Association between allergen component sensitisation and clinical allergic disease in children

Brand, Paul L. P.; Brohet, Richard M.; Schwantje, Olof; Dikkeschei, Lambert D.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

ORIGINAL ARTICLE

OPEN ACCESS

Association between allergen component sensitisation and clinical allergic disease in children

Paul L.P. Brand[a,b], **Richard M. Brohet**[c], **Olof Schwantje**[d], **Lambert D. Dikkeschei**[e]*

[a]*Isala Academy, Department of Medical Education and Faculty Development, Isala Hospital, Zwolle, The Netherlands*
[b]*Wenckebach Institute for Medical Education, University Medical Centre, Groningen, The Netherlands*
[c]*Isala Academy, Department of Research and Innovation, Isala Hospital, Zwolle, The Netherlands*
[d]*General Practice Schwantje & Groot, Zwolle, The Netherlands*
[e]*Central Laboratory, Isala Hospital, Zwolle, The Netherlands*

Abstract
Background: Allergen component sensitisation testing is becoming increasingly important in the diagnosis of peanut allergy. The aim of the present study was to evaluate the relationship between sensitisation and symptoms of allergic disease in children by testing a large panel of inhalants, food allergens, and allergen components.
Methods: For 287 children visiting our laboratory for allergy testing, symptoms of allergic disease were recorded by standardised validated questionnaires. Specific IgE to 11 whole allergens was assessed by ImmunoCAP, and to 112 allergen components by ISAC ImmunoCAP assay. We used latent class analysis (LCA) to distinguish clinical phenotypes.
Results: Inhalant and food allergen sensitisation was common, irrespective of the children's allergic symptom type. Less than 10% of the variance in symptom scores was explained by variations in the number of allergens (components) that the child was sensitised to. In LCA, 135 children (50.2%) had mild allergy, with few symptoms and sensitisation to no or few allergens, 74 children (27.5%) had more symptoms and sensitisation to inhalant allergens (respiratory allergy) and 60 children (22.3%) showed polysensitisation to a median of six allergens and had more severe symptoms of different organ systems. Adding allergen component test results to LCA failed to result in identifiable classes of allergic disease in children.
Conclusions: In this group of children with allergic symptoms, referred for allergy testing by their physician, broad screening for allergen component sensitisation did not contribute to distinguishing phenotypes of allergic disease.
© 2022 Codon Publications. Published by Codon Publications.

Corresponding author: Paul L.P. Brand, Isala Academy, Department of Medical Education and Faculty Development, Isala Hospital, PO Box 10400, 8000 GK Zwolle, The Netherlands. *Email address:* p.l.p.brand@isala.nl

Introduction

The diagnosis of clinical allergy in children relies on the combination of a history of symptoms suggestive of allergy and the demonstration of sensitisation to the suspected allergen by skin prick or specific IgE testing.[1,2] Although a convincing structured history plays a key part in the diagnostic work-up of both food and inhalant allergens, a symptom history alone carries a high risk of false positive and negative results.[3,4] Similarly, allergen sensitisation alone is insufficient to diagnose clinically relevant allergies.[1,2,5] The main problem with allergen sensitisation tests is their excessive sensitivity, resulting in a high degree of false positives.[1,2]

Component-resolved diagnostics (CRDs), that is, testing of sensitisation to specific allergen components instead of testing of sensitisation to the whole allergen, may improve the relationship between sensitisation and clinical allergies in children.[6] For example, after initial reports indicated that sensitisation to the component Arah2 was associated with a high risk of clinically relevant peanut allergy in children,[7] the diagnostic value of assessing sensitisation to peanut allergen components in the diagnostic work up of suspected peanut allergy in children became increasingly clear.[8] Investigations have also begun to explore the relationship between allergen component sensitisation and clinical allergy for other allergens, including pets and hen's egg,[9,10] to help in unravelling complex or rare allergies,[11] aid in decisions regarding specific allergen immunotherapy[12] and predict the risk and severity of asthma.[10,13] To date, Ara h2 testing in suspected peanut allergy is the allergen component test that has been most implemented in paediatric clinical allergy practice.[8] Although a few population-based studies have used CRDs in a wide range of allergen components to examine the risk of (developing) allergies over time,[13-15] there is a lack of studies on the relationship between CRD results and allergy symptoms in groups of patients with suspected allergies. Results of such studies may help clinicians to appreciate the potential value of CRD testing in their diagnostic approach to allergies in childhood.

The aim of the present study was to evaluate the relationship of CRDs and the clinical expression of common allergic diseases in children.

Materials and Methods

Design

This was a prospective cohort study of children, 0–18 years of age, for whom the general practitioner (GP) or hospital-based paediatrician ordered a specific IgE test at Isala's Central Laboratory in Zwolle, the Netherlands. This laboratory performs an average of 1000 specific IgE tests in children annually.[16]

Participants

From January 2015 to December 2017, parents/guardians of each child referred to the laboratory for allergy testing were asked to participate in the study and to allow for obtaining an additional 5 mL serum sample for study purposes. This did not require additional venipuncture.

Symptom questionnaires

Guided by their responses to a research assistant's question about the nature of their child's allergic symptoms, parents were asked to complete one or more of the following validated symptom questionnaires electronically, links for which were emailed to them by the research assistant: the Children's Dermatology Life Quality Index (CDLQI) to assess atopic dermatitis symptoms,[17] the paediatric Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) to assess allergic rhinitis symptoms,[18] the paediatric Asthma Control Questionnaire (ACQ) to assess asthma symptoms[19] and the food allergy quality of life questionnaire (FAQLQ) to assess food allergy symptoms.[20] Children aged 8 years or older completed the corresponding child versions of the questionnaires, aided by their parents. The CDLQI score ranges from 0 to 30, and the RQLQ, ACQ and FAQLQ from 0 to 6. Higher scores indicate more severe symptoms.

Parents also completed a generic paediatric quality of life questionnaire (the Quality of My Life (QML) questionnaire).[21] QML is recorded on a visual analogue scale ranging from 0 (poorest) to 100 (best quality of life).

Specific IgE testing

As described in more detail previously,[16,22] blood samples were investigated using a screening test for aeroallergens, food allergens, or both (Phadiatop, FX5 or Phadiatop infant, Thermo Fisher, Uppsala, Sweden). In the case of a positive screening test, specific IgE to a panel of common aeroallergens (house dust mite, cat dander, dog dander, grass pollen and tree pollen) and food allergens (cow's milk, hen's egg, peanut, tree nuts, wheat and soy) was assessed using the ImmunoCAP system (Thermo Fisher, Uppsala, Sweden). A specific IgE level of 0.35 kU/L or greater was considered to reflect sensitisation to the specific allergen.

Component-resolved diagnostics

The additional 5 mL serum sample was used to assess IgE to 112 allergenic molecules (components) using ImmunoCAP ISAC (ThermoFisher/Phadia AB, Uppsala, Sweden). In this assay, allergen components that are immobilized on a solid substrate in a microarray format react with the specific IgE in the patient sample. After washing away non-specific IgE, fluorescence-labelled anti-human IgE antibody is added to form a complex, and unbound fluorescence-labelled anti-human IgE antibodies are removed by washing. The procedure is followed by fluorescence measurement using a LuxScan 10k Microarray Scanner, and the results are expressed as ISU-E. The assay has demonstrated excellent reproducibility between laboratories.[23]

Statistical analysis

Standard statistical techniques were applied to examine the relationship between allergic symptoms (as assessed by standardised questionnaires), whole allergen sensitisation and CRD results. In addition, latent class analysis (LCA) was performed to find patient groups with clinically distinct profiles of allergic symptoms and patterns of sensitisation

to either whole allergens or allergen components (CRDs).[24] A maximum likelihood method was used to estimate patterns in patient characteristics summarised into groups or latent classes by providing a probability distribution over the cluster assignment for each patient. We compared models, allowing for different numbers of latent classes. We used likelihood ratios, Akaike's information criterion (AIC) and Bayesian information criterion (BIC) to compare the models, with smaller AIC and BIC values indicating better models in terms of parsimoniousness next to the goodness-of-fit estimate.

Data were analysed using SPSS Statistics version 24.0 and with STATA version 16.1 (Statacorp LLC) for LCA. In light of the exploratory nature of the study, we refrained from adjusting for multiple comparisons.

Ethics

This study was approved by Isala Hospital's Ethical Review Board (file number: 13.11128).

Results

From the 767 children approached for participation in the study, completed symptom questionnaires were obtained from 464 children (61%) (256 boys, 55%). These children had symptoms of allergic rhinitis (n=301, 65%), asthma (n=239, 52%), eczema (n=117, 25%) or (suspected) food allergy (n=129, 28%), and 23 (5%) had other non-specific symptoms (such as malaise or abdominal pain). Mean age was 7.9 (5.0) years.

Permission to obtain additional serum for CRDs was obtained from parents of 287 patients (149 boys, 52%). Demographic and symptomatic characteristics of these children are presented in Table 1. There were no statistically significant differences in age, gender, or type of symptoms among children with or without CRD analysis (all P values > 0.1).

Overall, 208 children (72.5%) were sensitised to one or more inhalant allergens (house dust mite, dog dander, cat dander, grass pollen or tree pollen), 92 (32.1%) to one or more food allergens (cow's milk, hen's egg, peanut, tree nuts, soy or wheat) and 86 (30.0%) to one or more inhalant and one or more food allergens. The median (interquartile range) number of children sensitised to whole allergens was 2 (2-5).

Supplementary Table A lists the number of children sensitised to each of the allergen components in the ISAC ImmunoCAP assay, and the median and range of the degree of sensitisation (in ISU-E) for each component.

The relationship of whole allergen sensitisation to the type of allergic symptoms is presented in Table 2. Sensitisation to inhalant allergens occurred in 73%, 76%, 84% and 71% of children with asthma, allergic rhinitis, atopic dermatitis and food allergy, respectively. Sensitisation to food allergens was found in 34%, 34%, 50% and 40% of children with asthma, allergic rhinitis, atopic dermatitis and food allergy, respectively.

Table 1 Age and gender of the 287 study participants for whom completed symptom questionnaires and component resolved diagnostics data were available and for those with different types of allergic symptoms.

	Mean (SD) age	Male gender, number (%)	Median (range) of symptom questionnaire
Asthma (n=111)	7.9 (4.8)	64 (58%)	ACQ median 0.9 (0-5.6)
Allergic rhinitis (n=170)	9.2 (5.2)	96 (56%)	RQLQ median 0.3 (0-6)
Atopic dermatitis (n=64)	7.7 (4.3)	32 (50%)	CDLQI median 0.3 (0-17)
(Suspected) food allergy (n=68)	6.4 (4.5)	36 (53%)	FAQLQ median 0.6 (0-3.0)
Non-specific symptoms (n=26)	7.5 (4.7)	17 (65%)	
Overall	**8.0 (5.0)**	**149 (52%)**	QML median 91 (29-100)

ACQ, asthma control questionnaire; RQLQ, rhinitis quality of life questionnaire; CDLQI, children's dermatology life quality index; FAQLQ, food allergy quality of life questionnaire; QML, quality of my life questionnaire.

Table 2 Relationship between whole allergen sensitisation and the type of allergic symptoms (n=287).

	Hay fever (n = 170)	Asthma (n = 111)	Eczema (n = 64)	(Suspected) food allergy (n = 68)	Non-specific symptoms (n = 26)
House dust mite	92 (54%)	64 (58%)	42 (66%)	34 (50%)	16 (62%)
Dog	40 (24%)	29 (26%)	21 (33%)	15 (22%)	6 (23%)
Cat	61 (36%)	44 (40%)	27 (42%)	21 (31%)	8 (31%)
Grass pollen	101 (59%)	63 (57%)	41 (64%)	42 (62%)	14 (54%)
Tree pollen	76 (45%)	49 (44%)	36 (56%)	28 (41%)	7 (27%)
Cow's milk	9 (5%)	4 (4%)	7 (11%)	5 (7%)	4 (15%)
Hen's egg	8 (5%)	5 (5%)	7 (11%)	7 (10%)	1 (4%)
Peanut	37 (22%)	23 (31%)	19 (30%)	14 (21%)	3 (12%)
Tree nuts	45 (27%)	31 (28%)	25 (39%)	21 (31%)	5 (19%)
Soy	30 (18%)	15 (14%)	14 (22%)	7 (10%)	2 (8%)
Wheat	12 (7%)	7 (6%)	6 (9%)	2 (3%)	2 (8%)

Table 3 Non-parametric correlation coefficients (Spearman's ρ) between symptom scores and the number of whole allergens and the number of allergen components to which children were sensitised.

	ACQ	RQLQ	CDLQI	FAQLQ	QML
Number of whole allergens child is sensitised to	0.041 (p=0.503)	0.160 (p=0.008)	0.183 (p=0.002)	0.007 (p=0.909)	0.004 (p=0.945)
Number of allergen components child is sensitised to	0.017 (p=0.777)	0.247 (p<0.001)	0.084 (p=0.167)	0.044 (p=0.473)	−0.015 (p=0.811)

ACQ, asthma control questionnaire; RQLQ, rhinitis quality of life questionnaire; CDLQI, children's dermatology life quality index; FAQLQ, food allergy quality of life questionnaire; QML: quality of my life questionnaire.
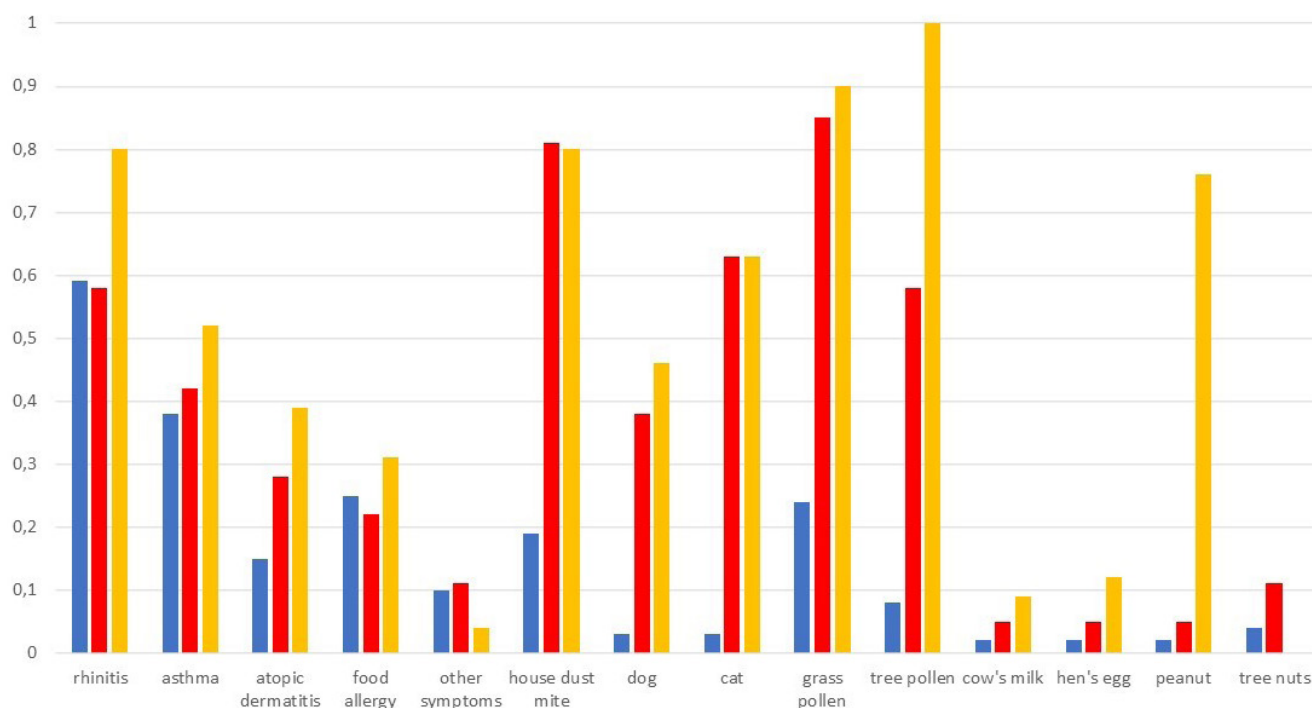

Figure 1 Distribution of symptoms and whole allergen sensitisation across the three classes distinguished by latent class analysis. Blue bars: class 1 (n = 135), red bars: class 2 (n = 74) and yellow bars: class 3 (n = 60).

Differences in the degree of symptoms between children with and without sensitisation to whole allergens were small and rarely significant (Supplementary Table B). Because of this, we refrained from testing differences in symptom scores between children with and without sensitisation to individual allergen components.

Correlations between symptom scores and the number of whole allergens and the number of allergen components children were sensitised to were weak overall, with less than 10% of variance in symptom scores explained by variations in the number of allergens (components) the child was sensitised to (Table 3).

In LCA models, including symptom scores and whole allergen sensitisation, a three-class model exhibited the best statistical fit (AIC 3551, BIC 3709, likelihood ratio chi-squared 906, P<0.001). Figure 1 and Table 4 show the distribution of variables across classes in this model. Class 1 (n=135) showed relatively few symptoms (in particular little atopic dermatitis) and sensitisation to no or few allergens and was called "mild allergy". Children in Class 2 (n=74) had more symptoms and showed sensitisation to a few, mostly inhalant, allergens ("respiratory allergy"),

and those in Class 3 (n=60) showed most symptoms and sensitisation to a range of inhalant and food allergens ("polysensitisation"). Differences in allergen component sensitisation rates among the three classes are shown in Supplementary Table C, and Table 4 reflects the differences among the classes in whole allergen sensitisation rates. In the LCA analysis models in which symptom scores and allergen component sensitisation rates were entered, the likelihood maximisation algorithms failed to converge, and no classes of symptom and sensitisation patterns could be distinguished.

Discussion

In this cohort of children referred for allergy testing by their GP or paediatrician, there was only a weak association of the type and severity of allergic symptoms to the patterns of sensitisation to whole allergens and allergen components. Inhalant and food allergen sensitisation was common, irrespective of the children's allergic symptom type. In LCA, half of the children had mild

Table 4 Distribution of variables across the three classes distinguished by latent class analysis.

	Class 1 (n = 135)	Class 2 (n = 74)	Class 3 (n = 60)	p
Male gender	70 (52%)	44 (60%)	36 (60%)	0.431
Age, mean (SD)	7.6 (5.3)	7.6 (4.7)	9.4 (4.7)	0.051
Hay fever symptoms	81 (60%)	41 (55%)	49 (82%)	0.003
RQLQ score, mean (SD)	0.56 (0.76)	0.44 (0.60)	0.87 (0.84)	0.003
Asthma symptoms	52 (39%)	29 (39%)	32 (53%)	0.130
ACQ, mean (SD)	1.76 (4.07)	1.48 (2.89)	1.92 (3.43)	0.772
Eczema symptoms	18 (13%)	24 (32%)	22 (37%)	<0.001
CDLQI score, mean (SD)	0.24 (0.95)	0.74 (1.92)	0.48 (1.14)	0.032
Food allergy symptoms	34 (25%)	17 (23%)	18 (30%)	0.641
FAQLQ score, mean (SD)	0.22 (0.60)	0.20 (0.62)	0.17 (0.40)	0.851
Other symptoms	13 (10%)	10 (14%)	2 (3%)	0.128
QML score, mean (SD)	86.5 (13.0)	82.2 (20.0)	85.6 (14.1)	0.153
Sensitised to house dust mite	24 (18%)	62 (84%)	48 (80%)	<0.001
Sensitised to grass pollen	32 (24%)	62 (84%)	54 (90%)	<0.001
Sensitised to tree pollen	10 (7%)	41 (55%)	60 (100%)	<0.001
Sensitised to dog	3 (2%)	29 (39%)	27 (45%)	<0.001
Sensitised to cat	2 (2%)	48 (65%)	38 (63%)	<0.001
Sensitised to cow's milk	3 (2%)	4 (5%)	5 (8%)	0.146
Sensitised to hen's egg	2 (2%)	4 (5%)	7 (12%)	0.009
Sensitised to peanut	2 (2%)	2 (3%)	45 (75%)	<0.001
Sensitised to tree nuts	5 (4%)	6 (8%)	53 (88%)	<0.001
Sensitised to soy	1 (1%)	2 (3%)	31 (52%)	<0.001
Sensitised to wheat	3 (2%)	2 (3%)	9 (15%)	0.001
Sensitised to inhalant allergens	59 (44%)	74 (100%)	60 (100%)	<0.001
Sensitised to food allergens	10 (7%)	14 (19%)	60 (100%)	<0.001
Sensitised to inhalant and food allergens	4 (3%)	14 (19%)	60 (100%)	<0.001
Number of allergens child is sensitised to, median (range)	0 (0-4)	3 (2-6)	6 (3-10)	<0.001
Number of allergen components child is sensitised to, median (range)	0 (0-13)	2 (0-15)	16.5 (0-58)	<0.001

RQLQ, rhinitis quality of life questionnaire; ACQ, asthma control questionnaire; CDLQI, children's dermatology life quality index; FAQLQ, food allergy quality of life questionnaire; QML, quality of my life questionnaire.

allergy, with few symptoms and sensitisation to no or few allergens. The other half of the children were equally divided between a group with respiratory allergy and a group with polysensitisation and more severe symptoms of different organ systems. Adding CRD results to the LCA failed to result in identifiable classes of allergic disease in children.

The identification of one or more allergens that play a causative role in allergic symptoms in children varies from relatively straightforward to extremely complicated. Taking a detailed and structured history into account plays an important role in making or refuting a diagnosis of a specific allergy. For example, in a series of 280 peanut-sensitised children, peanut allergy could be reliably excluded in 55% of patients, and reliably diagnosed in 17%, based on history alone.[4] Similarly, patients who report only symptoms of rhinitis or asthma during a specific pollen allergy season are likely to have a relevant allergy to that specific pollen.[25,26] In the large majority of cases, however, a diagnosis of allergy cannot be made by considering history alone, but sensitisation tests are needed to raise or lower the probability of clinically relevant allergy to the possible allergen(s).[1-3,25] Most clinicians and laboratories approach such testing in a stepwise panel approach,

similar to what we did in this study: first a screening test for inhalant, food allergens or both, followed by a breakdown into the most common allergens after a positive screening test. Interpreting the results of such sensitisation tests within the context of a detailed structured history requires knowledge on the principles and characteristics of the test, and on the pre-test probability of a positive test result.[1,25] The results of the present study confirm earlier observations that sensitisation to food and inhalant allergens frequently co-exist,[22] irrespective of the nature of the child's allergic symptoms (Table 2).[1,2,25] Given the high likelihood of asymptomatic sensitisation in children, particularly for food allergens,[1,2,5] a screening sensitisation test without a clear clinical suspicion is likely to generate more confusion than clarity. Therefore, the results of our study support the recommendation to screen only for suspected allergens dependent on the nature of the symptoms.[25]

The relationship between severity of allergic symptoms and sensitisation to individual allergens was weak (Supplementary Table B). This is in agreement with population-based studies, in which sensitisation to house dust mite shows only limited association to the presence or severity of asthma in children.[13] Recent work has shown, however, that interaction patterns among different

house dust mite allergen components show a considerably stronger relationship to asthma severity in children and adults,[13,15] and the same goes for sensitisation to pet allergen components.[10] Because of the high number of allergen components that can be tested, for example, in the ISAC ImmunoCAP assay, such relationships are difficult to tease out using simple bivariate statistics, such as correlation testing or *t* tests (Table 3 and Supplementary Table B). More advanced statistical tests, such as machine learning techniques,[15] appear more promising in elucidating the complex relationship between allergen and allergen component sensitisation and the presence and severity of allergic disease in children.

Unsupervised classification techniques such as cluster analysis and LCA have been used to identify and characterise different phenotypes of asthma in children, both in population studies[27,28] as well as in patient populations.[29] Recently, LCA has also been used to distinguish different phenotypes of children with allergic rhinitis.[30] We used LCA to identify patterns of different types of allergic symptoms (asthma, rhinitis, atopic dermatitis and food allergy) in relation to sensitisation to allergen and allergen components. The identification of a distinct phenotype of polysensitisation in this group of patients referred for allergy testing confirms earlier observations from population-based studies and clinical samples.[22,31,32] Polysensitised children have a higher likelihood of having allergic symptoms from multiple organ systems (Table 4), particularly atopic dermatitis,[31] and have more severe symptoms and reduced lung function.[28] As expected, the results of our study show that these children are also sensitised to a high number of allergen components (Table 4). Recent studies have shown that sensitisation to multiple allergen components is associated with more severe allergic rhinitis symptoms,[30] a higher likelihood of clinically relevant peanut allergy,[33] more severe asthma[13] and with the development of pet allergy.[14] In our study, LCA was unable to identify distinct phenotypes of allergic symptoms in relation to sensitisation patterns of allergen components. Although there are no clear guidelines on the desired sample size for LCA,[24] our study sample was relatively small compared to other studies using LCA,[27,28,30] which may have limited our power to identify distinct phenotypes. Future studies in larger clinical samples of children with allergic disease, using standardised methods to record the presence and severity of symptoms (like we did) and applying advanced statistical tests including machine learning techniques are needed to further elucidate the relationship between symptoms of allergic disease in children and their sensitisation patterns to multiple allergen components. Such data may help clinicians to fine-tune their diagnostic approach for suspected allergies in children and may contribute in establishing the role of allergen component screening tests in paediatric allergy practice.

In conclusion, the relationship between the extent and degree of sensitisation to whole allergens or allergen components to allergic disease severity in children is weak. There appears to be three classes of symptom/sensitisation patterns in children with symptoms of allergic disease: mild allergy, respiratory allergy and polysensitisation. Broad screening for allergen component sensitisation did not contribute to distinguishing phenotypes of allergic disease.

Conflict of interest

Funding

References

1. Roberts G, Ollert M, Aalberse R, Austin M, Custovic A, DunnGalvin A, et al. A new framework for the interpretation of IgE sensitization tests. Allergy. 2016;71:1540-51. https://doi.org/10.1111/all.12939

2. Eigenmann PA, Atanaskovic-Markovic M, O'B HJ, Lack G, Lau S, Matricardi PM, et al. Testing children for allergies: why, how, who and when: An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. Pediatr Allergy Immunol. 2013;24:195-209. https://doi.org/10.1111/pai.12066

3. Smith HE, Hogger C, Lallemant C, Crook D, Frew AJ. Is structured allergy history sufficient when assessing patients with asthma and rhinitis in general practice? J Allergy Clin Immunol. 2009;123:646-50. https://doi.org/10.1016/j.jaci.2008.11.005

4. van Veen WJ, Dikkeschei LD, Roberts G, Brand PL. Predictive value of specific IgE for clinical peanut allergy in children: relationship with eczema, asthma, and setting (primary or secondary care). Clin Transl Allergy. 2013;3:34. https://doi.org/10.1186/2045-7022-3-34

5. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: Food allergy. J Allergy Clin Immunol. 2012;129:906-20. https://doi.org/10.1016/j.jaci.2012.02.001

6. Fiocchi A, Nowak-Wegrzyn A. The fascinating world of molecular diagnosis in the management of food allergy: nondum matura est. Curr Opin Allergy Clin Immunol. 2011;11:200-3. https://doi.org/10.1097/ACI.0b013e32834694ae

7. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. J Allergy Clin Immunol. 2011;127:684-5. https://doi.org/10.1016/j.jaci.2010.12.012

8. Nilsson C, Berthold M, Mascialino B, Orme ME, Sjolander S, Hamilton RG. Accuracy of component-resolved diagnostics in peanut allergy: systematic literature review and meta-analysis. Pediatr Allergy Immunol. 2020;31:303-14. https://doi.org/10.1111/pai.13201

9. Gray CL, Levin ME, du Toit G. Egg sensitization, allergy and component patterns in African children with atopic dermatitis. Pediatr Allergy Immunol. 2016;27:709-15. https://doi.org/10.1111/pai.12615

10. Schoos AM, Nwaru BI, Borres MP. Component-resolved diagnostics in pet allergy: Current perspectives and future directions. J Allergy Clin Immunol. 2021;147:1164-73. https://doi.org/10.1016/j.jaci.2020.12.640

11. Konradsen JR, Borres MP, Nilsson C. Unusual and unexpected allergic reactions can be unraveled by molecular allergy diagnostics. Int Arch Allergy Immunol. 2021;182:904-16. https://doi.org/10.1159/000515708

12. Barber D, Diaz-Perales A, Escribese MM, Kleine-Tebbe J, Matricardi PM, Ollert M, et al. Molecular allergology and its impact in specific allergy diagnosis and therapy. Allergy. 2021;76:3642-58. https://doi.org/10.1111/all.14969

13. Roberts G, Fontanella S, Selby A, Howard R, Filippi S, Hedlin G, et al. Connectivity patterns between multiple allergen specific IgE antibodies and their association with severe asthma. J Allergy Clin Immunol. 2020;146:821-30. https://doi.org/10.1016/j.jaci.2020.02.031

14. Asarnoj A, Hamsten C, Waden K, Lupinek C, Andersson N, Kull I, et al. Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study. J Allergy Clin Immunol. 2016;137:813-21. https://doi.org/10.1016/j.jaci.2015.09.052

15. Fontanella S, Frainay C, Murray CS, Simpson A, Custovic A. Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: A cross-sectional analysis within a population-based birth cohort. PLoS Med. 2018;15:e1002691. https://doi.org/10.1371/journal.pmed.1002691

16. Koet LBM, Brand PLP. Increase in atopic sensitization rate among Dutch children with symptoms of allergic disease between 1994 and 2014. Pediatr Allergy Immunol. 2018;29:78-83. https://doi.org/10.1111/pai.12825

17. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132:942-9. https://doi.org/10.1111/j.1365-2133.1995.tb16953.x

18. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol. 1998;101:163-70. https://doi.org/10.1016/S0091-6749(98)70380-X

19. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J. 2010;36:1410-6. https://doi.org/10.1183/09031936.00117509

20. Flokstra-de Blok BM, Dunngalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy. 2009;39:127-37. https://doi.org/10.1111/j.1365-2222.2008.03120.x

21. Gong GW, Young NL, Dempster H, Porepa M, Feldman BM. The Quality of My Life questionnaire: the minimal clinically important difference for pediatric rheumatology patients. J Rheumatol. 2007;34:581-7.

22. Baatenburg de Jong A, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: A comparison of non-sensitized, monosensitized, and polysensitized children. Pediatr Allergy Immunol. 2011;22:166-71. https://doi.org/10.1111/j.1399-3038.2010.00993.x

23. van Hage M, Schmid-Grendelmeier P, Skevaki C, Plebani M, Canonica W, Kleine-Tebbe J, et al. Performance evaluation of ImmunoCAP(R) ISAC 112: a multi-site study. Clin Chem Lab Med. 2017;55:571-7. https://doi.org/10.1515/cclm-2016-0586

24. Weller BE, Bowen NK, Faubert SJ. Latent Class Analysis: A Guide to Best Practice. J Black Psychol. 2020;46:287-311. https://doi.org/10.1177/0095798420930932

25. Klok T, Ottink MD, Brand PLP. Question 6: What is the use of allergy testing in children with asthma? Paediatr Respir Rev. 2021;37:57-63. https://doi.org/10.1016/j.prrv.2020.07.007

26. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2013;68:1102-16. https://doi.org/10.1111/all.12235

27. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. J Allergy Clin Immunol. 2011;127:1505-12. https://doi.org/10.1016/j.jaci.2011.02.002

28. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med. 2014;11:e1001748. https://doi.org/10.1371/journal.pmed.1001748

29. Just J, Saint-Pierre P, Gouvis-Echraghi R, Laoudi Y, Roufai L, Momas I, et al. Childhood allergic asthma is not a single phenotype. J Pediatr. 2014;164:815-20. https://doi.org/10.1016/j.jpeds.2013.11.037

30. Yavuz ST, Oksel Karakus C, Custovic A, Kalayci O. Four subtypes of childhood allergic rhinitis identified by latent class analysis. Pediatr Allergy Immunol. 2021;32:1691-9. https://doi.org/10.1111/pai.13605

31. Broeks SA, Brand PL. Atopic dermatitis is associated with a fivefold increased risk of polysensitisation in children. Acta Paediatr. 2017;106:485-8. https://doi.org/10.1111/apa.13729

32. Herr M, Just J, Nikasinovic L, Foucault C, Le Marec AM, Giordanella JP, et al. Risk factors and characteristics of respiratory and allergic phenotypes in early childhood. J Allergy Clin Immunol. 2012;130:389-96. https://doi.org/10.1016/j.jaci.2012.05.054

33. Kaur N, Mehr S, Katelaris C, Wainstein B, Altavilla B, Saad R, et al. Added diagnostic value of peanut component testing: A cross-sectional study in Australian children. J Allergy Clin Immunol Pract. 2021;9:245-53. https://doi.org/10.1016/j.jaip.2020.08.060

Appendix

Supplementary Table A   Number of children sensitised to each allergen component in the ISAC CRD and the median and range (ISU-E) rate of sensitisation to each component (n=287).

Inhaled allergen	Component	Number (%) of children sensitised to this component	Median (range) sensitisation rate in those sensitised (ISU-E)
House dust mite	Blo t5	8 (2.8)	1.49 (0.1-15.0)
	Der f1	73 (25.4)	15.7 (0.2-69.1)
	Der f2	71 (24.7)	32.9 (0.5-107.1)
	Der p1	71 (24.7)	26.4 (0.6-101.7)
	Der p10	6 (2.1)	5.0 (0.1-7.0)
	Der p2	74 (25.8)	34.2 (0.4-112.7)
	Der p23	58 (20.2)	8.5 (0.1-103)
Storage mite	Lep d2	10 (3.5)	1.7 (1.0-6.0)
Dog	Can f1	18 (6.3)	1.7 (0.1-64)
	Can f2	9 (3.1)	10.0 (1.0-54.0)
	Can f3	3 (1.0)	2.2 (2.0-15.0)
	Can f 4	7 (2.4)	7.4 (1.0-65.0)
	Can f5	11 (3.8)	0.8 (0.1-23.0)
	Can f6	11 (3.8)	1.9 (0.1-66.0)
Cat	Fel d1	53 (18.5)	4.4 (0.1-71.0)
	Fel d2	3 (1.0)	1.2 (1.0-5.0)
	Fel d4	10 (3.5)	0.7 (0.1-27.0)
Alder pollen	Alng1	48 (16.7)	4.0 (0.4-48.9)
Birch pollen	Bet v1	67 (23.3)	9.6 (0.2-115.8)
	Bet v2	12 (4.2)	3.6 (0.1-86.0)
	Bet v4	0	—
Hazel pollen	Cor a 1.0101	44 (15.3)	2.4 (0.2-27.9)
Japanese cedar	Cry j1	6 (2.1)	0.6 (0.1-3.0)
Cypress pollen	Cup a1	6 (2.1)	0.7 (0.1-2.0)
Plane pollen	Pla a1	0	—
	Pla a3	2 (0.7)	3.6 (0.1-7)
Olive pollen	Ole e1	29 (10.7)	2.3 (0.2-115.0)
	Ole e7	1 (0.3)	1.0
	Ole e9	4 (1.4)	0.7 (0.1-1.0)
Bermuda grass pollen	Cyn d1	54 (18.8)	6.4 (0.3-109.5)
Timothy grass pollen	Phl p1	75 (26.1)	18.1 (0.2-117.4)
	Phl p2	34 (11.8)	8.0 (0.3-75.1)
	Phl p4	43 (15.0)	5.2 (0.3-92.4)
	Phl p5	39 (13.6)	34.0 (0.1-105.0)
	Phl p6	32 (11.1)	5.2 (0.1-40.0)
	Phl p7	0	—
	Phl p11	23 (8.0)	8.8 (0.1-52.0)
	Phl p12	7 (2.4)	6.2 (1.0-23.0)
Plantain pollen	Pla l1	2 (0.7)	2.7 (1.0-4.0)
Ragweed pollen	Amb a1	0	—
Mugwort pollen	Art v1	2 (0.7)	3.2 (2.0-5.0)
	Art v3	1 (0.3)	4.0
Goosefoot pollen	Che a1	8 (2.8)	1.0 (0.1-7.0)
Annual mercury pollen	Mer a1	12 (4.2)	4.8 (1.0-100.0)
Wall pellitory pollen	Par j2	4 (1.4)	0.5 (0.1-1.0)
Saltwort pollen	Sal k1	0	—
Cockroach	Bla g1	2 (0.7)	0.3 (0.2-0.4)
	Bla g2	0	—
	Bla g5	0	—
	Bla g7	2 (0.7)	4.5 (1.0-6.5)
Horse	Equ c1	20 (7.0)	1.1 (0.1-53.0)
	Equ c3	1 (0.3)	6.4
Mouse	Mus m1	6 (2.1)	13.4 (0.1-76.0)

Fungi	Component	Number (%) of children sensitised to this component	Median (range) sensitisation rate in those sensitised (ISU-E)
Alternaria	Alt a1	12 (4.2%)	1.0 (0.1-82.0)
	Alt a6	2 (0.7%)	8.2 (3.8-12.7)
Aspergillus	Asp f1	0	—
	Asp f3	3 (1.0)	4.0 (1.0-7.0)
	Asp f6	0	—
Cladosporium	Cla h8	3 (1.0)	0.4 (0.1-1.0)

Food allergen	Component	Number (%) of children sensitised to this component	Median (range) sensitisation rate in those sensitised (ISU-E)
Cow's milk	Bos d4	2 (0.7)	1.3 (0.6-2.0)
	Bos d5	2 (0.7)	0.8 (0.8-0.8)
	Bos d6	2 (0.7)	1.3 (1.0-2.0)
	Bos d8	3 (1.0)	0.6 (0.1-2.0)
	Bos d lactoferrin	2 (0.7)	1.0 (0.1-2.0)
Hen's egg	Gal d1	7 (2.4)	1.9 (0.1-36.0)
	Gal d2	8 (2.8)	0.8 (1.0-4.0)
	Gal d3	0	—
	Gal d5	0	—
Soy	Gly m4	29 (10.1)	2.8 (0.1-24)
	Gly m5	3 (1.0)	0.8 (0.7-3.4)
	Gly m6	5 (1.7)	0.6 (0.1-9)
Peanut	Ara h1	6 (2.1)	0.6 (1.0-2.0)
	Ara h2	8 (2.8)	9.6 (0.1-92.0)
	Ara h3	2 (0.7)	3.0 (2.0-4.0)
	Ara h6	5 (1.7)	10.0 (3.0-41.0)
	Ara h8	37 (12.9)	2.4 (0.1-33.0)
	Ara h9	2 (0.7)	1.3 (0.1-2.0)
Hazelnut	Cor a14	9 (3.1)	6.9 (0.1-15.0)
	Cor a 1.0401	53 (18.5)	3.8 (0.4-58.7)
	Cor a8	1 (0.3)	17.0
	Cor a9	4 (1.4)	0.9 (0.1-4.0)
Cashew	Ana02	4 (1.4)	0.4 (0.1-1.0)
	Ana 03	13 (14.5)	1.4 (0.1-83.0)
Brazil nut	Ber e1	2 (0.7)	0.7 (0.6-0.8)
Walnut	Jug r1	11 (3.8)	3.8 (0.1-9.0)
	Jug r3	2 (0.7)	3.3 (0.4-6.2)
Sesame seed	Ses i1	1 (0.3)	0.4
Wheat	Tri a14	1 (0.3)	1.3
	Tri a19.0101	2 (0.7)	0.4 (0.2-0.6)
	Tri aA_TI	1 (0.3)	0.8
Buckwheat	Fag e2	1 (0.3)	0.7
Kiwi	Actd1	10 (3.5)	1.0 (0.1-19.0)
	Actd2	5 (1.7)	1.5 (0.1-5.0)
	Actd5	0	—
	Actd8	28 (9.8)	1.6 (0.1-33.0)
Celery	Api g1	24 (8.4)	1.6 (0.7-23.0)
Red meat	Alpha-Gal	1 (0.3)	0.3
Cod	Gad c1	3 (1.0)	9.1 (0.6-39.1)
Shrimp	Pen m1	5 (1.7)	2.4 (0.5-5.0)
	Pen m2	4 (1.4)	0.7 (0.3-35.3)
	Pen m4	2 (0.7)	0.5 (0.4-0.6)
Apple	Mal d1	55 (19.2)	4.0 (0.3-79.7)
Peach	Pru p1	52 (18.1)	1.8 (0.1-9.3)
	Pru p3	2 (0.7)	3.2 (0.1-6.0)

Other allergens	Component	Number (%) of children sensitised to this component	Median (range) sensitisation rate in those sensitised (ISU-E)
Anisakis	Ani s1	0	—
	Ani s3	5 (1.7)	2.7 (0.1-6.0)
Latex	Hev b1	0	—
	Hev b3	0	—
	Hev b5	0	—
	Hev b6	0	—
	Hev b8	12 (4.2)	5.8 (0.1-94.0)

Supplementary Table B 95% confidence intervals of the difference in symptom scores between children with and without sensitisation to whole allergens.

	RQLQ	ACQ	CDLQI	FAQLQ	QML
House dust mite	−0.27 to 0.09	−1.24 to 0.53	−0.61 to 0.03	−0.11 to 0.16	−0.40 to 7.00
Dog	−0.34 to 0.08	−1.44 to 0.62	−0.94 to 0.18	−0.12 to 0.20	−1.37 to 7.55
Cat	−0.20 to 0.17	−1.23 to 0.66	−0.70 to −0.03 (P=0.033)	−0.12 to 0.17	−2.18 to 5.69
Grass pollen	−0.40 to −0.05 (P=0.011)	−0.44 to 1.34	−0.58 to 0.02	−0.15 to 0.12	−3.87 to 3.57
Tree pollen	−0.33 to 0.04	−0.50 to 1.30	−0.35 to 0.26	0.02 to 0.26 (P=0.023)	−4.78 to 2.78
Cow's milk	−0.61 to 0.38	−0.98 to 3.34	−1.80 to 0.08	−0.83 to 0.25	−8.90 to 12.82
Hen's egg	−0.33 to 0.52	−0.19 to 2.02	−3.59 to 0.60	−0.74 to 0.17	−9.57 to 2.24
Peanut	−0.57 to −0.07 (P=0.012)	−0.93 to 1.24	−0.47 to 0.31	−0.10 to 0.18	−5.04 to 3.35
Tree nuts	−0.46 to 0.00 (P=0.05)	−0.98 to 0.97	−0.50 to 0.21	−0.16 to 0.13	−3.27 to 5.28
Soy	−0.76 to −0.16 (P=0.03)	−1.30 to 1.43	−0.67 to 0.34	−0.06 to 0.24	−6.57 to 4.51
Wheat	−0.93 to −0.01 (P=0.049)	0.89 to 2.13 (p<0.001)	−1.27 to 0.32	−0.37 to 0.42	−7.82 to 10.19

ACQ, asthma control questionnaire; RQLQ, rhinitis quality of life questionnaire; CDLQI, children's dermatology life quality index; FAQLQ, food allergy quality of life questionnaire; QML, quality of my life questionnaire.

Supplementary Table C Allergen component sensitisation rates compared among the three classes as distinguished by latent class analysis (results only shown for allergen components with significantly different sensitisation rates among classes; all other components, P > −0.05).

	Class 1 (n = 135)	Class 2 (n = 74)	Class 3 (n = 60)	P
Act d8 (kiwi)	12 (9%)	2 (3%)	12 (20%)	0.003
Aln g1 (alder pollen)	17 (13%)	6 (8%)	21 (35%)	<0.001
Can f1 (dog)	5 (4%)	3 (4%)	8 (13%)	0.023
Can f2 (dog)	1 (1%)	0 (0%)	7 (12%)	<0.001
Can f4 (dog)	1 (1%)	0 (0%)	4 (7%)	0.007
Can f6 (dog)	4 (3%)	1 (1%)	6 (10%)	0.027
Ara h8 (peanut)	13 (10%)	5 (7%)	17 (28%)	<0.001
Bet v1 (birch pollen)	24 (18%)	15 (20%)	23 (38%)	0.006
Bos d Lactoferrin (cow's milk)	0 (0%)	0 (0%)	2 (3%)	0.030
Cor a1.0101 (hazel pollen)	15 (11%)	6 (8%)	20 (33%)	<0.001
Cor a1.0401 (hezelnut)	19 (14%)	8 (11%)	21 (35%)	<0.001
Cry j1 (Japanese cedar)	1 (1%)	0 (0%)	5 (8%)	0.001
Cynd1 (bermuda grass pollen)	20 (15%)	12 (16%)	18 (30%)	0.035
Blo t5 (house dust mite)	1 (1%)	1 (1%)	4 (7%)	0.029
Der f1 (house dust mite)	21 (16%)	15 (20%)	29 (48%)	<0.001

	Class 1 (n = 135)	Class 2 (n = 74)	Class 3 (n = 60)	P
Der f2 (house dust mite)	24 (18%)	17 (23%)	23 (38%)	0.008
Der p1 (house dust mite)	22 (16%)	13 (18%)	28 (47%)	<0.001
Der p2 (house dust mite)	26 (19%)	17 (23%)	24 (40%)	0.008
Der p23 (house dust mite)	20 (15%)	11 (15%)	21 (35%)	0.002
Fel d1 (cat)	12 (9%)	15 (20%)	20 (33%)	<0.001
Gad c1 (cod)	0 (0%)	0 (0%)	3 (5%)	0.005
Gly m4 (soy)	11 (8%)	2 (3%)	14 (23%)	<0.001
Mal d1 (apple)	19 (14%)	9 (12%)	21 (35%)	0.001
Ole e1 (olive pollen)	9 (7%)	8 (11%)	11 (18%)	0.048
Par j2 (wall pellitory pollen)	1 (1%)	0 (0%)	3 (5%)	0.035
Phl p1 (timothy grass pollen)	27 (20%)	20 (27%)	23 (38%)	0.026
Phl p2 (timothy grass pollen)	14 (10%)	4 (5%)	13 (22%)	0.011
Phl p4 (timothy grass pollen)	18 (13%)	6 (8%)	15 (25%)	0.019
Phl p5 (timothy grass pollen)	13 (10%)	8 (11%)	17 (28%)	0.002
Phl p6 (timothy grass pollen)	11 (8%)	7 (10%)	13 (22%)	0.020
Pru p1 (peach)	20 (15%)	6 (8%)	21 (35%)	<0.001
Tri a19.0101 (wheat)	0 (0%)	0 (0%)	2 (3%)	0.030