House dust mite sensitization, eczema, and wheeze increase risk of shellfish sensitization

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Author Contribution

Loo EXL and Tham EH conceptualized the study design, contributed to the analysis and writing of the manuscript. Lau HX analyzed the data and wrote the manuscript. Suaini NHA, Wong LSY, Goh AEN, Teoh OH, Van Bever HP, Shek LP-C, Lee BW, Tan KH, Godfrey KM, Eriksson JG, Chong YS contributed to the study design, collection of data and provided intellectual input. All authors critically reviewed the manuscript.

Conflict of Interest Statement

Godfrey KM has received reimbursement for speaking at conferences sponsored by Nestle and Shek LP has received reimbursement for speaking at conferences sponsored by Danone and Nestle and consulting for Mead Johnson and Nestle.

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To The Editor,

Shellfish allergy is more prevalent in South-East Asia (~5%[1]) than in Western populations (e.g. United States ~2-3%.[2]). Typically commencing in late childhood, it is the leading cause of anaphylaxis in adolescents and adults in Asia.[3]

Cross-sectional studies have demonstrated a high correlation between shellfish and house dust mite (HDM) sensitization in warm, humid climates and urban environments where HDM are ubiquitous.[4,5] The major shellfish allergen, tropomyosin, shares ~80% structural homology with HDM tropomyosin, and primary sensitization to dust mite tropomyosin has been hypothesized to induce cross-sensitization to shellfish.[6]

However, no prospective studies have investigated the temporal relationship between primary HDM sensitization and the development of shellfish sensitization/allergy. It is also unclear whether the mite-crustacean cross-reactivity syndrome originates from sensitization through the cutaneous or inhalational route.

We hypothesized that early life HDM sensitization predisposes to the development of shellfish sensitization in later childhood and aimed to evaluate its temporal relationship with early onset atopic dermatitis (AD) and wheezing in the prospective population-based Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort in Singapore.[7] Data were obtained from interviewer-administered questionnaires at birth, 3, 6, 9, 12, 15, 18 months and ages 2, 3, 4, 5, 6, 7 and 8 years. Skin prick testing (SPT) was conducted at 18 months, 3, 5 and 8 years, which included cow's milk, egg, peanut and HDM [*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* (Greer Laboratories, Lenoir, NC, USA) and *Blomia tropicalis* (developed in-house[8])] at 18 months, 3 and 5 years; and all of the above plus crab and shrimp (Greer Laboratories, Lenoir, NC, USA) at 5 and 8 years. Ethical approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group and the Centralised Institutional Review Board of SingHealth.

Atopic Dermatitis (AD) was defined as a parental-reported doctor's diagnosis of eczema at any of the above time-points. Wheeze was defined as positive responses to the questions "Has your child ever wheezed" and "Has your child ever been prescribed with nebulizer/inhaler treatment? at any of the above time-points. HDM sensitization was defined as a positive SPT to any of the 3 house dust mites. Shellfish sensitization was defined as a positive SPT to either crab or shrimp allergen.

Data was analyzed using SPSS Version 26.0 (IBM Corp, New York, NY, USA) for Windows. P values <0.05 were considered significant.

In this study, subjects who completed skin prick testing at 18 months, 3, 5 and 8 years and were not sensitized to shellfish at age 5 years were included in the analysis. Table 1 summarizes the demographic characteristics and allergic disease status of the cohort. The prevalence of HDM sensitization was 10.8% at age 18 months, 21.5% at 3 years and 32.3% at 5 years. The prevalence of shellfish sensitization at 8 years was 6.0%.

In multivariate analysis, HDM sensitization at ages 18 months, 3 and 5 years were associated with increased odds of shellfish sensitization at 8 years (Table 2). AD by 6 months in combination with HDM sensitization at age 18 months [AdjOR 10.1 (95% CI 2.0-50.4), p<0.01] and AD by 5 years with HDM sensitization at 5 years [AdjOR 3.4 (95% CI 1.4-8.6), p<0.01] increased the odds of shellfish sensitization at age 8 years. A trend of association between AD by 3 years in combination with HDM sensitization at 3 years with shellfish sensitization at 8 years was observed (p=0.05). Odds ratio of the eczema + HDM sensitization were greater than eczema alone.

Wheeze by age 3 years [AdjOR 2.7 (95% CI 1.1-6.3), p=0.02], HDM sensitized wheeze by 3 years [AdjOR 4.2 (95% CI 1.4-13.1), p=0.01] and HDM sensitized wheeze by 5 years [AdjOR 2.9 (95% CI 1.1-7.6), p=0.03] were associated with shellfish sensitization at age 8 years. A trend of association between wheeze by 5 years and shellfish sensitization at age 8 years was also observed (p=0.06). Odds ratio of the wheeze + HDM sensitization combination were greater than wheeze alone. Rates of sensitization to other food allergens and shellfish allergy were too low for analysis.

This is the first prospective study in a tropical climate demonstrating that early house dust mite sensitization is a risk factor for development of shellfish sensitization, and early onset AD and wheezing disorders are major co-factors which strengthen this risk.

We hypothesized from these findings that an impaired skin or airway epithelial barrier in early life, such as in early onset AD, and wheezing disorders, may predispose to sensitization to ubiquitous environmental allergens such as food allergens or HDM. Further research is needed to study the mechanism of sensitization. This has been well-established in epicutaneous sensitization in AD. A possible mechanism for airway sensitization is through protease allergens such as Der p 1 which possess cysteine proteinase activity that can cleave structural proteins in airway epithelial tight junctions, facilitating allergen sensitization.[9] It could be postulated that environmental

exposure to HDM from infancy together with a defective epithelial barrier in the presence of eczema and wheeze, predisposes to acquisition of HDM sensitization and cross-reactivity to shellfish tropomyosins. This hypothesis could partially explain the later onset of shellfish allergies in tropical Asian populations, which contrasts with the earlier onset of milk, egg and peanut allergies in most paediatric populations.

We hypothesize that an impaired airway or skin barrier could predispose to allergic sensitization. However, we did not study gut microbiome dysbiosis, a known risk factor for food allergy development. Gut microbiome dysbiosis precedes and affects food allergen sensitization by regulating intestinal barrier integrity, Th2 immune balance, allergen tolerance and basophil production.[10] Results from murine models showed that commensal bacteria such as Clostridia can induce IL-22 production in innate lymphoid cells and T cells to prevent the passage of allergens through the intestinal epithelium barrier and protect against food allergen sensitization.[11]

This study's strengths lie in its prospective data collection at multiple time-points which enables the analysis of temporal relationships between exposures and outcomes while adjusting for multiple confounders. Limitations include the lack of shellfish oral food challenges at year 8, and a very low prevalence of reported shellfish allergy in our cohort, which precluded further analysis. This is consistent with the known low prevalence of food allergy in our cohort.[12] Studies have shown the sensitivity of shrimp SPT to be around 60-70% and thus shrimp sensitization alone may misclassify some subjects' true clinical reactivity status.[13,14] However, our previous data also indicates that the prevalence of shellfish allergy is very low in early life and only increases in adolescence and young adulthood[1], thus follow-up studies are needed to evaluate the relationship between HDM sensitization and shellfish allergy later in life. We have observed temporal associations in this study but definitive causation and its mechanisms require further study. Questionnaire-based assessments of eczema and wheeze may also misclassify disease outcomes compared to physician's diagnosis and is another limitation of our study. The confidence intervals obtained in this study were wide due to modest sample sizes, hence larger studies will be needed to confirm these findings.

Further research is also needed to evaluate the possible role of early interventions such as environmental measures for reduction of HDM sensitization or immunotherapy against the development of shellfish sensitization and subsequent shellfish allergy.

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References

1. Shek LP, Cabrera-Morales EA, Soh SE, et al. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. *J Allergy Clin Immunol.* 2010;126(2):324-331, 331 e321-327.
2. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol.* 2004;114(1):159-165.
3. Lee AJ, Gerez I, Shek LP, Lee BW. Shellfish allergy--an Asia-Pacific perspective. *Asian Pac J Allergy Immunol.* 2012;30(1):3-10.
4. Wang J, Calatroni A, Visness CM, Sampson HA. Correlation of specific IgE to shrimp with cockroach and dust mite exposure and sensitization in an inner-city population. *J Allergy Clin Immunol.* 2011;128(4):834-837.
5. Rosenfield L, Tsoulis MW, Milio K, Schnittke M, Kim H. High rate of house dust mite sensitization in a shrimp allergic southern Ontario population. *Allergy Asthma Clinical Immunol.* 2017;13:5.
6. Shafique RH, Inam M, Ismail M, Chaudhary FR. Group 10 allergens (tropomyosins) from house-dust mites may cause covariation of sensitization to allergens from other invertebrates. *Allergy Rhinol (Providence).* 2012;3(2):e74-90.
7. Soh SE, Tint MT, Gluckman PD, et al. Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. *Int J Epidemiol.* 2014;43(5):1401-1409.
8. Yi F, Chew F, Jimenez S, Chua K, Lee B. Culture of Biomia tropicalis and IgE Immunoblot Characterization of Its Allergenicity. *Asian Pac J Allergy Immunol.* 1999;17(3):189.
9. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. *J Allergy Clin Immunol.* 2014;134(3):499-507.
10. Zhao W, Ho H-e, Bunyavanich S. The gut microbiome in food allergy. *Ann Allergy Asthma Immunol.* 2019;122(3):276-282.
11. Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization. *Proc Natl Acad Sci.* 2014;111(36):13145.
12. Tham EH, Lee BW, Chan YH, et al. Low Food Allergy Prevalence Despite Delayed Introduction of Allergenic Foods-Data from the GUSTO Cohort. *J Allergy Clin Immunol Pract.* 2018;6(2):466-475.e461.

13. Yang AC, Arruda LK, Santos ABR, et al. Measurement of IgE antibodies to shrimp tropomyosin is superior to skin prick testing with commercial extract and measurement of IgE to shrimp for predicting clinically relevant allergic reactions after shrimp ingestion. J Allergy Clin Immunol. 2010;125(4):872-878.
14. Srisuwatchari W, Vichyanond P. Oral food challenges: result of a 16-year experience at a major teaching hospital in Thailand. Asia Pac Allergy. 2018;8(2).

Table 1. Demographic Characteristics and allergic disease status

Demographics	**N (%)** **N=536**
Male	272 (50.7)
Ethnicity	
Chinese	307 (57.3)
Malay	144 (26.9)
Indian	85 (15.9)
Caesarean delivery	163 (30.4)
Maternal tertiary education	378 (71.1)
Maternal history of allergy	204 (38.9)
House Dust Mite (HDM) sensitization status	
Any HDM sensitization @ month 18	58 (10.8)
D. Pteronyssinus	44 (8.2)
D. Farinae	34 (6.3)
B. Tropicalis	5 (0.9)
Any HDM sensitization @ month 36	115 (21.5)
D. Pteronyssinus	101 (18.8)
D. Farinae	78 (14.6)
B. Tropicalis	12 (2.2)
Any HDM sensitization @ year 5	173 (32.3)
D. Pteronyssinus	157 (29.3)
D. Farinae	139 (25.9)
B. Tropicalis	36 (6.7)
Shellfish sensitization at 8 years	32 (6.0)
Atopic dermatitis (AD) status	
AD by 6 months of age	35 (7.2)
AD by 6 months + HDM sensitized at 18 months	7 (1.4)
AD by 3 years of age	106 (23.7)
AD by 3 years + HDM sensitized at 3 years	35 (7.8)

AD by 5 years of age	116 (26.9)
AD by 5 years + HDM sensitized at 5 years	58 (13.4)
Wheeze status	
Wheeze by 18 months	56 (12.5)
Wheeze + HDM sensitized at 18 months	9 (2.0)
Wheeze by 3 years	94 (20.9)
Wheeze + HDM sensitized at 3 years	31 (6.9)
Wheeze by 5 years	113 (26.4)
Wheeze + HDM sensitized at 5 years	52 (12.1)

HDM = House dust mite

Table 2. Multivariate analysis for the associations between early onset atopic dermatitis, wheeze, house dust mite sensitization and shellfish sensitization at 8 years

	Shellfish sensitization at 8 years	
	AdjOR (95% CI)	**p value**
HDM sensitized at 18 months	**2.6 (1.03-6.3)**	**0.04**
HDM sensitized at 3 years	**2.5 (1.1-5.3)**	**0.02**
HDM sensitized at 5 years	**3.6 (1.7-7.7)**	**<0.01**
Atopic dermatitis by 6 months	2.3 (0.7-7.3)	0.16
Atopic dermatitis by 6 months + HDM sensitized at 18 months	**10.1 (2.0-50.4)**	**<0.01**
Atopic dermatitis by 3 years	1.6 (0.7-3.8)	0.27
Atopic dermatitis by 3 years + HDM sensitized at 3 years	2.9 (1.0-8.4)	0.05
Atopic dermatitis by 5 years	1.4 (0.6-3.4)	0.42
Atopic dermatitis by 5 years + HDM sensitized at 5 years	**3.4 (1.4-8.6)**	**<0.01**
Wheeze by 18 months	2.3 (0.8-6.1)	0.10
Wheeze + HDM sensitized at 18 months	2.4 (0.3-21.0)	0.44
Wheeze by 3 years	**2.7 (1.1-6.3)**	**0.02**
Wheeze + HDM sensitized at 3 years	**4.2 (1.4-13.1)**	**0.01**
Wheeze by 5 years	2.2 (1.0-5.1)	0.06
Wheeze + HDM sensitized at 5 years	**2.9 (1.1-7.6)**	**0.03**

Adjusted for gender, ethnicity, mode of delivery, maternal education levels and maternal history of allergy

Bold text indicates statistical significance

HDM=house dust mite