Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study

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Background: Previous studies, mostly from Europe, suggest that early-life farming exposures protect against childhood asthma and allergy; few data exist on asthma and allergy in adults.
Objective: We sought to examine associations between early-life farming exposures and current asthma and atopy in an older adult US farming population.
Methods: We analyzed data from 1746 farmers and 1555 spouses (mean age, 63) from a case-control study nested within the Agricultural Health Study. Current asthma and early-life farming exposures were assessed via questionnaires. We defined atopy based on specific IgE > 0.70 IU/mL to at least 1 of 10 allergens measured in blood. We used logistic regression, adjusted for age, sex, race, state (Iowa or North Carolina), and smoking (pack years), to estimate associations between early-life exposures and asthma (1198 cases and 2031 noncases) or atopy (578 cases and 2526 noncases).
Results: Exposure to the farming environment *in utero* and in early childhood had little or no association with asthma but was associated with reduced odds of atopy. The strongest association was seen for having a mother who performed farm activities while pregnant (odds ratio, 0.60; 95% CI, 0.48-0.74) and remained significant in models with correlated early-life exposures including early childhood farm animal contact and raw milk consumption.
Conclusions: In a large US farming population, early-life farm exposures, particularly maternal farming activities while pregnant, were strongly associated with reduced risk of atopy in adults. These results extend previous work done primarily on childhood outcomes and suggest that protective associations of early-life farming exposures on atopy endure across the life course. (J Allergy Clin Immunol 2017;140:249-56.)

Key words: *Agriculture, agricultural workers' diseases, allergy and immunology, asthma, hygiene hypothesis, IgE, prenatal exposure delayed effects*

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Asthma and allergies are common chronic health problems in the United States and worldwide.[1,2] Rates have increased over the past 50 years but causes remain largely unknown.[3] *In utero* and childhood exposures to farm animals and consumption of raw (unpasteurized) milk have consistently been associated with reduced risk of childhood asthma and allergies in European farming environments (reviewed in Campbell et al,[4] von Mutius et al,[5] Brooks et al,[6] and Braun-Fahrlander et al[7]). Associations of early-life farm exposures and adult asthma have been null, and associations with adult atopy have been weaker than those reported for child atopy.[4,8-20] Few studies of early-life farm exposure and asthma or atopy have been conducted in the United States where farming practices may differ.

The putative protective effect of the farming environment for childhood asthma and allergic disease has generally been attributed to the hygiene hypothesis whereby diverse microbial exposure early in life stimulates immune tolerance, protecting against allergy to common antigens throughout life.[21,22] Recent work has identified molecular mechanisms whereby farm dust exposure modulates immune system cross talk between airway epithelium and dendritic cells, resulting in reduced allergic responses.[23]

We evaluated associations between early-life farm exposures and both adult asthma and allergic sensitization among 3301 participants in a case-control study of current asthma (the Agricultural Lung Health Study [ALHS]) nested within a US agricultural cohort (the Agricultural Health Study [AHS]).

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Supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (Z01-ES049030 and Z01-ES102385) and the National Cancer Institute (Z01-CP010119). Supported in part by American Recovery and Reinvestment Act (ARRA) funds through NIEHS contract number N01-ES-55546. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of any company or product does not constitute endorsement by National Institute for Occupational Safety and Health.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 11, 2016; revised September 1, 2016; accepted for publication September 8, 2016.

Available online November 12, 2016.

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0091-6749

Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2016.09.036

Abbreviations used
AHS: Agricultural Health Study
ALHS: Agricultural Lung Health Study
COPD: Chronic obstructive pulmonary disease
OR: Odds ratio

METHODS

Agricultural Lung Health Study

ALHS is a nested case-control study of current asthma within the parent AHS. AHS is a prospective cohort including private pesticide applicators, predominantly farmers, and henceforth referred to as farmers (n = 52,395), and their spouses (n = 32,347) from Iowa and North Carolina, who enrolled between December 1993 and December 1997 by completing a baseline questionnaire (data version AHSREL201304.00, P1REL201209.00).[24] ALHS participants were identified from among the 44,130 respondents (24,171 farmers and 19,959 spouses) to the AHS follow-up questionnaire administered by phone from November 2005 to February 2010 (data version P3REL201209.00).[25] Participants had to be capable of providing consent and residing in or within a 5-hour drive of North Carolina or Iowa.

From among the 2363 putative asthma cases identified in AHS based on the follow-up interview, 1223 enrolled in ALHS (response rate, 51.7%). To avoid missing undiagnosed current asthma and to minimize misclassification with chronic obstructive pulmonary disease (COPD), we identified 3 categories of asthma cases. The majority of enrolled cases (n = 876) responded "yes" to the 2 questions "have you ever been diagnosed with asthma?" and "do you still have asthma?"[26] and "no" to the 2 questions "have you ever been diagnosed with chronic obstructive pulmonary disease (COPD)?" and "have you ever been diagnosed with emphysema?" We also identified never smoking (n = 263) or minimal past smoking (≤10 pack years, n = 46) cases of likely undiagnosed asthma (total n = 309) based on report of current asthma symptoms and use of asthma medications and no diagnosis of either COPD or emphysema. In addition, because asthma and COPD can coexist, we also enrolled 38 subjects reporting current asthma and previous diagnosis of either COPD or emphysema as long as they were never-smokers (n = 28) or past-smokers (≤10 pack years, n = 10).

Noncases were randomly selected from among individuals who denied currently having asthma, experiencing asthma symptoms (ie, wheeze or awakened by respiratory symptoms), or using asthma medications or inhalers in the past 12 months. To achieve a suitably sized comparison group, we enrolled 2078 noncases in ALHS (response rate, 50.0%).

Among 3301 total participants enrolled in ALHS, the 3229 (1198 cases and 2031 noncases) with data on early-life exposures and all covariates were included in these analyses. Participants were enrolled between February 2009 and September 2013. This study was approved by the Institutional Review Board at the National Institutes of Health and its contractors.

Atopy

Blood samples drawn by field staff during home visits were measured for 10 allergen-specific IgEs at ImmuneTech (Foster City, Calif) using the Luminex (Luminex Corporation, Austin, Tex) platform: seasonal (Bermuda grass, ragweed, timothy grass, mountain cedar), perennial (*Alternaria*, dust mite, cat dander), and food (milk, egg, wheat). Based on recent literature, we classified atopy using a threshold of 0.70 IU/mL.[27,28] In sensitivity analyses we considered lower (0.35 IU/mL) and higher (3.5 IU/mL) thresholds. Atopy was defined as a positive test result to any of the 10 allergens. Seasonal, perennial, or food atopy was based on positivity to any allergen in the respective category. Inhaled atopy was defined as a positive test result to any seasonal or perennial allergen. Analyses of atopy included 3104 individuals with IgE measurements.

Early-life farming exposures

Through a self-administered questionnaire, participants were asked whether their mother lived on a farm when pregnant with them and whether she performed farm activities during the pregnancy, including working with animals. Participants were also asked about their own farming exposures during childhood, including whether they lived on a farm at birth, were exposed to farm animals before age 6, and drank raw milk. In addition, participants were asked about exposures not unique to farms, including whether they were breast-fed, exposed to indoor pets, and had parents who smoked during their childhood. Table E1 (in the Online Repository available at www.jacionline.org) provides specific questions verbatim.

Statistical analysis

Using logistic regression, we estimated odds ratios (ORs) and 95% CIs for associations between early-life farming exposures and the outcomes of current asthma (case vs noncase) and atopy (atopic vs nonatopic) separately, adjusting for participants' age, sex, race (white, nonwhite), state (Iowa, North Carolina), and pack years of cigarette smoking. Because ALHS is a nested case-control study of current asthma, the asthma status selection factor was included in models examining atopy outcomes. We additionally explored models adjusted for exposure to farm animals in the past 12 months and use of pesticides that were previously reported to be associated with asthma or hay fever in the larger cohort.[29-31] We also explored models stratified by sex, state, and exposure to farm animals in the past 12 months and examined corresponding interaction terms. We analyzed asthma and atopy in combination (atopy with asthma, atopy without asthma, asthma without atopy vs neither asthma nor atopy), using multinomial logistic regression adjusting for age, sex, race, state, and pack years of cigarette smoking. The Hosmer-Lemeshow test was calculated to assess goodness of fit. All analyses were performed in SAS (Cary, NC) version 9.3 using proc logistic and proc freq and SAS version 9.4 using proc corr for tetrachoric correlations.

RESULTS

Study population characteristics

Approximately one-half of ALHS participants (average age, 62.7 years) were farmers (52.9%) and the remainder spouses (47.4%) (Table I). Nearly all farmers were male (96.7%) and spouses were female (99.7%). Nearly all subjects were white (98.3%) and about 70% were from Iowa (Table I). Two-thirds reported never smoking, whereas only 4.2% reported currently smoking.

Asthma

In our primary logistic regression analysis comparing all 1198 current asthma cases to noncases, being born to a family that lived on a farm was associated with a slightly reduced asthma OR (0.89; 95%, 0.74-1.06) (Table II). When we excluded cases with either likely undiagnosed asthma (n = 309) or asthma plus COPD diagnosis (n = 38), this association was slightly stronger and statistically significant (OR, 0.81; 95% CI, 0.67-0.98) (see Table E2 in this article's Online Repository at www.jacionline.org). In contrast, asthma ORs for most other early-life exposures were slightly above 1 whether including all cases (Table II) or restricting (Table E2). For example, the OR (95% CI) for having a mother who worked with farm animals while pregnant was 1.10 (0.93-1.30) and for farm animal exposure before age 6 years was 1.18 (0.97-1.42) (Table II). We found no evidence for associations between exposure to specific types of farm animals and asthma (see Table E3 in this article's Online Repository at www.jacionline.org). Ever consumption of raw milk was associated with a small increased risk for asthma (OR, 1.23; 95% CI, 1.01-1.49) (Table II) that was reduced and no longer statistically significant when restricted to diagnosed asthma cases only (OR, 1.14; 95% CI, 0.92-1.41) (Table E2). Consuming raw milk as a main source of milk was not significantly associated