

Determinants of Longitudinal Changes in Spirometric Function Among Swine Confinement Operators and Farmers

DAVID A. SCHWARTZ, KELLY J. DONHAM, STEPHEN A. OLENCHOCK, WILLIAM J. POPENDORF, D. SCOTT VAN FOSSEN, LEON F. BURMEISTER, and JAMES A. MERCHANT

Divisions of Occupational and Environmental Health and Biostatistics, Department of Preventive Medicine, and the Pulmonary Disease Division, Department of Internal Medicine, U.S. Department of Veterans Administration Medical Center and the University of Iowa, Iowa City, Iowa

To assess whether working in a swine confinement facility causes an excess or accelerated decline in lung function, we conducted a population-based study to evaluate the determinants of longitudinal changes in airflow in a population of swine confinement operators. Spirometric measures of lung function were compared between swine confinement operators ($N = 168$) and neighborhood farmer control subjects ($N = 127$). Study subjects were randomly selected from a cohort of swine confinement operators in eastern Iowa. The control farming population was matched by geographic location, age, and sex to the swine confinement operators. On average, the follow-up time was approximately 2 yr, with a range of follow-up between 56 and 1,900 d. Although swine confinement operators and neighborhood farmers had similar demographic characteristics (age, gender, racial background, smoking history, and atopy status), swine confinement operators tended to have less farming experience and were more extensively followed (more measures of lung function and longer periods of observation) than the neighborhood farmer control group. Swine confinement operators were also exposed to higher environmental dust concentrations and other irritants than the farmer control subjects. Interestingly, the cross-sectional data indicated that swine confinement operators tended to have slightly lower measures of airflow and greater workshift declines in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and mid-expiratory flow (FEF_{25-75}) than the neighborhood farmer control group. After controlling for age, height, gender, cigarette smoking, and follow-up time, longitudinal declines in spirometric measures of lung function were independently related to cross-shift declines in spirometric measures of lung function (FEV_1 , FVC, AND FEF_{25-75}), higher concentrations of endotoxin present in the bioaerosol (FEV_1 and FEF_{25-75}), and working in the swine confinement setting (FEV_1 and FEF_{25-75}). Interestingly, cross-shift changes in lung function and higher concentrations of endotoxin in the bioaerosol interacted positively with follow-up time, indicating that these work-related responses and exposures accelerated the decline in FEV_1 and FEF_{25-75} during the period of observation. Our results indicate that cross-shift decrements in lung function and higher concentrations of endotoxin are important determinants of accelerated decrements in airflow among agricultural workers. Although work in the swine confinement setting was associated with lower measures of FEV_1 and FEF_{25-75} that persisted throughout the period of observation, work in these confinement facilities does not appear specifically to accelerate the progressive loss of lung function among agricultural workers. **Schwartz DA, Donham KJ, Olenchok SA, Popendorf WJ, Van Fossen DS, Burmeister LF, Merchant JA. Determinants of longitudinal changes in spirometric function among swine confinement operators and farmers. Am J Respir Crit Care Med 1995;151:47-53.**

(Received in original form June 3, 1993 and in revised form June 2, 1994)

The National Institute of Occupational Safety and Health Division of Respiratory Disease Studies at Morgantown, West Virginia also contributed to this investigation.

Supported in part by Education and Development Grant No. HL33128 from the National Heart, Lung, and Blood Institute, Grant No. OH00093-01 from the National Institute of Occupational Safety and Health, Centers for Disease Control, the National Institute of Environmental Health Sciences (ES 06537), and the Department of Veterans Affairs (Merit Review).

Correspondence and requests for reprints should be addressed to David A. Schwartz, M.D., M.P.H., Pulmonary Disease Division, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA 52242.

Dr. Schwartz is a recipient of Clinical Investigator Award No. ES00203 from the National Institute of Environmental Health Sciences.

Am J Respir Crit Care Med Vol 151, pp 47-53, 1995

Although not widely appreciated, the agricultural worker and possibly those living in rural environments appear to be at high risk of developing either asthma or bronchitis (1-5). Moreover, the risk associated with the development of airway disease appears to be more than threefold greater among those who are more heavily exposed to dusts generated in the agricultural environment (3). Interestingly, cigarette smoking does not appear to account for this excess risk, because farmers have relatively low rates of cigarette smoking (6). These epidemiologic observations are supported by an increasing number of exposure-specific studies in agricultural workers. In fact, airway disease is common among those exposed to cotton, flax, hemp, grain dust, and other organic dusts (7, 8).

The agricultural worker and those living in a rural environment

encounter a variety of airborne organic dusts, including molds and pollens in the air; dusts generated in silos and barns; and exposure to animal danders, grain dust, feed additives, and storage mites. Although "agricultural dusts" generally contain a large fraction (approximately 30 to 40%) of particles in the respirable range (9, 10), these dusts may differ in terms of individual constituents. For instance, dusts generated in the production of animals differ from dusts generated in the production and marketing of grain products. In fact, within the animal confinement setting, workers may be exposed to grain dust, gases (ammonia, hydrogen sulfide, and carbon dioxide) generated from the manure pit, microorganisms contaminating the manure, aerosolized fecal material, and animal proteins (11–14). In all cases, however, these organic dusts are characterized by a complex mixture of vegetable particles and fragments, microorganisms and their products, insects and insect fragments, feed additives, including fish meal and antibiotics, avian and rodent proteins, pesticides, and absorbed gases (9, 15). Importantly, endotoxin from gram-negative organisms has been measured in similar concentrations from several of these agricultural dusts (16–19).

Swine confinement operators appear to be at increased risk for developing asthma and bronchitis (20–25). Our previous results indicate that symptomatic swine confinement operators have airway disease that is manifested by air trapping, an enhanced airway response to methacholine, and remodeling of the airway architecture (25). Interestingly, specific exposures in the swine confinement setting (26), such as hydrogen sulfide and endotoxin, are related to acute workshift declines in airflow and may be responsible for the development of chronic airway disease. The etiology of airway disease in swine confinement workers remains unclear, however, and the long-term pulmonary consequences of work in the swine confinement setting have not been evaluated.

To assess whether working in a swine confinement facility causes an excess or accelerated decline in lung function, we conducted a population-based study to evaluate the determinants of longitudinal changes in airflow in a population of swine operators. We were also interested in determining whether specific elements of the agricultural aerosol or cross-shift changes in airflow were related to longitudinal decrements in lung function.

METHODS

Study Population

The population-based, longitudinal cohort was established in 1984 and followed through 1989. A sample consisting of 3,301 producers, each with at least 400 swine, were identified in eastern Iowa. These farms were stratified by number of swine produced and by county, and then 2,019 were randomly selected (all strata were represented equally) for further study. This selection process allowed us to identify a representative sample of total swine-producing farms with 95% confidence. Each of the 2,019 producers was sent a mailed questionnaire asking about certain production factors in their operations, including production capacity, duration of exposure, and subjective assessment of dustiness. Contact by either mail or phone resulted in 932 responses (46%). Of this group, 465 (50%) reported that confinement structures were used in their operations. This group was then stratified according to the estimated environmental exposures into high, moderate, and low exposure categories. Worker exposure estimates were based on an algorithm that included size of operation, number of hours worked in confinement buildings, subjective assessment of dustiness, and certain structural features of each building. In total, 207 swine confinement workers were randomly selected from the initial cohort of 465, and all 207 swine confinement workers underwent the initial survey. After the 207 swine confinement operators were selected, 158 neighborhood farmers were matched by geographic locale to the group of swine confinement operators. For neighborhood farmers, no regular work in swine confinement buildings was permitted to have

occurred for 5 yr before the onset of the study. Of those initially surveyed, 168, or 81%, of the swine confinement operators and 127, or 80%, of the neighborhood farmers had follow-up examinations and are included in this report. As illustrated in Table 1, these two groups of agricultural workers were reasonably similar in terms of age, gender, smoking history, and atopy status. However, swine confinement operators tended to have more extensive follow-up (more measures of lung function and longer periods of observation) than the neighborhood farmer control subjects. In addition, swine confinement operators participated in an educational program designed to improve knowledge regarding the prevention of respiratory illnesses (27). All phases of this study were approved by the Human Subjects Committee at the University of Iowa.

Field Visits

The field visits included the health and environmental evaluations and were planned to occur during the first, third, and fifth years of this project. For study subjects who had only two measures of lung function, in 87% of the swine confinement workers and 33% of the neighborhood farmers these measures of lung function were separated by 4 to 5 yr (Table 1). A mobile survey vehicle was used to perform these evaluations at the operating farm site of each study subject. The team staffing the mobile unit was comprised of a trained respiratory technician and an industrial hygiene technician. Only one respiratory technician was involved in this longitudinal study. The field team was equipped with medical and exposure questionnaires, a spirometer, skin-testing supplies, and environmental sampling equipment. The field visits were distributed throughout the year, and during each season, similar numbers of workers within each of the exposure categories (swine confinement operators and neighborhood farmers) were evaluated.

Health Evaluation

The health evaluation was performed by a respiratory technician who was trained to interview, perform pulmonary function tests, and apply skin tests. This evaluation consisted of completing a modified American Thoracic Society (ATS) questionnaire (28), spirometry testing before and after 4 h of regular work, and standard skin tests to assess atopy status. An ATS questionnaire (28) was used to assess the presence of chronic respiratory symptoms and atopic status. Additional questionnaires were used to assess acute symptoms, collect demographic data, and characterize the cigarette smoking history. Spirometric evaluations were conducted using a Spirotech 5520 spirometer (Spirotech, Atlanta, GA), which was statically and dynamically calibrated on a daily basis while in use. This spirometer meets ATS specifications, and all spirometric measures were performed in accordance with ATS guidelines (29). Nose clips were used on all study subjects, and tests were conducted in a sitting position in a temperature-controlled environment. The Spirotech software system permits spirometry data to be automatically stored in a computer file, which is available for data analysis and hard copy retrieval. Spirometry measures were made before a workshift and after completing 2 to 4 h or normal work in the confinement building or on the farm. All subjects were asked to refrain from the use of dust masks or respirators during the work period. Study subjects were asked not to smoke cigarettes for 1 h before spirometry testing or during the work period. The predicted normal values used were those of Morris and colleagues (30) for spirometry.

All subjects were skin tested by the respiratory technician using a standard battery of 10 aeroallergens and 10 additional allergens common in eastern Iowa (Centers Labs, Port Washington, NY). Skin tests were applied intradermally (positive = wheal 5 mm greater than diluent) at extract concentrations of 100 PNU/ml for pollens and danders, 1,000 PNU/ml for molds, and 10,000 PNU/ml for house dust. Histamine (2.5 mg/ml) was used as a positive control. Skin tests were read at 10 min and the diameter of the wheal was recorded. Study subjects were considered atopic if at least 1 of the 20 aeroallergen skin tests was positive.

Environmental Evaluation

The purpose of these environmental evaluations was to measure ambient conditions suspected of inducing acute and chronic pulmonary responses

following the workshift. The environmental evaluation consisted of an exposure questionnaire and personal sampling for aerosols and endotoxin.

The exposure questionnaire was administered by the industrial hygiene technician on the morning of the testing session. This questionnaire focused on current and remote exposures that occurred as a result of either work or home activities. This questionnaire also queried other known, nonagricultural exposures associated with the development of airflow obstruction.

The decision to use aerosol monitors was weighted heavily toward the technical considerations and to address the hypothesis that the concentration of particulate material or the level of endotoxin was responsible for the acute respiratory symptoms previously reported among swine confinement workers (27) and may contribute to the chronic pulmonary changes in that population. Thus, total dust samples were collected over the workshift in the breathing zone of each study participant on his or her side of preferred dexterity only during the initial testing session. For dust sampling, the Mine Safety Appliances (MSA) Type FWS-D polyvinylchloride membrane filter with pore size 0.5 μm (Mine Safety Appliances Co., Pittsburgh, PA) was used in a standard 37 mm polystyrene filter cassette with a cellulose backing pad. The filters were preweighed and reweighed after sampling using a Cahn electrobalance (to within 2 μg) to determine the dust loading over the sampling period. Ambient air was drawn through dust samplers using MSA Flow-Lite[®] Model H constant flow personal sampling pumps calibrated to draw 1.7 L/min. These pumps weigh only 800 g each and were affixed to an equipment belt worn by the participant. Total concentration of airborne dust was determined using standard methods (31), and airborne endotoxin concentrations were measured using the commercially available assay that employs the chromogenic *Limulus* amoebocyte lysate (LAL) methodology (32). It has been shown for many of the most common gram-negative bacteria that the activity in the LAL assay is a reasonable measure of pulmonary potency and pyrogenicity in humans and animal models (32–34). Measurements of endotoxin were performed by the National Institute of Occupational Safety and Health Division for Respiratory Disease Studies (Morgantown, WV).

Characterization of Smoking History

Participants were classified as never smokers (< 20 packs of lifetime cigarettes and no cigarettes in the month before the initiation of the study), former smokers (\geq 20 lifetime packs of cigarettes but stopped at least 1 mo before the initiation of the study), and current smokers (smoked within 1 mo of the initiation of the study). In the classification of pack-years of cigarette smoking, never smokers were classified as having 0 pack-years of cigarette smoking.

Statistical Analysis

The primary objective of this investigation was to identify whether working in a swine confinement building caused an excess or accelerated decline in lung function during the period of observation. Secondly, we were interested in determining whether specific elements of the agricultural aerosol or whether acute airway responses (lung function change during the workshift) to occupational conditions contributed to longitudinal decrements in airflow.

The generalized estimating equations (GEE) approach (35, 36) was used to develop regression models assessing the relationship between longitudinal changes in spirometric measures of lung function and a set of confounders and covariates of potential interest. This regression methodology for correlated observations permits unequal numbers (and spacings) of follow-up measurements across subjects, as well as both subject-specific (time-independent) and observation-specific (time-dependent) covariates. Because the GEE approach models the occasion-specific distribution of the response variable as a function of a set of explanatory variables, the regression coefficients estimate the marginal relationship between the response and covariates. An important practical advantage of the semiparametric GEE methodology is that it is not necessary to specify completely the joint distribution of a subject's repeated observations. Instead, it is necessary only to specify the relationship between the mean and the variance and a hypothesized "working" correlation structure. The resulting estimating equations have consistent solutions even

when the time dependence is misspecified. In addition, robust estimators of the variances and covariances of the estimated parameters are used.

The outcome variables are continuous and approximately normally distributed, so that the identity link function and constant variance function were used. Thus, the mean spirometric measures of lung function (FEV₁, FVC, and FEF₂₅₋₇₅, mid expiratory flow) were modeled as a linear function of follow-up time and other covariates. Dichotomous explanatory variables were coded as 0 (absent) or 1 (present), and categoric covariates with $k > 2$ levels, such as smoking history, were coded using $k - 1$ indicator (0, 1) variables. Because both the number and precise spacing of the repeated measurements varied across subjects, it is not possible to assume a general, unstructured "working" correlation matrix (the estimated correlation matrix is not guaranteed to be positive definite). Instead, the independence and exchangeable (equal correlation between all pairs of time points) correlation structures were used. The two approaches yielded similar results, and thus only the results from the independence working correlation model are reported.

The regression procedure was as follows. First, for FEV₁, FVC, and FEF₂₅₋₇₅, we determined whether our potential confounders (age, height, smoking status, and pack-years of cigarette smoking) interacted with follow-up time. Importantly, none of these potential confounders interacted with follow-up time. Next, we included the confounders or covariates (age, height, smoking status, pack-years of cigarette smoking, and follow-up time) in a model that evaluated the relationship between changes in FEV₁, FVC, or FEF₂₅₋₇₅ during the follow-up period and a variety of clinical characteristics. All the clinical characteristics that were found to be significantly related to changes in the outcome variable of interest were then tested to determine whether an interaction was observed between that characteristic and the follow-up time. Significant terms were then included in a regression model, and backward elimination was used to determine which clinical characteristics were independently associated with changes in FEV₁, FVC, or FEF₂₅₋₇₅ while controlling for age, height, smoking status, and pack-years of cigarette smoking. After eliminating nonsignificant covariates, two- and three-way interactions of the remaining independent variables were tested. Interaction terms were included only if the interaction was significantly ($p \leq 0.05$) related to changes in lung function.

The goal of the procedure was to obtain a parsimonious model describing the relationship between the outcome variable and a set of potential explanatory variables. Such an exploratory analysis examining the effects of multiple covariates is complicated by intercorrelations among the independent variables. In particular, the estimated regression coefficient for an independent variable depends on which variables are included and which are excluded. This problem cannot be eliminated in an observational study. Our procedure was first to examine interactions between potential confounders and follow-up time and then to examine separately individual clinical characteristics before the backward elimination of nonsignificant terms.

RESULTS

Swine confinement workers were found on average to have less farming experiences than the neighborhood farmers (Table 2). This may reflect the relatively recent contribution of animal confinement technology to livestock production in the United States and the potential tendency for newly employed farmers to be attracted to this form of livestock production. Of the neighborhood farmers, 33 (34%) had experience working in the swine confinement setting; on average, their years of work in the swine confinement setting was significantly less than that of the swine confinement workers (Table 2), and by definition, the neighborhood farmers had not worked in the confinement units within 5 yr of the initial evaluation. Importantly, swine confinement operators were found to have far greater exposure to total dust and endotoxin than the farmer control subjects (Table 2).

The yearly pulmonary function for the swine confinement operators and neighborhood farmer control group is presented in Table 3. These data indicate that swine confinement operators tended to have slightly lower absolute values for FEV₁, FVC, and FEF₂₅₋₇₅

TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS FOR ALL STUDY SUBJECTS

	Swine Confinement Workers (n = 168)	Neighborhood Control Farmers (n = 127)
Age	37.6 ± 11.0	39.4 ± 10.8
Gender		
Males	150 (89.3)	112 (88.2)
Females	18 (10.7)	15 (11.8)
White	168 (100)	127 (100)
Smoking history		
Never smoker	113 (67.3)	81 (63.8)
Former smoker	30 (17.9)	23 (18.1)
Current smoker	25 (14.9)	23 (18.1)
Pack-years smoking	4.3 ± 10.4	4.3 ± 9.8
Atopic	49 (29.2)	41 (32.3)
Pulmonary function testing periods		
Years 1 and 3	12 (7.1)	66 (52.0)
Years 1 and 5	83 (49.4)	33 (26.0)
Years 1, 3, and 5	73 (43.5)	28 (22.0)
Follow-up, days		
Mean	724.7 ± 153.8	544.0 ± 223.9
Median	731.5	423.0
Range	56-1,900	146-1,093

TABLE 2
EXPOSURE CHARACTERISTICS OF STUDY POPULATION AS DETERMINED DURING THE INITIAL EVALUATION

	Swine Confinement Workers (n = 168)	Neighborhood Control Farmers (n = 127)
Farm-years	18.9 ± 11.1	20.7 ± 11.1
Swine confinement years	10.6 ± 5.9*	1.6 ± 5.2
Total dust, mg/m ³	6.4 ± 5.6*	2.3 ± 4.5
Total endotoxin, E _u /m ³	588.3 ± 1,196.3*	410.6 ± 1,642.1

* p < 0.001.

TABLE 3
YEARLY PREWORKSHIFT MEASURES OF LUNG FUNCTION
IN SWINE CONFINEMENT WORKERS AND FARMERS

Pulmonary Function	Follow-up Year	Swine Confinement Workers (n)	Neighborhood Control Farmers (n)
FEV ₁ , L	1	4.13 ± 0.77 (168)	4.28 ± 0.79 (127)
	3	4.21 ± 0.88 (85)	4.17 ± 0.83 (94)
	5	4.07 ± 0.77 (156)	4.40 ± 0.75 (61)
FVC, L	1	5.20 ± 0.90 (168)	5.31 ± 0.94 (127)
	3	5.34 ± 1.05 (85)	5.21 ± 1.01 (94)
	5	5.16 ± 0.90 (156)	5.44 ± 0.85 (61)
FEF ₂₅₋₇₅ , L/s	1	3.89 ± 1.21 (168)	4.25 ± 1.30 (126)
	3	3.95 ± 1.22 (84)	4.12 ± 1.22 (94)
	5	3.79 ± 1.22 (156)	4.42 ± 1.34 (61)

than the neighborhood farmer control subjects. Using standard equations (30) to control for age, gender, and height, we also found minimal differences in the percentage predicted spirometric measures of lung function between swine confinement operators and neighborhood farmer control subjects for each of the follow-up periods (data not shown). When we compared the percentage change in lung function from the beginning of the study to the last observation point, we found that the neighborhood farmer control subjects tended to have a greater decline in FEV₁ and FVC than the swine confinement operators (Table 4).

Importantly, swine confinement operators consistently had greater declines in FEV₁, FVC, and FEF₂₅₋₇₅ during the workshift than the neighborhood farmers (Table 5). However, the farming control population also demonstrated consistent (albeit modest)

declines in spirometric measures of lung function that were associated with work in the agricultural setting.

To identify the independent contribution of clinical and environmental factors to the longitudinal changes in spirometric measures of lung function while controlling for potentially important demographic factors, including the period of follow-up, we used multivariate techniques. In these multivariate models, we control for variables known to affect spirometric measures of lung function, such as age, height, gender, smoking status, pack-years of cigarette smoking, and follow-up time. After controlling for age, height, gender, cigarette smoking, and follow-up time, long-term changes in spirometric measures of lung function were independently related to cross-shift declines in spirometric measures of lung function (FEV₁, FVC, and FEF₂₅₋₇₅), higher concentrations of

TABLE 4
PERCENTAGE CHANGE IN SPIROMETRIC MEASURES OF LUNG FUNCTION FROM THE
BEGINNING TO THE END OF THE STUDY

Pulmonary Function	Swine Confinement Workers (n = 168)	Neighborhood Control Farmers (n = 127)
FEV ₁ , L	-0.84 ± 5.24	-1.15 ± 5.04
FVC, L	-0.36 ± 4.51	-1.20 ± 4.52
FEF ₂₅₋₇₅ , L/s	-0.69 ± 13.01	-0.36 ± 11.76

endotoxin present in the bioaerosol (FEV₁ and FEF₂₅₋₇₅), and work in the swine confinement setting (FEV₁ and FEF₂₅₋₇₅) (Table 6). The regression coefficients indicate that swine confinement operators compared with neighborhood farmer control subjects have a persistently lower FEV₁ (190 ml) and FEF₂₅₋₇₅ (350 ml/s) during the period of observation. In addition, for every percentage decrease in lung function across the workshift, our results indicate that one could expect longitudinally a 100 ml decline in FEV₁, a 30 ml decline in FVC, and a 20 ml/s decline in FEF₂₅₋₇₅. Importantly, cross-shift changes in lung function and the concentration of endotoxin in the bioaerosol interacted positively with follow-up time, indicating that these factors were associated with an accelerated decline in lung function. In contrast, work in the swine confinement setting did not interact with follow-up time.

DISCUSSION

Our results indicate that working in swine confinement units is associated with lower measures of airflow but does not appear to accelerate the decline in lung function among agricultural workers. Within our cohort of agricultural workers, however, longitudi-

nal decrements in lung function were independently associated with greater cross-shift changes in lung function and higher concentrations of endotoxin in the bioaerosol. In fact, acute declines in airflow across the workshift and higher concentrations of endotoxin in the bioaerosol were associated with accelerated declines in airflow during the period of observation. These findings imply that, among agricultural workers, acute airway responses are predictive of chronic changes in airflow. Moreover, our finding suggest that the characteristics of the bioaerosol, such as microbiologic contamination, are more relevant to pulmonary function than are the more general categories of agricultural work.

Airflow obstruction observed among swine confinement workers appears to represent an airway response that is characteristically seen in other workers exposed to high concentrations of respirable organic dust. This hypothesis is best supported by the similar patterns of airway response among swine confinement operators (20-25), grain workers (37-43), and workers exposed to cotton dust (44). Although all these exposures may result in asthma, chronic cough and phlegm production are seen much more commonly than asthma and these symptoms are often associated with delayed chest tightness and modest decrements in expiratory flow rates over a workshift. The development of respiratory symptoms and airflow obstruction tends to be dose related, with chronic symptoms influenced by the duration of exposure. Cigarette smoking interacts with these exposures in an additive fashion, increasing symptoms of cough and chest tightness and worsening airflow obstruction (37, 41-43, 45). Compared with previously exposed workers, unexposed subjects develop a similar degree of airflow obstruction when challenged with either grain dust (46) or cotton dust (47). The common denominator linking these exposures appears to be the high concentration of respirable particles and organic components of the inhaled bioaerosol. In all cases, these organic dusts represent a complex mixture of vegetable particles, microorganisms and their products, insects and insect fragments, feed additives, including fish meal and antibiotics, avian and rodent proteins, and pesticides. Endotoxin from gram-negative organisms has been measured in similar concentrations from several of these vegetable dusts, including corn, wheat, oats, barley, and cotton (16-19). Moreover, recent findings indicate that among those exposed to cotton dust, vertical elutriated levels of endotoxin are more predictive of respiratory impairment (symptoms and airflow obstruction) than concentrations of airborne dust (47). Findings from the current investigation indicate that the concentration of endotoxin in the bioaerosol appears to be more relevant to longitudinal changes in pulmonary function than are the more general categories of agricultural work. In aggregate, these observations suggest that endotoxin and/or other components of the agricultural bioaerosol are responsible for the development and progression of airway inflammation and airflow obstruction among agricultural workers. We believe that a focused investigation of the role of endotoxin and other potential pathogens in organic dusts will markedly en-

TABLE 5
YEARLY CROSS-WORKSHIFT CHANGES IN LUNG FUNCTION
AMONG SWINE CONFINEMENT WORKERS AND FARMERS*

Pulmonary Function	Follow-up Year	Swine Confinement Workers (n)	Neighborhood Control Farmers (n)
FEV ₁ , L	1	-2.86 ± 3.86 (168)	-1.19 ± 3.11 (127)
	3	-2.44 ± 4.47 (85)	-0.98 ± 3.81 (94)
	5	-2.07 ± 4.27 (156)	-0.69 ± 3.23 (61)
FVC, L	1	-1.91 ± 3.30 (168)	-0.69 ± 2.16 (127)
	3	-1.95 ± 3.41 (85)	-0.84 ± 2.81 (94)
	5	-2.13 ± 3.69 (156)	-1.11 ± 2.78 (61)
FEF ₂₅₋₇₅ , L/s	1	-4.65 ± 9.49 (168)	-1.76 ± 10.10 (126)
	3	-2.61 ± 10.65 (84)	-1.00 ± 10.41 (94)
	5	-1.55 ± 10.80 (156)	-1.45 ± 7.85 (60)

* Expressed as the percentage change from the preshift value.

TABLE 6
MULTIVARIATE MODELS THAT IDENTIFY THE INDEPENDENT
DETERMINANTS OF LONGITUDINAL CHANGES IN
FEV₁, FVC, AND FEF₂₅₋₇₅*

	FEV ₁ (L)	FVC (L)	FEF ₂₅₋₇₅ (L/s)
Cross-shift change, %	0.10 (0.04)†	0.03 (0.01)†	0.02 (0.005)†
Total endotoxin, E _μ /m ³	-0.13 (0.04)†	NS	-0.28 (0.10)†
Swine confinement	-0.19 (0.06)†	NS	-0.35 (0.12)†

* Multivariate models controlled for age, height, smoking status, pack-years of cigarette smoking, and follow-up time. The values represent the regression coefficient (standard error), NS indicating a nonsignificant relationship. Thus, the regression coefficients indicate that swine confinement farmers compared with neighborhood farmer control subjects have a persistently lower FEV₁ (190 ml) and FEF₂₅₋₇₅ (350 ml/s) during the period of observation.

† p < 0.01.

hance our ability to control and treat airway disease in agricultural workers.

Our findings indicate that acute workshift-related changes in airflow are independently associated with accelerated longitudinal declines in lung function. Interestingly, other investigators have found that acute changes in airflow across either the workshift or the work week are consistently associated with accelerated longitudinal declines in lung function among grain handlers (38–40). It is possible that the physiologic response to agricultural dust serves simply to identify a cohort of individuals with a high intrinsic risk of airway disease, similar to the clinical use of a bronchoprovocative airway challenge. Alternatively, the acute physiologic response to these agricultural dusts may be associated with acute airway inflammation and cell injury. This possibility is supported by animal inhalation studies, which have shown that grain dust induces a profound neutrophilic response in the lower respiratory tract (48). Moreover, animal studies have shown that neutrophils are rapidly recruited to the lung (49, 50) and that alveolar macrophages are primed to release tumor necrosis factor α following inhalation of cotton dust (50). Similarly, humans challenged with aerosols of grain dust extract rapidly accumulate neutrophils in the upper and lower respiratory tract (51). Clearly, recurrent airway inflammation and injury may accelerate the decline in lung function and place individuals at higher risk of developing chronic lung disease. Moreover, this hypothesis supports preventing chronic lung disease by minimizing and potentially controlling the acute airway responses to organic dusts. Prospective intervention trials are needed to address this hypothesis fully.

Selection, on the part of the study subjects, may have contributed to our findings. Of the 2,019 swine producers, only 932, or 46%, responded to our initial inquiry. Importantly, of all eligible study subjects, 81% of swine confinement operators and 80% of neighborhood farmers participated in the follow-up examinations. However, despite the similar rate of participation, swine confinement operators participating in the longitudinal study had more measures of lung function and longer periods of observation than the neighborhood farmer control subjects. This suggests that the swine confinement operators represent a selected, more motivated population than the neighborhood farmers. Although one might assume that the confinement operators were more motivated to participate because of excess lung disease, we did not find this to be true. Rather, despite concerns that could be raised regarding selection bias, working in the swine confinement did not appear to influence longitudinal changes in airflow.

Our findings strongly suggest that excessive exposure to agricultural aerosols in any work setting should be avoided. Although not proven, the independent association between the concentration of endotoxin in the bioaerosol and accelerated longitudinal decrements in lung function suggests that minimizing exposure to agricultural aerosols may decrease the incidence of chronic lung disease among agricultural workers. Ideally, ventilation systems and other comprehensive methods to decrease dust levels would be engineered into enclosed agricultural structures. However, routine cleaning of farm buildings and equipment, use of personal respiratory protection, and proper management of manure pits would substantially improve the working conditions in most agricultural settings. Our findings indicate that further attention should be placed on new and innovative approaches to limiting exposure to these potentially hazardous aerosols.

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