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 2016;■■■:■■■-■■■.)

Key words: *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

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

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).

TABLE I. Demographics of participants in the ALHS, 2009-2013

Characteristic	Asthma analysis n (%) 3229	Atopy analysis n (%) 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)
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.

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

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)
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.

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]

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
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.

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.

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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.**

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METHODS

Quantitative bias assessment

The response rate among subjects targeted for the current study was about 50%. Although the comparable response rates between asthma cases and noncases provide some reassurance, selection bias could have occurred if nonresponse was jointly conditional on both early-life farm exposure and asthma or atopic status. Because we have some surrogate data on both the exposure and outcomes among the entire target population of 44,301 cohort members who completed the second follow-up interview, we were able to perform quantitative selection bias analyses.[E1] As a surrogate for early-life farm exposure, we had the question: "As a child, how much time did you spend around farm animals (for example, cattle, pigs, or chickens)?" Though not identical to our early-life questions, when dichotomized into categories of monthly or more frequently versus never or less than once per month, this surrogate was strongly correlated with the early-life farm exposure variables most associated with atopy in our study (tetrachoric correlations, 0.73-0.84; $P < .0001$ for all correlations).

When we analyzed the surrogate variable for farm animal contact before age 18 in the entire target population, the OR for asthma was 0.93, which is identical to that for the subjects enrolled in our study. For atopy, IgE measurements were only made in participants in our substudy so we used the following surrogate atopy end point available on all 44,301 cohort members: self-report of diagnosis of hay fever, seasonal allergies, or allergic rhinitis. When we examined the association between our surrogate early-life farm animal exposure variable and surrogate atopy end point in the entire target population, we observed reduced odds of atopy (OR, 0.86; 95% CI, 0.81-0.96). Among our study participants, the corresponding OR is nearly identical at 0.89 with a wider CI (0.72-1.10), reflecting the much smaller sample size. Thus, our quantitative bias assessment reassuringly indicates a lack of selection bias for the evaluation of the association of early-life farm exposure with asthma and atopy.

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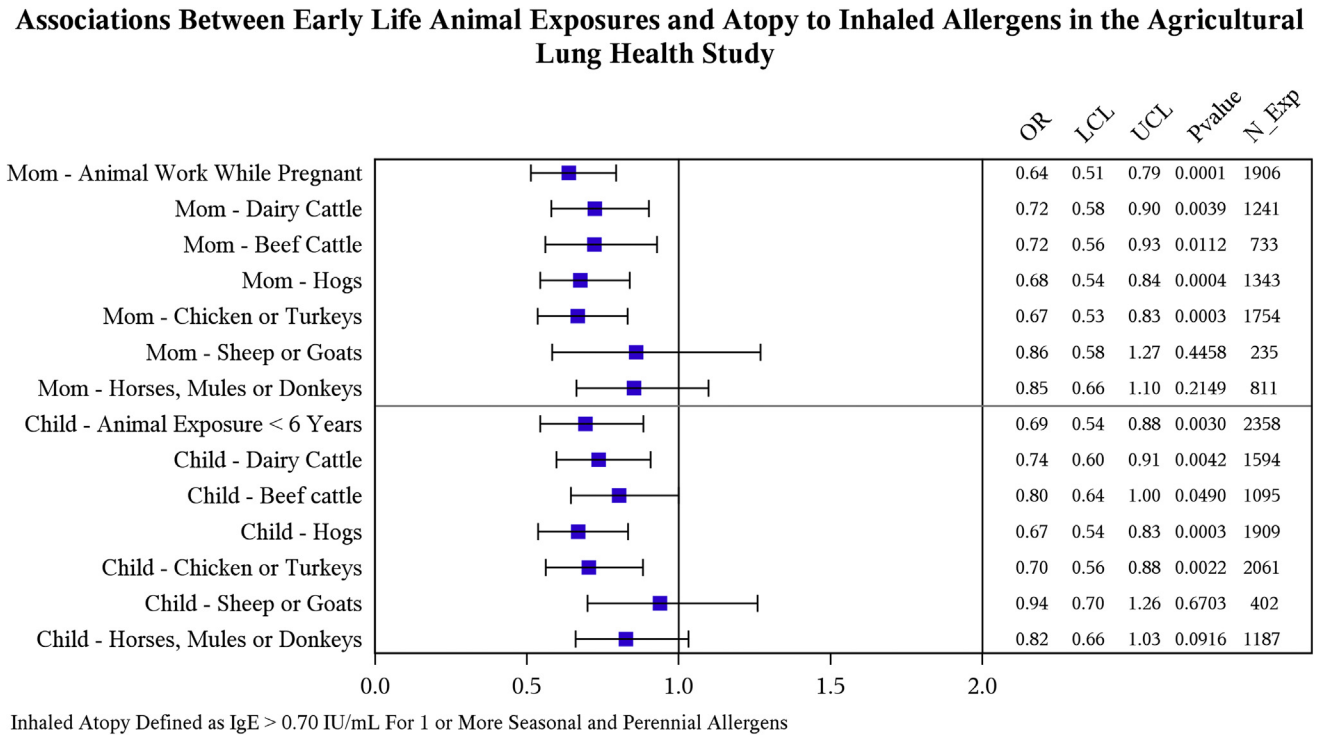

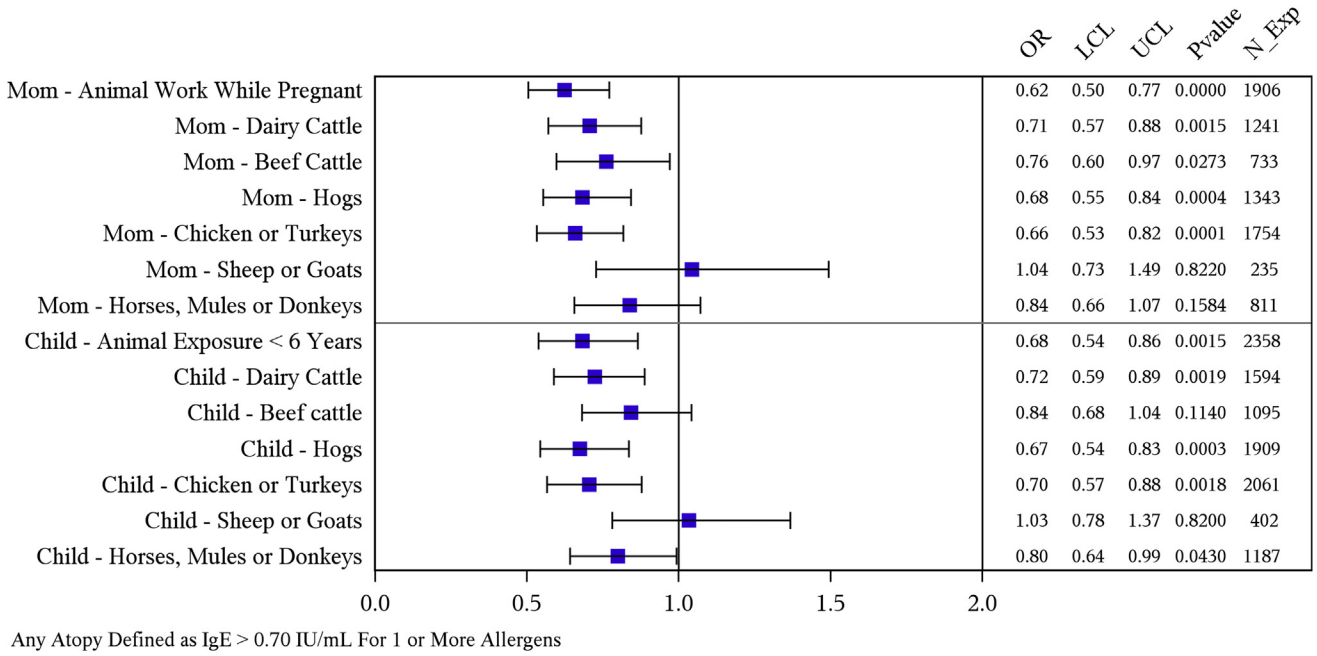

FIG E1. Associations between exposure to specific farm animals and adult atopy in the ALHS. Results are adjusted for age, sex, race, state, pack years, and asthma case-control status. *LCL/UCL*, Lower/upper confidence limit (95%); *N_Exp*, count of exposed individuals.

TABLE E1. Questions from the ALHS early life questionnaire analyzed for association with asthma or atopy

Question	Possible responses
Did your mother live on a farm while she was pregnant with you?	Yes, no, don't know
Did your mother perform any farm activities while she was pregnant with you?	Yes, no, don't know
Did your mother work with or around farm animals such as cattle, horses, hogs, poultry, sheep or goats while pregnant with you?	Yes, no, don't know
If yes, which of the following types of animals did your mother work with or around?	Yes, no, don't know
Dairy cattle	Yes, no, don't know
Beef cattle	Yes, no, don't know
Hogs	Yes, no, don't know
Chickens or turkeys	Yes, no, don't know
Sheep or goats	Yes, no, don't know
Horses, mules, or donkeys	Yes, no, don't know
Was your family living on a farm when you were born, regardless of whether they were doing farm work?	Yes, no, don't know
At any time before you were age 3, did you spend time around farm animals, such as cattle, horses, hogs, poultry, sheep or goats at least weekly or for months at a time?	Yes, no, don't know
At any time between age 3 and your sixth birthday, did you spend time around farm animals at least weekly or for months at a time?	Yes, no, don't know
Up until your sixth birthday, which of the following types of farm animals did you spend time around?	
Dairy cattle	Yes, no, don't know
Beef cattle	Yes, no, don't know
Hogs	Yes, no, don't know
Chickens or turkeys	Yes, no, don't know
Sheep or goats	Yes, no, don't know
Horses, mules, or donkeys	Yes, no, don't know
Were you ever breastfed as an infant?	Yes, no, don't know
When you were a child, what was the main type of milk served in your home?	Raw milk, pasteurized/store-bought milk, no milk was served at home, don't know
Have you ever drunk raw milk?	Yes, no, don't know
If yes, how old were you when you first drank raw milk? If you are not sure of your answer, please provide your best guess.	Less than 1 year, 1 year old, 2 years old, 3 years old, 4 years old, 5 years old, 6 or older
How old were you when you last drank raw milk? If less than 1 year old, write "00." If you still drink raw milk, write your current age. If you are not sure, please provide your best guess.	Open response
At any time before you were age 6, did you have any dogs, cats, other furry pets such as hamsters, or birds living inside your home?	Yes, no, don't know
Did your mother smoke cigarettes when she was pregnant with you?	Yes, no, don't know
At any time before you were age 6, did anyone living in your home smoke cigarettes?	Yes, no, don't know
If yes, at any time before you were age 6, did your mother smoke cigarettes?	Yes, no, don't know
If yes, at any time before you were age 6, did your father smoke cigarettes?	Yes, no, don't know

TABLE E2. Sensitivity analysis of associations between early-life farm exposures and current asthma in the ALHS

		Excluding asthma cases with COPD overlap		Excluding asthma cases with COPD overlap and likely undiagnosed asthma cases	
Early-life exposures*	**Noncases n**	**Cases n**	**OR (95% CI)†**	**Cases n**	**OR (95% CI)†**
Total	2031	1161		860	
Mother lived on farm while pregnant					
No	476	321	Ref	253	Ref
Yes	1534	822	0.88 (0.73-1.04)	594	0.81 (0.67-0.98)
Missing	21	18		13	
Mother performed farm activities while pregnant					
No	604	367	Ref	283	Ref
Yes	1332	728	1.01 (0.86-1.20)	535	0.96 (0.80-1.15)
Missing	95	66		42	
Mother worked with farm animals while pregnant					
No	624	364	Ref	275	Ref
Yes	1257	696	1.09 (0.92-1.29)	512	1.05 (0.87-1.27)
Missing	150	101		73	
Family lived on farm when born					
No	472	320	Ref	250	Ref
Yes	1537	826	0.88 (0.74-1.05)	596	0.81 (0.67-0.98)
Missing	22	15		14	
Farm animal exposure before age 3					
No	540	308	Ref	233	Ref
Yes	1313	739	1.10 (0.93-1.32)	542	1.08 (0.89-1.32)
Missing	178	114		85	
Farm animal exposure before age 6					
No	409	232	Ref	185	Ref
Yes	1538	887	1.18 (0.97-1.43)	643	1.08 (0.88-1.33)
Missing	84	42		32	
Breast-fed					
No	684	398	Ref	290	Ref
Yes	961	549	1.16 (0.97-1.39)	409	1.16 (0.96-1.42)
Missing	386	214		161	
Raw milk					
No	422	235	Ref	181	Ref
Yes	1498	856	1.23 (1.01-1.50)	629	1.14 (0.92-1.41)
Missing	111	70		50	
Indoor furry pets before age 6					
No	1480	810	Ref	584	Ref
Yes	507	332	1.15 (0.98-1.36)	263	1.26 (1.05-1.50)
Missing	44	19		13	
Mother smoked cigarettes when pregnant					
No	1764	991	Ref	723	Ref
Yes	169	113	1.12 (0.87-1.45)	94	1.27 (0.96-1.67)
Missing	98	57		43	
Parents smoked cigarettes in house before age 6					
No	936	485	Ref	338	Ref
Yes	1043	637	1.18 (1.02-1.38)	492	1.27 (1.08-1.51)
Missing	52	39		30	

*Exposures are modeled individually, one at a time.
†Logistic regression used to estimate ORs adjusted for age, sex, race, state, and pack years.

TABLE E3. Associations between early-life exposures to farm animals and current asthma in the ALHS

	Mother worked with farm animals while pregnant*				Farm animals before age 6*			
	Cases	Noncases	OR (95% CI)†	*P* value	Cases	Noncases	OR (95% CI)†	*P* value
Any farm animals								
No	371	624	Ref		238	409	Ref	
Yes	722	1257	1.10 (0.93-1.30)	.28	913	1538	1.18 (0.97-1.42)	.10
Missing	105	150			47	84		
Dairy cattle								
No	575	1002	Ref		511	842	Ref	
Yes	473	814	1.14 (0.97-1.34)	.11	612	1049	1.1 (0.94-1.29)	.24
Missing	150	215			75	140		
Beef cattle								
No	739	1263	Ref		662	1113	Ref	
Yes	272	498	0.97 (0.81-1.17)	.78	422	722	1.03 (0.87-1.21)	.73
Missing	187	270			114	196		
Hogs								
No	526	887	Ref		382	614	Ref	
Yes	490	902	1.03 (0.87-1.21)	.75	722	1260	1.04 (0.87-1.22)	.69
Missing	182	242			94	157		
Chickens or turkeys								
No	423	701	Ref		336	562	Ref	
Yes	659	1160	1.08 (0.91-1.27)	.39	788	1354	1.11 (0.93-1.32)	.23
Missing	116	170			74	115		
Sheep or goats								
No	950	1617	Ref		942	1572	Ref	
Yes	83	161	0.95 (0.71-1.25)	.70	155	265	1.05 (0.84-1.3)	.69
Missing	165	253			101	194		
Horses, mules, or donkeys								
No	735	1241	Ref		659	1092	Ref	
Yes	308	542	1.13 (0.94-1.36)	.20	459	773	1.14 (0.96-1.35)	.14
Missing	155	248			80	166		

*Exposures are modeled individually.
†Logistic regression used to estimate ORs adjusted for age, sex, race, state, and pack years.

TABLE E4. Associations between raw milk consumption and current asthma in the ALHS

Raw milk exposure*	Cases	Noncases	OR (95% CI)†	*P* value
Ever drank raw milk				
No	239	422	Ref	
Yes	889	1498	1.23 (1.01-1.49)	.04
Missing	70	111		
Raw milk before or after age 6				
Never	239	422	Ref	
Start after age 6	147	211	1.30 (1.00-1.70)	.05
Start before age 6	729	1278	1.19 (0.97-1.45)	.10
Missing	83	120		
Main milk was raw milk				
No	451	742	Ref	
Yes	698	1218	1.11 (0.93-1.32)	.25
Missing	49	71		
Ever raw milk, main milk				
Never raw milk	233	404	Ref	
Ever raw milk, main milk not raw	170	265	1.17 (0.91-1.51)	.23
Ever raw milk, main milk raw	692	1203	1.20 (0.97-1.47)	.10
Missing	103	159		

*Twenty-four participants (12 cases and 12 noncases) 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.

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

TABLE E5. Associations between early-life exposures and adult atopy by allergen type in the ALHS

	No exposure		Exposure			
Early-life exposures*	**Atopic†**	**Nonatopic**	**Atopic**	**Nonatopic**	**OR (95% CI)‡**	***P* value**
Mother lived on farm when pregnant						
Atopy to any allergen	174	588	394	1901	0.68 (0.55-0.85)	.001
Atopy to inhaled allergen	165	597	368	1927	0.69 (0.55-0.87)	.001
Atopy to perennial allergen	121	641	277	2018	0.74 (0.57-0.95)	.02
Atopy to seasonal allergen	75	687	171	2124	0.72 (0.53-0.99)	.04
Atopy to food allergen	27	735	76	2219	0.79 (0.49-1.27)	.33
Mother performed farm activities when pregnant						
Atopy to any allergen	217	711	326	1683	0.60 (0.48-0.74)	<.001
Atopy to inhaled allergen	205	723	305	1704	0.61 (0.49-0.75)	<.001
Atopy to perennial allergen	154	774	228	1781	0.63 (0.50-0.80)	<.001
Atopy to seasonal allergen	93	835	144	1865	0.65 (0.48-0.87)	.004
Atopy to food allergen	36	892	64	1945	0.67 (0.44-1.05)	.08
Mother worked with farm animals when pregnant						
Atopy to any allergen	217	734	305	1601	0.62 (0.50-0.77)	<.001
Atopy to inhaled allergen	204	747	286	1620	0.64 (0.51-0.79)	<.001
Atopy to perennial allergen	150	801	216	1690	0.68 (0.53-0.87)	.002
Atopy to seasonal allergen	95	856	131	1775	0.66 (0.49-0.89)	.006
Atopy to food allergen	39	912	58	1848	0.61 (0.39-0.94)	.03
Family lived on farm when born						
Atopy to any allergen	175	582	395	1911	0.67 (0.54-0.84)	<.001
Atopy to inhaled allergen	165	592	370	1936	0.68 (0.55-0.86)	.001
Atopy to perennial allergen	122	635	277	2029	0.72 (0.56-0.93)	.01
Atopy to seasonal allergen	76	681	171	2135	0.71 (0.52-0.96)	.03
Atopy to food allergen	32	725	71	2235	0.60 (0.38-0.94)	.03
Farm animal exposure before age 3						
Atopy to any allergen	182	638	337	1656	0.68 (0.54-0.84)	<.001
Atopy to inhaled allergen	173	647	315	1678	0.67 (0.54-0.84)	<.001
Atopy to perennial allergen	127	693	235	1758	0.70 (0.55-0.90)	.006
Atopy to seasonal allergen	80	740	148	1845	0.70 (0.52-0.95)	.02
Atopy to food allergen	26	794	71	1922	1.00 (0.62-1.60)	.99
Farm animal exposure before age 6						
Atopy to any allergen	141	476	419	1939	0.68 (0.54-0.86)	.002
Atopy to inhaled allergen	133	484	393	1965	0.69 (0.54-0.88)	.003
Atopy to perennial allergen	95	522	297	2061	0.76 (0.58-1.00)	.05
Atopy to seasonal allergen	63	554	182	2176	0.70 (0.50-0.97)	.03
Atopy to food allergen	19	598	84	2274	0.99 (0.58-1.69)	.97

*Exposures are modeled individually.
†Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL in that group.
‡Logistic regression used to estimate ORs adjusted for age, sex, race, state, pack years, and asthma case-control status.

TABLE E6. Associations between early-life exposures and adult atopy by cut point in the ALHS

	No exposure		Exposure			
Early-life exposures*	**Atopic†**	**Nonatopic**	**Atopic**	**Nonatopic**	**OR (95% CI)‡**	***P* value**
Mother lived on farm when pregnant						
0.35 IU/mL	353	409	954	1341	0.82 (0.69-0.98)	.03
0.70 IU/mL	174	588	394	1901	0.69 (0.55-0.85)	.001
3.50 IU/mL	65	697	146	2149	0.73 (0.52-1.01)	.06
Mother performed farm activities when pregnant						
0.35 IU/mL	438	490	816	1193	0.76 (0.64-0.90)	.001
0.70 IU/mL	217	711	326	1683	0.60 (0.49-0.74)	<.001
3.50 IU/mL	88	840	119	1890	0.56 (0.41-0.77)	<.001
Mother worked with farm animals when pregnant						
0.35 IU/mL	449	502	770	1136	0.76 (0.64-0.89)	.001
0.70 IU/mL	217	734	305	1601	0.62 (0.50-0.77)	<.001
3.50 IU/mL	88	863	110	1796	0.57 (0.42-0.79)	.001
Family lived on farm when born						
0.35 IU/mL	354	403	957	1349	0.81 (0.68-0.96)	.02
0.70 IU/mL	175	582	395	1911	0.67 (0.54-0.84)	<.001
3.50 IU/mL	66	691	146	2160	0.70 (0.50-0.98)	.04
Farm animal exposure before age 3						
0.35 IU/mL	385	435	820	1173	0.79 (0.67-0.94)	.009
0.70 IU/mL	182	638	337	1656	0.68 (0.54-0.84)	<.001
3.50 IU/mL	69	751	122	1871	0.67 (0.48-0.93)	.02
Farm animal exposure before age 6						
0.35 IU/mL	281	336	998	1360	0.88 (0.72-1.06)	.17
0.70 IU/mL	141	476	419	1939	0.68 (0.54-0.86)	.002
3.50 IU/mL	60	557	150	2208	0.57 (0.40-0.80)	.001

*Exposures are modeled individually.
†Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL in that group.
‡Logistic regression used to estimate ORs adjusted for age, sex, race, state, pack years, and asthma case-control status.

TABLE E7. Associations between the number of types of farm animals to which subjects were exposed *in utero* or early life and adult atopy in the ALHS

	Atopic*	Nonatopic	OR (95% CI)†	*P* value
No. of farm animal types exposed to *in utero*				
None	218	740	Ref	
1 vs 0	42	228	0.62 (0.43-0.91)	.02
2 vs 0	53	262	0.66 (0.47-0.93)	.02
3 vs 0	81	379	0.68 (0.51-0.92)	.01
4 vs 0	75	436	0.55 (0.41-0.75)	<.001
5 or more vs 0	53	288	0.61 (0.43-0.87)	.007
No. of farm animal types exposed to before age 6				
None	142	481	Ref	
1 vs 0	33	145	0.73 (0.47-1.13)	.16
2 vs 0	83	245	1.01 (0.73-1.40)	.95
3 vs 0	104	492	0.64 (0.47-0.86)	.003
4 vs 0	110	617	0.54 (0.40-0.74)	<.001
5 or more vs 0	87	429	0.64 (0.46-0.88)	.007

*Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL.
†Logistic regression used to estimate ORs adjusted for age, sex, race, state, pack years, and asthma case-control status.

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TABLE E8. Tetrachoric correlations between early life farming exposures in the ALHS

	Mother lived on farm while pregnant	Mother performed farm activities while pregnant	Mother worked with farm animals while pregnant	Family lived on farm when born	Farm animal exposure before age 3	Farm animal exposure before age 6	Breast-fed	Raw milk
Mother performed farm activities while pregnant	0.95	—	—	—	—	—	—	—
Mother worked with farm animals while pregnant	0.94	0.9997	—	—	—	—	—	—
Family lived on farm when born	0.996	0.94	0.93	—	—	—	—	—
Farm animal exposure before age 3	0.84	0.85	0.86	0.84	—	—	—	—
Farm animal exposure before age 6	0.85	0.85	0.87	0.84	0.999	—	—	—
Breast-fed	0.23	0.31	0.33	0.23	0.24	0.24	—	—
Raw milk	0.48	0.52	0.54	0.48	0.47	0.55	0.48	—
Main milk raw milk	0.62	0.64	0.64	0.63	0.62	0.69	0.45	0.999

Tetrachoric correlation values presented in this table are based on early SAS 9.4 proc corr. Depending on the pair of exposure variables in question, n values ranged from 2421 (mom worked with farm animals while pregnant vs breast-fed) to 3173 (mom lived on farm while pregnant vs family lived on farm when born). Limiting analysis to individuals with atopy data changed results by < 0.02 for all data points. $P < .0001$ for all correlations.

TABLE E9. Associations between early-life exposures and adult allergic symptoms in the ALHS

Early-life exposures*	Current allergic disease† (%)	No current allergic disease (%)	OR (95% CI)‡
Total	1920	1292	
Mother lived on farm while pregnant			
No	540 (28.1)	263 (20.4)	Ref
Yes	1353 (70.5)	1016 (78.6)	0.80 (0.66-0.97)
Missing	27 (1.4)	13 (1.0)	
Mother performed farm activities while pregnant			
No	629 (32.8)	348 (26.9)	Ref
Yes	1187 (61.8)	884 (68.4)	0.86 (0.72-1.03)
Missing	104 (5.4)	60 (4.6)	
Mother worked with farm animals while pregnant			
No	641 (33.4)	352 (27.2)	Ref
Yes	1124 (58.5)	840 (65.0)	0.86 (0.72-1.03)
Missing	155 (8.1)	100 (7.7)	
Family lived on farm when born			
No	544 (28.3)	254 (19.7)	Ref
Yes	1353 (70.5)	1024 (79.3)	0.75 (0.62-0.91)
Missing	23 (1.2)	14 (1.1)	
Farm animal exposure before age 3			
No	546 (28.4)	307 (23.8)	Ref
Yes	1194 (62.2)	869 (67.3)	0.91 (0.75-1.09)
Missing	180 (9.4)	116 (9.0)	
Farm animal exposure before age 6			
No	418 (21.8)	228 (17.7)	Ref
Yes	1430 (74.5)	1005 (77.8)	0.95 (0.77-1.16)
Missing	72 (3.8)	59 (4.6)	
Breast-fed			
No	683 (35.6)	408 (31.6)	Ref
Yes	908 (47.3)	611 (47.3)	1.02 (0.85-1.24)
Missing	329 (17.1)	273 (21.1)	
Indoor furry pets before age 6			
No	1336 (69.6)	970 (75.1)	Ref
Yes	543 (28.3)	300 (23.2)	1.16 (0.97-1.39)
Missing	41 (2.1)	22 (1.7)	
Mother smoked cigarettes while pregnant			
No	1633 (85.1)	1136 (87.9)	Ref
Yes	192 (10.0)	94 (7.3)	1.15 (0.87-1.53)
Missing	95 (4.9)	62 (4.8)	
Parents smoked cigarettes in house before age 6			
No	820 (42.7)	606 (46.9)	Ref
Yes	1044 (54.4)	650 (50.3)	1.01 (0.86-1.19)
Missing	56 (2.9)	36 (2.8)	

*Exposures are modeled individually.
†Respondents who answered yes to current eczema or atopic dermatitis in past 12 months and yes to itching/other eczema symptoms in past 12 months or answered yes to any of the following concerning the past 12 months: allergy symptoms, medication use to treat allergy symptoms, nasal problems without cold/flu, itchy/watery eyes with problems, and medication use for nasal problems (n = 149 for current eczema; n = 1899 for current allergies).
‡Logistic regression used to estimate ORs adjusted for age, sex, race, state, asthma case-control status, and pack years.

TABLE E10. Associations between early-life exposures and adult atopy and asthma using multinomial regression in the ALHS excluding asthma cases with COPD overlap and likely undiagnosed asthma cases

Early-life exposures*	No exposure	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	161	396	0.80 (0.63-1.00)	.05
Asthma = yes, atopy = yes	80	172	0.64 (0.47-0.88)	.006
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	170	369	1.05 (0.84-1.31)	.68
Asthma = yes, atopy = yes	100	141	0.62 (0.47-0.84)	.002
Mother worked with farm animals when pregnant				
Asthma = no, atopy = no	500	1070	Ref	
Asthma = no, atopy = yes	96	141	0.66 (0.49-0.88)	.006
Asthma = yes, atopy = no	165	357	1.17 (0.94-1.47)	.17
Asthma = yes, atopy = yes	97	133	0.72 (0.53-0.97)	.03
Family lived on farm when born				
Asthma = no, atopy = no	368	1302	Ref	
Asthma = no, atopy = yes	75	181	0.63 (0.46-0.86)	.004
Asthma = yes, atopy = no	159	400	0.81 (0.64-1.02)	.07
Asthma = yes, atopy = yes	80	170	0.62 (0.46-0.85)	.003
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	117	428	1.08 (0.84-1.39)	.53
Asthma = yes, atopy = yes	62	187	0.80 (0.58-1.12)	.20
Indoor furry pets before age 6				
Asthma = no, atopy = no	1243	410	Ref	
Asthma = no, atopy = yes	175	74	1.33 (0.99-1.80)	.06
Asthma = yes, atopy = no	387	173	1.28 (1.04-1.59)	.02
Asthma = yes, atopy = yes	173	78	1.33 (0.99-1.79)	.06
Parents smoked in house before age 6				
Asthma = no, atopy = no	770	872	Ref	
Asthma = no, atopy = yes	121	130	0.94 (0.71-1.23)	.64
Asthma = yes, atopy = no	225	322	1.22 (1.00-1.49)	.05
Asthma = yes, atopy = yes	94	153	1.42 (1.07-1.89)	.01
Breast-fed as infant				
Asthma = no, atopy = no	565	805	Ref	
Asthma = no, atopy = yes	91	114	0.96 (0.69-1.32)	.78
Asthma = yes, atopy = no	184	280	1.23 (0.97-1.56)	.09
Asthma = yes, atopy = yes	98	110	1.00 (0.72-1.37)	.98
Ever drank raw milk				
Asthma = no, atopy = no	337	1271	Ref	
Asthma = no, atopy = yes	62	173	0.76 (0.54-1.07)	.12
Asthma = yes, atopy = no	116	417	1.09 (0.84-1.41)	.52
Asthma = yes, atopy = yes	59	182	1.03 (0.73-1.46)	.85
Raw milk was main milk				
Asthma = no, atopy = no (ref)	593	1034	Ref	
Asthma = no, atopy = yes	109	140	0.74 (0.54-1.01)	.06
Asthma = yes, atopy = no	213	329	1.01 (0.80-1.27)	.95
Asthma = yes, atopy = yes	112	129	0.79 (0.57-1.08)	.13

Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL in that group. Asthma cases restricted to those who responded "yes" to ever have or still have asthma and "no" to ever diagnosed with COPD or emphysema.

*Exposures are modeled individually.

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

TABLE E11. Associations between farm animal exposure across life span and current asthma in the ALHS

Farm animal exposure	Cases	Noncases	OR (95% CI)*	*P* value
In utero, childhood				
In utero = no, childhood = no	208	339	Ref	
In utero = yes, childhood = no	17	48	0.63 (0.35-1.13)	.12
In utero = no, childhood = yes	159	260	1.09 (0.83-1.42)	.54
In utero = yes, childhood = yes	679	1177	1.12 (0.91-1.39)	.29
Missing	135	207		
Childhood, adulthood				
Childhood = no, adulthood = no	162	295	Ref	
Childhood = yes, adulthood = no	486	798	1.26 (1.00-1.58)	.05
Childhood = no, adulthood = yes	73	109	1.19 (0.83-1.70)	.34
Childhood = yes, adulthood = yes	410	731	1.17 (0.91-1.49)	.22
Missing	67	98		

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

TABLE E12. Associations between farm animal exposure across life span and adult atopy in the ALHS

Farm animal exposure	Atopic*	Nonatopic	OR (95% CI)†	*P* value
In utero, childhood prior to age 6				
In utero = no, childhood = no	119	401	Ref	
In utero = yes, childhood = no	11	54	0.75 (0.37-1.53)	.43
In utero = no, childhood = yes	93	311	0.94 (0.68-1.29)	.69
In utero = yes, childhood = yes	289	1499	0.61 (0.47-0.80)	<.001
Missing	66	261		
Childhood prior to age 6, adulthood				
Childhood = no, adulthood = no	99	343	Ref	
Childhood = yes, adulthood = no	227	1029	0.73 (0.55-0.97)	.03
Childhood = no, adulthood = yes	41	132	0.96 (0.62-1.48)	.85
Childhood = yes, adulthood = yes	191	906	0.61 (0.45-0.83)	.002
Missing	20	116		

*Atopy cut point defined as 1 or more allergen-specific IgEs > 0.70 IU/mL.
†Logistic regression used to estimate ORs adjusted for age, sex, race, state, pack years, and asthma case-control status.