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

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Abstract

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%

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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.

Keywords

Agriculture; agricultural workers'; diseases; allergy and immunology; asthma; hygiene hypothesis; IgE; prenatal exposure delayed effects

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]).

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 with asthma (OR, 1.11; 95% CI, 0.93–1.32) (see Table E4 in this article's Online Repository at www.jacionline.org). Further adjustment for current (past 12 months) farm animal exposure and previous pesticide use did not materially change asthma ORs (data not shown). Associations were generally similar across strata of sex, state, and recent farm animal exposure (data not shown).

Atopy

Our primary cut point of 0.70 IU/mL IgE classified 578 (18.6%) individuals as atopic. The strongest association was for having a mother who performed farm activities while pregnant (OR, 0.60; 95% CI, 0.48–0.74), but we observed similar inverse associations for other early-life exposures: living on a farm at birth, mother lived on a farm while pregnant, mother worked with farm animals while pregnant, or childhood exposure to farm animals before age 3 or 6 years (ORs, 0.63–0.69, $P < .002$) (Table III). In general, associations between early-life farming exposures and atopy to seasonal, perennial, or inhaled allergens were similar to those seen for atopy to any allergen (see Table E5 in this article's Online Repository at www.jacionline.org). Food sensitization was much less common and thus associations with early-life exposures were not consistent (Table E5). When using the less stringent IgE cut point of 0.35 IU/mL (42.8% atopic), associations were generally weaker (ORs, 0.76–0.88), though all but 1 remained statistically significant (see Table E6 in this article's Online Repository at www.jacionline.org). At the much stricter cut point of 3.5 IU/mL, the prevalence of atopy was correspondingly much lower (7.0% atopic), but associations remained statistically significant with slightly stronger effect estimates (ORs, 0.56–0.73) (Table E6).

Specific farm animal exposures during pregnancy or early childhood were also associated with a reduced risk for atopy (see Fig E1 in this article's Online Repository at www.jacionline.org). The inverse association between atopy and maternal animal exposure during pregnancy did not vary by number of animals (see Table E7 in this article's Online Repository at www.jacionline.org). For childhood exposures before age 6 years, a reduced risk of atopy was noted only among those exposed to 3 or more animal types (Table E7).

We observed no appreciable association with atopy for having been breast-fed, having parents who smoked, or having indoor furry pets prior to age 6 years (Table III). Ever consumption of raw milk was not associated with atopy (Table IV), but raw milk as the primary milk consumed in childhood was associated with reduced odds of atopy (OR, 0.73; 95% CI, 0.58–0.90) (Table IV). Only 62 individuals were IgE positive to milk and another 22 reported "no milk served at home" with no overlap between these 2 groups.

Adjustment for current farm animal exposure (past 12 months) did not materially alter the inverse associations between early-life farming exposures and atopy. For example, the OR for having a mother who performed farm activities while pregnant was essentially unchanged when recent farm animal exposure was included in the model (OR, 0.60; 95% CI, 0.49–0.75). Likewise, adjustment for previous exposure to pesticides did not change results (data not shown). Neither stratification by asthma status, sex, state, or current farm

animal exposure nor interaction *P* values suggested substantial modification of the associations between early-life exposures and atopy by these factors (data not shown).

We attempted to distinguish the independent contributions of the early-life exposures by modeling together those found to be individually associated with reduced risk of atopy: living on a farm when born, mother performing farm activities while pregnant (including working with animals), childhood farm animal exposure before age 6, and consuming raw milk as your main milk (Tables III and IV). Not surprisingly, some of these exposures were correlated (see Table E8 in this article's Online Repository at www.jacionline.org). Living on a farm when born and mother performing farm activities while pregnant were highly correlated (tetrachoric correlation, $\rho = 0.94$). Correlation was only slightly lower between living on a farm when born and childhood farm animal exposure before age 6 ($\rho = 0.84$) as well as mother performing farm activities while pregnant and childhood farm animal exposure before age 6 ($\rho = 0.85$). Given these correlations, including these exposures together resulted, not surprisingly, in mostly null estimates. However, in this multivariable model, having a mother who performed farm activities when pregnant remained significantly associated with decreased odds of adult atopy (OR, 0.69; 95% CI, 0.50–0.96). In addition, when we modeled whether the mother performed farm activities while pregnant pairwise with each of the other early-life exposures in Table III, adjusted ORs were always statistically significant only for the mother performed farm activities while pregnant exposure (ORs, 0.60–0.66; $P < .002$). For our logistic regression model examining atopy in relation to this early-life exposure of mother performing farm activities while pregnant, the Hosmer-Lemeshow test provided no evidence of lack of fit ($P = .95$).

We examined whether the associations between early-life exposures and atopy, as measured by IgE levels, were also observed for current allergic disease defined by self-reported symptoms of hay fever, allergic rhinitis, seasonal allergies, or eczema or use of medications for these conditions in the past 12 months (1920 cases and 1292 noncases) (see Table E9 in this article's Online Repository at www.jacionline.org). Associations for early-life exposures were similar but attenuated with this less specific self-reported outcome compared with the objective atopy outcome.

Asthma and atopy

To evaluate atopy and asthma together, we analyzed early-life exposures in relation to an outcome with 4 levels: neither asthma nor atopy (referent), atopy without asthma, asthma without atopy, and asthma with atopy. Results generally mirrored findings for asthma and atopy modeled separately; namely, early-life farming exposures were associated with a reduced risk of atopy and not asthma. For example, having a mother who performed farm activities while pregnant was associated with reduced risk of atopy with asthma (OR, 0.63; 95% CI, 0.48–0.83) and atopy without asthma (OR, 0.64; 95% CI, 0.47–0.85) but not asthma without atopy (OR, 1.12; 95% CI, 0.92–1.36) (Table V). Excluding cases with likely undiagnosed asthma or asthma/COPD overlap did not materially change these estimates (see Table E10 in this article's Online Repository at www.jacionline.org).

Timing of exposures

To examine the timing of exposures across the life course, we combined information on farm animal exposure *in utero* and farm animal exposure in childhood (before age 6) into 4 categories: exposure in neither time period (referent), *in utero* only, childhood only, and both time periods. No new asthma associations emerged (see Table E11 in this article's Online Repository at www.jacionline.org). For atopy, the inverse association was clearly seen for exposure both *in utero* and in childhood (289 cases; OR, 0.61; 95% CI, 0.47–0.80) (see Table E12 in this article's Online Repository at www.jacionline.org) but not for exposure only in childhood (93 cases; OR, 0.94; 95% CI, 0.68–1.29). Few subjects were exposed only *in utero* (11 cases; OR, 0.75; 95% CI, 0.37–1.53).

We also combined information on farm animal exposure in childhood and current (past year) adult farm animal exposure into 4 categories: exposure in neither time period (referent), childhood only, current adult only, and both time periods. Again we did not identify any new asthma associations (Table E11). For atopy, childhood farm exposure was related to reduced risk regardless of current exposure, but associations were stronger for exposure in both time periods (childhood only: OR, 0.73; 95% CI, 0.55–0.97; both childhood and current adult: OR, 0.61; 95% CI, 0.45–0.83) (Table E12). Current adult exposure only was not associated with atopy (OR, 0.96; 95% CI, 0.62–1.48).

DISCUSSION

In this study of older adults in a US farming cohort, we observed a reduced risk of atopy in relation to *in utero* exposure to the farming environment, living on a farm when born, and exposure to farm animals before the age of 6 years. Raw milk, if the main type of milk consumed in childhood, was also associated with reduced risk of atopy. To the extent that we can separate the effects of these somewhat correlated exposures, the most robust associations appeared to be for the mother performing farm activities while pregnant and atopy. Although being born to a family that lived on a farm was weakly associated with a reduced risk of current asthma, most early-life farming exposures were not associated with current asthma in our adult population.

Previous studies of early-life farm exposure have primarily focused on asthma and allergic disease in childhood rather than adulthood. In particular, the Allergies and Endotoxin Study (ALEX), Protection Against Allergy: Study in Rural Environments (PASTURE), Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL), and Prevention of Allergy Risk factors for Sensitization In Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) studies, conducted in Europe, have examined the impact of farming on asthma and atopy by comparing children who lived on small farms with children who did not[4–7] and identified several aspects of the farming environment as protective, including maternal exposure to farm animals while pregnant, childhood exposure to farm or household animals, and raw milk consumption.[4–7] One US study reported a protective association between living on a farm and childhood wheeze but only in 1 of the 2 counties studied.[32] Other US studies suggest that living on a farm or attending school near a concentrated animal-feeding operation may be associated with an increased risk of childhood asthma.[33–36] A recent meta-

analysis of studies worldwide on the association between exposure to farming in the first year of life and childhood atopy based on objective measures (ie, serum IgE or skin prick test) reported a summary OR of 0.60 (95% CI, 0.51–0.70).[4]

Overall, our results are consistent with the small existing literature in its general lack of support for a protective effect of early-life farming exposure on adult asthma. In the European Community Respiratory Health Survey ([ECRHS], N = 5703), the OR for living on a farm in childhood and adult asthma was 0.82 (95% CI, 0.53–1.27),[11] and in a separate paper among ECRHS participants in France, no association was seen for living on a farm in the first year of life with adult asthma (OR, 1.05; 95% CI, 0.49–2.21).[10] Similar null results for living on a farm in childhood and adult asthma were reported from studies in Germany[15] and Finland,[16] although the latter study reported a near statistically significant protective association for the family having farm animals. Some studies have also examined the impact of farming exposures in childhood and adulthood together. In New Zealand, farm exposure in both childhood and adulthood was strongly associated with a reduced risk of adult asthma and adult wheeze, but associations were attenuated when exposure occurred only in childhood.[17] A study in Poland reported mostly reduced, but nonsignificant ORs for associations of raw milk consumption in the first year of life with childhood and adulthood asthma.[18]

Previous papers from the parent AHS reported reduced prevalence of allergic symptoms among those who grew up on a farm.[25,37] In 2 reports from the ECRHS, the farming environment in the first year of life and growing up on a farm were strongly associated with a reduced risk of adult atopy (OR, 0.47; 95% CI, 0.24–0.93 and OR, 0.68; 95% CI, 0.50–0.94, respectively).[10,11] Similarly, a Danish study of young adults (mean age, 19), a German study of adults ages 18 to 44 years, and a Finnish study of adults age 31 years all reported reduced risk of atopic sensitization associated with early-life farming exposures.[12,13,16] Among 1236 Danish males ages 30 to 40 years, reduced allergic sensitization was seen for upbringing on a farm versus in a city (OR, 0.31; 95% CI, 0.21–0.46).[19] The Saskatchewan Rural Health Study of 1658 adults reported reduced atopy to cat in relation to growing up on a farm.[20] A meta-analysis of adult atopy in relation to exposure to the farming environment in the first year of life reported a summary OR of 0.63 (95% CI, 0.44–0.91),[4] similar to estimates obtained in our study of adults substantially older than those in most previous studies.

Ours is the first study to examine combined atopy and asthma outcomes in adults in relation to early-life environmental farming exposures. Among the studies of children, only the GABRIEL study reported on asthma phenotypes with and without atopy using objective measures. The GABRIEL investigators reported an association between the farming environment and childhood wheeze only in nonatopic participants.[38]

Our work suggests that various maternal and early-life exposures to the farming environment are associated with a persistent reduced risk of adult atopy but not asthma. The hygiene hypothesis has been primarily postulated for allergic disease, defined by hay fever or allergic sensitization, rather than asthma.[21,39] In rodent models of asthma, which serve as a proxy for human disease and have provided mechanistic support for the hygiene hypothesis,[23] what is

usually studied is acute allergic sensitization rather than bronchial hyperresponsiveness *per se*, which is the basis of asthma.[40] Asthma and atopy frequently coexist in children but this concordance decreases over time and does not prove that the asthma is due to the atopy.[41,42] In adults, asthma frequently occurs without atopy.[43] For these reasons, our finding of protective associations with early-life exposure predominantly for atopy, rather than asthma, may not be surprising. This finding may also reflect greater stability of IgE responses versus the more transient and heterogeneous nature of asthma across the life course.[44]

Several studies provide mechanistic evidence for a protective effect of early exposure to the farming environment on allergic disease through changes in the adaptive and innate immune systems. In farm children, higher blood expression levels were observed for the pattern-recognition receptor genes *CD14* (cluster of differentiation 14) and Toll-like receptor 2 (*TLR2*).[45] Another study replicated these findings and further reported increased expression of *TLR4* in children whose mother worked with farm animals while pregnant.[46] Recent work by Schuijs et al.[23] provides a molecular mechanism for protection against allergy by early-life exposure to farm dust; chronic low-dose exposure altered immune cytokine cross talk between epithelial and dendritic cells. This communication was dependent on the A20 enzyme and resulted in suppression of type 2 immune responses.[23]

Our study has several strengths. It is the largest study to examine the relationship of early-life exposures in the farming environment with adult asthma and atopy outcomes in the United States. Because 24.7% of participants in our study (12.6% of farmers and 38.2% of spouses) did not live on a farm at birth, we had the ability to examine associations between early-life farm exposures and asthma and atopy. Further, our study population consisted of older individuals (mean age, 63), which allowed us to assess whether associations between farming exposures and asthma and atopy persist long term into adulthood.

Asthma status was based on self-report. In adults, overlap or mistaken diagnosis between asthma and COPD is a concern. Therefore, we asked about diagnoses of COPD and emphysema and enrolled primarily asthmatics with no previous diagnosis of these conditions. The high prevalence of never-smokers in our study also makes overlap less problematic than in most studies of adults. Another strength of our study is that we assessed atopy objectively using specific IgE.

Because the response rate among subjects targeted for the current study was about 50%, we performed quantitative selection bias analyses using surrogate exposure and outcome data among the entire target population of 44,301 cohort members who completed the second follow-up interview.[47] A full description of the surrogate variables and analysis is provided in the Methods section in the Online Repository at www.jacionline.org). Reassuringly, this assessment indicated a lack of selection bias. Specifically, the ORs for the surrogate farm animal exposure and surrogate outcomes of asthma (0.93) and atopy (0.86) in the entire target population were nearly identical to the estimates obtained for the subjects enrolled in ALHS.

Radon et al[13] also cautioned that studies on farming exposures and adult asthma and atopy may be susceptible to selection bias if individuals with severe asthma or atopy leave

farming. We cannot assess this particular source of bias because participants are either farmers or farm spouses. However, when we asked participants if they had stopped working with farm animals due to respiratory or allergic symptoms, only 4% to 6% of our study population reported that they had. Further, the prevalence of asthma in AHS is 7.2%,[25] which is similar to population-based estimates for current asthma among adults in Iowa (6.9%) and North Carolina (7.7%).[48,49] For atopy, at the cut point of 0.35 IU/mL presented in the US National Health and Nutrition Examination Survey (NHANES), the prevalence in our study is 42.8%, comparable to that in the US general population (44.2%).[50]

Older adults can have difficulty recalling farming exposures in childhood, and no one can directly recall events that happen *in utero* or during infancy. Therefore, we asked whether the family was living on a farm at the time of the participant's birth, which is likely known with certainty. We also asked about exposures by 6 years, an age when memories are more reliably formed. In an effort to increase the quality of information about exposures, particularly *in utero* and during infancy, we sent participants the questionnaire in advance of home visits so that they could consult family members if needed. About 20% of respondents reported receiving help from family members to complete the early-life questionnaire. The frequency of most early-life exposures were similar among those who did or did not receive help (data not shown), though individuals who consulted family members had fewer missing values for raw milk consumption.

Our study suggests that early-life farming exposures have little or no association with adult asthma. In contrast, having a mother who performed farm activities (including working with animals while pregnant), living on a farm when born, farm animal exposure before age 6 years, and primarily consuming raw milk were all strongly associated with a reduced risk of adult atopy. Although disentangling the effects of correlated exposures is difficult, the strongest signal appears to come from having a mother who performed farm activities while pregnant, nearly all of whom worked with farm animals while pregnant. These results support the importance of *in utero* and early-life exposures in the etiology of allergic disease and specifically implicate atopy independent of asthma. This study extends previous research conducted in Europe by demonstrating that *in utero* and early-life exposures to the farming environment are strongly inversely associated with allergic sensitization in a large US-based farming cohort of older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

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

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Key messages

- *In utero* and early-childhood exposure to the farming environment had little or no association with current asthma in an older adult US farming population.
- In contrast, early-life farming exposures, particularly having a mother who performed farm activities while pregnant, were associated with reduced odds of atopy in adulthood.
- The protective association of early-life farming exposures on atopy previously noted in studies of children appears to endure across the life course well into adulthood.

TABLE I

Demographics of participants in the ALHS, 2009–2013

	Asthma analysis	Atopy analysis
	n (%)	n (%)
Characteristic	**3229**	**3104**
Sex		
Male	1647 (51.0)	1589 (51.2)
Female	1582 (49.0)	1515 (48.8)
Enrollment status		
Farmer	1698 (52.9)	1638 (52.8)
Spouse	1531 (47.4)	1466 (47.2)
State		
Iowa	2269 (70.3)	2180 (70.2)
North Carolina	960 (29.7)	924 (29.8)
Race		
White	3174 (98.3)	3052 (98.3)
Other	55 (1.7)	52 (1.7)
Asthma status		
Case	1198 (37.1)	1155 (37.0)
Control	2031 (62.9)	1949 (63.0)
Smoking status		
Never	2149 (66.6)	2061 (66.4)
Former	946 (29.3)	911 (29.4)
Current	134 (4.2)	132 (4.2)
Pack years, mean ± SD	6.0 ± 14.9	5.99 ± 15.0
Age (y), mean ± SD	62.7 ± 11.0	62.9 ± 11.1

TABLE II

Associations between early-life farm exposures and current asthma in the ALHS

Early-life exposures*	Cases n (%)	Noncases n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)†
Total	1198	2031		
Mother lived on farm while pregnant				
No	328 (27.4)	476 (23.4)	Ref	Ref
Yes	851 (71.0)	1534 (75.5)	0.81 (0.68–0.95)	0.88 (0.74–1.05)
Missing	19 (1.6)	21 (1.0)		
Mother performed farm activities while pregnant				
No	374 (31.2)	604 (29.7)	Ref	Ref
Yes	755 (63.0)	1332 (65.6)	0.92 (0.78–1.07)	1.02 (0.87–1.21)
Missing	69 (5.8)	95 (4.7)		
Mother worked with farm animals while pregnant				
No	371 (31.0)	624 (30.7)	Ref	Ref
Yes	722 (60.3)	1257 (61.9)	0.97 (0.83–1.13)	1.10 (0.93–1.30)
Missing	105 (8.8)	150 (7.4)		
Family lived on farm when born				
No	327 (27.3)	472 (23.2)	Ref	Ref
Yes	856 (71.5)	1537 (75.7)	0.80 (0.68–0.95)	0.89 (0.74–1.06)
Missing	15 (1.3)	22 (1.1)		
Farm animal exposure before age 3				
No	316 (26.4)	540 (26.6)	Ref	Ref
Yes	762 (63.6)	1313 (64.6)	0.99 (0.84–1.17)	1.11 (0.93–1.32)
Missing	120 (10.0)	178 (8.8)		
Farm animal exposure before age 6				
No	238 (19.9)	409 (20.1)	Ref	Ref
Yes	913 (76.2)	1538 (75.7)	1.02 (0.85–1.22)	1.18 (0.97–1.42)
Missing	47 (3.9)	84 (4.1)		
Breast-fed				
No	411 (34.3)	684 (33.7)	Ref	Ref
Yes	568 (47.4)	961 (47.3)	0.98 (0.84–1.16)	1.14 (0.95–1.35)
Missing	219 (18.3)	386 (19.0)		
Raw milk				
No	239 (19.9)	422 (20.8)	Ref	Ref
Yes	889 (74.2)	1498 (73.8)	1.05 (0.88–1.25)	1.23 (1.01–1.49)
Missing	70 (5.8)	111 (5.5)		
Indoor furry pets before age 6				
No	839 (70.0)	1480 (72.9)	Ref	Ref
Yes	340 (28.4)	507 (25.0)	1.18 (1.01–1.39)	1.14 (0.97–1.35)

Early-life exposures*	Cases n (%)	Noncases n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)†
Missing	19 (1.6)	44 (2.2)		
Mother smoked cigarettes when pregnant				
No	1022 (85.3)	1764 (86.9)	Ref	Ref
Yes	117 (9.8)	169 (8.3)	1.20 (0.93–1.53)	1.14 (0.88–1.47)
Missing	59 (4.9)	98 (4.8)		
Parents smoked cigarettes in house before age 6				
No	503 (42.0)	936 (46.1)	Ref	Ref
Yes	655 (54.7)	1043 (51.4)	1.17 (1.01–1.35)	1.17 (1.01–1.36)
Missing	40 (3.3)	52 (2.6)		

*Exposures are modeled individually, one at a time.

†Logistic regression used to estimate ORs adjusted for age, sex, race, state, and pack years.

TABLE III

Associations between early-life exposures and adult atopy in the ALHS

Early-life exposures*	Atopic n (%)†	Nonatopic n (%)	Crude OR (95% CI)	OR (95% CI)‡
Total	578	2526		
Mother lived on farm while pregnant				
No	174 (30.1)	588 (23.3)	Ref	Ref
Yes	394 (68.2)	1901 (75.3)	0.70 (0.57–0.86)	0.69 (0.55–0.85)
Missing	10 (1.7)	37 (1.5)		
Mother performed farm activities while pregnant				
No	217 (37.5)	711 (28.1)	Ref	Ref
Yes	326 (56.4)	1683 (66.6)	0.63 (0.52–0.77)	0.60 (0.48–0.74)
Missing	35 (6.1)	132 (5.2)		
Mother worked with farm animals while pregnant				
No	217 (37.5)	734 (29.1)	Ref	Ref
Yes	305 (52.8)	1601 (63.4)	0.64 (0.53–0.78)	0.62 (0.50–0.77)
Missing	56 (9.7)	191 (7.6)		
Family lived on farm when born				
No	175 (30.3)	582 (23)	Ref	Ref
Yes	395 (68.3)	1911 (75.7)	0.69 (0.56–0.84)	0.67 (0.54–0.84)
Missing	8 (1.4)	33 (1.3)		
Farm animal exposure before age 3				
No	182 (31.5)	638 (25.3)	Ref	Ref
Yes	337 (58.3)	1656 (65.6)	0.71 (0.58–0.87)	0.68 (0.54–0.84)
Missing	59 (10.2)	232 (9.2)		
Farm animal exposure before age 6				
No	141 (24.4)	476 (18.8)	Ref	Ref
Yes	419 (72.5)	1939 (76.8)	0.73 (0.59–0.90)	0.68 (0.54–0.86)
Missing	18 (3.1)	111 (4.4)		
Breast-fed				
No	208 (36)	846 (37.5)	Ref	Ref
Yes	257 (44.5)	1210 (56.4)	0.86 (0.71–1.06)	0.95 (0.76–1.20)
Missing	113 (19.6)	470 (6.1)		
Indoor furry pets before age 6				
No	396 (37.5)	1829 (37.5)	Ref	Ref
Yes	167 (56.4)	644 (56.4)	1.20 (0.98–1.47)	1.18 (0.95–1.45)
Missing	15 (6.1)	53 (6.1)		
Mother smoked cigarettes while pregnant				
No	483 (37.5)	2185 (37.5)	Ref	Ref
Yes	62 (56.4)	214 (56.4)	1.31 (0.97–1.77)	1.14 (0.84–1.57)

Early-life exposures*	Atopic n (%)†	Nonatopic n (%)	Crude OR (95% CI)	OR (95% CI)‡
Missing	33 (6.1)	127 (6.1)		
Parents smoked cigarettes in house before age 6				
No	243 (37.5)	1126 (37.5)	Ref	Ref
Yes	315 (56.4)	1322 (56.4)	1.10 (0.92–1.33)	1.05 (0.86–1.27)
Missing	20 (6.1)	78 (6.1)		

*Exposures are modeled individually, one at a time.

†Any atopy defined 1 or more allergen-specific IgEs > 0.70 IU/mL.

‡Logistic regression used to estimate ORs adjusted for age, sex, race, state, asthma case-control status, and pack years.

TABLE IV

Association between raw milk consumption and adult atopy in the ALHS

Raw milk exposure*	Atopic n (%)†	Nonatopic n (%)	OR (95% CI)‡	*P* value
Total	578	2526		
Ever drank raw milk				
No	132 (22.8)	498 (19.7)	Ref	
Yes	402 (69.6)	1895 (75.0)	0.85 (0.67–1.09)	.21
Missing	44 (7.6)	133 (5.3)		
Raw milk before or after age 6				
Never	132 (22.8)	498 (19.7)	Ref	
Start after age 6	78 (13.5)	264 (10.5)	1.10 (0.79–1.53)	.57
Start before age 6	320 (55.4)	1613 (63.9)	0.79 (0.61–1.02)	.07
Missing	48 (8.3)	151 (6.0)		
Was main milk raw milk				
No	248 (42.9)	888 (35.2)	Ref	
Yes	302 (52.2)	1544 (61.1)	0.73 (0.58–0.90)	.004
Missing	28 (4.8)	94 (3.7)		
Ever raw milk, main milk				
Never raw milk	129 (22.3)	478 (18.9)	Ref	
Ever raw milk, main milk not raw	90 (15.6)	325 (12.9)	1.03 (0.76–1.41)	.84
Ever raw milk, main milk raw	298 (51.6)	1530 (60.6)	0.75 (0.58–0.98)	.04
Missing	61 (10.6)	193 (7.6)		

*Twenty-two participants (7 atopic and 15 nonatopic) who reported not drinking any type of milk in childhood were included in the referent categories of these analyses (eg, never drank raw milk and main milk not raw). Excluding these individuals did not materially change estimates.

†Any atopy defined as 1 or more allergen-specific IgEs > 0.70 IU/mL.

‡Logistic regression used to estimate ORs adjusted for age, sex, race, state, asthma case-control status, and pack years.

TABLE V

Associations between early-life exposures and adult atopy and asthma using multinomial regression in the ALHS

Early-life exposures*	No exposure	Yes exposure	OR (95% CI)†	*P* value
Mother lived on farm when pregnant				
Asthma = no, atopy = no	372	1298	Ref	
Asthma = no, atopy = yes‡	75	180	0.63 (0.46–0.86)	.004
Asthma = yes, atopy = no	216	603	0.88 (0.72–1.08)	.22
Asthma = yes, atopy = yes‡	99	214	0.66 (0.50–0.88)	.004
Mother performed farm activities when pregnant				
Asthma = no, atopy = no	477	1132	Ref	
Asthma = no, atopy = yes	93	153	0.64 (0.47–0.85)	.003
Asthma = yes, atopy = no	234	551	1.12 (0.92–1.36)	.27
Asthma = yes, atopy = yes	124	173	0.63 (0.48–0.83)	.001
Mother worked with farm animals when pregnant				
Asthma = no, atopy = no	500	1070	Ref	
Asthma = no, atopy = yes	96	141	0.65 (0.49–0.88)	.006
Asthma = yes, atopy = no	234	531	1.21 (0.99–1.47)	.07
Asthma = yes, atopy = yes	121	164	0.72 (0.55–0.95)	.02
Family lived on farm when born				
Asthma = no, atopy = no	368	1302	Ref	
Asthma = no, atopy = yes	75	181	0.62 (0.46–0.85)	.003
Asthma = yes, atopy = no	214	609	0.89 (0.73–1.09)	.27
Asthma = yes, atopy = yes	100	214	0.64 (0.49–0.86)	.002
Farm animal exposure before age 6				
Asthma = no, atopy = no	321	1298	Ref	
Asthma = no, atopy = yes	65	183	0.64 (0.46–0.90)	.009
Asthma = yes, atopy = no	155	641	1.18 (0.94–1.48)	.15
Asthma = yes, atopy = yes	76	236	0.85 (0.63–1.16)	.30
Indoor furry pets before age 6				
Asthma = no, atopy = no	1243	410	Ref	
Asthma = no, atopy = yes	175	74	1.33 (0.98–1.79)	.06
Asthma = yes, atopy = no	586	234	1.18 (0.97–1.43)	.10
Asthma = yes, atopy = yes	221	93	1.23 (0.94–1.62)	.13
Parents smoked in house before age 6				
Asthma = no, atopy = no	770	872	Ref	
Asthma = no, atopy = yes	121	130	0.93 (0.71–1.22)	.60
Asthma = yes, atopy = no	356	450	1.13 (0.95–1.34)	.18
Asthma = yes, atopy = yes	122	185	1.33 (1.03–1.71)	.03

Early-life exposures*	No exposure	Yes exposure	OR (95% CI)†	*P* value
Breast-fed as infant				
Asthma = no, atopy = no	565	805	Ref	
Asthma = no, atopy = yes	91	114	0.95 (0.68–1.31)	.74
Asthma = yes, atopy = no	281	405	1.15 (0.93–1.41)	.19
Asthma = yes, atopy = yes	117	143	1.11 (0.83–1.48)	.48
Ever drank raw milk				
Asthma = no, atopy = no	337	1271	Ref	
Asthma = no, atopy = yes	62	173	0.76 (0.54–1.08)	.12
Asthma = yes, atopy = no	161	624	1.17 (0.93–1.48)	.17
Asthma = yes, atopy = yes	70	229	1.13 (0.82–1.55)	.46
Raw milk was main milk				
Asthma = no, atopy = no (ref)	593	1034		
Asthma = no, atopy = yes	109	140	0.74 (0.54–1.01)	.06
Asthma = yes, atopy = no	295	510	1.15 (0.94–1.40)	.18
Asthma = yes, atopy = yes	139	162	0.82 (0.62–1.09)	.18

*Exposures are modeled individually.

†Logistic regression used to estimate ORs adjusted for age, sex, race, state, and pack years.

‡Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL.