Actualités
Allergologie pédiatrique 2014

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Pas de conflit d'intérêt sur ce sujet

Facteurs prédictifs d'asthme chez l'enfant préscolaire

Hafkamp-de-Groen *JACI 2013* PIAMA study
(Hollande)

- Probabilité d'avoir de l'asthme à l'âge scolaire chez enfant d'âge préscolaire par le PIAMA risk score ?

- n=2877 enfants (1-4 ans), avec symptômes d'asthme (diagnostic d'asthme par questionnaire), évalués ensuite à 6 ans

➔ **Asthme persistant à 6 ans = 6%**

Hafkamp-de-Groen JACI 2013

TABLE II. Association between PIAMA risk score predictors and asthma at school age

Predictors	Univariable		Multivariable	
	Development study* (n = 2171)	Validation study (n = 2877)	Development study* (n = 2171)	Validation study (n = 2877)
1. Male sex	1.8 (1.4-2.4)	1.8 (1.3-2.5)	1.7 (1.3-2.3)	1.6 (1.1-2.2)
2. Postterm delivery	2.1 (1.3-3.5)	0.5 (0.3-1.1)	2.3 (1.3-4.0)	0.5 (0.2-1.5)
3. Medium/low parental education	1.6 (1.1-2.2)	1.8 (1.3-2.5)	1.6 (1.1-2.3)	1.6 (1.1-2.2)
4. Parental asthma†	2.6 (1.9-3.5)	3.2 (2.3-4.4)	2.4 (1.8-3.3)	2.6 (1.8-3.7)
5. Wheezing/dyspnea apart from colds‡§	2.9 (1.7-4.9)	1.2 (0.6-2.5)	2.3 (1.3-4.1)	1.0 (0.5-2.3)
6. Wheezing frequency‡				
Never	Reference	Reference	Reference	Reference
1-3 times/y	1.8 (1.3-2.5)	2.4 (1.6-3.7)	1.6 (1.1-2.3)	2.4 (1.6-3.6)
≥4 times/y	3.9 (2.7-5.6)	8.4 (5.3-13.2)	2.8 (1.9-4.2)	7.2 (4.5-11.6)
7. Respiratory tract infections‡‖				
Never	Reference	Reference	Reference	Reference
1-2 times/y	1.8 (1.2-2.6)	0.8 (0.5-1.3)	1.7 (1.3-2.2)	0.7 (0.4-1.2)
≥3 times/y	2.8 (1.9-4.1)	1.8 (1.3-2.5)	2.2 (1.4-3.3)	1.1 (0.8-1.6)
8. Eczema	3.1 (2.3-4.2)	5.5 (3.9-7.9)	2.6 (1.9-3.5)	4.6 (3.1-6.8)

Facteurs prédictifs d'asthme à 6 ans les plus pertinents :

-nombre d'épisodes sifflants/an < 4 ans

-dermatite atopique

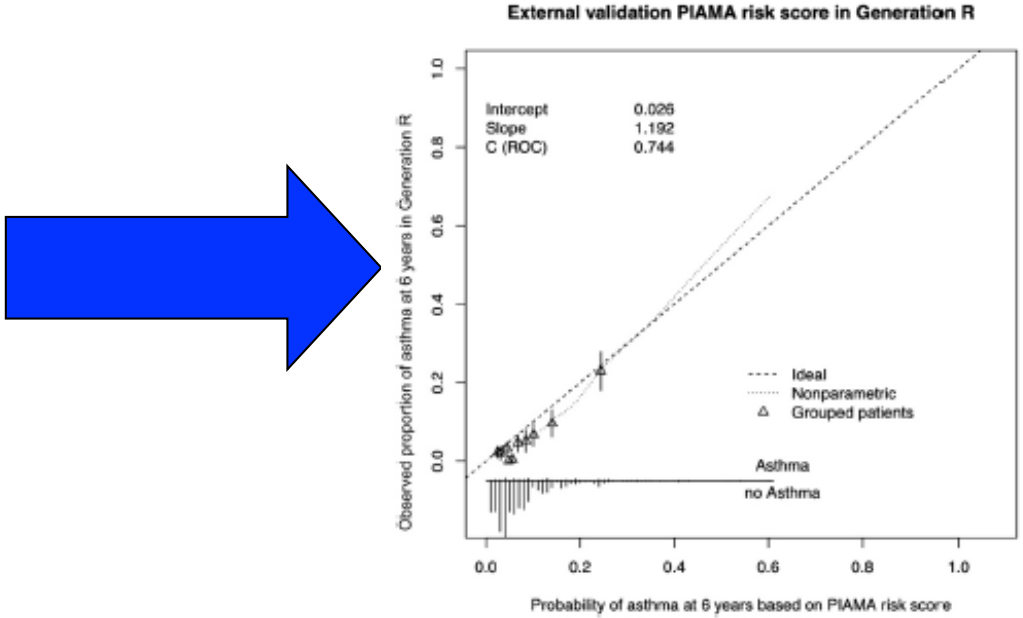
CIBLE POTENTIELLE EN PREVENTIF ?

TABLE IV. Score chart of the modified PIAMA risk score for predicting asthma in preschool children

Male sex	2
Medium/low parental education	1
Parental asthma	4
Preterm birth (<37 wk)	1
Wheezing frequency	
1-3 times/y	4
≥4 times/y	7
Wheezing/dyspnea apart from colds	2
Eczema	6
Range total score	0-23

Total score	Risk on asthma
0-7	≤5%
8-15	6%-22%
16-23	25%-60%

Postterm delivery and respiratory tract infections were deleted from the original PIAMA risk score.



Prévention

Virus

➔ **rhinovirus 16 induit cortico-résistance**

Papi JACI 2013

➔ **variants de locus 17q21 associés à risque d'asthme**

Granell JACI 2013, Caliskan NEJM 2013

➔ **rôle des réponses de l'immunité innée et adaptative**

Yoo JACI 2013

➔ **altérations de la composition du microbiome des voies respiratoires chez asthmatiques léger/sévère**

Reddy Marri JACI 2013

Prévention

Environnement

➔ **exposition chronique aux particules diesel dans l'enfance associée à méthylation d'une protéine forkhead box P3 et risque accru d'asthme**

Brunst JACI 2013

➔ **bisphenol A**

Donohue JACI 2013

Stress

➔ **obésité ou perturbations de l'axe corticotrope chez la femme en prénatal associées à un risque accru de sifflements dans l'enfance**

Wright AJRCCM 2013

Effets préventifs d'une ITSL ?

Global Prevention of Asthma in Children (GPAC) Study

Holt JACI 2013

- **Double aveugle, contrôlée versus placebo, suivi 3 ans**
- **Nourrissons (18-30 mois) + ATCD familiaux (DA, asthme, RA) + ATCD personnels (eczéma ET sensibilisation pour au moins 1 allergène alimentaire ET RAST pour les allergènes de traitement < 0,35 KU/L)**

  ➔ nourrissons A HAUT RISQUE
- **« Oral mucosal immunoprevention » (OMIP) therapy :**
  -mélange avec acariens, chat, graminées-gouttes
  -voie sublinguale, chaque jour, 1 an

  - **Objectif I : nouvelles sensibilisations ?**
  - **Objectif II : incidence de l'asthme ?**

- **Données préliminaires sur 37 enfants (18 ITSL) à 2 ans**

	Active	Placebo	Odds ratios (95% CI)*	Uncorrected *P* value	Corrected *P* value†
Allergic sensitization‡ (yes)					
ITT§	88.0% (22/25)	76.0% (19/25)	2.32 (0.51-10.5)	.28	1.00
PP‖	88.9% (16/18)	73.7% (14/19)	2.86 (0.48-17.1)	.25	.75
Current asthma (yes)¶					
ITT§	16.0% (4/25)	16.0% (4/25)	1.00 (0.16-6.1)	.85	1.00
PP‖	5.6% (1/18)	5.3% (1/19)	1.06 (0.01-87.7)	.74	.97
Allergic sensitization# to house dust mite, *Der P* (yes)					
ITT§	76.0% (1[illegible])	60.0% (15/25)	2.11 (0.63-7.1)	.23	1.00
PP‖	77.8% (1[illegible])	52.6% (10/19)	3.15 (0.75-13.2)	.12	.58
Allergic sensitization# to house dust mite, *Der F* (yes)					
ITT§	72.0% (1[illegible])	56.0% (14/25)	2.02 (0.62-6.6)	.24	1.00
PP‖	77.8% (1[illegible])	47.4% (9/19)	3.89 (0.93-16.3)	.06	.38
Allergic sensitization# to timothy grass (yes)					
ITT§	80.0% (2[illegible])	60.0% (15/25)	2.67 (0.75-9.5)	.13	.90
PP‖	83.3% (1[illegible])	52.6% (10/19)	4.50 (0.97-20.8)	.05	.38

Mais effectif faible et niveau d'absorption allergénique par la muqueuse incertain (cible = cellules dendritiques muqueuse) ++

La réponse est liée à la quantité d'allergènes effectivement en contact avec la muqueuse : problème de la voie SL chez le petit enfant qui ne garde pas le traitement sous la langue.

Asthme et phénotypes

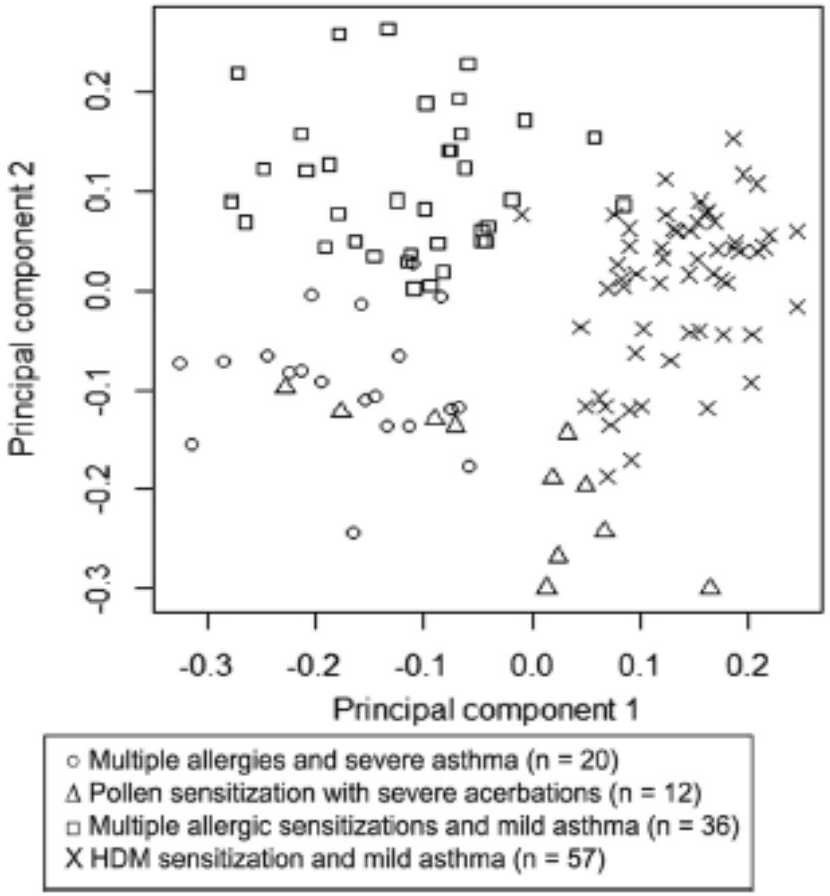
Pourquoi étudier les phénotypes dans l'asthme ?

- meilleure compréhension de la pathogénèse, en association aux marqueurs biologiques (?)
- évaluer le risque d'exacerbation
- choisir le traitement de fond le plus approprié (IT, omalizumab)

Asthme et phénotypes

Just *Pediatrics* 2014

- 125 enfants, 6-12 ans (moyenne 8.9 ans), asthme regroupés par cluster selon une analyse de 18 variables
- **4 cluster identifiés**



Just *Pediatrics* 2014

Table I. Characteristics of children according to cluster analysis in the entire population (n = 125)

	Total cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)	Cluster 2 "*Pollen Sensitization with Severe Exacerbations*" (n = 12)	Cluster 3 "*Multiple Allergic Sensitizations and Mild Asthma*" (n = 36)	Cluster 4 "*HDM Sensitization and Mild Asthma*" (n = 57)	*P* value*
Male sex n (%)	85 (68)	15 (75)	**11 (92)**	28 (78)	31 (54)	**.018**
Age (y)	8.9 ± 2.6	9.3 ± 2.2	8.9 ± 2.8	**10** ± 2.6	8.3 ± 2.4	**.016**
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9	5.0 ± 3.1	5.6 ± 3.1	5.1 ± 3.3	.136
Eczema n (%)	58 (46)	**18 (90)**	6 (50)	14 (39)	20 (35)	**<.001**
Food allergy n (%)	13 (10)	1 (5)	**4 (33)**	6 (17)	2 (4)	**.013**
Asthma severity† n (%)						
Moderate to severe asthma	46 (37)	**19 (95)**	11 (92)	1 (3)	15 (26)	**<.001**
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)	**11 (92)**	0 (0)	8 (14)	**<.001**
Controlled without high-dose of ICS	10 (8)	0 (0)	**0 (0)**	5 (14)	5 (9)	
Uncontrolled with high-dose of ICS	7 (6)	2 (10)	**1 (8)**	1 (3)	3 (5)	.173
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344	601 ± 410	581 ± 545	622 ± 1066	**.006**
Specific IgE n (%)						
against						
multiple allergens	61 (49)	**20 (100)**	5 (42)	35 (97)	1 (2)	**<.001**
HDM	96 (77)	**19 (95)**	3 (25)	32 (89)	42 (74)	**<.001**
Pollens	47 (38)	12 (60)	**11 (92)**	20 (56)	4 (7)	**<.001**
Cat or dog dander	45 (36)	**14 (70)**	2 (17)	25 (69)	4 (7)	**<.001**
Mold	15 (12)	4 (20)	0 (0)	**11 (31)**	0 (0)	**<.001**
Functional parameters						
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6	94 ± 10.3	99.8 ± 10.7	97.3 ± 12.2	.701
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2	98.4 ± 10.1	101.6 ± 10.8	97 ± 11.1	.182
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34	95.1 ± 21.6	90.2 ± 18.6	82.7 ± 26.2	**.009**
FeNO (ppb)	53.4 ± 27	**67.3** ± 30	56.5 ± 27.5	55.5 ± 24.7)	46.6 ± 25.7	**.031**

The variables age, asthma duration, serum total IgE, and functional characteristics are expressed as (mean ± SD); other variables are expressed in absolute number (%).
Boldface values indicate statistical significance.
*ANOVA or χ^2 test when conditions were respected, Kruskal–Wallis or Fisher exact test otherwise.
†According to the Global Initiative for Asthma. Uncontrolled: no control or partially controlled. High-doses of ICS were defined as ≥500 μg fluticasone equivalents per day.

- **3 variables (90% des patients)**

  ➔ **Mono/polysensibilisation**
  ➔ **Sévérité de l'asthme**
  ➔ **Sensibilisation pollens**

- **Points clés**
  - exacerbations sévères allergiques associées à la sensibilisation aux pollens
  - fonction respiratoire altérée associée au phénotype asthme allergique multiple (DA fréquente)
  - asthme léger le plus souvent associé à mono ou polysensibilisation allergique mais sans DA ou allergie alimentaire

Asthme et phénotypes

Schatz *JACI* 2013

- 518 enfants de 6-11 ans et adolescents-adultes > 12 ans (n=3612) asthme sévère ou difficile à traiter (cohorte TENOR)
- Évaluation par méthode des cluster
- **5 cluster identifiés**

TABLE II. Characteristics of 5 clusters in 518 children ages 6-11 years

	Cluster*				
Feature	**1**	**2**	**3**	**4**	**5**
No. patients (%)	115 (22.2)	81 (15.6)	162 (31.3)	87 (16.8)	73 (14.1)
% Boys	[illegible]	[illegible]	[illegible]	65.5	100†
% White race	[illegible]	[illegible]	58.0	69.0	**0**†
% Onset <3 y old	46.1	54.3	58.0	57.5	67.1
Obese					
% BMI > 95th percentile	20.0	[illegible]	34.6	35.6	35.6
Mean (SD) BMI	18.8 ± 3.7‡	19.9 ± 5.2	20.4 ± 5.2	[illegible] ± 10.4§	20.2 ± 4.5
% Passive smoke exposure	0†	0†	[illegible]	**100**†	0†
Atopy					
≥3 Allergic triggers	49.6‖	39.5	**25.3**‡§¶	57.5‖	54.8‖
% Allergic rhinitis	100†	100†	**0**†	[illegible]	[illegible]
% Atopic dermatitis	40.0‖	37.0‖	**2.8**‡§[illegible]	[illegible]	[illegible]‖
IgE					
% Total IgE ≥100	73.0	64.2	60.5	73.6	80.8
Mean (SD) IgE	505 ± 792	393 ± 520	469 ± 722	787 [illegible]	[illegible]
FEV_1:FVC ratio					
% <normal for age	57.4	50.6	73.5	72.4	72.6
Mean (SD) FEV_1:FVC	82.2 (9.5)‖¶	83.4 (9.3)‖¶	78.0 (10.6)§#	79.2 (11.0)	77.7 (10.9)§#

*Features that most distinguish one cluster from others in boldface.

†When a cluster has a boundary value (0, 100) for an item, this item is different by definition, and it is not a question of whether it may be different due to random chance, thus, a *P* value is not applicable.

‡Statistically significantly different from cluster 4 at the $P < .05$ level.

§Statistically significantly different from cluster 1 at the $P < .05$ level.

‖Statistically significantly different from cluster 3 at the $P < .05$ level.

¶Statistically significantly different from cluster 5 at the $P < .05$ level.

#Statistically significantly different from cluster 2 at the $P < .05$ level.

1. Garçons atopiques sans tabac
2. Filles
3. Non atopiques
4. Exposition tabac
5. Ethnie/non blancs

Asthme et phénotypes

Schatz *JACI* 2013

TABLE III. Characteristics of 5 clusters in 3612 adolescents and adults ages ≥12 years

	Cluster*				
Feature	**1**	**2**	**3**	**4**	**5**
No. patients (%)	1262 (34.9)	659 (18.2)	664 (18.4)	596 (16.5)	431 (11.9)
% Girls and women	100†	67.5‡	**0**†	61.1‡	76.8§
% White race	**100**†		100†	**0**†	73.1§
% Onset ≥		38.5‡#	43.7‡#	44.5‡#	58.0§‖¶
BMI					
% Obes			54.8	62.6	61.7
Mean (S		29.0 ± 8.0‡¶	28.3 ± 6.6‡¶#	30.4 ± 8.4§‖	30.6 ± 8.0§‖
% Smokers	35.7			36.7	31.8
Atopy					
≥3 Allergic triggers	56.7‡§‖	68.9‖¶#	47.9‡§#	51.5‡§	67.1‖¶#
% Allergic rhinitis	75.9‡§¶	85.1‖¶#		68.6‡§#	83.3‖¶#
% Atopic dermatitis	0†	**100**†		5.5‡	23.4¶
IgE					
% Total IgE ≥100	25.3	42.2	41.		
Mean (SD) IgE	204 ± 437§‖¶	512 ± 1302‡‖¶#	349 ±	1168‡#	289 ± 705§¶
% Aspirin sensitive	0†	0.2	0†	0†	**100**†
FEV_1:FVC ratio					
% <normal for age	43.0	49.5	61.8	54.2	
Mean (SD) FEV_1:FVC	72.5 ± 11.7‡‖	72.9 ± 12.1‡‖	69.1 ± 12.0§¶#	71.6 ± 12.5‖	70.1 ± 12.1§#

1. Femmes blanches début adulte sans HS aspirine et avec IgET basses
2. Atopiques (DA++)
3. Hommes
4. Ethnie/non blancs
5. HS aspirine

*Features that most distinguish one cluster from others are in boldface.

†When a cluster has a boundary value (0, 100) for an item, this item is different by definition, and it is not a question of whether it may be different due to random chance, thus, a *P* value is not applicable.

‡Statistically significantly different from cluster 5 at the $P < .05$ level.

§Statistically significantly different from cluster 2 at the $P < .05$ level.

‖Statistically significantly different from cluster 3 at the $P < .05$ level.

¶Statistically significantly different from cluster 4 at the $P < .05$ level.

#Statistically significantly different from cluster 1 at the $P < .05$ level.

Schatz *JACI* 2013

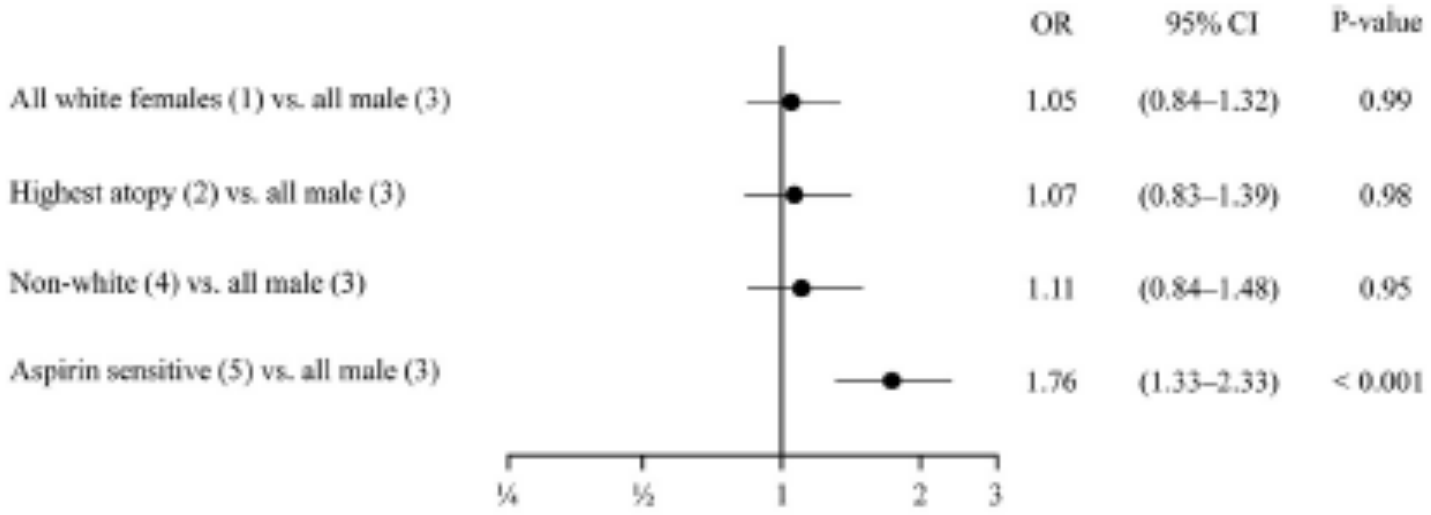


FIG 1. The relationship of cluster membership to the risk of asthma exacerbations (hospitalization, emergency department visit, or steroid burst) identified at month 6 or month 12 visits in adolescents and adults (n = 2691). *P* values were adjusted for multiple comparisons; $P < .05$ was considered statistically significant. C-index, 0.585; Hosmer and Lemeshow Test, 13.94, $P = .08$. Cluster numbers are shown in *brackets* after the text. *OR,* Odds ratio.

➔ Dans l'analyse pédiatrique, pas d'association entre gravité de l'asthme (exacerbation, qualité de vie, contrôle de l'asthme) et clusters.

Traitement Asthme sévère

Just *Pediatrics* 2014

Table I. Characteristics of children a cluster analysis in the entire population (n = 125)

	Total cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)	Cluster 2 "*Pollen Sensitization with Severe Exacerbations*" (n = 12)	Cluster 3 "*Multiple Allergic Sensitizations and Mild Asthma*" (n = 36)	Cluster 4 "*HDM Sensitization and Mild Asthma*" (n = 57)
Male sex n (%)	85 (68)	15 (75)	**11 (92)**	28 (78)	31 (54)
Age (y)	8.9 ± 2.6	9.3 ± 2.2	8.9 ± 2.8	**10** ± 2.6	8.3 ± 2.4
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9	5.0 ± 3.1	5.6 ± 3.1	5.1 ± 3.3
Eczema n (%)	58 (46)	**18 (90)**	6 (50)	14 (39)	20 (35)
Food allergy n (%)	13 (10)	1 (5)	**4 (33)**	6 (17)	2 (4)
Asthma severity† n (%)					
Moderate to severe asthma	46 (37)	**19 (95)**	11 (92)	1 (3)	15 (26)
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)	**11 (92)**	0 (0)	8 (14)
Controlled without high-dose of ICS	10 (8)	0 (0)	**0 (0)**	5 (14)	5 (9)
Uncontrolled with high-dose of ICS	7 (6)	2 (10)	**1 (8)**	1 (3)	3 (5)
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344	601 ± 410	581 ± 545	622 ± 1066
Specific IgE n (%) against					
multiple allergens	61 (49)	**20 (100)**	5 (42)	35 (97)	1 (2)
HDM	96 (77)	**19 (95)**	3 (25)	32 (89)	42 (74)
Pollens	47 (38)	12 (60)	**11 (92)**	20 (56)	4 (7)
Cat or dog dander	45 (36)	**14 (70)**	2 (17)	25 (69)	4 (7)
Mold	15 (12)	4 (20)	0 (0)	**11 (31)**	0 (0)
Functional parameters					
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6	94 ± 10.3	99.8 ± 10.7	97.3 ± 12.2
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2	98.4 ± 10.1	101.6 ± 10.8	97 ± 11.1
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34	95.1 ± 21.6	90.2 ± 18.6	82.7 ± 26.2
FeNO (ppb)	53.4 ± 27	**67.3** ± 30	56.5 ± 27.5	55.5 ± 24.7)	46.6 ± 25.7

The variables age, asthma duration, serum total IgE, and functional characteristics are expressed as (mean ± SD); other variables are expressed in absolute number (%).
Boldface values indicate statistical significance.
*ANOVA or χ^2 test when conditions were respected, Kruskal–Wallis or Fisher exact test otherwise.
†According to the Global Initiative for Asthma. Uncontrolled: no control or partially controlled. High-doses of ICS were defined as ≥500 μg fluticasone equivalents per day.

Traitement Asthme sévère

Deschildre *ERJ* 2013

- Omalizumab, étude en vie réelle après 1 an de traitement pour asthme sévère
- Enfants < 18 ans (âge moyen 11.9 ans), n=104

Allergy and allergic comorbidities	
Allergic rhinitis	88 (84.5)
Atopic dermatitis	35 (34)
Food allergy	36 (35)
Total IgE levels $kU \cdot L^{-1}$	1125 (934–1315)
Sensitisation to aeroallergens	101 (97)
>2 sensitisations	69 (66)
Asthma-related events in the previous year	
Exacerbation rate	4.4 (3.7–5.2)
>2 oral steroid courses	68 (65.5)
ED visit	70 (67)
Hospitalisation	46 (44)
>1 hospitalisation	20 (19)
Hospitalisation in ICU	8 (7.7)

Traitement Asthme sévère

Deschildre *ERJ* 2013/ Just *Pediatrics* 2014

	Total cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)
Male sex n (%)	85 (68)	15 (75)
Age (y)	8.9 ± 2.6	9.3 ± 2.2
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9
Eczema n (%)	58 (46)	**18 (90)**
Food allergy n (%)	13 (10)	1 (5)
Asthma severity† n (%)		
Moderate to severe asthma	46 (37)	**19 (95)**
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)
Controlled without high-dose of ICS	10 (8)	0 (0)
Uncontrolled with high-dose of ICS	7 (6)	2 (10)
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344
Specific IgE n (%)		
against		
multiple allergens	61 (49)	**20 (100)**
HDM	96 (77)	**19 (95)**
Pollens	47 (38)	12 (60)
Cat or dog dander	45 (36)	**14 (70)**
Mold	15 (12)	4 (20)
Functional parameters		
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34
FeNO (ppb)	53.4 ± 27	**67.3** ± 30

omalizumab

Allergy and allergic comorbidities	
Allergic rhinitis	88 (84.5)
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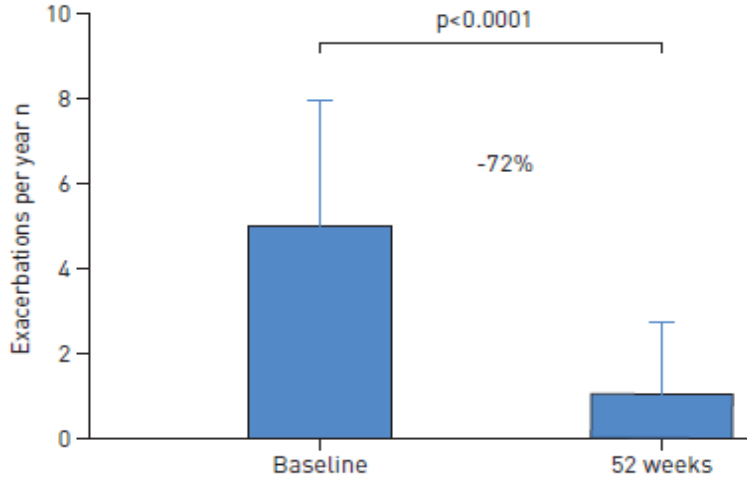
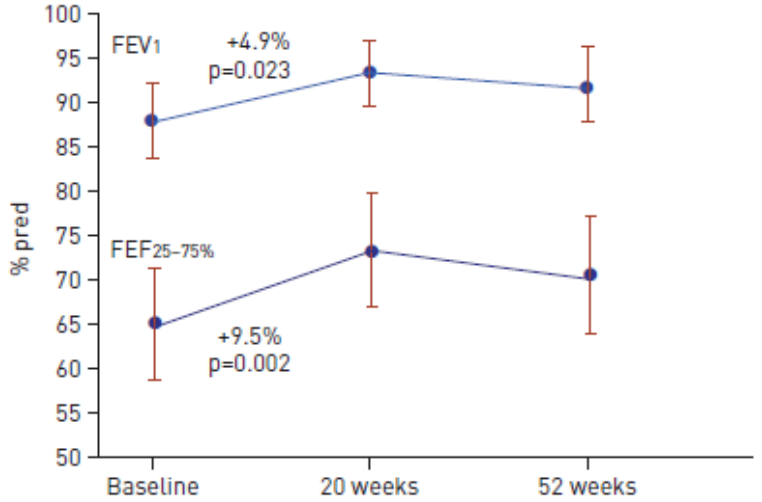
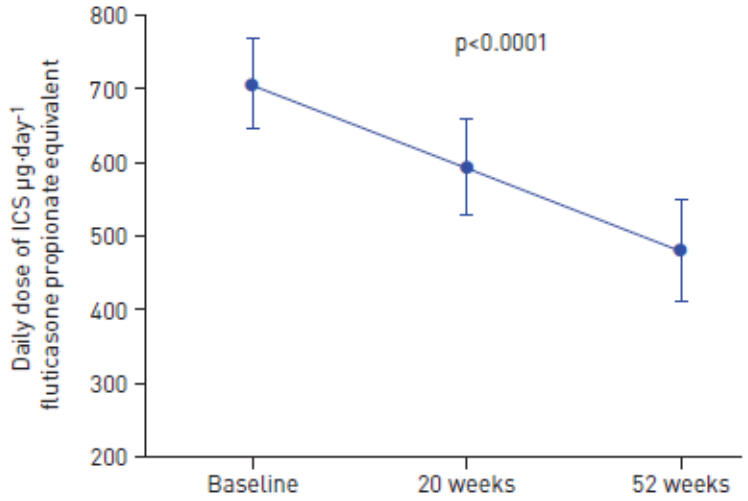
>2 oral steroid courses	68 (65.5)
ED visit	70 (67)
Hospitalisation	46 (44)
>1 hospitalisation	20 (19)
Hospitalisation in ICU	8 (7.7)
Lung function tests	
FEV_1 % pred	88 (83.8–92.2)
FEV_1/FVC %	75.8 (72.5–79.1)
$FEF_{25-75\%}$ % pred	65.1 (58.8–71.4)

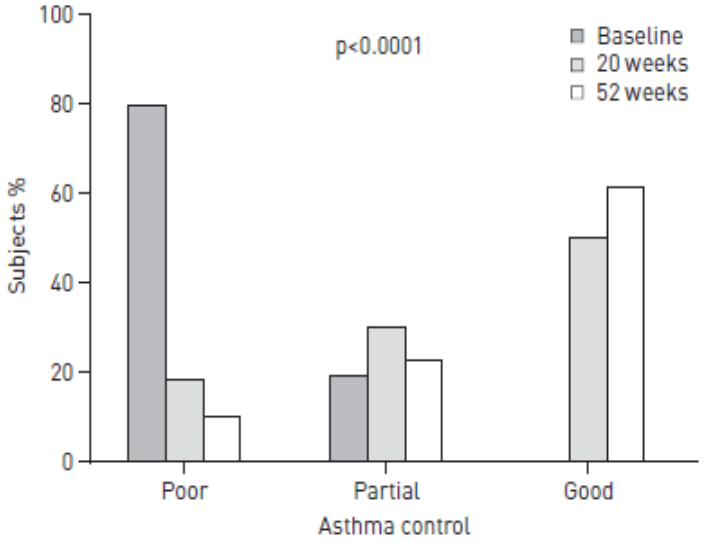
Traitement Asthme sévère

Deschildre *ERJ* 2013









Traitement Asthme sévère

Deschildre *ERJ* 2013

Effets secondaires

-**Douleurs à l'injection** (n=23), réactions locales (n=10), asthénie (n=6), céphalées ou douleurs abdominales ou malaise vagal (n=3)

-**Arrêt** (n=6) pour urticaire ou anaphylaxie ou douleurs abdominales/céphalées/asthénie

Traitement Asthme sévère

Deschildre *ERJ* 2013

Points clés

➔ Contrôle obtenu pour 50% des enfants dans les 20 premières semaines de traitement mais contrôle obtenu pour 2/3 des enfants traités 1 an

➔ Seulement 14% de non répondeurs en terme de contrôle à 1 an

➔ Réduction de 72% du nombre d'exacerbations sévères surtout dans les premiers mois de traitement

➔ Impact positif sur la dose de CSI et sur la fonction respiratoire (VEMS, DEM25-75)

Traitement Asthme sévère

Walker Cochrane 2014

- **Omalizumab,** pour 8 à 60 semaines, 25 études (n=6382, adultes et enfants 6-12 ans)

  Pour des patients avec un asthme modéré à sévère, omalizumab comme traitement additionnel aux CSI versus placebo =

  ↘ exacerbations (OR 0.55 ; IC95% : 0.42-0.60)

  ↘ hospitalisations (OR 0.16 ; IC95% : 0.06-0.42)

  ↘ doses de CSI/j

  ↗ réactions locales (9.1% versus placebo 5.6%)

Autres cibles potentielles ?

Chung *ERJ* 2014

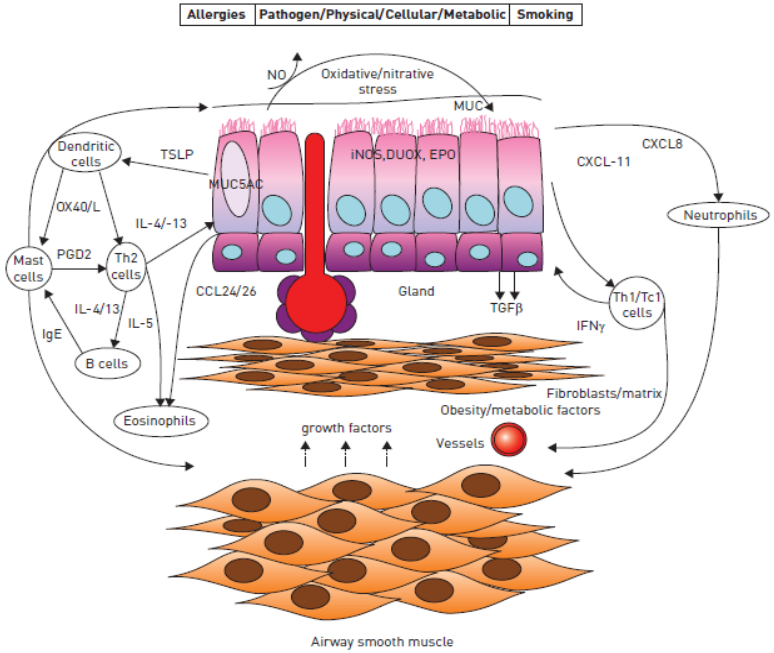


TABLE 9 Potential phenotype-targeted therapies in severe asthma[#]

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High F_{ENO}	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High F_{ENO}	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

Immunothérapie pneumallergènes

Just *Pediatrics* 2014

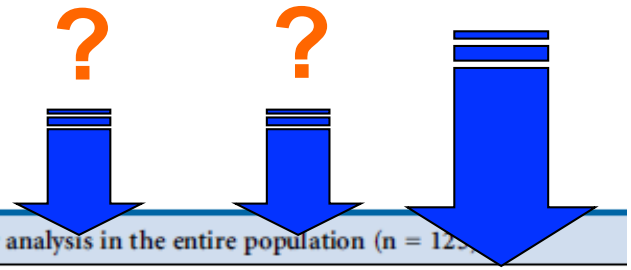


Table I. Characteristics of children according to cluster analysis in the entire population (n = 12

	Total cohort (n = 125)	Cluster 1 "*Multiple Allergies and Severe Asthma*" (n = 20)	Cluster 2 "*Pollen Sensitization with Severe Exacerbations*" (n = 12)	Cluster 3 "*Multiple Allergic Sensitizations and Mild Asthma*" (n = 36)	Cluster 4 "*HDM Sensitization and Mild Asthma*" (n = 57)
Male sex n (%)	85 (68)	15 (75)	**11 (92)**	28 (78)	31 (54)
Age (y)	8.9 ± 2.6	9.3 ± 2.2	8.9 ± 2.8	**10** ± 2.6	8.3 ± 2.4
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9	5.0 ± 3.1	5.6 ± 3.1	5.1 ± 3.3
Eczema n (%)	58 (46)	**18 (90)**	6 (50)	14 (39)	20 (35)
Food allergy n (%)	13 (10)	1 (5)	**4 (33)**	6 (17)	2 (4)
Asthma severity† n (%)					
Moderate to severe asthma	46 (37)	**19 (95)**	11 (92)	1 (3)	15 (26)
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)	**11 (92)**	0 (0)	8 (14)
Controlled without high-dose of ICS	10 (8)	0 (0)	**0 (0)**	5 (14)	5 (9)
Uncontrolled with high-dose of ICS	7 (6)	2 (10)	**1 (8)**	1 (3)	3 (5)
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344	601 ± 410	581 ± 545	622 ± 1066
Specific IgE n (%) against					
multiple allergens	61 (49)	**20 (100)**	5 (42)	35 (97)	1 (2)
HDM	96 (77)	**19 (95)**	3 (25)	32 (89)	42 (74)
Pollens	47 (38)	12 (60)	**11 (92)**	20 (56)	4 (7)
Cat or dog dander	45 (36)	**14 (70)**	2 (17)	25 (69)	4 (7)
Mold	15 (12)	4 (20)	0 (0)	**11 (31)**	0 (0)
Functional parameters					
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6	94 ± 10.3	99.8 ± 10.7	97.3 ± 12.2
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2	98.4 ± 10.1	101.6 ± 10.8	97 ± 11.1
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34	95.1 ± 21.6	90.2 ± 18.6	82.7 ± 26.2
FeNO (ppb)	53.4 ± 27	**67.3** ± 30	56.5 ± 27.5	55.5 ± 24.7)	46.6 ± 25.7

The variables age, asthma duration, serum total IgE, and functional characteristics are expressed as (mean ± SD); other variables are expressed in absolute number (%). Boldface values indicate statistical significance.
*ANOVA or χ^2 test when conditions were respected, Kruskal–Wallis or Fisher exact test otherwise.
†According to the Global Initiative for Asthma. Uncontrolled: no control or partially controlled. High-doses of ICS were defined as ≥500 μg fluticasone equivalents per day.

Voie sous cutanée

Asthme et RA

Erekosima *Laryngoscope* 2013

Revue de la littérature

Outcomes in asthma studies					
Asthma symptoms	10	628	Dust mite (6), *Cladosporium* (1), timothy (1), ragweed (1), cat (1)	SCIT vs. placebo (8), vs. pharmacotherapy (1), vs. no SCIT (1)	9 of 10 studies demonstrated greater improvement in the SCIT group than the comparator.
Asthma plus rhinitis/rhinoconjunctivitis symptoms	5	175	*Parietaria* (1), *Alternaria* (1), birch (1), timothy (1), cat (1)	SCIT vs. placebo (4) vs. pharmacotherapy (1)	All SCIT groups consistently showed greater improvement than the comparators.
Asthma medication scores	8	592	Dust mite (5), ragweed (1), *Cladosporium* (1), birch (1)	SCIT vs. placebo (6), vs. pharmacotherapy (1), vs. no SCIT (1)	5 studies showed greater reduction in medication in the SCIT group.2 studies did not report direction of change, and magnitude of effect could not be calculated.

Effet fort (>40%)

Effet modéré (15-40%)

Effet fort (>40%)

➔ **Pas d'impact clair démontré sur la fonction respiratoire ni la réactivité bronchique (études discordantes ++)**

Voie sublinguale

Asthme et RA

Kim *Pediatrics* 2013

Revue systématique

18 études, n=1583 (sans les études SL cp)

hétérogénéité ++

SLIT studies					
Asthma symptoms	9	471	Dust mite (7) Tree mix (1) *Parietaria* (1)	SLIT vs placebo (8) vs SLIT (1) (high versus low dose versus placebo)	All 9 studies demonstrated improvement in the SLIT group. Higher dose of SLIT showed greater improvement compared with lower dose/placebo. There was a strong magnitude of effect in 6 studies.

Effet fort (>40%)

Allergie alimentaire

Physiopathologie dans l'allergie alimentaire

- **Comparaison de 2 sensibilisations orale et épicutanée** dans des modèles murins =

➔ seules les souris sensibilisées par **voie cutanée** ont une expansion de mastocytes intestinaux et une augmentation de IL4, une anaphylaxie après TPO

Bartnikas *JACI* 2013

- **Rôle du microbiome**

➔ modèle murin à risque allergique (mutation α récepteur IL4) et phénotype sauvage, sensibilisation orale avec ovalbumine de l'œuf de poule

➔ les mutants sensibilisés ont un **microbiome spécifique** caractérisé par une abondance de nombreuses bactéries distinctes des sujets contrôles sensibilisés

Noval *JACI* 2013

Physiopathologie

➔ **Un déficit en vitamine D pourrait être un facteur de risque d'allergie alimentaire.**

Weisse *Allergy* 2013

Allen *JACI* 2013

Baiz *JACI* 2014

➔ **Les anti-sécrétoires pourraient favoriser l'allergie alimentaire au moins chez les enfants atopiques.**

De Muth *Allergy Asthma Proc* 2013

Trikka *PAI* 2013

Epidémiologie

Grimshaw *Pediatrics* 2013

- **Impact de l'allaitement maternel et diversification sur allergie alimentaire**
- Etude de cohorte (PIFA), cas-contrôle de 41 enfants avec allergie alimentaire confirmée, à 2 ans comparée à 82 enfants.
- Données précises prospectives sur alimentation depuis naissance (diversification, allaitement maternel jusqu'à 1 an).

Grimshaw *Pediatrics* 2013

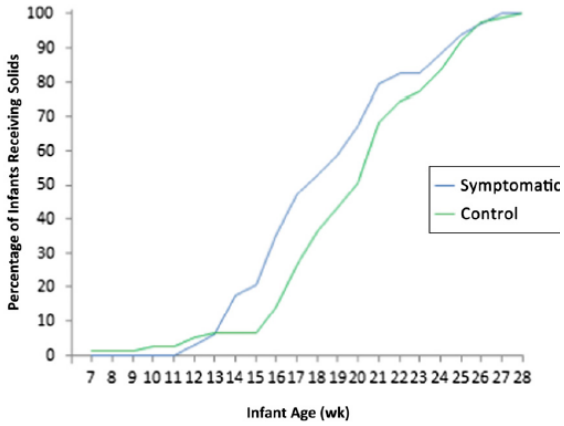


FIGURE 3
Timing of introduction of solids to food-allergic and control infants.

TABLE 5 Adjusted Multivariable Logistic Model for Assessment of Variables Associated With Food Allergy Development

Variable	Adjusted OR (95% CI)
Age at solid introduction (≥17 wk vs <17 wk)	0.245 (0.088–0.679)[a]
Concurrent feeding with breast milk and cow's milk protein (concurrent feeding versus no concurrent feeding)	0.267 (0.086–0.828)[a]
Maternal asthma (no asthma versus asthma)	0.568 (0.177–1.821)
Maternal allergy (no allergy versus allergy)	0.579 (0.226–1.482)

OR, odds ratio; CI, confidence interval.
[a] $P < .05$.

Une diversification précoce (12-16 semaines de vie) est associée à l'allergie alimentaire.

➔ **Pas de diversification avant 17 semaines de vie**

Effet protecteur des PLV en association à l'allaitement maternel sur l'allergie alimentaire.

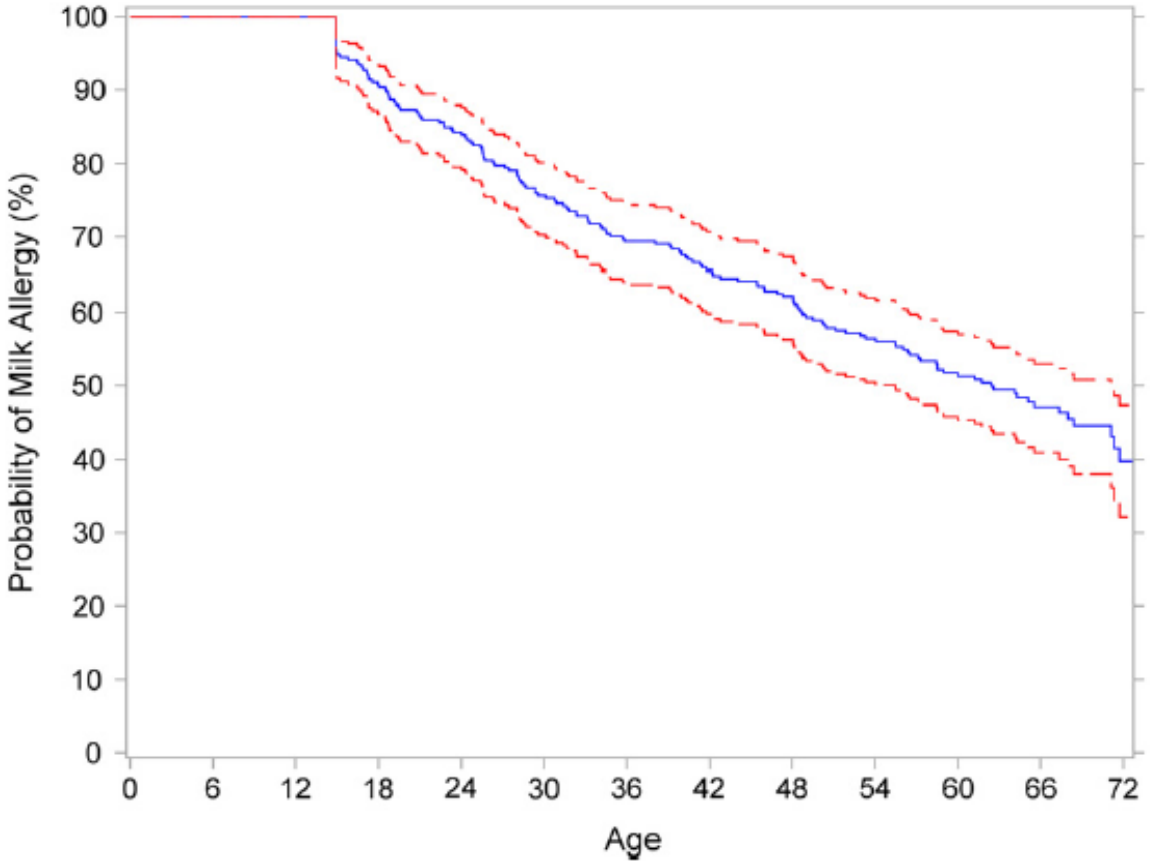
➔ **Poursuivre l'allaitement maternel si possible après la diversification ou l'utilisation des PLV.**

Histoire naturelle Lait de vache

Wood *JACI* 2013

- Etude de cohorte longitudinale, n=244 nourrissons (3-15 M) avec allergie PLV

➔ Guérison dans 53% des cas (âge médian=63 mois)



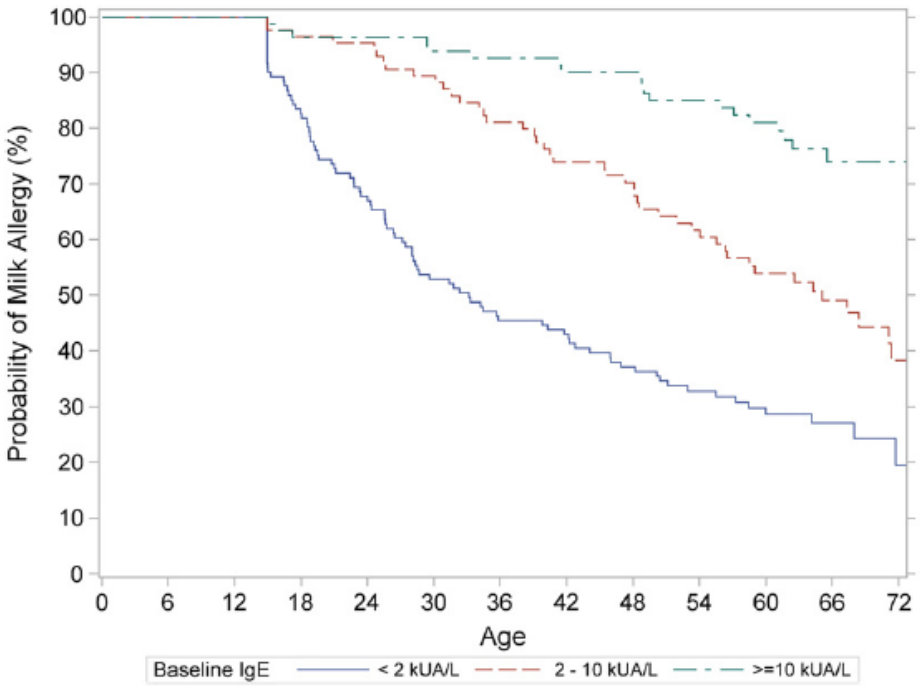
Wood *JACI* 2013

- **Facteurs prédictifs (à 3-15 mois) de guérison :**
  - **RAST PLV**
  - **Valeur prick tests PLV**
  - **Sévérité de la DA**

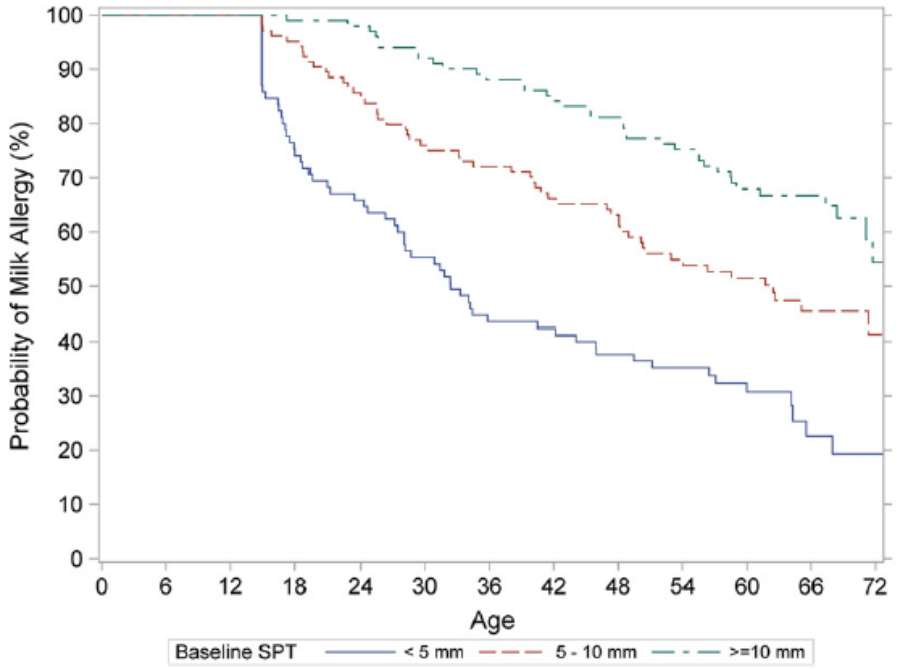
	All milk allergy, no.	Milk allergy resolved				*P* value*
		No		Yes		
		No.	Percent	No.	Percent	
Baseline milk IgE level (kU_A/L)†						<.001
<2	122	34	27.9	88	72.1	
≥2.0-10	85	39	45.9	46	54.1	
≥10	82	63	76.8	19	23.2	
Baseline milk SPT response (wheal, mm)‡						<.001
<5	86	24	27.9	62	72.1	
5-10	105	50	47.6	55	52.4	
>10	101	64	63.4	37	36.6	
Baseline AD severity						<.001
None	32	6	18.8	26	81.3	
Mild	34	12	35.3	22	64.7	
Moderate	146	77	52.7	69	47.3	
Severe	81	44	54.3	37	45.7	

Wood *JACI* 2013

RAST PLV



prick tests PLV



Factor for resolution of milk allergy	Hazard ratio	95% Hazard ratio confidence limits	*P* value*
Baseline milk-specific IgE level (kU_A/L)			
<2 vs ≥10	5.74	3.48-9.46	<.001
2-<10 vs ≥10	2.66	1.56-4.54	
Baseline AD			
Mild/none vs moderate/severe	2.09	1.48-2.94	<.001
Baseline milk SPT response (mm)			
<5 vs >10	3.65	2.42-5.51	<.001
5-10 vs >10	1.86	1.22-2.82	

Lait de vache

Salmivesi *Acta Paediatr* 2013 (Finlande)

Étude randomisée, double aveugle

N=28 enfants (6-14 ans) OIT lait de vache, 18 patients OIT et 10 placebo

OIT augmentation progressive quotidienne de 0.06 à 6400 mg de protéines, sur 23 semaines

- **➔ dans le bras OIT poursuite 6400 mg/j**
- **➔ dans le bras placebo, OIT en ouvert**

89% OIT et 80% placebo ont achevé le protocole.

OIT 2 arrêts pour douleurs abdominales

Placebo : 2 arrêts (motivation, anaphylaxie par PLV)

Lait de vache

Salmivesi *Acta Paediatr* 2013

OIT

médiane de protéines tolérées 6 mg (0.05-162)

14/18 enfants tolèrent 6400 mg et 2/18 tolèrent 960 et 1920 mg

Table 1 Parent-reported symptoms during the 24 weeks of OIT in the 24 children who completed the double-blind study protocol and in the 10 children who completed the open-label study protocol

	Double-blind OIT		Open-label OIT
Symptoms	Active group (N = 16)[A]	Placebo group (N = 8)[B]	Placebo group (N = 10)[C]
Intestinal	8 (50.5%)	3 (37.5%)	8 (80%)
Oral	8 (44.4%)	1 (12.5%)	3 (30%)
Nasal	2 (11.1%)	2 (25%)	1 (10%)
Dermal	4 (22.2%)	3 (37.5%)	1 (10%)
Angioedema	2 (12.5%)	0	1 (10%)
No symptoms	0	3 (37.5%)*	2 (20%)†

Lait de vache

Salmivesi *Acta Paediatr* 2013

OIT dans le groupe placebo

médiane de protéines tolérées 6 mg (0.05-162)

10/10 enfants tolèrent 6400 mg

Points clés

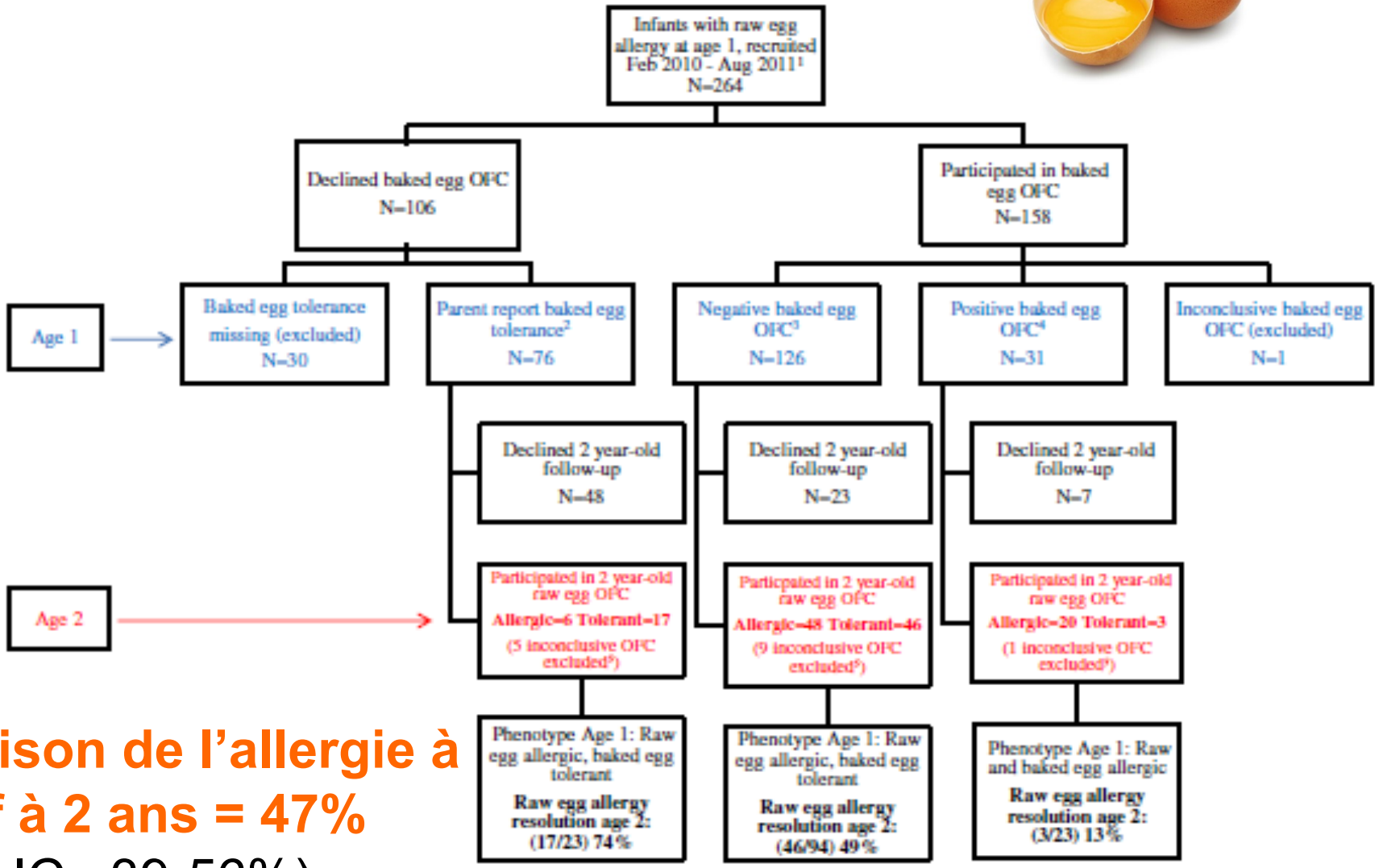
➔ **12 mois après OIT 13/18 et 6 mois dans le groupe placebo 10/10 consommaient 6400 mg/j de PLV**

Oeuf

Peters *JACI* 2014 HealthNuts study

- Histoire naturelle et facteurs prédictifs de persistance de l'allergie à 2 ans
- Données contradictoires sur la fréquence de guérison de l'allergie à l'œuf
- Cohorte prospective de nourrissons de 12 mois (Australie)

Peters *JACI* 2014



Guérison de l'allergie à l'œuf à 2 ans = 47%

(95% IC : 39-56%)

Peters *JACI* 2014

TABLE I. Demographic and clinical characteristics of children with persistent and resolved raw egg allergy at 2 years of age

	Resolved raw egg allergy: age 2 y (n = 66)	Persistent raw egg allergy: age 2 y (n = 74)	*P* value
Demographic factors			
Sex (male)	45% (30/66)	68% (56/74)	.008
Preterm (≤36 wk)	8% (5/62)	0% (0/69)	.02
Duration of breast-feeding			
Not breast-fed	5% (3/64)	3% (2/74)	
1-6 mo	27% (17/64)	16% (12/74)	
7-12 mo	34% (22/64)	38% (28/74)	
>12 mo	34% (22/64)	43% (32/74)	.40
Any siblings	39% (26/66)	39% (29/74)	.98
Parents' country of birth			
Both Australia	65% (43/66)	47% (34/72)	
One overseas	17% (11/66)	35% (25/72)	
Both overseas	18% (12/66)	18% (13/72)	.04
Family history of food allergy	15% (10/65)	18% (13/73)	.70
Family history of any allergy*	83% (55/66)	78% (58/74)	.46
Clinical factors			
Eczema†	59% (39/66)	67% (49/73)	.33
Baked egg allergy at 1 y‡	5% (3/66)	27% (20/74)	<.001
Other food allergy at 1 y§	13% (8/63)	35% (25/71)	.003
GIT/respiratory symptoms at 1-y raw egg OFC‖	9% (6/66)	31% (23/74)	.001
Egg SPT at 1 y (mm)¶	3 (2.5-4)	5 (3.5-7)	<.001
Egg SPT at 2 y (mm)¶	0 (0-1)	4 (3-6)	<.001
Egg sIgE at 1 y (kU_A/L)¶	0.56 (0.26-1.30)	3.59 (1.77-9.94)	<.001
Egg sIgE at 2 y (kU_A/L)¶	0.15 (0.07-0.35)	1.34 (0.59-4.44)	<.001
Egg SPT ≥4 mm at 1 y#	35% (23/65)	72% (53/74)	<.001
Egg sIgE ≥1.7 kU_A/L at 1 y#	14% (8/58)	79% (49/62)	<.001
FLG mutation	9% (5/54)	13% (9/68)	.49

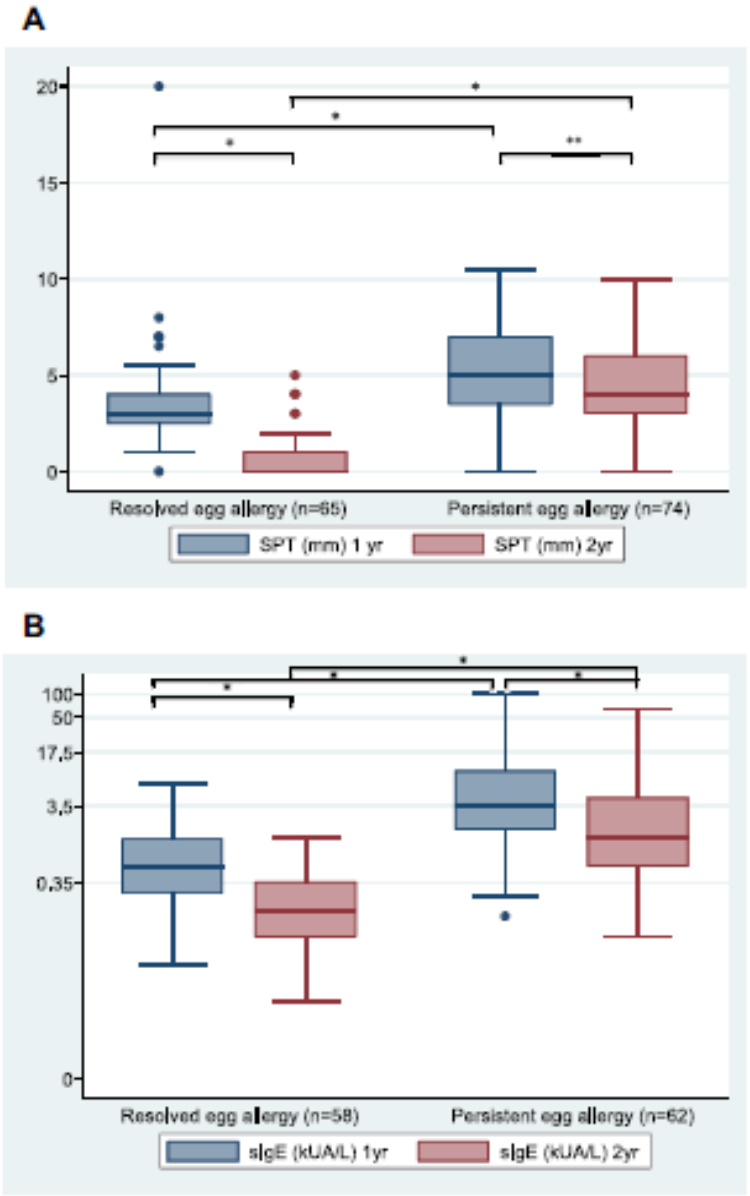


FIG 2. **A,** Average SPT wheal size at age 1-year and 2-year raw egg OFCs in children with persistent and resolved egg allergy. *$P < .001$ and **$P = .11$. **B,** Egg-specific sIgE levels (logged) at age 1-year and 2-year raw egg OFCs in children with persistent and resolved egg allergy. *$P < .001$.

Peters *JACI* 2014

TABLE II. Clinical predictors of persistent egg allergy at 2 years of age

	No.	Crude OR*	*P* value	No.	Adjusted OR	*P* value	Confounders adjusted for in addition to *a priori* confounders†
Eczema‡	119	1.34 (0.64-2.83)	.44	119	0.55 (0.18-1.62)	.27	OFC symptoms, sIgE
Baked egg allergy	140	7.78 (2.19-27.61)	.002	136	5.27 (1.36-20.50)	.02	OFC symptoms, SPT
Other food allergy§	115	5.79 (2.00-16.69)	.001	115	2.55 (0.59-10.99)	.21	SPT, sIgE
GIT/respiratory symptoms at age 1-y raw egg OFC‖	120	4.68 (1.62-13.57)	.004	128	1.78 (0.40-7.83)	.44	Baked egg allergy, sIgE
SPT ≥4 mm at age 1 y¶	139	4.61 (2.25-9.44)	<.001	136	3.34 (1.52-7.38)	.003	Baked egg allergy
sIgE ≥1.7 kU/L at age 1 y¶	120	23.56 (8.98-61.82)	<.001	119	29.46 (8.86-97.92)	<.001	OFC symptoms, eczema
FLG mutation	111	1.42 (0.43-4.63)	.57	111	2.44 (0.40-14.70)	.33	SPT, sIgE

Points clés

➔ 80% des nourrissons qui ont réagi à l'œuf cru tolèrent œuf cuit

➔ seulement 13% des nourrissons allergiques à l'œuf cuit à 1 an guérissent à 2 ans avec un risque 5 fois supérieur par rapport aux enfants tolérants l'œuf cuit à 1 an (OR=5.27 ; 95% IC=1.36-20.50 ; p=0.02)

➔ pas d'association entre la dose réactogène lors du TPO à 1 an et la persistance de l'allergie à 2 ans

Peters *JACI* 2014

Fréquence des nourrissons tolérants à l'œuf cuit à 1 an guéris de l'allergie à l'œuf à 2 ans

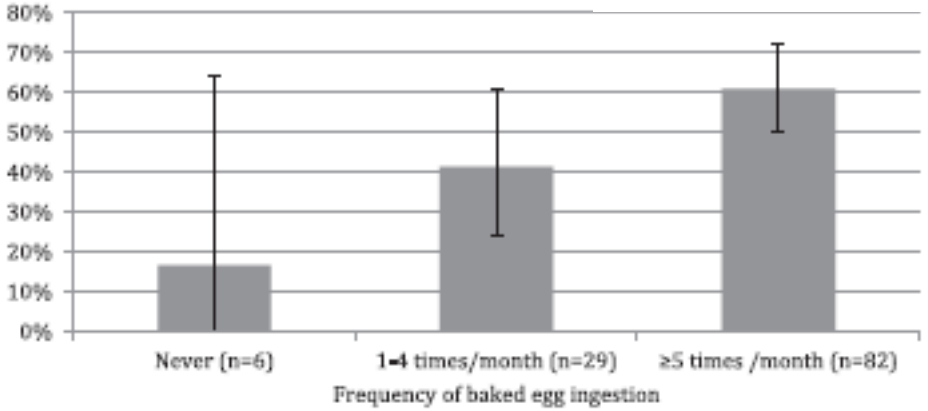


FIG 3. Association between the frequency of baked egg ingestion between 1 and 2 years of age and the resolution of egg allergy at 2 years of age among infants with tolerance to baked egg at 1 year of age (n = 117).

Points clés

➔ **Tolérance à l'œuf cru à 2 ans 3 fois plus fréquente chez les nourrissons consommant entre 1 et 2 ans de l'œuf > 5 fois /mois (par rapport à ceux consommant < 5 fois /mois)** (OR 3.51 95%IC:1.38-8.98 ; p=0.009)

Arachide

Fleischer *JACI* 2013

Etude double-aveugle randomisée *vs* placebo

N=40 patients 12-37 ans (âge médian 15 ans), allergie arachide

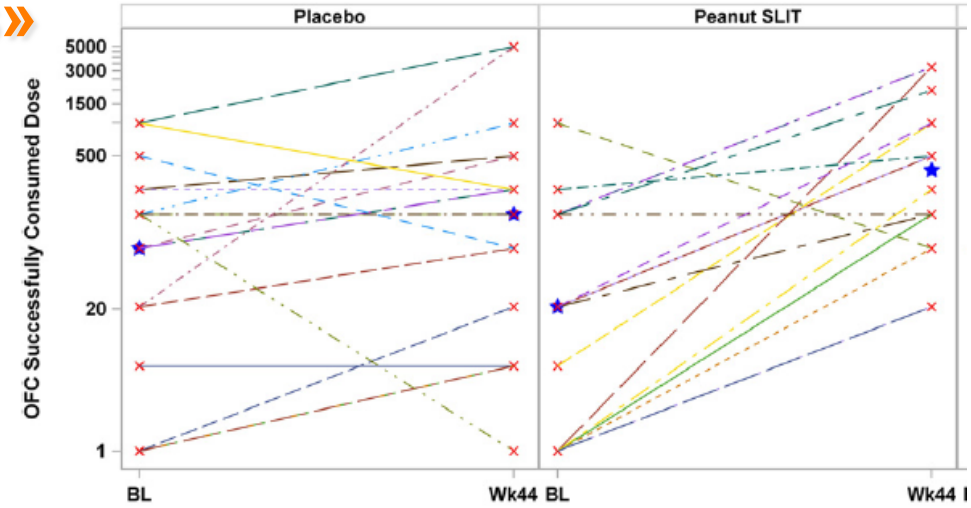
► 1er TPO puis randomisés 1/1 ITSL arachide et placebo /j pendant 44 semaines (escalade et maintien)

► **70% de «bons répondeurs»**

(dose > 5 g ou > 1er TPOx10)

soit de 3,5 à 496 mg

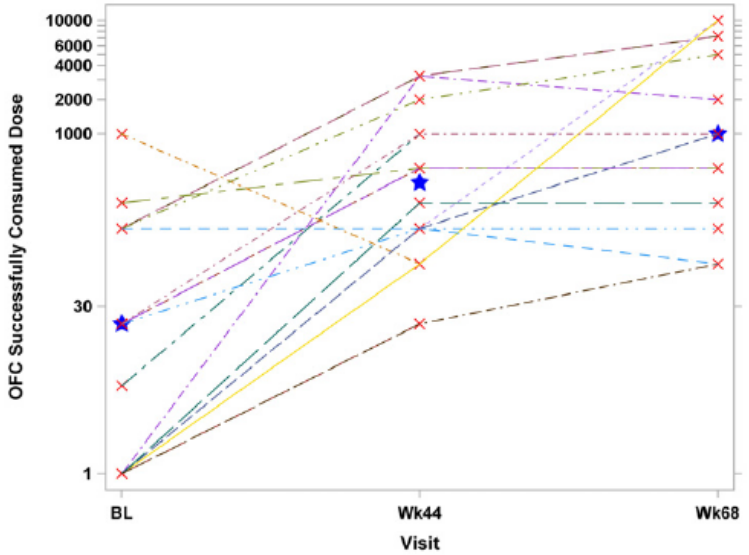
(*vs* 15% groupe placebo)



Arachide

Fleischer *JACI* 2013

puis 996 mg à 68 semaines

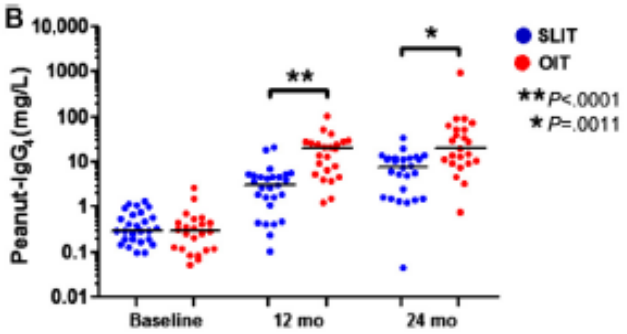


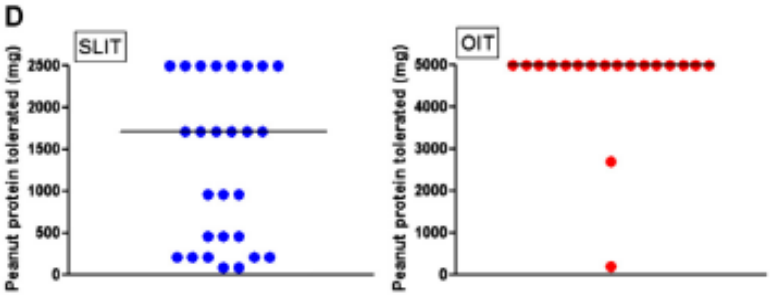
► Pas de différence entre les groupes « bon » ou « mauvais » répondeur selon l'âge, RAST, TC, dose TPO

Arachide SLIT ou OIT ?

Chin *JACI* 2013

- **Etude rétrospective sur 2 études publiées d'IT arachide DA contrôlées vs placebo, OIT (n=23) vs SLIT (n=27)**
- **Evaluation à 12 et 24 mois de traitement**





Points clés

► ↗ **progressive des IgG4sp dans les 2 groupes avec un effet OIT > SLIT**

► **A 12 mois, la dose réactogène est plus faible dans le groupe SLIT avec un risque d'échec 3 fois supérieur dans le groupe SLIT (95%IC : 1.64-5.49).**

Conclusions

- **Du phénotype à l'endotype = vers une médecine personnalisée…**
- **Intérêt d'identifier des biomarqueurs en compléments des phénotypes cliniques pour cibler les patients à risque et mieux choisir les traitements ?**
- **Efficacité de l'omalizumab dans l'asthme sévère**
- **Efficacité et sûreté d'utilisation de l'ITS dans la RC et l'asthme**
- **ITS efficace dans l'allergie alimentaire mais sélection des patients/familles, protocoles nécessitant une expertise, pour sécurité optimale des patients**
- **ITO ? ITSL ? IT épicutanée ?**

Devenir de l'asthme vers l'âge adulte

Andersson *Pediatrics* 2013

- Cohorte de 248 enfants (7-8 ans), asthme, en Suède, en 1996, suivis chaque année jusqu'à 19 ans (83%)

➔ **Rémission (aucun traitement ni sifflement dans les 36 mois précédents) = 21%**

➔ **41% avaient un asthme persistant**

Devenir de l'asthme vers l'âge adulte

Andersson *Pediatrics* 2013

TABLE 4 Factors Related to Remission and Periodic Asthma, Respectively, Analyzed by Multinomial Logistic Regression With Persistent Asthma as Reference

Independent Baseline Variables	Remission		Periodic Asthma	
	OR (95%CI)	OR (95%CI)[a]	OR (95%CI)	OR (95%CI) [a]
Male gender	2.66 (1.00-7.03)	2.53 (1.04–6.15)	1.01 (0.46–2.25)	
Positive SPT to any animal	0.14 (0.04–0.55)	0.17 (0.06–0.48)	0.21 (0.07–0.66)	(0.22 0.09–0.58)
Positive SPT to any pollen	1.84 (0.41–8.37)		1.29 (0.35–4.80)	
Positive SPT to any mold	1.44 (0.16–12.9)		0.64 (0.06–7.40)	
Physician-diagnosed rhinitis	0.41 (0.14–1.20)		0.71 (0.29–1.72)	
Physician-diagnosed eczema	0.51 (0.19–1.42)		0.30 (0.12–0.73)	0.28 (0.12–0.64)
Asthma score ≥2/5	0.19 (0.07–0.54)	0.22 (0.08–0.57)	0.24 (0.10–0.57)	0.23 (0.10–0.52)
Living in an apartment	1.05 (0.32–3.50)		3.12 (1.15–8.44)	3.86 (1.51–9.86)
Mother smokes	0.75 (0.22–2.54)		1.84 (0.68–4.97)	
Mother smoked during pregnancy	1.87 (0.52–6.80)		1.08 (0.36–3.26)	

[a] Results from the stepwise backward multinomial regression model.

Facteurs associés à la persistance de l'asthme

-sexe masculin

-sensibilisation pour au moins un animal

-sévérité de l'asthme

Devenir vers l'âge adulte

Andersson *Pediatrics* 2013

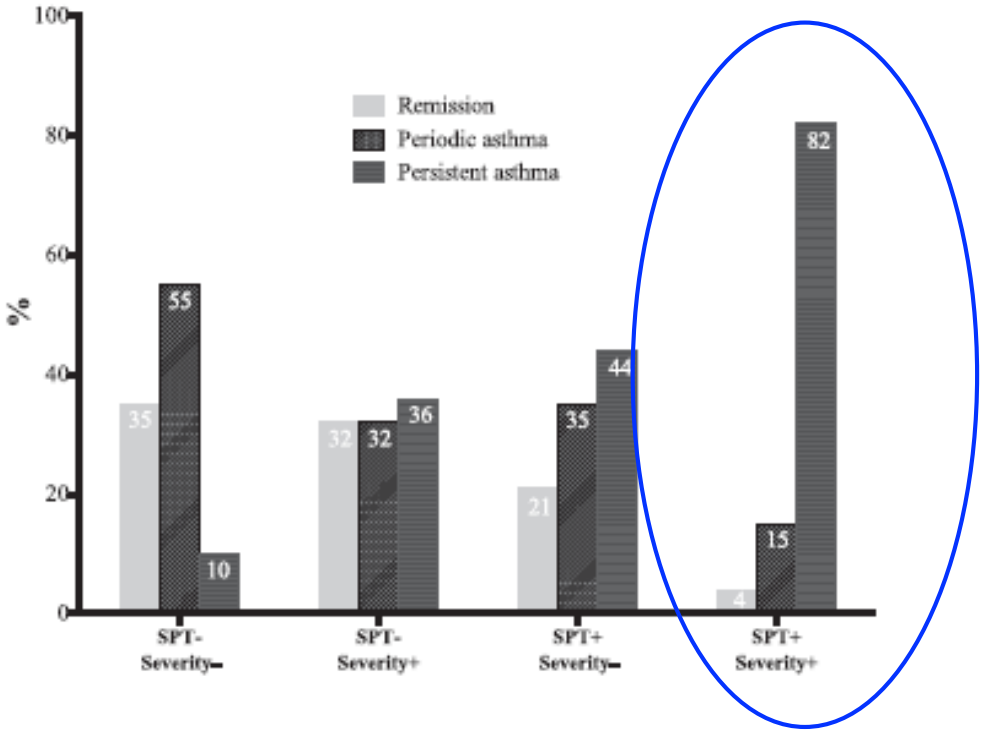


FIGURE 2
The prognosis of childhood asthma by sensitization to animals and asthma severity at age 7 to 8 years. *P* for distribution across groups <.001. Severity+, asthma severity score ≥2, SPT+, Positive skin prick testing to any furred animal, Severity−, asthma severity score <2, SPT−, Negative skin prick testing to furred animals.

Score de sévérité de l'asthme ≥ 2 et PT + animal poils = 82% ont un asthme persistant

Biomarqueurs dans l'asthme ?

- **NO exhalé et hyperéosinophilie** associés de façon indépendante à la prévalence des sifflements et au diagnostic d'asthme

  Malinovschi *JACI* 2013

  ➔ Intérêt en association aux phénotypes cliniques ?

- **IgE**

- **Périostine**

- **Leucotriènes urinaires** : évaluation dans la réponse aux antileucotriènes, intérêt dans l'évaluation de la R aux CSI ?

  Guan *JACI* 2013

Asthme et phénotypes

Chipps Curr Respir Care Rep 2012

- Asthme difficile à traiter/sévère
- Enfants (6-12 ans) n=770 et adolescents (7-17 ans) n=497

Table 2 Predictors of future exacerbations in children aged 6–11 years [17•]

Predictor[a]	Model I[b]			Model II[c]		
	Stepwise model where future exacerbation includes 6-month and 12-month time frames			Additional stepwise reduction of model including only 6-month events		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Recent exacerbation	1.99	1.51, 2.61	<0.001	3.08	2.21, 4.28	<0.001
Non-white vs. white	1.76	1.34, 2.32	<0.001	1.77	1.25, 2.51	0.001
Allergic triggers[d]						
1 or 2 allergic triggers	1.39	0.99, 1.95	0.059	1.26	0.82,1.93	0.29
3 or 4 allergic triggers	2.01	1.40, 2.89	<0.001	2.05	1.31, 3.20	0.002
NHLBI guidelines control impairment domain[e]						
VPC vs. NWC	1.40	1.08, 1.80	0.010	1.59	1.14, 2.23	0.007
WC vs. NWC	0.89	0.45, 1.75	0.73	0.85	0.37, 1.92	0.69
Duration of asthma (per year)	1.06	1.01, 1.12	0.021	–	–	–
Non-allergic triggers[f], 1–2 vs. 0	1.52	1.07, 2.16	0.019	–	–	–

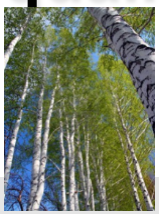
Voie sublinguale

Asthme

Larenas Linnemann *Ann Allergy Asthma Immunol* 2013

Revue systématique 29 études pédiatriques (2009-2012)

Evaluation de la qualité selon la méthode GRADE

Effets+  **Pas d'effet**

Asthma symptoms	Blaiss et al, 2012 (for asthma G3), and Stelmach et al, 2012 (G3)	Effet très faible
Bufe et al, 2009 (G4) Total Tablets: Pajno et al, 2011 (G3) (first year) Stelmach et al, 2009 (G2) Total Drops:		Yes: ●○○○ Yes: ●○○○
Asthma medication Stelmach et al, 2009 (G2) Lung function tests and bronchial provocation PFT: Stelmach et al, 2009 (G2) Methacholine: Stelmach et al, 2009 (G2) (trend $P = .058$) FeNO: Stelmach et al, 2012 (G3) Total Drops:	None PFT: Stelmach et al, 2012 (G3), and methacholine: Stelmach et al, 2012 (G3)	Yes: ●●○○ Effet faible PFT: No: ●○○○ Methacholine: No: ●●○○ Effet modéré FeNO reduction: Yes: ●●●○

Voie sublinguale

Asthme

Larenas Linnemann *Ann Allergy Asthma Immunol* 2013

Effets+

Pas d'effet

Effet très faible

Effet fort

Asthma symptoms Eifan et al, 2012 (G4)	Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5)	Yes: ●○○○
Asthma medication Keles et al, 2011 (G4) (SLIT group) Eifan et al, 2012 (G4) Total	Yukselen et al, 2012 (G2.5)	Yes: ●●●●
Pulmonary function tests No positive studies	Eifan et al, 2012 (G4) (methacholine), Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5)	No: ●●●○
Specific/specific bronchial challenge Marogna et al, 2011 (G3) (passive smokers)	Eifan et al, 2012 (G4) (methacholines), Keles et al, 2011 (G3) (SLIT group), Yukselen et al, 2012 (G2.5)	Methacholine: No: ●●●○

Voie sous cutanée

Asthme et RA

Kim *Pediatrics* 2013

Revue systématique

13 études pédiatriques, n=925, dont 7 ont évalué l'asthme en critère principal, acariens (8/13), durée de traitement de 4 mois à 3 ans, hétérogénéité ++

SCIT studies				
Asthma symptoms	6	550	Dust mite (1) *Cladosporium* (1) Rye (1) *Alternaria* (1) Multiple (2)	SCIT (2) vs placebo (4) vs pharmacotherapy (2)
Asthma medication scores	4	470	Dust mite (1) Rye (1) Multiple (2)	SCIT vs placebo (2) vs pharmacotherapy (2)

Effet modéré (15-40%)

Effet faible (<15%)

Voie sublinguale

Asthme

Lin *JAMA* 2013

Revue systématique de 9 études pédiatriques

N=471 patients

Outcome	No. of Participants	No. of Studies	Allergens	Comparators	Summary of Grading Data	Findings	Strength of the Evidence
Asthma symptoms	625	13	Dust mite[25-27,35-37,42] *Alternaria*[22,45] Grass mix[46] Tree mix[41] Birch[47] *Parietaria*[48]	Sublingual immunotherapy vs placebo[22,25-27,35-37,42,45,47,48] vs inhaled steroids[46] vs placebo-controlled trial of sublingual immunotherapy[41]	Two studies with low risk of bias and strong magnitude of effect.[25,35]	All placebo-controlled studies demonstrated greater improvement in the sublingual immunotherapy group. The study[46] of sublingual immunotherapy vs inhaled steroids showed improvement in both groups.	High

enfants

+

adultes

Effet fort (>40%)

Epidémiologie

Du Toit *JACI* 2013 LEAP study

- Etude prospective monocentrique observationnelle (UK)
- **But** : déterminer la meilleure stratégie de prévention de l'allergie arachide chez l'enfant
- Prévalence de l'allergie arachide = 1,8-3%, doublement en 10 ans
- Nourrissons de 4 à 10 mois à risque d'allergie arachide

  = avec DA sévère ET/OU allergie œuf

  ET sensibilisation arachide (PT arachide < 4 mm)

Du Toit *JACI* 2013

TABLE II. OR estimates (95% CIs) for predictors of peanut-specific IgE comparing 0.35 kU/L or greater to less than 0.35 kU/L

Variable	Unadjusted	Adjusted for all variables except peanut SPT response	Adjusted for all variables including peanut SPT response
Female (yes vs no)	0.81 (0.58-1.14)	0.82 (0.56-1.19)	0.72 (0.46-1.12)
Race (black vs white)	4.26 (2.49-7.29)	5.30 (2.85-9.86)	7.13 (3.58-14.21)
Egg allergy (yes vs no)	5.97 (3.87-9.21)	4.67 (2.95-7.40)	4.08 (2.45-6.82)
Duration of eczema (quarters)	1.40 (1.10-1.78)	1.31 (0.99-1.75)	1.02 (0.73-1.42)
Severe eczema (yes vs no)	4.35 (2.35-8.06)	3.21 (1.65-6.25)	2.23 (1.09-4.57)
Eosinophilia percentage	1.16 (1.11-1.22)	1.11 (1.06-1.17)	1.12 (1.06-1.18)
Peanut SPT-induced wheal, 1-4 mm (vs 0 mm)	7.35 (4.64-11.64)	—	6.69 (3.97-11.28)
Peanut SPT-induced wheal >4 mm (vs 0 mm)	55.02 (21.30-142.13)	—	51.96 (18.88-142.97)

TABLE III. OR estimates (95% CIs) for predictors of skin test–induced wheal sizes in models comparing 1- to 4-mm and greater than 4-mm wheals with 0-mm wheals

	Unadjusted		Adjusted for all variables except peanut-specific IgE level		Adjusted for all variables including peanut-specific IgE level	
Variable	1-4 vs 0 mm	>4 vs 0 mm	1-4 vs 0 mm	>4 vs 0 mm	1-4 vs 0 mm	>4 vs 0 mm
Female sex (yes vs no)	0.89 (0.57-1.38)	1.29 (0.73-2.27)	0.93 (0.59-1.46)	1.38 (0.76-2.51)	1.06 (0.64-1.75)	2.43 (1.03-5.76)
Race (black vs white)	0.82 (0.34-1.98)	1.83 (0.77-4.33)	0.79 (0.32-1.96)	1.87 (0.75-4.70)	0.26 (0.09-0.72)	0.15 (0.04-0.61)
Egg allergy (yes vs no)	2.86 (1.74-4.69)	5.71 (2.54-12.87)	2.31 (1.39-3.86)	4.03 (2.00-10.57)	1.10 (0.62-1.97)	1.12 (0.36-3.51)
Duration of eczema (quarters)	1.50 (1.09-2.05)	2.29 (1.50-3.50)	1.38 (0.98-1.93)	2.05 (1.31-3.22)	1.40 (0.95-2.04)	1.79 (0.91-3.51)
Severe eczema (yes vs no)	3.07 (1.45-6.49)	14.08 (1.93-102.85)	2.47 (1.14-5.34)	12.53 (1.69-93.14)	1.72 (0.76-3.90)	8.64 (0.92-81.09)
Eosinophilia percentage	1.07 (1.02-1.12)	1.05 (0.99-1.12)	1.04 (0.99-1.09)	1.02 (0.95-1.09)	0.96 (0.91-1.03)	0.88 (0.79-0.99)
Peanut-specific IgE (kU/L), log10	3.17 (2.51-3.99)	8.19 (5.20-12.9)	—	—	3.53 (2.65-4.71)	14.55 (7.61-27.83)

Sensibilisation arachide [PT=1-4 mm vs PT=0 ou RAST > vs < 0.35 KU/L] associée un DA sévère et allergie œuf

Les enfants avec allergie à l'œuf ou DA sévère sont susceptibles de faire l'objet d'une étude de prévention pour allergie arachide.

Epidémiologie

- **Aux Etats-Unis, la prévalence de l'allergie alimentaire en pédiatrie est de 6,5%.**
- **La prévalence est augmentée chez les noirs, non-hispaniques et asthmatiques.**

Greenhawt *JACIP* 2013

- **L'allergie alimentaire est un facteur de risque d'hospitalisation chez asthmatique (OR = 2,35 ; 95% IC =1,3-4,24)**

Friedlander *JACIP* 2013

Physiopathologie

- **Déficits en filaggrine** liés à des mutations génétiques ou down regulation médiée par cytokines apparaissent comme un des FdR importants de DA.

  ➔ Des mutations de la filaggrine responsables d'altérations de la barrière cutanée sont associées à l'allergie arachide.

- **Rôle des graisses**

  Souris nourries avec protéines arachide, TCM, TCL ou TCL + inhibiteur de la formation des chylomicrons

  ➔ La réponse immunitaire peut être influencée par les processus de fabrication et le type des aliments et dans ce cas les TCM modifient l'absorption allergénique et les réponses allergéniques.

Li *JACI* 2013

Lait de vache

Ford *JACI* 2013

- **Recherche de biomarqueurs de tolérance aux PLV**
- 75% des allergiques au lait de vache tolèrent les PLV sous forme cuite
- N=132 (4-10 ans) (**exclusion RAST > 35 KU/L, anaphylaxie**), **TPO lait 3 groupes** (tolérant lait cuit – muffin, pizza, riz au lait-, allergie, guérison)
- IgE spécifiques, IgG4 spécifiques, test d'activation des basophiles, PT

Lait de vache

Ford *JACI* 2013

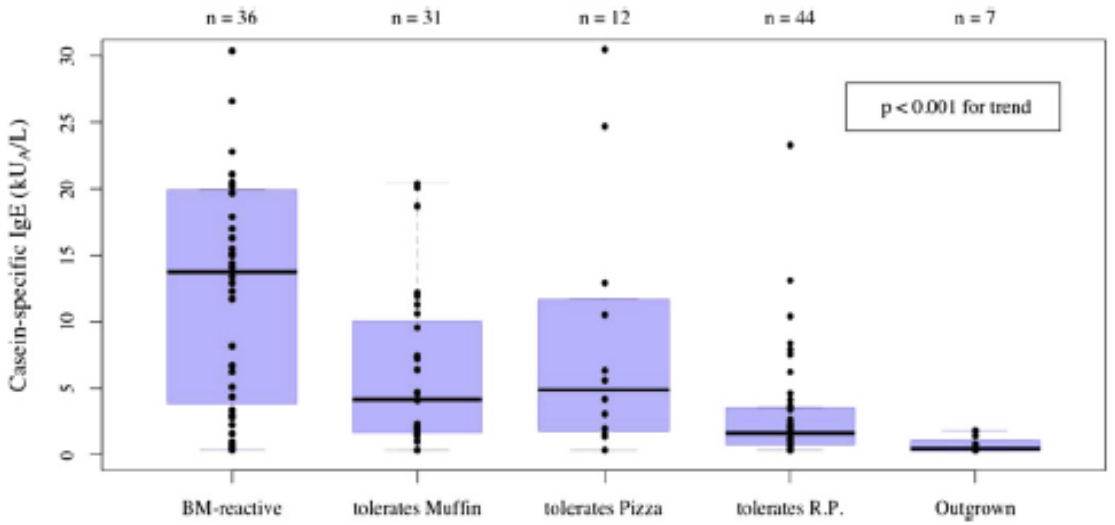


FIG 1. Casein-specific IgE measurements by 5 levels of challenge outcome. With the 3 central groups pooled, *post hoc* analysis showed a significant difference between those who reacted to baked milk and those who tolerated it ($P < .001$) and between those who tolerated baked milk and those who had fully outgrown their milk allergy ($P < .005$). *BM*, Baked milk; *R.P.*, rice pudding.

Prick tests

« allergie » médiane 10 mm (5.5-20) *versus*

« guérison » 6 mm (1-9)

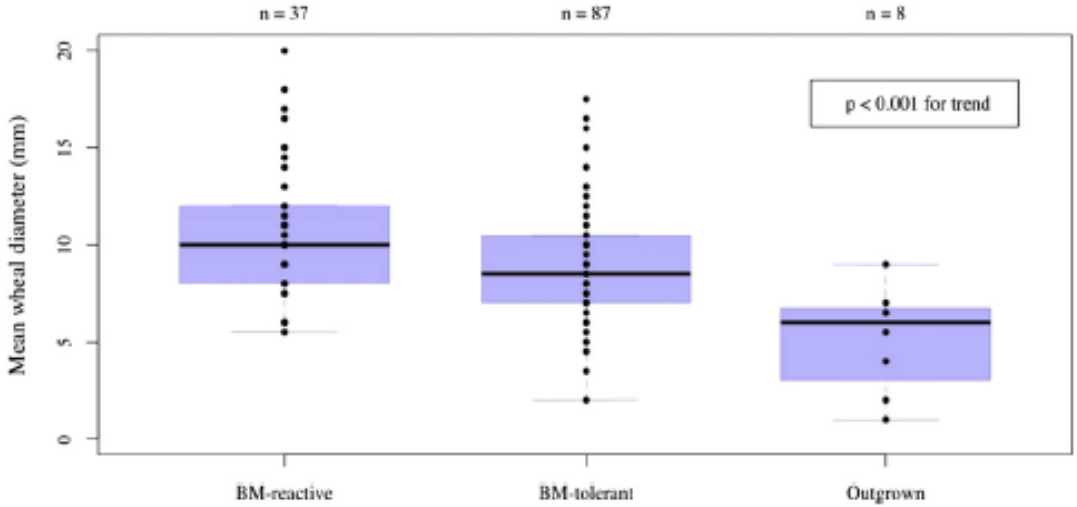


FIG 6. Wheal reaction on SPTs with commercial milk extract by 3 levels of challenge outcome (baked milk–tolerant subjects have been pooled). *Post hoc* analysis shows a significant decrease in wheal size in those who tolerated baked milk compared with those who reacted to it ($P < .005$) and in those who have fully outgrown their milk allergy compared with those who tolerate baked milk ($P < .005$). *BM*, Baked milk; *PST*, skin prick test.

Lait de vache

Ford *JACI* 2013

RAST caséine

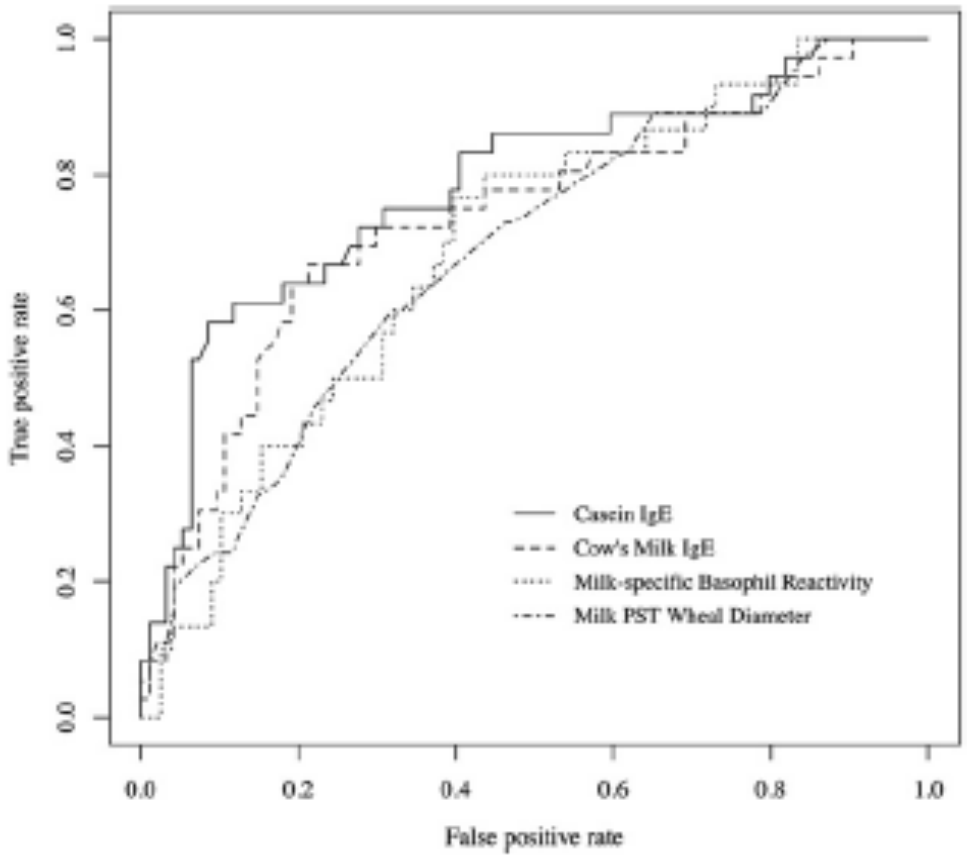
AUC 0.78 (95%IC: 0.69-0.88)

RAST PLV

AUC 0.73 (95%IC: 0.63-0.83)

Test d'activation basophiles

AUC 0.69 (95%IC:0.59-0.80)

Prick tests

AUC 0.68 (95%IC:0.58-0.78)