike the adult studies, which primarily occurred in Europe, most of the studies on children have been in the U.S. – 2 studies in Iowa,[30,31] 1 in Washington,[217] 1 in North Carolina,[218] and 1 in Germany.[36] Additionally, three of the studies among adults mentioned above which used Electronic Medical Records (EMR) also included children,[9,11,16] however, only one of them separated analyses by age group.[9] A recent review article criticized the combining of adults and children since the same dose of exposure affects children differently than adults, but also the process by which children and adults get diagnosed and treated is likely different. Not to mention children could be negatively impacted by emissions from nearby CAFOs at much smaller doses due to their developing respiratory systems.[219] This research among children is still in its infancy. Only six studies thus far have assessed the relationship between proximity to CAFOs and respiratory health among children (separate from adults) and more research is needed.[9,30,31,35,36,217]

The study populations used in the children studies tended to focus on small sample sizes with children of narrow age ranges, located in specific geographic locations. Common age ranges were 5-6, 12-14 and 5-11 years.[31,36,218] However, the Washington study did not specify the age ranges of the schoolchildren in their sample,[217] and one Iowa study included 0-17 year olds.[30] The Washington study recruited children (n=51) from a farm workers clinic servicing the Yakima Valley.[217] Pavilonis (2013) used a cohort of children from Keock County, Iowa (n=565), and Siguardson and Kline

(2006) only used children (n=572) from two schools in Iowa (one near a pig CAFO and one far form a CAFO). Only two studies had larger sample sizes – The North Carolina study spanned 499 public schools (n=58,169) throughout counties with pig CAFOs[35] and the German study recruited participants (n=7,943) form the Lower Saxony region.[36] The North Carolina study[35] and Siguardson and Kline (2006) study in Iowa were the only two to examine exposure to CAFO(s) from the children's school whereas the remaining three studies examined exposure from the children's residence. No study to-date has assessed both school and residence proximity to CAFO(s).

The majority of studies among adults relied on proxy measures of distance from the residence to the nearest CAFO or the number of CAFOs within a certain radius from the residence, with distances of exposure ranging from <= 0.31-3 miles. Three of the studies among children considered one or more CAFOs within 3 miles of the residence or school to be "exposed" to air emissions from nearby CAFO(s).[30,35,217] The one German study used a distance of 1.24 miles,[36] and the one Iowa study, which only looked at children from two schools, on school was less than 800m from a pig CAFO and the other school was greater than 16 km from any CAFOs.[31] Two of the studies used an exposure metric, which used the inverse square law to calculate a cumulative estimate of exposure based on the number of AFOs within 3 miles of the school or residence, along with the average wind speed and direction of the AFO from the residence or school.[30,35]

While the studies among adults tended to include a variety of animal-type CAFOs, only the German study[36] among children included a mixture of animal types. All others were only among swine CAFOs or AFOs,[30,31,35] except for the study in Washington,[217] which looked specifically at dairy AFOs. However, only two studies, Siguardson and Kline (2006) and Mirabelli et al (2006) included animal operations that met EPA's definition of a large CAFO, the remaining studies included animal operations which do not meet the size requirement of a CAFO, and are considered to be AFOs. The two studies which had CAFOs, and not AFOs, had the strongest positive associations with asthma and allergy outcomes. However, the Siguardson and Kline (2006) study compared children from only two elementary schools. Exposure status was based on whether the child was from the school near an AFO or the school far from an AFO, while the binary outcome (asthma, yes/no) was measured at the individual level. The results were potentially confounded by other factors associated with differences between schools and the types of children and families attending those schools.

All studies relied on self-reported outcomes of asthma and allergy diagnoses and symptoms. Only two studies conducted exams on a subset of their sample to gather IgE,[36,217] and one study measured lung function via spirometry.[217] The Washington study which measured lung function in children and compared it to measured ammonia levels in the levels, found no association between ammonia levels and FEV1.[217]

1.3 Research Gap & Significance

While the increased risk of respiratory health effects among CAFO workers is well documented,[7,8,200,203,220] evidence of potential respiratory health effects among residents living near CAFOs is limited, and findings inconsistent.[6,12,168,200,221] About half of the studies have been conducted in Europe, where confined animal operations are often smaller than ones seen in the United States.[9–14,222] Additionally, they are typically located in more densely populated areas in Europe, and as a result have more environmental regulations and constraints put on them.[124,223]

CAFOs are regulated in the US under the Clean Water Act (CWA) as point sources which discharge pollutants into navigable waters of the US.[224] However, they are exempt from regulation under the Clean Air Act (CAA), with no permit requirements, mandatory air monitoring or use of technologies to reduce air emissions.[225,226] Recent amendments (i.e. the FARM Act) have additionally exempt all livestock farms from the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and the Emergency Planning and Community Right-to-Know Act (EPCRA), two laws which require reporting of releases of hazardous substances that meet or exceed reportable quantities in a 24-hour period.[100,227] Yet, preliminary results from an ongoing EPA National Air Emissions Monitoring Program of CAFOs have revealed the air at some CAFOs may be unsafe with levels of PM, ammonia, and hydrogen sulfide at many sites to be well above federal health-based standards.[228] Other studies have found elevated levels of concern up to 2-5 miles from a CAFO.[37,73,229,230] The majority of epidemiology studies to-date, which have found null or inverse associations between proximity to CAFOs and respiratory ailments have been conducted in Europe.[9–11] Whereas U.S.-based studies have found a higher prevalence of respiratory ailments among residents living near CAFOs.[15,16,231,232] This difference suggests results from European studies may not be generalizable to the U.S., but more U.S-based research is needed to strengthen our understanding of living near CAFOs and potential health effects.

Epidemiology studies that investigate residential proximity to CAFOs and respiratory health in the US have predominantly taken place in Iowa and North Carolina,[35,218,231,232] with a couple studies in Pennsylvania and Washington.[16,32] However, CAFOs exist in 47 of the 50 states,[1] with Iowa, Texas, California, Nebraska, Kansas, North Carolina, Minnesota, Colorado, Idaho, and Wisconsin being the top 10 states with the largest number of animal units.[233,234] In most states, the EPA has delegated regulatory authority of NPDES to state agencies.[3] This has resulted in some states developing additional regulations for smaller AFOs, or regulations pertaining to odors and air emissions, while other states are set to meet the bare minimum requirements through the CWA.[235]

As seen in Figure A6 and A7, the concentration and settlement of CAFOs varies greatly across the U.S., and CAFO regulations tailored to the state allows states to regulate based on their

[1] CAFOs do not exist in Alaska, Massachusetts, and Rhode Island

needs.[234] Additionally, varying resources available for states to monitor and enforce regulations has resulted in some states having undocumented CAFOs and violations under NPDES due to the agency's inability to properly regulate.[96,236] This has not only resulted in states having different public-use data sets of CAFOs (some including all AFOs, some only CAFOs), but with a varying degree of accuracy. This has made comparisons and conclusions across the few studies in the US difficult. Studies thus far are a contribution to the literature and strengthen our understanding of the potential health risks or benefits of living near CAFOs. However their greatest impact is likely at the state-level, where legislation and policy-making can be tailored to the unique settlement of people, CAFOs, and conflicts between the two. Additional studies would strengthen our understanding of the potential human health risks and benefits of CAFOs at the local and state-level.

Wisconsin is second only to California in terms of the number of dairy CAFOs, total dairy animal units, and milk produced, and continues to lead the country in cheese production.[74] Over 90% of the CAFOs in Wisconsin are dairy, and University of Wisconsin-Madison economists estimate that CAFOs accounted for 40% of state milk production in 2013 compared to 22% in 2007, and the percent of production from CAFOs continues to grow.[237] Wisconsin's dairy farms are an enormous benefit to the state economy, generating 43.4 Billion each year for the state's economy.[78] This is more than the combined value of citrus to Florida, potatoes to Idaho, apples to Washington and raisins to California.[78] Improved efficiency in production over the last several decades has resulted in fewer, but larger farms.[78] A survey among farmers in Wisconsin in 2008 from the UW found 74% of farmers said efficiencies in production, which included the ability to increase their herd, afforded them more time with family, less stress, and improved quality of life.[238]

Yet, Midwest Environmental advocates have reported increasing conflicts between CAFOs and communities with an increase in the number lawsuits as farm sizes continue to increase.[80,88,118,239,240] While Wisconsin has improved siting laws around large farms,[241] it has not done much more beyond the minimum NPDES regulations under the CWA. Not only does Wisconsin not have any mandatory air and odor regulations, but Wisconsin has removed the ability for local communities to regulate CAFOs beyond what the state level sets.[242] They have also strengthened protection of CAFOs from civil tort litigations under the state's right-to-farm law.[242] Changes made to the 1997 legislation now require that a citizen prove both that they 1) did not come to the nuisance AND 2) that the nuisance is a threat to their health.[111,242] Proving a nuisance is a threat to one's health is more akin to a public nuisance claim, than a private one.[118] With litigation fees falling on the citizen if they lose their case, most are not willing to risk filing a tort claim.[243] Not to mention, proving a specific source is the cause of a health condition is difficult to do for professionals in a court of law, let alone for an untrained citizen. Yet, there have been no epidemiology studies in the state which aim to objectively assess any relationship between living near CAFOs and respiratory health effects. In fact, this is common across most states, where delegation of the NPDES permitting by the EPA is typically to an agency such as the Department of Natural Resources, without a primary mandate to address public health.[93]

This study aims to add to the growing national and international literature assessing whether there are any associations between residential proximity to CAFOs and respiratory health. This study is also the first epidemiology study in Wisconsin to specifically look at residential and school proximity to CAFOs and respiratory health in Wisconsin. While this study will not provide any answers for residents in the state living near CAFOs, it does start to build the foundation of research which is needed to help inform future policy and regulation decisions. Additionally, this study adds to the rural asthma and allergy literature. More research is warranted as researchers and experts continue to tease out what factors potentially make farming exposure protective and which factors potentially make farming deleterious. Lastly, with natural resource protection as the current regulatory focus under NPDES, more research is need which addresses health-based concerns of

CAFOs and whether future regulations should consider human health as an additional primary regulatory focus.

1.4 Specific Aims

Aim 1: Determine whether residential proximity to concentrated animal feeding operations is associated with the prevalence of allergies, asthma, or reduced lung function (via spirometric measures) among an adult population.

> ***H1a.*** Among adults residents, asthma and allergy outcomes will be more prevalent among those living closer to a CAFO than among those living further away.
>
> ***H1b.*** Average lung function will be lower among rural residents living closer to a CAFO when compared to those living further away.
>
> ***H1c.*** A dose-response effect will be seen where stronger positive associations will be found when closer to a CAFO and lessen as one moves away from a CAFO, when compared to someone living very far from a CAFO.

Aim 2: Determine whether residential proximity to concentrated animal feeding operations is associated with the prevalence of asthma or reduced lung function (via spirometric measures) among children and adolescents

> ***H2a.*** Among children and adolescents, asthma outcomes will be more prevalent among those living closer to a CAFO than among those living further away.
>
> ***H2b.*** Average lung function will be lower among residents living closer to a CAFO when compared to those living further away.
>
> ***H2c.*** A dose-response effect will be seen where stronger positive associations will be found when closer to a CAFO and lessen as one moves away from a CAFO, when compared to someone living very far from a CAFO.

Aim 3: Develop a more refined relative potential risk of exposure to air emissions from nearby CAFOs using data on fate and transport from atmospheric modeling and biological systems engineering. Compare model fit of relative exposure metric versus distance alone as a proxy measure of exposure to CAFO air emissions. Assess whether higher relative exposure metric is associated with increased prevalence of asthma and decreased lung function among children and adolescents.

H3a. The cumulative relative exposure metric, which accounts for number of animal units, distance, wind speed and wind direction from CAFOs to the participant's home and school, will produce a better model fit with asthma and lung function outcomes than distance alone.

H3b. Those with a higher potential risk of exposure will have increased prevalence of asthma and reduced lung function.

1.5 Theory and Conceptual Framework

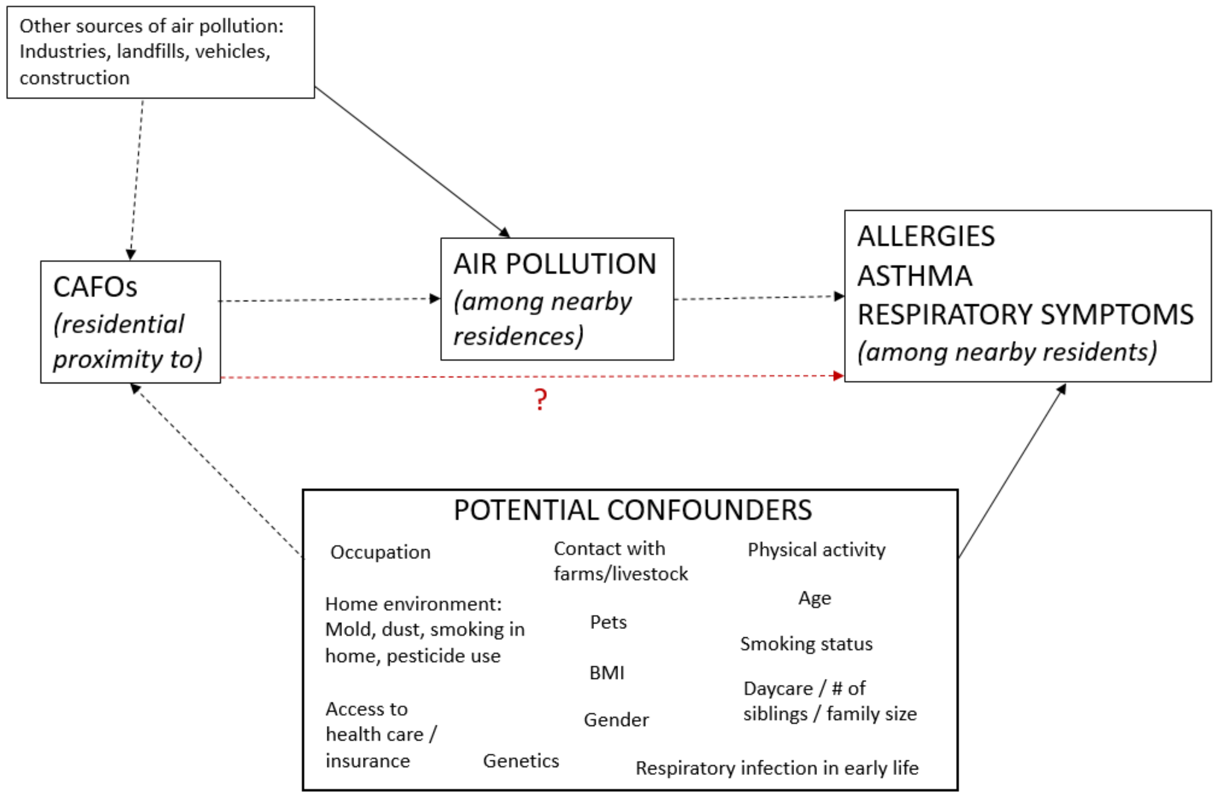


Figure 2. Overall conceptual framework for Aims 1 and 2. The dotted lines represented potential associations, while the solid lines represent established associations from prior research. While it is well documented that CAFOs release air emissions which can increase the risk of asthma and respiratory among CAFO workers, it is not well established the extent to which CAFOs contribute to local air pollution and affect the respiratory health of community members. Aim 1 and 2 investigate the association between residential proximity to a CAFO and allergy, asthma, and lung function (red dotted line), where proximity to a CAFO is a surrogate for the potential relative exposure to air pollution from a nearby CAFO since actual air emissions near the home are not being measured. Other sources of air pollution, such as industries and vehicles, have been associated with increased prevalence of asthma and decreased lung function among nearby residents. These other sources of air pollution are tested as confounders to ensure those living near CAFOs are also not more or less likely to live near other sources of air pollution. Additional environmental and individual characteristics that have been found to be associated with the asthma and allergies were tested as confounders to a ensure those living near CAFOs were also not more likely to have other known risk factors which may be explaining any associations seen with the outcome.

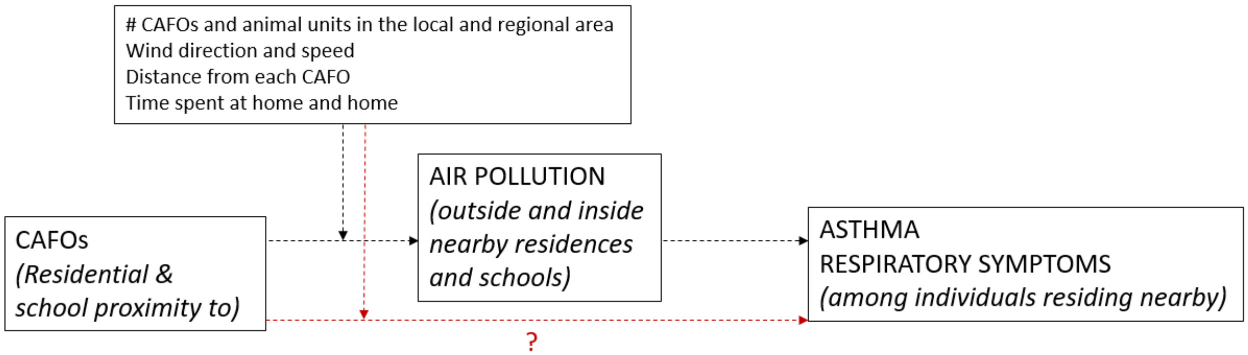


Figure 3. Simplified conceptual framework for Aim 3. Several factors have been identified as influencing the quantity of air emissions outside of a CAFO facility – including wind direction, wind speed, distance from the site, as well the number of livestock and management practice/facility technologies. Aim 3 investigates if proximity to CAFOs is associated with asthma and lung function, taking into account distance, wind direction, wind speed, approximate time spent at both home and school, and local/regional effects of all CAFOs. Aim 3 combines a proxy measure of potential exposure while at school and home among children and adolescents, and uses a framework similar to Figure 2 for testing confounders.

Chapter 2. Residential proximity to concentrated animal feeding operations and allergic and respiratory disease

2.1 Abstract

Background: Air emissions from concentrated animal feeding operations (CAFO) have been associated with respiratory and allergic symptoms among farm workers, primarily on swine farms. Despite the increasing prevalence of CAFOs, few studies have assessed respiratory health implications among residents living near CAFOs and few have looked at the health impacts of dairy CAFOs.

Objectives: The goal of this study was to examine objective and subjective measures of respiratory and allergic health among rural residents living near dairy CAFOs in a general population living in the Upper Midwest of the United States.

Methods: Data were from the 2008-2016 Survey of the Health of Wisconsin (SHOW) cohort (n=5338), a representative, population based sample of rural adults (age 18 +). The association between distance to the nearest CAFO and the prevalence of self-reported physician-diagnosed allergies, asthma, episodes of asthma in the last 12 months, and asthma medication use was examined using logistic regression, adjusting for covariates and sampling design. Similarly, the association between distance to the nearest CAFO and lung function, measured using spirometry, was examined using multivariate linear regression. Restricted cubic splines accounted for nonlinear relationships between distance to the nearest CAFO and the aforementioned outcomes.

Results:

Living 1.5 miles from a CAFO was associated with increased odds of self-reported nasal allergies (OR=2.08; 95% CI: 1.38, 3.14), lung allergies (OR=2.72; 95% CI: 1.59, 4.66), asthma (OR=2.67; 95% CI: 1.39, 5.13), asthma medication (OR=3.31; 95% CI: 1.65 6.62), and uncontrolled asthma, reported as an asthma episode in last 12 months (OR=2.34; 95% CI: 1.11, 4.92) when compared to living 5 miles from a CAFO. Predicted FEV1 was 7.72% (95% CI: -14.63, -0.81) lower at a residential distance 1.5 miles from a CAFO when compared with a residence distance of 3 miles from a CAFO.

Conclusions: Results suggest CAFOs may be an important source of adverse air quality associated with reduced respiratory and allergic health among rural residents living in close proximity to a CAFO.

Abbreviations: Odds Ratio, OR; Confidence Interval, CI; Forced Expiratory Volume in one second, FEV1

Keywords: Air pollution, concentrated animal feeding operation, lung function, allergies, asthma

2.2 Introduction

Over the last several decades, large livestock farms, including concentrated animal feeding operations (CAFOs), have increasingly replaced small farms across the globe. The change in normative agricultural practices from smaller farms to large-scale farming productions, while more efficient for meat production, may have unintended public health risks. CAFOs increase both the quantity and concentration of airborne particulates, gases, and vapors associated with farming.[4] More than 400 compounds have been found in and around CAFO facilities, including volatile organic compounds (VOCs), endotoxins, ammonia, and hydrogen sulfide.[4] While respiratory health effects among CAFO farm workers are well documented,[7,8,219] less is known about the extent to which CAFO air emissions affect the health of nearby residents.

Beyond increasing air emissions, potential for increased exposure to emerging antibiotic resistance microorganisms and outbreaks of zoonotic viral and bacterial pathogens have drawn attention to potential health risks among residents living near CAFOs.[176,177,244] Several agents, such as ammonia, hydrogen sulfide, endotoxins, and viral and bacterial pathogens from animal manure can be absorbed by dust particles and stay airborne for long periods and travel several miles, potentially exposing nearby residents to elevated levels of livestock-related agents.[5,6,26]

Three studies in the United States (U.S.) found the prevalence of asthma to be higher among children and adolescents attending schools,[31,35] and living,[30] near swine CAFOs. Studies among adults have found more mixed results. Two ecological studies among adults in the Netherlands[9] and Greece[14] found null results when assessing residential proximity to livestock farms with allergy and asthma outcomes. Yet, an ecological study in North Carolina, U.S. found the prevalence of wheezing to be higher among adults living near swine CAFOs.[15] Two studies in rural Germany found the number of animal houses near a residence and measured ammonia levels to be associated with decreased lung function in adults.[12,13] However, only measured ammonia levels were associated with sensitization of allergies.[13]

Three Netherlands studies found mixed results using general practice electronic medical records (EMR) to identify cases and controls of asthma and allergies. Inverse associations were found between distance to the nearest farm and asthma, allergies, and COPD [10,11] and negative associations between the numbers of livestock farms within 1000 m of residence and lung function.[222] Yet living within 1000 m of more than 11 farms had increased odds of wheezing and COPD,[10] and measured ammonia was associated with decreased lung function.[222] The only adult study in the U.S. to use EMR found living near a CAFO was associated with increased odds of asthma medication use and asthma-related hospitalizations.[16]

Several of the aforementioned studies relied on convenience samples[14,15,31] of people living near 2-3 identified livestock operations, or small regions consisting of a few rural towns in Germany[12,13] or a rural county in the U.S.[30] While studies in the Netherlands[10,11,222] have used population-based study samples using electronic medical records from general practices, only one study in the United States has attempted to done so by using asthma hospitalization, emergency, and medication data from Geisinger Clinic in Pennsylvania.[16] Generating generalizable results from clinic data in the United States can be challenging as those who do not seek medical care due to inconvenience, cost, or lack of insurance go unreported.

The number of studies on the effect of CAFO air emissions exposure on respiratory health among nearby residents are limited and results are inconsistent. Furthermore, many prior studies have grouped exposure to CAFOs, removing individually variability. This study advances understanding of public health implications of CAFOS by using cubic spline regression to examine the association between residential proximity to CAFOs and respiratory health effects in order to account for non-linearity and retain individual levels of exposure This study also uses a well-characterized, rural sample of Wisconsin residents. Wisconsin ranks second after California as the state with the largest number of dairy cows,[245] over 90% of its CAFOs being dairy CAFOs.[47] To our knowledge, no studies to date have looked at respiratory effects among residents living near dairy CAFOs.

2.3 Materials and Methods

2.3.1 Study Sample

Data came from the 2008-2016 Survey of the Health of Wisconsin (SHOW) state-wide sample of adults ages 18 and older (n = 5,338). SHOW participants are randomly selected using a probability sampling proportion to size with replacement (PPSWR) approach.[246] Between 2008-2013, a two-stage probability-based cluster sampling was used to randomly select census block groups (stage 1) and household addresses (stage 2) annually within strata of region and poverty level.[246] SHOW 2014-2016 cohort was designed as a three-year sample instead of an annual sample as in prior years. A three stage cluster-sampling approach was employed. One county per strata was randomly selected within strata of county mortality rates, followed by random selection of census block groups by poverty status strata. Then 30-35 residential households were randomly selected via US postal service listings.

SHOW recruits 400-1,000 participants every year. Across all years of the study, on average 67% of individuals who screen eligible complete each study component (interview and exam).

However, participation rates vary from 47% in some urban communities to greater than 80% in some rural communities.

Figure 4 describes the analytic sample selected for this study which includes a subset of 1856 (35%) rural participants among the 5338 SHOW subjects. Participants were considered rural if their residence was located in rural census block group defined by the U.S. Census Bureau as having fewer than 2,500 people.[247] Additionally, 32 subjects who reported farming as their current occupation were excluded due to increased likelihood of occupational contact with livestock. Subjects with missing data on any of the respiratory outcomes or confounders of interest were also excluded from analyses, resulting in a final sample size of 1547 for asthma and allergy outcomes, and 1395 for objectively measured lung function outcomes. Detailed allergy data was only collected for 2008-2013 SHOW cohort, resulting in n=1019 for detailed allergy analyses. All residential household addresses were geocoded using CENTRUS software (Pitney Bowes Inc., Stamford, CT) and linked to the nearest CAFO using ArcGIS v10.3 software (ESRI, Redlands, CA). Figure 5 displays a map of the study sample by census block group.

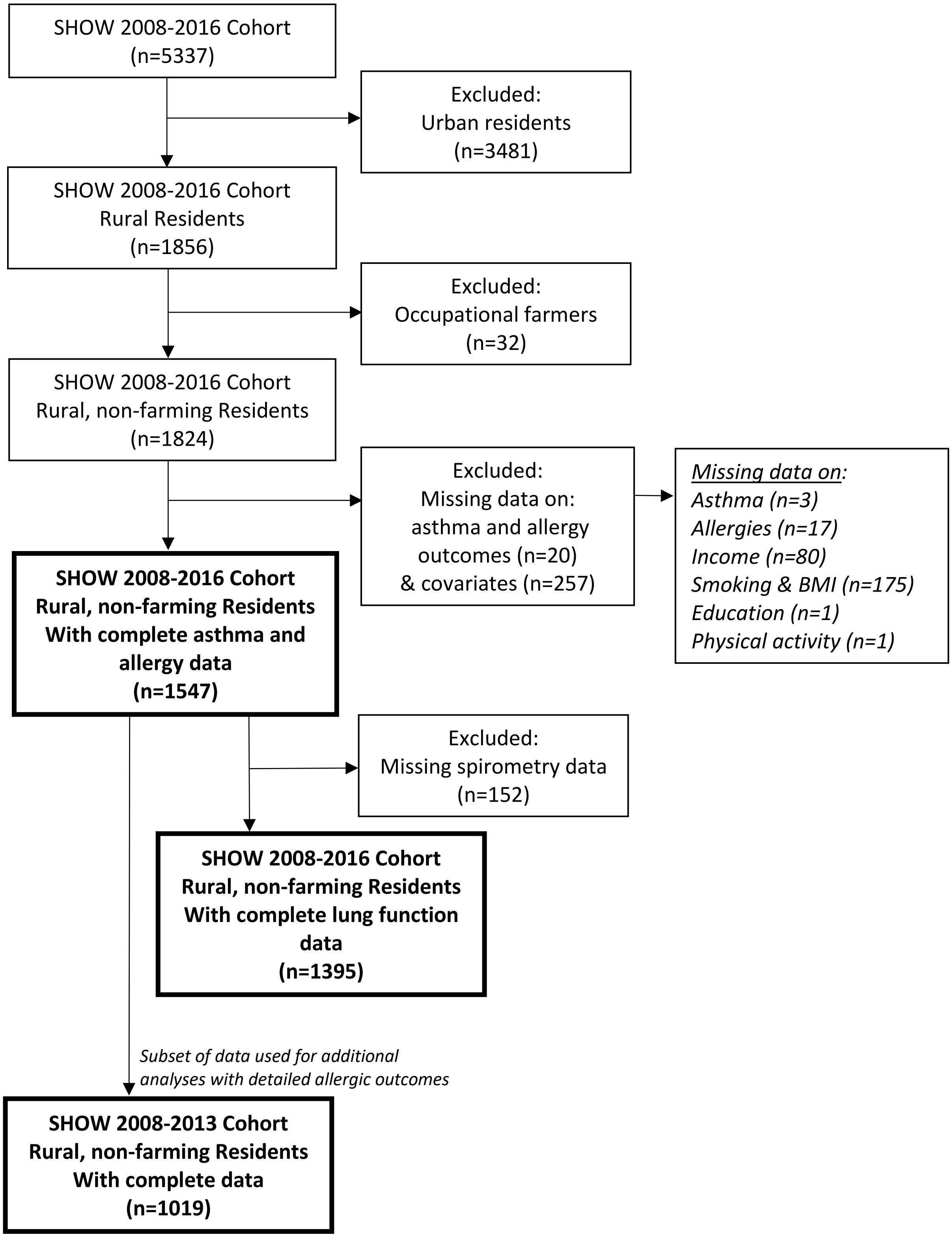


Figure 4. Flow chart of the study sample, depicting exclusion criteria and sample size.

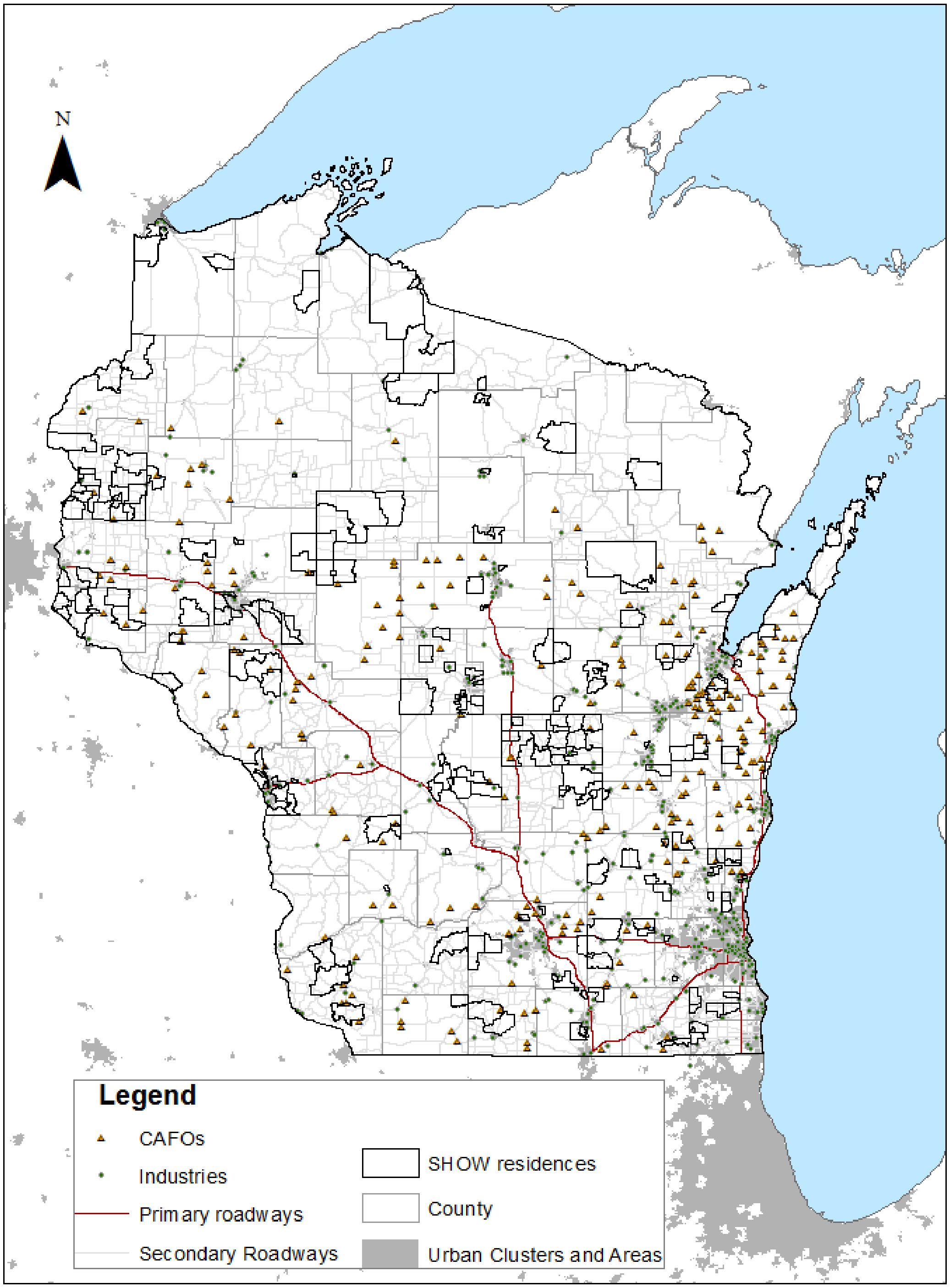


Figure 5. Map of study sample depicting rural SHOW participant residences by census block group.

2.3.2 Concentrated animal feeding operations (CAFOs)

Data on CAFO location, type (dairy cow, hog, chicken, or turkey), years of operation and total animal units are maintained by the Wisconsin Department of Natural Resources' (WDNR) and Department of Agriculture, Trade and Consumer Protection (DATCP) under the Wisconsin Pollutant Discharge Elimination System (WPDES) program. WPDES falls under the Clean Water Act (CWA) National Pollutant Discharge Elimination System (NPDES) which requires states to regulate point source pollution to waters of the entire United States. CAFOs are defined by the CWA [Section 502(14)] as point sources, thus requiring a discharge permit and monitoring by WPDES.

CAFOs are defined as an animal feeding operation (AFO) where the following conditions are met: 1) animals are confined for a total of 45 days or more in any 12-month period and 2) animals do not have access to crops, vegetation or forage growth in the normal growing season. AFOs that have 1000 or more animal units (1 animal unit = 1000 pounds of live animal weight) are considered a large CAFO (1000+ cattle, 700+ dairy cows, 2,500+ swine, 55,000+ turkeys). Medium CAFOs (300-999 cattle, 200-699 dairy cows, 750-2,499 swine, 16,500-54,999) are additionally regulated under WPDES if the facility has a manmade ditch or pipe that carries manure or wastewater to surface water or if the animals come into contact with surface water that passes through the area where they are confined.[48]

According to publicly available data downloaded from WDNR WPDES program there were a total of 284 CAFOs operating in Wisconsin in 2016. Ninety percent (244 large, 2 medium) were dairy CAFOs, followed by swine (5 large, 9 medium), beef (10 large, 3 medium), poultry (1 medium, 10 small).

Publicly available data were limited, therefore additional data including the location, start date, and end date of all permitted CAFOs established between 2007 and 2015 was obtained via an open records request to the Wisconsin DATCP. The DATCP data was used to ensure CAFOs were in existence during SHOW participants' year of participation in the study (when residential address and health data were collected). Figure 1 from the WDNR shows the proportion of CAFOs by animal type has remained stable over the last decade, with over 90% of the CAFOs in Wisconsin being dairy.

Residential proximity to the nearest CAFO was used as a proxy to estimate potential exposure to air emissions from CAFOs. Distance from a participant's residence to the nearest CAFO was calculated using the "Near" tool in ArcGIS (ESRI, Redlands, CA). Participants were linked by cohort year to the nearest CAFO, only including CAFOs that were in existence during both the year they participated AND the year prior.

2.3.4 Allergy, asthma, and lung function

Self-report history of respiratory allergies and asthma was collected during in-home interviews. Current allergies was defined as having reported "yes" to the survey question "Do you still have allergies or hay fever?" as a follow-up to the question "Has a doctor or other health professional ever told you that you had allergies or hay fever?" Allergy type was defined based on response to the question "Where do allergy symptoms occur?" For this analysis individuals with nasal, sinus, lung, eye, and skin as sites of allergies most likely to be triggered by CAFO air emissions were included. Those reporting digestion, food, or insect allergies were unlikely to be related to proximity to CAFOs and were defined as not having respiratory allergies.

Participants were defined as having current asthma if they responded yes to the survey question "Do you still have asthma?" which is a follow-up to the question "Has a doctor or other health professional ever told you that you had asthma?" Those who report having current asthma are also asked "During the last 12 months, have you had an episode of asthma or an asthma attack?" and if they have taken prescription medication to prevent or stop asthma attacks within the last 30 days.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured via spirometry using an electronic peak flow meter (Jaeger AM, Yorba Linda, CA), and validated protocol.[248] Trained technicians gave study participants explicit directions on how to breathe into the spirometry device. Measurements were considered valid if two FEV1 and FVC readings were within 10% of the highest value measured. FEV1 to FVC ratio (Tiffeneau index) and percent predicted FEV1 (FEV1 divided by predicted FEV1) were also assessed to account for inter-individual variability in lung function measurement. Predicted FEV1 was calculated using sex, race, age, and height as defined by the NHANES general U.S. population.[249]

2.3.5 Covariates and confounding

Self-reported demographic data including age (years), gender (male vs. female), education (high school or less, some college, and bachelor's degree or higher) and household income were gathered via personal interviews. Poverty to income ratios were calculated using U.S. Department of Health and Human Services poverty guidelines and the midpoint of the household income range identified by the participant. Body mass index (BMI) was calculated from measured weight and height as kg/m^2. Physical activity was defined as Metabolic Equivalent of Task (MET)-minutes/week of moderate or vigorous activity using self-report data from a modified International Physical Activity Questionnaire – IPAQ.[250] Income, BMI and MET-minutes/week were used as continuous variables in all statistical models, but log transformed to adjust for skewness. Additional self-reported questionnaire items assessed as potential confounders include: home smoking policy, household pets, smell of mildew or mold inside, and the use of any pesticides inside the home in the last 12 months. Sensitivity analyses were also run to test for potential confounding by previously identified environmental sources of allergies and respiratory health in the population[251] residential proximity to the nearest primary or secondary roadway and industry were also examined.

2.3.6 Statistical analysis

Restricted cubic splines functions were applied to the residential distance in order to account for nonlinear relationships between distance to the nearest CAFO and respiratory health. Knots were placed at the minimum, maximum, and 25th, 50th, 75th percentiles of the distance variable (0.24, 6.17, 9.07, 17.9, 69.9 miles). Univariate as well adjusted multiple linear (lung function outcomes) and logistic (allergic and asthma outcomes) regression models were used to examine associations between residential proximity to a CAFO and respiratory health. Potential confounders selected *a priori* from the literature. Covariates that did not change the main effect estimate by more than 10% were excluded from the multivariate models. An adjusted odds ratio (OR) or an adjusted beta-coefficient value with two-sided p-value < 0.05 was regarded as statistically significant. To acquire estimates from the spline regression, comparisons were made between different residential distances, while holding confounders constant. Residential distances of interest were chosen *a priori* from literature estimating air pollution and distance from CAFOs[14,20,22,37,252], and from univariate spline regression trends between distance to nearest CAFO and each outcome. SAS version 9.4 (SAS Institute Inc. Cary, NC) was used for all statistical analyses. All adjusted analyses included sampling weights to account for sampling design, response rates and spatial clustering.

2.4 Results

Unadjusted cubic spline plots revealed the log odds of asthma and allergy outcomes decreased, and lung function increased, as distance from a CAFO increased, leveling off at around 5 miles (Figure B1). Therefore, results include comparisons between distances of 1-3 miles compared with 5 miles from a CAFO. Descriptive characteristics of the study population by residential proximity to the nearest CAFO are presented in Table 1. The majority of the study population (72%) lived > 5 miles from a CAFO, four percent (n=65) lived < 1.5 miles of a CAFO and 23 percent (n=361) lived 1.5-5 miles from a CAFO. Those living near a CAFO (< 1.5 miles) were more likely to be males, never-smokers, younger, less educated and diagnosed with asthma when compared with those living middle-distance (1.5-5 miles) and far (> 5 miles) from a CAFO. Those living near a CAFO were also less likely to live near a major roadway and have allergies when compared to the populations living middle-distance and far from a CAFO (Table 1).

Close residential proximity to a CAFO (living within 1-3 miles) remained positively associated with reporting any allergy symptoms even after controlling for gender, age, BMI, smoking status, education, income, pet ownership (Figure 5). Mold in the home, smoking policy in the home, indoor chemical use, and residential proximity to an industrial site and roadway did not change the main effects and were not included in final models. Odds of allergies was more than 2-fold when comparing living 1 and 1.5 miles from a CAFO to 5 miles from a CAFO

Table 1. Characteristics of the study population.

	Total Study Sample (n = 1547)	Residential distance from nearest CAFO <= 1.5 miles *2.4 km* (n = 65)	1.5-5 miles *2.4-8 km* (n = 361)	>= 5 miles *8 km* (n = 1121)	
	N	%	%	%	p-trend
Gender					0.82
Male	682	47.7	44.3	43.8	
Female	865	52.3	55.7	56.2	
Age (in years)					0.48
18-39	320	23.1	18.8	21.1	
40-59	711	44.6	50.1	44.7	
60-94	516	32.3	31.0	34.2	
Race					0.12
White (non-Hispanic)	485	98.5	93.9	92.3	
Non-white	42	1.5	6.1	7.7	
Education					0.67
H.S./GED or less	475	38.5	31.0	30.2	
Some college	606	36.9	38.2	39.6	
Bachelors or higher	466	24.6	30.7	30.2	
Income					0.0001
< $25,000	246	6.2	11.6	17.8	
$25,000 - $49,999	401	43.1	23.8	25.6	
$50,000 - $99,999	590	35.4	45.7	35.9	
>$99,999	310	15.4	18.8	20.7	
Smoking Status					0.84
Current	247	13.8	15.0	16.4	
Former	488	27.7	32.1	31.6	
Never	812	58.5	52.9	52.0	0.39
BMI					
< 25	381	20.0	28.0	23.8	
25-30	501	38.5	29.9	32.8	
> 30	665	41.5	42.1	43.4	
Physical Activity					
< 600 Met Min / wk	392	24.6	27.7	24.6	0.50
>= 600 Met min / wk	1155	75.4	72.3	75.4	
Proximity to major roadway					0.02
< 300 meters	493	20.0	28.5	33.6	
>= 300 meters	1054	80.0	71.5	66.4	

CAFO: concentrated animal feeding operation; km: kilometer; N: number; H.S.: high school; GED: General Education Development test; BMI: body mass index; wk: week.
P-trend: statistical significance by Chi-square test

(OR=2.55; 95% CI: 1.49, 4.36 and OR=2.02; 95% CI: 1.33, 3.08) and decreased as distance from a CAFO increased. Similar associations were seen among those with nasal- and lung-specific allergies, with the strongest associations seen with lung allergies. The adjusted odds of lung allergies was consistently more than 2-fold higher among those living 1-3 miles from a CAFO when compared to those living 5 miles from a CAFO. Tables B1 and B2 show results of all distance comparisons made for the previously mentioned allergy outcomes, along with current allergies assessed with the entire 2008-2016 cohort. While results indicate residential proximity is associated with eye and dermal allergies, none of the results were statistically significant (Table B2).

Residential proximity to a CAFO was similarly associated with asthma and asthma control measures, including one or more asthma attacks in the last 12 months or taking asthma medication. Reporting current asthma was consistently about 1.8-1.9 times greater among those living 1-3 miles versus 5 miles from a CAFO (Figure 6). The odds of ever being diagnosed with asthma was 3.11 (95% CI: 1.49, 4.36) and 2.67 (95% CI: 1.33, 3.08) when comparing 1 and 1.5 miles from a CAFO to 5 miles from a CAFO. Similar to the associations seen with current and nasal-specific allergies, the odds of doctor diagnosed asthma and asthma medication use decreased as distance from a CAFO increased. Those living 1, 1.5, 2, 2.5 miles from a CAFO, asthma medication was 4, 3, 2.5, and 2 times greater, respectively, when compared to those living 5 miles from a CAFO; all associations statistically significant. Odds of an asthma attack were consistently 2-fold higher at 1-3 miles versus 5 miles from a CAFO, with the odds being 2.34 (95% CI: 1.11, 4.92) times higher at 1.5 miles versus 5 miles from a CAFO.

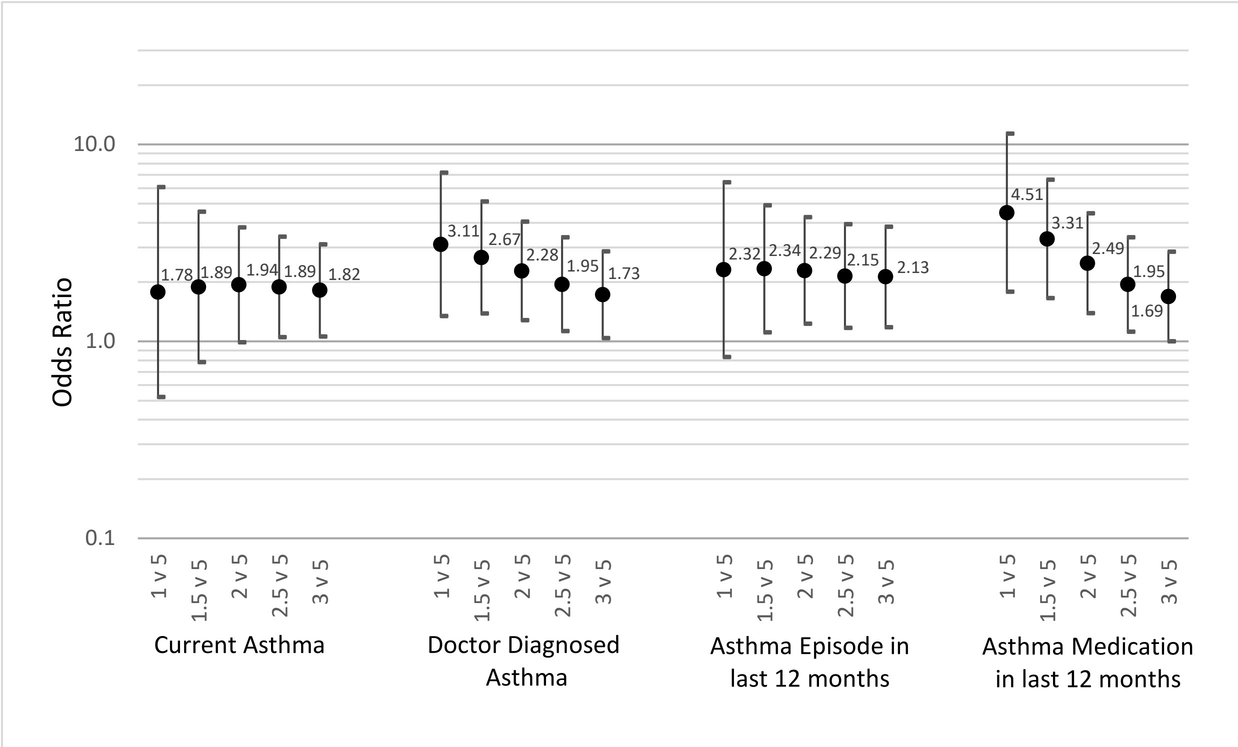


Figure 6. Results of logistic regression assessing asthmatic outcomes by restricted cubic spline of residential distance to the nearest CAFO. Residential distances of 1, 1.5, 2, 2.5 and 3 miles (1.6, 2.4, 3.4, 4.0, 4.8 km) from a CAFO were compared with a residential distances of 5 miles (8.0 km) from a CAFO. Models are adjusted for gender, age, poverty to income ratio, education, BMI, smoking status, pet ownership and proximity to major roadways.

Among the SHOW 2008-2013 cohort, the odds of reporting both allergies of nose or lungs and current asthma was 2.67 (95% CI: 0.97, 6.38) times greater and 2.14 times greater among those living 1 and 1.5 miles from a CAFO when compared to those living 5 miles from a CAFO (Figure 7). Associations were lower at 2 and 2.5 miles but increased again to 2.74 (95% CI: 1.43, 5.23) when comparing 3 miles to 5 miles from a CAFO. This finding suggests that those in this study population with the presence of asthma or allergies may have allergic asthma. Results of all distance comparisons made with the aforementioned asthma outcomes can be seen in Table B3. Similar directional associations are seen when distances of 1-3 miles are compared with 3, 4, and 6 miles as a reference value instead of 5 miles.

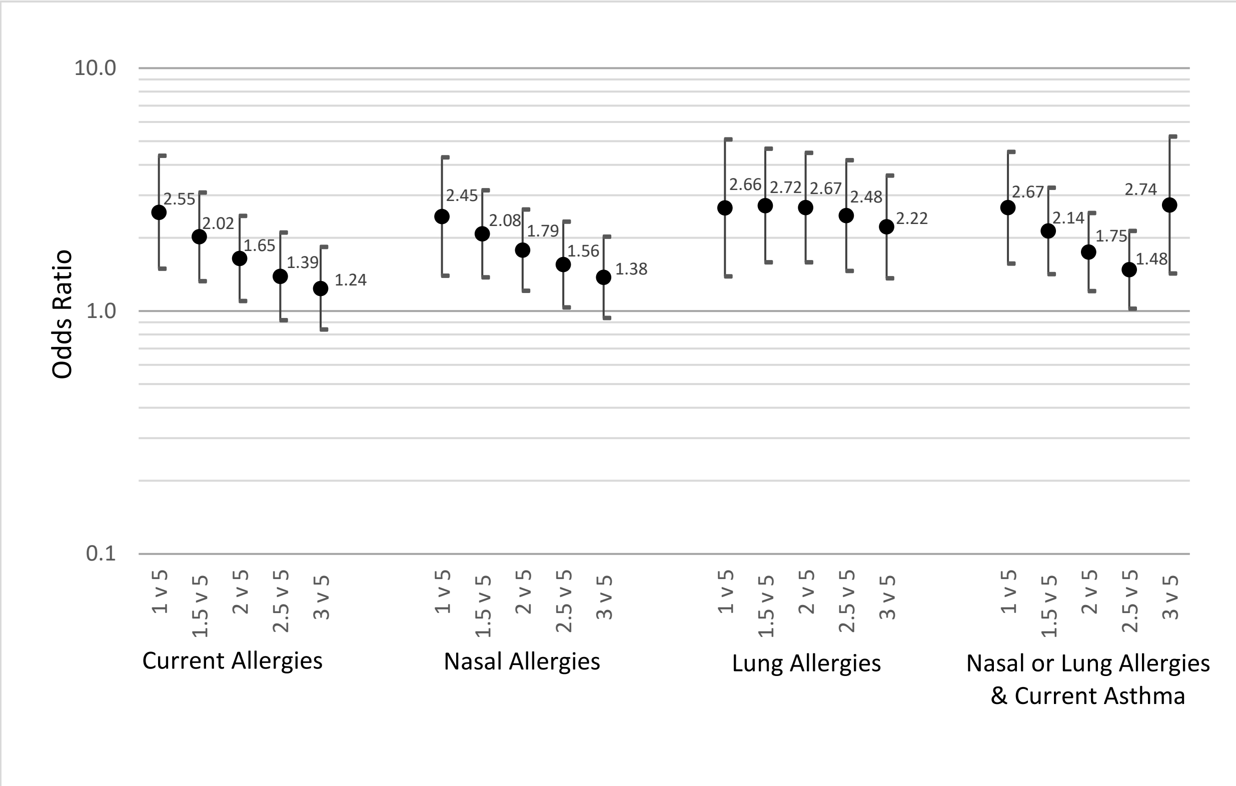


Figure 7. Results of logistic regression assessing allergic outcomes by restricted cubic spline of residential distance to the nearest CAFO. Residential distances of 1, 1.5, 2, 2.5 and 3 miles (1.6, 2.4, 3.4, 4.0, 4.8 km) from a CAFO were compared with a residential distances of 5 miles (8.0 km) from a CAFO. Models are adjusted for gender, age, poverty to income ratio, education, BMI, smoking status, pet ownership and proximity to major roadways.

FEV1 percent predicted and FEV1/FVC were significantly lower among individuals living 1-3 miles from a CAFO when compared to those living 5 miles from CAFO (Figure 8).While not statistically significant, Figure 8 shows FEV1 percent predicted was 11.31 L/s (95% CI: 0.51, 23.14) lower at 1 mile, and 7.00 L/s (95% CI: 2.26, 16.26) lower at 1.5 miles, when compared with 5 miles from a CAFO. The difference in FEV1 percent predicted decreased at 2 and 2.5 miles versus 5 miles until it reached 0 when comparing 3 miles versus 5 miles from a CAFO. FEV1/FVC was 0.039 (95% CI: 0.008, 0.07) lower at 1 mile, and 0.027 (95% CI: 0.003, 0.051) lower at 1.5 miles, when compared with 5 miles from a CAFO. Results of all distance comparisons, including FEV1 and FVC outcomes, can be found in Table B4.

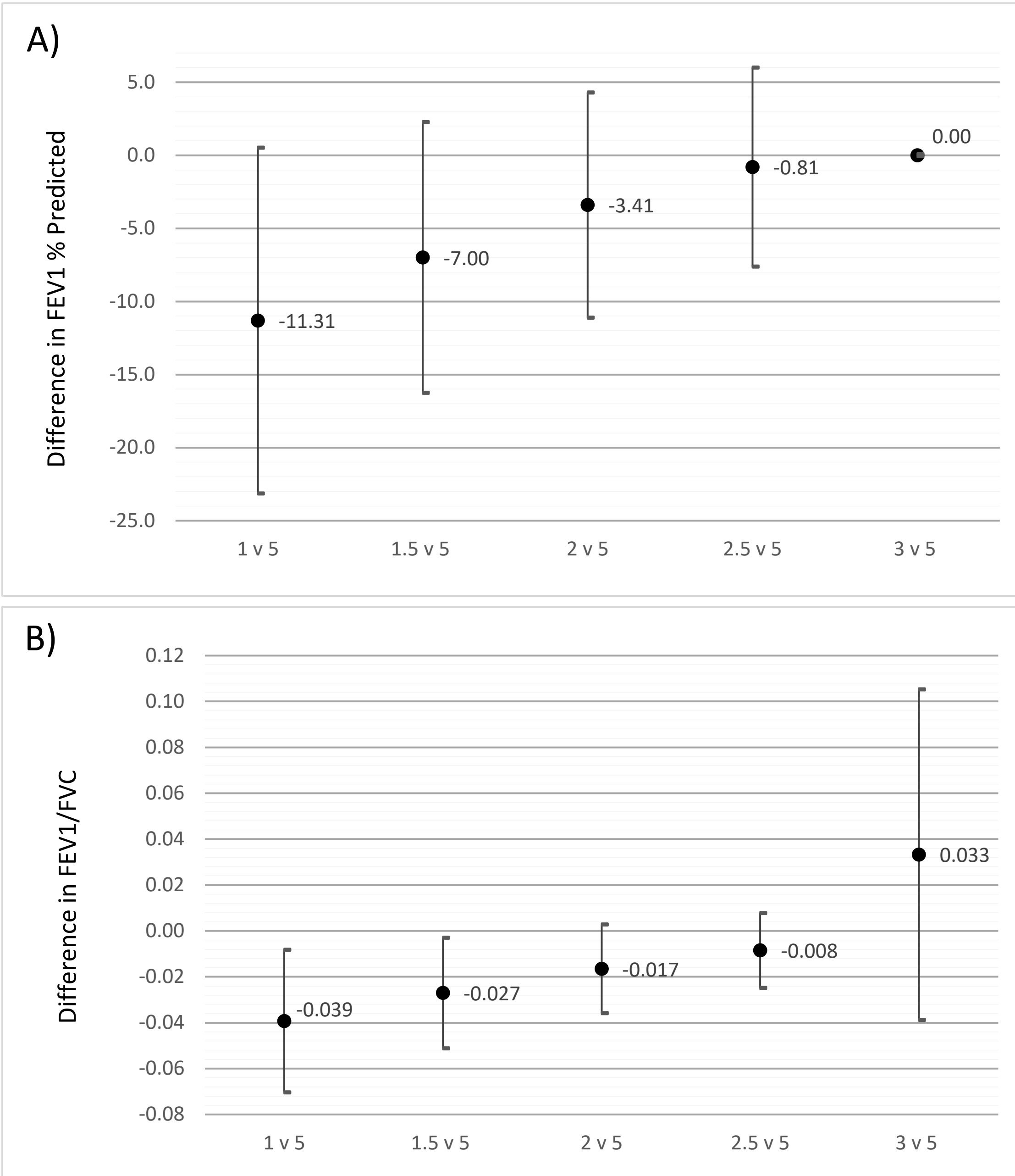


Figure 8. Results of linear regression assessing (A) FEV1% predicted and (B) FEV1/FVC ratio by restricted cubic spline of residential distance to the nearest CAFO. Residential distances of 1, 1.5, 2, 2.5 and 3 miles (1.6, 2.4, 3.4, 4.0, 4.8 km) from a CAFO were compared with a residential distances of 5 miles (8.0 km) from a CAFO. Models are adjusted for gender, age, poverty to income ratio, education, BMI, smoking status, pet ownership, height, and physical activity.

2.5 Discussion

These findings add to the emerging body of literature regarding public health impacts of concentrated animal feeding operations among rural populations. Much of the existing research has been conducted in Europe. This one of the first studies to examine how rural respiratory health is potentially influenced by farming practices in a general population based sample of adults in the United States. Among this well-characterized population-based sample, household proximity to a CAFO was associated with numerous respiratory outcomes including increased odds of self-reported allergies and asthma, and decreased lung function.

Our ability to explore nonlinear relationships between proximity to a CAFO and respiratory health outcomes was a strength of this study. We found spatial associations between living within 3 miles of a CAFO and increased prevalence of allergies, asthma, and decreased lung function. A 5 mile reference cut point was determined from visual plots of the cubic spline function of distance to the nearest CAFO regressed by each respiratory outcome. Our study found health effects tend to follow a similar nonlinear decline with distance from CAFOs as O'Shaughnessy and Altmaier's (2011) atmospheric dispersion modeling found when modeling H_2S emitted from swine CAFOs in Iowa showed where background levels were reached at 3-4 miles from a CAFO.[46]

Study findings are consistent with, and add strength to other U.S.-based studies of asthma and allergy symptoms among people living near AFOs or CAFOs. Pavilonis et al., (2013) found cumulative exposure to AFOs < 3 miles from residence was associated with an increased odds of asthma (1.51 p=0.014) and asthma medication or wheeze (1.38 p =0.023) among school age children.[231] Similarly, Rasmussen et al. (2017) found adult asthmatics recruited from a clinic based sample and living within 3 miles of a CAFO compared > 3 miles had increased odds of ordering asthma medications (OR =1.11 (95% CI: 1.04, 1.19) and asthma hospitalizations (OR=1.29; 95% CI: 1.15, 1.46).[16] The smaller farm sizes may have contributed to the smaller effect sizes seen in

Pavilonis et al. (2013) study. Not to mention, children may not present asthma symptoms until later in life, or may be less likely to have received a diagnosis than adults. The focus on hospitalizations and emergency department visits[16] may have underestimated asthma events by excluding those who live near CAFOs but do not seek medical care due to being uninsured, financially insecure, or far from services.

To our surprise, we found stronger associations with doctor diagnosed asthma than with current asthma. This was likely due to misinterpretation and timing of the survey questionnaire. Cross-tab frequencies on current asthma and asthma medication in the last 12 months revealed several participants reported not having current asthma because it is under control from taking asthma medication. Therefore, asthma medication use, episodes, and doctor diagnosed asthma may be more reflective of asthma prevalence

Current allergies of any type and nasal allergies were 2.5 times higher at 1 mile from a CAFO, and decreased to 1.3 times higher at 3 miles from a CAFO when compared to 5 miles from a CAFO. Lung allergies remained 2.2-2.6 times higher at distances 1-3 miles from a CAFO when compared to 5 miles. Our ability to assess allergy by type is a unique contribution, and something few studies have been able to do. Our study confirms findings from a few U.S. studies that have looked at proximity to CAFOs and allergies or allergy-like symptoms. Wing and Wolf (2000) found those living within 2 miles of a CAFO had increased prevalence of running nose, coughing, headache, itchy eyes, running nose, and sore throat.[15] Mirabelli et al. (2006) found stronger associations with adolescents attending schools within 3 miles of a CAFO and asthma when stratified by those with allergies.[35]

Findings in the U.S, are largely in contrast to those found in Europe, particularly in Germany and Netherlands, where proximity cut points are typically at 500m (0.31 miles) or 1000m (0.62 miles).[10,13,222] Several factors may contribute to this. For example, European confined livestock farms are generally smaller than in the U.S., densely clustered, and located in areas of higher population density. Thus, shorter distance cut points and livestock farm counts within 500 or 1000m are more appropriate. Borlée et al. (2017, 2015) is one of the few studies to assess nonlinear associations using cubic splines of CAFO proximity and nasal allergies, finding inverse results to those seen in this study.[10,222] Borlée et al. (2015) and Smit et al. (2014) both found inverse associations with doctor diagnosed asthma and allergies using EMR data in the Netherlands.[10,11] Hooiveld et al. (2016), another Netherlands study which used EMR data found null results, but did not use individually measured exposure data as seen in the other two Netherlands studies.[12] found self-reported asthma and nasal allergies were associated with increased livestock farm odor in Germany, but the number of animal houses near the home was not a predictor of allergies or specific sensitization.[13] is one of the few European studies to find those exposed to higher ammonia levels from livestock farms to be 4.2 times more likely to be sensitized against ubiquitous allergens.

Findings from European studies largely suggest livestock farms provide a protective, if any, effect and support the hygiene hypothesis, specifically with allergy endpoints. Recent research suggest that it may not just be the dose of microbial products from farming exposure which promotes a protective or harmful effect, but the type of microbial products may also play an important role.[178] Exposure to small-scale farming has been associated with having a more diverse microbiome which may increase immune function and may explain the protective effect seen against allergies and respiratory outcomes seen in Europe.[124] While distance cut points and settlement of livestock farms in relation to residences are different, the contrast in results suggests other differences may exist between the studies in the U.S. and Europe. Differences in the livestock farms themselves, the microbial diversity emitted, the regulations imposed on them, or the populations living near them may contribute to the different study findings.

Lung function was positively associated with proximity to a CAFO, with lung function improving as distance from a CAFO increased. Unlike with allergies and asthma, we found similar effect sizes, although most non-significant, as seen in European studies among adults. A distance of

1.5 miles was associated with -7.0% predicted FEV when compared with a distance of 5 miles from a CAFO. Schulze et al. (2011) found a -8.19 % predicted FEV1 among those with average ammonia concentration greater than or equal to 19.71 µg/m3 when compared to those with levels below. Similarly, Radon et al. (2007) reported a -7.4 % predicted FEV1 among those more than twelve animals houses within 500m of home. While definitions of exposure to CAFO varied, the fact that all three studies found very similar results suggests residential proximity to a CAFO, or many AFOs, is likely associated with decreased lung function.

As one of the first studies in the U.S. to use a statewide, population-based sample of adult residents to assess multiple respiratory health effects among people living in proximity to CAFOs, this study has numerous strengths. Prior U.S. studies have tended to rely on grouped exposures, removing individually variability among the exposure.[15,16,31,35] Our study was able to report on the nonlinear association between proximity to the nearest CAFO and respiratory health outcomes in the U.S., providing an important link between dispersion modeling of CAFO emissions and human health effects.

While utilizing a population-based statewide sample is a strength of this study, it is also a limitation. Rare exposures, such as living near a CAFO in the U.S., can result in low power and are best studied with cohort studies where subjects are selected by exposure status. Low power may have resulted in our inability to detect interaction with proximity to a CAFO and smoking status. Though we carefully controlled for multiple confounding factors, residual confounding or confounding by other unmeasured factors may affect estimated associations. We attempted to remove participants with current livestock exposure by excluding those with a farming occupation; we were not able to separate all current or historical occupational or lifestyle exposures to livestock. If we had been able to it may have influenced our results on allergies. Furthermore, the cross sectional nature of this study limits our ability to ascertain the temporal association between exposure and disease in this study. Self-report is not ideal and can lead to recall bias, however asthmatic and allergic symptoms may go clinically underreported in rural Wisconsin, where people may be less likely to seek medical care due to inconvenience, cost, or lack of insurance. While we had objective and self-report data on asthma, we relied on self-report of allergies. Therefore, we were unable to definitively tease out allergic and non-allergic asthma, something that would have strengthened the study and allowed more comparability with other studies. Furthermore, the lack of allergic sensitization data limits comparisons with other studies.

We were able to acquire retrospective CAFO data and ensure CAFOs linked to participant residences were in existence prior and during their study participation. However, the farm size and type could not be validated from this data. Additionally, we were unable to account for proximity to non-CAFO livestock farms. The assumption being made here is that the distribution of smaller farms is random throughout the study sample, resulting in non-differential misclassification bias. This assumption results in estimates biased towards the null.

2.6 Conclusion

In summary, residential proximity to a CAFO among individuals from a randomly sampled general population health survey was positively associated with self-reported nasal and lung allergies, asthmatic outcomes, and objectively measured lung function. This study provides evidence for respiratory health effects among residents living near dairy CAFOs. CAFOs may be an important source to regulate as current evidence suggest that concentrated animal feeding operations, irrespective of animal type, contribute to health disparities among rural residents.

Chapter 3. Residential proximity to concentrated animal feeding operations, asthma, and lung function among children and adolescents

3.1 Abstract

Background: Numerous studies have demonstrated a protective benefit of farm living on the development of asthma by rural children and adolescents. Most of the evidence in support of the hygiene hypothesis comes from small farm living. Yet, in the U.S. small-sized farms are decreasing in numbers while large-scale farms are on the rise. Emerging evidence suggests exposure to large-scale livestock farms may not offer the same protective benefits of small farm living. However, more research is needed as to whether children living near large-scale farms are at risk of impaired respiratory health.

Objectives: The goal of this study was to examine whether living in close proximity to a CAFO is associated with the prevalence of asthma and decreased lung function among children and adolescents across Wisconsin.

Methods: Data came from the 2014-2017 Survey of the Health of Wisconsin (SHOW) cohort of children and adolescents ages 0-17 (n=867). The association between distance to the nearest CAFO and the prevalence of self-reported physician-diagnosed allergies, current asthma, episodes of asthma in the last 12 months, and asthma medication use in the last 3 months was examined using logistic regression, adjusting for individual and household level confounders. Similarly, the association between distance to the nearest CAFO and lung function, measured using spirometry, was examined using multivariate linear regression. Restricted cubic splines accounted for nonlinear relationships between distance to the nearest CAFO and the aforementioned outcomes.

Results: Living 1.5 miles from a CAFO was associated with increased odds of wheezing (OR=2.19; 95% CI: 1.37, 3.51), asthma medication use (OR=2.96; 95% CI: 1.62, 5.42), and uncontrolled asthma, reported as an asthma episode in last 12 months (OR=2.42; 95% CI: 1.27, 4.61) when compared to living 6 miles from a CAFO. No associations were found with Predicted FEV1 or FEV1/FVC ratio and residential proximity to a CAFO.

Conclusions: Results suggest that CAFOs may be an important source of adverse air quality associated with asthma symptoms among children and adolescents living nearby.

Abbreviations: Concentrated Animal Feeding Operation, CAFO; Odds Ratio, OR; Confidence Interval, CI; Forced Expiratory Volume in one second, FEV1

Keywords: Air pollution, concentrated animal feeding operation, lung function, asthma

3.2 Introduction

Asthma is one of the most common chronic illnesses of children and adolescents in the US,[253] and is a leading cause of school days missed.[254] While the cause of asthma is still under debate, a mixture of environmental, lifestyle and genetic factors are known to be likely contributors of both asthma onset and asthma exacerbations.[255,256] Among these risk factors are air pollution, an environmental exposure for which children are particularly vulnerable [125] Children take in more air per unit body weight at a given level of exertion than adults do, equating to a higher dose of particulates, gases, and vapors in the air.[257,258] In addition, their developing immune system makes them potentially more vulnerable to airborne bacteria and viruses.[179] While outdoor air pollution is generally thought to be a problem of urban settings,[259] agricultural activities can also contribute to rural air quality.[57,58,260] [57,58,260]

Asthma has long been understood to disproportionately affect urban dwellers, with prior epidemiology studies focused on urban populations.[259] Studies of childhood asthma in rural communities have consistently found farm children to be less atopic, and in many cases, have lower rates of asthma than rural non-farm children and urban children.[33,261–266] However, recent studies are beginning to demonstrate rural pediatric asthma prevalence to be similar to urban and suburban asthma prevalence.[267–269] The challenge of teasing out the unique intersections of factors associated with asthma and rurality likely contributed to previous perceptions of rural/urban dichotomy in asthma prevalence.[270] Variations in "rural" definitions, asthma diagnoses, access to healthcare, and demographics made comparisons of these prior studies challenging as well.[270]

Numerous studies have demonstrated a protective benefit of farm living on the development of asthma by rural children and adolescents.[223] Explanations for this include exposure to dust and environmental microbial agents,[271–273] and increased diversity of the nasal microbiota which can strengthen the immune response and provide protective benefit.[171] Exposure to farm environments in early childhood has been shown to influence DNA methylation patterns in asthma and IgE-related genes in peripheral blood cells.[274] These findings are consistent with the hygiene hypothesis, which posits that childhood allergy and asthma risk is immunologically modulated in early life by exposure to infectious agents.[142,150,275] Most evidence in support of the hygiene hypothesis comes from small farm living.[276] Yet, in the U.S. small-sized farms are decreasing in numbers while large-scale farms are on the rise.[163,165,277]

Research examining children's exposure to large-scale, concentrated animal feeding operations (CAFOs) and asthma is in its infancy. Only a handful of studies have assessed the relationship between residential or school proximity to CAFOs and respiratory health among children and adolescents.[9,11,32,35,36,231,232] Three studies in the United States (U.S.) found the prevalence of asthma to be higher among children and adolescents attending schools,[31,35] and living,[30] near large swine operations in Iowa and North Carolina. A study in Yakima Valley, Washington recruited 51 children from a farm workers clinic and longitudinally measured ammonia levels every 6 days, and collected biweekly asthma symptoms and daily FEV1 measurements over 13 months.[32] The study found ammonia concentrations were correlated with proximity to dairy animal feeding operations, and FEV1% predicted was lower per IQR increase in 1 and 2 day lagged ammonia levels.[32] A study in Germany estimated individual exposure to bioaerosols from livestock facilities using a dispersion model and found estimated levels of bioaerosols to be correlated with the prevalence of asthma symptoms among atopic children of atopic parents.[36]

The emerging evidence suggests CAFOs may have negative respiratory health effects on children and adolescents living nearby. However, the number of studies thus far is limited. All but two studies[32,231] grouped exposure to CAFOs, removing individual variability of exposure. In addition, exposures have focused on AFOs, smaller in size than CAFOs. States have discretion to regulate large-scale livestock farms beyond the scope of what is required under the EPA's Clean Water Act National Pollutant Discharge Elimination System (NPDES) program.[224] This has resulted in variations in statewide public datasets on livestock farms, with some states having more accurate databases of AFOs rather than CAFO-sized operations. Furthermore, the settlement, quantity, and type of livestock farms vary across the nation. It is estimated that Iowa and North Carolina have about 10,000 and 6,500 CAFOs (mostly swine), respectively.[94,278] Whereas Washington and Wisconsin each have between 200-300 CAFOs each (mostly dairy).[47,279] Swine, poultry, and dairy operations can vary in terms of housing and manure storage. In fact, levels and types of bacteria and viruses have been found to vary inside CAFO housing facilities of different animal types.[26–28] More research is needed which expands this area of research to other geographic regions. Additionally, research which considers individual measurement of the exposure and includes objective measures of asthma, would strengthen the current literature.

This study aims to assess the association between residential proximity to CAFOs in Wisconsin and respiratory health effects among children and adolescents. Wisconsin ranks second after California as the state with the largest number of dairy cows [245] with over 90% of its CAFOs being dairy CAFOs.[47] Both self-report asthma outcomes and objectively measured lung function are assessed in a well-characterized, rural sample of 6-17 year old children in Wisconsin. A cubic spline regression is used to examine the association between residential proximity to CAFOs and respiratory health effects in order to account for non-linearity and retain individual levels of exposure.

3.3 Materials and Methods

3.3.1 Study Sample

Data came from the 2008-2017 Survey of the Health of Wisconsin (SHOW) statewide sample of children (n=867) and adults (n=6062). SHOW is an ongoing annual survey that began in 2008 and aims to recruit 400-1,000 participants every year. From 2008-2013 SHOW enrolled adults ages 21-74 (n=3380). From 2014-2016, adults ages 18+ (n=1957) and children ages 0-17 (n=645) were enrolled. In 2017, longitudinal follow-up was completed among 2008-2013 participants (n=725), and 222 children and adolescents completed the SHOW study for the first time.

SHOW participants are randomly selected using a probability sampling proportion to size without replacement (PPSWOR) approach.[246] Between 2008-2013, a two-stage probability-based cluster sampling was used to randomly select census block groups (stage 1) and household addresses (stage 2) annually within strata of region and poverty level.[246] SHOW 2014-2016 cohort was designed as a three-year sample. A three stage cluster-sampling approach was employed. One county per strata was randomly selected within strata of county mortality rates, followed by random selection of census block groups by poverty status strata. Then 30-35 residential households were randomly selected via US postal service listings.

Across 2008-2016 years of the study, participation ranged from 56-70% among all those who screened eligible. Response rates were higher in rural areas, and lower in urban areas. In 2017, 85% of eligible adults from 2008-2013 successfully completed longitudinal follow-up.

Figure 9 describes the analytic sample selected for this study. This study includes a subset of 571 children and adolescents ages 6-18. Children ages <6 years were excluded due to diagnoses of asthma rarely occurring before age 6. Subjects with missing data on any of the asthma outcomes or confounders of interest were also excluded from analyses, resulting in a final sample size of 542 for asthma outcomes, and 502 for lung function outcomes. All residential household addresses were geocoded using CENTRUS software (Pitney Bowes Inc., Stamford, CT) and linked to the nearest CAFO using ArcGIS v10.3 software (ESRI, Redlands, CA). Figures 10a-b display maps of the SHOW children and adolescent study population by census block group.

3.3.2 Concentrated animal feeding operations (CAFOs)

Data on CAFO location, type (dairy cow, hog, chicken, or turkey), years of operation and total animal units are maintained by the Wisconsin Department of Natural Resources' (WDNR) and Department of Agriculture, Trade and Consumer Protection (DATCP) under the Wisconsin Pollutant Discharge Elimination System (WPDES) program. WPDES falls under the Clean Water Act (CWA) National Pollutant Discharge Elimination System (NPDES) which requires states to regulate point source pollution to waters of the entire United States. CAFOs are defined by the CWA [Section 502(14)] as point sources, thus requiring a discharge permit and monitoring by WPDES.

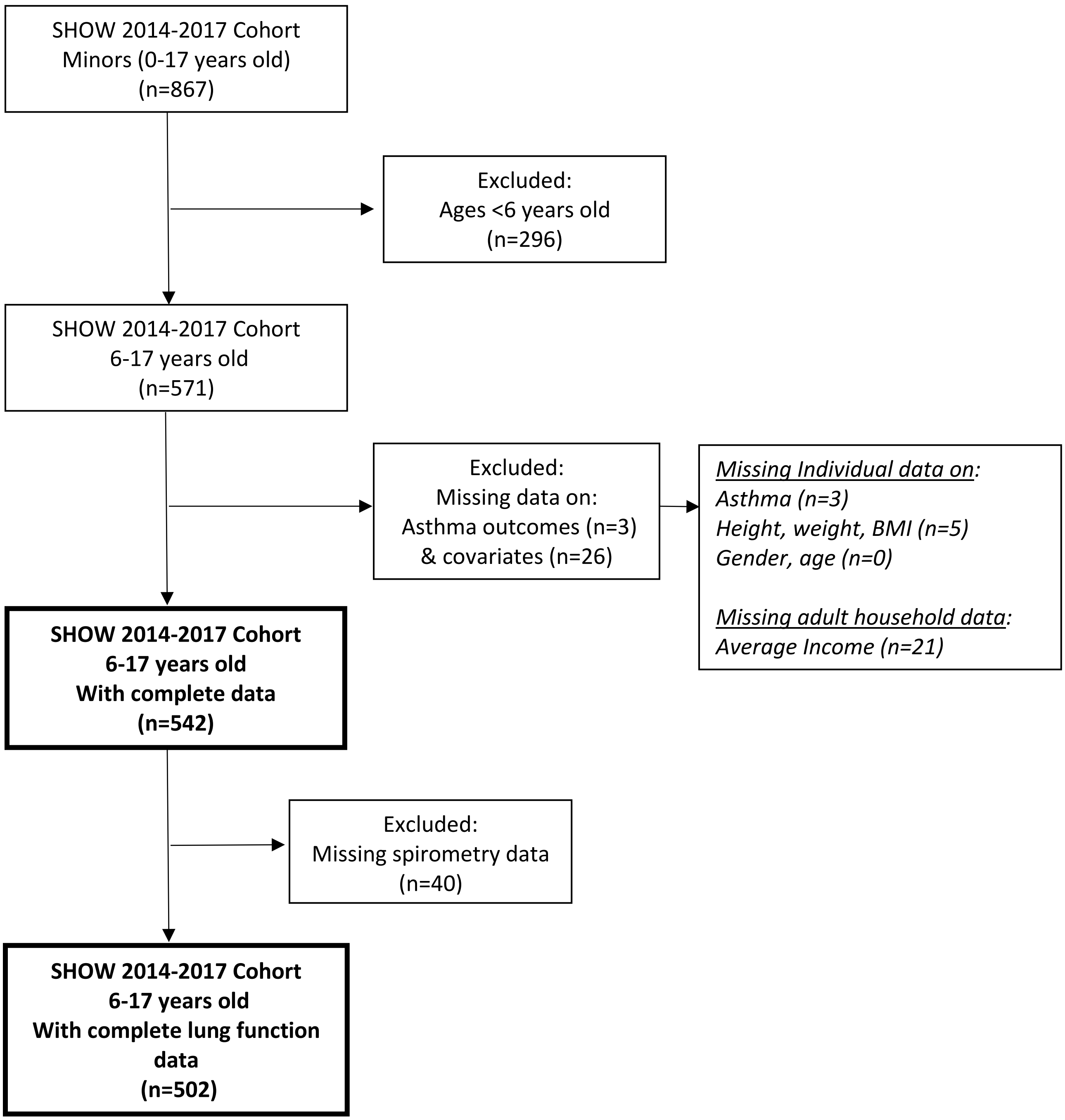


Figure 9. Flow chart of the study sample, depicting exclusion criteria and sample size.

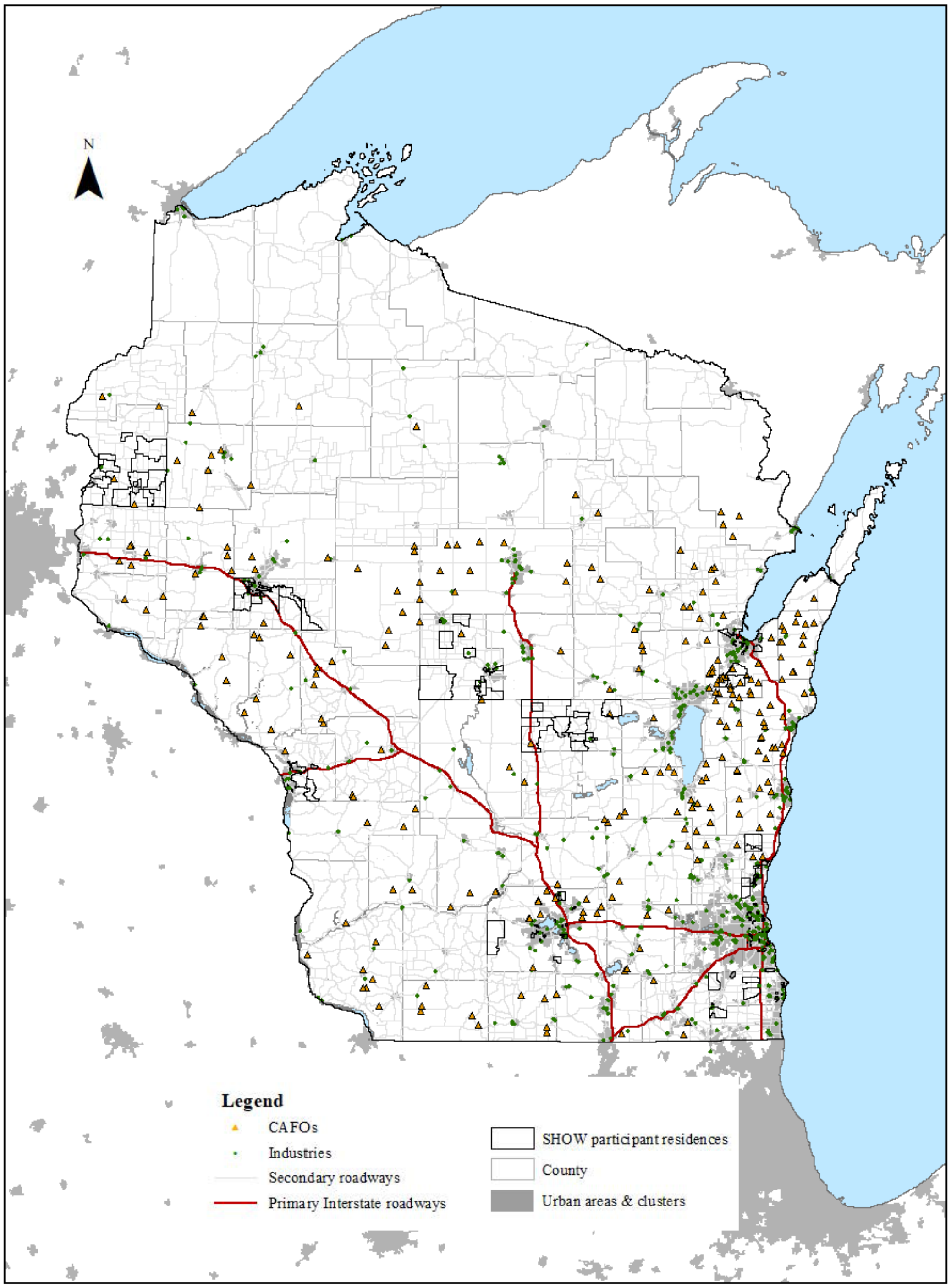
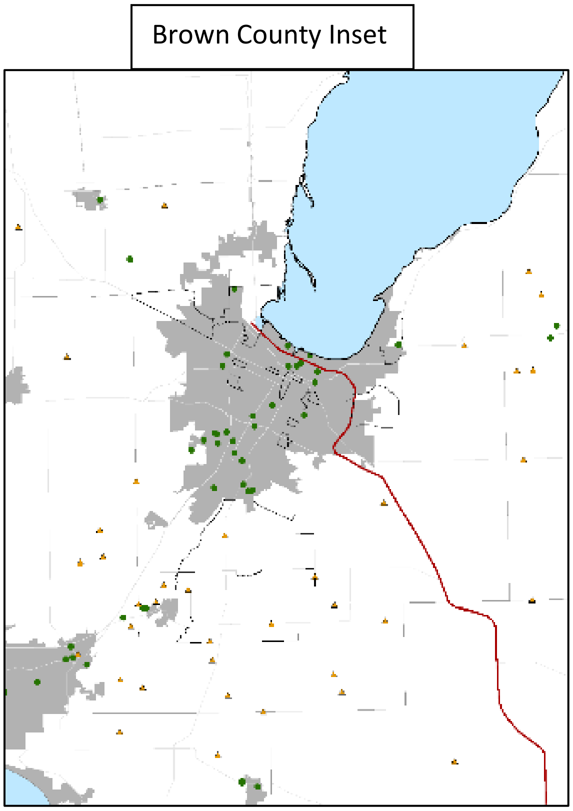
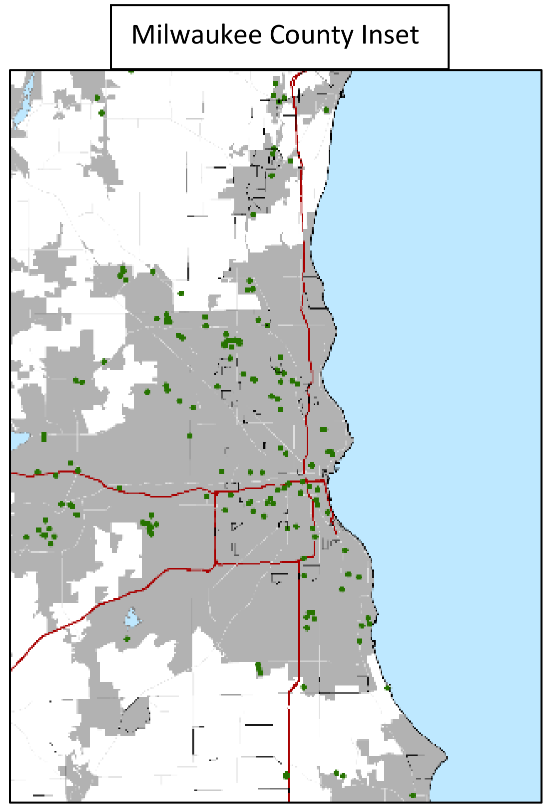
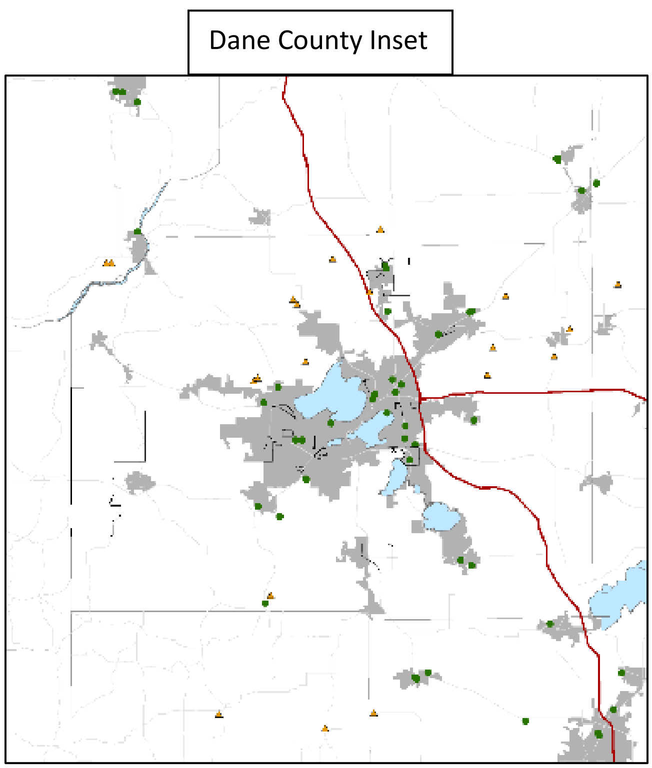


Figure 10a. Map of the study sample by cenus block group.







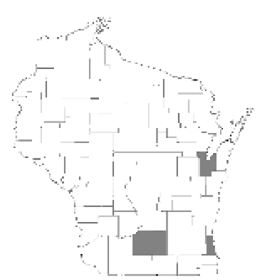


Figure 10b. Map insets of Brown, Milwaukee, and Dane county from Figure 10a Map. See legend on Figure 2a Map.

CAFOs are defined according to these standard definitions as an animal feeding operation (AFO) where the following conditions are met: 1) animals are confined for a total of 45 days or more in any 12-month period and 2) animals do not have access to crops, vegetation or forage growth in the normal growing season. AFOs that have 1000 or more animal units (1 animal unit = 1000 pounds of live animal weight) are considered a large CAFO (1000+ cattle, 700+ dairy cows, 2,500+ swine, 55,000+ turkeys). Medium CAFOs (300-999 cattle, 200-699 dairy cows, 750-2,499 swine, 16,500-54,999) are additionally regulated under WPDES if the facility has a manmade ditch or pipe that carries manure or wastewater to surface water or if the animals come into contact with surface water that passes through the area where they are confined.[48] See Table A1 for a table of the EPAs regulatory definitions for CAFOs.

According to publicly available data downloaded from WDNR WPDES program there were a total of 284 CAFOs operating in Wisconsin in 2016. Ninety percent (244 large, 2 medium) were dairy CAFOs, followed by swine (5 large, 9 medium), beef (10 large, 3 medium), poultry (1 medium, 10 small). Publicly available data were limited, therefore additional data including the location, start date, and end date of all permitted CAFOs established between 2013 and 2015 was obtained via an open records request to the Wisconsin DATCP. The DATCP data was used to ensure CAFOs were in existence during SHOW participants' year of participation in the study (when residential address and health data were collected). Figure 1 from the WDNR shows the proportion of CAFOs by animal type has remained stable over the last decade, with over 90% of the CAFOs in Wisconsin being dairy.

Children's residential proximity to the nearest CAFO was used as a proxy to estimate potential exposure to air emissions from CAFOs. Distance from a child's residence to the nearest CAFO was calculated using the "Near" tool in ArcGIS (ESRI, Redlands, CA). Participants were linked by cohort year to the nearest CAFO, only including CAFOs that were in existence during both the year they participated AND the year prior.

3.3.4 Asthma and lung function

Self-report history of asthma and wheezing was collected during in-home interviews with an adult proxy (a parent or guardian living in the home) for child and adolescents. Participants were defined as having current asthma if their adult proxy responded “yes” to the survey question “Does [child’s name] still have asthma?” which is a follow-up to the question “Has a doctor or other health professional ever told you that [child’s name] had asthma?” Adult proxies were also asked whether the child had an “episode of asthma or an asthma attack” during the last 12 months, and whether the child participant had taken medication prescribed by a doctor or other health professional for asthma in the last 3 months. Participants were considered to have wheezing if their adult proxy reported that their “chest sounded wheezy during or after exercise or physical activity” in the last 12 months.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured via spirometry using an electronic peak flow meter (Jaeger AM, Yorba Linda, CA), and validated protocol.[248] Trained technicians gave study participants explicit directions on how to breathe into the spirometry device. Measurements were considered valid if two FEV1 and FVC readings were within 10% of the highest value measured. FEV1 to FVC ratio (Tiffeneau index) and percent predicted FEV1 (FEV1 divided by predicted FEV1) were also assessed to account for inter-individual variability in lung function measurement. Predicted FEV1 was calculated using sex, race, age, and height as defined by the NHANES general U.S. population.[249]

3.3.5 Covariates and confounding

Adult proxies provided child participant demographics and health behaviors for children under 12 years of age. Adolescents (12-17 years) provided these data directly, which include age (years), gender (male vs. female), minutes/week spent in moderate to vigorous activity, and daily servings of fruits and vegetables. Body mass index (BMI) was calculated from measured weight and height as kg/m^2 and analyzed as the child's BMI-for-age percentile. BMI-for-age percentiles were calculated using 2000 CDC Growth Charts. While body compositions remain stable in adulthood, children's body compositions vary as they age and they vary between the sexes. Therefore, children's weight status and BMI levels need to be expressed relative to other children of the same age and gender rather than as categories used for adults.

Household level characteristics were derived from data collected from all adults in the home who participated in the SHOW study. Adult data used in this study included their average household education level, income, smoking status (if anyone in the household reported smoking yes/no), and whether there are pets in the home. Poverty to income ratios (PIR) were calculated for all adult's self-reported individual incomes using U.S. Department of Health and Human Services poverty guidelines and the midpoint of the household income range identified by the participant.

The following variables were derived from all adult participants in the home:

Derived variable:	Description:
Highest Education Level	The highest education reported among all adults in the home (high school or less, some college, bachelors degree or higher)
Poverty-to-Income Ratio	The average among all poverty-to-income ratios calculated for the adults in the home
Household smoking status	"Yes" if any adult in the home reported current smoking status "No" if all adults in the home reported former or never smokers
Household pets	"Yes" if any adult in the home reported pets in the home "No" if all adults in the home reported no pets in the home
Number of people residing in the home	The average among the total number of people living in the home reported by the adults in the home
Health insurance	"Yes" if any adult reported >= 1 month Medicaid/private in last yr. "No" if all adults reported <1 month or no insurance in last yr

To minimize confounding by previously identified environmental sources of asthma and respiratory health in the population[251] residential proximity to the nearest primary or secondary roadway and industry were also tested as confounders. Roadway data were obtained from the United States Census 2010, and the MAF/TIGER Feature Class Code (MTFCC) and Road Type Code (RTTYP) were used to identify roadway segments as primary and secondary (See Table A2 for US Census roadway type details).[280] Industries that are required to report fugitive[†] or stack[‡] air emission annually to the EPA were downloaded for the years 2013-2016 from the EPA website data came from the USEPA's 2014 Toxic Release Inventory (TRI) site database.[281]

3.3.6 Statistical analysis

Restricted cubic splines functions were applied to the residential distance to the nearest CAFO in order to account for nonlinear relationships between distance to the nearest CAFO and respiratory health. Knots were placed at the quartiles of the distance variable (0.46, 6.2, 8.8, 20.1, 36.5 miles). Univariate as well adjusted multiple linear (lung function outcomes) and logistic (asthma outcomes) regression models were used to examine associations between residential proximity to a CAFO and respiratory health.

Potential confounders were selected *a priori* from the literature. Age, BMI percentile (based on BMI for age z-score from NHANES growth charts) physical activity, servings of fruits and vegetable, PIR, number of household members, and distances to TRI site and roadways were used as continuous variables in all statistical models. Gender, smoking status, urbanicity, and pets were binary, and highest education level was categorical (<= high school or equivalent, some college,

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[†] Fugitive air emission are all releases to air that do not occur through a confined air stream. They include equipment leaks, releases from building ventilation systems and evaporative losses from surface impoundments and spills.

[‡] Point source air emissions, also called stack emissions, are releases to air that occur through confined air streams, such as stacks, ducts or pipes

Bachelors or higher) in models. Urbanicity was defined based on population density at the census block group level by the U.S Census Bureau as rural (<2,500), urban cluster (2,500-50,000) and urban area (50,000+). BMI-for-age percentile, physical activity, servings of fruits and vegetables, and proximity to roadways and TRI sties were categorized in Table 2 for ease of describing characteristics of the study population by exposure status. Cut points for BMI-for-age (<85 percentile vs. >= 85th percentile) were chosen from the Centers for Disease Control (CDC) which considers BMI-for-age at or above the 85th percentile to be overweight.[282] Physical activity cut points (<420 min/wk vs. >= 420 min/wk) came from the US Department of Health and Human Services recommendation that children and adolescents ages 6-17 years do at least 60 minutes of moderate-to-vigorous physical activity daily.[283] Fruit and vegetable servings were based on the American Heart Association's recommendation that children ages 4+ years have 4 servings of fruits and vegetables daily.[284] Cut points for proximities to roadways (<=400 meters vs. > 400 meters) and industries (<= 800 meters vs. > 800 meters) were chosen based on studies of dispersion modeling of vehicle emissions and distances where respiratory health impacts have been found.[251,285,286]

Covariates that did not change the main effect estimate by more than 10% were excluded from the multivariate models. AIC and BIC model fit statistics were used when determining the best fit model. An adjusted odds ratio (OR) or an adjusted beta-coefficient value with two-sided p-value < 0.05 was regarded as statistically significant. To acquire estimates from the spline regression, comparisons were made between different residential distances, while holding confounders constant. Residential distances of interest were chosen *a priori* from literature estimating air pollution and distance from CAFOs,[14,20,22,37,252] and from univariate spline regression trends between distance to nearest CAFO and each outcome. SAS version 9.4 (SAS Institute Inc. Cary, NC) was used for all statistical analyses. Due to clustering of the study sample within census block groups and within households, all analyses were performed as mixed models with random effects of census block group and household.

Sensitivity analyses were run to explore the extent to which residual confounding occurs when including urban residents in the study sample. Urban residents may be exposed to additional sources of air pollutants (vehicle and industry emissions) which rural residents may not be exposed to. See Figure C1. for a map of annual average fine particulate matter across the state, which shows urban areas to have higher levels on average. Furthermore, Table C1 shows the prevalence of asthma outcomes to be higher in urban areas compared to rural areas in our study sample. While the main analyses attempt to account for potential confounding by urbanicity, all models were run among a subset of participants where those residing in urban areas (n=334) were excluded. This resulted in a sample size of n=224 for asthma outcomes and n=211 for lung function outcomes. See Figure C2 for a study sample flow chart for sensitivity analyses.

Table 2. Characteristics of the study sample. Column percents of characteristics by residential distance are shown.

		Residential distance from nearest CAFO		
	Total Study Sample (n = 542)	**<= 5 miles** *2.4 km* **(n = 149)**	**> 5 miles** *8 km* **(n = 393)**	**p-value**
Individual characteristics	N	%	%	
Gender				0.6
Male	284	54.8	51.9	
Female	258	45.2	48.1	
Age (in years)				0.9
6-12	358	66.7	65.9	
13-17	184	33.3	34.1	
BMI percentile[a]				0.9
< 85th percentile *(not overweight)*	369	67.7	68.2	
>= 85th percentile *(overweight)*	173	32.3	31.8	
Time / week in moderate to vigorous Physical activity[b]				1.0
< 420 minutes	64	11.8	11.8	
>= 420 minutes	478	88.2	88.2	
Servings fruit & veggies[c]				0.002
< 4 per day	254	32.3	49.9	
>= 4 per day	288	67.7	50.1	
Household characteristics				
Current smoker				0.2
Yes	114	17.8	22.1	
No	390	82.2	77.9	
Household income				0.02
< $50,000	214	26.9	42.1	
$50,000 - $99,999	153	33.3	27.2	
>$99,999	175	39.8	30.7	
Health insurance				0.7
Yes	493	93.3	90.1	
No	49	6.7	9.9	
Highest Education				0.1
H.S./GED or less	75	8.6	14.9	
Some college	182	25.8	35.2	
Bachelors or higher	285	65.6	49.9	
Pet(s)				0.001
Yes	363	81.7	63.9	
No	179	18.3	36.1	
Household members (No.)				0.4
Less than 5	309	52.7	57.9	
5 or more	233	47.3	42.1	
Residence length				0.7
< 1 year	69	10.3	13.5	
>= 1 year	475	89.7	86.5	
Adult(s) with allergies				0.8
Yes	125	58.9	60.8	
No	191	41.1	39.2	
Adult(s) with asthma				0.02
Yes	106	10.8	21.4	
No	436	89.2	78.6	
Adult(s) asthma diagnosed				0.3
Yes	166	25.8	31.6	

No	376	74.2	68.4	
Proximity to TRI site				0.01
<= 800 meters	50	16.1	7.8	
> 800 meters	492	83.9	92.2	
Proximity to Primary road				0.2
<= 800 meters	42	4.3	8.5	
> 800 meters	500	95.7	91.5	
Proximity to Secondary road				0.3
<= 400 meters	224	36.6	42.3	
> 400 meters	318	63.4	57.7	
Census block group population				0.4
Rural or urban cluster	224	45.2	40.5	
Urban area	318	54.8	59.5	

CAFO: concentrated animal feeding operation; km: kilometer; N: number; H.S.: high school; GED: General Education Development test; BMI: body mass index; wk: week; TRI: Toxic release inventory.
p-trend: statistical significance by Chi-square test
[a]https://www.cdc.gov/obesity/childhood/defining.html
[b]https://www.cdc.gov/healthyschools/physicalactivity/guidelines.htm
[c]https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/dietary-recommendations-for-healthy-children

3.4 Results

Descriptive characteristics of the study sample by residential proximity to the nearest CAFO are presented in Table 2. Children and adolescents living within 5 miles of a CAFO were more likely to eat 4 or more servings of fruits and vegetables per day, have pets in the home, and live near an industry site when compared with children and adolescents living more than 5 miles from a CAFO. Participants living near a CAFO were also slighty more likely to have adult participants report having health insurance and higher household incomes compared to participants living more than 5 miles from a CAFO. However, participants living near a CAFO were less likely to have one or more adults in the home who smoke or have current asthma. Interestingly enough, slightly more participants living in urban areas (census block groups with >50,000 residents) live within 5 miles of a CAFO when compared with urban cluster and rural participants, defined based on census definitions of urbanicity. Gender, age, BMI, physical activity, and number of household members did not vary significantly between exposure groups.

Unadjusted cubic spline plots revealed the log odds of asthma outcomes decreased and FEV1 / FVC ratio increased, as distance from a CAFO increased from 0 to 6 miles (See Figure C3). After about 6 miles from a CAFO, the log odds of asthma outcomes increases again. Contrary to the FEV1 / FVC ratio plot, the FEV % predicted, FEV1 (not shown), and FVC (not shown) plots all displayed decreases as distance from a CAFO increases.

Residential proximity to a CAFO was associated with asthma, wheezing, and asthma control measures, including one or more asthma attacks in the last 12 months or asthma medication use in the last 3 months. Figure 11 shows the results of multivariate models of distance to the nearest CAFO and asthma outcomes, adjusting for gender, age, BMI percentile, household-based poverty-to-income ratio, smoking status, number of people in the home, and proximity to secondary roadways and industries. Wheezing in the last 12 months, asthma medication use in the last 3 months, and asthma attach in the last 12 months had the largest effect sizes with proximity to the nearest CAFO, with estimated odds of 1.6 to 3.3 times greater among those living 1 to 3 miles from a CAFO when compared to those living 6 miles from a CAFO. Current asthma and doctor diagnosed asthma was 1.8 to 1.3 times greater at residential distances of 1 to 3 miles from a CAFO, respectively, but the results were not statistically significant. Table C2 shows the unadjusted and adjusted results of all distance comparisons made with the aforementioned asthma outcomes, including a reference distance of 10 miles in addition to 6 miles. Effect size increased once adjusted for confounders, except for asthma attack in the last 12 months, which saw a decrease in the effect sizes seen once adjusted.

FEV1 percent predicted and FEV1/FVC were not significantly different at residential distances near a CAFO when compared to 6 miles from a CAFO (Figure 12). FEV1 percent predicted and FEV1 / FVC remained slightly higher among those living 1-3 miles from a CAFO when compared to living 6 miles from a CAFO. No significant trend was seen even after adjusting for gender, age, BMI, height, physical activity, smoking status, poverty-to-income ratio and proximity to roadways and industries. Table C3 shows the unadjusted and adjusted results of all distance comparisons made with FEV1, FVC, FEV1 % Predicted, and FEV1/FVC ratio, including a reference distance of 10 miles in addition to 6 miles.

Results from the sensitivity analysis can be viewed in Appendix C. Unadjusted cubic splines with urban area residents excluded revealed similar trends as the main study sample, with the log odds of asthma decreasing as distance from a CAFO increases from 1 to 6 miles (Figure C3). However, the while the main study sample saw an increase in log odds of asthma after about 6 miles, the subset without urban participants tended to level off at sound 10-15 miles from a CAFO. Furthermore, lung function show a decreasing trend past 10 miles from a CAFO in the main study sample, but showed the exact opposite trend when urban residents were excluded. Tables C4-C8 shows results comparing main study sample, urban area residents excluded, and Milwaukee residents excluded among selected outcomes. Similar effects were seen among all three study samples, with the largest effect sizes seen when urban area residents were excluded and the lowest effect sizes seen when urban and rural residents are included.

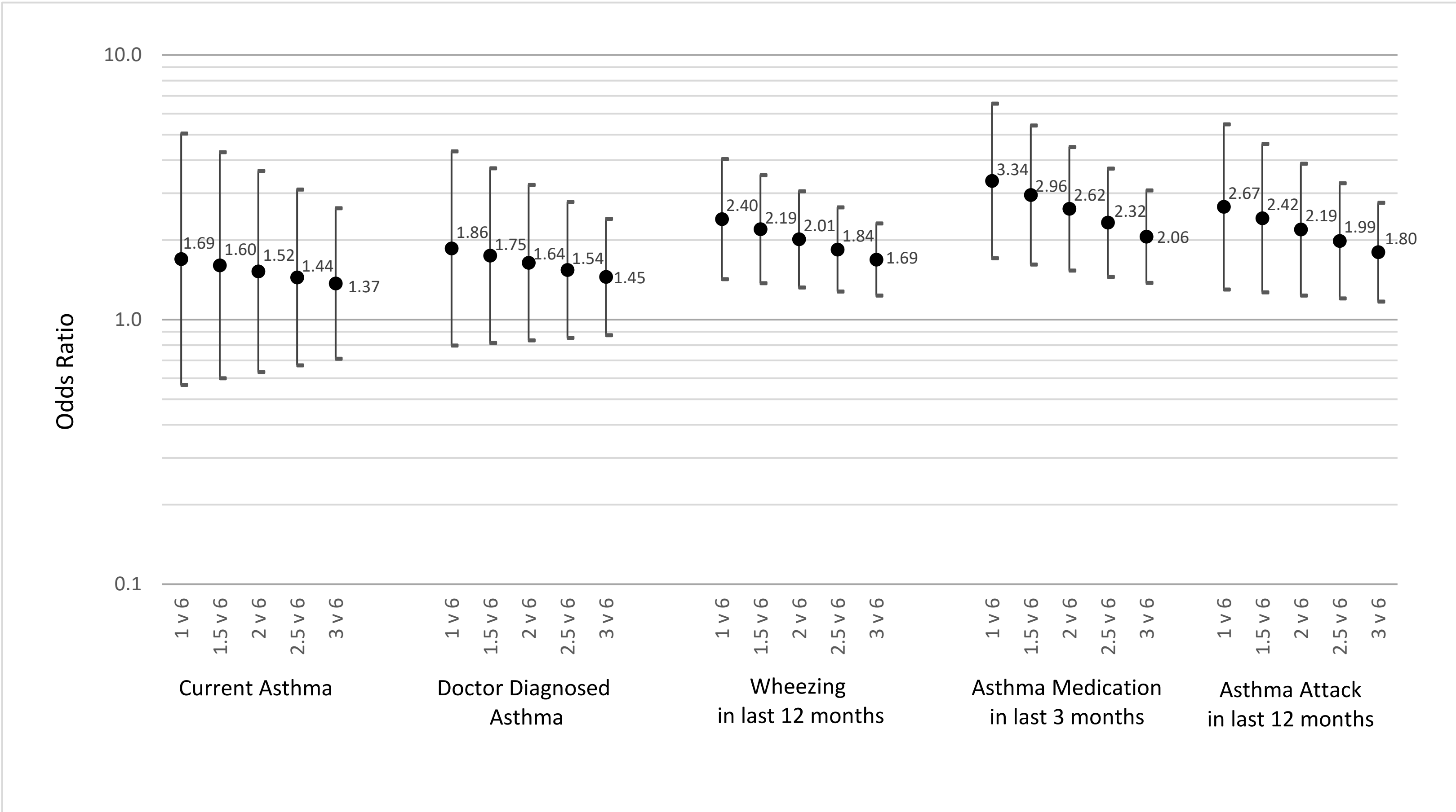

Figure 11. Results of logistic regression assessing asthmatic outcomes by restricted cubic spline of residential distance to the nearest CAFO. Residential distances of 1, 1.5, 2, 2.5 and 3 miles (1.6, 2.4, 3.4, 4.0, 4.8 km) from a CAFO were compared with a residential distances of 6 miles (9.7 km) from a CAFO. Models are adjusted for individuals gender, age, BMI, and household-based poverty to income ratio, smoking status, number of people in the home, and proximity to major roadways and industries.

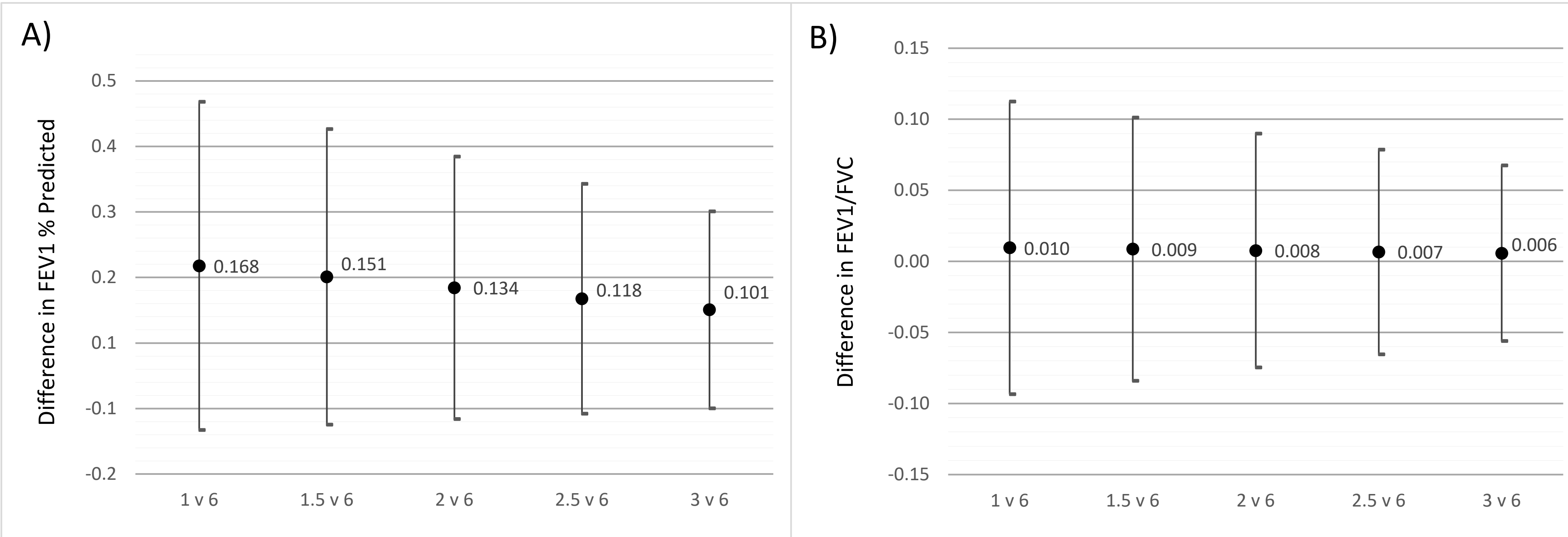

Figure 12. Results of linear regression assessing (A) FEV1% predicted and (B) FEV1/FVC ratio by restricted cubic spline of residential distance to the nearest CAFO. Residential distances of 1, 1.5, 2, 2.5 and 3 miles (1.6, 2.4, 3.4, 4.0, 4.8 km) from a CAFO were compared with a residential distances of 6 miles (9.7 km) from a CAFO. Models are adjusted for individuals' gender, age, BMI, height, physical activity and household-based poverty to income ratio, smoking status, and proximity to major roadways and industries.

3.5 Discussion

Our results provide unique insight into potential exposures children living near dairy CAFOs may face, and their associations with respiratory health. We found children and adolescents living in proximity to a CAFO were more likely to have had a wheezing episode in the last 12 months and have taken asthma medication in the last 3 months. While we found similar associations with doctor diagnosed asthma, current asthma, and asthma attack in the last 12 months, they were not statistically significant. Lung function measured via spirometry was not found to be associated with proximity to a CAFO. This study adds to the paucity of research to-date which has investigated the potential effects CAFO air emissions may have on children living nearby.

The elevated prevalence of wheezing and asthma outcomes among children living near CAFOs found in this study is plausible given the known bioaerosols, endotoxins, particulate matter and gases CAFOs emit.[32,54–56] Although exposure is likely to be orders of magnitude smaller at nearby residences when compared to levels measured inside and near CAFO facilities, children may be vulnerable to low doses of air pollutants compared to adults due to their developing immune and respiratory symptoms.[125] This evidence is supported by prior studies in North Carolina, Iowa and Washington.[30,35,232] In North Carolina, a statewide school study found students who attended schools nearby swine CAFOs (within 3 miles) were 24% more likely to report current wheezing symptoms.[35] Children in an Iowa who had a larger relative exposure to AFOs (based on distance, size and direction of AFOs within 3 miles of home) had an increased odds of both asthma and medication for wheeze.[30] Another Iowa study found children who attended an elementary school located within 800m of a swine AFO had an increased prevalence of physician-diagnosed asthma (OR=5.71, p = 0.004) compared to children who went to school far from a AFO (>16 km away).[232]

These results are in contrast to decades of research which have indicated children who live on farms or have livestock exposure in early life have a decreased risk of developing atopy and asthma.[151,165,264,287–289] This protective effect, known as the Hygiene Hypothesis, is still heavily researched and debated, but exposure to microbial burden and diversity is thought to play a major role in both the protective and deleterious effects associated with farming.[124,289] Alpha and Beta diversity of children's nasal microbiome have been associated with having a protective effect against atopy and asthma, which has been linked to farm exposure.[290] However, most studies finding a protective effect with farm exposure in early life have been on non-CAFO sized farms, where children are exposed to different livestock, grasses, hay, dirt, dust, feed, and fodder.[124,163,170,265,275,291] Among these studies, is a study in Wisconsin which found children in rural areas on farms were less likely to have asthma compared to children from nonfarming environments in rural areas.[167]

There is limited research comparing microbial differences on CAFO-size livestock farms to smaller livestock farms, and so the conflicting health effects seen in studies exposed to small farms when compared to larger farms is not clear. It may be that exposure to CAFOs results in too high of a dose of microbial burden and other particulates and gases. It may also be that living near CAFOs results in exposure to a decrease in the diversity of microbes with an abundance of a few inflammatory microbes, when compared with smaller farms. Sequencing of 16SrRNA components of aerosols at varying distances from dairy CAFOs in Colorado revealed a microbiome derived predominantly from animal sources with bacterial genera dominate by Staphlyococcus, Streptococcus, Haemphilus and Pseudomonas, all of which have pro-inflammatory and pathogenic capacity in humans.[174]

Research comparing microbial diversity found on different types and sizes of farms is scarce. However, there is some supporting evidence suggesting that antibiotics may play a role in decreased microbial diversity and result in an increased risk of allergic disease. A rural pediatric asthma study in Iowa found asthma prevalence was higher among children growing up on swine farms that use antibiotics in the feed when compared to those growing up farm without antibiotic use and those from non-farm environments.[33] This evidence is plausible as dairy cattle are principal reservoirs of reservoirs of Staphylococcus, an opportunistic pathogen among humans that can rapidly evolve toward an antibiotic-resistant phenotype.[174] Antibiotic usage and resistance is a well-known disruptor of asymptomatic colonization patterns and can result in reduced microbial diversity.[175] As livestock farms grow in quantity and concentration, so does the risk of disease and antibiotic usage.[66–68] In fact, high concentrations of several veterinary antibiotics have been found in airborne PM downwind and upwind of cattle CAFOs, where microbial communities of PM downwind were enriched with ruminant-associated taxa and were distinct when compared to upwind PM.[70,71] Furthermore, gene encoding resistance to tetracycline antibiotics were significantly more abundant in PM collected downwind.[70]

One strength of our study is our use of cubic splines to account for non-linear associations between residential proximity to CAFOs and respiratory outcomes. The unadjusted splines revealed those living <3 miles from a CAFO had a higher log odds of asthma outcomes, which decreased as residential proximity increased towards 3 miles from a CAFO. At residential distances between 3-7 miles from a CAFO, the log odds of asthma outcomes were lowest, and then the rose again as distance from a CAFO increased. While we cannot be certain what this dip in prevalence of asthma outcomes is due to, it may be suggestive of a protective effect against asthma from having a lower, but not too dose of microbes and other air pollution. In constant, living very near a CAFO may equate to a high microbial burden (and exposure to other air emissions) which may influence respiratory symptoms, it could be that those who live 3-7 miles from a CAFO experience a dose of microbial burden low enough that protective effects are attained.

It is equally possible that those residing 3-7 miles from a CAFO are no longer influenced by a nearby CAFO, but perhaps are experiencing increased microbial diversity because they more likely to live on smaller farms, with more livestock variety, or are different in other ways from those living nearer to CAFOs. However, this cannot be determined from the data in this study. Evidence of residential proximity to a CAFO and respiratory health effects have been seen within 3 miles of a

CAFO, with little to no evidence of effects past 3 miles.[16,30,32,35,232] Unfortunately, the use of distance to the nearest CAFO is a crude measure of exposure which does not account for other CAFO and non-CAFO size exposures, and is a limitation in this study. It is possible livestock farms just below CAFO-size may emit just as much or more air emissions due to having less regulation, and as a result less advanced technologies to reduce air emissions. Accounting for exposure to other non-CAFO farms in this study was something that could not be done, and is a limitation of this study. Furthermore, management practices, facility equipment, manure and livestock storage, building and ventilation structures can all influence CAFO air emissions, which were also not considered.[27,229,230,292,293] Lastly, distance to the nearest CAFO does not capture exposure to local and regional air pollution from having several CAFOs or AFOs in the area. All of these factors may have resulted in misclassification of the exposure such that our spline and results may not be reflective of true exposure to CAFO air emissions and its association with asthma and lung function.

While trends were similar for all asthma outcomes, current asthma, doctor diagnosed asthma, and having an asthma attack in the last 12 months were not statistically significant. Childhood asthma is commonly underdiagnosed by physicians and asthma status obtained through self-report through questionnaires may not be sensitive enough to detect all cases.[33,294,295] A study investigating childhood asthma prevalence in two rural Iowa counties found that among the 14% of participants who reported asthma symptoms, only 42% had been given a diagnosis by a doctor. Asthma medication may be better indicator of asthma.[295] Furthermore, a cross-tabs with current asthma and asthma medication use revealed some participants who responded to not having current asthma due it being controlled via their current asthma medication use. Therefore, misinterpretation of a potentially poorly worded question may have contributed to non-significant results with current asthma. No associations or trends were found with lung function and proximity to a CAFO. This was contrary to results seen in a longitudinal study in Washington which found measured ammonia levels to be correlated with residential proximity to CAFOs, and associated with a decrease in FEV1 % predicted, but only with one and two day lagged concentrations.[32] Few studies have assessed lung function among children living near CAFOs and thus there is not a lot of supporting evidence to suggest lung function is associated with proximity to a CAFO or not. While one would perhaps expect lung function to be lower among those living closer to a CAFO due to the increased exposure to air emission, it is also collected just once in this study and may be more reflective of acute exposure. Whereas as the asthma outcomes were asked about symptoms and diagnoses over 3 month months, 12 months, and the entire life period and may be more reflective of chronic exposure from nearby air emissions.

This study was unique in that its study sample came from statewide sample. Prior studies have primarily sampled in very specific communities, counties, or used panels of volunteers.[4,15,24,30,32,232] However, this posed an additional challenge many prior studies did not face, which was the geographical differences among study participant – specifically the inclusion of urban and rural participants who are known to be exposed to different sources of air pollutants. Sensitivity analysis revealed results from the main analyses likely have residual confounding from urban areas. While proximity to the nearest industry and roadway attempted to account for confounding air pollution from sources in urban areas, they are imperfect proxy measures of air emission exposure from other source. True exposure to other sources of air emissions was likely was not accurately accounted for, and perhaps there are differences between urban and rural participants confounding the associations seen that could not be accounted for. When Milwaukee county residences are excluded, effect sizes increase, and are even stronger when all urban areas residents are excluded. One would expect the inclusion of urban residents to bias results towards the null since air pollution and asthma prevalence is higher in the urban areas (See Figure C1 and Table C1). However, due to a small sample size, and the high number of participants classified as living in an urban area but also live within 5 miles of a CAFO, we decided to not excluded participants due to geography in our model.

A significant limitation of this study was the study sample. Population-based samples are not ideal for rare exposures, such as living near a CAFO. As such, we had limited power and ability to adequately look at all potential confounders in models, and test for interactions. Furthermore, while the SHOW program collects a lot of information on the study subjects, we did not have information on the history of respiratory infection at an early age, prenatal/material exposure, or daycare information, all known factors associated with asthma.

3.6 Conclusion

This study adds to the growing national and international literature assessing whether there are any associations between residential proximity to CAFOs and respiratory health. This study is also the first epidemiology study in Wisconsin to specifically look at residential proximity to CAFOs and respiratory health in Wisconsin. It is important this research extend to new geographical areas. The number of CAFOs, settlement patterns of CAFOs near other communities, and CAFO regulations vary by state. While this study will not provide any answers for residents in the state living near CAFOs, it does start to build the foundation of research which is needed to help inform future policy and regulation decisions in the state. Future research should consider either a cohort sample where participants are selected by their exposure status to ensure adequate power to detect associations, or a case-control study in selected counties where CAFOs are prevalent. An assessment of participants' community, livestock exposure, other non-CAFOs in the area, and personal air monitoring would strength this study and reduce misclassification of the exposure. More research is warranted as researchers and experts continue to tease out what factors potentially make farming exposure protective and which factors potentially make farming deleterious, specifically how microbial burden and diversity differs by varying degrees of exposure to farming and livestock.

Chapter 4. Cumulative school and home exposure to concentrated animal feeding operations and pediatric and adolescent asthma

4.1 Abstract

Background: Residential and school proximity to a CAFO have both been found to be separately associated with asthma among children. However, no studies have attempted to create a relative exposure metric which accounts for a child's combined exposure to CAFOs at both school and home. Estimating exposure at both locations may better capture potential exposure to CAFO air emissions.

Objectives: This study aims to assess the association between residential and school proximity to CAFOs in Wisconsin and respiratory health effects among children and adolescents.

Methods: Data came from the 2014-2017 Survey of the Health of Wisconsin (SHOW) cohort of children and adolescents ages 0-17 (n=867). ArcGIS is used to link CAFO and wind data to children's homes and schools. A relative exposure metric ($LogE_{relative}$) is used to estimate the additive exposure from all CAFO air emissions from both time spent at home and school, taking into account CAFO size, distance, wind direction and wind speed from all CAFOs in the state.
The association between relative exposure to CAFOs and the prevalence of self-reported physician-diagnosed allergies, current asthma, episodes of asthma in the last 12 months, and asthma medication use in the last 3 months was examined using logistic regression, adjusting for individual and household level confounders. Similarly, the association between relative exposure to CAFOs and lung function, measured using spirometry, was examined using multivariate linear regression. Restricted cubic splines accounted for nonlinear relationships between relative exposure to CAFOs and the aforementioned outcomes.

Results:
The odds of having been diagnosed with asthma and having a wheezing episode in the last 12 months was 50-90% higher at the 95th percentile of the relative exposure to CAFOs when compared to the 50th-85th percentile of $LogE_{relative}$. Asthma medication use and current asthma showed similar trends, although with smaller effect sizes, and non-significant results. No associations were found with Predicted FEV1 or FEV1/FVC ratio and residential proximity to a CAFO.

Conclusions: Associations were found between having a large potential exposure to CAFOs and physician diagnosed asthma and wheezing, while no associations were found with lung function. This study is an important contribution to the field in its development of an exposure metric which considers potential exposure to CAFOs from the two locations where children tend to spend most of their time.

Abbreviations: Concentrated Animal Feeding Operation, CAFO; Odds Ratio, OR; Confidence Interval, CI; Forced Expiratory Volume in one second, FEV1

Keywords: Air pollution, concentrated animal feeding operation, lung function, asthma

4.2 Introduction

The number of livestock farms in the U.S has been decreasing since the 1980s, while the number of animals has increased and are increasingly being housed on large-scale farms, called concentrated animal operations (CAFOs).[233] CAFOs are defined as 1000 or more pounds of live animal weight (i.e. 1000+ cattle, 700+ dairy cows, 2,500+ swine, or 55,000+ turkeys), confined in close quarters for 45 days or more with no access to vegetation.[49,65] Livestock farms are known to emit non-biological aerosols from animal feed, skin cells, hair, and dried manure, as well as biological aerosols including endotoxins, bacteria, and fungi from liquid manure.[32,54–56] While these emissions may be protective at lower doses, the increase in quantity and concentration of air emissions produced as livestock farms increase to CAFO-size may be at too high of a dose to reap protective immune system benefits. This has been shown to be the case among adult farmers and CAFO workers whose exposure to livestock emissions is higher than children who grow up on a farm but are not in direct and frequent contact with livestock.[17,197–203]

CAFOs are also of concern due to the nature of the agricultural practices required for large scale farming. The primary exposures of concern may differ not only in concentration and type when compared with exposures from smaller farms. Large scale farming has been associated with greater levels of particulate matter, gases, and vapors containing a mixture of natural and man-made products.[32,54–56] Antibiotics and potential for increased risk of antimicrobial resistance are an additional concern. Antibiotic use increases as the quantity and concentration of livestock increase,[66–68] and is known to disrupt asymptomatic microbial colonization patterns and cause a loss of microbial diversity.[42,124,175] Prevalence of asthma was found to be higher among children who grew up on swine farms in a rural health Iowa study, but the highest prevalence was among children on farms with antibiotic added to the feed.[33] Dairy cattle are principal reservoirs of Staphylococcus aureus, an opportunistic pathogen among humans that can rapidly evolve toward an antibiotic-resistant phenotype.[174] Staphylococcus, Pseudomonas, and Streptococcus have been found to be the most abundant taxa originating from animal feces when bioaerosols were measured in and around dairy CAFOs in Colorado.[174] Early asymptomatic nasal colonization with Streptococcus in early childhood has also been found a strong predictor of asthma.[175]

Children take in more air per unit body weight at a given level of exertion than adults do, lending them to be more susceptible to their environment.[257,258] Research on exposure to CAFOs and the development of the immune system is complicated by the fact that some farm-life exposures are thought to be beneficial, while other evidence suggests that beyond a certain threshold of exposure, an increased risk of respiratory heath effect may ensure. For example, xposure to farming in early childhood is known to stimulate the immune system and be associated with decreased risk of developing allergies and asthma.[124,264,277,296] The increase in microbial burden from farm life (i.e. exposure to livestock, pets, endotoxin and nonpasteurized milk) can help to promote healthy development of the immune system.[124,154,173,264] This is further supported by studies showing household dust and the nasal microbiota from farm children to have higher alpha and beta diversity than those found from nonfarm children, and lower nasal microbiota diversity to be associated with asthma prevalence.[171] Yet, the studies supporting the protective effect of farm exposure (i.e. the hygiene hypothesis) have been conducted on children growing up on small-scale farms, mostly in Europe.[124,165,264,265]

Epidemiologic evidence of childhood exposure to CAFOs and respiratory health are limited. There is a need for studies that consider cumulative exposure from multiple CAFOs in the area, and consider exposure children may encounter when at both school and home. Two studies have found school proximity to CAFOs to be associated with asthma and wheezing.[35,232] An Iowa study found children who attended an elementary school located within 800m of a swine AFO had an increased prevalence of physician-diagnosed asthma (OR=5.71, $p = 0.004$) compared to children who went to school far from a AFO (>16 km away).[232] In North Carolina, a statewide school study found students who attended schools nearby swine CAFOs (within 3 miles) were 24% more likely to report current wheezing symptoms.[35]

There is additional evidence that residential proximity to large-scale livestock farms may be associated with an increased prevalence of pediatric asthma and lung function. Children in an Iowa who had a larger relative exposure to animal feeding operations (based on distance, size and direction of AFOs within 3 miles of home) had an increased odds of both asthma and medication for wheeze.[30] A longitudinal study among schoolchildren in Washington found measured ammonia levels was found to be correlated with residential proximity to CAFOs, and associated with a decrease in FEV1 % predicted among children living near CAFOs in Washington, but only with one and two day lagged concentrations.[32]

This research is in its infancy, and as such, preliminary studies have relied on proxy measures of exposure to CAFOs, often using distance to a CAFO as a surrogate for CAFO air emissions exposure. Studies have examined exposure to CAFOs and respiratory health without consideration of a cumulative risk approach, and have not considered the combined impact exposure to CAFOs while children are at school and home and its potential impact on their respiratory health. More refined exposures that account for children's potential exposure to CAFOs while at both school and home, and integrate information on wind direction and speed, could improve overall estimates of exposure to CAFOs and reduce concerns of mis-classification bias in observational epidemiology studies.

Wind direction, wind speed and size of farm are known factors which can influence air emissions measured upwind and downwind from CAFOs facilities,[37,174,297–300] and a few studies have additionally incorporated these factors into estimating exposure to CAFO air emissions.[30,32,35] Furthermore, studies have relied on estimates of exposure to CAFOs within 3 miles from a CAFO, without considering how multiple CAFOs in area beyond 3-5 miles of a residence or school may affect local and regional air emissions.

This study aims to assess the association between residential and school proximity to CAFOs in Wisconsin and respiratory health effects among children and adolescents. A relative exposure metric is used to estimate the additive exposure from all CAFO air emissions from both time spent at home and school, taking into account CAFO size, distance, wind direction and wind speed. This study not only adds to the literature by attempting to refine estimates of exposure to CAFO air emissions, but it extends this area of research into a new geographical region in the United States. States have authority delegated by the EPA to regulate CAFOs, which has resulted in states' tailoring CAFO regulations to suit the needs and concerns unique to their state, where settlement of CAFOs vary. Not only is this a relevant study at the national and internally level, but it provides important insight into potential health concerns residents near CAFOs may face at the state level in Wisconsin.

4.3 Materials and Methods

4.3.1 Study Sample

Data came from the 2008-2017 Survey of the Health of Wisconsin (SHOW) statewide sample of children (n=867) and adults (n=6062). SHOW is an ongoing annual survey that began in 2008 and aims to recruit 400-1,000 participants every year. From 2008-2013 SHOW enrolled adults ages 21-74 (n=3380). From 2014-2016, adults ages 18+ (n=1957) and children ages 0-17 (n=645) were enrolled. In 2017, longitudinal follow-up was completed among 2008-2013 participants (n=725), and 222 children and adolescents completed the SHOW study for the first time.

SHOW participants are randomly selected using a probability sampling proportion to size without replacement (PPSWOR) approach.[246] Between 2008-2013, a two-stage probability-based cluster sampling was used to randomly select census block groups (stage 1) and household addresses (stage 2) annually within strata of region and poverty level.[246] SHOW 2014-2016 cohort was designed as a three-year sample. A three stage cluster-sampling approach was employed. One county per strata was randomly selected within strata of county mortality rates, followed by random selection of census block groups by poverty status strata. Then 30-35 residential households were randomly selected via US postal service listings.

Across 2008-2016 years of the study, participation ranged from 56-70% among all those adults who screened eligible. Separate response rates for children are not available, however, it is known that response rates were higher in rural areas, and lower in urban areas. In 2017, 85% of eligible adults from 2008-2013 successfully completed longitudinal follow-up, during which time children who were not previously included in SHOW were invited to participate.

Figure 13 describes the analytic sample selected for this study. This study includes a subset of 571 children and adolescents ages 6-18 recruited into SHOW in 2014-2017. Children ages <6 years were excluded due to diagnoses of asthma rarely occurring before age 6. Subjects with missing data on any of the asthma outcomes (n=3), school location (n=8) or confounders (n=26) of interest were also excluded from analyses, resulting in a final sample size of 536 for asthma outcomes, and 496 for lung function outcomes. All residential household addresses were geocoded using CENTRUS software (Pitney Bowes Inc., Stamford, CT) and linked to the nearest CAFO using ArcGIS v10.3 software (ESRI, Redlands, CA). Figures 14a-b display maps of the SHOW children and adolescent study population by census block group.

4.3.2 Concentrated animal feeding operations (CAFOs)

Data on CAFO location, type (dairy cow, hog, chicken, or turkey), years of operation and total animal units are maintained by the Wisconsin Department of Natural Resources' (WDNR) and Department of Agriculture, Trade and Consumer Protection (DATCP) under the Wisconsin Pollutant Discharge Elimination System (WPDES) program. WPDES falls under the Clean Water Act (CWA) National Pollutant Discharge Elimination System (NPDES) which requires states to regulate point source pollution to waters of the entire United States. CAFOs are defined by the CWA [Section 502(14)] as point sources, thus requiring a discharge permit under the NPDES and monitoring completed by the Wisconsin Department of Natural Resources (WDNR), where pollutants are tracked by the Wisconsin Pollution Discharge Elimination System (WPDES).[301]

CAFOs are defined as an animal feeding operation (AFO) where the following conditions are met: 1) animals are confined for a total of 45 days or more in any 12-month period and 2) animals do not have access to crops, vegetation or forage growth in the normal growing season. AFOs that have 1000 or more animal units (1 animal unit = 1000 pounds of live animal weight) are considered a large CAFO (1000+ cattle, 700+ dairy cows, 2,500+ swine, 55,000+ turkeys). Medium CAFOs (300-999 cattle, 200-699 dairy cows, 750-2,499 swine, 16,500-54,999) are additionally regulated under WPDES if the facility has a manmade ditch or pipe that carries manure or wastewater to surface

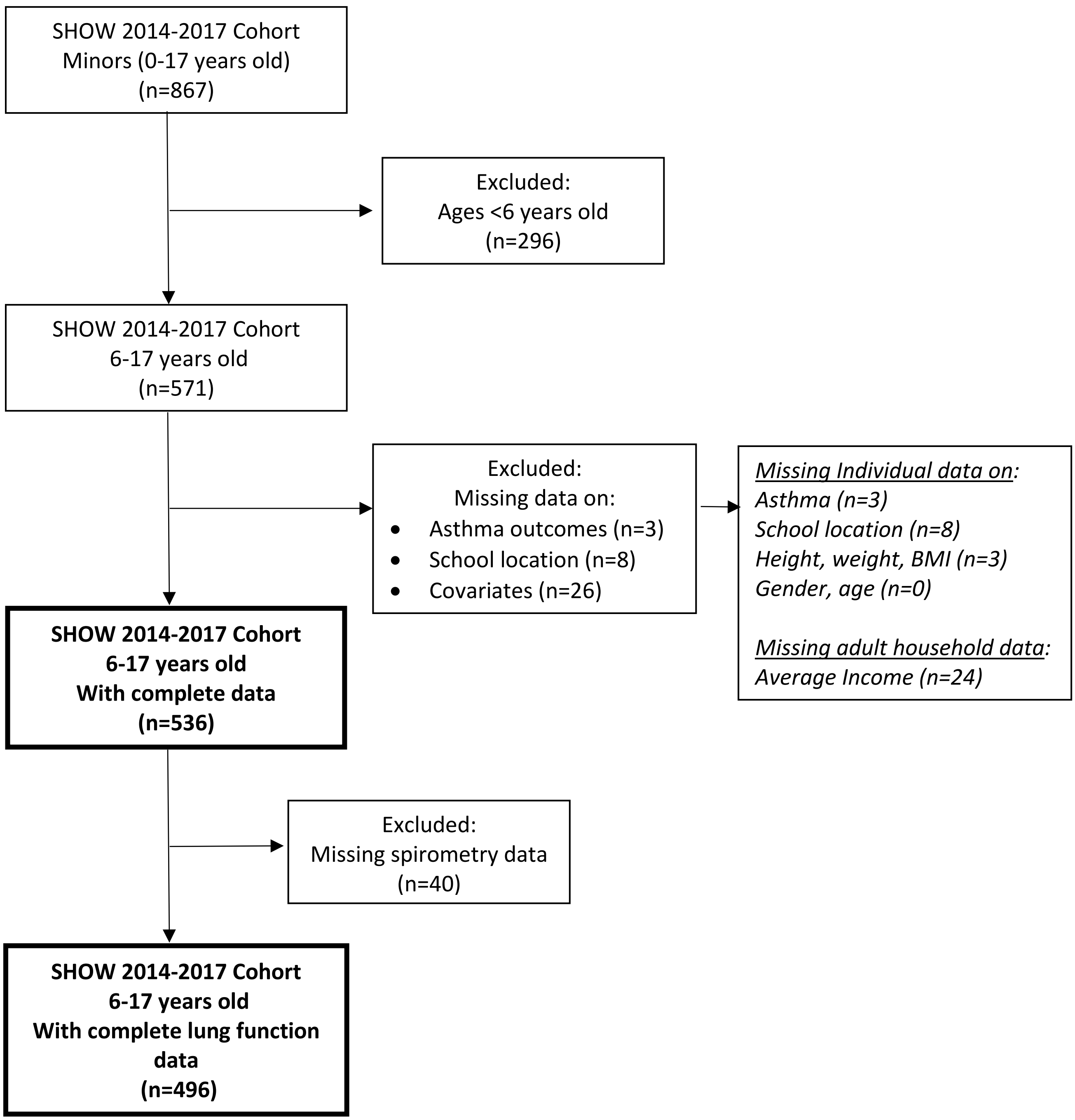

Figure 13. Flow chart of the study sample depicting inclusion and exclusion criteria.

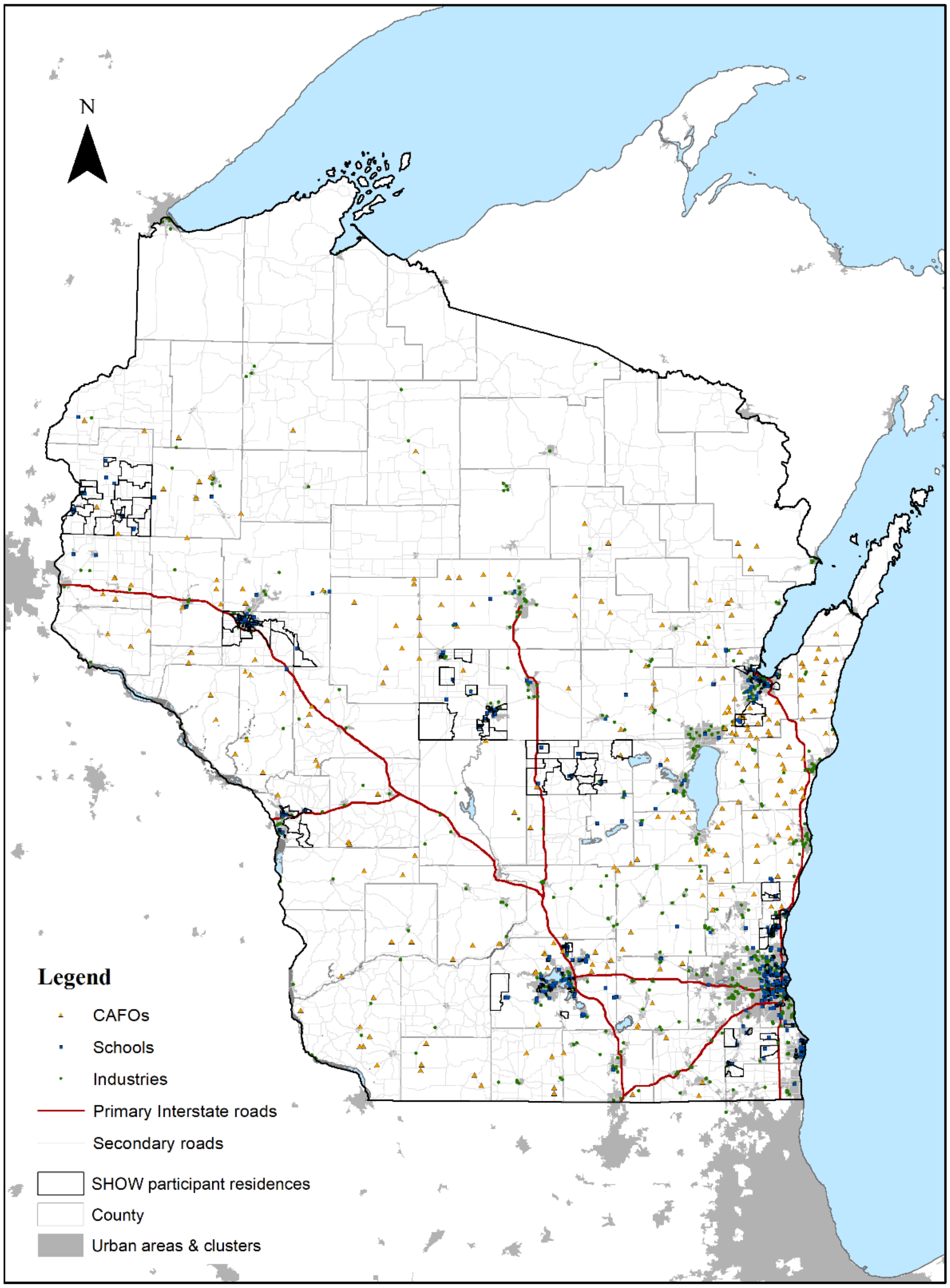

Figure 14a. Map of study sample area, depicting participant residences by census block group.

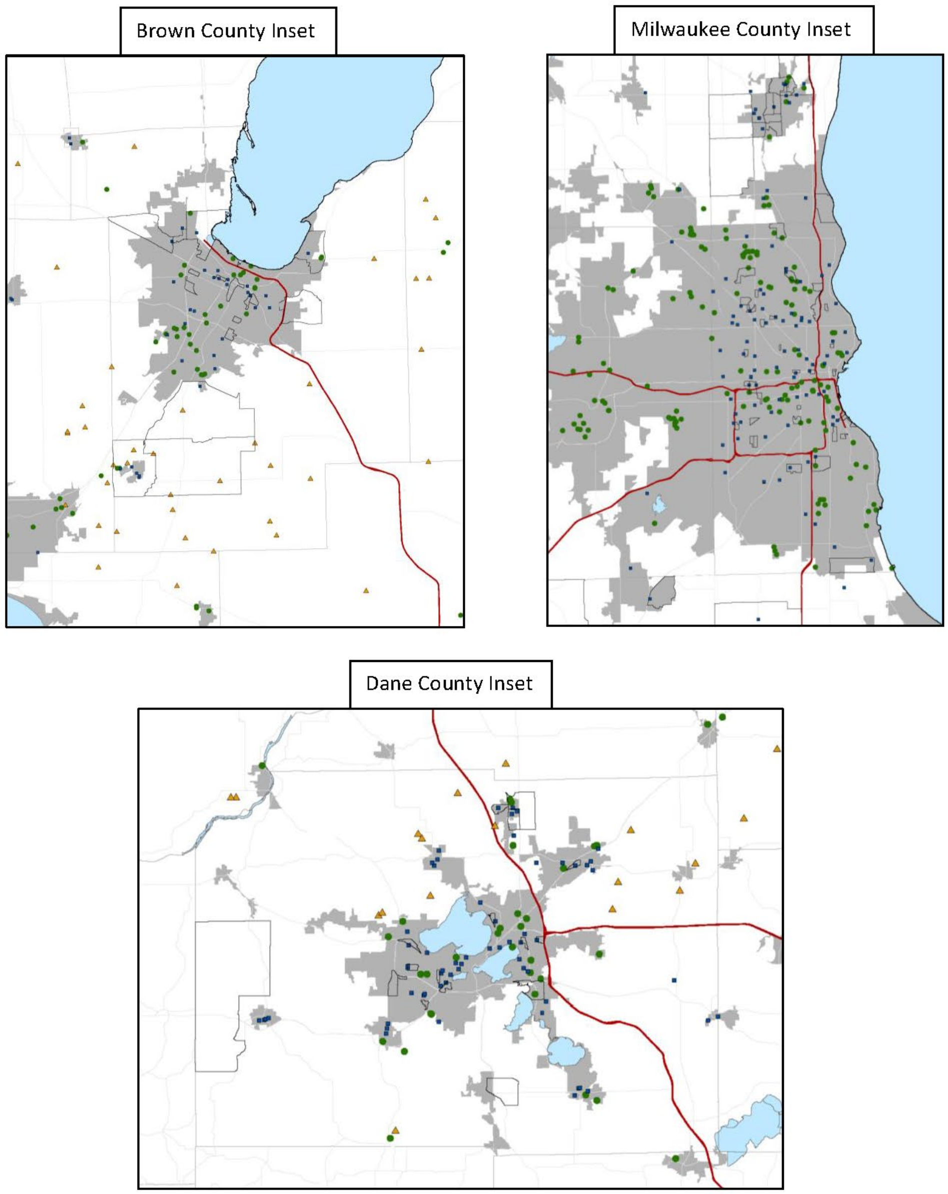

Figure 14b. Map insets of Brown, Milwaukee, and Dane County from Figure 14a Map. See legend on

water or if the animals come into contact with surface water that passes through the area where they are confined.[48] See Table A1 for a table of the EPAs regulatory definitions for CAFOs.

According to publicly available data downloaded from WDNR WPDES program there were a total of 284 CAFOs operating in Wisconsin in 2016. Ninety percent (244 large, 2 medium) were dairy CAFOs, followed by swine (5 large, 9 medium), beef (10 large, 3 medium), poultry (1 medium, 10 small). Publicly available data were limited, therefore additional data including the location, start date, and end date of all permitted CAFOs established between 2013 and 2015 was obtained via an open records request to the Wisconsin DATCP. The DATCP data was used to ensure CAFOs were in existence during SHOW participants' year of participation in the study (when residential address and health data were collected). Figure 1 from the WDNR shows the proportion of CAFOs by animal type has remained stable over the last decade, with over 90% of the CAFOs in Wisconsin being dairy.

4.3.3 Asthma and lung function

Self-report history of asthma and wheezing was collected during in-home interviews with an adult proxy (a parent or guardian living in the home) for child and adolescents. Participants were defined as having current asthma if their adult proxy responded "yes" to the survey question "Does [child's name] still have asthma?" which is a follow-up to the question "Has a doctor or other health professional ever told you that [child's name] had asthma?" Adult proxies were also asked whether the child participant had an "episode of asthma or an asthma attack" during the last 12 months, and whether the child participant had taken medication prescribed by a doctor or other health professional for asthma in the last 3 months. Participants were considered to have wheezing if their adult proxy reported that their "chest sounded wheezy during or after exercise or physical activity" in the last 12 months.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured via spirometry using an electronic peak flow meter (Jaeger AM, Yorba Linda, CA), and validated protocol.[248] Trained technicians gave study participants explicit directions on how to breathe into the spirometry device. Measurements were considered valid if two FEV1 and FVC readings were within 10% of the highest value measured. FEV1 to FVC ratio (Tiffeneau index) and percent predicted FEV1 (FEV1 divided by predicted FEV1) were also assessed to account for inter-individual variability in lung function measurement. Predicted FEV1 was calculated using sex, race, age, and height as defined by the NHANES general U.S. population.[249]

4.3.4 Covariates and confounding

Adult proxies provided child participant demographics and health behaviors for children under 12 years of age. Adolescents (12-17 years) provided these data directly, which include age (years), gender (male vs. female), minutes/week spent in moderate to vigorous activity, and daily servings of fruits and vegetables. Body mass index (BMI) was calculated from measured weight and height as kg/m^2 and analyzed as the child's BMI-for-age percentile. BMI-for-age percentiles were calculated using 2000 CDC Growth Charts. While body compositions remain stable in adulthood, children's body compositions vary as they age and they vary between the sexes. Therefore, children's weight status and BMI levels need to be expressed relative to other children of the same age and gender rather than as categories used for adults.

Household level characteristics were derived from data collected from all adults in the home who participated in the SHOW study. Adult data used in this study included their education level, household income, smoking status, and whether there are pets in the home. Poverty to income ratios (PIR) were calculated for all adult's self-reported individual incomes using U.S. Department of

Health and Human Services poverty guidelines and the midpoint of the household income range identified by the participant.

The following variables were derived from all adult participants in the home:

Derived variable:	Description:
Highest Education Level	The highest education reported among all adults in the home (high school or less, some college, bachelors degree or higher)
Poverty-to-Income Ratio	The average among all poverty-to-income ratios calculated for the adults in the home
Household smoking status	"Yes" if any adult in the home reported current smoking status "No" if all adults in the home reported former or never smokers
Household pets	"Yes" if any adult in the home reported pets in the home "No" if all adults in the home reported no pets in the home
Number of people residing in the home	The average among the total number of people living in the home reported by the adults in the home
Health insurance	"Yes" if any adult reported >= 1 month Medicaid/private in last yr "No" if all adults reported <1 month or no insurance in last yr

To minimize confounding by previously identified environmental sources of asthma and respiratory health in the population[251] residential proximity to the nearest primary or secondary roadway and industry were also tested as confounders. Roadway data were obtained from the United States Census 2010, and the MAF/TIGER Feature Class Code (MTFCC) and Road Type Code (RTTYP) were used to identify roadway segments as primary and secondary (See Table A2 for US Census roadway type details).[280] Industries that are required to report fugitive[§] or stack[**] air emission

[§] Fugitive air emission are all releases to air that do not occur through a confined air stream. They include equipment leaks, releases from building ventilation systems and evaporative losses from surface impoundments and spills.

[**] Point source air emissions, also called stack emissions, are releases to air that occur through confined air streams, such as stacks, ducts or pipes

annually to the EPA were downloaded for the years 2013-2016 from the EPA website data came from the USEPA's 2014 Toxic Release Inventory site database.[281]

4.3.5 Wind data

Wind direction percentage from 2013-2017 were ascertained from meteorological data compiled by the 69 Automated Surface Observing System (ASOS) stations in the state of Wisconsin. ASOS stations collect minute-by-minute observations and data provided are essential observations for the National Weather Service (NWS), the Federal Aviation Administration (FAA), and the Department of Defense (DOD). Details on the methods used to clean and derive the wind data used in this study are described in Appendix D. In brief, an 8-point wind rose was created at every station, for every year. The wind rose data included (1) the annual percentage of time wind blew in each of the 8 directions, each year, and (2) the annual percentage of time wind blew in each of the 8 directions ONLY when wind speeds were less than 4 m s-1 since near source areas are affected greater during low wind conditions. Plume dispersion models from CAFOs have found air emissions affect nearby areas, or rather levels of emissions remain elevated locally, during low wind conditions. It has been found that high wind conditions tend to disperse the air emissions leading to their levels reaching background levels sooner.[44]

4.3.6 Relative environmental exposure to CAFOs

In order to estimate the relative exposure to study participants from CAFOs in their environment, a qualitative exposure metric was devised (Equation 1). This metric accounts for the cumulative effects of all CAFOs and their proximity to the participant's home and school, while taking into consideration the distance, wind speed and direction, CAFO size, and time the participant spends at home versus at school. The purpose of developing this metric was not to predict actual concentrations of pollutants emitted by CAFOs, but to qualify study participant's potential risk of exposure to CAFOs based on prior knowledge of air pollutant dispersion and factors that affect their fate and transport.

This metric may allow for better representation of potential exposure to CAFO air emissions rather than relying on distance alone as a proxy. While many studies have relied on categorical or linear distance from CAFOs as an estimate of exposure, there is evidence to suggest air emissions tend to degrade exponentially with distance from their source. Therefore, inverse square law was used in the exposure equation, as opposed to a simple linear function, in order to account for the known exponential decay of emissions (such as ammonia and H_2S) from CAFOs. Exponential decay of air emissions (PM2.5, VOCs) from other sources (such as roadways and industrial sites) has also been found.

$$log(E_{Relative}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i} * p_{s_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i} * p_{s_i}\right) * 0.15\right]_{school}\right) \qquad \textit{equation 1}$$

Variable Definitions:
d = distance to the nearest CAFO in miles
n = total number of CAFOs in Wisconsin
u = total animal units at the i^{th} CAFO
d_R = distance between i^{th} CAFO and residence in miles
d_S = distance between i^{th} CAFO and school in miles
p_S = Percentage of time wind blows < 9 mph (4 m/s) in the direction from i^{th} CAFO to the residence (or school)

While this may be more representative of pollutant dispersion, Erelative is still a simplification of a number of factors known to influence air emissions generated inside and outside of CAFO facilities, including animal density, ventilation systems, and manure storage and application management. Since facility management and application systems were unknown, the number of animal units permitted was used as a surrogate for the total amount of air emissions produced by the facility and is assumed proportional to exposure. This exposure estimate was then multiplied by the percent of time wind blew < 4m/s from the CAFO to the home (or school). The exposure estimates for each CAFO are summed. Exposure estimates are summed separately for the CAFOs in proximity to the school rather than the home. This is to account for the difference in time participants spend at home and school. The summation of the exposure estimates for CAFO(s) in proximity to the home was multiplied by 0.85 to account for the percent of time a participant spends at home relative to 0.15, the percent of time a participant spends at school. An average estimation of the amount of time a participant spends at school vs. at home was based on Wisconsin Legislature PI 0.01(2)(f) minimum number of instructional hours required[302] and National Center for Education Statistics' account of average instructional hours and days in Wisconsin. Details on methods for deriving these estimations can be found in Appendix D. For participants who report being home schooled, 1.00 instead of 0.85 is multiplied by their summation exposure to CAFOs at home.

In order to calculate Erelative, all residential household addresses, school locations, CAFOs, and wind stations were geocoded using CENTRUS software (Pitney Bowes Inc., Stamford, CT) and ArcGIS v10.3 software (ESRI, Redlands, CA) was used to link participant households to CAFOs and wind data from the year prior to their participation in SHOW.

More detailed methods on how Erelative was derived can be found in Appendix D. In brief, the ArcGIS Analysis-Proximity tool "Generate Near Table" was used to calculate the distance and angle from the participant households (and schools) to all CAFOs. Angles were converted to follow the wind data's 8 wind rose directions. Participants were linked to the nearest wind station via the "Near" tool in ArcGIS also. SAS 9.4 was used to merge participant household and school CAFO distances and directions with the wind direction percentages by station, year and direction.

4.3.7 Statistical analysis

Restricted cubic splines functions were applied to the relative exposure metric in order to account for nonlinear relationships between potential relative exposure to CAFOs and respiratory health. Knots were placed at the minimum, maximum, and 25th, 50th, 75th percentiles of the exposure. Univariate as well adjusted multiple linear (lung function outcomes) and logistic (asthma outcomes) regression models were used to examine associations between residential proximity to a CAFO and respiratory health.

Potential confounders were selected *a priori* from the literature. Age, BMI-for-age, physical activity, servings of fruits and vegetable, PIR, number of household members, and distances to TRI site and roadways were used as continuous variables in all statistical models. Gender, smoking status, and pets were binary, and highest education level was categorical (<= high school or equivalent, some college, Bachelors or higher) in models. BMI-for-age percentile, physical activity, servings of fruits and vegetables, and proximity to roadways and TRI sties were categorized in Table 3 for ease of describing characteristics of the study population by exposure status. Cut points for BMI-for-age (<85 percentile vs. >= 85th percentile) were chosen from the Centers for Disease Control (CDC) which considers BMI-for-age at or above the 85th percentile to be overweight.[282] Physical activity cut points (<420 min/wk vs. >= 420 min/wk) came from the US Department of Health and Human Services recommendation that children and adolescents ages 6-17 years do at least 60 minutes of moderate-to-vigorous physical activity daily.[283] Fruit and vegetable servings were based on the American Heart Association's recommendation that children ages 4+ years have 4 servings of fruits and vegetables daily.[284] Cut points for proximities to roadways (<=400 meters vs. > 400 meters) and industries (<= 800 meters vs. > 800 meters) were chosen based on studies of dispersion modeling of vehicle emissions and distances where respiratory health impacts have been found.[251,285,286]

The relative exposure metric was log transformed to account for skewness. The log transforming was not necessary for analyses, it aided in visualization of the cubic splines and was left as log transformed in all models. Covariates that did not change the main effect estimate by more than 10% were excluded from the multivariate models. An adjusted odds ratio (OR) or an adjusted beta-coefficient value with two-sided p-value < 0.05 was regarded as statistically significant. To acquire estimates from the spline regression, percentiles of the potential relative exposure to CAFOs were compared (high percentiles vs. low percentiles of exposure). SAS version 9.4 (SAS Institute Inc. Cary, NC) was used for all statistical analyses. Due to clustering of the study sample within census block groups and within households, all analyses were performed as mixed models with random effects of census block group and household.

4.4 Results

Table 3 displays characteristics of the study sample by their relative exposure to CAFOs ($\log E_{relative}$). Participants with a high relative exposure to CAFOs (in the 85th-100th percentile range) were on average more likely to eat fruits and vegetables, have pets in the home, and come from a home with a higher income and more educated adults when compared with participants with a lower relative exposure metric to CAFOs (0-85th percentile). Those with a high relative exposure were also less likely to live in a home with asthmatic adults and less likely to live near an industry when compared to those with a lower relative exposure metric. Not surprisingly, participants with a high relative exposure to CAFOs were more likely to live near a primary and secondary roadway, and more likely to live in an urban census block group when compared to those with a low relative exposure.

The relative exposure metric to CAFOs in this study sample ranged from -7.14 (high relative exposure) to -17.3 (low relative exposure). Table D1 summarizes components of the relative exposure metric and asthma outcomes by quartiles of $\log E_{relative}$. On average, those in the highest quartile of exposure to CAFOs had a residential distance 4.4 miles from a CAFO, a school distance 4.9 miles from a CAFO. Those in the highest quartile of exposure also had more than one CAFO within 5 miles of their home on average. Unadjusted cubic splines of the log odds of asthma outcomes regressed on $\log(E_{relative})$ depicted U-shaped curves (see Figure D1). Log odds of doctor diagnosed asthma, current asthma, asthma medication use and asthma episode in the last 12 months is high at high values of the relative exposure to CAFOs metric, decreases as the relative exposure to CAFOs decreases until around -13.5 (~ 50th percentile), at which point the log odds of asthma outcomes increases again as the relative exposure metric decreases. A similar pattern in seen with FEV1/FVC ratio, where an inverted U-shape shows that lung function increases as relative exposure to CAFOs decreases, until about the 50th percentile of exposure, at which point, lung function decreases as exposure decreases.

Relative exposure to CAFOs, which includes distance, animal units, wind direction and speed from every CAFO in the state to the participants residence and school, was associated with asthma and wheezing. Figure 15 displays the results of multivariate models of relative exposure to CAFOs and asthma outcomes adjusting for gender, age, household-based poverty to income ratio, number of people in the home and residential proximity to an industry. Doctor diagnosed asthma and wheezing in the last 12 months showed the strongest association with relative exposure to CAFOs.

The odds of having been diagnosed with asthma and having a wheezing episode in the last 12 months was 50-90% higher at the 95th percentile of the relative exposure to CAFOs when compared to the 50th-85th percentile of $\log(E_{relative})$. At the 95th percentile of exposure, the odds of asthma outcomes continued to increase as the 95th percentile of exposure was compared to lower percentiles of exposure until about 50-75th percentile. At low relative exposures (0-50th percentiles), the odds of having an asthma is about the same, or greater than the odd of asthma at high relative exposure (95th percentile). Asthma medication use and current asthma showed similar trends, although with smaller effect sizes, and non-significant results. Table D2 shows the unadjusted and adjusted results of additional percentile comparisons of $\log(E_{relative})$ made with the aforementioned asthma outcomes. Additionally, Tables D3a-c show model building results, which largely depict unadjusted and adjusted models with similar main effects where additional variables do not appear to explain much confounding.

Table 3. Characteristics of the study sample. Column percents of characteristics by percentile ranges of log($E_{relative}$).

	Total Study Sample (n = 536)	Percentile ranges of log($E_{relative}$)		
		85th-100th (n = 78)	0-85th (n = 458)	p-value
Individual characteristics	N	%	%	
Gender				0.5
Male	280	48.7	52.3	
Female	256	51.3	47.2	
Age (in years)				0.9
6-12	354	65.4	66.2	
13-17	182	34.6	33.8	
BMI percentile[a]				0.7
< 85th percentile *(not overweight)*	366	66.7	68.6	
>= 85th percentile *(overweight)*	170	33.3	31.4	
Time / week in moderate to vigorous Physical activity[b]				0.7
< 420 minutes	63	10.3	12.0	
>= 420 minutes	473	89.7	88.0	
Servings fruit & veggies[c]				0.004
< 4 per day	252	32.1	49.4	
>= 4 per day	284	67.9	50.4	
Household characteristics				
Current smoker				0.2
Yes	114	16.2	22.0	
No	385	83.8	88.0	
Household income				0.001
< $50,000	211	24.4	41.9	
$50,000 - $99,999	151	19.2	29.7	
>$99,999	174	56.4	28.4	
Health insurance				-
Yes	493	100	89.3	
No	49	0	10.7	
Highest Education				0.01
H.S./GED or less	75	11.5	14.4	
Some college	177	19.2	35.4	
Bachelors or higher	284	69.2	50.2	
Pet(s)				0.02
Yes	359	78.2	65.1	
No	177	21.8	34.9	
Household members (No.)				0.9
Less than 5	306	56.4	57.2	
5 or more	230	43.6	42.8	
Residence length				0.8
< 1 year	64	10.2	12.1	
>= 1 year	472	89.8	87.9	
Adult(s) with allergies				0.2
Yes	294	52.6	56.1	
No	242	47.4	43.9	
Adult(s) with asthma				0.0006
Yes	104	5.1	21.8	
No	432	94.9	78.2	
Adult(s) asthma diagnosed				0.07
Yes	164	21.8	32.1	
No	372	78.2	67.9	
Proximity to TRI site				0.18

<= 800 meters	49	5.1	9.8	
> 800 meters	487	94.9	90.2	
Proximity to Primary road				0.2
<= 800 meters	42	3.8	2.2	
> 800 meters	494	96.2	97.8	
Proximity to Secondary road				0.004
<= 400 meters	224	25.6	43.2	
> 400 meters	314	74.4	56.8	
Census block group population				0.6
Rural or urban cluster	224	29.5	32.5	
Urban area	318	70.5	67.5	

CAFO: concentrated animal feeding operation; km: kilometer; N: number; H.S.: high school; GED: General Education Development test; BMI: body mass index; wk: week; TRI: Toxic release inventor.
p-trend: statistical significance by Chi-square test
[a]https://www.cdc.gov/obesity/childhood/defining.html
[b]https://www.cdc.gov/healthyschools/physicalactivity/guidelines.htm
[c]https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/dietary-recommendations-for-healthy-children

Figure 16 displays the results of multivariate linear regression assessing FEV1 % predicted and FEV1/FVC ratio by restricted cubic spline of the log($E_{relative}$). Results show lung function to not be associated with relative exposure to CAFOs. While none of the results were statistically significant, results indicate lung function to be slightly better among those with high relative exposure to CAFOs when compared to those with lower relative exposure to CAFOs. Modeling building Table D3d shows that while high relative exposure to CAFOs was associated with decreased FEV1/FVC ratio in unadjusted and other adjusted models, poverty to income ratio explained this association. Table D4 shows the unadjusted and adjusted results of additional percentile comparisons of log($E_{relative}$) and additional lung function measurements, including FEV1 and FVC.

4.5 Discussion

This study aimed to assess whether a larger relative exposure to CAFOs was associated with asthma, wheezing, and lung function among a sample of children and adolescents across the

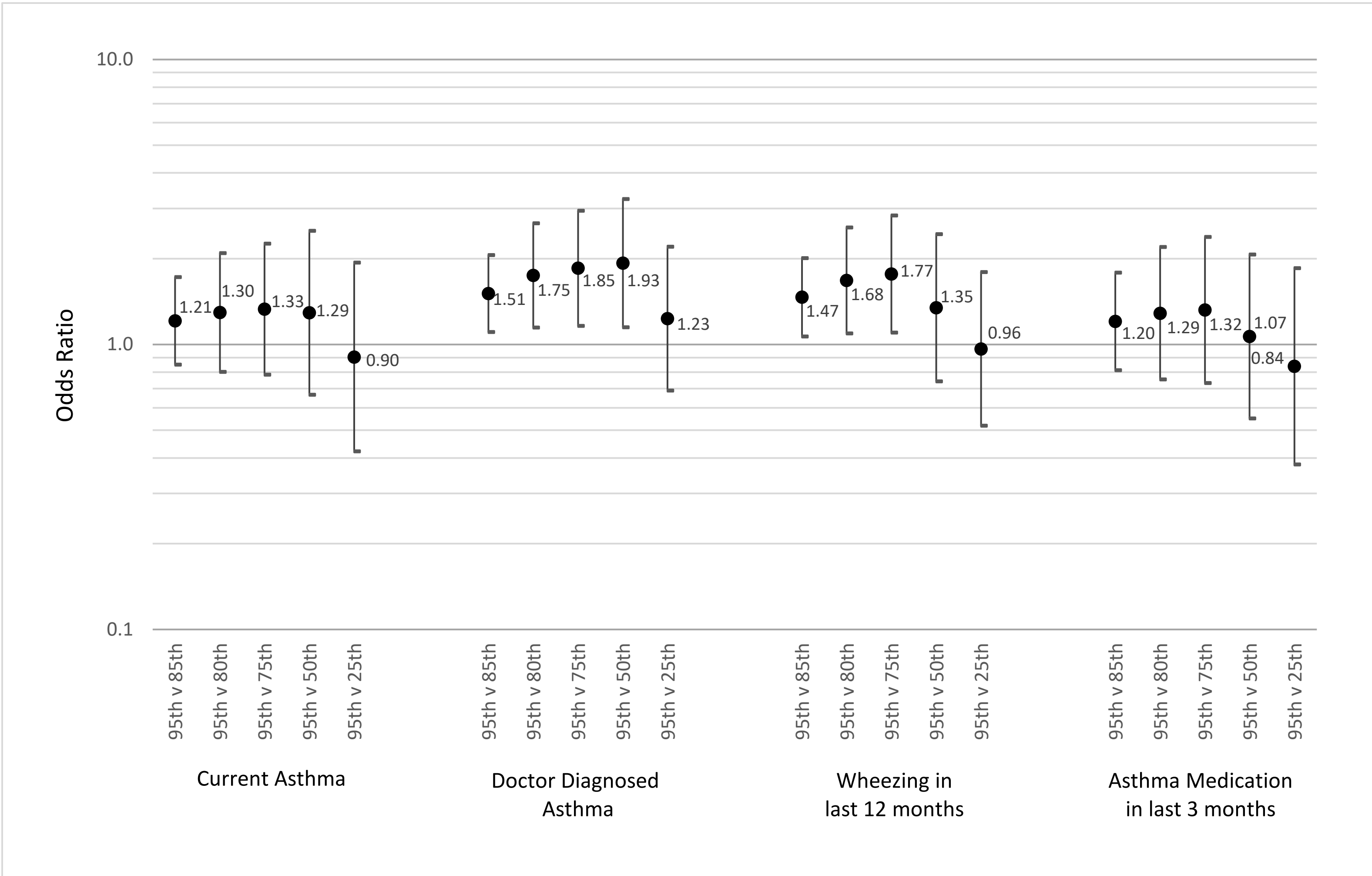

Figure 15. Results of logistic regression assessing asthmatic outcomes by restricted cubic spline of $\log E_{relative}$ exposure metric – an estimated relative metric of exposure to CAFOs. The $\log E_{relative}$ at the 95th percentile is compared to the 85th, 80th, 75th, 50th, and 25th percentiles. Models are adjusted for individuals gender, age, household-based poverty to income ratio, number of people in the home, and proximity to industries.

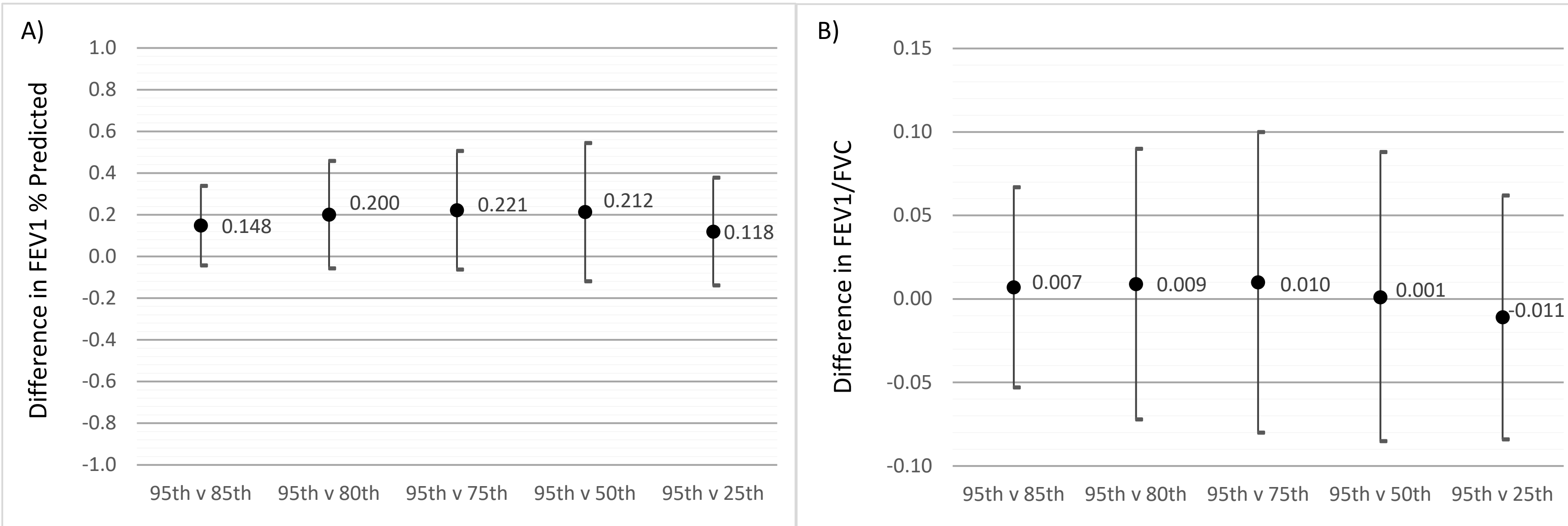

Figure 16. Results of linear regression assessing (A) FEV1% predicted and (B) FEV1/FVC ratio by restricted cubic spline of $logE_{relative}$ exposure metric – an estimated relative metric of exposure to CAFOs. The $logE_{relative}$ at the 95^{th} percentile is compared to the 85^{th}, 80^{th}, 75^{th}, 50^{th}, and 25 quantiles. Models are adjusted for gender, age, height, poverty to income ratio, number of people in the home, and proximity to industries.

State of Wisconsin. This study is unique in that it is the first to use an exposure metric which accounts for both potential exposure to CAFOs while at home and school. A participant's relative exposure to CAFOs was estimated using a metric which considered distance, size, wind direction and wind speed from every CAFO in the state in relation to the participant's home and school. We found children and adolescents with a larger relative exposure to CAFOs were more likely to be diagnosed with asthma and to have had a wheezing episode in the last 12 months when compared to participants with a lower relative exposure to CAFOs. However, no associations were found between relative exposure to CAFOs and lung function. This study adds to the limited research on children's exposure to CAFOs and respiratory health by considering multiple locations by which exposure to CAFOs can occur throughout a child's life.

We were concerned children with a high $logE_{relative}$ would differ in terms of socioeconomic status when compared to children and adolescents with a low $logE_{relative}$. Environmental justice issues have been raised in North Carolina where CAFOs are located in predominately low-income and minority communities, and researchers are finding it difficult to tease out whether the higher prevalence of asthma and respiratory symptoms among residents near CAFOs is associated with proximity to CAFOs or is due to other factors associated with the population living the CAFOs.[19,20,23,303,304] In fact, in our study we found just the opposite. Those with a higher $logE_{relative}$ had a higher household income, were more likely to have an adult in the home with a college degree, and were more likely to have health insurance when compared with those with lower $logE_{relative}$. Similar findings were seen in an Iowa study, where children living <=4.8 km from a swine AFO were compared to children living more than 4.8 km from a swine AFO, and found those living near an AFO to have a slightly higher household income and found parental education did not differ between the exposure groups.[30] This is an important finding and highlights the regional differences in the settlement of large animal livestock operations in the U.S. and the need for this research to extend into different states and regions. The landscape in Wisconsin, where several CAFOs are the result of smaller family farms which have grown over time into CAFO-sized family farms, is different than seen in North Carolina.[75,78]

Results from this study are consistent with other studies which have assessed exposure to livestock operations and respiratory health among children and adolescents. Pavilonis et al. (2013) used an exposure metric which included distance, AFO land size, wind direction and wind speed, of swine AFOs within 3 miles of a child's home in Keock County, Iowa.[30] He found those with a larger exposure metric to AFOs had an increased odds of having physician-diagnosed asthma (OR=1.51, p=0.014) and physician diagnosed asthma or medication for wheeze (OR=1.38, p=0.023).[30] Another study in Iowa found children who attended an elementary school within 800m of a swine CAFO were 5.71(p=0.004) times more likely to have physician diagnosed asthma when compared with children who attend school 16 km from a CAFO.[31] A large cross-sectional study among children from public schools across North Carolina (n=58,169) found children who attend school within 3 miles of swine CAFO were more likely to have physician-diagnosed asthma (PR=1.07, 95% CI: 1.01–1.15).[35] Our study did not find statistically significant results with current asthma and asthma medication use in the last 3 months. This could be due to our limited power to detect associations between relative exposure to CAFOs and asthma medication use. Cross tabs on current asthma and medication use also revealed that some participants reported not having current asthma, but reported taking asthma medication. Participants' interpretation of current asthma seemed to vary in terms of whether controlled asthma via medication equated to having current asthma or not.

Loftus et al. (2015) is the only study to assess lung function measured via spirometry and exposure to CAFOs.[32] Their study was conducted on 51 children in Washington State and found measured ammonia concentrations (one and two day lagged) to be associated with decreased FEV1% predicted.[32] Ammonia levels were mostly explained (77%) by residential proximity to CAFOs, but were not associated with any asthma symptoms, diagnosis, or prevalence.[32] Our study did not find significant associations between relative exposure to CAFOs and lung function. The Washington study measured lung function 1 and 2 days after measuring ammonia concentrations. Our study measured lung function during one home visit during when the main survey was completed and participants completed the study at different times throughout the year. While we attempted to control for the month and season of when the lung function test was performed, it did not prove to confound results in our study. However, lung function is variable and dependent not only on the day of collection, but how accurately the participant understands the directions and performs the test adequately; something that can be particularly challenging for children. It's possible the self-reported asthma and wheezing outcomes are a better reflection of overall respiratory health and are less sensitive to factors that may have influenced the lung function measurement on the particular day of collection.

One of the strengths of this study was the amount of personal and household characteristics and health data collected on participants. Another strength of the study is the amount of complete data and the reduced risk of selection bias. Only 8 age-eligible children from the study population were missing school location data, and only 5% were missing data on asthma outcomes or confounders. This is also one of the first studies to use cubic spline regression and show visual plots of the association between relative exposure to CAFOs and asthma and lung function. While a few other studies have developed exposure metrics, the exposure was grouped for analyses, or quartiles were compared and no visual plots were shown. Borlee et al (2015) is the only study to-date which provided cubic spline plots of the association between residential distance to the nearest CAFO and log odds of asthma among adults in the Netherlands.[10] Our spline plots offer a unique insight into potential patterns and trends seen as potential exposure to CAFOs increases. Similar U-shaped curves were seen in Aim 2 when distance to the nearest CAFO was used as an exposure measure. This finding suggests at close distances to a CAFO, or when exposure to CAFOs is high, emissions may be high enough to cause irritation and asthma or respiratory symptoms. Whereas lower exposures may still provide a protective effect. This protective effect is no longer seen in the spline plots when exposure to CAFOs is very low, or essentially non-existent. Comparison between our cubic spline plots are difficult to compare to Borlee et al (2015), where splines were only assessed from 0 to 1500m from a livestock farm, distances from livestock farms that are common in the Netherlands where farms are smaller in size, more regulated, and located in more densely populated areas.[10]

This study is the first to try and capture a more complete window of exposure to CAFOs, by incorporating potential exposure that may occur at home and at school, and considering wind direction, wind speed, and CAFO size rather than just relying on distance as a proxy measure of exposure to the nearest CAFO. While this is a strength, it still highlights the need for better data collection and public records of livestock farms. There are over 8,000 dairy farms in Wisconsin, yet less than 300 are regulated as CAFOs with public data including size, animal type and location.[47,305] Data on farms smaller than CAFO-size are scare and provide limited information. Yet many dairy farms could be in operation at just under the threshold deemed to be a CAFO and releasing similar amounts of air emissions. Health effects have been seen among children living in proximity to smaller AFO-sized farms in Iowa,[30,33] suggesting that cumulative effects from many smaller farms may have similar effects on residents as living in areas of high relative exposure to CAFOs.[30,33] The fact that exposure to non-CAFO sized livestock farms were not included in this study may have biased results. If non-CAFO sized livestock farms are more or less likely to exist in areas of high relative exposure to CAFOs, than results may be biased. The assumption in this study is that smaller livestock farms are not more or less likely to be in areas of high relative CAFO exposure when compared to low relative CAFO exposure, resulting in non-differential classification bias.

Other limitations of this study include potential misclassification of the exposure due our imperfect proxy measure of the exposure. Our exposure measure, while more sophisticated than most, does not consider variability in air emissions from CAFOs due to differences in management practices, facility types, and ventilation systems, all factors which can impact concentrations of airborne particulates and vapors. Furthermore, the wind data derived from the nearest wind station may not be an accurate representation of the wind patterns seen at the participant's residence and school. While SHOW collects a lot of personal data, we did not have information on respiratory infections in early life, or any information on whether the child lives on a farm, or grew up on a farm. We also had limited available data on the occupations of the adults or parents in the home. These are all factors associated with asthma that we were unable to control for. Furthermore, population-based samples are not ideal for investigating rare exposures such as residential and school proximity to CAFOs. Due to the exposure being rare, and some of the outcomes not being very prevalent (i.e. Asthma episode in last 12 months), this study may have lacked the power to detect associations in some of the models. The small sample size, rare exposure, and low prevalence of some of the outcomes resulted in parsimonious models where residual confounding may be present. This study also relied on self-report of outcomes which may have resulted in measurement error of the outcomes due to recall bias. Lastly the cross-sectional nature of the study means causality cannot be inferred.

Geography posed a unique challenge in this study which prior studies did not face. Prior studies which have used an exposure metric or distance to the nearest CAFO and investigated associations with respiratory outcomes considered only people living within < 3 miles from a CAFO or within a small rural community, resulting in a more homogenous study sample. While SHOW collects an abundance of participant characteristics and health data from which we were able to test many different confounders, our ability to account for confounding by geography and urbanicity was limited. This was further complicated by the unique settlement of CAFOs being near urban-defined census block groups in the Green Bay area. We found those with a higher $logE_{relative}$ (85^{th}-100^{th} percentile) were only slightly less likely to live in an urban defined census block group than those with lower $logE_{relative}$ (0-85^{th} percentile); 55% compared with 60%. While residential proximity to an industry and major roadway were used to adjust for additional sources of air pollution participants in urban areas may be more likely to encounter, our study likely suffered from residual confounding. Confounders tested in our models did not result in significant changes in the main effects seen between $\log E_{relative}$ and asthma outcomes. While there are clearly differences seen between those with a high $\log E_{relative}$ when compared to those with a lower $\log E_{relative}$, it is possible these differences may be due to some other unknown confounder, and not their estimated potential exposure to CAFOs.

4.6 Conclusion

This study builds upon the limited research concerning exposure to CAFOs and asthma and respiratory health among children and adolescents. A relative exposure metric was used, which considered both cumulative exposure to CAFOs when participants at home and at school, taking into account distance, size, and wind direction and speed. Associations were found between large potential exposure to CAFOs and physician diagnosed asthma and wheezing, while no associations were found with lung function. This study is an important contribution to the field in its development of an exposure metric which considers potential exposure to CAFOs from the two locations where children spend most of their time. This study is also significant in that it extends the field of research to new geographical area. The number of CAFOs, settlement patterns of CAFOs near other communities, and CAFO regulations vary by state, making it important each state start to investigate whether there are any health concerns CAFOs pose and whether any additional regulations need to be considered.

This study also highlights the importance of better data collection on reporting of smaller livestock farms, which collectively may pose even more concerns than CAFOs. Future research should consider a cohort or case-control study in a smaller geographical areas in Wisconsin, such as Brown County, where there is a large concentration of both CAFOs as well as non-CAFOs. Data collection which incorporates satellite imagery, or neighborhood assessment of smaller livestock farms, and incorporates both exposure from CAFOs and well as non-CAFOs would strengthen our understanding of farming exposures protective and deleterious effects. More research is warranted as we continue to figure out what factors associated with farming are protective and which are potentially pro-inflammatory.

Chapter 5. Conclusion

5.1 Summary of Results and Conclusions

The last few decades have seen a shift in agriculture from many smaller farms to fewer large-scale farms. While large-scale farming practices offer more efficiency and profit, the public health impacts of these changes are not well understood. It is well established that particulates, gases, and vapors from large, concentrated animal feeding operations (CAFOs) pose a health risk among livestock workers,[4,7,8] where an increased risk of respiratory ailments is well documented in the literature.[7,8,200,203,208,216,220,306] However, there is a paucity of data on whether health effects are seen among residents living near CAFO facilities. Epidemiology studies that investigate residential proximity to CAFOs and respiratory health in the US have predominantly taken place in Iowa and North Carolina,[35,218,231,232] with a couple studies in Pennsylvania and Washington.[16,32] However, CAFOs exist in 47 of the 50 states,[††] with Iowa, Texas, California, Nebraska, Kansas, North Carolina, Minnesota, Colorado, Idaho, and Wisconsin being the top 10 states with the largest number of animal units.[233,234] The concentration and settlement of CAFOs varies greatly across the US, and since states have authority to regulate CAFOs beyond the minimum requirements set under the Clean Water Act's NPDES program, regulation and monitoring of CAFOs varies by state. Additional research examining population level exposures from CAFOs and potential respiratory health risks is needed, particularly research which expands into new areas, such as Wisconsin.

The purpose of this study was to determine whether residential proximity to a CAFO was associated with allergies, asthma and lung function among a statewide representative adult sample. It was additionally important that this study investigated the same relationship among children, who take in more air per unit body weight at a given level of exertion than adults do, leaving them more vulnerable to air pollutants.[257,258] Furthermore, this study developed a unique exposure metric which

[††] CAFOs do not exist in Alaska, Massachusetts, and Rhode Island

considered a child's exposure to CAFOs when both at home and school, and incorporated the size, distance, wind direction and speed of every CAFO in the state. Whereas many prior studies grouped exposure, this study used cubic spline regression to allow for non-linear associations. The visual plots of the non-linear associations between proximity to CAFOs and relative exposure to CAFOs with allergies, asthma, and lung function adds to the literature and provides important insight into the nonlinear relationship seen between potential exposure to CAFOs and respiratory health outcomes, showing both potential deleterious and protective effects.

This study is significant in that it extends the research concerning residential proximity to CAFOs and respiratory health to a new state and region in the United States. Research thus far has taken place in only a handful of states in the U.S. (North Carolina, Iowa, Pennsylvania, and Washington).[15,16,18,22,30–33,35] Yet, CAFOs exist in nearly every state in the U.S. and the quantity, settlement, and regulations of CAFOs vary by state.[233,234] Wisconsin, with just under 300 CAFOs, is second only to California in terms of the number of dairy CAFOs, total dairy animal units and milk produced.[47,74] Wisconsin also has some of the strongest protections of CAFOs from private nuisance claims under the state's Right to Farm law.[243] Residents facing air or odor externalities from nearby CAFOs are required to prove both that they did not come to a nuisance AND that the nuisance is a threat to their health.[242,307–309] Proving nearby air emissions are affecting a person's health is more akin to public nuisance, and one which relies on epidemiological evidence. Yet, there is no epidemiological evidence to indicate whether CAFOs may pose a respiratory health risk to nearby residents in Wisconsin.

This study also provides important evidence to suggest CAFOs may be a source of important public health concerns, and more research is needed to further address the primary sources of concern and to protect human health. While this study does not provide any conclusive answers regarding the causal relationship between CAFO emissions and respiratory health problems among adults and children living near CAFOs, it does start to build the foundation of research that is needed to help inform future state policy and regulation decisions in the state. This study found proxy measures of exposure to CAFOs were associated with allergies among adults, and doctor diagnosed asthma, wheezing, and asthma medication use among adults and children. Evidence from this preliminary research suggests that future research regarding respiratory health among residents living near CAFOs in Wisconsin, and other regions of the United States is warranted.

Chapter 2, Aim 1, investigated the association between residential proximity to the nearest CAFO and the prevalence of allergies, asthma, and lung function among a statewide representative sample of rural adults in Wisconsin. The study found residential proximity to a CAFO was associated with reduced lung function and self-reported asthma, uncontrolled asthma and asthma medication use. Residential proximity to a CAFO was associated with allergies. Our ability to assess allergy by type was a unique contribution of this study, and something few studies have been able to do. One would expect the strongest associations between air pollution and allergies to be at the site of the nose, sinus, and lungs, which is what we found to be the case in this study. This study was a contribution to the U.S.-based literature thus far, and confirmed findings from a study in North Carolina which found a panel of residents living near CAFOs were more likely to experience asthma and asthma-like symptoms.[15,20,303,310] Our study also found similar findings to an adult clinic-based study in Pennsylvania which found those living within 3 miles of a CAFO had an increased odds of asthma medication use and asthma-related hospitalizations.[16]

This study also highlights the differences seen between studies in Europe when compared to the United States. European studies, which have investigated residential proximity to CAFOs and respiratory health, have mostly found inverse or null results.[9,11,36] This has largely been attributed to their livestock farms being smaller in size, located in more densely populated areas, and as a result have more restrictions and regulations placed on them.[124,223] It is also possible other factors contribute to the contradictory results, such as different management practices, including variation in the use of antibiotics and feed additives, and potential differences in the types of people that live near

CAFOs. Exposure to farm life and livestock are known to have protective effects against asthma and allergies.[142,160,163,264,277] These protective effects are largely thought to be attributed to the increase in exposure to microbial diversity found on farms.[124,170] However, findings from this study, and the few other observational studies in the U.S.[15,16,30–32,35] suggest there is something about the exposure to CAFOs which may present inflammatory responses, rather than protective responses. The exact reason is unknown, but evidence showing farm workers are risk of this suggest that it could be exposure to a higher concentration of air emissions and microbes. [17,18,166,208,221,311,312] It has been suggested that low doses of microbial burden may be beneficial, while high doses may be too much for the immune system whereby introducing a pro-inflammatory response.[124,160,223,289,313]

A strength of this study was its ability to explore nonlinear relationships between proximity to a CAFO and respiratory health outcomes. Unadjusted cubic spline function of distance to the nearest CAFO regressed by asthma and allergy outcomes revealed the odds of asthma and allergies decreased as distance to the nearest CAFO increased from 0-5 miles. At around 5-6 miles from a CAFO the odds of asthma and allergies was lowest and increased until about 10-11 miles from a CAFO, at which point it appeared to level off. Prior studies have tended to group the exposure measure, and only Borlee et al (2015) showed cubic spline plots of distance to the nearest CAFO and wheezing in the Netherlands.[10] Distances investigated only went from 0 to 1500m, making results largely incomparable to the U.S. where residents are not in as close proximity to CAFOs. The relationship seen in this study confirms cut points used in prior studies in the U.S. which tended to compare residents living <3 miles to a CAFO to those living greater than 3 miles from a CAFO.[16,30,32,35] The cubic spline curves also support evidence of both the negative and protective health effects from exposure livestock seen from prior studies. Splines suggest at close proximity to a CAFO, odds of asthma and allergies are higher than at far distances, but that distances of 3-7 miles from a CAFO, protective effects may be possible, as the odds are lower than those seen at distances greater than 7 miles. However, it is important to emphasize this is an exploratory, observational study. Proxy measures of exposure to CAFOs are not ideal and may have resulted in misclassification of the exposure. Furthermore, residual confounding is likely present, and we cannot be certain as to why there is a dip in the odds of asthma and allergies at 5-7 miles from a CAFO. It is possible that at this distance residents are different in other ways – i.e. they may have exposure to more microbial diversity, more likely to have grown up on farm, or are more likely to be exposed to fewer air emissions through their occupation. We could not completely account all these factors in this study.

Chapter 3, Aim 2, investigated the association between residential proximity to the nearest CAFO and the prevalence of asthma and lung function among a study sample of children and adolescents from across the state. While most prior studies among adults have taken place in Europe, most of the studies investigating health effects among children living near CAFOs come from the U.S., primarily Iowa, North Carolina, and Washington State.[30–32] This study was an important contribution as it brought the research to another state, where CAFO type, settlement, management, and regulations differ.

This study found children and adolescents living in proximity to a CAFO were more likely to have had a wheezing episode in the last 12 months and have taken asthma medication in the last 3 months. While similar associations with doctor diagnosed asthma, current asthma, and asthma attack in the last 12 months were observed, they were not statistically significant. These results were in contrast to another rural pediatric asthma cohort study in Wisconsin of children aged 5-17 (n=1000 children) which compared children born on dairy farms to children who grew up in similar rural area but without farm exposure.[167] They found those who grew up on dairy farms were less likely to be asthmatic compared to children from non-farms in rural areas. However, this did not specifically investigate exposure to large-scale CAFOs and was more suggestive of exposure to small-scale farm life.   In fact, the handful of studies finding school and residential proximity to CAFOs to be associated with a higher prevalence of asthma is in contrast to decades of research which have indicated children who live on farms or have livestock exposure in early life have a decreased risk of developing atopy and asthma.[163,264,277,314] These findings are also in support of the hypotheses which speculate that exposure to small farm life may offer protection from asthma and allergies due to the diversity of exposures to grasses, hay, dirt, dust, feed, livestock and fodder, which can lead to a more diverse microbiome in children living on these farms.[124,157,170,289] Alpha and Beta diversity of children's nasal microbiome have been associated with having a protective effect against atopy and asthma, which has been linked to farm exposure.[175,290]

Results from this study strengthen and confirm emerging evidence that proximity to CAFOs may have negative effects on children's respiratory health. This study supports the hypothesis that living near CAFOs may result in exposure to a decrease in the diversity of microbes with an abundance of a few inflammatory microbes, when compared with smaller farms, due to the large abundance and concentration of one specific type of animal, feed, and manure.[124,157,170] Sequencing of 16SrRNA components of aerosols at varying distances from dairy CAFOs in Colorado revealed a microbiome derived predominantly from animal sources with bacterial genera dominate by Staphylococcus, Streptococcus, Haemphilus and Pseudomonas, all of which have pro-inflammatory and pathogenic capacity in humans.[174] Furthermore, antibiotic use is higher on CAFOs and high concentrations of several veterinary antibiotics have been found in airborne PM downwind and upwind of cattle CAFOs, where microbial communities of PM downwind were enriched with ruminant-associated taxa and were distinct when compared to upwind PM.[70,71]

Antibiotic use and resistance is a well-known disruptor of asymptomatic colonization patterns and can result in reduced microbial diversity.[175] It is also plausible that antibiotics may play a role in the different health effects seen among children living near CAFOs when compared to studies which have found protective effects among children growing on small, traditional-style farms. The results of this study provide further rationale for more research which investigates the microbial differences seen near livestock farms of different sizes, with different management styles, to see how they can affect air emissions, and specifically microbial diversity near the facilities and among nearby residents.

Unlike with the adults, this study did not find associations with lung function and proximity to a CAFO. Few studies have assessed lung function among children living near CAFOs and thus there is not a lot of supporting evidence to suggest lung function is associated with proximity to a CAFO or not. While one would perhaps expect lung function to be lower among those living nearer to a CAFO due to the increased exposure to air emissions, lung function measurements are also collected just once in this study and may be more reflective of acute exposure. Results from this study are contrary to results seen in a longitudinal study in Washington which found measured ammonia levels to be correlated with residential proximity to CAFOs, and associated with a decrease in FEV1 % predicted, but only with one and two day lagged concentrations.[32] In this study, the asthma outcomes asked were about symptoms and diagnoses over 3 months, 12 months, and the lifespan, and may be more reflective of chronic exposure from nearby air emissions.

Having a statewide sample of children was both a strength and a weakness of this study, and presented a unique challenge many prior studies did not face – having a mix of urban and rural residents. Sensitivity analyses revealed stronger associations between proximity to the nearest CAFO and asthma outcomes when Milwaukee county residents (largest urban metropolitan area in the state) were removed from analysis; and even larger effect sizes when all urban residents were removed from analyses. This finding suggests that by including urban residents in the analyses, residual confounding is introduced. This could be due to higher exposures to air pollutants from other sources such as vehicles or industries which are more prevalent in urban areas. It could also be due to other factors related to asthma prevalence that may be different in an urban setting when compared to a rural setting. Fine particulate matter is higher in the urban areas of Wisconsin (Figure C1) and the prevalence of asthma is also higher among our study sample in urban areas. However, prevalence estimates of asthma may not reflect true prevalence of asthma due to reporting bias from variation in access to healthcare. By including urban participants in analyses, who are more likely to be far from CAFOs, but have a higher prevalence of asthma, results may potentially be biased towards the null. The unadjusted cubic splines showed a similar pattern as seen with the adults in Chapter 2 (Aim 1). When urban residents were included, the log odds of asthma outcomes tended to be higher than at near distances, likely representing the higher prevalence in the cities that was not seen in Chapter 2 where only rural adults were included in analyses. It was decided that Chapter 3 (Aim 2) retain all urban and rural children participants due to the small sample size and low prevalence of both the exposure and outcome.

In Chapter 4 (Aim 3), a relative exposure metric was developed which estimated cumulative exposures using an the additive model estimating exposure from all CAFO air emissions from both time spent at home and school, taking into account CAFO size, distance, wind direction and wind speed. A couple studies in Iowa and Washington found residential proximity to be associated with pediatric asthma prevalence,[30,32] while two additional studies in Iowa and North Carolina found school attendance near a CAFO to also be associated with an increased prevalence of asthma.[31,35] These prior findings suggest that exposure to CAFOs from time spent at home and at school may affect pediatric respiratory health. Yet, no study had attempted to refine the relative estimate of exposure to capture both potential exposure to CAFOs while at home and at school. Furthermore, many prior studies focused on cumulative effects of AFOs within 3 miles or distance to the nearest CAFO, not taking into account potential local and regional elevated air emissions from CAFOs which may extend beyond those distance cut point. This study considered exposure to all CAFOs in the state, using the inverse square law to weight exposure to nearby CAFOs more heavily than those far away.

Similar to Aim 2, this study found relative exposure to CAFOs to be associated with doctor diagnosed asthma and wheezing when using a more refined estimate of exposure. Similar trends for all respiratory outcomes were seen with the relative exposure metric as were seen with distance to the nearest CAFO. Lung function was not found to be associated with relative exposure to CAFOs, and unadjusted cubic spline plots showed a similar trend in association between exposure and asthma outcomes.

One important finding from Aim 3 was an increased understanding regarding the potential variability in exposure to CAFOs estimated from home and school locations. While we may have anticipated children who live near a CAFO to also be more likely to attend school near a CAFO, and vice versa, we found exposure to CAFOs from both locations to be variable. Around 6% of the study sample lived within 3 miles of a CAFO and attended school within 3 miles of CAFO. Whereas 9% either lived, or attended school, within 3 miles of CAFO, but not both (Table D5).

Findings across all three aims are consistent and robust which suggest future research that builds off these observational studies are warranted. Effects observed between adults and children, with both distance to the nearest CAFO and also with a relative exposure metric, were relatively similar. To improve understanding of causal mechanisms, future research should refine measurements of exposure and outcomes and consider a longitudinal, cohort or case-control design.

A somewhat surprising outcome, as shown in Tables D6-D8, was that distance to the nearest CAFO was perhaps a better predictor of asthma outcomes in children, with better model fit statistics, when compared to the relative exposure metric. However, the fit statistics did not differ greatly among the various exposure metrics, and should be interpreted with caution. It cannot be determined from this study which proxy measure of exposure to CAFOs is a better estimate of actual exposure to air emissions from CAFOs. Based on prior atmospheric dispersion modeling, fate and transport research of endotoxin, antibiotics, PM2.5, H2S, and ammonia can be influenced by direction, wind, size and type of livestock farms, as well as management practices.[4,26,44,45,297,298,300,315–317] We have every reason to believe the more refined exposure metric used in Chapter 4 is a better surrogate measure of potential exposure to CAFOs, although actual measurement of air emissions at both the sources and the residence or school would need to be gathered in order to determine whether that is true or not.

This study also highlights need for better data on livestock farms that do not meet regulatory standards under NPDES under the CWA. The relative exposure metric suggests that the concentration and size of livestock may play a role and that living downwind from two AFOs with 500 animal units each may be no different than living near one CAFO with 1000 animal units. However, there is no regulatory measures on non-CAFO in the state which provide public data on them, or any passive surveillance which would allow us to better research and understand their role in community respiratory health.

5.2 Strengths and limitations

Strengths

This study contributes to the national and international literature and offers many strengths. This study used a statewide sample of both adults and residents, which provided a unique population, as many prior studies were conduct on panels or smaller communities living near CAFOs. By using SHOW's statewide study sample, this study was able to span different geographical regions within the state. SHOW's breadth of data enabled this research to be analyzed among both adults and children, and assess many behavioral and environmental characteristics as confounders. Having both objective measures of lung function and subjective measures of asthma and allergies was an additional strength, only a few studies have been able to do.

This study offered strengths in its ability to refine proxy measures of exposure. Individual levels of exposure were retained and cubic splines were used which provided important insights into the potential exposure-outcome relationship between CAFOs and respiratory health among nearby residents. Furthermore a refined estimate of exposure was used, which attempted to capture children's exposure to CAFO from both time spent at home and school, something no other studies have done. Most of all, this study provides a well thought out and thorough exploratory and descriptive analysis of respiratory health among child and adult residents living near CAFOs in Wisconsin, which are mostly dairy. Bringing this research into a new state, which has different settlement and regulation of CAFOs offers a very valuable foundation of knowledge upon which to inform the direction of future studies in the state.

Limitations

While observational studies such as this one are an important contribution to the field, they also have limitations which must be acknowledged and realized when interpreting results. The statewide, population-based study sample presented challenges when investigating a rare exposure, such as living near CAFOs. Furthermore, the prevalence of some of the asthma outcomes – such as asthma medication use and asthma episodes in the last 12 months – likely resulted in having low power to detect associations and Odds Ratios may be an overestimation of true associations in the state population. The statewide sample also introduced a spatial challenge which prior studies did not face – having a mix of urban and rural participants, in combination with CAFOs existing in and near urban-defined census block groups. Teasing out potential residual confounding from urban sources of air pollution, or other factor unique to urban vs. rural settings that may be related to air pollution exposure and asthma, allergies, and lung function was difficult to do in this study. The low power and small study sample in Aim 2 and 3 of this study allowed for little ability to assess many confounders at once, or to investigate potential interactions. In addition, several of the data available on potential confounders were imperfect measures. For example, proxy measures of exposure to vehicle and industry emissions likely did not adequately capture relative exposure to other sources of air pollution, which may have led to misclassification of confounders as well as the main exposure. Limited data was available on occupational exposures to air pollution, or livestock – something which may have greatly altered associations seen in Aim 1 in particular, since adults spend a lot of time at their job. Not having information on childhood respiratory infection or exposure to farm-life/livestock may have also affected results seen in Aim 2 and 3. This study was also cross-sectional, and as such causality cannot be assessed. Ascertainment of the outcomes relied on self-reported data which may suffer from recall bias, and objective measures of lung function which may not reflect overall lung function but rather reflect an acute measure of lung function.

One of the biggest limitations of this study is in its proxy measure of exposure to CAFOs. While more refined than most, it has likely resulted in misclassification of the exposure. Not only were other factors which are known to influence the concentration, fate and transport of air emission not included in Aim 1 and 2, but exposure to other non-CAFO sized livestock farms were not accounted, of which there are over 8,000 in Wisconsin.[305] Exposure to nearby crop field emissions, which include airborne uptake from manure and chemicals spread on crop fields, were also not considered in this study, something that could be a driving factor in associations seen, rather than the CAFO facilities themselves. Identifying the exact cause of associations found in this study was not possible, but it is important to recognize that differences seen in respiratory health among those living near CAFOs vs. those living far from CAFOs may be due to other farming exposures, or due to differences between the two study populations which are unknown confounders.

Implications

Overall this collective work represents an important first step in the process of discovery in environmental health sciences research. As Kaufman and Curl (2019) point out with their latest Translational Research Framework for Environmental Health Sciences, while some important translational research fits the bench-to-bedside model and is discovered in the lab, most important environmental health discoveries are driven by observations from clinicians, researchers, and the public themselves.[318] The source of London's cholera outbreak was discovered by John Snow's observation of the geographical distribution of cases.[319] In 1930, Merewether and Price's observational study of the asbestos industry was what launched are current understanding of risks of occupational exposure to asbestos.[320]

The value of observational studies often relies on the generation of many of observational studies over time, each playing an important role in the genesis of health improvement.[318] For example, it was the consistent results from a series of many well-designed observational studies in the late 1980s, which lead to our current understanding of the effect of second-hand smoke on low birth weight.[321,322] Additionally, the value of the public and media in making important observations and contributions to environmental health discoveries cannot be understated.[318] For example, undertakers and florists were the ones who first observed effects of the Great London Smog when they began running out of coffins and fresh flowers due to a very high untick in the number of funeral arrangement requests.[323]

This study demonstrates another example of observational research, largely fueled from public and media observations. While the Right to Farm law in Wisconsin makes it difficult for individuals to file private nuisance claims in response to potential exposures from CAFOs and human health effects,[242] communities in Wisconsin have banded together to form coalitions to fund litigation fees, and have drawn media attention.[80–82,88,89,324] There have been several media splashes and articles highlighting neighbors who can't breathe due to the strong ammonia odors and who face respiratory symptoms from nearby large livestock farms.[76,83,88,242,325] As Kaufman and Curl (2019) state, "The initial discovery phase in environmental health sciences most often takes the form of an observation of an environmental exposure that has the potential to cause harm to human health."[318] This study does just that – it (1) leverages existing knowledge of air emission releases from CAFOs, known fate and transport of those emissions, and their known potential for triggering asthma symptoms and inflammation of the respiratory system; it (2) takes current public and media observations which suggest a potential harm to human health may be occurring among residents living near CAFOs in the state; (3) it finds a paucity of research on the topic, and no studies in Wisconsin, where state regulations of CAFOs may alter exposure levels and the effects of exposures compared to other states; and it (4) adds to the T1 Discovery Phase in Kaufman and Curl's Framework Model by conducting an observational study where there is a potential environmental exposure which has the potential to cause harm to human health.

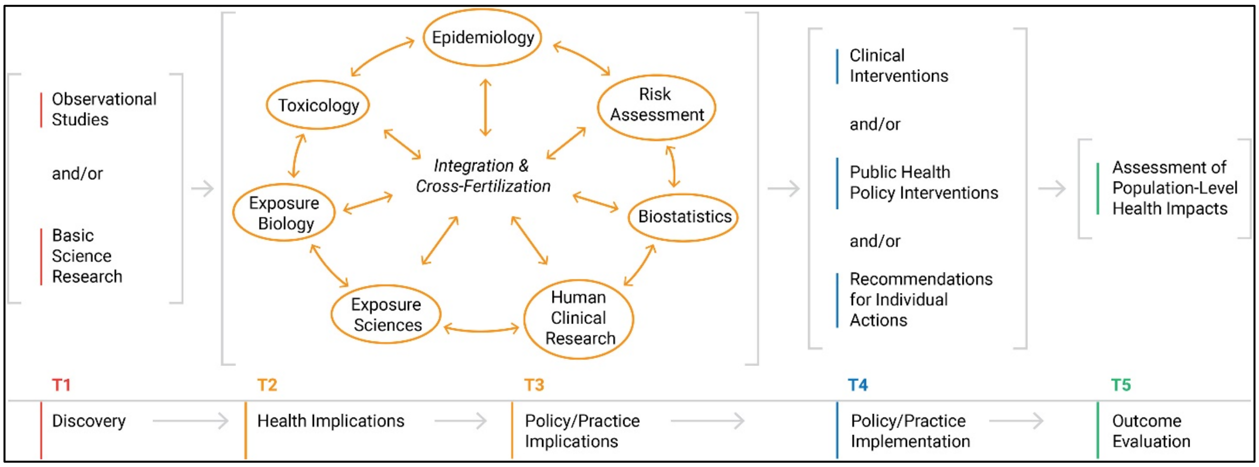

Figure 17. Kaufman and Curl's (2019) framework for translational research in the context of environmental health sciences.[318]

5.3 Future Directions

Results from this study suggest additional research is warranted in Wisconsin around exposure to CAFOs and asthma, allergies and lung function. Future studies should consider addressing limitations of this study around study design, estimates of exposure and the outcomes. In order to account for the low prevalence of the exposure, a cohort study which selects study participants by exposure status should be considered. An additional method which addresses the potential low prevalence of asthma outcomes, would be to design a case-control study in a county or area with a large concentration of CAFOs, such as Brown County, where the likelihood having both cases and controls with and without the exposure is higher.

Addressing current gaps in knowledge around the role the microbiome plays would greatly contribute to our understanding of how and why livestock farms may have protective or deleterious effects on respiratory health, and what role antibiotic use and the size of farms plays in this connection. Recent protocol developments and pilot studies within the SHOW infrastructure could be leveraged to write a grant for an ancillary study that takes this research a step further. The Wisconsin Microbiome Follow-up study recently collected participant stool samples, as well as household dust, high touch surface swab, and soil samples from SHOW participants and participant households. In addition, SHOW assisted in the protocol development and data collection of the Cumulative Risks, Early Development, and Academic Trajectories study (CREATE), where personal air pollution exposure was collected on 3-4 year old children via a small monitor in a backpack the children wore over 2 days, across 2 time points. Also, urine, cheek swabs, and hair samples were successfully collected on the children. Evidence suggests early life exposure to farm life, livestock, and microbial diversity are likely an important window by which asthma and allergy status are affected.[124,171,173] Capturing gut microbiome and personal air exposure among children, in addition to household microbiome, household air pollution data, and nearby CAFO air pollution data would strengthen the measurement of exposure, as well as our understanding of how microbes and other air constituents play a role in the asthma and allergy development. An additional study which focuses on data collection pertaining to this specific research question also enables better data collection around parental occupations, residential mobility and early life exposure to livestock and respiratory infections – all important confounders that were not easy to account for in this study.

This study highlights the importance of surveillance data. Passive surveillance can be an effective and inexpensive way to start observational research around a potential environmental exposure. In this study, CAFO data obtained via WPDES permits were used. However additional surveillance that includes livestock farms of all sizes would be useful. Iowa for example requires permitting of all Animal Confined Operations, regardless of their size, and has public use datasets, which include their location, animal type, and quantity of animals. Beyond just data pertaining to livestock farms, this study highlights the need for data on crop fields and their manure applications and chemical applications. It is certainly plausible that associations seen in this study could be due to other nearby farming practices, which were not accounted for.

While this study does not provide conclusive evidence by which to drive policy changes, other states have made changes in how they regulate livestock farms, recognizing the potential for human health effects and being proactive. Wisconsin could look to other states for models and make changes to how they regulate agriculture that help mitigate conflict and reduce potential human health effects from living near CAFOs until more research is realized. Schultz and Harvey (2017) provide several examples of changes other states have made to their Right to Farm laws (See Table #) which Wisconsin could consider in an effort to protect potential human health effects from living near CAFOs until further evidence is provided.[242]

Table 4. Suggested changes to Wisconsin's Right to Farm Law.

Suggested change	Reasoning
Removing proof of threat to public health and safety as necessity for private nuisance	Proving public health and safety is akin to a public nuisance and not a private nuisance. The inability to file a private nuisance claim was in fact found to be an unconstitutional takings according to Iowa's state constitution, and Washington State narrowly defined their Right to Farm law protection only against urban encroachment.
Change in definition of agricultural use and practice	Minnesota provides more explicit and detailed definitions of agricultural uses and practices so that some categories of uses and practices may be exempt or singularly included under specific aspects of the Right to Farm law, such as expansions or change in use permits.
Add recognition of "change in agricultural use" as either exemption from Right to Farm, or open period for contested nuisance claims	Some state, Indiana for example, not only recognize change in use in their Right to Farm statute, but exempt the change in use from Right to Farm protection at least for a certain period of time (typically 1 year), so that private and public nuisance have minimal limitations by which to file claims.
Add mandatory regulation of odor, air, and adjacent property private well water	Since the federal government minimally regulates air pollution, states can take it upon themselves to regulate it. Minnesota regulates and monitors Hydrogen Sulfide on CAFOs and Missouri enforces regulation of an odor control plan and a numerical odor test on CAFOs in the state.
Exempt farms with over a certain number of animal units from Right to Farm laws	Minnesota explicitly exempts CAFOs from Right to Farm protections under its statute, opening them up for nuisance claims like any other property owner would face.
Ban manure irrigation use and winter spreading of manure	Michigan and Minnesota, among other states, have banned manure irrigation in counties where the most conflict would ensue. In three counties in Wisconsin, local efforts to ban winter spreading of manure have statistically significantly decreased the contaminant levels in nearby wells, supporting this proposed change.

Source: Schultz and Harvey (2017)

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Appendices

Appendix A: Tables

Table A1. Regulatory Definitions of Large CAFOs, Medium CAFOs, and Small CAFOs

Animal Sector	Size Thresholds (number of animals)		
	Large CAFOs	Medium CAFOs[1]	Small CAFOs[2]
cattle or cow/calf pairs	1,000 or more	300 - 999	less than 300
mature dairy cattle	700 or more	200 - 699	less than 200
veal calves	1,000 or more	300 - 999	less than 300
swine (weighing over 55 pounds)	2,500 or more	750 - 2,499	less than 750
swine (weighing less than 55 pounds)	10,000 or more	3,000 - 9,999	less than 3,000
horses	500 or more	150 - 499	less than 150
sheep or lambs	10,000 or more	3,000 - 9,999	less than 3,000
turkeys	55,000 or more	16,500 - 54,999	less than 16,500
laying hens or broilers (liquid manure handling systems)	30,000 or more	9,000 - 29,999	less than 9,000
chickens other than laying hens (other than a liquid manure handling systems)	125,000 or more	37,500 - 124,999	less than 37,500
laying hens (other than a liquid manure handling systems)	82,000 or more	25,000 - 81,999	less than 25,000
ducks (other than a liquid manure handling systems)	30,000 or more	10,000 - 29,999	less than 10,000
ducks (liquid manure handling systems)	5,000 or more	1,500 - 4,999	less than 1,500

Data: Environmental Protection Agency

https://www3.epa.gov/npdes/pubs/sector_table.pdf

[1] Must also meet one of two "method of discharge" criteria to be defined as a CAFO or must be designated.

[2] Never a CAFO by regulatory definition, but may be designated as a CAFO on a case-by-case basis.

[3] Liquid manure handling system

[4] Other than a liquid manure handling system

Table A2. United States Census Roadway Type Definitions

Primary Roadways:	Secondary Roadways:	Local Neighborhood Road, Rural Road, City Street Road/Path:
Primary roads are limited-access highways that connect to other roads only at interchanges and not at at-grade intersections. This category includes Interstate highways, as well as all other highways with limited access (some of which are toll roads). Limited-access highways with only one lane in each direction, as well as those that are undivided.	Secondary roads are main arteries that are not limited access, usually in the U.S. highway, state highway, or county highway systems. These roads have one or more lanes of traffic in each direction, may or may not be divided, and usually have at-grade intersections with many other roads and driveways. They often have both a local name and a route number.	Generally, a paved non-arterial street, road, or byway that usually has a single lane of traffic in each direction. Roads in this feature class may be privately or publicly maintained. Scenic park roads would be included in this feature class, as would some unpaved roads.

https://www.census.gov/geo/reference/rttyp.html
https://www2.census.gov/geo/pdfs/reference/mtfccs2018.pdf

Appendix A: Figures

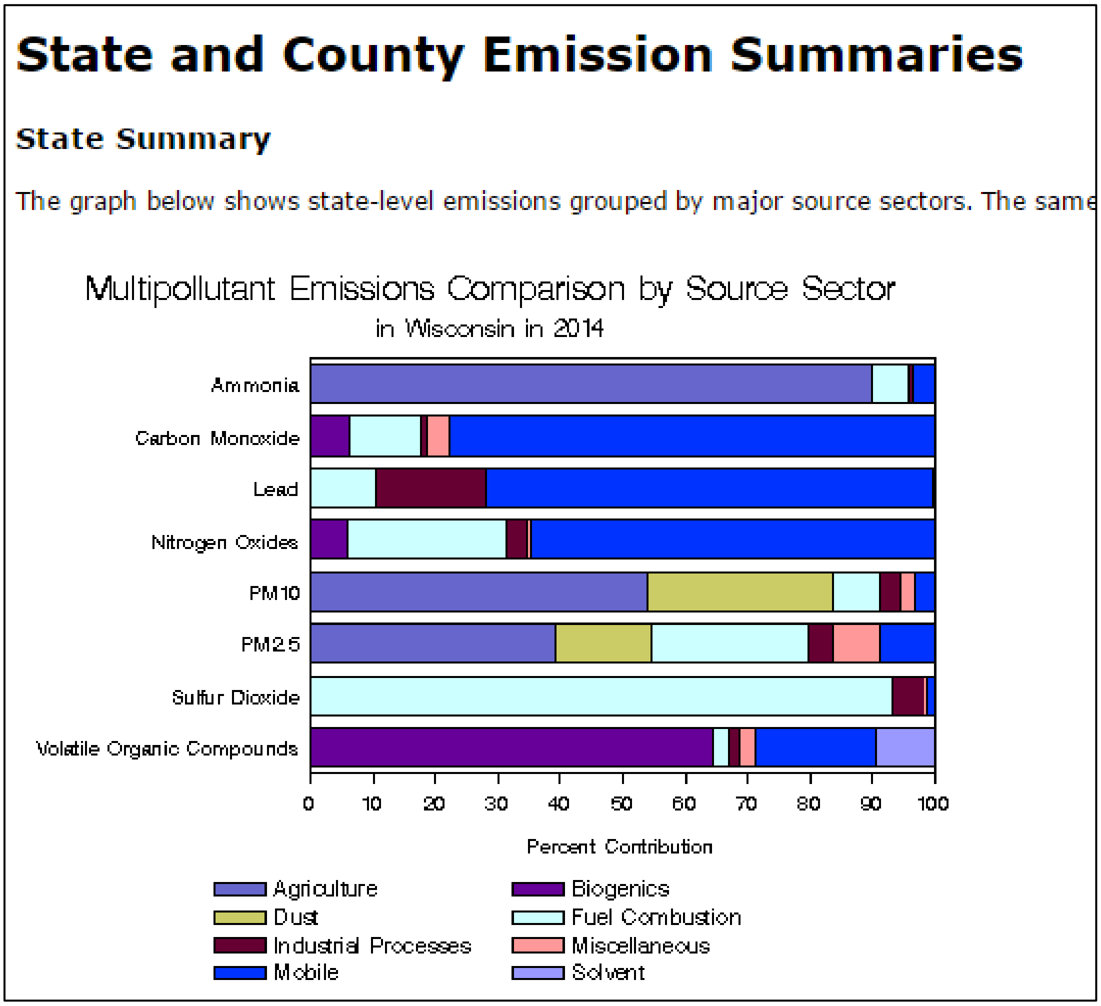


Figure A1. Wisconsin State Emissions Comparison by Source Sector in 2014
Source: https://www.epa.gov/air-emissions-inventories/air-emissions-sources

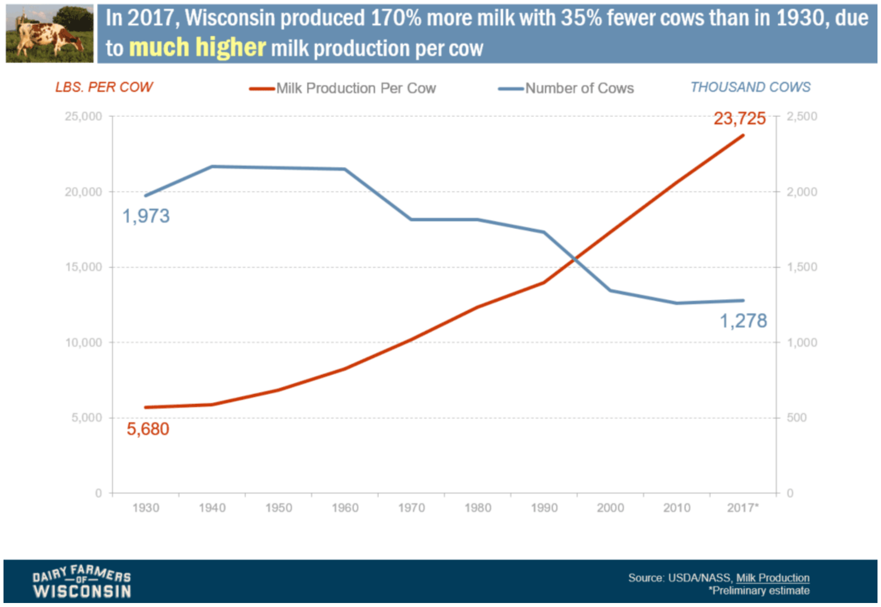


Figure A2. Wisconsin milk production and number of cows: 1930-2017
Source: USDA/NASS, Milk Production & Dairy Farmers of Wisconsin[77]

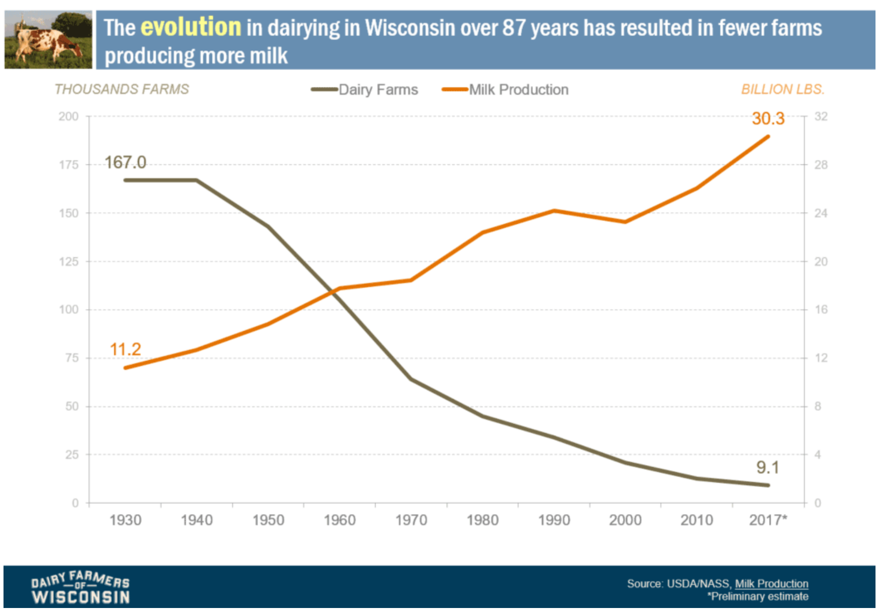


Figure A3. Wisconsin Dairy farms and milk production: 1930-2017
Source: USDA/NASS, Milk Production & Dairy Farmers of Wisconsin[77]

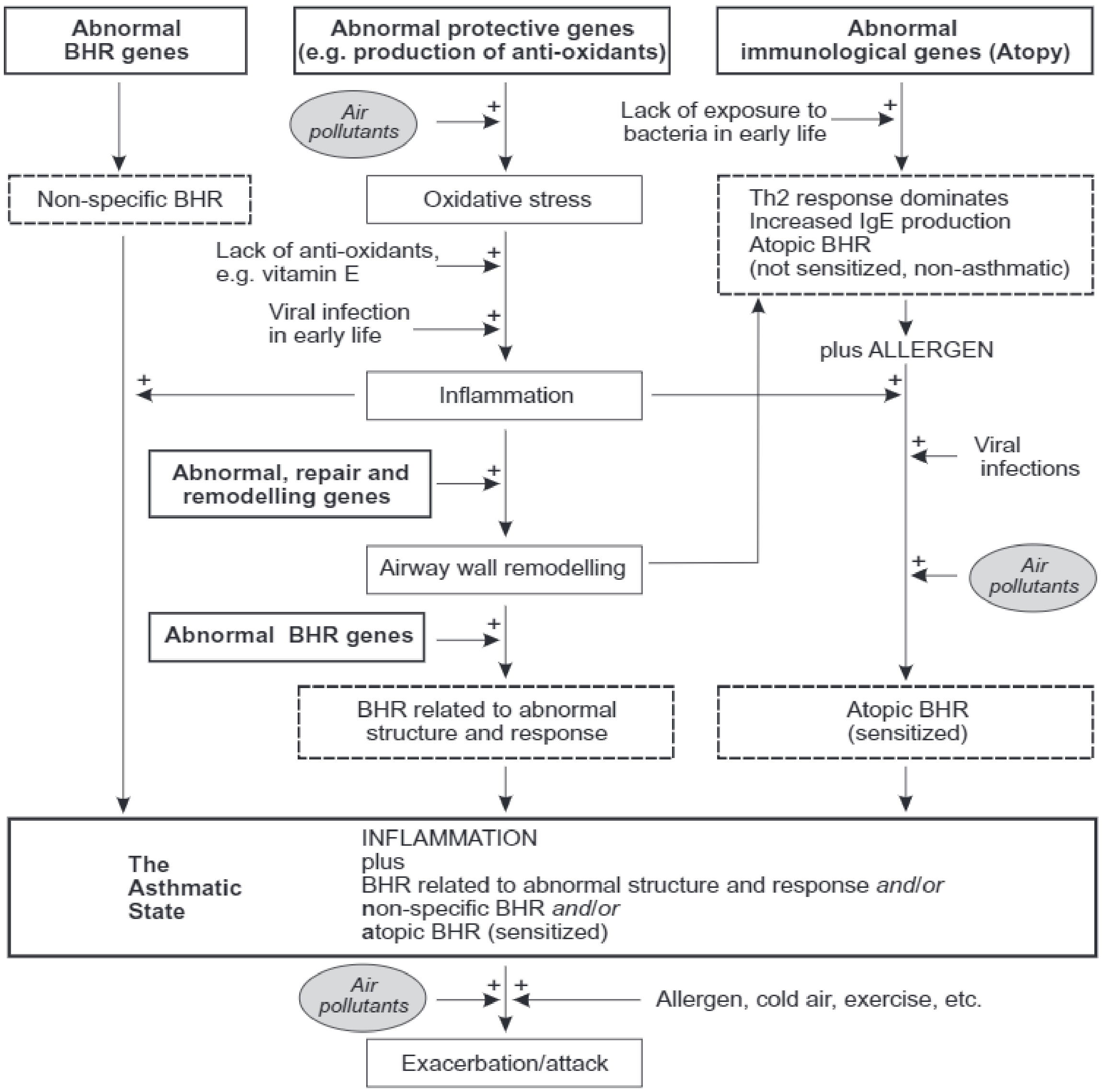


Figure A4. Diagram depicting the hypothetical network of how air pollution exposure is related to asthma from Gowers et al., 2012[133]

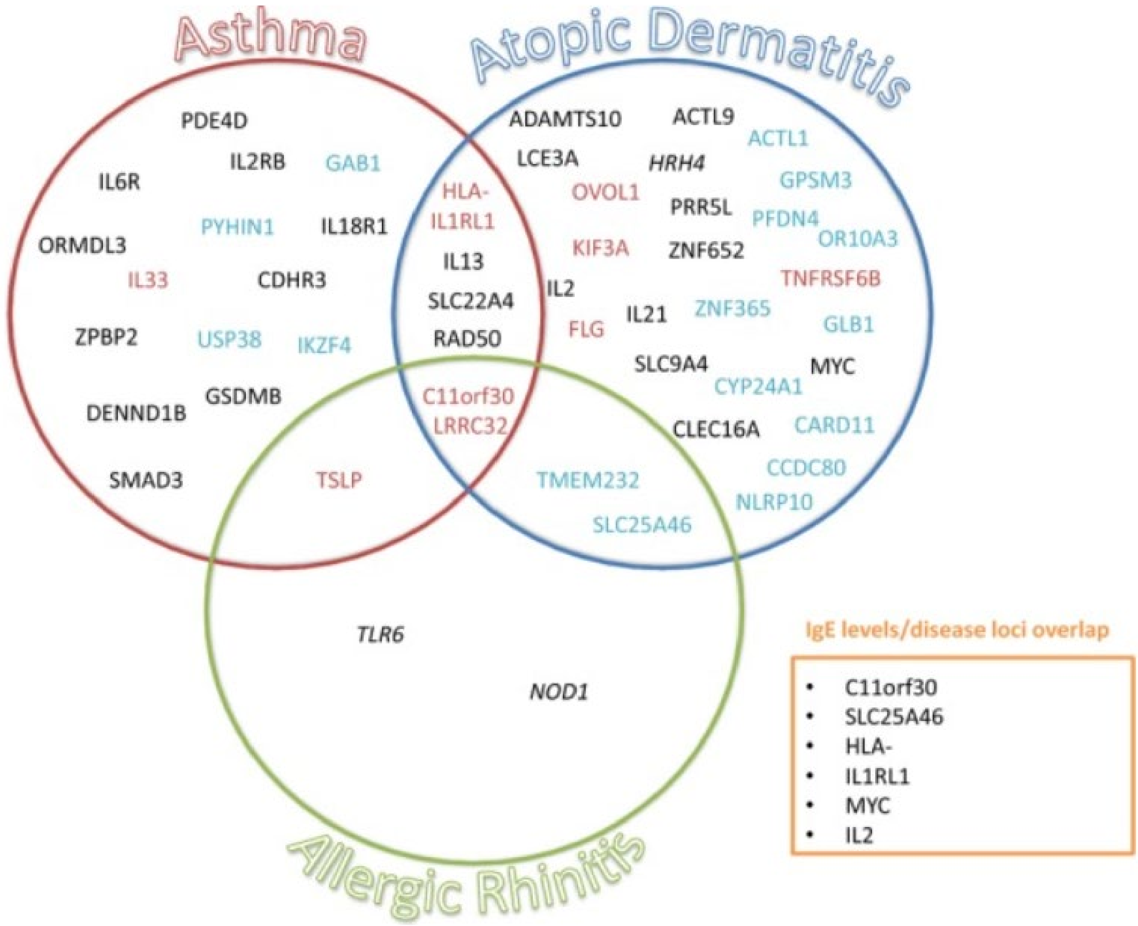


Figure A5. Diagram displaying genes identified through GWAS studies as being associated with allergic diseases and their overlap. Genes are color-coded based on population-type discovered in (black = Caucasian, italics = nearly achieved GWAS significance, blue = non-Caucasian, red = many different populations). Diagram is from Portelli et al. 2015 [184]

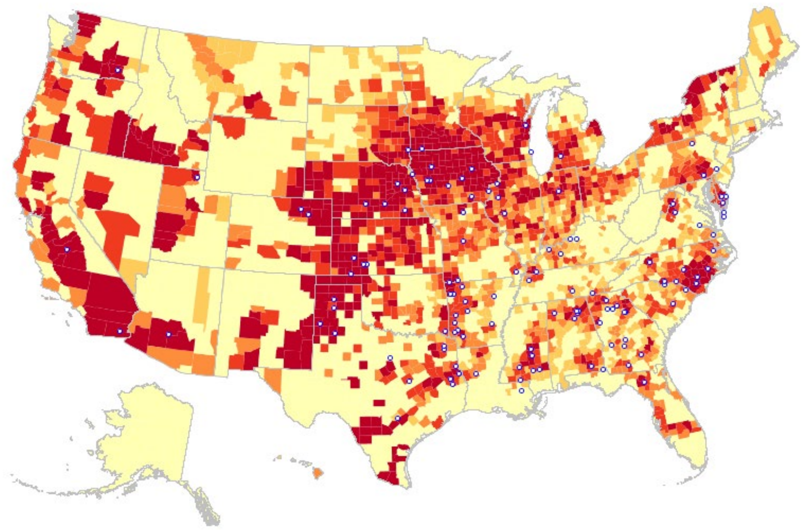


Figure A6. Relative density of CAFOs (all animal types) with NPDES permits depicted at the county level *(Dark red = most dense; light yellow = least dense or none*
Source: Food and Water Watch[234]

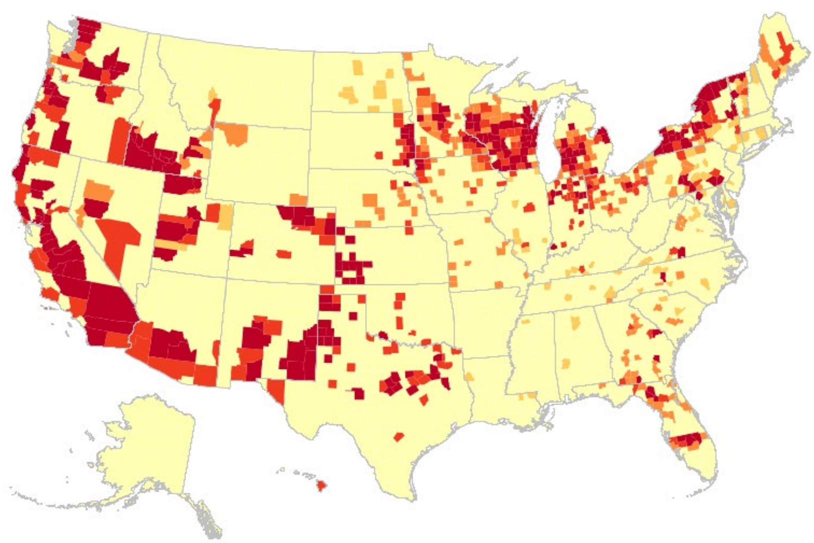


Figure A7. Relative density of Dairy CAFOs with NPDES permits depicted at the county level *(Dark red = most dense; light yellow = least dense or none)*
Source: Food and Water Watch[234]

Appendix B: Tables

Table B1.

Odds Ratio (OR) of current allergies and asthma by residential distance to the nearest CAFO

	Current Allergies *SHOW 2008-2016*		**Current Allergies** *SHOW 2008-2013*		**Current allergies & asthma** *SHOW 2008-2013*	
Residential Distance Compared	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 mile *(1.6 km)* vs:						
2 miles *(3.4 km)*	1.29 (0.93, 1.78)	1.52 (1.06, 2.19)	1.25 (0.84, 1.86)	1.55 (1.00, 2.40)	1.26 (0.85, 1.88)	1.52 (1.02, 2.27)
3 miles *(4.8 km)*	1.55 (0.95, 2.54)	2.01 (1.19, 3.4)	1.51 (0.82, 2.76)	2.08 (1.12, 3.87)	1.55 (0.85, 2.83)	2.06 (1.16, 3.66)
4 miles *(6.4 km)*	1.73 (1.02, 2.93)	2.29 (1.35, 3.89)	1.73 (0.91, 3.3)	2.43 (1.34, 4.41)	1.82 (0.96, 3.45)	2.46 (1.38, 4.36)
5 miles *(8.0 km)*	1.81 (1.10, 2.99)	2.36 (1.42, 3.92)	1.90 (1.03, 3.49)	2.55 (1.49, 4.36)	2.03 (1.11, 3.72)	2.67 (1.57, 4.53)
6 miles *(9.7 km)*	1.81 (1.13, 2.89)	2.3 (1.37, 3.87)	1.97 (1.12, 3.49)	2.53 (1.48, 4.31)	2.15 (1.22, 3.78)	2.72 (1.61, 4.61)
1.5 miles *(2.4 km)* vs:						
2 miles *(3.4 km)*	1.13 (0.97, 1.31)	1.22 (1.04, 1.43)	1.11 (0.93, 1.34)	1.23 (1.01, 1.49)	1.12 (0.94, 1.34)	1.22 (1.02, 1.46)
3 miles *(4.8 km)*	1.36 (0.99, 1.86)	1.61 (1.16, 2.23)	1.34 (0.91, 1.98)	1.65 (1.13, 2.42)	1.37 (0.93, 2.02)	1.65 (1.15, 2.36)
4 miles *(6.4 km)*	1.51 (1.06, 2.17)	1.83 (1.28, 2.63)	1.54 (0.99, 2.40)	1.92 (1.30, 2.85)	1.61 (1.04, 2.50)	1.97 (1.34, 2.89)
5 miles *(8.0 km)*	1.59 (1.11, 2.27)	1.89 (1.26, 2.84)	1.69 (1.09, 2.61)	2.02 (1.33, 3.08)	1.8 (1.17, 2.77)	2.14 (1.42, 3.22)
6 miles *(9.7 km)*	1.58 (1.10, 2.28)	1.84 (1.13, 3.00)	1.76 (1.13, 2.73)	2.00 (1.20, 3.36)	1.9 (1.23, 2.95)	2.18 (1.34, 3.54)
2 miles *(3.4 km)* vs:						
3 miles *(4.8 km)*	1.20 (1.01, 1.43)	1.32 (1.11, 1.57)	1.21 (0.97, 1.49)	1.35 (1.11, 1.63)	1.23 (0.99, 1.51)	1.35 (1.12, 1.63)
4 miles *(6.4 km)*	1.34 (1.07, 1.69)	1.50 (1.17, 1.93)	1.39 (1.05, 1.84)	1.57 (1.21, 2.04)	1.44 (1.09, 1.9)	1.61 (1.25, 2.08)
5 miles *(8.0 km)*	1.41 (1.08, 1.84)	1.55 (1.06, 2.26)	1.52 (1.10, 2.10)	1.65 (1.10, 2.47)	1.61 (1.17, 2.21)	1.75 (1.21, 2.54)
6 miles *(9.7 km)*	1.40 (1.02, 1.93)	1.51 (0.9, 2.52)	1.58 (1.07, 2.32)	1.63 (0.92, 2.88)	1.70 (1.16, 2.49)	1.79 (1.07, 2.98)
2.5 miles *(4.0 km)* vs:						
3 miles *(4.8 km)*	1.09 (1.01, 1.16)	1.12 (1.05, 1.21)	1.09 (1.00, 1.19)	1.14 (1.05, 1.22)	1.10 (1.01, 1.20)	1.14 (1.06, 1.23)
4 miles *(6.4 km)*	1.21 (1.05, 1.40)	1.28 (1.06, 1.56)	1.26 (1.05, 1.5)	1.32 (1.08, 1.63)	1.29 (1.08, 1.54)	1.36 (1.13, 1.65)
5 miles *(8.0 km)*	1.27 (1.01, 1.59)	1.32 (0.91, 1.91)	1.37 (1.05, 1.8)	1.39 (0.92, 2.11)	1.44 (1.10, 1.89)	1.48 (1.02, 2.14)
6 miles *(9.7 km)*	1.27 (0.93, 1.73)	1.29 (0.76, 2.19)	1.43 (0.98, 2.08)	1.38 (0.75, 2.54)	1.53 (1.05, 2.22)	1.51 (0.88, 2.59)
3 miles *(4.8 km)* vs:						
4 miles *(6.4 km)*	1.25 (1.01, 1.54)	1.16 (1.02, 1.33)	1.09 (0.85, 1.40)	1.19 (1.03, 1.37)	1.11 (0.72, 1.70)	1.51 (1.17, 1.94)
5 miles *(8.0 km)*	1.24 (0.96, 1.60)	1.18 (0.85, 1.66)	1.18 (0.87, 1.61)	1.24 (0.84, 1.84)	1.48 (0.82, 2.69)	2.74 (1.43, 5.23)
6 miles *(9.7 km)*	1.12 (0.81, 1.55)	1.13 (0.66, 1.92)	1.24 (0.83, 1.85)	1.21 (0.64, 2.28)	1.94 (0.82, 4.61)	4.43 (1.55, 12.65)

CAFO: concentrated animal feeding operation; km: kilometers; OR: odds ratio; CI: confidence interval

[b]Adjusted for gender, age, body mass index, smoking status, education, income, pet ownership

Table B2.

Odds Ratio (OR) of allergy type by residential distance to the nearest CAFO

	Nasal Allergies		Lung Allergies		Eye Allergies		Dermal Allegies	
Residential Distance Compared	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 mile *(1.6 km)* vs:								
2 miles *(3.4 km)*	1.17 (0.78, 1.76)	1.37 (0.85, 2.23)	0.95 (0.56, 1.58)	1.00 (0.61, 1.62)	1.13 (0.72, 1.77)	1.28 (0.73, 2.25)	1.01 (0.53, 1.92)	0.86 (0.50, 1.48)
3 miles *(4.8 km)*	1.37 (0.74, 2.54)	1.78 (0.90, 3.53)	0.99 (0.45, 2.16)	1.23 (0.62, 2.45)	1.28 (0.65, 2.52)	1.53 (0.67, 3.5)	1.00 (0.37, 2.68)	0.85 (0.39, 1.88)
4 miles *(6.4 km)*	1.6 (0.83, 3.09)	2.15 (1.12, 4.15)	1.12 (0.48, 2.57)	1.79 (0.90, 3.54)	1.44 (0.70, 2.97)	1.70 (0.73, 3.97)	0.97 (0.34, 2.80)	0.95 (0.42, 2.13)
5 miles *(8.0 km)*	1.82 (0.98, 3.39)	2.45 (1.40, 4.29)	1.29 (0.58, 2.85)	2.66 (1.39, 5.09)	1.59 (0.80, 3.15)	1.79 (0.81, 3.97)	0.93 (0.34, 2.55)	1.11 (0.51, 2.44)
6 miles *(9.7 km)*	1.98 (1.11, 3.54)	2.63 (1.55, 4.44)	1.43 (0.68, 3.01)	3.5 (1.77, 6.92)	1.68 (0.88, 3.19)	1.80 (0.82, 3.97)	0.89 (0.35, 2.27)	1.27 (0.56, 2.86)
1.5 miles *(2.4 km)* vs:								
2 miles *(3.4 km)*	1.08 (0.90, 1.3)	1.17 (0.94, 1.44)	0.98 (0.78, 1.24)	1.02 (0.82, 1.26)	1.06 (0.87, 1.30)	1.13 (0.87, 1.45)	1.00 (0.75, 1.34)	0.94 (0.74, 1.20)
3 miles *(4.8 km)*	1.27 (0.86, 1.89)	1.51 (0.99, 2.30)	1.02 (0.62, 1.70)	1.26 (0.82, 1.93)	1.2 (0.78, 1.87)	1.35 (0.80, 2.27)	0.99 (0.52, 1.88)	0.93 (0.56, 1.53)
4 miles *(6.4 km)*	1.48 (0.95, 2.32)	1.83 (1.21, 2.78)	1.16 (0.65, 2.05)	1.83 (1.15, 2.91)	1.36 (0.83, 2.23)	1.49 (0.84, 2.65)	0.97 (0.47, 2.00)	1.04 (0.59, 1.81)
5 miles *(8.0 km)*	1.69 (1.08, 2.63)	2.08 (1.38, 3.14)	1.34 (0.76, 2.36)	2.72 (1.59, 4.66)	1.50 (0.92, 2.44)	1.57 (0.85, 2.88)	0.93 (0.46, 1.89)	1.22 (0.64, 2.30)
6 miles *(9.7 km)*	1.83 (1.17, 2.87)	2.23 (1.36, 3.66)	1.49 (0.84, 2.63)	3.58 (1.82, 7.03)	1.58 (0.96, 2.60)	1.58 (0.79, 3.18)	0.88 (0.44, 1.79)	1.39 (0.64, 2.98)
2 miles *(3.4 km)* vs:								
3 miles *(4.8 km)*	1.18 (0.95, 1.46)	1.3 (1.05, 1.60)	1.04 (0.79, 1.37)	1.23 (0.99, 1.54)	1.13 (0.89, 1.44)	1.20 (0.91, 1.58)	0.99 (0.70, 1.40)	0.99 (0.76, 1.29)
4 miles *(6.4 km)*	1.37 (1.03, 1.83)	1.57 (1.21, 2.04)	1.18 (0.82, 1.70)	1.8 (1.29, 2.50)	1.28 (0.93, 1.75)	1.33 (0.91, 1.95)	0.96 (0.61, 1.53)	1.10 (0.75, 1.64)
5 miles *(8.0 km)*	1.56 (1.12, 2.17)	1.79 (1.21, 2.63)	1.36 (0.90, 2.07)	2.67 (1.59, 4.49)	1.41 (0.98, 2.03)	1.39 (0.83, 2.36)	0.93 (0.55, 1.55)	1.29 (0.72, 2.32)
6 miles *(9.7 km)*	1.69 (1.14, 2.51)	1.92 (1.1, 3.34)	1.52 (0.92, 2.49)	3.51 (1.7, 7.27)	1.49 (0.96, 2.31)	1.41 (0.70, 2.83)	0.88 (0.49, 1.60)	1.47 (0.67, 3.25)
2.5 miles *(4.0 km)* vs:								
3 miles *(4.8 km)*	1.08 (1.00, 1.18)	1.13 (1.04, 1.22)	1.04 (0.93, 1.15)	1.14 (1.05, 1.25)	1.07 (0.97, 1.17)	1.08 (0.97, 1.21)	0.99 (0.87, 1.14)	1.01 (0.91, 1.13)
4 miles *(6.4 km)*	1.27 (1.06, 1.52)	1.37 (1.12, 1.67)	1.17 (0.93, 1.47)	1.67 (1.28, 2.17)	1.20 (0.98, 1.47)	1.20 (0.91, 1.58)	0.97 (0.73, 1.28)	1.13 (0.84, 1.53)
5 miles *(8.0 km)*	1.44 (1.09, 1.90)	1.56 (1.04, 2.34)	1.35 (0.95, 1.92)	2.48 (1.47, 4.18)	1.32 (0.97, 1.81)	1.26 (0.76, 2.08)	0.93 (0.61, 1.41)	1.33 (0.75, 2.34)
6 miles *(9.7 km)*	1.56 (1.06, 2.30)	1.67 (0.9, 3.08)	1.5 (0.93, 2.43)	3.25 (1.51, 6.99)	1.40 (0.91, 2.16)	1.27 (0.62, 2.62)	0.88 (0.50, 1.56)	1.51 (0.67, 3.42)
3 miles *(4.8 km)* vs:								
4 miles *(6.4 km)*	0.96 (0.75, 1.23)	1.22 (1.07, 1.40)	1.10 (0.82, 1.46)	1.42 (1.18, 1.72)	0.99 (0.74, 1.32)	1.12 (0.93, 1.35)	1.15 (0.79, 1.67)	1.09 (0.89, 1.34)
5 miles *(8.0 km)*	1.09 (0.80, 1.49)	1.38 (0.94, 2.03)	1.24 (0.84, 1.83)	2.22 (1.37, 3.62)	1.03 (0.72, 1.47)	1.16 (0.74, 1.83)	1.10 (0.69, 1.74)	1.27 (0.76, 2.10)
6 miles *(9.7 km)*	1.29 (0.85, 1.95)	1.46 (0.77, 2.75)	1.37 (0.81, 2.34)	3.08 (1.42, 6.67)	1.10 (0.69, 1.75)	1.16 (0.56, 2.38)	0.96 (0.52, 1.76)	1.43 (0.64, 3.20)

CAFO: concentrated animal feeding operation; km: kilometers; OR: odds ratio; CI: confidence interval

[b]Adjusted for gender, age, body mass index, smoking status, education, income, pet ownership

Table B3.

Odds Ratio (OR) of asthma outcomes by residential distance to the nearest CAFO

	Current Asthma[a]		Doctor Diagnosed Asthma		Asthma Episode in last 12 months		Asthma medication use in last 12 months	
Residential Distance Compared	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted O [b] (95%CI)**
1 mile *(1.6 km)* vs:								
2 miles *(3.4 km)*	1.40 (0.84, 2.35)	0.92 (0.40, 2.11)	1.62 (1.06, 2.47)	1.36 (0.77, 2.42)	1.56 (0.85, 2.86)	1.01 (0.47, 2.18)	2.00 (1.24, 3.20)	1.81 (0.94, 3.47)
3 miles *(4.8 km)*	1.71 (0.79, 3.70)	1.02 (0.29, 3.55)	2.10 (1.11, 3.96)	1.86 (0.80, 4.34)	2.18 (0.89, 5.35)	1.20 (0.39, 3.71)	2.89 (1.43, 5.85)	2.85 (1.09, 7.46)
4 miles *(6.4 km)*	1.80 (0.80, 4.08)	1.32 (0.36, 4.89)	2.20 (1.13, 4.30)	2.49 (1.04, 5.95)	2.68 (1.05, 6.84)	1.64 (0.53, 5.10)	3.07 (1.48, 6.39)	3.85 (1.43, 10.36)
5 miles *(8.0 km)*	1.73 (0.80, 3.75)	1.78 (0.52, 6.07)	2.03 (1.08, 3.82)	3.11 (1.35, 7.19)	2.98 (1.23, 7.22)	2.32 (0.83, 6.43)	2.72 (1.37, 5.38)	4.51 (1.79, 11.35)
6 miles *(9.7 km)*	1.60 (0.77, 3.31)	2.25 (0.72, 7.05)	1.80 (0.99, 3.26)	3.50 (1.51, 8.11)	3.07 (1.31, 7.19)	3.09 (1.19, 8.06)	2.26 (1.19, 4.32)	4.63 (1.91, 11.21)
1.5 miles *(2.4 km)* vs:								
2 miles *(3.4 km)*	1.17 (0.93, 1.47)	0.98 (0.67, 1.42)	1.25 (1.03, 1.51)	1.17 (0.90, 1.51)	1.24 (0.94, 1.62)	1.02 (0.72, 1.44)	1.37 (1.11, 1.70)	1.33 (0.99, 1.78)
3 miles *(4.8 km)*	1.42 (0.86, 2.34)	1.08 (0.49, 2.41)	1.61 (1.07, 2.43)	1.6 (0.93, 2.73)	1.72 (0.97, 3.06)	1.21 (0.60, 2.47)	1.98 (1.27, 3.11)	2.09 (1.14, 3.85)
4 miles *(6.4 km)*	1.50 (0.86, 2.62)	1.40 (0.57, 3.41)	1.70 (1.07, 2.67)	2.13 (1.17, 3.88)	2.12 (1.12, 4.02)	1.65 (0.78, 3.51)	2.11 (1.28, 3.46)	2.83 (1.45, 5.54)
5 miles *(8.0 km)*	1.44 (0.83, 2.52)	1.89 (0.79, 4.56)	1.57 (0.99, 2.47)	2.67 (1.39, 5.13)	2.36 (1.22, 4.55)	2.34 (1.11, 4.92)	1.86 (1.14, 3.06)	3.31 (1.66, 6.62)
6 miles *(9.7 km)*	1.33 (0.75, 2.37)	2.39 (0.97, 5.90)	1.39 (0.86, 2.23)	3.00 (1.40, 6.41)	2.43 (1.18, 4.97)	3.13 (1.36, 7.17)	1.55 (0.91, 2.64)	3.40 (1.58, 7.33)
2 miles *(3.4 km)* vs:								
3 miles *(4.8 km)*	1.22 (0.93, 1.59)	1.11 (0.72, 1.71)	1.30 (1.04, 1.62)	1.37 (1.02, 1.82)	1.39 (1.02, 1.90)	1.19 (0.82, 1.73)	1.45 (1.14, 1.84)	1.58 (1.14, 2.19)
4 miles *(6.4 km)*	1.28 (0.90, 1.83)	1.44 (0.81, 2.53)	1.36 (1.02, 1.82)	1.82 (1.21, 2.75)	1.71 (1.13, 2.61)	1.62 (1.01, 2.61)	1.54 (1.12, 2.11)	2.13 (1.37, 3.31)
5 miles *(8.0 km)*	1.24 (0.81, 1.89)	1.94 (0.99, 3.80)	1.26 (0.89, 1.79)	2.28 (1.28, 4.06)	1.91 (1.11, 3.27)	2.29 (1.23, 4.28)	1.36 (0.92, 2.02)	2.49 (1.39, 4.47)
6 miles *(9.7 km)*	1.14 (0.68, 1.93)	2.45 (1.07, 5.60)	1.11 (0.72, 1.72)	2.57 (1.19, 5.53)	1.96 (0.98, 3.92)	3.06 (1.30, 7.21)	1.13 (0.68, 1.88)	2.56 (1.19, 5.53)
2.5 miles *(4.0 km)* vs:								
3 miles *(4.8 km)*	1.08 (0.97, 1.20)	1.08 (0.91, 1.28)	1.10 (1.01, 1.2)	1.17 (1.04, 1.31)	1.16 (1.03, 1.31)	1.12 (0.97, 1.29)	1.15 (1.05, 1.26)	1.23 (1.08, 1.40)
4 miles *(6.4 km)*	1.14 (0.91, 1.44)	1.40 (0.97, 2.01)	1.16 (0.96, 1.40)	1.56 (1.15, 2.11)	1.43 (1.07, 1.90)	1.52 (1.10, 2.11)	1.22 (0.99, 1.51)	1.66 (1.22, 2.27)
5 miles *(8.0 km)*	1.10 (0.76, 1.59)	1.89 (1.05, 3.40)	1.07 (0.79, 1.46)	1.95 (1.13, 3.38)	1.59 (0.97, 2.61)	2.15 (1.17, 3.94)	1.08 (0.76, 1.54)	1.95 (1.12, 3.38)
6 miles *(9.7 km)*	1.01 (0.60, 1.71)	2.38 (1.03, 5.50)	0.95 (0.61, 1.47)	2.20 (1.00, 4.83)	1.63 (0.81, 3.31)	2.87 (1.15, 7.18)	0.90 (0.54, 1.51)	2.00 (0.90, 4.44)
3 miles *(4.8 km)* vs:								
4 miles *(6.4 km)*	0.85 (0.59, 1.21)	1.27 (1.00, 1.62)	0.89 (0.58, 1.38)	1.34 (1.09, 1.65)	0.89 (0.58, 1.38)	1.36 (1.09, 1.71)	1.07 (0.77, 1.48)	1.39 (1.13, 1.72)
5 miles *(8.0 km)*	0.80 (0.51, 1.27)	1.82 (1.06, 3.11)	0.97 (0.54, 1.76)	1.73 (1.04, 2.87)	0.97 (0.54, 1.76)	2.13 (1.18, 3.82)	0.91 (0.59, 1.40)	1.69 (1.00, 2.86)
6 miles *(9.7 km)*	0.80 (0.45, 1.45)	2.43 (1.02, 5.79)	1.14 (0.51, 2.54)	2.00 (0.89, 4.49)	1.14 (0.51, 2.54)	3.14 (1.17, 8.38)	0.73 (0.41, 1.31)	1.78 (0.75, 4.22)

CAFO: concentrated animal feeding operation; km: kilometers; OR: odds ratio; CI: confidence interval; [a] Asthma defined as doctor diagnosed and currently still have asthma;
[b]Adjusted for gender, age, body mass index, smoking status, education, income, height, physical activity, pet ownership

Table B4.
Change in lung function by residential distance to the nearest CAFO

Residential Distance Compared	FEV1 (Liters) Unadjusted β (95%CI)	FEV1 (Liters) Adjusted β[a] (95%CI)	FVC (Liters/second) Unadjusted β (95%CI)	FVC (Liters/second) Adjusted β[a] (95%CI)	FEV1 % PRD Unadjusted β (95%CI)	FEV1 % PRD Adjusted β[a] (95%CI)	FEV1/FVC Unadjusted β (95%CI)	FEV1/FVC Adjusted β[a] (95%CI)
1 mile *(1.6 km)* vs:								
2 miles *(3.4 km)*	-0.11 (-0.24, 0.02)	-0.05 (-0.24, 0.02)	-0.05 (-0.24, 0.02)	-0.16 (-0.25, -0.06)	-3.89 (-7.2, -0.58)	-7.91 (-14.95, -0.86)	-0.016 (-0.032, 0.000)	-0.023 (-0.040, -0.005)
3 miles *(4.8 km)*	-0.16 (-0.37, 0.04)	-0.24 (-0.39, -0.10)	-0.06 (-0.37, 0.04)	-0.24 (-0.39, -0.10)	-5.24 (-10.17, -0.31)	-12.03 (-22.7, -1.37)	-0.026 (-0.051, -0.002)	-0.036 (-0.063, -0.009)
4 miles *(6.4 km)*	-0.16 (-0.38, 0.05)	-0.26 (-0.43, -0.10)	-0.04 (-0.38, 0.05)	-0.26 (-0.43, -0.10)	-4.40 (-9.53, 0.74)	-12.64 (-24.26, -1.01)	-0.031 (-0.057, -0.005)	-0.041 (-0.071, -0.010)
5 miles *(8.0 km)*	-0.13 (-0.34, 0.07)	-0.24 (-0.41, -0.08)	0.01 (-0.34, 0.07)	-0.24 (-0.41, -0.08)	-2.66 (-7.4, 2.07)	-11.31 (-23.14, 0.51)	-0.031 (-0.056, -0.006)	-0.039 (-0.07, -0.008)
6 miles *(9.7 km)*	-0.09 (-0.29, 0.10)	-0.21 (-0.37, -0.04)	0.05 (-0.29, 0.10)	-0.21 (-0.37, -0.04)	-1.37 (-5.8, 3.07)	-9.67 (-21.81, 2.47)	-0.029 (-0.053, -0.005)	-0.035 (-0.067, -0.004)
1.5 miles *(2.4 km)* vs:								
2 miles *(3.4 km)*	-0.05 (-0.11, 0.01)	-0.07 (-0.12, -0.03)	-0.02 (-0.11, 0.01)	-0.07 (-0.12, -0.03)	-1.70 (-3.19, -0.21)	-3.59 (-6.78, -0.40)	-0.008 (-0.015, 0.000)	-0.01 (-0.018, -0.003)
3 miles *(4.8 km)*	-0.10 (-0.23, 0.03)	-0.16 (-0.25, -0.06)	-0.03 (-0.23, 0.03)	-0.16 (-0.25, -0.06)	-3.06 (-6.2, 0.09)	-7.72 (-14.63, -0.81)	-0.018 (-0.034, -0.002)	-0.024 (-0.042, -0.006)
4 miles *(6.4 km)*	-0.10 (-0.25, 0.05)	-0.18 (-0.29, -0.06)	-0.01 (-0.25, 0.05)	-0.18 (-0.29, -0.06)	-2.21 (-5.69, 1.27)	-8.32 (-16.59, -0.06)	-0.022 (-0.04, -0.004)	-0.028 (-0.05, -0.007)
5 miles *(8.0 km)*	-0.07 (-0.22, 0.08)	-0.16 (-0.28, -0.03)	0.04 (-0.22, 0.08)	-0.16 (-0.28, -0.03)	-0.48 (-3.88, 2.92)	-7.00 (-16.26, 2.26)	-0.023 (-0.041, -0.004)	-0.027 (-0.051, -0.003)
6 miles *(9.7 km)*	-0.03 (-0.18, 0.12)	-0.12 (-0.26, 0.02)	0.08 (-0.18, 0.12)	-0.12 (-0.26, 0.02)	0.82 (-2.74, 4.37)	-5.36 (-15.70, 4.98)	-0.02 (-0.039, -0.002)	-0.023 (-0.05, 0.003)
2 miles *(3.4 km)* vs:								
3 miles *(4.8 km)*	-0.05 (-0.13, 0.02)	-0.09 (-0.14, -0.03)	-0.01 (-0.13, 0.02)	-0.09 (-0.14, -0.03)	-1.36 (-3.05, 0.34)	-4.13 (-7.97, -0.29)	-0.01 (-0.019, -0.002)	-0.013 (-0.024, -0.003)
4 miles *(6.4 km)*	-0.05 (-0.15, 0.04)	-0.10 (-0.18, -0.02)	0.02 (-0.15, 0.04)	-0.10 (-0.18, -0.02)	-0.51 (-2.76, 1.74)	-4.73 (-10.49, 1.03)	-0.015 (-0.027, -0.003)	-0.018 (-0.033, -0.003)
5 miles *(8.0 km)*	-0.02 (-0.13, 0.09)	-0.08 (-0.18, 0.02)	0.06 (-0.13, 0.09)	-0.08 (-0.18, 0.02)	1.22 (-1.44, 3.89)	-3.41 (-11.11, 4.30)	-0.015 (-0.029, -0.001)	-0.017 (-0.036, 0.003)
6 miles *(9.7 km)*	0.02 (-0.11, 0.15)	-0.05 (-0.17, 0.07)	0.10 (-0.11, 0.15)	-0.05 (-0.17, 0.07)	2.52 (-0.83, 5.86)	-1.76 (-11.29, 7.77)	-0.013 (-0.029, 0.003)	-0.013 (-0.036, 0.011)
2.5 miles *(4.0 km)* vs:								
3 miles *(4.8 km)*	-0.02 (-0.05, 0.01)	-0.03 (-0.06, -0.01)	0.00 (-0.05, 0.01)	-0.03 (-0.06, -0.01)	-0.32 (-0.99, 0.35)	-1.53 (-3.13, 0.08)	-0.004 (-0.008, -0.001)	-0.005 (-0.01, -0.001)
4 miles *(6.4 km)*	-0.02 (-0.08, 0.04)	-0.05 (-0.11, 0.00)	0.03 (-0.08, 0.04)	-0.05 (-0.11, 0.00)	0.52 (-0.97, 2.01)	-2.13 (-6.23, 1.96)	-0.009 (-0.016, -0.001)	-0.010 (-0.02, 0.001)
5 miles *(8.0 km)*	0.01 (-0.08, 0.11)	-0.03 (-0.11, 0.05)	0.07 (-0.08, 0.11)	-0.03 (-0.11, 0.05)	2.25 (-0.14, 4.65)	-0.81 (-7.62, 6.00)	-0.009 (-0.02, 0.002)	-0.008 (-0.025, 0.008)
6 miles *(9.7 km)*	0.05 (-0.07, 0.18)	0.00 (-0.11, 0.12)	0.11 (-0.07, 0.18)	0.00 (-0.11, 0.12)	3.55 (0.09, 7.00)	0.83 (-8.29, 9.96)	-0.007 (-0.022, 0.009)	-0.005 (-0.026, 0.017)
3 miles *(4.8 km)* vs:								
4 miles *(6.4 km)*	0.82 (-0.99, 2.63)	-1.13 (-3.85, 1.59)	0.99 (0.98, 1.00)	0.99 (0.99, 1.00)	-0.02 (-0.10, 0.06)	-0.03 (-0.06, 0.01)	0.035 (-0.083, 0.153)	-0.003 (-0.036, 0.029)
5 miles *(8.0 km)*	3.91 (-0.10, 7.92)	0.45 (-5.42, 6.33)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)	0.03 (-0.07, 0.13)	0.00 (-0.07, 0.07)	0.091 (-0.049, 0.232)	0.033 (-0.039, 0.105)
6 miles *(9.7 km)*	6.32 (0.67, 11.98)	2.50 (-6.22, 11.22)	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)	0.09 (-0.04, 0.22)	0.05 (-0.06, 0.15)	0.136 (-0.032, 0.305)	0.073 (-0.039, 0.185)

FEV1: Forced Expiratory Volume in One Second; FVC: Forced expiratory Vital Capacity; L: Liters; s: seconds; PRD: Predicted; km: kilometers; CAFO; concentrated animal feeding operation
[a]Adjusted for gender, age, body mass index, smoking status, education, income, height, physical activity, pet ownership

Table B5.
Total number of participants with current asthma and allergy by distance from nearest CAFO.

	SHOW 2008-2016 (N=1547)			SHOW 2008-2013 (N=1019)		
Distance to nearest CAFO	*Total n*	*Current asthma*	*Current allergy*	*Total n*	*Current allergy*	*Current allergy & asthma*
<= 1 miles *(1.6 km)*	**25**	7	10	16	8	2
<= 1.5 miles *(2.4 km)*	**65**	8	24	43	20	5
<= 2 miles (*3.2 km)*	**93**	10	35	67	27	7
<= 2.5 miles *(4.0 km)*	**131**	11	52	95	37	8
<= 3 miles *(4.8 km*)	**179**	15	69	130	50	11

Appendix B: Figures

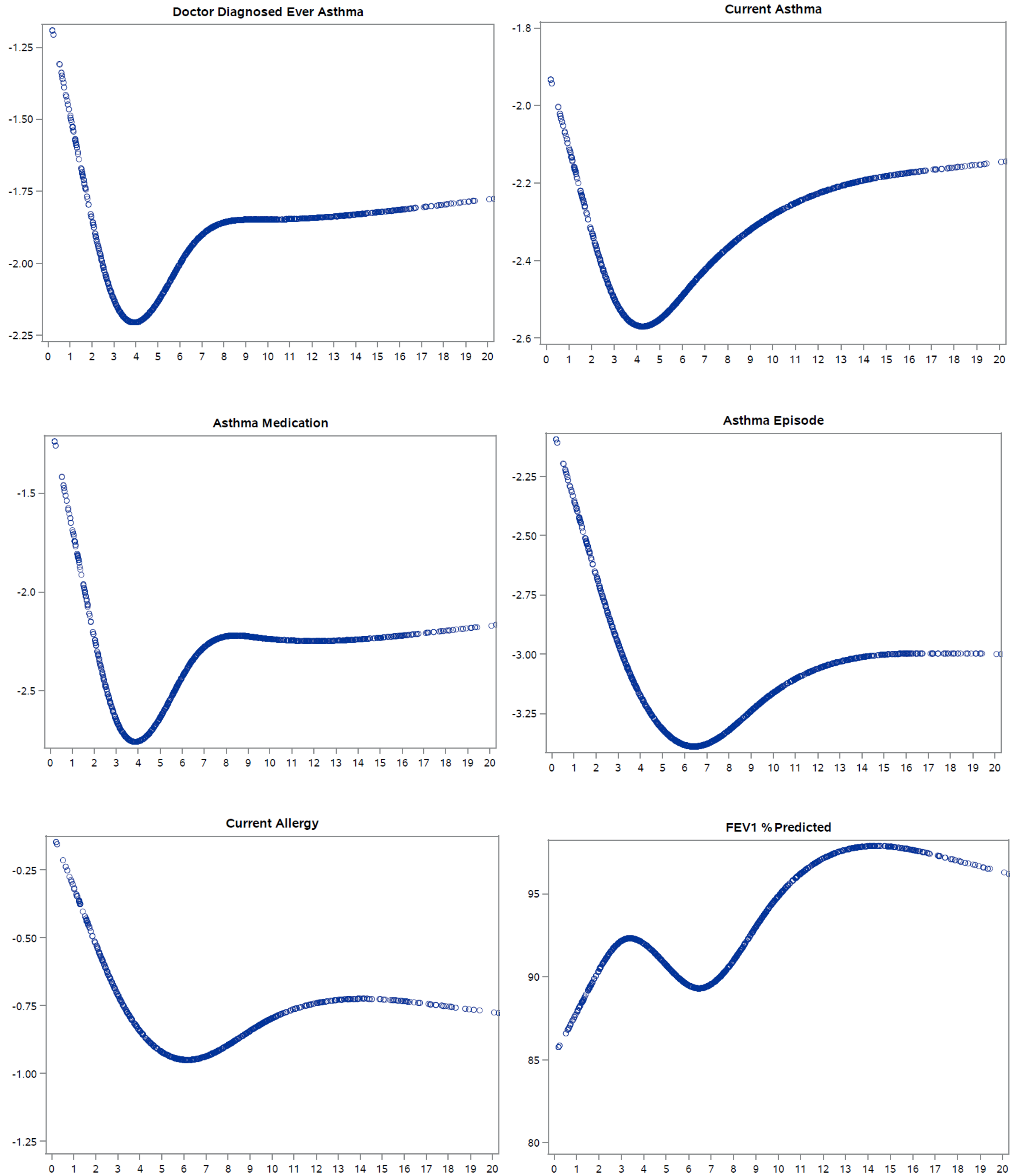


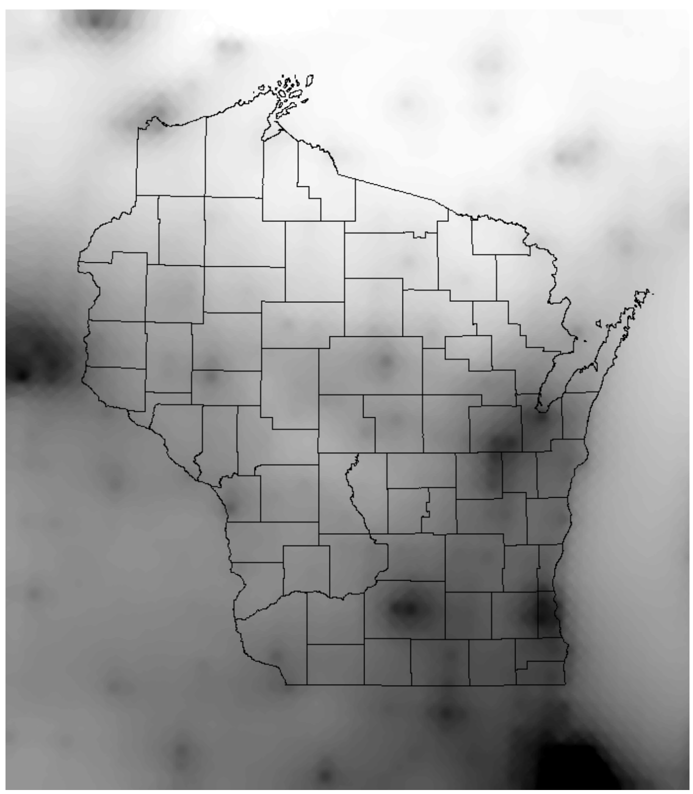
Figure B1. Unadjusted cubic splines of residential proximity to the nearest CAFO (x axis: distance in miles) and the log odds of asthma and allergy outcomes (y axis); and linear predictor (y axis) of FEV1 percent predicted.

Appendix C: Figures

Sensitivity Analysis

Results tables include results from both the main analysis, this subset analysis, and a third analysis where only those residing in Milwaukee County are excluded. This third analysis was run as an alternative method for removing urban residents without reducing sample size as much. Since Milwaukee city is the largest, most urbanized area in Wisconsin, residents of this county would have the greatest urban air pollution exposure. Supplementary Figure 3 shows the annual average fine particulate matter (PM2.5 in μg/m^3) for the state of Wisconsin in 2013. Data comes from the EPA's 12 x 12 kilometer grid of estimated PM2.5 from a hierarchical Bayesian model including point and non-point air emission sources (agriculture, forest fires, roadways, traffic, industry, population density) as well as geography and climate (topography, temperature, humidity). As you can see, urban areas such as Milwaukee, Madison, and Green Bay show higher annual average PM2.5 air pollution when compared to rural areas, with Milwaukee having the highest estimated annual average PM2.5.

Figure C1. Annual average fine particulate matter (PM2.5) interpolated using inverse distance weighting from 12 x 12 km grid of PM2.5 daily values from EPA's Hierarchical Bayesian Time Modeling System (HBM).



Results tables and figures in this supplementary include results from both the main analysis, this subset analysis, and a third analysis where only those residing in Milwaukee County are excluded. This third analysis was run as an alternative method for removing urban residents without reducing sample size as much. Since Milwaukee city is the largest, most urbanized area in Wisconsin, residents of this county would have the greatest urban air pollution exposure, as depicted in SF3. Furthermore, the prevalence of asthma outcomes is higher in urban areas (ST2.)

Figure C2. Study flow chart of the subset study sample where urban area residents are excluded.

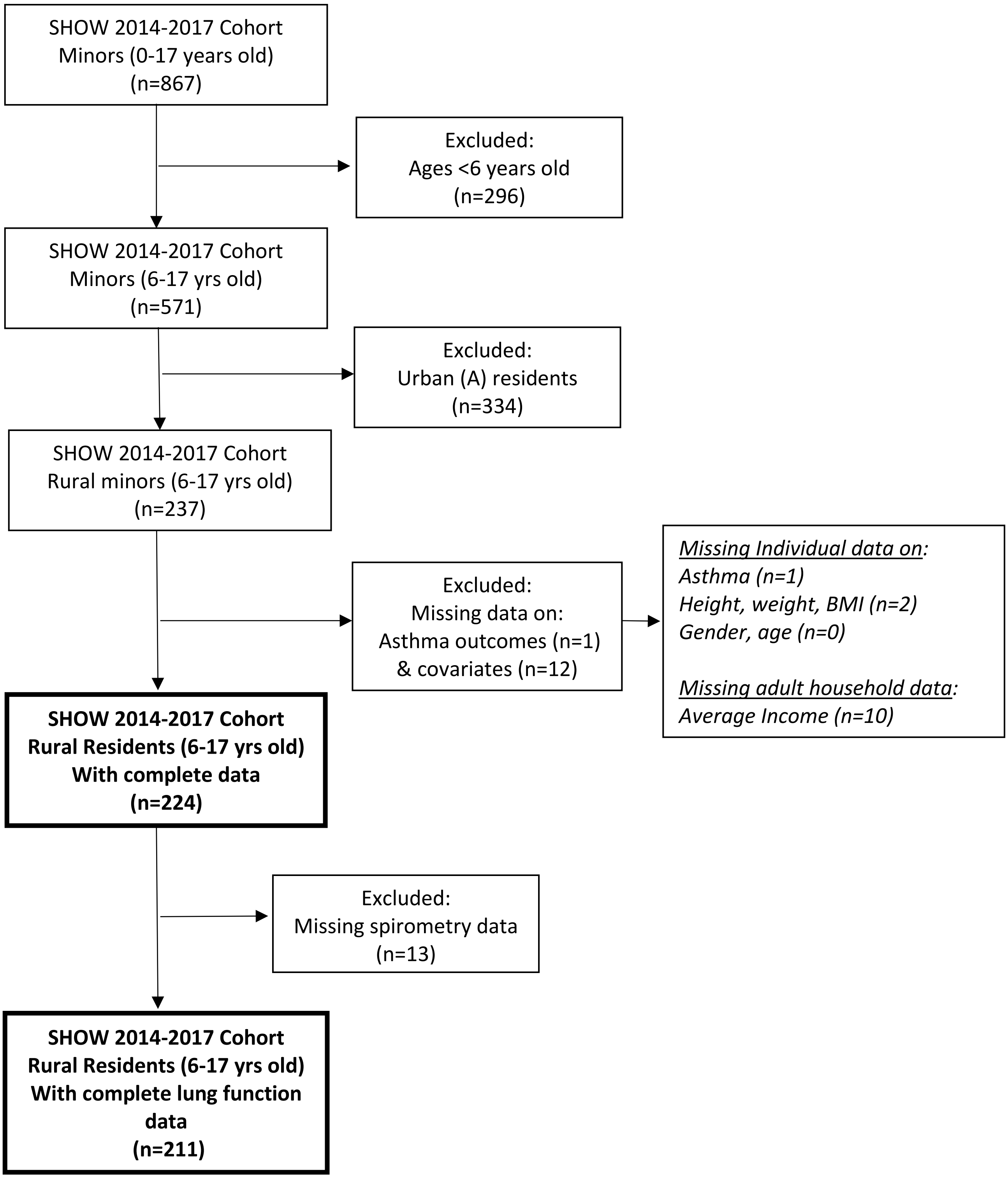
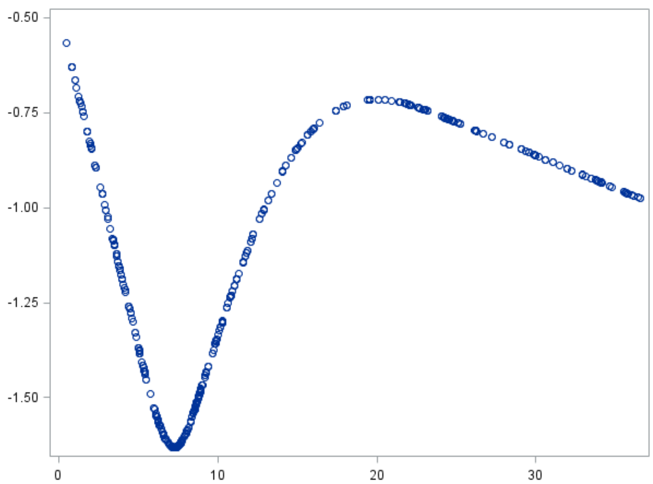


Figure C3. Unadjusted cubic splines of residential proximity to the nearest CAFO (x axis: distance in miles) and the log odds of asthma outcomes (y axis); and linear predictor (y axis) of FEV1 percent predicted.

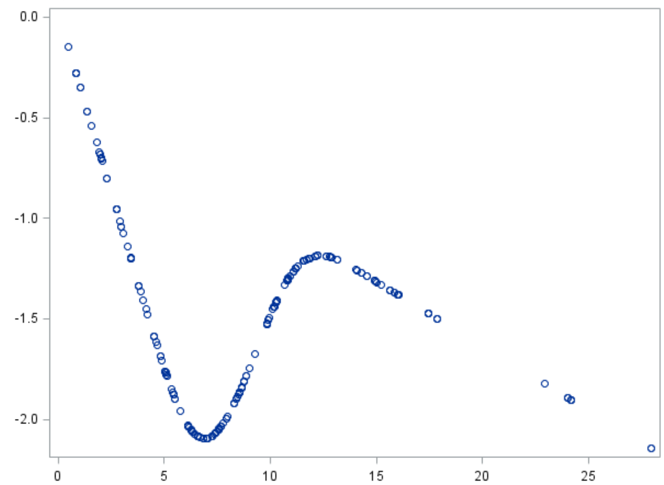
(A) Plots with <u>entire study sample</u> from main analyses (includes urban and rural participants).
(B) Plots with <u>subset of study sample</u> (**excludes** urban area participants).

Doctor Diagnosed Ever Asthma:

(A):

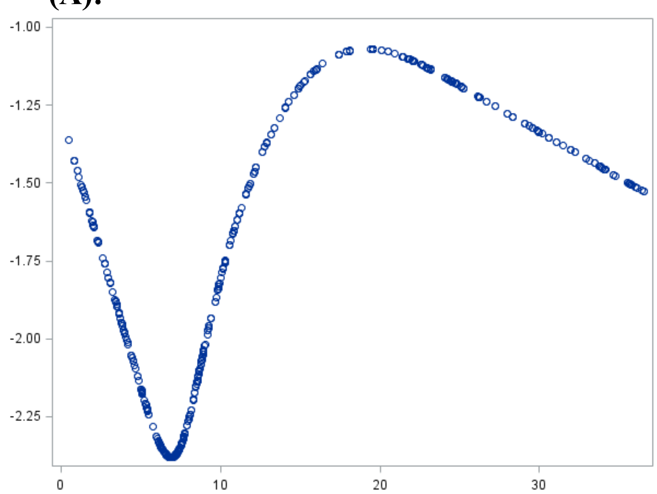


(B):



Current Asthma:

(A):



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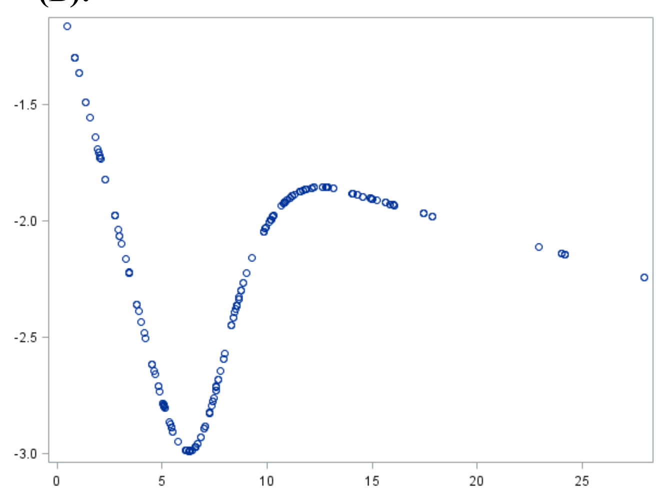
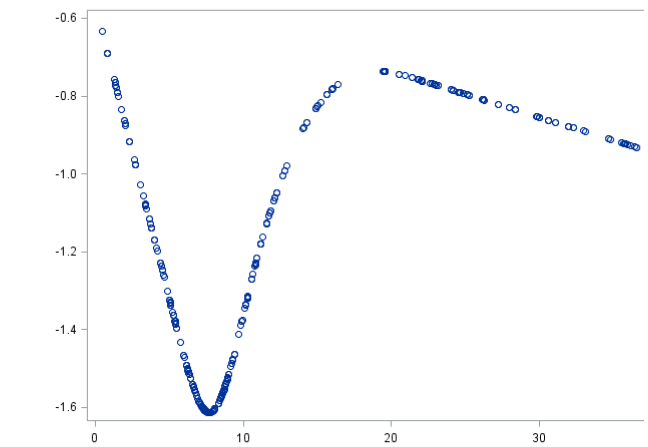
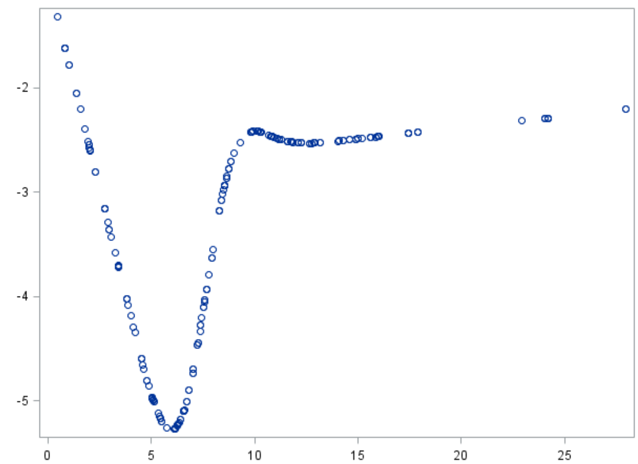


Asthma Episode:

(A):

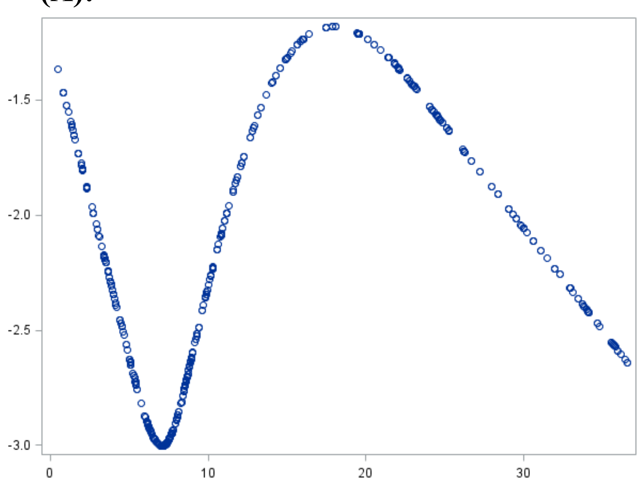


(B):



Asthma Medication:

(A):



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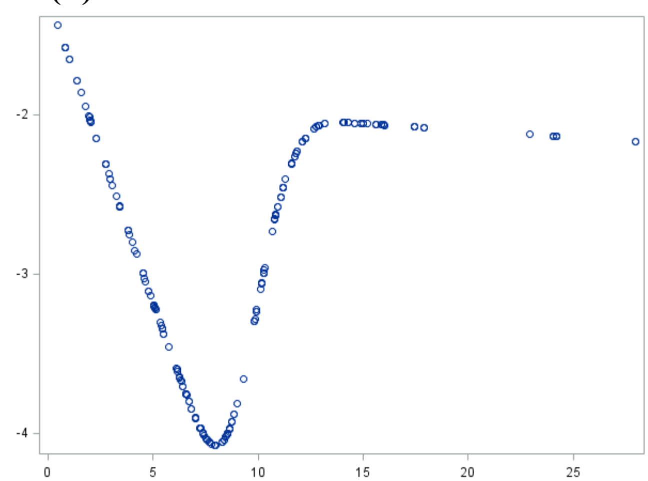
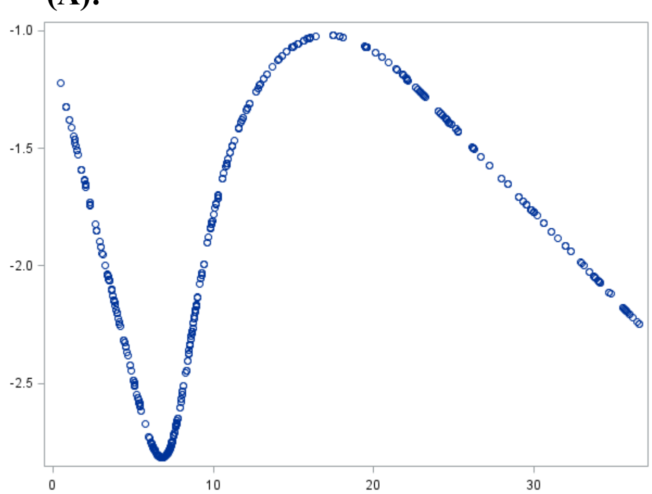


Wheezing:

(A):



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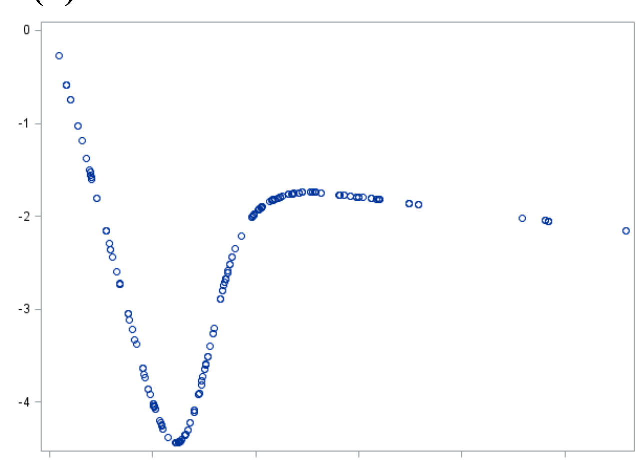
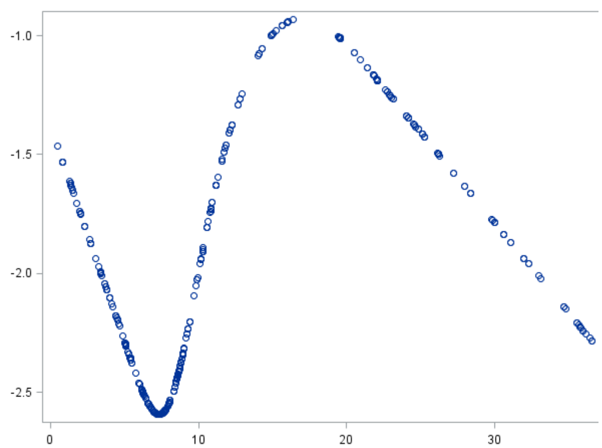


FEV1 % Predicted:

(A):



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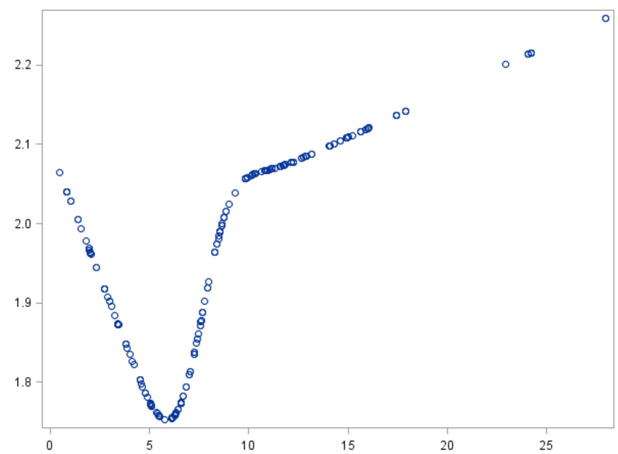
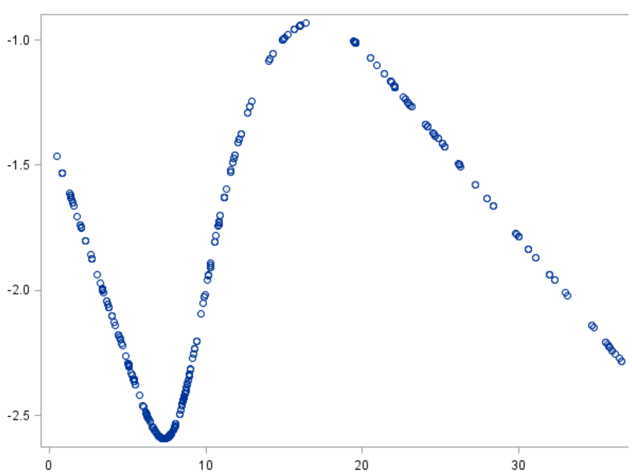


FEV1 / FVC:

(A):



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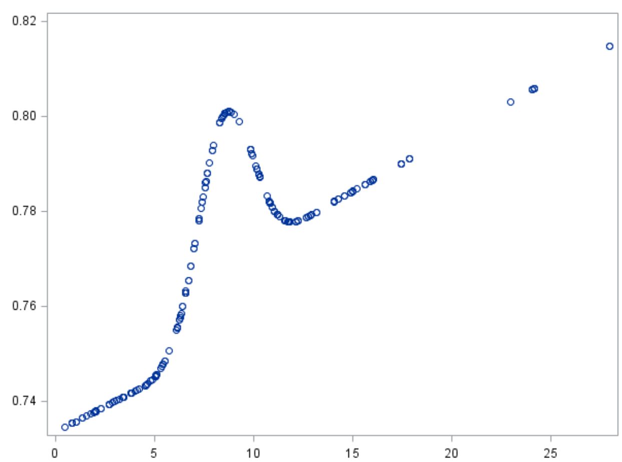


Appendix C: Tables

Table C1. Prevalence of asthma outcomes among SHOW 2014-2017 (ages 6-17) by urbanicity.

	Total (n=542)	Urban area resident (n=289)	Urban cluster resident (n=48)	Rural area resident (n=165)
	N	*N (%)*	*N (%)*	*N (%)*
Ever asthma	118	80 (24.8)	7 (14.0)	30 (17.1)
Current asthma	74	52 (16.2)	2 (4.0)	19 (10.9)
Wheezing	72	50 (15.2)	4 (8.0)	18 (10.3)
Asthma attack	40	30 (9.4)	1 (2.0)	9 (5.1)
Asthma meds	55	43 (13.3)	1 (2.0)	11 (6.3)

Table C2. Odds Ratio (OR) of asthma outcomes by residential distance to the nearest CAFO. Table displays results from main study sample (n=504)

Residential Distances Compared (in miles)	Current Asthma[a]		Doctor Diagnosed Asthma		Wheezing in last 12 months		Asthma medication use in last 3 months		Asthma attack in last 12 months	
	Unadjusted OR (95%CI)	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted O[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted O[b] (95%CI)**
1 v 6	1.89 (0.57, 6.28)	1.69 (0.57, 5.05)	2.13 (0.85, 5.29)	1.86 (0.80, 4.32)	2.46 (1.57, 3.86)	2.40 (1.42, 4.04)	3.18 (1.66, 6.06)	3.34 (1.71, 6.55)	2.50 (1.25, 4.98)	2.67 (1.30, 5.47)
1.5 v 6	1.77 (0.60, 5.22)	1.60 (0.60, 4.30)	1.97 (0.87, 4.47)	1.75 (0.82, 3.73)	2.25 (1.50, 3.37)	2.19 (1.37, 3.51)	2.83 (1.58, 5.06)	2.96 (1.62, 5.42)	2.28 (1.23, 4.24)	2.42 (1.27, 4.61)
2 v 6	1.66 (0.64, 4.34)	1.52 (0.63, 3.65)	1.83 (0.88, 3.79)	1.64 (0.84, 3.22)	2.05 (1.43, 2.95)	2.01 (1.32, 3.05)	2.52 (1.50, 4.22)	2.62 (1.53, 4.49)	2.08 (1.20, 3.61)	2.19 (1.23, 3.89)
2.5 v 6	1.56 (0.67, 3.61)	1.44 (0.67, 3.10)	1.69 (0.90, 3.20)	1.54 (0.85, 2.78)	1.88 (1.37, 2.57)	1.84 (1.28, 2.65)	2.24 (1.43, 3.53)	2.32 (1.45, 3.72)	1.90 (1.17, 3.07)	1.99 (1.20, 3.28)
3 v 6	1.46 (0.71, 3.01)	1.37 (0.71, 2.64)	1.57 (0.91, 2.71)	1.45 (0.87, 2.40)	1.71 (1.31, 2.25)	1.69 (1.23, 2.31)	2.00 (1.36, 2.94)	2.06 (1.38, 3.08)	1.73 (1.14, 2.62)	1.80 (1.17, 2.77)
4 v 6	1.29 (0.80, 2.08)	1.23 (0.80, 1.91)	1.35 (0.94, 1.94)	1.28 (0.91, 1.79)	1.43 (1.20, 1.71)	1.42 (1.15, 1.74)	1.58 (1.22, 2.05)	1.62 (1.24, 2.11)	1.44 (1.09, 1.90)	1.48 (1.11, 1.97)
5 v 6	1.13 (0.89, 1.44)	1.11 (0.89, 1.38)	1.16 (0.97, 1.39)	1.13 (0.96, 1.34)	1.19 (1.09, 1.31)	1.19 (1.07, 1.32)	1.26 (1.11, 1.43)	1.27 (1.11, 1.45)	1.20 (1.04, 1.37)	1.21 (1.05, 1.40)
1 v 10	1.38 (0.32, 5.90)	1.04 (0.23, 4.73)	1.91 (0.68, 5.42)	1.51 (0.53, 4.31)	1.55 (0.87, 2.75)	1.2 (0.64, 2.25)	2.12 (0.96, 4.70)	1.60 (0.62, 4.13)	1.69 (0.72, 4.01)	1.38 (0.53, 3.58)
1.5 v 10	1.29 (0.34, 4.92)	0.98 (0.24, 4.03)	1.78 (0.69, 4.60)	1.42 (0.54, 3.73)	1.41 (0.83, 2.41)	1.10 (0.61, 1.97)	1.89 (0.91, 3.93)	1.42 (0.59, 3.43)	1.54 (0.70, 3.43)	1.25 (0.51, 3.04)
2 v 10	1.21 (0.36, 4.10)	0.93 (0.25, 3.43)	1.65 (0.69, 3.9)	1.33 (0.55, 3.23)	1.29 (0.79, 2.12)	1.00 (0.58, 1.73)	1.68 (0.86, 3.30)	1.25 (0.55, 2.85)	1.41 (0.68, 2.94)	1.13 (0.49, 2.59)
2.5 v 10	1.14 (0.38, 3.42)	0.89 (0.27, 2.92)	1.53 (0.70, 3.31)	1.25 (0.56, 2.80)	1.18 (0.75, 1.86)	0.92 (0.56, 1.52)	1.50 (0.81, 2.76)	1.11 (0.52, 2.37)	1.29 (0.65, 2.52)	1.02 (0.48, 2.21)
3 v 10	1.07 (0.40, 2.86)	0.84 (0.28, 2.49)	1.42 (0.71, 2.81)	1.18 (0.57, 2.43)	1.08 (0.71, 1.64)	0.84 (0.53, 1.33)	1.33 (0.77, 2.32)	0.98 (0.49, 1.97)	1.17 (0.63, 2.17)	0.93 (0.46, 1.89)
4 v 10	0.94 (0.44, 2.00)	0.76 (0.32, 1.81)	1.22 (0.73, 2.04)	1.04 (0.59, 1.83)	0.90 (0.63, 1.28)	0.71 (0.48, 1.04)	1.06 (0.68, 1.64)	0.77 (0.44, 1.37)	0.98 (0.59, 1.61)	0.76 (0.42, 1.39)
5 v 10	0.83 (0.48, 1.41)	0.68 (0.35, 1.33)	1.05 (0.73, 1.49)	0.92 (0.60, 1.40)	0.75 (0.56, 1.01)	0.59 (0.42, 0.83)	0.84 (0.60, 1.18)	0.61 (0.39, 0.96)	0.81 (0.54, 1.22)	0.63 (0.38, 1.04)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, number of people in the home

Table C3. Change in lung function by residential distance to the nearest CAFO. Table displays results from main study sample (n=504)

Residential Distance Compared	FEV1 (Liters)		FVC (Liters/second)		FEV1 % PRD		FEV1/FVC	
	Unadjusted β (95%CI)	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**
1 v 6	0.277 (-0.13, 0.683)	0.135 (-0.169, 0.439)	0.502 (-0.101, 1.106)	0.245 (-0.692, 1.182)	0.251 (-0.078, 0.58)	0.168 (-0.083, 0.418)	-0.007 (-0.127, 0.113)	0.01 (-0.093, 0.112)
1.5 v 6	0.249 (-0.117, 0.614)	0.122 (-0.152, 0.395)	0.452 (-0.091, 0.995)	0.22 (-0.623, 1.064)	0.226 (-0.07, 0.522)	0.151 (-0.074, 0.377)	-0.007 (-0.115, 0.101)	0.009 (-0.084, 0.101)
2 v 6	0.221 (-0.104, 0.546)	0.108 (-0.135, 0.351)	0.402 (-0.081, 0.884)	0.196 (-0.554, 0.946)	0.201 (-0.062, 0.464)	0.134 (-0.066, 0.335)	-0.006 (-0.102, 0.09)	0.008 (-0.075, 0.09)
2.5 v 6	0.193 (-0.091, 0.477)	0.095 (-0.118, 0.307)	0.351 (-0.071, 0.774)	0.171 (-0.485, 0.827)	0.176 (-0.055, 0.406)	0.118 (-0.058, 0.293)	-0.005 (-0.089, 0.079)	0.007 (-0.065, 0.079)
3 v 6	0.166 (-0.078, 0.409)	0.081 (-0.101, 0.263)	0.301 (-0.061, 0.663)	0.147 (-0.415, 0.709)	0.151 (-0.047, 0.348)	0.101 (-0.05, 0.251)	-0.004 (-0.076, 0.067)	0.006 (-0.056, 0.067)
4 v 6	0.11 (-0.052, 0.272)	0.054 (-0.068, 0.176)	0.2 (-0.041, 0.441)	0.098 (-0.277, 0.473)	0.1 (-0.031, 0.232)	0.067 (-0.033, 0.167)	-0.003 (-0.051, 0.045)	0.004 (-0.037, 0.045)
5 v 6	0.055 (-0.026, 0.136)	0.027 (-0.034, 0.088)	0.1 (-0.02, 0.22)	0.049 (-0.138, 0.236)	0.05 (-0.016, 0.116)	0.034 (-0.017, 0.084)	-0.001 (-0.025, 0.022)	0.002 (-0.019, 0.022)
1 v 10	0.101 (-0.348, 0.55)	0.104 (-0.223, 0.431)	0.401 (-0.304, 1.105)	0.252 (-0.918, 1.421)	0.178 (-0.216, 0.571)	0.166 (-0.177, 0.508)	-0.018 (-0.177, 0.14)	0.012 (-0.129, 0.154)
1.5 v 10	0.073 (-0.34, 0.486)	0.09 (-0.207, 0.387)	0.35 (-0.298, 0.999)	0.227 (-0.85, 1.304)	0.152 (-0.21, 0.515)	0.149 (-0.169, 0.466)	-0.018 (-0.164, 0.129)	0.012 (-0.12, 0.143)
2 v 10	0.046 (-0.332, 0.424)	0.077 (-0.191, 0.344)	0.3 (-0.294, 0.894)	0.203 (-0.781, 1.186)	0.127 (-0.205, 0.459)	0.132 (-0.161, 0.425)	-0.017 (-0.152, 0.118)	0.011 (-0.111, 0.132)
2.5 v 10	0.018 (-0.326, 0.362)	0.063 (-0.175, 0.301)	0.25 (-0.29, 0.789)	0.178 (-0.713, 1.069)	0.102 (-0.2, 0.404)	0.115 (-0.153, 0.383)	-0.016 (-0.139, 0.106)	0.01 (-0.102, 0.121)
3 v 10	-0.01 (-0.322, 0.302)	0.05 (-0.159, 0.259)	0.199 (-0.288, 0.687)	0.154 (-0.646, 0.953)	0.077 (-0.196, 0.35)	0.098 (-0.145, 0.342)	-0.016 (-0.126, 0.095)	0.009 (-0.092, 0.11)
4 v 10	-0.065 (-0.321, 0.19)	0.023 (-0.129, 0.175)	0.099 (-0.291, 0.488)	0.105 (-0.512, 0.721)	0.027 (-0.191, 0.245)	0.065 (-0.129, 0.259)	-0.014 (-0.101, 0.073)	0.007 (-0.074, 0.087)
5 v 10	-0.121 (-0.336, 0.094)	-0.004 (-0.104, 0.095)	-0.002 (-0.31, 0.306)	0.056 (-0.381, 0.492)	-0.023 (-0.193, 0.147)	0.031 (-0.114, 0.177)	-0.013 (-0.077, 0.052)	0.005 (-0.056, 0.065)

FEV1: Forced Expiratory Volume in One Second; FVC: Forced expiratory Vital Capacity; L: Liters; s: seconds; PRD; CAFO; concentrated animal feeding operation

[a]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Table C4. Odds Ratio (OR) of current asthma by residential distance to the nearest CAFO. Table displays results from main study sample, when urban area residents are excluded, and when Milwaukee county residents are excluded.

Residential Distances Compared (in miles)	**Entire study sample** (n=504)		**Milwaukee county excluded** (n=413)		**All urban areas excluded** (n=215)	
	Unadjusted OR (95% CI)	**Unadjusted OR (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 v 6	1.89 (0.57, 6.28)	1.69 (0.57, 5.05)	2.77 (0.49, 15.78)	2.47 (0.52, 11.73)	3.44 (1.49, 7.91)	8.63 (3.2, 23.2)
1.5 v 6	1.77 (0.60, 5.22)	1.60 (0.60, 4.30)	2.5 (0.52, 11.92)	2.25 (0.55, 9.13)	3.04 (1.44, 6.43)	6.95 (2.85, 16.9)
2 v 6	1.66 (0.64, 4.34)	1.52 (0.63, 3.65)	2.25 (0.56, 9.01)	2.05 (0.59, 7.11)	2.68 (1.38, 5.23)	5.60 (2.54, 12.3)
2.5 v 6	1.56 (0.67, 3.61)	1.44 (0.67, 3.10)	2.03 (0.6, 6.81)	1.87 (0.63, 5.53)	2.37 (1.32, 4.25)	4.51 (2.26, 9.03)
3 v 6	1.46 (0.71, 3.01)	1.37 (0.71, 2.64)	1.83 (0.65, 5.14)	1.7 (0.67, 4.31)	2.01 (1.27, 3.45)	3.64 (2.01, 6.59)
4 v 6	1.29 (0.80, 2.08)	1.23 (0.80, 1.91)	1.48 (0.75, 2.93)	1.41 (0.77, 2.61)	1.64 (1.17, 2.28)	2.36 (1.59, 3.51)
5 v 6	1.13 (0.89, 1.44)	1.11 (0.89, 1.38)	1.2 (0.87, 1.67)	1.17 (0.87, 1.58)	1.28 (1.08, 1.51)	1.53 (1.26, 1.87)
1 v 10	1.38 (0.32, 5.90)	1.04 (0.23, 4.73)	1.37 (0.33, 5.78)	0.95 (0.2, 4.5)	2.59 (0.93, 7.19)	7.83 (2.08, 29.5)
1.5 v 10	1.29 (0.34, 4.92)	0.98 (0.24, 4.03)	1.24 (0.35, 4.38)	0.87 (0.21, 3.56)	2.29 (0.89, 5.87)	6.31 (1.82, 21.8)
2 v 10	1.21 (0.36, 4.10)	0.93 (0.25, 3.43)	1.12 (0.37, 3.32)	0.79 (0.22, 2.82)	2.02 (0.85, 4.8)	5.09 (1.59, 16.2)
2.5 v 10	1.14 (0.38, 3.42)	0.89 (0.27, 2.92)	1.01 (0.4, 2.53)	0.72 (0.23, 2.24)	1.78 (0.81, 3.93)	4.10 (1.39, 12.0)
3 v 10	1.07 (0.40, 2.86)	0.84 (0.28, 2.49)	0.91 (0.43, 1.92)	0.66 (0.24, 1.8)	1.58 (0.77, 3.22)	3.30 (1.21, 9.04)
4 v 10	0.94 (0.44, 2.00)	0.76 (0.32, 1.81)	0.74 (0.48, 1.14)	0.55 (0.25, 1.19)	1.23 (0.70, 2.18)	2.14 (0.9, 5.13)
5 v 10	0.83 (0.48, 1.41)	0.68 (0.35, 1.33)	0.6 (0.46, 0.77)	0.45 (0.24, 0.86)	0.96 (0.61, 1.5)	1.39 (0.65, 2.99)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Table C5. Odds Ratio (OR) of <u>doctor diagnosed asthma</u> by residential distance to the nearest CAFO. Table displays results from main study sample, when urban area residents are excluded, and when Milwaukee county residents are excluded.

Residential Distances Compared (in miles)	**Entire study sample** (n=504)		**Milwaukee county excluded** (n=413)		**All urban areas excluded** (n=215)	
	Unadjusted OR (95% CI)	**Adjusted OR (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 v 6	2.13 (0.85, 5.29)	1.86 (0.80, 4.32)	2.61 (1.01, 6.75)	2.1 (0.98, 4.51)	3.44 (1.49, 7.91)	8.63 (3.2, 23.2)
1.5 v 6	1.97 (0.87, 4.47)	1.75 (0.82, 3.73)	2.37 (1.01, 5.57)	1.95 (0.98, 3.88)	3.04 (1.44, 6.43)	6.95 (2.85, 16.9)
2 v 6	1.83 (0.88, 3.79)	1.64 (0.84, 3.22)	2.15 (1.01, 4.59)	1.81 (0.98, 3.33)	2.68 (1.38, 5.23)	5.60 (2.54, 12.3)
2.5 v 6	1.69 (0.90, 3.20)	1.54 (0.85, 2.78)	1.95 (1.01, 3.78)	1.68 (0.98, 2.86)	2.37 (1.32, 4.25)	4.51 (2.26, 9.03)
3 v 6	1.57 (0.91, 2.71)	1.45 (0.87, 2.40)	1.77 (1.01, 3.12)	1.55 (0.98, 2.45)	2.01 (1.27, 3.45)	3.64 (2.01, 6.59)
4 v 6	1.35 (0.94, 1.94)	1.28 (0.91, 1.79)	1.46 (1, 2.12)	1.34 (0.99, 1.81)	1.64 (1.17, 2.28)	2.36 (1.59, 3.51)
5 v 6	1.16 (0.97, 1.39)	1.13 (0.96, 1.34)	1.2 (1, 1.44)	1.15 (0.99, 1.33)	1.28 (1.08, 1.51)	1.53 (1.26, 1.87)
1 v 10	1.91 (0.68, 5.42)	1.51 (0.53, 4.31)	1.89 (0.73, 4.91)	1.44 (0.48, 4.34)	2.59 (0.93, 7.19)	7.83 (2.08, 29.5)
1.5 v 10	1.78 (0.69, 4.60)	1.42 (0.54, 3.73)	1.71 (0.72, 4.07)	1.34 (0.47, 3.78)	2.29 (0.89, 5.87)	6.31 (1.82, 21.8)
2 v 10	1.65 (0.69, 3.90)	1.33 (0.55, 3.23)	1.55 (0.72, 3.37)	1.24 (0.47, 3.29)	2.02 (0.85, 4.8)	5.09 (1.59, 16.2)
2.5 v 10	1.53 (0.70, 3.31)	1.25 (0.56, 2.80)	1.41 (0.71, 2.79)	1.15 (0.46, 2.87)	1.78 (0.81, 3.93)	4.10 (1.39, 12.0)
3 v 10	1.42 (0.71, 2.81)	1.18 (0.57, 2.43)	1.28 (0.7, 2.32)	1.07 (0.45, 2.52)	1.58 (0.77, 3.22)	3.30 (1.21, 9.04)
4 v 10	1.22 (0.73, 2.04)	1.04 (0.59, 1.83)	1.05 (0.68, 1.62)	0.92 (0.43, 1.95)	1.23 (0.70, 2.18)	2.14 (0.9, 5.13)
5 v 10	1.05 (0.73, 1.49)	0.92 (0.60, 1.40)	0.87 (0.64, 1.17)	0.79 (0.4, 1.54)	0.96 (0.61, 1.5)	1.39 (0.65, 2.99)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Table C6. Odds Ratio (OR) of wheezing in last 12 months by residential distance to the nearest CAFO. Table displays results from main study sample, when urban area residents are excluded, and when Milwaukee county residents are excluded.

Residential Distances Compared (in miles)	**Entire study sample** (n=504)		**Milwaukee county excluded** (n=413)		**All urban areas excluded** (n=215)	
	Unadjusted OR (95% CI)	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 v 6	2.46 (1.57, 3.86)	2.40 (1.42, 4.04)	4.92 (2, 12.13)	5.58 (2.3, 13.53)	7.68 (3.49, 16.9)	44.7 (21.75, 91.9)
1.5 v 6	2.25 (1.50, 3.37)	2.19 (1.37, 3.51)	4.18 (1.86, 9.4)	4.68 (2.11, 10.36)	6.26 (3.08, 12.7)	30.5 (15.9, 58.4)
2 v 6	2.05 (1.43, 2.95)	2.01 (1.32, 3.05)	3.55 (1.73, 7.28)	3.92 (1.94, 7.93)	5.1 (2.72, 9.59)	20.8 (11.7, 37.1)
2.5 v 6	1.88 (1.37, 2.57)	1.84 (1.28, 2.65)	3.02 (1.62, 5.64)	3.29 (1.78, 6.07)	4.16 (2.4, 7.22)	14.25 (8.61, 23.5)
3 v 6	1.71 (1.31, 2.25)	1.69 (1.23, 2.31)	2.56 (1.51, 4.37)	2.76 (1.63, 4.65)	3.39 (2.11, 5.44)	9.74 (6.32, 14.99)
4 v 6	1.43 (1.20, 1.71)	1.42 (1.15, 1.74)	1.85 (1.31, 2.62)	1.94 (1.38, 2.73)	2.25 (1.64, 3.09)	4.54 (3.41, 6.05)
5 v 6	1.19 (1.09, 1.31)	1.19 (1.07, 1.32)	1.34 (1.13, 1.58)	1.36 (1.16, 1.6)	1.50 (1.28, 1.75)	2.12 (1.84, 2.44)
1 v 10	1.55 (0.87, 2.75)	1.20 (0.64, 2.25)	1.39 (0.7, 2.78)	1.07 (0.61, 1.86)	4.23 (1.88, 9.50)	18.02 (8.56, 37.9)
1.5 v 10	1.41 (0.83, 2.41)	1.10 (0.61, 1.97)	1.18 (0.61, 2.3)	0.9 (0.53, 1.53)	3.45 (1.66, 7.19)	12.31 (6.1, 24.85)
2 v 10	1.29 (0.79, 2.12)	1.00 (0.58, 1.73)	1 (0.52, 1.92)	0.75 (0.44, 1.27)	2.81 (1.45, 5.45)	8.41 (4.32, 16.36)
2.5 v 10	1.18 (0.75, 1.86)	0.92 (0.56, 1.52)	0.85 (0.45, 1.63)	0.63 (0.37, 1.07)	2.29 (1.27, 4.13)	5.74 (3.04, 10.84)
3 v 10	1.08 (0.71, 1.64)	0.84 (0.53, 1.33)	0.72 (0.38, 1.4)	0.53 (0.3, 0.92)	1.87 (1.11, 3.14)	3.92 (2.13, 7.23)
4 v 10	0.90 (0.63, 1.28)	0.71 (0.48, 1.04)	0.52 (0.26, 1.07)	0.37 (0.2, 0.7)	1.24 (0.84, 1.83)	1.83 (1.02, 3.29)
5 v 10	0.75 (0.56, 1.01)	0.59 (0.42, 0.83)	0.38 (0.17, 0.85)	0.26 (0.12, 0.55)	0.82 (0.62, 1.1)	0.85 (0.47, 1.56)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Table C7. Odds Ratio (OR) of asthma meds in last 3 months by residential distance to the nearest CAFO. Table displays results from main study sample, when urban area residents are excluded, and when Milwaukee county residents are excluded.

Residential Distances Compared (in miles)	**Entire study sample** (n=504)		**Milwaukee county excluded** (n=413)		**All urban areas excluded** (n=215)	
	Unadjusted OR (95% CI)	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**
1 v 6	3.18 (1.66, 6.06)	3.34 (1.71, 6.55)	5.18 (2.71, 9.92)	4.9 (2.76, 8.71)	7.68 (3.49, 16.9)	44.7 (21.75, 91.9)
1.5 v 6	2.83 (1.58, 5.06)	2.96 (1.62, 5.42)	4.38 (2.45, 7.86)	4.17 (2.49, 6.98)	6.26 (3.08, 12.7)	30.5 (15.9, 58.4)
2 v 6	2.52 (1.50, 4.22)	2.62 (1.53, 4.49)	3.71 (2.21, 6.22)	3.54 (2.24, 5.59)	5.1 (2.72, 9.59)	20.8 (11.7, 37.1)
2.5 v 6	2.24 (1.43, 3.53)	2.32 (1.45, 3.72)	3.13 (1.99, 4.92)	3.01 (2.02, 4.48)	4.16 (2.4, 7.22)	14.25 (8.61, 23.5)
3 v 6	2.00 (1.36, 2.94)	2.06 (1.38, 3.08)	2.65 (1.8, 3.9)	2.56 (1.82, 3.59)	3.39 (2.11, 5.44)	9.74 (6.32, 14.99)
4 v 6	1.58 (1.22, 2.05)	1.62 (1.24, 2.11)	1.89 (1.47, 2.44)	1.85 (1.48, 2.31)	2.25 (1.64, 3.09)	4.54 (3.41, 6.05)
5 v 6	1.26 (1.11, 1.43)	1.27 (1.11, 1.45)	1.35 (1.2, 1.53)	1.33 (1.2, 1.48)	1.50 (1.28, 1.75)	2.12 (1.84, 2.44)
1 v 10	2.12 (0.96, 4.70)	1.60 (0.62, 4.13)	1.81 (0.78, 4.17)	1.22 (0.44, 3.36)	4.23 (1.88, 9.50)	18.02 (8.56, 37.9)
1.5 v 10	1.89 (0.91, 3.93)	1.42 (0.59, 3.43)	1.53 (0.69, 3.38)	1.03 (0.38, 2.85)	3.45 (1.66, 7.19)	12.31 (6.1, 24.85)
2 v 10	1.68 (0.86, 3.30)	1.25 (0.55, 2.85)	1.29 (0.61, 2.75)	0.88 (0.32, 2.42)	2.81 (1.45, 5.45)	8.41 (4.32, 16.36)
2.5 v 10	1.50 (0.81, 2.76)	1.11 (0.52, 2.37)	1.09 (0.53, 2.24)	0.75 (0.27, 2.07)	2.29 (1.27, 4.13)	5.74 (3.04, 10.84)
3 v 10	1.33 (0.77, 2.32)	0.98 (0.49, 1.97)	0.92 (0.46, 1.84)	0.64 (0.23, 1.77)	1.87 (1.11, 3.14)	3.92 (2.13, 7.23)
4 v 10	1.06 (0.68, 1.64)	0.77 (0.44, 1.37)	0.66 (0.35, 1.26)	0.46 (0.16, 1.31)	1.24 (0.84, 1.83)	1.83 (1.02, 3.29)
5 v 10	0.84 (0.60, 1.18)	0.61 (0.39, 0.96)	0.47 (0.25, 0.88)	0.33 (0.11, 0.98)	0.82 (0.62, 1.1)	0.85 (0.47, 1.56)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Table C8. Change in FEV1 / FVC ratio by residential distance to the nearest CAFO. Table displays results from main study sample, when urban area residents are excluded, and when Milwaukee county residents are excluded.

Residential Distances Compared (in miles)	Entire study sample (n=464)		Milwaukee county excluded (n=378)		All urban areas excluded (n=202)	
	Unadjusted β (95% CI)	Unadjusted β (95%CI)	Unadjusted β (95%CI)	Unadjusted β (95%CI)	Unadjusted β (95%CI)	Adjusted β [b] (95%CI)
1 v 6	-0.007 (-0.127, 0.113)	0.010 (-0.093, 0.112)	-0.021 (-0.234, 0.192)	-0.015 (-0.217, 0.186)	-0.045 (-0.337, 0.247)	-0.045 (-0.306, 0.216)
1.5 v 6	-0.007 (-0.115, 0.101)	0.009 (-0.084, 0.101)	-0.019 (-0.210, 0.173)	-0.014 (-0.195, 0.167)	-0.041 (-0.303, 0.222)	-0.041 (-0.275, 0.194)
2 v 6	-0.006 (-0.102, 0.090)	0.008 (-0.075, 0.090)	-0.016 (-0.186, 0.153)	-0.012 (-0.173, 0.149)	-0.036 (-0.269, 0.197)	-0.036 (-0.244, 0.172)
2.5 v 6	-0.005 (-0.089, 0.079)	0.007 (-0.065, 0.079)	-0.014 (-0.163, 0.134)	-0.011 (-0.151, 0.130)	-0.032 (-0.235, 0.172)	-0.031 (-0.214, 0.151)
3 v 6	-0.004 (-0.076, 0.067)	0.006 (-0.056, 0.067)	-0.012 (-0.139, 0.114)	-0.009 (-0.129, 0.111)	-0.027 (-0.201, 0.147)	-0.027 (-0.183, 0.129)
4 v 6	-0.003 (-0.051, 0.045)	0.004 (-0.037, 0.045)	-0.008 (-0.092, 0.076)	-0.006 (-0.086, 0.074)	-0.018 (-0.133, 0.097)	-0.018 (-0.121, 0.086)
5 v 6	-0.001 (-0.025, 0.022)	0.002 (-0.019, 0.022)	-0.004 (-0.045, 0.037)	-0.003 (-0.042, 0.036)	-0.009 (-0.065, 0.047)	-0.009 (-0.060, 0.042)
1 v 10	-0.018 (-0.177, 0.140)	0.012 (-0.129, 0.154)	-0.018 (-0.20, 0.163)	0.017 (-0.161, 0.196)	-0.062 (-0.331, 0.207)	-0.042 (-0.335, 0.252)
1.5 v 10	-0.018 (-0.164, 0.129)	0.012 (-0.120, 0.143)	-0.016 (-0.177, 0.144)	0.019 (-0.14, 0.178)	-0.058 (-0.297, 0.182)	-0.037 (-0.305, 0.231)
2 v 10	-0.017 (-0.152, 0.118)	0.011 (-0.111, 0.132)	-0.014 (-0.154, 0.126)	0.021 (-0.119, 0.160)	-0.053 (-0.264, 0.158)	-0.032 (-0.275, 0.210)
2.5 v 10	-0.016 (-0.139, 0.106)	0.010 (-0.102, 0.121)	-0.012 (-0.131, 0.107)	0.022 (-0.098, 0.143)	-0.049 (-0.231, 0.134)	-0.028 (-0.244, 0.188)
3 v 10	-0.016 (-0.126, 0.095)	0.009 (-0.092, 0.110)	-0.010 (-0.108, 0.089)	0.024 (-0.078, 0.126)	-0.044 (-0.198, 0.110)	-0.023 (-0.214, 0.167)
4 v 10	-0.014 (-0.101, 0.073)	0.007 (-0.074, 0.087)	-0.006 (-0.066, 0.054)	0.027 (-0.041, 0.095)	-0.035 (-0.134, 0.064)	-0.014 (-0.155, 0.126)
5 v 10	-0.013 (-0.077, 0.052)	0.005 (-0.056, 0.065)	-0.002 (-0.037, 0.034)	0.030 (-0.015, 0.076)	-0.026 (-0.079, 0.028)	-0.005 (-0.098, 0.087)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;

[b]Adjusted for gender, age, body mass index, household smoking status, poverty to income ratio, distance to roadway, distance to industry, height, and physical activity

Additional Supplementary materials:

Table C9. Prevalence of asthma outcomes among SHOW 2014-2017 (ages 6-17) by residential distance to nearest concentrated animal feeding operation.

Distance to nearest CAFO	Total (n=542)	Ever asthma (n = 118)	Current asthma (n= 74)	Wheezing (n=72)	Asthma attack (n=40)	Asthma meds (n=55)
<= 1 miles	**14**	4	1	2	1	1
<= 2 miles	**35**	9	3	5	2	3
<= 3 miles	**52**	11	5	8	3	4
<= 4 miles	**83**	16	10	11	4	7
<= 5 miles	**101**	20	11	13	5	9

C10. Model building - Odds ratio estimates for **doctor diagnosed asthma** – entire study sample.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
1.5 v 6 miles	1.95 (0.87, 4.36)	1.79 (0.83, 3.87)	1.67 (0.79, 3.55)	1.72 (0.88, 3.37)	1.75 (0.71, 4.31)	1.86 (0.92, 3.78)	1.82 (0.86, 3.83)	1.92 (0.74, 4.94)
3 v 6 miles	1.56 (0.91, 2.67)	1.47 (0.88, 2.46)	1.41 (0.85, 2.33)	1.44 (0.92, 2.25)	1.45 (0.8, 2.65)	1.51 (0.94, 2.43)	1.49 (0.91, 2.45)	1.54 (0.82, 2.9)
2 v 10 miles	1.67 (0.7, 3.99)	1.62 (0.71, 3.7)	1.34 (0.54, 3.31)	1.33 (0.59, 3.01)	1.4 (0.5, 3.94)	1.4 (0.59, 3.31)	1.33 (0.55, 3.25)	1.43 (0.51, 4.02)
Age		1.15 (1.06, 1.26)	1.15 (1.05, 1.26)	1.14 (1.04, 1.25)	1.14 (1.03, 1.26)	1.05 (1.05, 1.27)	1.16 (1.06, 1.26)	1.13 (1.02, 1.24)
Gender (Male vs. Female)		1.16 (0.86, 1.55)	1.24 (0.91, 1.67)	1.25 (0.93, 1.69)	1.28 (0.87, 1.88)	0.85 (0.85, 1.77)	1.23 (0.88, 1.7)	1.3 (0.92, 1.83)
Distance nearest industry			0.92 (0.83, 1.01)	0.91 (0.85, 0.97)	0.91 (0.84, 0.98)	0.84 (0.84, 0.96)	0.92 (0.81, 1.05)	0.91 (0.85, 0.98)
Distance nearest pri rd			1 (1, 1)					
Pet(s) in home (Y vs. N)				1.27 (0.7, 2.3)				
No. of people in home				0.84 (0.72, 0.97)				0.83 (0.72, 0.94)
Smoker in home (Y vs. N)					1.47 (0.92, 2.36)			
Poverty to income ratio					1.14 (1.02, 1.27)			1.08 (0.97, 1.19)
Fruit/Veggie consumption						0.91 (0.78, 1.06)		
Min/week physical activity						1 (1, 1)		
BMI percentile						1.01 (1, 1.02)		
Season (Other vs. winter)							0.82 (0.25, 2.72)	
Urbanicity (urban vs. rural)							0.95 (0.57, 1.57)	

C11. Model building - Odds ratio estimates for **wheezing in last 12 months** – entire study sample.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
1.5 v 6 miles	2.33 (1.56, 3.5)	2.14 (1.45, 3.15)	2.32 (1.53, 3.51)	2.4 (1.53, 3.79)	2.83 (1.64, 4.88)	2.2 (1.38, 3.51)	2.18 (1.4, 3.39)	2.87 (1.74, 4.73)
3 v 6 miles	1.76 (1.34, 2.3)	1.66 (1.28, 2.15)	1.75 (1.32, 2.31)	1.79 (1.32, 2.43)	2 (1.39, 2.87)	1.69 (1.24, 2.31)	1.68 (1.25, 2.25)	2.02 (1.44, 2.81)
2 v 10 miles	1.27 (0.78, 2.08)	1.23 (0.77, 1.99)	1 (0.68, 1.48)	1.01 (0.61, 1.68)	1.31 (0.79, 2.18)	1.04 (0.63, 1.7)	0.99 (0.64, 1.54)	1.35 (0.83, 2.18)
Age		1.11 (0.99, 1.24)	1.1 (0.97, 1.25)	1.1 (0.97, 1.25)	1.1 (0.96, 1.25)	1.1 (0.94, 1.28)	1.09 (0.97, 1.22)	1.09 (0.97, 1.22)
Gender (Male vs. Female)		0.85 (0.38, 1.94)	0.96 (0.44, 2.1)	0.97 (0.45, 2.07)	1.04 (0.45, 2.44)	0.87 (0.37, 2.05)	1 (0.44, 2.28)	0.98 (0.46, 2.08)
Distance nearest industry			0.91 (0.83, 0.99)	0.88 (0.83, 0.94)	0.88 (0.82, 0.95)	0.89 (0.83, 0.94)	0.93 (0.84, 1.03)	0.88 (0.82, 0.95)
Distance nearest sec rd			1 (1, 1)					
Pet(s) in home (Y vs. N)				1.11 (0.47, 2.65)				
No. of people in home				0.93 (0.76, 1.13)				0.92 (0.73, 1.16)
Smoker in home (Y vs. N)					0.86 (0.32, 2.31)			
Poverty to income ratio					0.99 (0.84, 1.17)			0.99 (0.89, 1.1)
Fruit/Veggie consumption						0.9 (0.67, 1.19)		
Min/week physical activity						1 (1, 1)		
BMI percentile						1.01 (1, 1.02)		
Season (Other vs. winter)							1.13 (0.53, 2.43)	
Urbanicity (urban vs. rural)							0.66 (0.27, 1.64)	

C12. Model building - Odds ratio estimates for **asthma medication use in last 3 months** – entire study sample.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
1.5 v 6 miles	2.91 (1.63, 5.2)	2.9 (1.81, 4.65)	2.8 (1.72, 4.58)	3.03 (1.88, 4.89)	2.71 (1.19, 6.18)	2.89 (1.69, 4.92)	2.82 (1.8, 4.41)	2.92 (1.22, 7.02)
3 v 6 miles	2.04 (1.38, 3)	2.03 (1.48, 2.78)	1.98 (1.43, 2.75)	2.09 (1.52, 2.87)	1.95 (1.12, 3.37)	2.03 (1.42, 2.89)	1.99 (1.48, 2.68)	2.04 (1.14, 3.67)
2 v 10 miles	1.64 (0.84, 3.19)	1.66 (0.93, 2.97)	1.19 (0.66, 2.14)	1.17 (0.58, 2.35)	1.19 (0.41, 3.5)	1.25 (0.62, 2.52)	1.17 (0.62, 2.22)	1.29 (0.47, 3.55)
Age		1.04 (0.95, 1.14)	1.05 (0.97, 1.14)	1.03 (0.93, 1.13)	1.04 (0.93, 1.17)	1.03 (0.93, 1.14)	1.05 (0.97, 1.14)	1.01 (0.92, 1.11)
Gender (Male vs. Female)		1.42 (0.61, 3.32)	1.55 (0.61, 3.96)	1.64 (0.64, 4.16)	1.49 (0.55, 4.07)	1.59 (0.53, 4.74)	1.57 (0.59, 4.15)	1.56 (0.64, 3.8)
Distance nearest industry			0.83 (0.75, 0.92)	0.81 (0.73, 0.91)	0.82 (0.74, 0.92)	0.82 (0.74, 0.91)	0.85 (0.74, 0.99)	0.82 (0.74, 0.91)
Distance nearest sec rd			1 (1, 1)					
Pet(s) in home (Y vs. N)				1.46 (0.68, 3.14)				
No. of people in home				0.9 (0.72, 1.13)				0.87 (0.68, 1.12)
Smoker in home (Y vs. N)					1.06 (0.56, 2)			
Poverty to income ratio					1.04 (0.89, 1.22)			
Fruit/Veggie consumption						0.89 (0.75, 1.07)		
Min/week physical activity						1 (1, 1)		
BMI percentile						1.01 (0.99, 1.03)		
Season (Other vs. winter)							0.81 (0.44, 1.5)	
Urbanicity (urban vs. rural)							0.65 (0.21, 2.02)	

C13a. Model building - Change in estimates for **FEV1 % Predicted** – entire study sample.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
1.5 v 6 miles	-0.007 (-0.115, 0.101)	-0.008 (-0.041, 0.024)	-0.017 (-0.122, 0.089)	-0.016 (-0.109, 0.078)	-0.015 (-0.126, 0.096)
3 v 6 miles	-0.004 (-0.076, 0.067)	-0.010 (-0.049, 0.029)	-0.011 (-0.081, 0.059)	-0.010 (-0.073, 0.052)	-0.010 (-0.084, 0.064)
2 v 10 miles	-0.017 (-0.152, 0.118)	-0.019 (-0.073, 0.036)	-0.020 (-0.153, 0.112)	-0.015 (-0.135, 0.105)	-0.014 (-0.149, 0.121)
Age		0.008 (0.005, 0.011)	0.008 (0.005, 0.011)	0.008 (0.005, 0.011)	0.009 (0.005, 0.012)
Gender (Male vs. Female)		0.034 (-0.011, 0.078)	0.032 (-0.012, 0.077)	0.035 (-0.010, 0.080)	0.035 (-0.010, 0.080)
Distance nearest industry			0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)
Distance nearest sec rd			0.00 (-0.001, 0.001)		
Pet(s) in home (Y vs. N)				0.004 (-0.001, 0.008)	0.002 (-0.001, 0.005)
No. of people in home				0.00 (-0.001, 0.002)	
Smoker in home (Y vs. N)					-0.009 (-0.048, 0.030)
Poverty to income ratio					0.01 (-0.011, 0.030)
Fruit/Veggie consumption					
Min/week physical activity					
BMI percentile					
Season (Other vs. winter)					
Urbanicity (urban vs. rural)					

C13b. Model building - Odds ratio estimates for **FEV1/FVC** – entire study sample.

Variable	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)	Model 9 OR (95% CI)
1.5 v 6 miles	0.003 (-0.096, 0.102)	-0.018 (-0.122, 0.086)	-0.007 (-0.041, 0.026)	0.005 (-0.045, 0.054)
3 v 6 miles	0.002 (-0.064, 0.068)	-0.012 (-0.081, 0.057)	-0.009 (-0.049, 0.032)	0.006 (-0.053, 0.065)
2 v 10 miles	0.007 (-0.125, 0.138)	-0.017 (-0.147, 0.112)	-0.015 (-0.073, 0.043)	-0.003 (-0.081, 0.076)
Age	0.008 (0.006, 0.011)	0.008 (0.004, 0.013)	0.008 (0.001, 0.015)	0.008 (-0.001, 0.015)
Gender (Male vs. Female)	0.034 (-0.015, 0.083)	0.031 (-0.016, 0.077)	0.035 (-0.008, 0.077)	0.034 (-0.010, 0.078)
Height	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)
BMI				
Distance nearest industry	0.002 (-0.002, 0.006)	0.002 (0, 0.005)	0.002 (-0.003, 0.006)	0.001 (-0.003, 0.005)
Distance nearest sec rd				
Pet(s) in home (Y vs. N)				
No. of people in home				0.009 (-0.009, 0.027)
Smoker in home (Y vs. N)	0.038 (-0.050, 0.126)			
Poverty to income ratio	-0.001 (-0.014, 0.012)			
Fruit/Veggie consumption		0.001 (-0.017, 0.019)		
Min/week physical activity		0.00 (-0.001, 0.001)		
asthma med use			-0.014 (-0.080, 0.052)	
Season (Other vs. winter)			0.022 (-0.021, 0.065)	

Appendix D: Figures

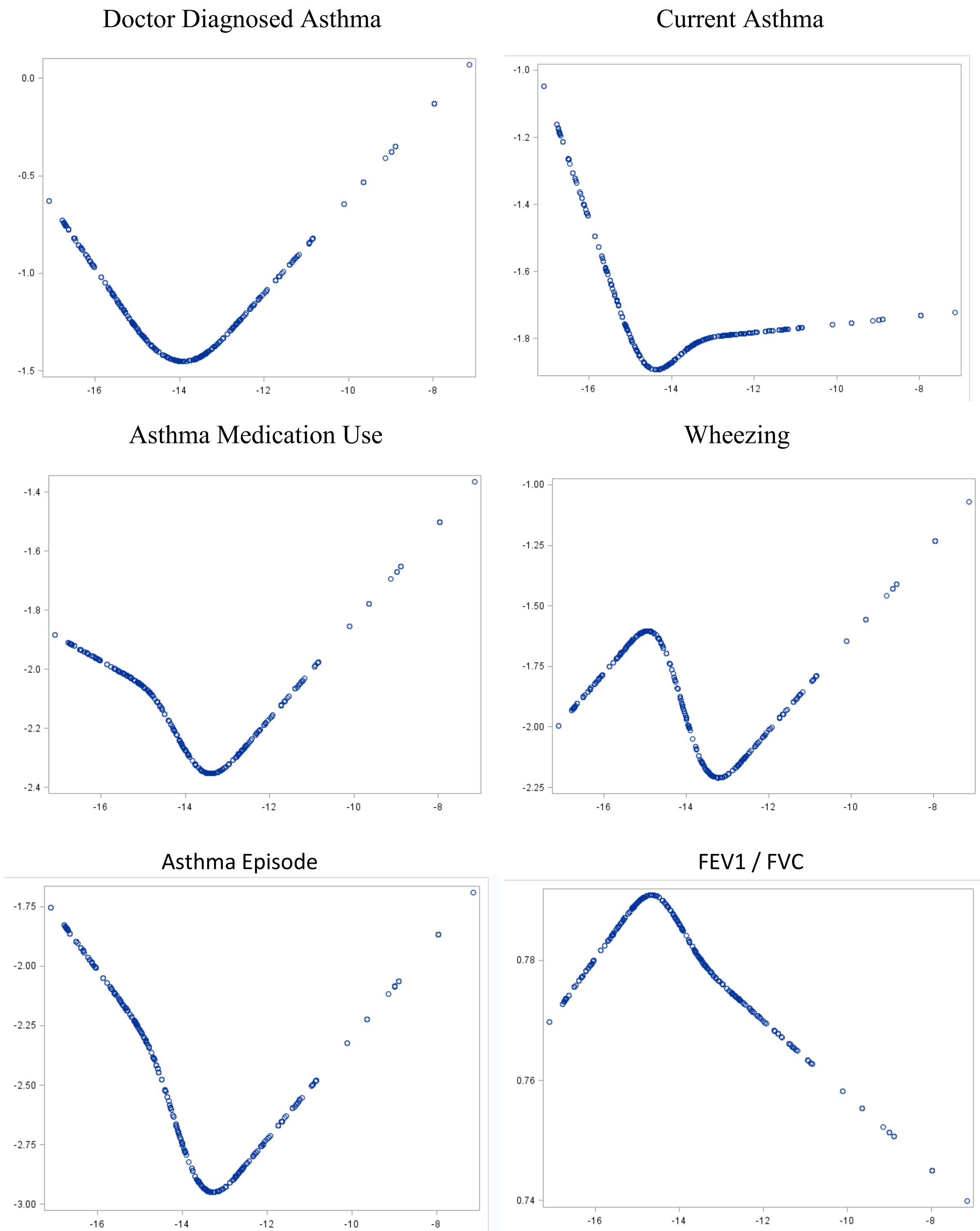


Figure D1. Unadjusted cubic splines of log (Erelative) on the x-axis and the log odds of asthma outcomes (y axis); and linear predictor (y axis) of FEV1 / FVC ratio.

Appendix D: Tables

Table D1. Summary of exposure metrics and prevalence of asthma outcomes by quartiles and percentile ranges of Log($E_{relative}$)

		Mean Values by Quartiles of log (Erelative)				Mean Values by Percentile ranges of high relative exposure to log (Erelative)		
RELATIVE EXPOSURE METRICS	*Range*	*75-100th*	*50-75th*	*25-50th*	*0-25th*	*90-100th*	*80-90th*	*70-80th*
Residential distance to nearest CAFO (in miles)	*0.45-36.5*	4.4	8.2	12.3	25.6	3.68	4.54	7.33
Animal Units at nearest CAFO to home (# animal units)	*420-10,638*	3008	2409	1734	1548	4121	2109	2436
Percent of time wind blows from nearest CAFO to home (%)	*2.4-30.6*	18.2	17.6	15.7	20	19.4	16.9	20.8
Percent of time wind blows <9mi/h from nearest CAFO to home (%)	*2.4-26.8*	13.8	12.3	11.1	13.9	14.7	12.8	16.8
Number of CAFOs within 5 miles of home (count)	*1-10*	1.75	1	1	1	2.58	1.29	1.05
Number of CAFOs within 5 miles of school (count)	*1-14*	1.83	1	1	1	2.89	1.21	1.03
School distance to nearest CAFO (in miles)	*0.42-37.8*	4.9	7.9	13.1	25	4.23	5.34	7
ASTHMA OUTCOMES	*Total*	*75-100th*	*50-75th*	*25-50th*	*0-25th*	*90-100th*	*80-90th*	*70-80th*
Asthma ever	*116*	31	22	25	38	17	10	12
Current asthma	*72*	18	12	16	26	9	6	8
Wheezing	*71*	17	12	16	26	9	6	7
Asthma meds	*53*	12	11	11	19	7	3	7
Asthma Episode	*39*	6	7	10	16	4	1	3

Table D2. Odds Ratio (OR) of asthma outcomes by residential distance to the nearest CAFO. Table displays <u>results from main study sample</u> (n=536)

	Current Asthma[a]		Doctor Diagnosed Asthma		Wheezing in last 12 months		Asthma medication use in last 3 months		Asthma attack in last 12 months	
Percentiles compared:	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted O[b] (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted O[b] (95%CI)**
95th vs 85th	1.02 (0.72, 1.43)	1.21 (0.85, 1.73)	1.36 (1.02, 1.81)	1.51 (1.11, 2.06)	1.28 (0.93, 1.76)	1.47 (1.07, 2.01)	1.23 (0.94, 1.63)	1.20 (0.81, 1.79)	1.31 (0.99, 1.74)	1.07 (0.56, 2.04)
95th vs 80th	1.02 (0.64, 1.63)	1.30 (0.80, 2.09)	1.52 (1.03, 2.23)	1.75 (1.15, 2.66)	1.40 (0.91, 2.15)	1.68 (1.09, 2.57)	1.33 (0.91, 1.94)	1.29 (0.75, 2.20)	1.45 (0.99, 2.12)	1.09 (0.46, 2.63)
95th vs 75th	1.02 (0.61, 1.71)	1.33 (0.78, 2.26)	1.59 (1.04, 2.42)	1.85 (1.16, 2.95)	1.45 (0.90, 2.33)	1.77 (1.10, 2.84)	1.37 (0.91, 2.07)	1.32 (0.73, 2.38)	1.50 (0.99, 2.29)	1.10 (0.42, 2.90)
95th vs 50th	1.12 (0.58, 2.14)	1.29 (0.67, 2.50)	1.86 (1.12, 3.09)	1.93 (1.15, 3.24)	1.14 (0.69, 1.87)	1.35 (0.74, 2.44)	1.32 (0.80, 2.19)	1.07 (0.55, 2.07)	1.25 (0.64, 2.42)	0.75 (0.26, 2.18)
95th vs 25th	0.88 (0.43, 1.82)	0.90 (0.42, 1.94)	1.38 (0.79, 2.41)	1.23 (0.69, 2.21)	0.89 (0.55, 1.42)	0.96 (0.52, 1.79)	1.04 (0.54, 2.01)	0.84 (0.38, 1.85)	0.71 (0.39, 1.29)	0.45 (0.19, 1.04)
95th vs 20th	0.88 (0.43, 1.82)	0.90 (0.42, 1.94)	1.38 (0.79, 2.41)	1.23 (0.69, 2.21)	0.89 (0.55, 1.42)	0.96 (0.52, 1.79)	1.04 (0.54, 2.01)	0.84 (0.38, 1.85)	0.71 (0.39, 1.29)	0.45 (0.19, 1.04)
95th vs 15th	0.81 (0.40, 1.67)	0.86 (0.40, 1.84)	1.29 (0.75, 2.22)	1.17 (0.65, 2.08)	0.93 (0.60, 1.43)	1.02 (0.57, 1.84)	1.02 (0.53, 1.97)	0.86 (0.39, 1.94)	0.68 (0.40, 1.15)	0.44 (0.19, 1.04)
90th vs 80th	1.01 (0.79, 1.30)	1.15 (0.89, 1.50)	1.26 (1.02, 1.55)	1.36 (1.08, 1.71)	1.20 (0.95, 1.52)	1.33 (1.05, 1.68)	1.17 (0.95, 1.43)	1.15 (0.86, 1.54)	1.22 (0.99, 1.51)	1.05 (0.65, 1.69)
90th vs 75th	1.01 (0.75, 1.37)	1.18 (0.87, 1.62)	1.31 (1.02, 1.68)	1.44 (1.09, 1.89)	1.24 (0.94, 1.64)	1.40 (1.06, 1.85)	1.20 (0.94, 1.54)	1.18 (0.83, 1.67)	1.27 (0.99, 1.63)	1.06 (0.60, 1.87)
90th vs 50th	1.11 (0.66, 1.85)	1.15 (0.69, 1.92)	1.54 (1.03, 2.31)	1.50 (1.01, 2.23)	0.97 (0.67, 1.41)	1.06 (0.67, 1.69)	1.16 (0.76, 1.78)	0.95 (0.58, 1.57)	1.06 (0.60, 1.85)	0.72 (0.35, 1.48)
90th vs 25th	0.87 (0.45, 1.70)	0.80 (0.39, 1.64)	1.14 (0.67, 1.95)	0.96 (0.54, 1.68)	0.76 (0.47, 1.24)	0.76 (0.41, 1.41)	0.91 (0.47, 1.78)	0.75 (0.35, 1.60)	0.60 (0.35, 1.03)	0.43 (0.23, 0.80)
90th vs 20th	0.87 (0.45, 1.70)	0.80 (0.39, 1.64)	1.14 (0.67, 1.95)	0.96 (0.54, 1.68)	0.76 (0.47, 1.24)	0.76 (0.41, 1.41)	0.91 (0.47, 1.78)	0.75 (0.35, 1.60)	0.60 (0.35, 1.03)	0.43 (0.23, 0.80)
90th vs 15th	0.81 (0.42, 1.55)	0.76 (0.38, 1.55)	1.07 (0.64, 1.78)	0.9 (0.52, 1.57)	0.79 (0.50, 1.25)	0.81 (0.45, 1.46)	0.90 (0.46, 1.74)	0.77 (0.36, 1.66)	0.57 (0.36, 0.91)	0.43 (0.23, 0.79)
85th vs 75th	1.01 (0.85, 1.19)	1.10 (0.92, 1.31)	1.17 (1.01, 1.34)	1.23 (1.05, 1.43)	1.13 (0.97, 1.32)	1.21 (1.03, 1.41)	1.11 (0.97, 1.27)	1.10 (0.90, 1.33)	1.14 (1.00, 1.32)	1.03 (0.75, 1.42)
85th vs 50th	1.10 (0.69, 1.74)	1.07 (0.68, 1.68)	1.37 (0.95, 1.98)	1.28 (0.89, 1.83)	0.89 (0.64, 1.23)	0.92 (0.61, 1.37)	1.07 (0.71, 1.61)	0.89 (0.57, 1.37)	0.95 (0.56, 1.60)	0.71 (0.41, 1.21)
85th vs 25th	0.87 (0.45, 1.68)	0.75 (0.37, 1.52)	1.01 (0.59, 1.75)	0.82 (0.45, 1.47)	0.69 (0.41, 1.18)	0.66 (0.35, 1.25)	0.84 (0.42, 1.69)	0.70 (0.32, 1.51)	0.54 (0.32, 0.92)	0.42 (0.24, 0.75)
85th vs 20th	0.87 (0.45, 1.68)	0.75 (0.37, 1.52)	1.01 (0.59, 1.75)	0.82 (0.45, 1.47)	0.69 (0.41, 1.18)	0.66 (0.35, 1.25)	0.84 (0.42, 1.69)	0.70 (0.32, 1.51)	0.54 (0.32, 0.92)	0.42 (0.24, 0.75)
85th vs 15th	0.80 (0.42, 1.52)	0.71 (0.35, 1.44)	0.95 (0.56, 1.60)	0.77 (0.44, 1.37)	0.72 (0.43, 1.20)	0.70 (0.37, 1.31)	0.83 (0.42, 1.64)	0.72 (0.33, 1.57)	0.51 (0.33, 0.81)	0.42 (0.24, 0.74)

CAFO: concentrated animal feeding operation; v: verses; OR: odds ratio; CI: confidence interval;
[b]Adjusted for gender, age, poverty to income ratio, distance to industry, number of people in the home

Table D3a. Odds ratio estimates for **doctor diagnosed asthma** by percentile comparison of LogE$_{relative}$ – results from several models.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
90th vs. 80th log(Erelative)	1.26 (1.02, 1.55)	1.27 (1.04, 1.55)	1.24 (1.02, 1.51)	1.28 (1.04, 1.57)	1.36 (1.06, 1.74)	1.23 (1.01, 1.50)	1.23 (1.00, 1.58)	1.36 (1.08, 1.71)
90th vs. 75th log(Erelative)	1.31 (1.02, 1.68)	1.39 (1.06, 1.82)	1.35 (1.03, 1.77)	1.40 (1.05, 1.86)	1.52 (1.08, 2.14)	1.28 (1.01, 1.62)	1.28 (0.98, 1.72)	1.44 (1.09, 1.89)
90th vs. 50th log(Erelative)	1.54 (1.03, 2.31)	1.77 (1.14, 2.75)	1.49 (0.96, 2.33)	1.52 (0.97, 2.38)	1.64 (0.98, 2.75)	1.45 (0.96, 2.19)	1.42 (0.96, 2.14)	1.50 (1.01, 2.23)
Age		1.16 (1.07, 1.25)	1.16 (1.07, 1.26)	1.16 (1.07, 1.25)	1.15 (1.06, 1.26)	1.17 (1.05, 1.29)	1.16 (1.07, 1.27)	1.14 (1.04, 1.26)
Gender (Male vs. Female)		1.17 (0.75, 1.84)	1.23 (0.78, 1.95)	1.24 (0.78, 1.96)	1.25 (0.78, 2.03)	1.21 (0.83, 1.75)	1.21 (0.88, 1.66)	1.28 (0.90, 1.82)
Distance nearest industry			0.94 (0.86, 1.02)	0.92 (0.86, 0.99)	0.92 (0.85, 1.00)	0.91 (0.85, 0.98)	0.93 (0.81, 1.06)	0.92 (0.86, 0.99)
Distance nearest pri rd			1.00 (0.99, 1.01)					
Pet(s) in home (Y vs. N)				1.14 (0.64, 2.04)				
No. of people in home				0.83 (0.70, 0.99)	0.86 (0.72, 1.01)			0.81 (0.72, 0.92)
Smoker in home (Y vs. N)					1.53 (0.82, 2.85)			
Poverty to income ratio					1.11 (0.97, 1.26)			1.05 (0.96, 1.15)
Fruit/Veggie consumption						0.9 (0.78, 1.05)		1.36 (1.08, 1.71)
Min/week physical activity						1.00 (0.98, 1.01)		
BMI percentile						1.01 (1.00, 1.02)		
Season (Other vs. winter)							1.01 (0.58, 1.75)	
Urbanicity (urban vs. rural)							0.92 (0.26, 3.19)	

Table D3b. Odds ratio estimates for **wheezing in the last 12 months** by percentile comparison of $LogE_{relative}$ – results from several models.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
90^{th} vs. 80^{th} log(Erelative)	1.20 (0.95, 1.52)	1.20 (0.88, 1.64)	1.18 (0.85, 1.63)	1.19 (0.85, 1.66)	1.34 (1.04, 1.73)	1.16 (0.94, 1.43)	1.17 (0.94, 1.46)	1.33 (1.05, 1.68)
90^{th} vs. 75^{th} log(Erelative)	1.24 (0.94, 1.64)	1.28 (0.83, 1.97)	1.25 (0.80, 1.96)	1.27 (0.8, 2.01)	1.42 (1.04, 1.92)	1.19 (0.93, 1.53)	1.20 (0.92, 1.57)	1.40 (1.06, 1.85)
90^{th} vs. 50^{th} log(Erelative)	0.97 (0.67, 1.41)	1.01 (0.56, 1.79)	0.88 (0.49, 1.59)	0.90 (0.48, 1.69)	1.03 (0.65, 1.65)	0.88 (0.64, 1.21)	0.87 (0.60, 1.25)	1.06 (0.67, 1.69)
Age		1.12 (1.00, 1.25)	1.12 (0.99, 1.26)	1.12 (0.99, 1.26)	1.12 (0.98, 1.27)	1.11 (0.96, 1.3)	1.13 (1.01, 1.26)	1.12 (0.98, 1.27)
Gender (Male vs. Female)		0.85 (0.47, 1.54)	0.92 (0.50, 1.67)	0.92 (0.51, 1.67)	1.00 (0.51, 1.97)	0.84 (0.39, 1.84)	0.87 (0.39, 1.93)	1.00 (0.51, 1.97)
Distance nearest industry			0.96 (0.89, 1.03)	0.92 (0.86, 0.99)	0.93 (0.86, 1.00)	0.91 (0.84, 1.00)	0.94 (0.83, 1.06)	0.93 (0.86, 1.00)
Distance nearest sec rd			1.00 (.099, 1.01)					
Pet(s) in home (Y vs. N)				0.97 (0.44, 2.15)				
No. of people in home				0.95 (0.78, 1.15)				0.93 (0.73, 1.19)
Smoker in home (Y vs. N)					0.96 (0.33, 2.75)			
Poverty to income ratio					1.00 (0.87, 1.15)			0.97 (0.88, 1.07)
Fruit/Veggie consumption						0.89 (0.67, 1.18)		
Min/week physical activity						1.00 (0.99, 1.01)		
BMI percentile						1.01 (0.99, 1.02)		
Season (Other vs. winter)							1.22 (0.51, 2.89)	
Urbanicity (urban vs. rural)							0.79 (0.37, 1.70)	

Table D3c. Odds ratio estimates for **asthma medication use in the last 3 months** by percentile comparison of $LogE_{relative}$ – results from several models.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)
90^{th} vs. 80^{th} log(Erelative)	1.17 (0.95, 1.43)	1.19 (0.95, 1.49)	1.16 (0.91, 1.48)	1.15 (0.89, 1.47)	1.12 (0.82, 1.53)	1.13 (0.90, 1.42)	1.12 (0.89, 1.42)	1.15 (0.86, 1.54)
90^{th} vs. 75^{th} log(Erelative)	1.20 (0.94, 1.54)	1.27 (0.93, 1.73)	1.22 (0.87, 1.72)	1.21 (0.85, 1.70)	1.18 (0.77, 1.80)	1.18 (0.86, 1.63)	1.18 (0.86, 1.61)	1.18 (0.83, 1.67)
90^{th} vs. 50^{th} log(Erelative)	1.16 (0.76, 1.78)	1.23 (0.75, 2.02)	0.99 (0.60, 1.65)	1.08 (0.58, 2.00)	1.03 (0.53, 1.99)	1.00 (0.61, 1.64)	0.96 (0.59, 1.55)	0.95 (0.58, 1.57)
Age		1.06 (0.95, 1.19)	1.05 (0.94, 1.18)	1.05 (0.94, 1.18)	1.07 (0.93, 1.23)	1.06 (0.93, 1.20)	1.07 (0.95, 1.20)	1.09 (0.96, 1.25)
Gender (Male vs. Female)		1.39 (0.71, 2.72)	1.49 (0.75, 2.96)	1.50 (0.76, 2.97)	1.36 (0.62, 2.99)	1.48 (0.72, 3.01)	1.46 (0.73, 2.91)	1.37 (0.64, 2.94)
Distance nearest industry			0.91 (0.83, 1.01)	0.86 (0.78, 0.95)	0.88 (0.80, 0.97)	0.86 (0.78, 0.94)	0.88 (0.79, 0.97)	0.88 (0.80, 0.97)
Distance nearest sec rd			1.00 (0.99, 1.00)					
Pet(s) in home (Y vs. N)				1.24 (0.57, 2.70)				
No. of people in home				0.93 (0.76, 1.13)				0.89 (0.69, 1.15)
Smoker in home (Y vs. N)					1.26 (0.48, 3.32)			
Poverty to income ratio					1.05 (0.88, 1.24)			
Fruit/Veggie consumption						0.91 (0.75, 1.09)		
Min/week physical activity						1.00 (0.99, 1.01)		
BMI percentile						1.01 (1.00, 1.02)		
Season (Other vs. winter)							0.84 (0.45, 1.59)	
Urbanicity (urban vs. rural)							0.81 (0.36, 1.82)	

Table D3d. Change in **FEV1/FVC** ratio by percentile comparison of $LogE_{relative}$ – results from several models.

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
90th vs. 80th log(Erelative)	-0.006 (-0.046, 0.035)	-0.009 (-0.042, 0.025)	-0.008 (-0.04, 0.024)	-0.006 (-0.040, 0.027)	-0.007 (-0.050, 0.036)
90th vs. 75th log(Erelative)	-0.007 (-0.055, 0.041)	-0.012 (-0.057, 0.034)	-0.010 (-0.048, 0.028)	-0.008 (-0.048, 0.032)	-0.008 (-0.060, 0.043)
90th vs. 50th log(Erelative)	-0.019 (-0.067, 0.028)	-0.023 (-0.085, 0.039)	-0.019 (-0.069, 0.032)	-0.017 (-0.057, 0.023)	-0.016 (-0.065, 0.033)
Age		0.008 (0.002, 0.015)	0.008 (0.002, 0.015)	0.008 (0.005, 0.011)	0.009 (0.005, 0.012)
Gender (Male vs. Female)		-0.034 (-0.067, -0.001)	-0.033 (-0.066, 0.00)	0.035 (-0.010, 0.08)	0.035 (-0.01, 0.08)
Distance nearest industry			0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00(-0.001, 0.001)
Distance nearest sec rd			0.00 (-0.001, 0.001)		
Pet(s) in home (Y vs. N)				0.004 (0.00, 0.008)	0.002 (-0.001, 0.005)
No. of people in home				0.00 (0.001, 0.002)	
Smoker in home (Y vs. N)					-0.009 (-0.048, 0.030)
Poverty to income ratio					0.009 (-0.012, 0.030)
Fruit/Veggie consumption					
Min/week physical activity					
BMI percentile					
Season (Other vs. winter)					
Urbanicity (urban vs. rural)					

Table D3d continued. Change in **FEV1/FVC** ratio by percentile comparison of LogE$_{relative}$ – results from several models

Variable	Model 6 OR (95% CI)	Model 7 OR (95% CI)	Model 8 OR (95% CI)	Model 9 OR (95% CI)
90^{th} vs. 80^{th} log(Erelative)	0.005 (-0.036, 0.047)	-0.008 (-0.046, 0.031)	-0.007 (-0.046, 0.031)	0.005 (-0.039, 0.049)
90^{th} vs. 75^{th} log(Erelative)	0.006 (-0.043, 0.056)	-0.009 (-0.055, 0.037)	-0.009 (-0.055, 0.037)	0.006 (-0.047, 0.059)
90^{th} vs. 50^{th} log(Erelative)	-0.001 (-0.05, 0.048)	-0.015 (-0.058, 0.027)	-0.015 (-0.057, 0.027)	-0.003 (-0.054, 0.049)
Age	0.008 (0.006, 0.011)	0.008 (0.004, 0.013)	0.008 (0.001, 0.015)	0.008 (0.00, 0.015)
Gender (Male vs. Female)	0.034 (-0.015, 0.083)	0.031 (-0.016, 0.077)	0.035 (-0.008, 0.077)	0.034 (-0.010, 0.078)
Height	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)	0.00 (-0.001, 0.001)
BMI				
Distance nearest industry	0.002 (-0.002, 0.006)	0.002 (0.00, 0.005)	0.002 (-0.003, 0.006)	0.001 (-0.003, 0.005)
Distance nearest sec rd				
Pet(s) in home (Y vs. N)				
No. of people in home				0.009 (-0.013, 0.031)
Smoker in home (Y vs. N)	0.036 (-0.057, 0.129)			
Poverty to income ratio	-0.001 (-0.015, 0.012)			
Fruit/Veggie consumption		0.001 (-0.017, 0.019)		
Min/week physical activity		0.00 (0.001, 0.002)		
asthma med use			-0.014 (-0.080, 0.052)	
Season (Other vs. winter)			0.022 (-0.021, 0.065)	

Table D4. Change in lung function by residential distance to the nearest CAFO. Table displays results from main study sample (n=496)

	FEV1 (Liters)		**FVC (Liters/second)**		**FEV1 % PRD**		**FEV1/FVC**	
Percentiles compared:	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**	**Unadjusted β (95%CI)**	**Adjusted β[a] (95%CI)**
95th vs 85th	0.053 (-0.068, 0.174)	0.047 (-0.102, 0.196)	0.143 (-0.11, 0.396)	0.084 (-0.457, 0.625)	0.126 (-0.029, 0.281)	0.148 (-0.043, 0.338)	-0.008 (-0.063, 0.047)	0.007 (-0.053, 0.067)
95th vs 80th	0.072 (-0.092, 0.236)	0.064 (-0.139, 0.266)	0.194 (-0.149, 0.536)	0.114 (-0.618, 0.846)	0.17 (-0.04, 0.380)	0.200 (-0.058, 0.458)	-0.011 (-0.085, 0.063)	0.009 (-0.072, 0.09)
95th vs 75th	0.079 (-0.102, 0.261)	0.070 (-0.153, 0.294)	0.214 (-0.164, 0.593)	0.126 (-0.683, 0.935)	0.188 (-0.044, 0.42)	0.221 (-0.064, 0.506)	-0.012 (-0.094, 0.07)	0.010 (-0.08, 0.100)
95th vs 50th	-0.009 (-0.279, 0.262)	0.022 (-0.168, 0.212)	0.245 (-0.108, 0.598)	0.192 (-0.525, 0.91)	0.135 (-0.154, 0.424)	0.212 (-0.120, 0.543)	-0.024 (-0.103, 0.055)	0.001 (-0.085, 0.088)
95th vs 25th	0.00 (-0.295, 0.295)	-0.003 (-0.158, 0.153)	0.280 (-0.046, 0.606)	0.253 (-0.281, 0.787)	0.088 (-0.214, 0.390)	0.118 (-0.140, 0.377)	-0.023 (-0.095, 0.05)	-0.011 (-0.084, 0.062)
95th vs 20th	0.00 (-0.295, 0.295)	-0.003 (-0.158, 0.153)	0.280 (-0.046, 0.606)	0.253 (-0.281, 0.787)	0.088 (-0.214, 0.390)	0.118 (-0.140, 0.377)	-0.023 (-0.095, 0.05)	-0.011 (-0.084, 0.062)
95th vs 15th	0.032 (-0.251, 0.314)	0.013 (-0.141, 0.167)	0.303 (-0.025, 0.631)	0.265 (-0.337, 0.867)	0.114 (-0.187, 0.415)	0.128 (-0.135, 0.391)	-0.021 (-0.098, 0.057)	-0.011 (-0.091, 0.069)
90th vs 80th	0.039 (-0.05, 0.129)	0.035 (-0.076, 0.145)	0.106 (-0.081, 0.293)	0.062 (-0.337, 0.462)	0.093 (-0.022, 0.208)	0.109 (-0.032, 0.250)	-0.006 (-0.046, 0.035)	0.005 (-0.039, 0.049)
90th vs 75th	0.047 (-0.06, 0.153)	0.041 (-0.090, 0.173)	0.126 (-0.097, 0.349)	0.074 (-0.402, 0.551)	0.111 (-0.026, 0.247)	0.130 (-0.038, 0.298)	-0.007 (-0.055, 0.041)	0.006 (-0.047, 0.059)
90th vs 50th	-0.041 (-0.276, 0.193)	-0.007 (-0.126, 0.112)	0.157 (-0.11, 0.424)	0.141 (-0.257, 0.539)	0.058 (-0.152, 0.267)	0.121 (-0.095, 0.337)	-0.019 (-0.067, 0.028)	-0.003 (-0.054, 0.049)
90th vs 25th	-0.033 (-0.300, 0.235)	-0.031 (-0.187, 0.125)	0.192 (-0.086, 0.407)	0.202 (-0.061, 0.464)	0.011 (-0.233, 0.254)	0.027 (-0.122, 0.177)	-0.018 (-0.065, 0.029)	-0.015 (-0.058, 0.028)
90th vs 20th	-0.033 (-0.300, 0.235)	-0.031 (-0.187, 0.125)	0.192 (-0.086, 0.470)	0.202 (-0.061, 0.464)	0.011 (-0.233, 0.254)	0.027 (-0.122, 0.177)	-0.018 (-0.065, 0.029)	-0.015 (-0.058, 0.028)
90th vs 15th	-0.001 (-0.249, 0.247)	-0.016 (-0.163, 0.131)	0.215 (-0.036, 0.466)	0.213 (-0.102, 0.529)	0.037 (-0.201, 0.275)	0.037 (-0.116, 0.190)	-0.016 (-0.067, 0.035)	-0.015 (-0.063, 0.033)
85th vs 75th	0.026 (-0.034, 0.086)	0.023 (-0.051, 0.097)	0.071 (-0.054, 0.197)	0.042 (-0.227, 0.31)	0.062 (-0.015, 0.139)	0.073 (-0.021, 0.168)	-0.004 (-0.031, 0.023)	0.003 (-0.027, 0.033)
85th vs 50th	-0.062 (-0.284, 0.160)	-0.025 (-0.120, 0.070)	0.102 (-0.149, 0.352)	0.108 (-0.11, 0.327)	0.009 (-0.159, 0.177)	0.064 (-0.081, 0.208)	-0.016 (-0.047, 0.015)	-0.005 (-0.037, 0.026)
85th vs 25th	-0.053 (-0.313, 0.206)	-0.049 (-0.231, 0.132)	0.137 (-0.153, 0.427)	0.169 (-0.047, 0.385)	-0.038 (-0.258, 0.183)	-0.029 (-0.122, 0.063)	-0.015 (-0.053, 0.023)	-0.018 (-0.050, 0.014)
85th vs 20th	-0.053 (-0.313, 0.206)	-0.049 (-0.231, 0.132)	0.137 (-0.153, 0.427)	0.169 (-0.047, 0.385)	-0.038 (-0.258, 0.183)	-0.029 (-0.122, 0.063)	-0.015 (-0.053, 0.023)	-0.018 (-0.050, 0.014)
85th vs 15th	-0.021 (-0.257, 0.214)	-0.034 (-0.204, 0.136)	0.160 (-0.085, 0.405)	0.181 (-0.037, 0.399)	-0.012 (-0.223, 0.199)	-0.020 (-0.114, 0.074)	-0.013 (-0.052, 0.027)	-0.017 (-0.051, 0.017)

Table D5. Number of study participants who live and/or attend school by distance to the nearest CAFO.

Distance to nearest CAFO	*From Home only*	*From School only*	*From Home AND School*	*From Home only OR School only*
<= 1 miles *(1.6 km)*	8	20	1	28
<= 1.5 miles *(2.4 km)*	14	18	8	32
<= 2 miles (*3.2 km)*	20	18	9	38
<= 2.5 miles *(4.0 km)*	15	28	23	43
<= 3 miles *(4.8 km*)	14	35	32	49
<= 4 miles *(6.4 km*)	21	29	56	50
<= 5 miles *(8.0 km*)	22	39	72	61

Table D6. Model fit comparisons for physician diagnosed and current asthma regressed on log(Erelative2) presented in the main analyses, distance to the nearest CAFO, and components of the log(Erelative2). All models are adjusted for age, gender, distance to industry, number of people in the home, and poverty to income ratio.

ASTHMA EVER

Relative Exposure Metric:	AIC	BIC
d	370.07	416.44
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{w_i}\right)$	373.63	420
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{s_i}\right)$	374.37	420.73
$log(E_{Relative_1}) = log\left(\left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{w_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_S}^2_i} * p_{w_i}\right) * 0.15\right]_{school}\right)$	374.83	421.2
$log(E_{Relative_2}) = log\left(\left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{s_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_S}^2_i} * p_{s_i}\right) * 0.15\right]_{school}\right)$	375.02	421.39
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i}\right)$	375.76	422.12

CURRENT ASTHMA

Relative Exposure Metric:	AIC	SC
d	285.5	331.8
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{s_i}\right)$	291.56	337.86
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{w_i}\right)$	291.82	338.12
$log\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i}\right)$	291.99	338.29
$log(E_{Relative_1}) = log\left(\left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{w_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_S}^2_i} * p_{w_i}\right) * 0.15\right]_{school}\right)$	292.07	338.37
$log(E_{Relative_2}) = log\left(\left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_R}^2_i} * p_{s_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n} \frac{u_i}{{d_S}^2_i} * p_{s_i}\right) * 0.15\right]_{school}\right)$	292.15	338.44

Table D7. Model fit comparisons for wheezing and asthma medication use regressed on log(Erelative$_2$) presented in the main analyses, distance to the nearest CAFO, and components of the log(Erelative$_2$). All models are adjusted for age, gender, distance to industry, number of people in the home, and poverty to income ratio.

WHEEZING

Relative Exposure	AIC	SC
d	267.98	314.35
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{s_i}\right)$	278.57	324.93
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{w_i}\right)$	278.71	325.08
$log(E_{Relative_1}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{w_i}\right)*0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i}*p_{w_i}\right)*0.15\right]_{school}\right)$	279.54	325.9
$log(E_{Relative_2}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{s_i}\right)*0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i}*p_{s_i}\right)*0.15\right]_{school}\right)$	280.65	327.01
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}\right)$	280.84	327.2

ASTHMA MEDS

Relative Exposure	AIC	SC
d	221.33	267.72
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{s_i}\right)$	230	276.4
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{w_i}\right)$	230.17	276.57
$log(E_{Relative_2}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{s_i}\right)*0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i}*p_{s_i}\right)*0.15\right]_{school}\right)$	231.13	277.53
$log(E_{Relative_1}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}*p_{w_i}\right)*0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i}*p_{w_i}\right)*0.15\right]_{school}\right)$	231.22	277.62
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}\right)$	231.59	277.99

Table D8. Model fit comparisons for FEV1 / FVC u regressed on log(Erelative2) presented in the main analyses, distance to the nearest CAFO, and components of the log(Erelative2). All models are adjusted for age, gender, height, distance to industry, number of people in the home, and poverty to income ratio.

FEV1 / FVC	
Relative Exposure	RMSE
$log(E_{Relative_2}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i} * p_{s_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i} * p_{s_i}\right) * 0.15\right]_{school}\right)$	0.21
$log(E_{Relative_1}) = log\left(\left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i} * p_{w_i}\right) * 0.85\right]_{home} + \left[\left(\sum_{i=1}^{n}\frac{u_i}{{d_S}^2_i} * p_{w_i}\right) * 0.15\right]_{school}\right)$	0.20
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i} * p_{w_i}\right)$	0.20
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i} * p_{s_i}\right)$	0.20
$log\left(\sum_{i=1}^{n}\frac{u_i}{{d_R}^2_i}\right)$	0.19
d	0.18

Variable Definitions:
d = distance to the nearest CAFO in miles
n = total number of CAFOs in Wisconsin
u = total animal units at the i^{th} CAFO
d_R = distance between i^{th} CAFO and residence in miles
d_S = distance between i^{th} CAFO and school in miles
p_w = Percentage of time wind blows in the direction from i^{th} CAFO to the residence (or school)
p_s = Percentage of time wind blows < 9 mph (4 m/s) in the direction from i^{th} CAFO to the residence (or school)

Methods for Linking Wind Data to SHOW participants:

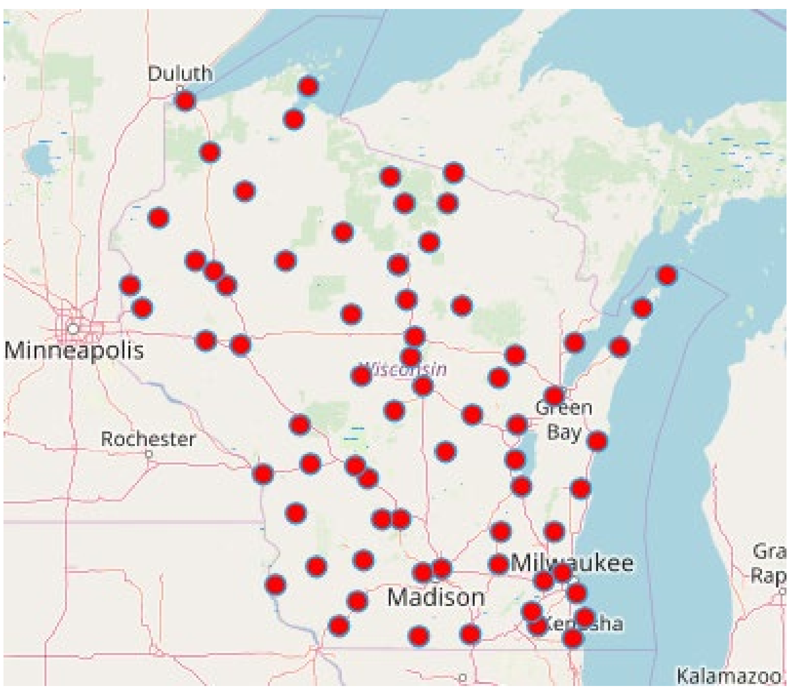
DATA DOWNLOAD:

- Data was downloaded from here: http://mesonet.agron.iastate.edu/request/download.phtml?network=WI_ASOS
- The Automated Surface Observing System (ASOS) data for the state of Wisconsin was downloaded.

ABOUT ASOS:

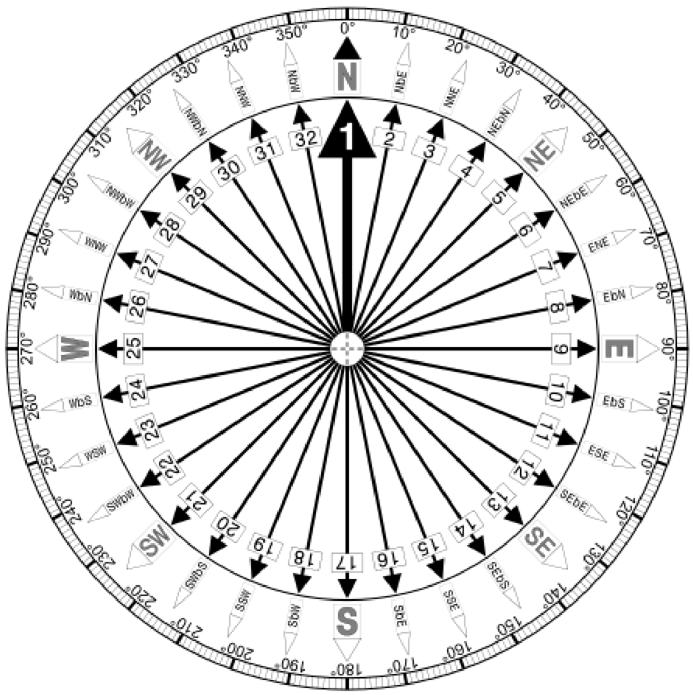
The ASOS is considered to be the flagship automated observing network. Located at airports, the ASOS stations provide essential observations for the National Weather Service (NWS), the Federal Aviation Administration (FAA), and the Department of Defense (DOD). The primary function of the ASOS stations are to take minute-by-minute observations and generate basic weather reports. Observations from the ASOS network are nationally monitored for quality 24 hours per day.

- There are 69 stations located in Wisconsin. The follow data were downloaded for the years 2007-2017 for all 69 stations (over 6 million records in long format):
    - Wind direction (in degrees 0-360), wind speed (mph)



PREPPING THE WIND DATA FOR MERGE:

1. Wind direction is defined as **<u>the direction the wind originated from</u>**
2. Wind direction is provided in degrees 0-360 relative to true north, where 0 = N, 90 = E, 180 = S, 270 = W.



3. Derived variable called **"Direction"** was created defined by the following 8 rose compass directions:
   - N >= 340 or <= 20
   - NE >= 30 and <= 60
   - E >= 70 and <= 110
   - SE >= 120 and <= 150
   - S >= 160 and <= 200
   - SW >= 210 and <= 240
   - W >= 250 and <= 290
   - NW >=300 and <= 330

4. Derived variable called **"Wind Speed"** was created defined by
   - 1 if <= 8.94775 miles per hour (or 4 meters / second)
   - 2 if > 8.94775 miles per hour (or 4 meters / second)

5. Calculated the total number of minutes per year wind blows, grouped by year, station and direction. Resulting in variable **"sum_obs_winddir_stationyr"** where every station has a 8 unique values (the 8 different directions) for every year 2007-2017.

6. Derived variable **"Percent time wind blows"** was created:
   ("sum_obs_winddir_stationyr" / total # minutes data collected that year at that station)* 100

7. Calculated the total number of minutes wind blows less than 4m/s, grouped by year, station and direction. Resulting in variable **"sum_obs_winddir_spd_stationyr"** where every station has 8 unique values (the 8 different directions) for every year 2007-2017.

8. Derived variable **"Percent time wind blows under 4m/s"** was created
   ("sum_obs_winddir_spd_stationyr" / total # minutes data collected that year at that station)* 100

9. Kept dataset in long format, removed duplicate records based on derived variables. Total n = 10,943 records

10. As a wide formatted dataset by the wind derived variable, n = 5487 records

PREPPING THE SHOW HHID AND CAFO DATA FOR MERGE WITH WIND DATA:

1. In ArcGIS, used the "Analysis Tools -> Proximity -> Generate Near Table" to calculate the distance and angle from SHOW household to all CAFOs within a 5 mile radius of the home

2. For those folks who do not live within 5 miles of a CAFO, the "Analysis Tools -> Proximity -> Near" tool was used to calculate the distance and angle from SHOW home to the nearest CAFO

3. The angle calculated follows such that 0 = E, 90 = N, W = 180 and -180, S = -90

4. A new data table field was created and using the field calculator, python script was used to derive the "Direction" variable to match that of the Wind Data:

```
def Direction(angle):
 if (angle >= 25 and angle < 65):
  return "NE"
 if (angle >= 65 and angle <115):
  return "N"
 if (angle >= 115 and angle <155):
  return "NW"
 if (angle >=155 or angle < -155):
  return "W"
 if (angle >= -155 and angle <-115):
  return "SW"
 if (angle >= -115 and angle <-65):
  return "S"
 if (angle >= -65 and angle <-25):
  return "SE"
```

```
if (angle >= -25 and angle <25):
  return "E"

Direction(!NEAR_ANGLE!)
```

5. The angle field in ArcGIS gives the direction the "near" data (CAFO) is relative to the "input" data (household). The below example would give the degrees of 180 or -180 and therefore give the direction of "W". Since the wind data is identified by the direction in which it originates, if we link the below example to wind data based on the direction "W" for the wind station nearest to the HHID, we would be linking the % of time wind blows from CAFO to home. – WHICH IS WHAT WE WANT!

    1. ʘ CAFO ʘ HHID

6. A derived variable "Year" was created which is the year prior to the SHOW HHIDs participation in SHOW.

MERGING DATASETS

- Both the ArcGIS SHOW household CAFO data set and the Wind data set were brought into SAS. The ArcGIS dataset was kept in long format since more than one CAFO could be linked to each home.

- Data were merged based on the following "group by" variables using SQL script:
    - Station, year, direction