ehp Environmental Health Perspectives
ehponline.org
Published by the National Institute of Environmental Health Sciences

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doi:10.1289/ehp.7240 (available at http://dx.doi.org/)
Online 7 December 2004

The National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services

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WORD COUNT: Abstract – 250

Text/References – 5055

Tables/Figures – 1750

Total – 6805

Acknowledgements/Grant Information/Disclaimers: Supported by NIOSH-funded grant, "Childhood Health Outcomes in a Rural Cohort," # 5 R01/CCR714364 and NIOSH-funded grant to the Great Plains Center for Agricultural Health, "Keokuk County Rural Health Study," # U07/CCU706145. These findings do not necessarily represent the United States Environmental Protection Agency. The authors would like to acknowledge the many contributions of the KCRHS staff.

Running title: Asthma-Farm Exposures in a Cohort of Rural Iowa Children

Key words: asthma, chronic wheeze, cough with exercise, rural, farming, children, animal feeding operations, agricultural occupational exposures, hygiene hypothesis, genetic selection, hydrogen sulfide, ammonia, odor, asthma under-diagnosis, asthma under-treatment, asthma school screening, asthma health care policy, asthma diagnosis and treatment

Abbreviations: US=United States, USDA=United States Department of Agriculture, AFOs=Animal Feeding Operations, KCRHS=Keokuk County Rural Health Study, PFT=Pulmonary Function Test, FEV1=forced expiratory volume in one second, PC20=concentration of methacholine that induces a 20% decline in FEV1, SPT=skin prick test, SAS=from SAS Institute, Inc., SUDAAN=Software for the Statistical Analysis of Correlated Data from Research Triangle Institute.

Definitions: *Doctor diagnosed asthma*=If the child's parent responded "yes" to the question: "Has a doctor ever diagnosed your child as having asthma?"; *Asthma/medication for wheeze*=If the child's parent responded "yes" to either of the following questions: "Has a doctor ever diagnosed your child as having asthma?", and/or "Has your child needed medication for his/her wheezing in the past 12 months?"; *Current wheeze*=If the child's parent responded "yes" to the two questions: "Has he/she ever wheezed when he or she did not have a cold? Has this happened in the last 12 months?"; *Cough with exercise*=If the child's parent responded "yes" to: "Does he/she cough during or shortly after vigorous exercise or exertion?"; *Family history of atopy*=any child whose biological siblings or parents had a history of asthma and/or hay fever and/or history of allergies; *Severe symptoms consistent with asthma*=if the child's parent responded "yes" to the question: "Has he/she ever wheezed for three or more days a week for a month or longer in the past 12 months?", and/or if the child had visited an emergency room or had ever been hospitalized for asthma, bronchospasm or wheezing; A child was considered to have *diagnosed allergies* if the child's parent answered "yes" to the question: "Has a doctor or other health practitioner ever said that (child's name) has allergies?"; a child was considered to have an *early respiratory illness* if the parent responded "yes" to the question: "Was he/she seen by a doctor or other health care practitioner for a severe chest illness BEFORE the age of two years?"; *A high risk birth* was defined as a premature birth, hospitalization in the neonatal intensive care unit (NICU), use of oxygen following birth (not including resuscitation at birth), or use of oxygen at home after leaving the hospital; *Cigarette smoker*=child whose parent reported that he/she had smoked cigarettes for 30 days or more; *Smoking during pregnancy*=child whose biological mother smoked while pregnant with child, including time pregnant but did not yet know she was; *Household exposure to tobacco smoke*="yes" to the question: "Does anyone living in (child's) home currently smoke cigarettes, cigars, or pipes on a daily basis INSIDE THE HOME?";

Parental education group was determined by categorical response to the question="What is the highest grade or year of school you have FINISHED?" (Then given a respondent card with the following categories: 8th grade or less, some high school, high school graduate or GED certificate, some technical school, technical school graduate, some college, college graduate, college/university graduate, some graduate school, masters degree, professional school degree (e.g., MD, DDS, DVM, JD, LLB, LLD), doctorate degree (e.g., PhD, EdD), other, specify; *Exposure to wood smoke*=child whose parent reported owning a wood stove or heating with wood; *Exposure to pesticides*=child whose parent reported the use of pesticides in the home or in the immediate vicinity of the home; *Exposure to animal antibiotics*=child whose parent reported using animal feed to which antibiotics had been added; *parental income* was determined from the question: "Was your total combined household income last year, that is GROSS INCOME, more or less than $20,000 before taxes?"

Outline of section headers:

Abstract

Epidemiological studies of farm children are of international interest because farm children have been found to be less often atopic, to have less allergic disease, and to often have less asthma than non-farm children, findings consistent with the hygiene hypothesis. We studied a cohort of rural Iowa children to determine the association between farm and other environmental risk factors with four asthma outcomes—*doctor-diagnosed asthma, doctor-diagnosed asthma/medication for wheeze, current wheeze, and cough with exercise.* Doctor-diagnosed asthma prevalence was 12%, but at least one of these four health outcomes was found in over a third of the cohort. Multivariable models of the four health outcomes found independent associations between male gender (three asthma outcomes), age (three asthma outcomes), a personal history of allergies (four asthma outcomes), family history of allergic disease (two asthma outcomes), premature birth (one asthma outcome), early respiratory infection (three asthma outcomes), high risk birth (two asthma outcomes) and farm exposure to raising swine given antibiotics with feed (two asthma outcomes). The high prevalence of rural childhood asthma and asthma symptoms underscores the need for asthma screening programs and improved asthma diagnosis and treatment. The high prevalence of asthma health outcomes among farm children living on farms that raise swine (44.1%, p=0.01) and raise swine and add antibiotics to feed (55.8%, p=0.013), despite lower rates of atopy and personal histories of allergy, suggest the need for awareness and prevention measures and more population-based studies to further assess environmental and genetic determinants of asthma among farm children.

Introduction

Most epidemiological studies of childhood asthma have been conducted among inner city or urban populations and have found asthma prevalence to vary by location, likely attributable to differing environmental exposures (ISAAC Steering Committee 1998). Studies of rural childhood asthma are of particular interest because they have consistently reported that farm children are less often atopic (Braun-Fahrlander et al. 1999; Downs et al. 2001; Riedler et al. 2000; Riedler et al. 2001), have lower rates of allergic diseases (Braun-Fahrlander et al. 1999; Kilpelainen et al. 2000; Riedler et al. 2000; Riedler et al. 2001; Von Ehrenstein et al. 2000; Wickens et al. 2002) and in several reports also have lower rates of asthma (Ernst and Cormier 2000; Kilpelainen et al. 2000; Riedler et al. 2000; Riedler et al. 2001; Von Ehrenstein et al. 2000). These findings are consistent with the hygiene hypothesis which posits that childhood allergy risk is immunologically modulated in early life by exposure to infectious agents. However, several studies have not found positive associations between asthma and asthma symptoms among children and farm exposures, raising questions regarding the influence of unmeasured risk factors and/or selection in these cross-sectional studies (Chrischilles et al. 2004; Downs et al. 2001; Salam et al. 2003; Wickens et al. 2002).

It is recognized that asthma risk is conveyed by a complex interaction of genetic and environmental determinants which makes the epidemiological investigation of farm-related asthma difficult (Douwes et al. 2001; Niven 2003; Schwartz 2001). International studies of childhood asthma among farm children have typically measured atopy to gauge genetic predisposition to asthma but have less consistently described and measured farm environment risk factors, often using endotoxin as an indicator of exposure to infectious agents early in life. While endotoxin is an ubiquitous exposure in agriculture, its concentration varies within and between farm types and it is but one of many agricultural respiratory exposures children may encounter (Douwes et al. 2003; Reynolds et al. 1996; Schenker et al. 1998).

Over the last three decades, the development of a vertically integrated livestock industry has significantly reduced the number of U.S. family farms raising hogs, poultry and cattle, but has rapidly increased the number of large, animal feeding operations (AFOs) (NAS 2003). While inflammatory airway diseases including asthma, chronic bronchitis, organic dust toxic syndrome and progressive airway obstruction are now well documented among AFO workers (Schenker et al. 1998), there has been much less research regarding exposures and health outcomes among AFO exposed children and community-based residents (Reynolds et al. 1997a; Salam et al. 2003; Thu et al. 1997; Wing and Wolf 2000).

The Keokuk County Rural Health Study (KCRHS) is a large, population-based study of a cohort of rural families living in an intensely agricultural region of southeastern Iowa (Merchant et al. 2002). The aim of the present study was to estimate asthma prevalence and assess whether farm exposures result in less atopy, less allergic disease and less asthma, while taking into account multiple personal and other environmental risk factors, among this cohort of farm children.

MATERIALS AND METHODS

The Study Population

This study reports data on children from birth through age 17 collected in Round 1 of the KCRHS which began in 1994 and ended in 1998. Keokuk County was chosen because it is intensely agricultural and entirely rural. A stratified, random sample that identified households from farm, town and rural non-farm locations was utilized. A total of 2496 eligible households were identified. Details regarding the sampling methodology and survey methods have been reported previously (Merchant et al. 2002). All members of enrolled households were invited to a centrally located research facility for interviews, and all adults and children age 8 and over were invited for medical examinations. One adult per household was interviewed by a trained interviewer about the health of all of the children (from birth but less than 18) living in the household.

Questionnaire

The childhood respiratory questionnaire chosen for this study was that used in University of Southern California studies of childhood asthma in Los Angeles (Peters et al. 1999). Four asthma outcomes were used to estimate asthma prevalence--*doctor diagnosed asthma*, *asthma/medication for wheeze* (doctor diagnosed asthma and/or medication for wheeze in the last 12 months), *current wheeze* and *cough with exercise.* These four asthma outcomes, *severe symptoms* consistent with asthma, *atopy*, an *early respiratory illness* and a *high risk birth* are fully defined in the electronic definition section of this paper. The parent's response to the questionnaire also provided information regarding parental farm exposures, maternal smoking during pregnancy, household exposure to tobacco smoke, parental education and household income.

Clinical Assessment

Children age 8 and older were invited to complete a medical examination that included skin prick testing (SPT), spirometry, methacholine challenge testing and height and weight measurements to calculate 95th percentile Body Mass Index (kg/m^2) (Must et al. 1991). A total of 18 aeroallergens common to the Midwest, a histamine positive and normal saline negative control, were used for skin prick tests. Common rural aeroallergens included: *tree pollen mix, grass pollen mix, ragweed pollen, weed pollen mix, cockroach mix, mold mix, insect mix, caddis fly/moth/mayfly mix, cat pelt, dog hair, mouse and rat mix and dust mite Df and Dp mix.* Farm aeroallergens included: *grain dust mix or grain smut mix, soybean dust or soybean whole grain, cattle hair, horse hair, chicken feathers and turkey feathers.* Children taking antihistamines and other medications known to affect skin test results, those with histories of past systemic reactions to allergy skin testing and any participant who might have been pregnant were excluded from skin testing. A wheal equal to or greater than 3 mm in diameter was defined as a positive reaction; subjects were considered *atopic by SPT* if they had a positive reaction to any two of the allergens tested. Spirometry was completed on a rolling-seal spirometer that conformed to ATS guidelines (ATS 1995). Contraindications to methacholine testing included participants with a baseline FEV1 of less than 70% of predicted or FEV1 less than 1.5 liters, pregnancy or suspected pregnancy, lactation, current use of a beta adrenergic blocking agent and a decline in FEV1 of 15% or more to the diluent. Methacholine was administered by dosimeter in five serial doses of 0.025 mg/ml, 0.25 mg/ml, 2.5 mg/ml, 10.0 mg/ml and 25.0 mg/ml, with three minutes between doses (Crapo et al. 2000). Bronchial hyper-responsiveness was defined as having a drop in FEV1 of 20% or more from the post-saline control, *the PC20*, following inhalation of less than or equal to 8 mg/ml of methacholine (Anto 1998; Crapo et al. 2000).

Serum Analysis

Sera were collected from subjects (N=217) at the time of skin prick testing and analyzed for total and specific IgE. Total IgE was measured by immunoassay using murine monoclonal anti-human IgE as the capture antibody (CLB, Sanguin Blood Supply Foundation, Amsterdam, The Netherlands), rabbit anti-human IgE as the second antibody (Dako, Corp., Carpinteria, CA) and peroxidase-conjugated donkey anti-rabbit IgG as the labeling antibody (RDI, Flanders, NJ) in a TMB substrate system (Pierce Endogen, Rockford, IL). Standard curves were generated using an IgE CAP system standards (Pharmacia Diagnostics, Uppsala, Sweden) with the standard curve from 0.02 to 10 kU/L. Sera were studied at initial dilutions of 1:20, 1:40, 1:80 and 1:160 with higher dilutions run for high IgE sera. Individuals were considered to be *atopic by IgE* if their total IgE was equal to or greater than 60 kU/L (Contreras et al. 2003).

Environmental Assessment

An industrial hygienist visited each household shortly after the clinic visit and completed a Home Environmental Questionnaire and Checklist, when applicable a Farm Environmental Questionnaire and Farm Environmental Checklist, and measurement of a limited number of environmental parameters. Details of these environmental assessments have been published previously (Reynolds et al. 1997b; Park et al. 2003). Assessments of specific environmental exposures were taken from these instruments, including several farm operation questions, livestock and antibiotics in animal feed questions, questions regarding gas stoves, heating with wood, exposure to pesticides, exposure to cats and dogs as pets and dehumidifier use.

Household type was determined at the time of the child's birth from the biological mother's reproductive history questionnaire and through follow-up phone interviews with the biological mother regarding residence type (farm, rural non-farm or home) at the time of birth. Children's various farm tasks, and the age each task was first performed, were determined from a questionnaire on childhood tasks from available KCRHS Round 2 data, and from follow-up phone administration of this questionnaire to Round 1 participants who had not participated in Round 2.

Statistical Analysis

Chi-squared tests and analysis of variance were used to evaluate any differences among demographic, personal and environmental risk factors for farm, rural-non farm and town households. Univariable logistic regression was used to identify variables that were significant ($p<0.1$) for *doctor diagnosed asthma*, *asthma/medication for wheeze, chronic wheeze and cough with exercise.* Multivariable logistic regression was then used to identify significant ($p<0.05$) variables in the final models.

Initial data analyses was performed with SAS, Version 8 (SAS Institute, Inc., Cary, NC) software. SUDAAN software (RTI, Chapel Hill, NC) was then used to adjust variance estimates for potential intra-household correlation resulting from the inclusion of more than one child per household.

The study was approved annually by The University of Iowa Institutional Review Board. A parent or legally authorized representative of each child participant provided written informed consent. Children 8-17 years of age gave their assent.

RESULTS

Cohort Description

Of the 2,496 Keokuk County households eligible for this study, 1675 households (67.1%) initially contacted by letter and telephone agreed to participate immediately or to be contacted at a later date. Enrollment stopped when the goal of 1000 households was reached. A total of 1,004 households (336 farm, 206 rural non-farm, 462 town households) enrolled and participated in Round 1 of the study.

The cohort, which consisted of 644 children (224 farm, 155 rural non-farm and 265 town), did not differ in age among household types, was somewhat over-represented by boys in farm and rural non-farm households and was 97.7% Caucasian. Of the 336 farms in the cohort, 109 had children. Complete data on all farming characteristics were available on 89 farms with children and on 172 farms without children. These farms produced primarily corn, soybeans and hogs, but very few other livestock. Farms with children were somewhat smaller (434 total acres in production) than farms without children (468 total acres in production), but were otherwise similar, except that farms with children on average raised more hogs (298 versus 141, p=0.03). Fifty percent of farm children were reported by a parent to perform tasks around hogs, compared to 16% or less for rural non-farm or town children, while 40% of farm children were reported to perform tasks around cows compared to 13% or less for rural non-farm or town children.

Health Outcomes

Ninety-five percent of the children's data was provided by the child's biological mother or female guardian. Complete data on asthma outcomes were available on 610 children. Concordance between the four asthma outcomes varied from strong to weak—*doctor diagnosed asthma* (*asthma/medication for wheeze*--Kappa 0.81, p<.0001*, current wheeze*—Kappa 0.31, p<.0001, *and cough with exercise*—Kappa 0.26, p<.0001); *asthma/medication for wheeze* (*current wheeze*—Kappa, 0.53, p<.0001, *cough with exercise*—Kappa, 0.39, P=0.11); *current wheeze* and *cough with exercise*—Kappa 0.27, p=0.73). Only 4.4% of participants were captured by all four asthma outcomes, while 33.6% of all 610 participants were captured by at least one asthma outcome. Children with *doctor diagnosed asthma* included only a third (8/24) of the children with *severe symptoms* consistent with asthma, while children with any one of the four asthma outcomes captured 23 of 24 children with *severe symptoms*. Of the 394 children ages 8-17, 351 (89.1%) had SPT, 347 (88.1%) had PFTs and 215 (61.2%) agreed to have blood drawn for sera. Agreement between total individual IgE and SPT results (aspergillus, cat hair, cockroach, weed mix, tree pollen, Der p and Der f) ranged from 72.8% to 89.1%.

Children who were *born on a farm* had a lower prevalence of atopy (IgE), a lower prevalence of diagnosed allergies and a higher FVC (likely attributable to hyperinflation) (Table 1). Children who *currently lived on a farm* were somewhat more likely to be boys and somewhat less likely to have diagnosed allergies (Table 1).

A very high proportion of children who lived on a farm at the time of study (*currently lives on a farm*) were born when their parents lived on a farm (*born on a farm*), and continued to live on a farm (in the first year of life, through age 5, or had a parent who continued to work on a farm were also analyzed but not reported). Because univariable associations were similar for all farm versus non-farm groups, only comparisons of *born on a farm* and *currently living on a farm* exposure results are presented (Table 2). Farm children were consistently exposed to less tobacco smoke, but were more often exposed to wood stoves, conditions resulting in dehumidifier use, cats as pets and application of pesticides outside the home. Farm children's parents were more often better educated and had a household annual income of $20,000 or more (Table 2).

Univariable associations between the four asthma outcomes and environmental risk factors are presented in Table 3. A weak association was observed between *doctor diagnosed asthma* and less parental education. A near significant association was observed between *doctor diagnosed asthma/medication for wheeze* and living on a farm raising swine and a significant association with living on a farm that adds antibiotics to feed; no significant association was observed with environmental exposures and *current wheeze*; but significant negative associations were observed between *cough with exercise* and exposure to wood smoke and applied pesticides outside home in the last year, and significant positive associations were observed with dogs as household pets and near significant positive associations were observed with living on a swine farm, and living on a farm that added antibiotics to feed. Tables 4 and 5 present univariable associations between the four asthma health outcomes and personal and clinical risk factors and health measures and revealed similar association patterns, but a few significant differences.

Multivariable models that included personal or environmental risk factors with univariable significance of p<0.1 for any of the four asthma outcomes are presented in Table 6. In addition to gender, age, history of allergies, family history of allergies, premature birth, early respiratory infection and high risk birth, an interaction term (living on a farm that raised swine and added antibiotics to feed) was independently associated with asthma/medication for wheeze, current wheeze (p=0.06) and cough with exercise. Of farms that raised swine, 24 of 43 (55.8%) added antibiotics to feed. Of livestock farms that add antibiotics to feed, 24 of 31 farms or 77.4% raise swine. Those farms that add antibiotics to feed were found to have larger mean numbers of livestock than those who did not add antibiotics to feed (750 vs. 392 animals; p=0.0002). Examination of children who lived on farms raising swine and adding antibiotics to feed found that 55.8% (p=0.013) reported at least one of the four asthma outcomes (Figure 1).

DISCUSSION

This study reports uniformly high prevalence of estimates of asthma and asthma-related symptoms that are consistent with asthma prevalence observed in studies of U.S. urban populations (Bauer et al. 1999; ISAAC Steering Committee 1998). These high asthma prevalence estimates, and our finding of a high proportion (2/3) of children with *severe symptoms* consistent with asthma, but without a doctor diagnosis of asthma, are consistent with the findings of our Rural Childhood Asthma Study (Chrischilles et al. 2004), and underscore the need for asthma screening programs, for improved rural health care provider asthma diagnostic and management skills, and for health policies that would improve access and insurance coverage for rural children.

A history of diagnosed allergies was found to be less common among children who lived on a farm in the first year of life, a finding consistent with many other studies of farm children (Braun-Fahrlander et al. 1999; Kilpelainen et al. 2000; Riedler et al. 2000; Riedler et al. 2001; Von Ehrenstein et al. 2000). The three estimates of atopy also tended to be lower among children who lived on a farm in the first year of life, as reported by others (Braun-Fahrlander et al. 1999; Riedler et al. 2000; Riedler et al. 2001). However, asthma and asthma-like symptom prevalences were found to be high and to not differ between children with farm exposures and those without farm exposures, unlike the findings of others (Ernst and Cormier 2000; Kilpelainen et al. 2000; Riedler et al. 2000; Riedler et al. 2001; Von Ehrenstein et al. 2000), despite these children having less allergic disease, less atopy and a significantly lower exposure to household tobacco smoke among farm children. However, as is depicted in Figure 1, these excesses are found only among children living on farms raising swine while a lower prevalence of asthma was observed among farm children not raising swine in comparison to non-farm children, which is consistent with the aforementioned studies.

Farms in Northern Europe tend to be smaller than Iowa farms, to have livestock that are often housed in immediate proximity to living quarters and these farm families have been described as more traditional in their way of life. Farms in Canada, Australia, and New Zealand are described as larger, but typically not as livestock-intensive as Iowa farms. Keokuk County farm families do not live in immediate proximity to livestock buildings, but do usually live on the same acreage with many farm family members typically participating in the farm operation. It is common for young children to be exposed to farming operations, including animal feeding operations, as they accompany a parent or sibling in assisting with farm tasks (Park et al. 2003). Farm children in Keokuk County were reported by their parents to be exposed to farm tasks around livestock as early as age one; however, such tasks around livestock were more typically done by male adolescents. While no environmental measurements of farm task exposures were made, several studies conducted in Iowa document high levels of occupational exposures to respirable and total dust, endotoxin, hydrogen sulfide and ammonia which have been associated with asthma, chronic bronchitis, cross-shift declines in lung function and progressive declines in lung function over time among those working in animal feeding operations (Reynolds et al. 1996; Schenker et al. 1998; Schwartz et al. 1995). It is, therefore, probable that swine farm exposed children had high exposures to endotoxin and other AFO exposures and that some of the asthma and asthma symptoms observed among these farm youth are attributable to occupational exposures.

Multivariable models for *doctor diagnosed asthma/medication for wheeze* and *cough with exercise* found that swine operations that add antibiotics to feed were independently associated with these health outcomes. As farms that add antibiotics to feed were much larger than those that did not add antibiotics to feed, it may be that adding antibiotics to feed may serve as an indicator of larger swine operations. However, it is plausible that antibiotic exposures may be playing some causal role as antibiotics have been documented to be components of emissions from AFOs (Hamscher et al. 2003; Svendsen et al. 2003), and when consumed for medical purposes have been associated with childhood asthma (Wickens et al. 1999). These high asthma estimates make clear that on-farm exposure to swine production is associated with asthma among children living on these farms and that swine production contributes to the higher prevalence of asthma outcomes in this livestock intensive rural community. More detailed assessment of the temporal relationships between childhood farm exposures, including measurements of endotoxin-laden dust, irritant gases and antibiotics in relation to asthma estimates, are needed to further our understanding of these relationships.

Other events early in life, apart from farm exposures, including premature birth, a respiratory infection under the age of three and high risk birth were found to be independently associated with asthma outcomes in this study, also consistent with other studies of childhood asthma (Farooqi and Hopkin 1998; von Mutius et al. 1993). These early life risk factors, which did not differ between farm and non-farm participants in this study, may confound assessment of farm exposures in populations where farm families are poorer and have less adequate prenatal health care.

Two studies of non-farm infants have evaluated the role of endotoxin exposures early in life and have reported no relationship between endotoxin levels and atopy, allergic disease and asthma (Bolte et al. 2003; Park et al. 2001), findings inconsistent with the hygiene hypothesis. Another contributing explanation, which has been recognized, but only indirectly assessed (Braun-Fahrlander et al. 1999; Downs et al. 2001; Ernst and Cormier 2000; Leynaert et al. 2001), is the potential unmeasured effect of systematic genetic selection of those susceptible to farm-related respiratory disease away from farming over successive generations. It is common for farm youth to leave the farm in Keokuk County, so much so that we have reported a significant deficit of asthma among adult farm men compared to other men in Keokuk County (Merchant et al. 2002).

As indicators of asthma associated with common farm exposures have been shown to be influenced by genotypic patterns (Arbour et al. 1999; Gilliland et al. 2004), epidemiological studies of genotype among farm family generations could help define patterns of differential selection of atopic, allergic, and asthmatic members of farm families away from farming.

Limitations of this study include the relatively small numbers of children with clinical data. Also, this study was not designed to address the question of whether exposures to dust, irritant gases and odors arising from AFOs may be associated with respiratory symptoms or health conditions among rural residents living in proximity to farms with AFOs. However, the few community-based studies of AFO exposures have reported higher rates of airway symptoms (Reynolds et al. 1997a; Thu et al. 1997; Wing and Wolf 2000), and significant peaks in asthma hospital visits have been observed following peak exposures to total reduced sulfur (for children) and to hydrogen sulfide (for adults) from a large animal waste treatment complex (Campagna et al. 2004). As the result of these findings and community complaints about odor, several states now regulate some combination of hydrogen sulfide, total reduced sulfur, ammonia and odor. Given our finding of a high prevalence of asthma outcomes among farm children living on swine farms, and especially those that add antibiotics to feed, it is clear that farm parents should be aware of this risk and take precautions to reduce childhood respiratory exposures from animal feeding operations. Evaluation of asthma outcomes and environmental exposures among school children and rural residents living proximate to AFOs remains an important research priority.

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Table 1. Farm exposures, personal and family risk factors, and asthma outcomes

Variable	Born on a Farm	Not Born on a Farm	Odds Ratio (95% CI)	p value	Currently Lives on a Farm	Does Not Currently Live on a Farm	Odds Ratio (95% CI)	p value
Male gender	56.2% (122/217)	52.0% (196/377)	1.19 (0.84-1.67)	0.3277	58.5% (131/224)	51.0% (214/420)	1.36 (0.98-1.88)	0.0654
Age (mean, yrs)	9.6 (±5.0) [n=217]	9.6 (±4.9) [n=377]	1.00 (0.96-1.04)	1.00	10.0 (±4.9) [n=224]	9.5(±4.9) [n=420]	1.02 (0.98-1.06)	0.36
Number of siblings under 18 yrs of age	1.6 (±1.2) [n=217]	1.4 (±1.0) [n=377]	1.15 (0.87-1.53)	0.33	1.5 (±1.2) [n=224]	1.5 (±1.0) [n=420]	1.04 (0.77-1.40)	0.79
Atopy (IgE)	29.3% (24/82)	42.0% (50/119)	0.57 (0.31-1.04)	0.0661	32.5% (27/83)	38.8% (52/134)	0.76 (0.43-1.36)	0.3477
Atopy (skin prick test)	13.6% (15/110)	18.7% (34/182)	0.69 (0.34-1.40)	0.2926	18.6% (21/113)	17.5% (36/206)	1.08 (0.57-2.06)	0.8196
Atopy (by questionnaire)	21.2% (46/217)	22.8% (86/377)	0.91 (0.53-1.57)	0.7333	24.1% (54/224)	22.9% (96/420)	1.07 (0.61-1.90)	0.8122
Diagnosed allergies	10.8% (23/212)	17.7% (64/362)	0.57 (0.32-0.99)	0.0324	11.0% (24/218)	16.9% (66/402)	0.61 (0.35-1.06)	0.0612
Overweight (BMI/95th)	8.1% (10/123)	5.5% (11/201)	1.53 (0.63-3.71)	0.3661	4.8% (6/124)	8.3% (19/228)	0.56 (0.22-1.43)	0.1836
Low birth weight (<2500 g)	3.8% (8/211)	5.0% (18/357)	0.74 (0.31-1.78)	0.4804	2.8% (6/214)	5.3% (21/399)	0.52 (0.19-1.40)	0.1793
Premature birth	10.4% (22/212)	12.2% (44/362)	0.84 (0.44-1.57)	0.5749	8.7% (19/218)	11.9% (48/402)	0.70 (0.34-1.44)	0.3216
Early respiratory infection	13.7% (29/212)	9.9% (36/362)	1.44 (0.80-2.57)	0.2446	12.8% (28/218)	10.7% (43/402)	1.23 (0.68-2.23)	0.5049
NICU admission	9.0% (19/212)	12.2% (44/362)	0.71 (0.38-1.33)	0.2660	11.5% (25/218)	11.7% (47/402)	0.98 (0.54-1.76)	0.9418
High risk birth[a]	17.0% (36/212)	22.4% (81/362)	0.71 (0.44-1.15)	0.1545	19.3% (42/218)	20.9% (84/402)	0.90 (0.56-1.45)	0.6730
Dr. diagnosed asthma	13.2% (28/212)	10.5% (38/362)	1.30 (0.69-2.43)	0.4234	11.9% (26/218)	11.7% (47/402)	1.02 (0.55-1.91)	0.9433
Asthma/meds for wheezing	17.0% (36/212)	15.2% (55/362)	1.14 (0.67-1.95)	0.6301	17.9% (39/218)	15.7% (63/402)	1.17 (0.71-1.95)	0.5427
Current wheeze	19.3% (41/212)	18.2% (66/362)	1.08 (0.65-1.77)	0.7769	19.3% (42/218)	20.2% (81/402)	0.95 (0.58-1.53)	0.8194
Cough with exercise	18.4% (39/212)	19.3% (70/362)	0.94 (0.58-1.53)	0.8022	19.7% (43/218)	18.9% (76/402)	1.05 (0.65-1.72)	0.8331
FVC[b]	3.38 (1.20)	3.34 (1.11)	1.96 (1.07-3.58)	0.03	3.47 (1.18)	3.25 (1.09)	1.64 (0.90-3.01)	0.11
FEV1[b]	2.88 (0.96)	2.88 (0.97)	1.30 (0.67-2.52)	0.44	2.98 (0.95)	2.78 (0.94)	1.54 (0.77-3.08)	0.22
FEV1/FVC[b]	86.20 (7.09)	86.48 (7.11)	0.97 (0.93-1.02)	0.26	86.47 (6.99)	86.88 (6.24)	1.02 (0.97-1.06)	0.52
FEF 25-75[b]	3.20 (1.12)	3.23 (1.12)	0.91 (0.64-1.29)	0.60	3.32 (1.10)	3.07 (1.20)	1.19 (0.84-1.68)	0.33
Positive methacholine challenge	49.2% (64/130)	52.0% (120/231)	0.90 (0.57-1.40)	0.6308	49.6% (69/139)	53.9% (137/254)	0.84 (0.54-1.31)	0.4445

[a]High risk birth is defined as premature birth, hospitalization in an NICU, use of oxygen following birth (not including resuscitation at birth), or use of oxygen at home after leaving the hospital.
[b]Adjusted for age, height and gender

Table 2. Farm exposures and environmental risk factors

Variable	Born on a Farm	Not Born on a Farm	Odds Ratio (95% CI)	p value	Currently Lives on a Farm	Does Not Currently Live on a Farm	Odds Ratio (95% CI)	p value
Born on a farm	--	--	--	--	80.3% (171/213)	12.1% (46/381)	29.65 (16.63-52.86)	<0.0001
Lived on farm for at least 3 mo under 1 yr of age	98.1% (212/216)	4.0% (15/375)	1272 (342.50-4724.07)	<0.0001	82.1% (174/212)	14.0% (53/379)	28.16 (15.90-49.88)	<0.0001
Lived on farm for at least 3 mo under 5 yrs of age	99.1 (214/216)	11.2% (42/375)	848.36 (203.16-3542.64)	<0.0001	87.7% (186/212)	18.5% (70/379)	31.58 (16.95-58.84)	<0.0001
Farm residence	78.8% (171/217)	11.1% (42/377)	29.65 (16.63-52.86)	<0.0001	--	--	--	--
Parent does farm work	79.3% (172/217)	27.8% (105/377)	9.90 (5.80-16.90)	<0.0001	95.1% (213/224)	20.2% (85/420)	76.32 (27.42-212.41)	<0.0001
Maternal smoking during pregnancy	21.2% (45/212)	29.0% (105/362)	0.66 (0.36-1.20)	0.1467	18.4% (40/218)	31.6% (127/402)	0.49 (0.25-0.93)	0.0161
Current household exposure to tobacco smoke	13.5% (28/208)	26.1% (94/360)	0.44 (0.23-0.83)	0.0057	10.8% (23/214)	30.8% (123/400)	0.27 (0.13-0.54)	0.0001
Ever household exposure to tobacco smoke	20.7% (43/208)	42.3% (153/362)	0.36 (0.21-0.62)	0.0001	13.1% (28/214)	47.5% (191/402)	0.17 (0.09-0.32)	<0.0001
Gas stove in home for cooking	48.7% (95/195)	46.4% (161/347)	1.10 (0.66-1.84)	0.7232	46.8% (95/203)	46.6% (176/378)	1.01 (0.58-1.75)	0.9730
Burn wood for fuel	31.3% (61/195)	20.8% (72/347)	1.74 (0.97-3.11)	0.0728	32.0% (65/203)	20.9% (79/378)	1.78 (0.97-3.28)	0.0680
Current dehumidifier use in home	54.4% (106/195)	30.8% (107/347)	2.67 (1.59-4.49)	0.0003	55.2% (112/203)	29.6% (112/378)	2.92 (1.66-5.15)	0.0002
Parent education (highest years of school)	14.2 (±2.1) [n=215]	13.5 (±2.0) [n=377]	1.17 (1.04-1.32)	0.01	14.3 (±2.0) [n=222]	13.5 (±1.9) [n=412]	1.22 (1.07-1.39)	<0.01
Household income (<$20,000)	2.4% (5/204)	10.6% (38/360)	0.21 (0.04-1.16)	0.0068	2.8% (6/211)	11.3% (45/399)	0.23 (0.05-1.03)	0.0084
Household pets – cats	66.7% (130/195)	49.0% (170/347)	2.08 (1.25-3.48)	0.0045	66.5% (135/203)	49.2% (186/378)	2.05 (1.19-3.54)	0.0092
Household pets – dogs	69.2% (135/195)	64.8% (225/347)	1.22 (0.69-2.16)	0.4869	70.9% (144/203)	65.3% (247/378)	1.29 (0.71-2.37)	0.3898
Applied pesticides in home during past yr	57.4% (112/195)	58.2% (202/347)	0.97 (0.58-1.62)	0.9035	58.6% (119/203)	58.7% (222/378)	1.00 (0.57-1.74)	0.9873
Applied pesticides outside home during past yr	49.7% (97/195)	33.4% (116/347)	1.97 (1.17-3.33)	0.0130	49.8% (101/203)	33.6% (127/378)	1.96 (1.12-23.43)	0.0220
Raise Swine	40.4% (76/188)	3.8% (14/366)	17.06 (7.55-38.58)	<0.0001	52.5% (96/183)	0.0% (0/420)	--	<0.0001
Raise livestock	68.6% (129/188)	7.4% (27/366)	27.45 (14.66-51.40)	<0.0001	89.6% (164/183)	0.0% (0/420)	--	<0.0001
Add antibiotics in feed	27.1% (51/188)	3.6% (13/366)	10.11 (4.24-24.08)	<0.0001	37.7% (69/183)	0.0% (0/420)	--	<0.0001

Table 3. Asthma outcomes and environmental risk factors

Variable	Dr. Diagnosed Asthma (n=72)	Non-asthmatic (n=538)	Odds Ratio (95% CI)	p value	Asthma/Medications for Wheeze (n=101)	Non-Asthmatic (n=509)	Odds Ratio (95% CI)	p value
Parent education (highest years of school)	13.2 (±1.9) [n=71]	13.9 (±2.0) [n=533]	0.90 (0.80-1.02)	0.08	13.5 (±1.9) [n=99]	13.9 (±2.0) [n=505]	0.86 (0.73-1.02)	0.10
Raise swine	23.6% (17/72)	15.0% (76/507)	1.75 (0.85-3.63)	0.1861	24.0% (24/100)	14.4% (69/479)	1.88 (1.02-3.45)	0.0762
Add antibiotics in feed	15.3% (11/72)	10.8% (55/507)	1.48 (0.68-3.24)	0.3707	19.0% (19/100)	9.8% (47/479)	2.16 (1.15-4.04)	0.0407

No significant association (p<0.1) was observed for any asthma outcome for the following variables: farm residence, born on a farm, lived on a farm for at least 3 mo under 1 yr of age, lived on farm for at least 3 mo under 5 yrs of age, parent does farm work, maternal smoking during pregnancy, current household exposure to tobacco smoke, ever household exposure to tobacco smoke, gas stove in home for cooking, burn wood for fuel, current dehumidifier use in home, household income (<$20,000), household pets – cats, household pets – dogs, applied pesticides in home during past yr, applied pesticides outside home during past yr, raise livestock

Variable	Current Wheeze (n=120)	No (n=490)	Odds Ratio (95% CI)	p value	Cough with Exercise (n=117)	No (n=493)	Odds Ratio (95% CI)	p value
Burn wood for fuel	21.6% (24/111)	25.8% (117/454)	0.79 (0.46-1.37)	0.3896	16.8% (18/107)	26.9% (123/458)	0.55 (0.31-0.97)	0.0255
Household pets – dogs	67.6% (75/111)	67.6% (307/454)	1.00 (0.62-1.62)	0.9921	76.6% (82/107)	65.5% (300/458)	1.73 (1.01-2.94)	0.0350
Applied pesticides outside home during past yr	33.3% (37/111)	41.8% (190/454)	0.69 (0.43-1.11)	0.1255	29.9% (32/107)	42.6% (195/458)	0.58 (0.35-0.96)	0.0282
Raise swine	20.3% (24/118)	15.0% (69/461)	1.45 (0.79-2.65)	0.2636	22.8% (26/114)	14.4% (67/465)	1.76 (0.97-3.19)	0.0970
Add antibiotics in feed	14.4% (17/118)	10.6% (49/461)	1.42 (0.74-2.71)	0.3328	17.5% (20/114)	9.9% (46/465)	1.94 (1.00-3.77)	0.0917

No significant association (p<0.1) was observed for any asthma outcome for the following variables: farm residence, born on a farm, lived on farm for at least 3 mo under 1 yr of age, lived on farm for at least 3 mo under 5 yrs of age, parent does farm work, maternal smoking during pregnancy, current household exposure to tobacco smoke, ever household exposure to tobacco smoke, gas stove in home for cooking, current dehumidifier use in home, parent education (highest years of school), household income (<$20,000), household pets – cats, applied pesticides in home during past yr, raise livestock

Table 4. Doctor diagnosed asthma and asthma/medication for wheeze, family and personal risk factors, respiratory symptoms and function

Variable	Dr. Diagnosed Asthmatic (n=73)	Non-Asthmatic (n=538)	Odds Ratio (95% CI)	p value	Asthma/Medication for Wheeze (n=101)	Non-Asthmatic (n=509)	Odds Ratio (95% CI)	p value
Male Gender	72.6% (53/73)	51.6% (282/547)	2.49 (1.31-4.72)	0.0021	71.6% (73/102)	50.6% (262/518)	2.46 (1.46-4.13)	0.0003
Age (mean, years)	11.0 (±4.4)	9.3 (±4.9)	1.1 (1.03-1.13)	<0.01	9.5 (±4.8)	9.5 (±4.9)	1.0 (0.96-1.04)	0.96
Number of siblings under 18 yrs of age	1.5 (±1.0)	1.5 (±1.1)	0.97 (0.75-1.26)	0.81	1.4 (±1.0)	1.5 (±1.1)	0.93 (0.74-1.16)	0.52
Atopy (IgE)	56.7% (17/30)	32.6% (58/178)	2.71 (1.22-6.00)	0.0235	54.3% (19/35)	32.4% (56/173)	2.86 (1.35-6.05)	0.0208
Atopy (SPT)	30.8% (12/39)	16.2% (43/266)	2.30 (1.03-5.18)	0.0824	34.1% (15/44)	15.3% (40/261)	1.61 (0.83-3.15)	0.1671
SPT mean positives	1.46	0.98		0.0493	1.45	0.67		0.0286
Atopy (by questionnaire)	43.8% (32/73)	21.6% (118/547)	2.84 (1.43-5.62)	0.0172	41.2% (42/102)	20.8% (108/518)	2.66 (1.49-4.74)	0.0063
Diagnosed allergies	39.7% (29/73)	11.5% (63/547)	5.06 (2.92-8.77)	<0.0001	39.2% (40/102)	10.0% (52/518)	5.78 (3.46-9.66)	<0.0001
Overweight (BMI[a]>95th)	9.6% (5/52)	6.7% (19/285)	1.49 (0.54-4.14)	0.4927	8.8% (5/57)	6.8% (19/280)	1.32 (0.48-3.66)	0.6183
Low birth weight (<2500 g)	6.8% (5/73)	4.1% (22/540)	1.73 (0.60-5.02)	0.3798	4.9% (5/102)	4.3% (22/511)	1.15 (0.40-3.31)	0.8066
Premature birth	20.6% (15/73)	9.5% (52/547)	2.46 (1.21-5.00)	0.0513	21.6% (22/102)	8.7% (45/518)	2.89 (1.60-5.23)	0.0066
NICU[b] admission	19.2% (14/73)	10.6% (58/547)	2.00 (0.98-4.10)	0.1128	18.6% (19/102)	10.2% (53/518)	2.01 (1.07-3.78)	0.0603
High risk birth[c]	34.2% (25/73)	18.5% (101/547)	2.30 (1.33-3.97)	0.0145	35.3% (36/102)	17.4% (90/518)	2.59 (1.61-4.19)	0.0011
Early respiratory infection	21.9% (16/73)	10.0% (55/547)	2.51 (1.23-5.14)	0.0463	21.6% (22/102)	9.5% (49/518)	2.63 (1.42-4.88)	0.0124
FVC[d]	3.45 (1.18)	3.32 (1.13)	0.69 (0.27-1.77)	0.44	3.42 (1.17)	3.31 (1.13)	0.63 (0.25-1.58)	0.32
FEV1[d]	2.87 (1.00)	2.84 (0.94)	0.43 (0.15-1.27)	0.13	2.84 (0.97)	2.85 (0.95)	0.37 (0.13-1.06)	0.07
FEV1/FVC[d]	83.55 (7.29)	86.40 (6.38)	0.95 (0.90-1.01)	0.08	83.40 (7.57)	86.48 (6.27)	0.95 (0.90-1.00)	0.07
FEF 25-75[d]	2.99 (1.21)	3.18 (1.15)	0.66 (0.39-1.10)	0.11	2.93 (1.18)	3.19 (1.16)	0.62 (0.37-1.02)	0.06
Positive methacholine challenge	63.6% (35/55)	51.4% (164/319)	1.65 (0.91-3.02)	0.0960	65.6% (40/61)	50.8% (159/313)	1.84 (1.03-3.30)	0.0343

[a]BMI=body mass index
[b]NICU=neonatal intensive care unit
[c]High risk birth is defined as premature birth, hospitalization in an NICU, use of oxygen following birth (not including resuscitation at birth), or use of oxygen at home after leaving the hospital
[d]Adjusted for age, height and gender

Table 5. Current wheeze and chronic cough, family and personal risk factors, respiratory symptoms and function

Variable	Current Wheeze (n=120)	No (n=490)	Odds Ratio (95% CI)	p value	Cough with Exercise (n=117)	No Cough (n=493)	Odds Ratio (95% CI)	p value
Male gender	56.9% (70/123)	53.3% (265/497)	1.16 (0.77-1.74)	0.4839	66.4% (79/119)	51.1% (256/501)	1.89 (1.22-2.93)	0.0046
Age (mean, years)	8.0 (±4.9)	9.9 (±4.8)	0.93 (0.89-0.97)	<0.01	10.7 (±4.5)	9.2 (±5.0)	1.06 (1.02-1.11)	<0.01
Number of siblings Under 18 yrs of age	1.4 (±1.0)	1.5 (±1.1)	0.89 (0.72-1.11)	0.30	1.4 (±0.9)	1.6 (±1.1)	0.85 (0.69-1.05)	0.13
Atopy (IgE)	45.4% (15/33)	34.3% (60/177)	1.60 (0.80-3.19)	0.2030	35.3% (18/51)	36.3% (57/157)	0.96 (0.48-1.91)	0.9000
Atopy (SPT)	45.4% (20/44)	13.4% (35/261)	5.38 (2.68-10.79)	0.0004	29.7% (19/64)	14.9% (36/241)	2.40 (1.29-4.49)	0.0145
SPT mean positives	1.95	0.58		0.0005	1.38	0.62		0.0097
Atopy (by questionnaire)	26.0% (32/123)	23.7% (118/497)	1.13 (0.66-1.95)	0.6676	26.0% (31/119)	23.8% (119/501)	1.13 (0.66-1.94)	0.6593
Diagnosed allergies	30.9% (38/123)	10.9% (54/497)	3.67 (2.25-5.97)	<0.0001	30.2% (36/119)	11.2% (56/501)	3.45 (2.16-5.49)	<0.0001
Overweight (BMI[a]>95[th])	13.0% (7/54)	6.0% (17/283)	2.33 (0.92-5.92)	0.1509	12.0% (9/75)	5.7% (15/262)	2.25 (0.96-5.25)	0.1143
Low birth weight (<2500 g)	6.5% (8/123)	3.9% (19/490)	1.72 (0.75-3.95)	0.2752	6.0% (7/117)	4.0% (20/496)	1.51 (0.60-3.85)	0.4182
Premature birth	17.1% (21/123)	9.3% (46/497)	2.02 (1.14-3.59)	0.0399	18.5% (22/119)	8.9% (45/501)	2.30 (1.23-4.31)	0.0243
NICU[b] admission	15.4% (19/123)	10.7% (53/497)	1.53 (0.85-2.76)	0.1892	18.5% (22/119)	9.9% (50/501)	2.05 (1.14-3.67)	0.0395
High risk birth[c]	27.6% (34/123)	18.5% (92/497)	1.68 (1.05-2.68)	0.0413	31.9% (38/119)	17.6% (88/501)	2.20 (1.38-3.51)	0.0033
Early respiratory infection	17.9% (22/123)	9.9% (49/497)	1.99 (1.10-3.60)	0.0487	18.5% (22/119)	9.8% (49/501)	2.09 (1.20-3.64)	0.0232
FVC[d]	3.35 (1.10)	3.33 (1.14)	0.94 (0.41-2.15)	0.88	3.47 (1.08)	3.29 (1.15)	0.90 (0.46-1.73)	0.74
FEV1[d]	2.81 (0.89)	2.85 (0.96)	0.60 (0.27-1.33)	0.21	2.90 (0.89)	2.83 (0.97)	0.57 (0.29-1.14)	0.11
FEV1/FVC[d]	84.27 (6.87)	86.26 (6.52)	0.95 (0.91-1.00)	0.06	83.94 (7.02)	86.51 (6.38)	0.95 (0.91-0.99)	0.01
FEF 25-75[d]	2.98 (1.13)	3.18 (1.17)	0.69 (0.47-1.02)	0.06	3.05 (1.16)	3.17 (1.17)	0.69 (0.49-0.99)	0.04
Positive methacholine challenge	60.7% (34/56)	51.9% (165/318)	1.43 (0.81-2.54)	0.2160	61.0% (50/82)	51.0% (149/292)	1.50 (0.89-2.52)	0.1214

[a]BMI=body mass index
[b]NICU=neonatal intensive care unit
[c]High risk birth is defined as premature birth, hospitalization in an NICU, use of oxygen following birth (not including resuscitation at birth), or use of oxygen at home after leaving the hospital
[d]Adjusted for age, height and gender

Table 6. Multivariable models for asthma outcomes

Parameter	Doctor Diagnosed Asthma		Asthma/Medication for Wheeze		Current Wheeze		Cough with Exercise	
	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Male gender	2.62 (1.38-4.95)	<0.01	2.41 (1.38-4.22)	<0.01	--	--	1.75 (1.07-2.86)	0.03
Child's age	1.09 (1.03-1.15)	0.01	--	--	0.93 (0.88-.097)	<0.01	1.07 (1.02-1.13)	0.01
Ever been diagnosed with allergies	4.60 (2.56-8.25)	<0.01	5.48 (3.10-9.70)	<0.01	3.88 (2.26-6.66)	<0.01	3.34 (1.97-5.67)	<0.01
Atopy (by questionnaire)	2.58 (1.22-5.45)	0.01	2.40 (1.24-4.65)	0.01	--	--	--	--
Premature Birth	2.43 (1.16-5.12)	0.02	--	--	--	--	--	--
Early respiratory infection	--	--	1.92 (0.87-4.23)	0.10	1.84 (0.92-3.70)	0.09	1.91 (1.01-3.62)	0.05
High risk birth	--	--	2.08 (1.23-3.52)	0.01	--	--	2.13 (1.30-3.48)	<0.01
Add antibiotics to feed and raise swine	--	--	2.47 (1.29-4.74)	0.01	1.91 (0.98-3.73)	0.06	2.72 (1.34-5.52)	0.01
Have dogs as pets	--	--	--	--	--	--	1.73 (0.98-3.06)	0.06

-- Risk factors not selected in the stepwise logistic regression

Figure 1.
Prevalence of One or More Asthma Outcomes
Rural Iowa Children