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Early-life farm exposures and eczema among adults in the Agricultural Lung Health Study

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Background: Several studies conducted in Europe have suggested a protective association between early-life farming exposure and childhood eczema or atopic dermatitis; however, few studies have examined associations in adults.
Objectives: We investigated associations between early-life exposures and eczema among 3217 adult farmers and farm spouses (mean age, 62.8 years) in a case–control study nested within an US agricultural cohort.
Methods: We used sampling-weighted logistic regression to estimate odds ratios and 95% confidence intervals for associations between early-life exposures and self-reported doctor-diagnosed eczema (273 cases) and polytomous logistic regression to estimate odds ratios (95% confidence intervals) for a 4-level outcome combining information on eczema and atopy (specific IgE ≥ 0.35). Additionally, we explored genetic and gene–environment associations with eczema.
Results: Although early-life farming exposures were not associated with eczema overall, several early-life exposures were associated with a reduced risk of having both eczema and atopy. Notably, results suggest stronger protective associations among individuals with both eczema and atopy than among those with either alone. For example, odds ratios (95% confidence intervals) for having a mother who did farm work while pregnant were 1.01 (0.60, 1.69) for eczema alone and 0.80 (0.65, 0.99) for atopy alone, but 0.54 (0.33, 0.80) for having both. A genetic risk score based on previously identified atopic dermatitis variants was strongly positively associated with eczema, and interaction testing suggested protective effects of several early-life farming exposures only in individuals at lower genetic risk.
Conclusions: *In utero* and childhood farming exposures are associated with decreased odds of having eczema with atopy in adults. (J Allergy Clin Immunol Global 2022;1:248-56.)

Key words: *Eczema, atopic dermatitis, epidemiology, agricultural workers, prenatal exposure delayed effects, genetic epidemiology*

Eczema is a chronic inflammatory skin disease characterized by erythematous itchy rash.[1] Historically, eczema, also referred to as atopic dermatitis, was considered a childhood disease.[1-3] However, recent studies demonstrating a high prevalence among adults have led to the hypothesis that eczema may be a lifelong disease with variable expression.[1-3] The estimated prevalence of eczema among US adults is 7% to 10%.[1,4,5]

In accordance with the hygiene hypothesis, early-life microbial exposures are believed to help stimulate the immune system affecting susceptibility to eczema in both childhood and adulthood.[5,6] Several studies of the farm environment have suggested a protective relationship between *in utero* and childhood farm exposures and childhood eczema.[7] However, associations between these exposures and adult eczema have not been widely studied.[8-12] The few studies in adults were conducted primarily in Europe and reported inconsistent results. Furthermore, to our knowledge, no previous study has considered associations with intrinsic (absence of atopy) and extrinsic (presence of atopy) dermatitis according to IgE measurements.

Therefore, we investigated associations of early-life farm exposures with eczema overall and by atopy among 3217 US adult farmers and their spouses participating in the Agricultural Lung Health Study (ALHS).

METHODS

The ALHS is a case–control study of current asthma nested within the Agricultural Health Study (AHS) cohort (data version P3REL201209.00). Details of the ALHS study design have been previously published.[13] Briefly, the ALHS includes 3301 farmers or spouses (1223 asthma cases, 2078 noncases) from Iowa and North Carolina enrolled onto the study in 2009-2013. The present study considered the 3217 participants with data on early-life exposures, eczema, and covariates. The ALHS was approved by the institutional review board at the National Institutes of Health and its contractors, and participants provided informed consent.

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Abbreviations used
AHS: Agricultural Health Study
ALHS: Agricultural Lung Health Study
CI: Confidence interval
FLG: Filaggrin
GRS: Genetic risk score
OR: Odds ratio
SNP: Single nucleotide polymorphism

Participants were asked about *in utero* and early childhood exposures through a self-administered questionnaire.[13] Questions are provided in this article's Methods section in the Online Repository at www.jaci-global.org. Eczema and atopic dermatitis outcomes were ascertained through a separate computer-assisted interview using the following questions: "Have you ever had eczema or atopic dermatitis?," "Was eczema or atopic dermatitis ever diagnosed by a doctor?," and "In the past 12 months, have you had any itching or other symptoms of eczema or atopic dermatitis?" Because few reported eczema cases were not diagnosed by a doctor (n = 59), our primary analysis compared ever diagnosed eczema versus never having eczema (n = 3158). A secondary analysis compared current diagnosed eczema versus never having eczema (n = 3034). Finally, in a sensitivity analysis we examined onset of eczema in childhood (<18 years) and adulthood (≥18 years) separately by dichotomizing ever diagnosed eczema based on the question, "At about what age did you first have eczema or atopic dermatitis?"

We also examined a 4-level outcome that combined information on ever diagnosed eczema and atopy as follows: neither eczema nor atopy (eczema = no, atopy = no), atopy without eczema (eczema = no, atopy = yes), eczema without atopy (eczema = yes, atopy = no), and both eczema and atopy (eczema = yes, atopy = yes). Details of the atopy data have been previously published,[13] and a summary is provided in this article's Methods section in the Online Repository. Briefly, atopy was defined as IgE levels of ≥0.35 IU/mL to at least 1 of the following 10 allergens: Bermuda grass, ragweed, timothy grass, mountain cedar, *Alternaria,* dust mite, cat dander, milk, egg, and wheat. After excluding 128 individuals without atopy data, analyses of the combined eczema and atopy outcome included 3030 participants.

Finally, we created a weighted genetic risk score (GRS) that was based on 27 single nucleotide polymorphisms (SNPs) associated with atopic dermatitis in a large genome-wide association meta-analysis.[14] SNP IDs and minor allele frequencies are provided in Table E1 in the Online Repository at www.jaci-global.org. Specifically, we natural-log–transformed the odds ratios (ORs) reported in the meta-analysis by Paternoster et al[14] to obtain beta coefficients. We recoded risk alleles for SNPs according to the sign of the beta coefficient. For each SNP, we counted the number of risk alleles and multiplied the count by the absolute value of its corresponding beta coefficient, considered as a weight. The weighted GRS was then calculated as the sum of all weighted risk alleles. We also created a dichotomous variable to examine filaggrin (*FLG*) mutations according to whether participants had at least 1 risk allele for any of the following 3 common loss-of-function mutations: rs61816761, rs138726443, rs150597413.[15] Another common loss-of-function *FLG* mutation (rs558269137)[15] was not available in our study. Details of the ALHS genetic data have been previously published.[16,17] We analyzed GRS and *FLG* mutations among the 2919 participants of European ancestry with genotype data.

To estimate ORs and 95% confidence intervals (CIs) for associations between outcomes and exposures of interest, we used logistic regression for binary outcomes and polytomous regression for multicategory outcomes. Binary outcomes included ever diagnosed eczema (vs never having eczema) and the subset of current diagnosed eczema (vs never having eczema). Age at onset was a 3-category outcome: eczema onset in childhood (<18 years) and onset in adulthood (≥18 years) compared to those never reporting eczema. Eczema and atopy combined was a 4-category outcome: eczema alone (ie, eczema without atopy), atopy alone (ie, atopy without eczema), and both eczema and atopy compared to those with neither eczema nor atopy. Exposures of interest included each early-life exposure, the weighted GRS, and the *FLG* mutation variable; we used separate models for each exposure variable.

To evaluate whether genetic predisposition modifies the association between early-life exposure and eczema, we stratified by the GRS (dichotomized at its overall median of 1.9856) and fitted a model of the early-life exposure and ever eczema within each stratum. We also fitted a model that included an interaction term between the early-life exposure and the dichotomized GRS as well as a model with an interaction term between the early-life exposure and the continuous GRS; *P* values for these interaction terms would not be influenced by whether the analysis was based on environmental exposure associations stratified by genetic factors (as we have done) or as genetic associations stratified by environmental factors.

All analyses used inverse probability weighting to account for the asthma-based case–control sampling in the ALHS.[18] Specifically, we estimated sampling probabilities using the proportion of asthma cases (1192/3024) and controls (2025/41,106) from AHS included in this ALHS analysis and then used the inverse of these probabilities as sample weights for cases (w_{case} = 2.54) and controls ($w_{control}$ = 20.30). Analyses were adjusted for age, sex, race (White, non-White), state (Iowa, North Carolina), pack-years of cigarette smoking, and the first 10 ancestral principal components (for GRS and *FLG* analyses only). Covariates were selected *a priori* primarily on the basis of previous ALHS literature;[13,19] other studies of early-life farming and adult eczema adjusted for many of the same variables[8-12] and main results did not appear to materially change with exclusion or inclusion of other covariates (eg, excluding cigarette smoking or including number of siblings and parental smoking). Analyses were performed by SAS 9.4 software (SAS Institute, Cary, NC) using 'proc surveylogistic.'

RESULTS

Approximately half of the study population were male and farmers, and the other half were female and spouses (Table I). Most participants self-reported as White (98.3%) and were from Iowa (70.3%). The average age was 62.8 years. Over one third (37.1%) were enrolled into the ALHS as having asthma. Ever having eczema was reported by 332 individuals (10.3%), including 273 who reported that their eczema had been diagnosed by a doctor. Current eczema (experiencing symptoms in the past 12 months) was reported by 183 individuals (5.7%), including 149 who reported their eczema had been diagnosed by a doctor.

Eczema

Early-life exposures were not statistically significantly associated with ever diagnosed eczema (273 cases), though ORs were below 1 for several farming variables, suggesting the possibility of a modest protective effect (Table II). For example, the ORs (95% CIs) for living on a farm at birth and mother doing farm work while pregnant with ever diagnosed eczema were 0.80 (0.55, 1.16) and 0.81 (0.57, 1.15) respectively. In analyses restricted to current diagnosed eczema, ORs were similar but CIs were wider, as expected, given the smaller number of cases (149 cases, Table II). In sensitivity analyses examining the timing of eczema onset, ORs (95% CIs) for eczema that started in childhood (109 cases) did not statistically differ from ORs (95% CIs) for eczema that started in adulthood (163 cases) ($P_{difference} \geq .22$; see Table E2 in the Online Repository at www.jaci-global.org). Additionally, results did not appear to materially differ when various time points of exposure in childhood were considered for farm animal exposure and raw milk consumption (see Table E3 in the Online Repository).

TABLE I. Demographics of participants in the ALHS, eczema analysis

Characteristic	Value
Total no. of participants	3217
Sex	
Male	1637 (50.9)
Female	1580 (49.1)
Enrollment status	
Farmer	1688 (52.5)
Spouse	1529 (47.5)
State	
Iowa	2261 (70.3)
North Carolina	956 (29.7)
Race	
White	3162 (98.3)
Other	55 (1.7)
Smoking status	
Never	2141 (66.6)
Former	942 (29.3)
Current	134 (4.2)
Asthma status	
Asthma	1192 (37.1)
No asthma	2025 (63.0)
Atopy status*	
Atopic	1319 (41.0)
Not atopic	1767 (54.9)
Missing	131 (4.1)
Eczema status	
Never	2885 (89.7)
Ever (not diagnosed)	59 (1.8)
Ever (diagnosed)	273 (8.5)
Age (years), mean ± SD	62.8 ± 11.0
Pack-years among ever smokers, mean ± SD	17.7 ± 21.1

Data are presented as nos. (%) unless otherwise indicated.
*Atopy was defined as IgE ≥ 0.35 IU/mL to at least 1 of the following allergens: Bermuda grass, ragweed, timothy grass, mountain cedar, *Alternaria,* dust mite, cat dander, milk, egg, and wheat.

Eczema and atopy

When we analyzed the outcome variable that combined information on ever diagnosed eczema and atopy, 4 exposures were significantly associated with reduced odds of having eczema and atopy together (vs having neither): having a mother who lived on a farm while pregnant, having a mother do farm work while pregnant, having a mother work with farm animals while pregnant, and living on a farm at birth (Table III). Notably, ORs for these early-life exposures indicated slightly stronger protective associations for having both diagnosed eczema and atopy (ORs ranging from 0.54 to 0.58 depending on the exposure) than for having atopy alone (ORs ranging from 0.79 to 0.83 depending on the exposure). However, the OR (95% CI) values for having both eczema and atopy were not significantly different from those for atopy alone (*P* values for whether the estimates differed by outcome ranging from .12 to .23, depending on exposure). For example, the OR (95% CI) for having a mother who did farm work while pregnant was 0.54 (0.33, 0.89) for having both eczema and atopy and 0.80 (0.65, 0.99) for atopy alone (with $P = .12$ for whether these estimates differed). In addition, we noted 2 exposures which were significantly associated with atopy alone, but not with having both eczema and atopy: ever drinking raw milk and having been breast-fed. For example, the OR (95% CI) for ever drinking raw milk was 0.73 (0.57, 0.93) for atopy alone and 1.40 (0.72, 2.71) for having both eczema and atopy (with $P = .06$ for whether these estimates differed). Early-life farming exposures did not appear to be strongly associated with eczema alone (Table III). When we additionally considered an outcome variable that combined information restricted to current diagnosed eczema and atopy, ORs were similar but CIs were wider, as expected, given the smaller number of cases (73 cases with current eczema only and 69 cases with current eczema and atopy; see Table E4 in the Online Repository at www.jaci-global.org).

GRS and *FLG* mutation

The weighted GRS was strongly positively associated with ever diagnosed eczema, with an OR (95% CI) 2.61 (1.47, 4.64) per unit increase in GRS that ranged from 0.99 to 3.16 (Table IV). When we considered eczema and atopy together, the GRS was most strongly associated with having both diagnosed eczema and atopy (OR = 3.03, 95% CI = 1.38, 6.66).

When we examined associations between early-life exposures and ever diagnosed eczema stratified by the GRS, which was dichotomized at the GRS median of 1.9856, we found several early-life exposures to be associated with significantly reduced risk of eczema among those in the lower GRS group, but not among those in the higher GRS group (Table V). For example, the ORs (95% CIs) for farm animal exposure before age 6 and ever diagnosed eczema was 0.44 (0.25, 0.78) among those with low GRS and 1.56 (0.86, 2.85) among those with high GRS ($P_{\text{interaction\_dichotomous}} = .0008$ and $P_{\text{interaction\_continuous}} = .003$). We observed a similar pattern of stronger protective associations with ever diagnosed eczema among those with a lower genetic predisposition for mother living on a farm while pregnant, mother doing farm work while pregnant, mother working with farm animals while pregnant, and living on a farm at birth.

The *FLG* mutation variable was not significantly associated with ever diagnosed eczema (OR = 1.09, 95% CI = 0.42, 2.87); however, only 3% of participants had at least 1 risk allele for the 3 common loss-of-function *FLG* mutation variants (7 individuals with diagnosed eczema and 86 individuals without eczema).

DISCUSSION

In this study of older adults from a US farming population, early-life farm exposures were not associated with diagnosed eczema in analyses that did not consider atopy. However, in analyses examining eczema and atopy together, 4 early-life exposures (mother living on a farm while pregnant, mother doing farm work while pregnant, mother working with farm animals while pregnant, and living on a farm at birth) were associated with a reduced risk of having both eczema and atopy. Notably, ORs suggested stronger protective associations among individuals with both eczema and atopy than among those with either atopy alone or eczema alone.

Although several studies have suggested a protective effect of the farm environment for childhood atopic dermatitis, few have considered the adult condition. Only 5 previous studies, including 2 conducted within the same population, examined associations between childhood farm exposure and adult atopic dermatitis and none considered eczema and atopy together.[8-12] A large study from Sweden, including a subset of individuals with IgE

TABLE II. Associations between early-life exposures and diagnosed eczema among adults in the ALHS

		Ever diagnosed eczema			Current diagnosed eczema		
Early-life exposures	**Never eczema (no.)**	**No.**	**OR (95% CI)**	***P* value**	**No.**	**OR (95% CI)**	***P* value**
Total	2885	273			149		
Mother lived on farm while pregnant							
No	684	101			55		
Yes	2171	165	0.90 (0.62, 1.30)	.57	89	0.84 (0.50, 1.43)	.52
Missing	30	7			5		
Mother did farm work while pregnant							
No	840	118			62		
Yes	1895	144	0.81 (0.57, 1.15)	.23	79	0.79 (0.47, 1.33)	.38
Missing	150	11			8		
Mother worked with farm animals while pregnant							
No	857	116			63		
Yes	1799	136	0.87 (0.61, 1.25)	.45	74	0.78 (0.47, 1.31)	.35
Missing	229	21			12		
Lived on farm at birth							
No	672	106			58		
Yes	2179	166	0.80 (0.55, 1.16)	.24	90	0.77 (0.45, 1.31)	.33
Missing	34	1			1		
Farm animal exposure before age 6							
No	551	83			44		
Yes	2214	183	0.92 (0.62, 1.36)	.66	102	0.91 (0.53, 1.59)	.75
Missing	120	7			3		
Ever consumed raw milk							
No	578	69			32		
Yes	2151	186	1.01 (0.66, 1.53)	.98	108	1.31 (0.71, 2.42)	.38
Missing	156	18			9		
Breast-fed							
No	965	112			56		
Yes	1376	117	0.83 (0.56, 1.24)	.37	67	1.06 (0.61, 1.84)	.84
Missing	544	44			26		
Indoor pets before age 6							
No	2095	181			102		
Yes	736	87	1.06 (0.73, 1.52)	.77	45	0.90 (0.53, 1.52)	.69
Missing	54	5			2		

Data for 59 individuals with eczema that was not doctor diagnosed were excluded so 3158 individuals were included in analyses. "Never eczema" was defined as responding "no" to "Have you ever had eczema or atopic dermatitis?." "Ever diagnosed eczema" was defined as responding "yes" to both the following: "Have you ever had eczema or atopic dermatitis?" and "Was eczema or atopic dermatitis ever diagnosed by a doctor?." "Current diagnosed eczema" was defined as responding "yes" to all 3 of the following: "Have you ever had eczema or atopic dermatitis?," "Was eczema or atopic dermatitis ever diagnosed by a doctor?," and "In the past 12 months, have you had any itching or other symptoms of eczema or atopic dermatitis?"

Early-life exposures are modeled individually, one at a time. ORs were calculated using logistic regression with inverse probability weighting for proportion of asthma cases (1192/3024) and controls (2025/41106) from AHS who participated in this ALHS analysis and adjustment for age, sex, state (Iowa, North Carolina), race (White, non-White), and pack-years.

measurements, found that being raised on a farm was associated with a decreased odds of current eczema (OR = 0.89, 95% CI = 0.77, 1.03, and OR = 0.51, 95% CI = 0.27, 0.99, for the subset).[8,12] However, this study did not examine the relationship between being raised on a farm and adult eczema and allergic sensitization combined.[8] Another study from Finland noted a significantly decreased OR for having a family who farmed in one's infancy and current eczema (OR = 0.81, 95% CI = 0.69, 0.95).[9] That study also noted protective associations of both *in utero* (OR = 0.80, 95% CI = 0.64, 1.00) and infant (OR = 0.77, 95% CI = 0.66, 0.91) exposure to farm animals with adult eczema.[9] In contrast, a study from New Zealand found no association between growing up on a farm and ever having eczema (OR = 0.98, 95% CI = 0.85, 1.13), and a study from Germany found no association between regular visits to animal buildings in childhood and adult atopic dermatitis (OR [95% CI] ranging from 0.75 [0.52, 1.08] to 1.13 [0.53, 2.45], depending on age).[10,11]

In a previous analysis using ALHS data that considered atopy but not eczema, we found that having a mother who lived on a farm while pregnant, having a mother who performed farm activities while pregnant, having a mother working with farm animals while pregnant, and living on a farm at birth was each associated with a lower odds of atopy (specific IgE ≥ 0.70: ORs 0.60-0.69, $P < .002$; specific IgE ≥ 0.35: ORs 0.76-0.82, $P < .03$).[13] In the present analysis where we considered both atopy (specific IgE ≥ 0.35) and eczema, ORs for these same exposures ranged from 0.79 to 0.83 ($P = .02$ to .09) among individuals with atopy but no eczema, but from 0.54 to 0.58 ($P = .02$ to .04) among individuals with both atopy and doctor-diagnosed eczema. These results suggest that the observed protective effect of early-life farm exposures may be greater for the combination of atopy and eczema than atopy alone.

In addition, in our previous analysis,[13] we found a suggestive protective association between ever drinking raw milk and atopy

TABLE III. Associations between early-life exposures and eczema and atopy (4 level combined outcome variable) among adults in the ALHS

Early-life exposures	Neither eczema nor atopy (no.)	Atopy only			Eczema only			Both eczema and atopy		
		No.	OR (95% CI)	*P* value	No.	OR (95% CI)	*P* value	No.	OR (95% CI)	*P* value
Total	1613	1157			128			132		
Mother lived on farm while pregnant										
No	363	288			40			54		
Yes	1233	856	0.83 (0.66, 1.03)	.09	84	1.27 (0.75, 2.18)	.38	75	0.57 (0.34, 0.96)	.04
Missing	17	13			4			3		
Mother did farm work while pregnant										
No	437	364			46			63		
Yes	1096	728	0.80 (0.65, 0.99)	.04	74	1.01 (0.60, 1.69)	.98	66	0.54 (0.33, 0.89)	.02
Missing	80	65			8			3		
Mother worked with farm animals while pregnant										
No	450	373			44			65		
Yes	1043	688	0.79 (0.64, 0.97)	.02	71	1.07 (0.64, 1.80)	.79	61	0.57 (0.34, 0.96)	.03
Missing	120	96			13			6		
Lived on farm at birth										
No	354	288			43			54		
Yes	1241	857	0.82 (0.65, 1.02)	.08	84	1.08 (0.63, 1.83)	.78	78	0.58 (0.34, 0.98)	.04
Missing	18	12			1			0		
Farm animal exposure before age 6										
No	293	234			37			42		
Yes	1249	882	0.84 (0.66, 1.07)	.16	88	1.06 (0.61, 1.82)	.85	88	0.66 (0.38, 1.15)	.14
Missing	71	41			3			2		
Ever consumed raw milk										
No	304	248			35			30		
Yes	1237	837	0.73 (0.57, 0.93)	.01	85	0.66 (0.38, 1.16)	.15	92	1.40 (0.72, 2.71)	.32
Missing	72	72			8			10		
Breast-fed										
No	516	418			47			57		
Yes	808	511			59			54		
Missing	289	228	0.78 (0.62, 0.97)	.03	22	0.80 (0.45, 1.41)	.44	21	0.85 (0.47, 1.54)	.58
Indoor pets before age 6										
No	1184	828			82			90		
Yes	399	307	1.13 (0.92, 1.39)	.26	45	0.96 (0.58, 1.60)	.88	38	1.25 (0.73, 2.14)	.42
Missing	30	22			1			4		

Data for 187 individuals were excluded (59 with eczema not doctor diagnosed and 128 missing atopy) so 3030 individuals were included in anlayses. "Neither eczema nor atopy" was defined as eczema = no and atopy = no; "atopy only" was defined as eczema = no and atopy = yes; "eczema only" was defined as eczema = yes and atopy = no; and "both eczema and atopy" was defined as eczema = yes and atopy = yes. Eczema was "no" if response was "no" to "Have you ever had eczema or atopic dermatitis?," and eczema was "yes" if response was "yes" to both of the following: "Have you ever had eczema or atopic dermatitis?" and "Was eczema or atopic dermatitis ever diagnosed by a doctor?." Atopy was "yes" if IgE ≥ 0.35 IU/mL to at least 1 of the following allergens: Bermuda grass, ragweed, timothy grass, mountain cedar, *Alternaria,* dust mite, cat dander, milk, egg, and wheat; atopy was "no" otherwise.

Exposures are modeled individually, one at a time. ORs were calculated using polytomous logistic regression with inverse probability weighting for the proportion of asthma cases (1192/3024) and controls (2025/41106) from AHS who participated in this ALHS analysis and adjustment for age, sex, state (Iowa, North Carolina), race (White, non-White), and pack-years.

(specific IgE ≥ 0.70: OR = 0.85, $P = .21$). In the present analysis, we noted a similar association between raw milk consumption and atopy alone (OR = 0.73, $P = .01$) and eczema alone (OR = 0.66, $P = .15$), but not both (OR = 1.40, $P = .32$). Raw milk has been previously associated with a decreased risk of childhood allergic diseases collectively.[7,20] Studies of raw milk and childhood eczema specifically are few,[7,20] and to our knowledge, our study is the first to examine the association between raw milk and eczema among adults. Raw milk differs from commercial milk in total fat content, specific fatty acid composition, and microorganisms, which are hypothesized to influence immune system development.[7,20] We also previously reported that childhood raw milk consumption was associated with higher FEV_1 and FVC in adulthood, supporting beneficial effects on lung growth.[19]

One of the challenges of studying eczema is disentangling atopic dermatitis from other forms of dermatitis, prompting some researchers to differentiate between intrinsic (absence of atopy) and extrinsic (presence of atopy) dermatitis on the basis of IgE measurements.[21] Our results suggest that the associations we observed between early-life farming exposures and eczema in adults may largely be driven by extrinsic atopic dermatitis. In other words, incorporating specific IgE measures with self-reported eczema helped differentiate cases of atopic dermatitis

TABLE IV. Associations between weighted GRS and diagnosed eczema among adults in the ALHS

Outcome eczema	Not cases (No.)	Cases (No.)	OR (95% CI)	*P* value
Ever diagnosed eczema	2661	258	2.61 (1.47-4.64)	.001
Current diagnosed eczema	2661	141	1.75 (0.90-3.40)	.10
Outcome eczema and atopy	**No.**	**OR (95% CI)**		***P* value**
Neither eczema nor atopy	1515			
Atopy only	1087	1.04 (0.75-1.43)		.83
Eczema only	118	1.98 (0.83-4.70)		.12
Both eczema and atopy	129	3.03 (1.38-6.66)		.01
Missing	70			

GRS was based on 27 variants identified by Paternoster et al.[14] Range of values for weighted GRS is 0.99 to 3.16. GRS was calculated only for participants ascertained to be of European ancestry based on the genetic data so 2919 individuals were included in anlayses.

"Never eczema" was defined as responding "no" to "Have you ever had eczema or atopic dermatitis?." "Ever diagnosed eczema" was defined as responding "yes" to both the following: "Have you ever had eczema or atopic dermatitis?" and "Was eczema or atopic dermatitis ever diagnosed by a doctor?." "Current diagnosed eczema" was defined as responding "yes" to all 3 of the following: "Have you ever had eczema or atopic dermatitis?," "Was eczema or atopic dermatitis ever diagnosed by a doctor?," and "In the past 12 months, have you had any itching or other symptoms of eczema or atopic dermatitis?" Atopy was defined as IgE ≥ 0.35 IU/mL to at least 1 of the following allergens: Bermuda grass, ragweed, timothy grass, mountain cedar, *Alternaria,* dust mite, cat dander, milk, egg, and wheat.

ORs were calculated using logistic regression with inverse probability weighting for the proportion of asthma cases (1192/3024) and controls (2025/41106) from AHS who participated in this ALHS analysis and adjustment for age, sex, state (Iowa, North Carolina), pack-years, and the first 10 ancestral principal components.

with elevated specific IgE from dermatitis without sensitization. Associations between the farming environment and reduced risk of allergic diseases is often attributed to the hygiene hypothesis—namely, that microbial exposure early in life stimulates the immune system to protect against allergic diseases throughout life.[22] Although other studies have shown an association between farming and asthma independent of atopic sensitization,[23,24] our results suggest that the relationship between early-life farming and eczema in adults is more pronounced among those with atopy.

In addition to environmental factors, genetics plays an important role in allergic diseases such as eczema.[5] In our study, a GRS summarizing 27 previously identified atopic dermatitis variants[14] was strongly positively associated with eczema. We found evidence of an interaction between the GRS and the following early-life exposures: mother living on a farm while pregnant, mother doing farm work while pregnant, mother working with farm animals while pregnant, living on a farm at birth, and working with farm animals before the age of 6. In particular, we noted protective associations between these *in utero* and childhood exposures and diagnosed eczema only among those with a lower genetic predisposition, suggesting that the modest effects of these early exposures may be more evident in those without already increased baseline disease risk as a result of greater genetic predisposition. Genetic risk scores, also known as polygenic risk scores, have been increasingly used to summarize genetic risk identified by genome-wide association studies for numerous health outcomes.[25] Because of the statistical power challenges of studying environmental interactions with multiple genetic variants, GRS have been recommended as an efficient way to identify whether environmental factors modify associations with health outcomes in people at higher or lower genetic predisposition.[25] This approach has been applied to a number of chronic conditions, including cardiovascular disease, adiposity, and cancer.[25-28] However, risk scores can be limited by the sample sizes of genome-wide association studies used to identify the SNPs as well as by SNP selection; further, they may combine variants that act on the phenotype through different mechanisms.[25,29]

Despite a substantial body of research showing the importance of filaggrin in moderating skin permeability and therefore susceptibility to eczema,[30,31] we did not find an association between 3 common loss-of-function *FLG* mutations and eczema among the participants in our study. However, given that the minor allele frequencies for rs61816761, rs138726443, and rs150597413 are less than 2% in European ancestry populations (Ensembl Release 98),[32] and likewise only 3% of ALHS participants had at least 1 risk allele for these 3 common loss-of-function *FLG* mutation variants, our study was likely underpowered to detect associations between these variants and eczema.

Our study had several potential limitations and strengths. Regarding generalizability, we note that the AHS includes only farmers and farm spouses, who tend to be more physically active, smoke less, and experience more farming-related exposures than the general population.[33,34] An earlier quantitative selection-bias analysis that was based on childhood exposure to farm animals and asthma did not indicate selective entry into ALHS from the parent AHS cohort.[13] Further, as discussed in previous studies, selection bias can also occur if individuals with severe allergic diseases leave farming.[13,35] We cannot directly assess this particular source of bias because our study includes only current farmers or spouses, and we do not have information on individuals who may have left farming (or never started farming) as a result of eczema. However, we did ask ALHS participants if they had ever stopped working with farm animals because of allergies; only 4% of those in the present analysis responded they had. In addition, the prevalence of eczema in ALHS (8.5% had ever diagnosed eczema and 4.6% had current diagnosed eczema) is similar to other population-based estimates. Specifically, the National Health Interview Survey, a US population-based household survey conducted by the National Center for Health Statistics, found that 10.2% of adults had current eczema and 7.2% of adults had current diagnosed eczema.[36,37]

Another potential limitation of our study was that information on early-life exposures and eczema were self-reported and ascertained retrospectively. However, early-life questions were similar to previous studies,[7] and questionnaires were sent to ALHS participants in advance of home visits so they could consult family members.[13] About 20% of respondents reported receiving help from family members, and the frequency of most

TABLE V. Associations between early-life exposures and diagnosed eczema stratified by GRS among adults in the ALHS

	Lower genetic risk (GRS < 1.985646) (n = 1460)			Higher genetic risk (GRS ≥ 1.985646) (n = 1459)			*P* interaction early life	
Early-life exposure	Never eczema (no.)	Ever diagnosed eczema (no.)	OR (95% CI)	Never eczema (no.)	Ever diagnosed eczema (no.)	OR (95% CI)	Dichotomous GRS	Continuous GRS
Total no.	1354	106		1307	152			
Mother lived on farm while pregnant								
No	332	43		302	52			
Yes	1007	61	0.61 (0.35, 1.06)	993	95	1.07 (0.63, 1.84)	.06	.04
Missing	15	2		12	5			
Mother did farm work while pregnant								
No	390	48		386	61			
Yes	892	54	0.53 (0.30, 0.94)	854	85	1.07 (0.65, 1.76)	.03	.19
Missing	72	4		67	6			
Mother worked with farm animals while pregnant								
No	396	48		398	58			
Yes	845	51	0.51 (0.29, 0.90)	810	81	1.37 (0.81, 2.30)	.01	.07
Missing	113	7		99	13			
Lived on farm at birth								
No	327	44		295	55			
Yes	1012	62	0.57 (0.33, 1.00)	998	96	0.92 (0.53, 1.59)	.09	.03
Missing	15	0		14	1			
Farm animal exposure before age 6								
No	260	40		246	37			
Yes	1034	63	0.44 (0.25, 0.78)	1015	111	1.56 (0.86, 2.85)	.0008	.003
Missing	60	3		46	4			
Ever consumed raw milk								
No	269	31		259	32			
Yes	1005	69	1.04 (0.55, 1.97)	985	108	0.99 (0.54, 1.81)	.62	.66
Missing	80	6		63	12			
Breast-fed								
No	461	41		447	65			
Yes	640	46	1.03 (0.52, 2.03)	610	66	0.73 (0.42, 1.26)	.93	.68
Missing	253	19		250	21			
Indoor pets before age 6								
No	965	71		963	103			
Yes	358	35	0.99 (0.53, 1.85)	326	44	1.04 (0.64, 1.69)	.91	.98
Missing	31	0		18	5			

GRS was based on 27 variants identified by Paternoster et al.[14] Range of weighted GRS is 0.99 to 3.16. GRS was calculated only for participants ascertained to be of European ancestry based on the genetic data so 2919 individuals were included in anlayses. GRS was dichotomized on the basis of overall median (n = 2919, median = 1.985646). *P* values for interaction were based on separate models, where one set of models included an interaction term between the early-life farming exposure and GRS dichotomized at 1.985646 and the other set of models included an interaction term between the early-life farming exposure and continuous GRS.

"Never eczema" was defined as responding "no" to "Have you ever had eczema or atopic dermatitis?." "Ever diagnosed eczema" was defined as responding "yes" to both the following: "Have you ever had eczema or atopic dermatitis?" and "Was eczema or atopic dermatitis ever diagnosed by a doctor?"

Exposures are modeled individually, one at a time. ORs calculated using logistic regression with inverse probability weighting for the proportion of asthma cases (1192/3024) and controls (2025/41106) from AHS who participated in this ALHS analysis and adjustment for age, sex, state (Iowa, North Carolina), pack-years, and the first 10 ancestral principal components.

early-life exposures were similar among those who did or did not receive help.[13] Although it might be difficult to recall timing of early-life exposures, we believe that this recall is unlikely to have differed by the presence of eczema. Eczema questions were also similar to previous studies, including the National Health Interview Survey. Participants were asked several questions about eczema, including ever diagnosis, current symptoms, and age at onset. Our primary analysis considered ever diagnosed eczema because it has the largest sample size and therefore enhances the power to assess associations between early-life exposures and eczema. However, we also analyzed current diagnosed eczema, age at onset, and eczema and atopy combined, as these were also informative outcomes—although estimates from these analyses were somewhat less precise as a result of smaller sample sizes.

Five of the early-life exposures examined here are highly correlated in the ALHS:[13,19] living on a farm at birth, mother doing farm work while pregnant, mother living on a farm while

pregnant, mother working with farm animals while pregnant, and exposure to farm animals before the age of 6 had tetrachoric correlations ranging from 0.84 to 0.99 (see Table E5 in the Online Repository at www.jaci-global.org). Therefore, modeling these exposures together in a single model for ever diagnosed eczema results in unstable estimates. Further, we did not consider creating a single combined measure of all early-life exposures because aggregating information across multiple recalled exposures into a single valid and generalizable measure is a complex methodological problem. Moreover, unlike with the GRS, we lacked the resource of a large meta-analysis to provide guidance about creating a defensible composite measure for early-life exposures. Instead, we modeled each exposure separately and reported CIs without adjusting for multiple comparisons. This approach trades an increased risk of false-positive results for enhanced statistical power.

Our study extends the existing literature by investigating associations between early-life farming exposures and eczema in adults in a large (n = 3217), older (mean age, 62.8 years) farming population in the United States. Although previous studies in adults had similar sample sizes (n = ~1000 to >5000), their participants were younger (mean, <50 years), and no prior studies were conducted in the United States.[8-12] Further, to our knowledge, our study is the first to estimate associations between early-life farming exposures and eczema among adults with and without atopy using IgE levels, and to investigate interactions with a GRS.

Given the growing prevalence of atopic dermatitis and its substantial effect on quality of life and health care utilization, atopic dermatitis remains an important public health concern.[1,5,38,39] Our study supports a protective effect of several early-life farming exposures on eczema with atopy in adults and provides further evidence suggesting that early-life microbial exposures may stimulate the immune system, offering protection against allergic diseases throughout life as postulated by the hygiene hypothesis.

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