

DR SUSANNE GLAUMANN (Orcid ID : 0000-0002-1967-2312)

DR CAROLINE NILSSON (Orcid ID : 0000-0003-2040-8428)

Article type : Letter to the Editor

Positive Phadiatop Infant (Phinf) can predict allergic disease during childhood.

To the Editor,

An early detection and follow-up of children at risk of developing allergic diseases is crucial to optimize treatment and increase well-being (1-3). A clinical history is the most important tool when diagnosing allergic diseases; however, IgE-antibody (IgE) testing can obtain additional information (3). We have previously evaluated Phadiatop Infant® (Phinf), a test analyzing IgE to 11 common inhalant and food allergens, at 2 and 5 years of age (4, 5), showing a sensitivity and specificity over 84 % for detecting IgE sensitizations during childhood (4-7). In the present study we evaluated the predictive capacity of Phinf at 2 years in relation to IgE sensitization and occurrence of allergic symptoms at 10 years of age. Further, the diagnostic capacity of Phinf in relation to IgE sensitization against 10 common allergens (10xIgE) and presence of allergic symptoms at 10 years of age was also studied.

The original cohort has been described elsewhere (1). In summary, 281 children, born into the cohort, to parents with allergic diseases (biparental allergy, n=120, maternal allergy, n=84) and non-allergic parents, n=77), have been followed prospectively. The parental medical history was verified with skin-prick-test (SPT) during pregnancy. The children were examined at 2 and 10 years of age and those with complete data (10xIgE, Phinf and clinical examination) at the 10-years follow-up formed the study population (n=205). In the

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13266](https://doi.org/10.1111/PAI.13266)

This article is protected by copyright. All rights reserved

comparative analysis, children with complete data at both 2 and 10 years were included (n=184). Asthma, rhino-conjunctivitis, eczema and food allergy, were evaluated according to predefined definitions (1).

Phinf is based on extract and detects IgE to 11 different food and inhalant allergens (Hen's egg, Cow's milk, Shrimp, Peanut, Cat, Dog, Birch pollen, Timothy pollen, *Dermatophagoides Pteronyssinus*, Ragweed, and Wall pellitory [*Parietaria Judaica*]) using the ImmunoCAP® system. The results were expressed as Phadia Arbitrary Units (PAU/L) and values ≥ 0.35 PAU/L were considered to be positive. Circulating IgE (positive at ≥ 0.35 kU_A/L) against 10 allergens ([10xIgE]; Extract from Hen's egg, Cow's milk, Codfish, Soybean, Peanut, Cat, Dog, Birch pollen, Timothy pollen, and *Dermatophagoides Farinae*) were analyzed with ImmunoCAP®. Children were classified as sensitized if they had IgE to at least one of the tested allergens.

IgE sensitization, positive Phinf as well as positive 10xIgE, at 2 years of age showed an increased risk, for being IgE sensitized (Phinf OR 9.5 [95% CI 3.8-24.0] and 10xIgE OR 7.3 [95% CI 3.2-16.5]), and for having allergic symptoms (Phinf OR 9.3 [95% CI 3.3-24.3] and 10xIgE OR 6.0, [95% CI 2.5-14.4]) at 10 years of age (Table 1). Furthermore, being IgE sensitized, both for Phinf and 10xIgE at 2 years of age was associated with an increased risk for asthma (OR 7.9 [95% CI 3.5-17.5] for Phinf and 8.8 [95% CI 3.9-19.7] for 10xIgE), food-allergy (OR 9.9 [95% CI 4.3-22.8] for Phinf and 9.4 [95% CI 4.1-21.5] for 10xIgE) and rhino-conjunctivitis (OR 7.6 [95% CI 3.6-16.3] for Phinf and OR 5.3 [95% CI 2.5-11.2] for 10xIgE) when the children were 10 years old (Table 1). Another interesting finding was that IgE sensitized (Phinf and 10xIgE) 2 years olds without any allergic symptoms also had a statistically significant increased risk of being IgE sensitized (OR; between 3.7 to 5.2) at 10 years of age (Table 1).

We noticed that some children lost, and others acquired IgE sensitization during the observation period, 2 to 10 years of age, and that the increase in IgE sensitization was mainly related to inhalant allergens. At 2 years of age 42/184 children (23%) were sensitized to Phinf and 23% to 10xIgE (n=43/184) (Figure 1). Six Phinf positive children lost their IgE sensitization and 55 children acquired IgE sensitization with Phinf until 10 years of age. The corresponding figures for 10xIgE was 9 children losing and 48 gaining IgE sensitization from 2 to

10 years of age. The total number of IgE sensitized among the 10 years olds with complete data at both 2 and 10 years were 91 (50%) for Phinf and 82 (45%) for 10xIgE.

The diagnostic capacity of Phinf was compared to results of Immuno-CAP analyzing IgE sensitization to the 10 selected allergen extracts in the 10 years old children (n=205). Positive Phinf was found in 49% and the corresponding figure for 10xIgE was 42%. We found that Phinf (cut-off; 0.35 PAU/L) had a sensitivity of 99% [95% CI, 94-100], and a specificity of 88% [95% CI, 81-93], to detect IgE sensitization (10xIgE) among the 10-year-olds. Only one child, who was negative in Phinf, had an elevated IgE level (milk 0.66 kU_A/L). On the other hand, there were fourteen children with a positive Phinf value (0.35-0.98 PAU/L) who had no IgE to the 10xIgE.

Some limitations in the present study have to be considered. It is a high-risk cohort, with a medium sample size which might be a limitation for the generalization of the study results. Besides, the ten selected allergens in this study (10xIgE) does not perfectly match the allergens included in the Phinf test. The allergens in Phinf are based on experience from international studies on the prevalence of IgE sensitization among children (8). The 10 allergens selected for analysis by Immuno-Cap are based on a Swedish national perspective. Eight allergens (Cow's milk, Hen's egg, Peanut, Cat, Dog, Birch, Timothy and Mites) are responsible for more than 95% of IgE sensitization among Swedish children (9) and was evaluated in the present study by both Phinf and Immuno-CAP. Thus, the difference of allergens tested in Phinf and 10xIgE only have limited impact on the study results. The reason

for an increased number of positive Phinf compared to the number of positive ImmunoCap can be explained by an additive effect of sub-threshold levels of IgE against allergen included in the Phinf test. A strength of our study is that the children have been followed prospectively since birth and were examined by the same pediatrician during the whole follow-up.

In summary, Phinf evaluated at 2 years of age, predicts the development of IgE sensitization and allergic diseases during childhood and can therefore be a candidate for allergy screening during early childhood. We also conclude that Phinf had a high sensitivity and specificity to detect IgE sensitization (10xIgE) among the 10-year-olds. Furthermore, Phinf is also an attractive alternative to multiple IgE analyses since a single blood test is less expensive and only a small amount of blood is needed and can thus easily be used in young children.

Conflict of Interest

Caroline Nilsson has received advisory board fees from Aimmune and Novartis and lecturer fees from MEDA, ALK, ThermoFisher and GSK. All other author reports no conflict of interest.

S Glaumann, MD, PhD^{1,2}; G Lilja MD, Ass.Professor^{1,2}; A Nopp, Ass.Professor^{1,2};
C Nilsson, MD, Ass.Professor^{1,2}

¹Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet

² Sachs' Childrens and Youth Hospital, Södersjukhuset, Stockholm

Corresponding author: Susanne Glaumann, MD PhD

Department of Clinical Science and Education, Södersjukhuset,
Karolinska Institutet, 118 83 Stockholm

e-mail: susanne.glaumann@ki.se

REFERENCES

1. Bjorkander S, Hallberg J, Persson JO, Lilja G, Nilsson C, Sverremark-Ekstrom E. The allergic phenotype during the first 10 years of life in a prospective cohort. *Immun Inflamm Dis.* 2019;7(3):170-82.
2. Lukkarinen M, Vuorinen T, Lehtinen P, Ruuskanen O, Jartti T. Sensitization at the first wheezing episode increases risk for long-term asthma therapy. *Pediatr Allergy Immunol.* 2015;26(7):687-91.
3. Eigenmann PA, Atanaskovic-Markovic M, J OBH, 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(2):195-209.

4. Ballardini N, Nilsson C, Nilsson M, Lilja G. ImmunoCAP Phadiatop Infant--a new blood test for detecting IgE sensitisation in children at 2 years of age. *Allergy.* 2006;61(3):337-43.
5. Nilsson C, Lilja G, Nordlund M, Berthold M, Borres MP. Phadiatop Infant((R)) detects IgE-mediated diseases among pre-school children: a prospective study. *Pediatr Allergy Immunol.* 2012;23(2):159-65.
6. Lau S, Nilsson M, Sulser C, Schulz G, Borres MP, Wahn U. Use of Phadiatop Infant in diagnosis of specific sensitization in young children with wheeze or eczema. *Pediatr Allergy Immunol.* 2008;19(4):337-41.
7. Halvorsen R, Jenner A, Hagelin EM, Borres MP. Phadiatop infant in the diagnosis of atopy in children with allergy-like symptoms. *Int J Pediatr.* 2009;2009:460737.
8. Fiocchi A, Besana R, Ryden AC, Terracciano L, Andreotti M, Arrigoni S, et al. Differential diagnosis of IgE-mediated allergy in young children with wheezing or eczema symptoms using a single blood test. *Ann Allergy Asthma Immunol.* 2004;93(4):328-33.
9. Schoos AM, Chawes BL, Melen E, Bergstrom A, Kull I, Wickman M, et al. Sensitization trajectories in childhood revealed by using a cluster analysis. *J Allergy Clin Immunol.* 2017;140(6):1693-9.

Table 1. Relation between sensitization at 2 and sensitization/symptoms at 10 years of age in all children and in symptom-free children.

n shows the number of children sensitized to Phinf and 10xIgE at 2 that had a persistent sensitization or symptoms at 10 years of age. Odds ratio (OR) is given for positive Phinf and 10x IgE test results as compared to negative test results among 184 children.

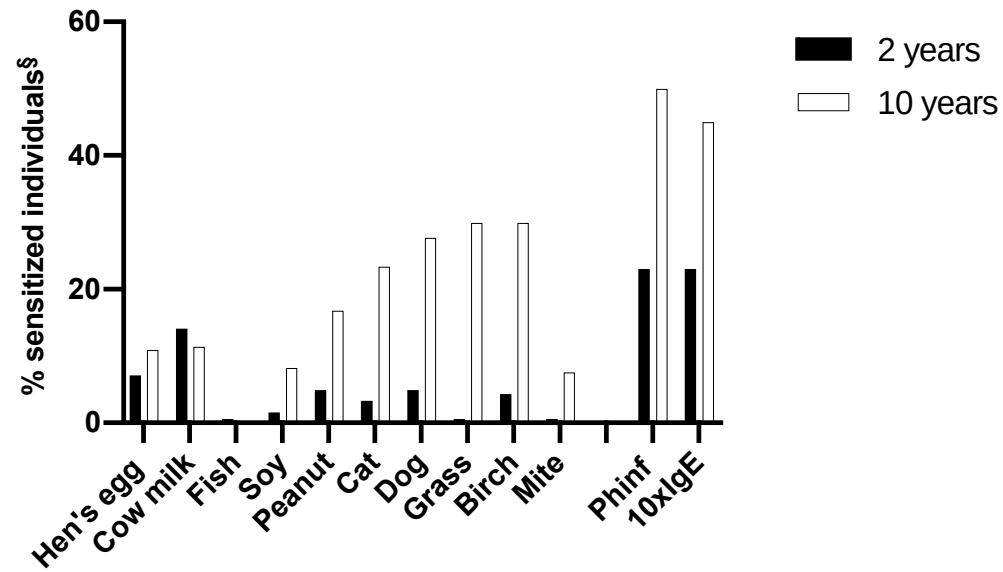
Sensitisation	Symptoms at 10 years of age										Sensitisation at 10 years of age	
	Any		Asthma		Eczema		Rhino-conjunctivitis		Food allergy		Positive Phinf [†]	Positive IgE [‡]
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Phinf[†] at 2 years of age												
All children (n=184)												
Positive (n= 42)	37		21		20		25		21		36	
Negative (n=142)	64	9.3 (3.3-24.3)	16	7.9 (3.5-17.5)	43	2.1 (1.0-4.2)	23	7.6 (3.6-16.3)	13	9.9 (4.3-22.8)	55	10.1 (4.2-24.5)
Symptom-free children (n= 82)												
Positive (n=10)	7		2		2		3		2		7	
Negative (n=72)	24	4.7 (1.1-19.7)	5	3.4 (0.6-20.2)	14	1.0 (0.2-5.4)	9	3.0 (0.7-13.7)	6	2.7 (0.5-16.0)	23	5.2 (1.3-20.9)
IgE-ab[‡] at 2 years of age												
All Children (n=184)												
Positive (n=43)	36		22		19		23		21		35	
Negative (n=141)	65	6.0 (2.5-14.4)	15	8.8 (3.9-19.7)	44	1.8 (0.9-3.5)	25	5.3 (2.5-11.2)	13	9.4 (4.1-21.5)	56	7.3 (3.2-16.5)
Symptom-free children (n=82)												
Positive (n=11)	7		3		1		3		3		7	
Negative (n=71)	24	3.4 (0.9-12.9)	4	6.3 (1.2-33.3)	15	0.4 (0.4-3.2)	9	2.6 (0.6 -11.6)	5	5.0 (1.0-24.7)	23	6.5 (1.7-25.3)

[†] Phinf sensitization ≥ 0.35 PAU/L

[‡] IgE sensitization (10xIgE) to one or more allergens ≥ 0.35 kU_A/L

Figure 1. Fraction of Children (%) IgE-sensitized to 10 individual allergens at 2 and 10 years of age.

Note that each child may be sensitized to more than one allergen (n=184).



[§]IgE sensitization ≥ 0.35 kU_A/L; Phinf sensitization ≥ 0.35 PAU/L