

Endotoxin exposure and atopic sensitization in adult pig farmers

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Background: Recent studies have reported a low prevalence of atopic sensitization and respiratory allergy in children growing up on farms.

Objectives: We sought to evaluate the dose-response relationship between endotoxin and atopic sensitization in adult farmers and to assess the effect on respiratory health outcomes.

Methods: Data on endotoxin exposure and serum IgE levels were available for 162 pig farmers from a cross-sectional case-control study, with case selection on the basis of respiratory symptoms. Exposure to endotoxin was modeled in detail, and respiratory health effects were assessed during a medical examination. Exploratory analysis was done by using nonparametric modeling and was followed by classical parametric regression.

Results: IgE to one or more common allergens was detected in sera from 28 (17%) farmers. The average (geometric mean) total serum IgE levels was 37 IU/mL (geometric SD, 4 IU/mL). A strong inverse relationship was found between endotoxin and sensitization to common allergens for exposures of 75 ng/m³ or less, with an odds ratio of 0.03 (95% CI, 0.0-0.34) for a 2-fold increase in endotoxin. For endotoxin exposure of greater than 75 ng/m³, the association was weak (odds ratio, 1.2 [95% CI, 0.38-3.6]). No association was found between endotoxin exposure and total serum IgE levels. Endotoxin was associated with increased airway hyperresponsiveness to histamine and lower lung function in sensitized farmers, without evidence of a nonlinear relationship.

Conclusions: The prevalence of atopic sensitization in adult pig farmers is low. Endotoxin or related exposures might protect from sensitization, even in an adult working population exposed to high levels of endotoxin, but is a risk factor for increased airway hyperresponsiveness and low lung function. (*J Allergy Clin Immunol* 2005;115:797-802.)

Key words: Endotoxins, hypersensitivity, IgE, allergens, adult, occupational exposure, epidemiology

Abbreviations used

AHR: Airway hyperresponsiveness

OR: Odds ratio

Recent epidemiologic studies have reported a considerably lower prevalence of atopic sensitization and symptoms of respiratory allergy in children, young adolescents, and even adults growing up on farms when compared with their peers living in the same rural areas.¹ Contact with livestock during the first year of life was identified as the factor that best explained the protective effect on atopic sensitization,^{2,3} which is consistent with the view that early life is a critical period for initiation of allergic immune responses and asthma.⁴ It has been speculated that respiratory exposure to endotoxin (particularly in livestock farming) might be important.⁵ Several studies have shown that animal keeping is associated with exposure to high levels of bacterial endotoxin.⁶⁻⁸ There are strong indications that endotoxin exposure might cause or aggravate respiratory symptoms,⁹⁻¹² but experimental studies have shown that timing might be crucial. Consequently, studies on the possible protective effect of endotoxin exposure have focused almost exclusively on early childhood exposure.¹³⁻¹⁶

Some studies have indicated that rural living¹⁷ or being a farmer¹⁸ is associated with a reduced risk of atopy and atopic disease in adulthood as well, and we have shown earlier that growing up on a farm and current farming were independently associated with a lower prevalence of atopic sensitization.¹⁹ Only one study has investigated the separate effects of having been born on a farm and current endotoxin exposure.¹³ Having been born on a farm was associated with a reduced risk of sensitization in school-age children, but there was an additional protective effect of current endotoxin exposure.

It is not clear whether adult farmers also have a reduced risk of atopic sensitization, whether this is associated with their endotoxin exposure, and whether this has an effect on respiratory health outcomes. We therefore analyzed these relationships in a study among pig farmers. Exposure to endotoxin was measured on more than one occasion and used to model average long-term exposure. Earlier analyses have shown that high endotoxin exposure was associated with increased respiratory symptoms and

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airway hyperresponsiveness (AHR) to histamine and with lower lung function in sensitized farmers.^{20,21} The relationship between endotoxin exposure and atopic sensitization was not studied in detail, although it was apparent that the prevalence of sensitization to common allergens in the population was low. We analyzed the relationship between exposure to endotoxin and atopic sensitization and assessed the effect on respiratory health outcomes.

METHODS

Population and health data

Data were from a cross-sectional survey in pig farmers conducted in the early 1990s. A detailed description of the design and methods of data collection have been reported previously.^{20,21}

The population consisted of 194 pig farmers living in the 2 southeastern provinces of the Netherlands, which were selected from a group of 1133 male owners of pig farms who worked at least 5 hours per day in pig farming. Selection was based on chronic respiratory symptoms reported in the Dutch version of a self-administered shortened questionnaire on respiratory symptoms of the British Medical Research Council.²² All farmers (n = 94) with more than one symptom of chronic cough, chronic phlegm, ever or frequent wheezing, shortness of breath, and chest tightness (asthma) were included, and a group of 100 control subjects was selected at random from the symptom-free farmers. In a subsequent medical survey held in winter 1990-1991, venous blood samples were taken for IgE analysis. The medical ethical committee of the University Nijmegen approved the study. Subjects received information about the trial and consented to participate in writing.

IgE measurements

Sera were stored at -20°C until IgE analysis. Total IgE and specific IgE antibodies to the common allergens house dust mite, grass pollen (mix of 2 species), birch pollen, and cat were measured by means of enzyme immunoassays.²³

Allergen-specific IgE was assessed with 1:10 diluted sera in allergen-coated microwells. A serum was considered positive if the optical density at 492 nm exceeded the mean optical density + 3 SD of the reagent blank (no serum control). Total serum IgE levels were measured by means of sandwich enzyme immunoassay with sera diluted 1:10, 1:20, and 1:40, and the IgE standard for the Pharmacia CAP system was used as a calibration standard.²³

Lung function and AHR

Forced expiratory lung function measurements were conducted with a Vicatest V dry rolling seal spirometer (Mijnhardt, Bunnik, The Netherlands). Measurements were performed according to the lung function protocol of the European Community for Steel and Coal.²⁴

Airway responsiveness was tested by using histamine provocation according to a modified procedure of the method of Cockcroft et al.²⁵ Histamine concentration ranged from 0.03 to 16 mg/mL. AHR was defined as a decrease in FEV₁ of at least 10% at a histamine concentration of 16 mg/mL or less.²⁶

Exposure measurements and modeling

Personal inhalable dust samples were taken twice: once in the summer and once in the winter. Dust was collected by using PAS6 sampling heads and 1-μm Teflon filters (Millipore, Billerica, Mass) at an airflow of 2 L/min.⁶ Samples were stored at -20°C until extraction. Endotoxin was extracted in 0.05% (vol/vol) Tween 20 in pyrogen-free water and stored at -20°C until analysis.²⁷ Endotoxin levels were measured with the Lymulus Amebocyte Test, according to procedures

described earlier.²⁷ Endotoxin units were converted to nanograms of endotoxin by using a factor of 0.1 ng/EU.

Endotoxin levels were expressed in nanograms per cubic meter. On the basis of the relationship between endotoxin concentration and farm characteristics and time spent on activities in pig farming during 2 full weeks, the long-term time-weighted average exposure to endotoxin was estimated.²⁸ Estimation was based on log-transformed exposure levels to standardize variance and obtain normally distributed residuals. The measurements in the summer and winter were used as independent observations because the correlation between them was low. The final model included outdoor temperature, 12 farm characteristics, and 8 activities in pig farming and explained 37% (adjusted $R^2 = 33\%$) of the variation in log-transformed time-weighted average endotoxin exposure. In this article endotoxin exposure is defined as modeled individual long-term average exposure to endotoxin.

Data analysis

IgE sensitization to common allergens was defined as a positive reaction to one or more common allergens. Endotoxin exposure and total IgE levels were best described by using a log-normal distribution. Total IgE levels were either log transformed or dichotomized by using 100 IU/mL as a cutoff level. For exploratory analysis, the relationship between log-transformed endotoxin exposure and sensitization to common allergens, (log-transformed) total IgE, and respiratory outcomes was studied by means of generalized additive modeling (smoothing) with PROC GAM (SAS for Windows version 8.0; SAS Institute, Cary, NC).²⁹ For dichotomous response variables, a logistic model was used, and smoothed curves were computed by using a logit-link function and transformed to prevalences by applying the inverse of the logit function. The smoothness of the function was determined by means of generalized cross-validation.³⁰

On the basis of results from this analysis, log-transformed endotoxin exposure was used in multiple regression analysis by using more conventional parametric models. A *P* value of less than .05 was considered statistically significant.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Subject characteristics, atopic sensitization, and total IgE levels

Complete data on endotoxin exposure, personal characteristics, and serology were available for 81 cases and 81 control subjects. Subject characteristics, IgE sensitization, and respiratory health outcomes in the study population stratified by case-control status are presented in Table I. Cases were somewhat older, smoked more often, and had been working with pigs for a longer time than control subjects.

Specific IgE to at least one of the 4 common allergens was detected in 28 (17%) farmers and was weakly associated with case-control status (odds ratio [OR], 1.4 [95% CI, 0.63-3.3]). Most sensitized farmers had IgE to house dust mite (61%) or grass pollen (36%); only 5 (18%) were sensitized to birch pollen, and none were sensitized to cat allergen. Four (14%) subjects were sensitized to more than one allergen. The average (geometric mean) total

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