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Adult farming exposure does not protect against sensitization to the storage mite Lepidoglyphus destructor

To the Editor,

Storage mite infestations are common in grain, straw, and hay storages.[1] Sensitization and allergy to storage mites have been found primarily in occupationally exposed individuals such as farmers, millers, and grain and also meat production workers where storage mite exposure is high.[1-4] Growing up in a farm environment, however, is a well-established protective factor against atopic sensitization to common allergens.[5,6] Working as a farmer in young adulthood may also provide protection against incident sensitization and persistence of existing sensitization, especially to pollen allergens.[7,8] As storage mites are most abundant in barns and stables, we assume that adults working in farming are exposed to much higher levels of storage mite allergens than children growing up in farm homes, with an at highest intermittent presence in barns and stables. However, it is so far unknown whether and how early-life and adult farming exposures affect specific storage mite sensitization over time. As far as we are aware, we here present the first longitudinal data on new-onset and loss of sensitization to the storage mite Lepidoglyphus destructor (Lep d).

The change in Lep d sensitization in relation to farming exposure and elevated Lep d concentrations was examined in a cohort of 1166 young Danish farmers and controls, with a mean age of 19 years at baseline. Baseline data were collected between 1992 and 1994 and at follow-up approximately 14 years later.[9] Sensitization to Lep d was measured by specific IgE (sIgE) levels and skin prick test (SPT) at both baseline and follow-up. Serum was stored at −80°C, and baseline and follow-up sera were tested simultaneously in IgE duplex analyses (carried out at ALK Abello), to minimize interassay and day-to-day variation. A positive specific IgE response was defined as ≥0.35 kU/L, and a positive SPT response was defined as a mean wheal reaction ≥3 mm in the presence of a negative control. Changes in sensitization (new-onset and loss) were analyzed in relation to farm exposure using self-reported information on exposures, as well as quantitative estimates of dust and endotoxin exposures based on actual personal exposure measurements.[8] The thus modeled dust and endotoxin exposure levels were in this study also used as surrogates for the lifetime levels of exposure to barns and animal stables where levels of Lep d and other storage mites are known to be high.[4]

New-onset sensitization was defined as negative at baseline and positive at follow-up, and loss of sensitization was defined as positive at baseline and negative at follow-up. Childhood exposure was categorized as having grown up in an urban environment, in the countryside but not on a farm, or on a farm with animals. Farmwork during the follow-up period was categorized as "never," "ex-," or "current farmer" with participants leaving farming during the follow-up period categorized as ex-farmers, and those still working as farmers at follow-up as "current farmers." Animal husbandry was subdivided into four exposure groups of "no animals," "swine," "cattle," and "mixed swine and cattle." Dust and endotoxin exposure was measured in a subpopulation, and the results were used in combination with detailed work diaries to estimate the cumulative exposure for all study participants. Analyses were based on exposure quartiles, the 4th quartile representing the highest exposure.[8,9] Changes in sensitization in relation to farm exposures during follow-up were analyzed by logistic regression to compare the participants with new-onset sensitization with those never sensitized, and those who lost sensitization with the participants with persistent Lep d sensitization. Changes in sensitization in relation to endotoxin exposures were also analyzed by logistic regression models adjusted for farm childhood, pet-keeping during childhood and smoking status.

At baseline, the Lep d sensitization prevalence was 4.9% measured by SPT and 6.1% measured by sIgE. At follow-up, the Lep d sensitization prevalence was 13.5% measured by SPT and 5.9% measured by sIgE. The unadjusted odds ratios in Table 1 show less new-onset sensitization to Lep d among participants with a rural or farm childhood and a greater loss of sensitization consistent with findings for other aeroallergens.[8] In contrary, farming exposure during adulthood appeared to be consistently associated with increased new-onset Lep d sensitization and with less loss of sensitization, although rarely significant due to low numbers. Significantly less loss of sensitization was observed particularly for work with swine and for high dust and endotoxin exposure.

Adjusted analyses of endotoxin exposure confirmed that an exposure environment with moderate and high endotoxin exposure, and presumably paralleled by an elevated Lep d exposure, was associated with increased new-onset sensitization to Lep d and significantly less loss of Lep d IgE sensitization independent of childhood exposure (Figure 1 for IgE test results; Figure S1 shows the results of the adjusted SPT analyses).

We previously showed that current farming exposure was protective against new pollen sensitization. This protective effect was, however, not seen for HDM, but neither was an increased risk of new HDM sensitization among current farmers,[7,8] as now suggested for Lep d sensitization. General storage mite sensitization levels may

Abbreviations: CI, confidence interval; HDM, house dust mite; IgE, immunoglobulin E; kU/L, kilo units per liter; OR, odds ratio; SPT, skin prick test.

TABLE 1. Unadjusted new-onset and loss of Lep d sIgE sensitization by exposure

	New sensitization					Loss of sensitization				
	N[a]	N[b]	%	OR	95%CI	N[a]	N[b]	%	OR	95%CI
Childhood environment	*1049*	*18*	*1.7*			*67*	*19*	*28.4*		
Farm childhood	529	9	1.7	0.50	(0.19-1.37)	29	10	34.5	2.80	(0.66-11.98)
Rural childhood	309	2	0.6	**0.19**	(0.04-0.92)	19	6	31.6	2.45	(0.51-11.80)
Urban childhood	211	7	3.3	1		19	3	15.8	1	
Adult exposure during follow-up										
Farmer status	*1029*	*17*	*1.7*			*67*	*19*	*28.4*		
Current farmer	411	9	2.2	3.55	(0.42-26.73)	26	6	23.1	0.24	(0.05-1.19)
Ex-farmer	467	7	1.5	2.28	(0.28-18.70)	32	8	25.0	0.27	(0.06-1.24)
Never farmer	151	1	0.7	1		9	5	55.6	1	
Working with animals	*1030*	*17*	*1.7*			*67*	*19*	*28.4*		
Swine only	214	4	1.9	3.07	(0.34-27.70)	8	0	0.0		
Cow only	179	5	2.8	4.63	(0.55-40.02)	17	2	11.8	**0.13**	(0.02-0.92)
Swine and cow	475	7	1.5	2.41	(0.29-19.72)	32	12	37.5	0.6	(0.14-2.51)
No animals	162	1	0.6	1		10	5	50.0	1	
Dust (mg*m^{-3}*y)	*1025*	*17*	*1.7*			*66*	*18*	*27.3*		
4. quartile	257	5	1.9	5.10	(0.59-43.95)	14	6	42.9	0.75	(0.17-3.33)
3. quartile	256	7	2.7	7.22	(0.88-59.15)	17	2	11.8	**0.33**	(0.02-0.81)
2. quartile	254	4	1.6	4.11	(0.46-37.04)	21	3	14.3	**0.17**	(0.03-0.83)
1. quartile	258	1	0.4	1		14	7	50.0	1	
Endotoxin (EU*m^{-3}*y)	*1025*	*17*	*1.7*			*66*	*18*	*27.3*		
4. quartile	257	4	1.6	4.08	(0.45-36.74)	14	6	42.9	0.64	(0.14-2.94)
3. quartile	259	6	2.3	6.12	(0.73-51.18)	15	2	13.3	**0.13**	(0.02-0.83)
2. quartile	250	6	2.4	6.34	(0.76-53.08)	24	3	12.5	**0.12**	(0.02-0.62)
1. quartile	259	1	0.4	1		13	7	53.8	1	

[a]N, total numbers of participants in each exposure category without (left) or with (right) IgE sensitization to Lep d at baseline. [b]Numbers in each category who changed IgE sensitization status from negative to positive (left) or from positive to negative (right). Dust and endotoxin exposure is given as exposure quartiles, the 4th quartile representing the highest exposure. OR, odds ratio; 95% CI, 95% confidence interval. Statistically significant values ($p<0.05$) are marked in bold.

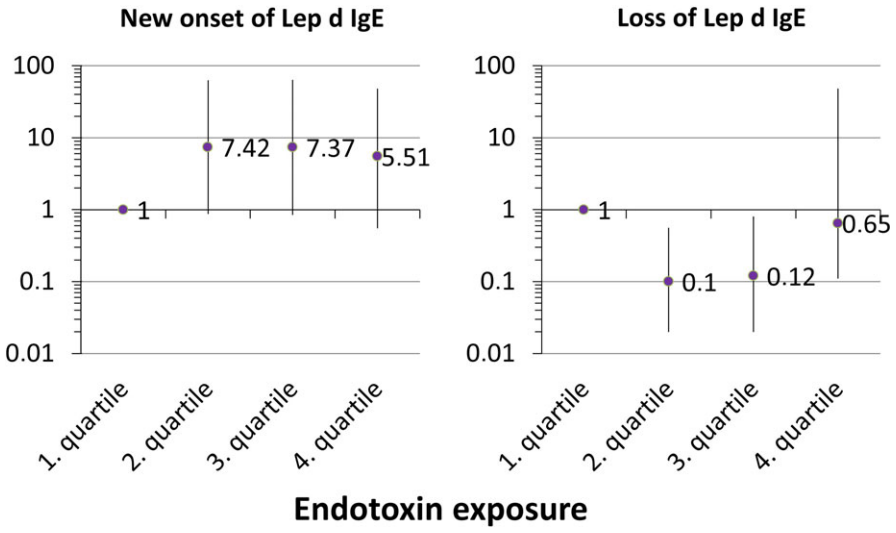

FIGURE 1. The Effect of Endotoxin Exposure on New-onset and Loss of Lep d sIgE Sensitization given as Adjusted Odds Ratios with 95% Confidence Intervals (OR 95% CI). Endotoxin exposure is given as exposure quartiles, the 4th quartile representing the highest exposure. The analyses were adjusted for farm childhood, pet-keeping during childhood and smoking status

be affected by house dust mite (HDM) exposures and sensitization, due to cross-reactivity between HDM and storage mites. However, several major storage mites' allergens (Lep d 2, Tyr p 2, and Gly d 2) show high homology and mutual cross-reactivity but share only approximately 40% amino acid identity with Der p 2, and cross-reactivity with HDM does not appear as often as previously suspected.[10,11] In this study, we could determine both the HDM and the Lep d sensitization status. Among participants with persistent HDM IgE sensitization, 33% also had persistent Lep d IgE sensitization, which might be thought to result from cross-reactivity. However, 53% of the persistent HDM IgE-sensitized participants never had a positive Lep d IgE test, and 21% of the persistent Lep d IgE-sensitized participants never had HDM IgE sensitization (Table S2 [IgE] and Table S3 [SPT]). Thus, Lep d and HDM sensitization showed, as expected, some overlap, which though by no means corresponded to an exact reflection of each other. This also supports our previous finding of new-onset and loss of HDM sensitization not being associated with farming exposure.[7,8]

Although this study lacks actual measurements of specific exposure levels of storage mite allergens, the positive association of new-onset as well as persistence of Lep d sensitization with farmwork can be explained by the exposure to farm dust during adult farmwork, which is known to contain high levels of storage mites in Danish farms. Although storage mites are found outside farming,[12] the concentration levels in farms are substantially higher compared with urban households.[13] Hence, exposure to Lep d allergens during adulthood is a major risk factor for Lep d sensitization irrespective of childhood exposure. The study is challenged by limited power, but consistent patterns are still found. This effect of adult farming exposure on changes in Lep d sensitization shows a reverse pattern compared with those observed for sensitization to common aeroallergens.[8] We speculate that this effect is due to a high occupational exposure to storage mites in general when working on a farm. While for the common allergens, exposure levels presumably remain relatively constant in adulthood as in childhood and adolescence, it is probable that the levels of general storage mite exposure increase considerably for young adults who start working as farmers. Thus, storage mites, in this study specifically Lep d, is a typical occupational allergen for which new sensitization might occur in the first years of a farmer's work life.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Plasminogen gene mutation with normal C1 inhibitor hereditary angioedema: Three additional French families

To the Editor

Hereditary angioedema should be divided into 2 forms according to the function of C1 inhibitor: HAE with C1 inhibitor deficiency (C1-INH-HAE)[1] and HAE with normal C1 inhibitor level (nC1-INH-HAE). Within this second form, some mutations have been described, such as *F12* gene mutation.[2] A missense variant in angiopoietin-1 gene (*ANGPT1*, c.807G > 1, p.Ala119Ser) seems also to be associated with nC1-INH-HAE.[3] However, in many cases, no mutation was found in nC1-INH-HAE patients.

Recently, Bork et al[4] described a new mutation associated with nC1-INH-HAE with variable penetrance. This mutation affected the plasminogen (*PLG*, NM_000301.3) gene and corresponded to the mutation c.988A > G in exon 9. This mutation led to the missense mutation p.Lys330Glu (K330E) in the kringle 3 domain of the PLG protein. It was identified in 60 patients belonging to 13 different German families. The phenotype of PLG-HAE in this cohort seemed to have some particularities: Patients preferentially developed face and tongue swelling. Oral contraceptive did not seem to be a frequent

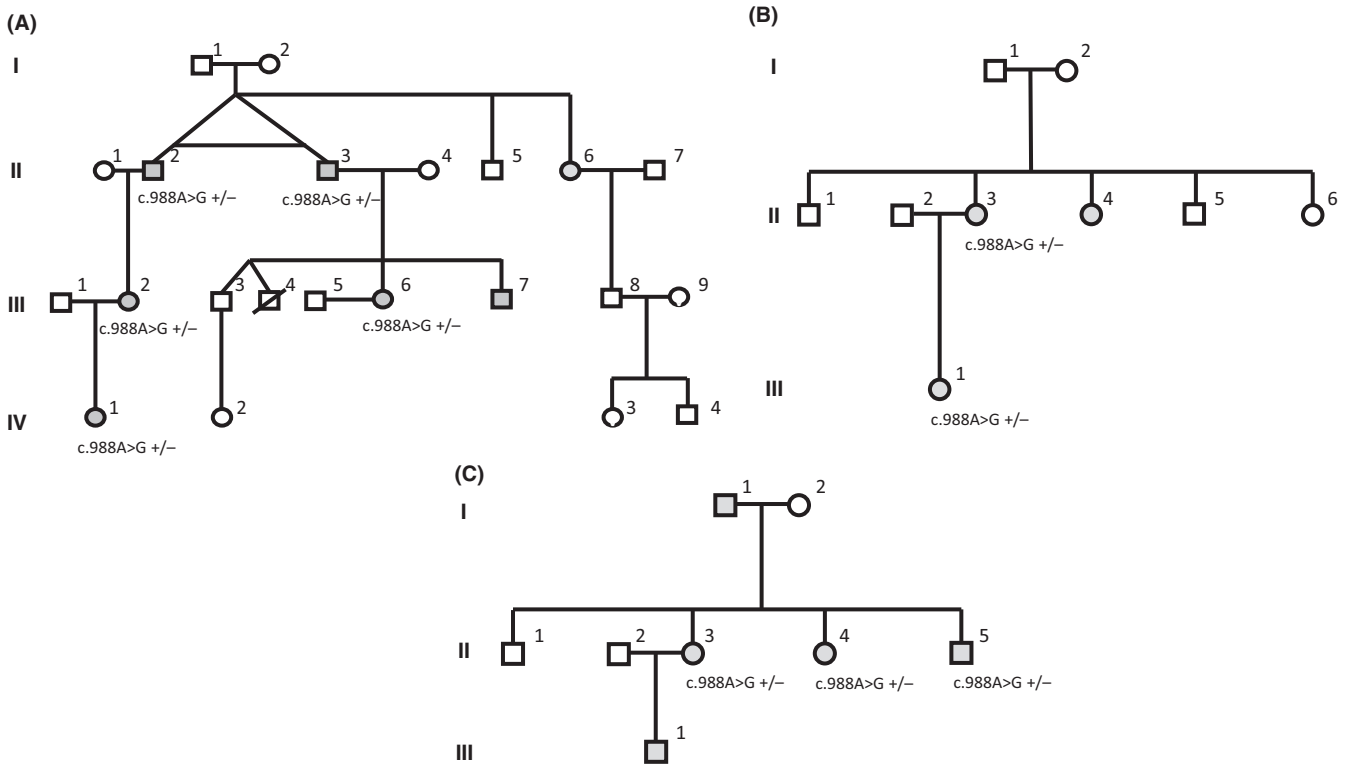

FIGURE 1 Families with mutation in the gene encoding for plasminogen. A, Family 01; B, family 02; C, family 03