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

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Abbreviations

CI Confidence interval

HDM House dust mite

IgE Immunoglobulin E

kU/L Kilo units per liter

OR Odds ratio

SPT Skin prick test

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, 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 exposure 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 was 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^{o}C, and baseline and follow-up sera were tested simultaneously in IgE duplex analyses (carried out at ALK Abello), to minimize inter-assay and day-to-day variation. A positive specific IgE response was defined as $\geq$ 0.35 kU/L, and a positive SPT response as a mean wheal reaction

>=3mm in the presence of a negative control. Changes in sensitization (new-onset and loss) were analyzed in relation to farm exposure by 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 modelled 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 testing negative at baseline and positive at follow-up, and loss of sensitization 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. Farm work 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; Supplementary 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 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 crss-reactivity. However, 53% of the persistent HDM IgE sensitized never had a positive Lep d IgE test, and 21% of the persistent Lep d IgE sensitized participants never had HDM IgE sensitization (supplementary Table S2 (IgE) and supplementary 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 between new-onset as well as persistence of Lep d sensitization with farm work can be explained by the exposure to farm dust during adult farm work, 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 to 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 to 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 farmers work life.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

TS conceived the study. TS and ØO designed the study. GE analyzed the data and drafted the manuscript. GE, VS, GD, IB, ØO, OMG and TS interpreted the data and revised the manuscript critically. All authors approved the final manuscript as submitted.

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

	New sensitization					Loss of sensitization				
	N[*)]	**N[#)]**	**%**	**OR**	**95%CI**	**N[*)]**	**N[#)]**	**%**	**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} *yrs)*	*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} *yrs)*	*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	

[*)] N = total numbers of participants in each exposure category without (left) or with (right) IgE sensitization to Lep d at baseline. [#)] 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.

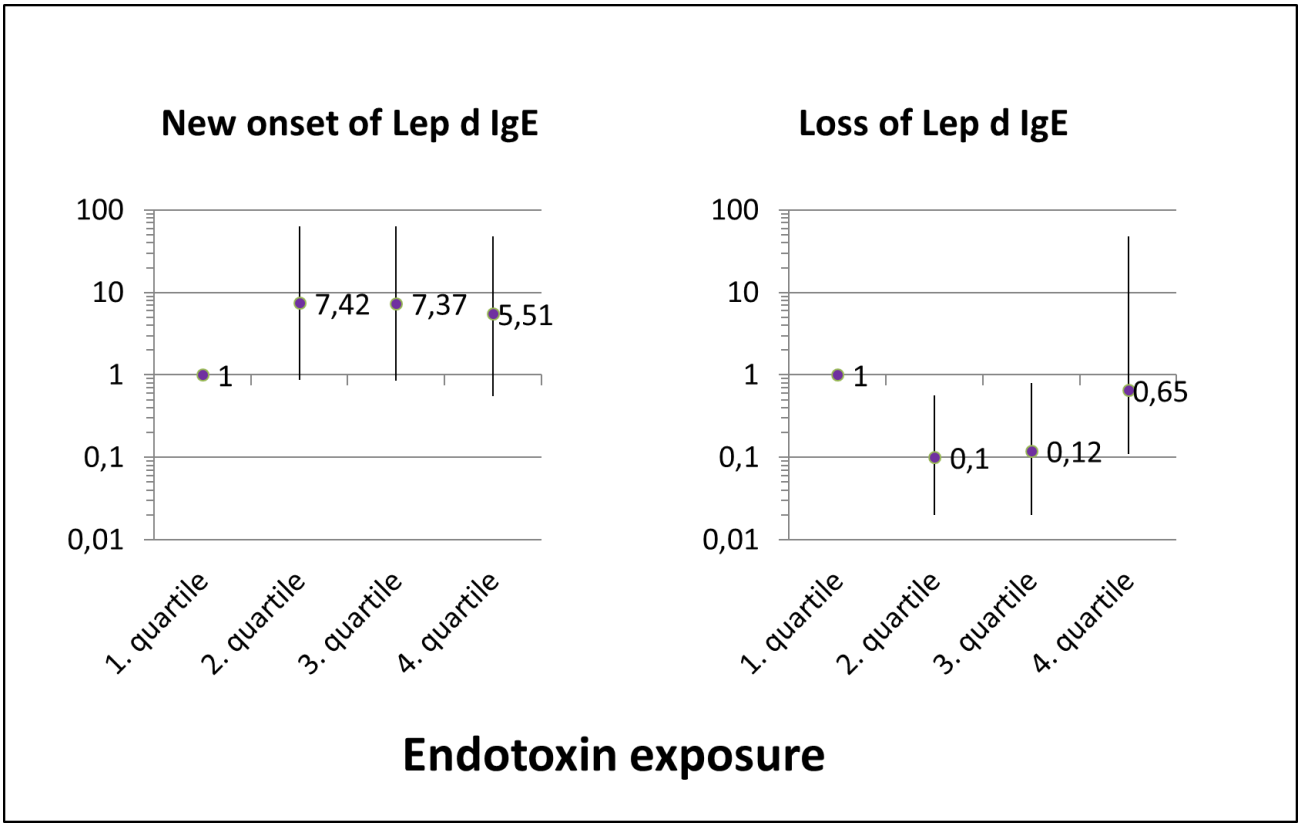

Figure 1. The effect of endotoxin exposure on new-onset and loss of Lep d sIgE sensitization given as adjusted odds ratios with 95% confidence intervals (OD 95% CI). Endotoxin exposure is given as exposure quartiles, the 4th quartile representing the highest exposure. The analyses were adjusted for farm childhood, pets during childhood and smoking status.