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1 **Natural history of allergic sensitization in infants with early-onset atopic**
2 **dermatitis: results from ORCA Study**

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18 **Running title** : biological outcomes of infants from ORCA Study

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28 **ABSTRACT**

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32 **Natural history of allergic sensitization in infants with early-onset atopic
33 dermatitis: results from ORCA Study**

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35 **Pediatr Allergy Immunol**

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37 **BACKGROUND:** Early-onset atopic dermatitis (AD) is a particular phenotype that

38 may convey a risk of developing multiple sensitizations to allergens but little is known

39 about the pathway of sensitization. The aims of this study were to describe the

40 natural history of sensitization to allergens for this phenotype and to identify the most

41 predictive marker associated with the risk of developing sensitization to inhaled

42 allergens in a well-selected cohort of infants with AD. **METHODS:** Infants with active

43 AD were enrolled and prospectively explored for biological markers of atopy every

44 year until the age of 6 years. Allergic sensitization was defined as the presence of

45 positive specific IgEs to allergens and multiple sensitizations as being sensitized to

46 ≥ 2 allergens. Elevated blood eosinophilia was defined as an eosinophil blood count

47 ≥ 470 eosinophils/mm³ and elevated total IgE as a serum IgE level ≥ 45 kU/L.

48 **RESULTS:** 229 infants were included. Elevated blood eosinophilia was observed at

49 baseline in 60 children (26.2%) and elevated total IgE in 85 (37.1%). When elevated

50 at baseline, eosinophilia and IgE levels remained significantly higher during the

51 follow-up period. Sensitization to food allergens decreased from 58% to 34%

52 whereas sensitization to inhaled allergens increased over time from 17% to 67%.

53 Initial multiple sensitizations to food allergens were the most predictive factor for the

54 risk of developing sensitization to inhaled allergens at 6 years (OR 3.72 [1.68-8.30]

55 $p < 0.001$). **CONCLUSIONS:** In the early-onset AD phenotype, multiple sensitization

56 to food allergens conveys a higher risk of sensitization to inhaled allergens than
57 single sensitization.

58 **Key words** Atopic dermatitis, sensitization, food allergens, inhaled allergens,
59 phenotypes, cohort

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89 **Introduction**

90 Atopic dermatitis (AD), which often begins in infancy, is a chronic inflammatory
91 disorder of the skin that affects 10 to 30% of children {1}. Prevalence of sensitization
92 to inhaled allergens in the general population is between 16 to 25% [2]. It is
93 suspected that there is a link between AD and the occurrence of sensitization to
94 inhaled allergens during childhood. This could be because of percutaneous entry of
95 the allergens through an impaired skin barrier due to inflammation. Moreover, early-
96 onset AD, as well as the severity of AD, has been shown to be associated with a risk
97 of sensitization to food allergens at 3 months of age [3]. Sensitization to food
98 allergens in birth cohorts, particularly elevated egg-specific IgE, has also been shown
99 to be a risk marker for sensitization to inhaled allergens later in life {4}. Furthermore,
100 sensitization to inhaled allergens can predict the occurrence of respiratory disease
101 which can start years before the first symptoms of allergic rhinitis or asthma [5]. All in
102 all, AD could be the first step leading to asthma, particularly in children with severe
103 [6] or early-onset AD [7]. However, the early-onset and severe phenotype of AD is
104 quite rare; e.g., in Flohr *et al.*'s study {3} conducted in 619 infants from a population
105 of breastfed infants, only 3.6% had severe AD and 5.4% were sensitized to at least
106 one food allergen. This makes it relatively difficult to explore this phenotype. We
107 therefore set out to explore a cohort of children suffering from early-onset AD from
108 the prospective longitudinal ORCA (Observatory of Respiratory risks linked with
109 Cutaneous Atopy) study to try to describe this phenotype more precisely. The
110 objectives of the present analysis were to describe the natural history of sensitization
111 in this cohort and then to identify the best marker associated with the risk of
112 developing sensitization to inhaled allergens.

113 **Methods**

114 ***Design***

115 Patients were part of the ten-year (2002-2012) Observatory of Respiratory risks
116 linked with Cutaneous Atopy (ORCA) Study resulting from the collaboration between
117 two tertiary care centers, the Allergology Department at the Armand Trousseau
118 Children's Hospital and the Dermatology Department at the Saint-Louis Hospital,

119 both in Paris, France. The study prospectively included children with AD referred to
120 the Saint-Louis Hospital by a primary care physician.

121 ***Ethics***

122 Parents of each child provided written informed consent at inclusion. The protocol
123 was endorsed by the Institutional Review Board of the Medical Ethics Committee on
124 Research of the Saint-Louis Hospital. Data were collected for the study with respect
125 to the confidentiality of patient records.

126 ***Inclusion criteria*** We considered for inclusion all the children meeting the following
127 criteria: i. aged younger than 12 months, ii. with an active AD diagnosed by a
128 dermatologist according to the United Kingdom Working Party criteria (UKWP) {8}
129 and ISAAC questionnaire {9}, iii. without a history of wheezing.

130 ***Data collection at inclusion***

131 Clinical data collected were:

- 132 1. Gender
- 133 2. Active AD defined by ISAAC questionnaire {9} and AD severity assessed by
134 the SCORAD questionnaire [10]. We defined a low severity group for children
135 when the SCORAD was under 15, a medium severity group when the
136 SCORAD was between 15 and 40, and a high severity group when the
137 SCORAD was above 40.
- 138 3. Any documented food allergy defined by relevant allergic symptoms following
139 consumption of a food allergen associated with a sensitization to the same
140 allergen.

141 Biological markers of atopy measured in peripheral blood included:

- 142 1. Specific IgEs for inhaled and food allergens (ImmunoCAP Phadiatop Infant;
143 Uppsala, Sweden). Sensitization was defined as a specific IgE concentration

144 ≥ 0.35 kU/L in serum against one of the following inhaled and food allergens:
145 house dust mite (HDM), cat and dog dander, pollens (birch tree, timothy grass,
146 mugwort), cockroaches; cow's milk, hen's egg, peanut, soy, fish and wheat.
147 Multiple sensitizations were defined as at least two positive specific IgEs to
148 allergens.

149 2. Other biological markers such as blood eosinophilia (cell counting by
150 automated Sysmex; France), and total IgE (measured by ImmunoCAP;
151 Uppsala, Sweden). Thresholds were used to define increased levels:
152 increased blood eosinophilia was defined as a concentration of 470
153 eosinophils/mm³ or more and increased total IgE as a concentration of 45 kU/L
154 or more [11].

155 ***Prospective data collection***

156 Children were followed up on biological parameters at the age of 6 months and then
157 annually until the age of 6 years. Biological parameters assessed at each visit were:
158 specific IgE levels against inhaled and food allergens; blood eosinophilia; and total
159 IgE levels, as described above.

160

161 **Statistical analysis**

162 All the results were calculated from the export database. Statistical analysis was
163 performed using the Open Source R software ($>$ R 2.13.1) [R Development Core
164 Team (2009). R: A language and environment for statistical computing. R Foundation
165 for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL [http://www.R-](http://www.R-project.org)
166 [project.org](http://www.R-project.org)]. Observed distributions of variables are described as numbers and
167 percentages for categorical variables and means, standard deviations and ranges for
168 continuous variables. The baseline characteristics of the patients were compared by

169 the chi-square test or Fisher's exact test for categorical variables and Welsh's
170 student test for continuous variables. The variables defining severity of AD were
171 discretized in three classes according to the SCORAD questionnaire as described
172 above. Clinical and biological features associated with the risk of developing
173 sensitization to inhaled allergens by the end of the follow-up period were calculated
174 with a logistic regression model. These prognostic factors ($p < 0.2$) were then included
175 in the multivariate analysis. Estimated OR are given with a 95% Confidence Interval.
176 Survival analysis, describing time to sensitization (sensitization to inhaled allergens),
177 was performed by Kaplan–Meier analysis. For Kaplan–Meier analysis, we analysed
178 all clinical events by time to first event.

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182 **Results**

183 Three hundred children were initially considered for inclusion. Twenty-nine were
184 excluded (21 for lack of parental consent, 7 for a previous history of wheezing and
185 one for gluten intolerance). 42 were lost to follow-up immediately after the inclusion
186 visit and were not included in the analysis. The remaining 229 patients were included
187 for baseline characteristics analysis. 190 completed the last visit and formed the final
188 sample. The baseline characteristics of the children who were not included in the
189 final analysis did not differ from those of the final sample (data not shown). Figure 1
190 summarizes the patients flowchart.

191 **Descriptive data at baseline**

192 **Clinical parameters.** There were 134 boys (58.5%) and the mean age was 6.5 ± 2.7
193 months (mean \pm SD). Mean SCORAD was 34.2 ± 21.0 (mean \pm SD). Food allergy was
194 present in 6% (13/229) of the children. 173 children (75.6%) had a parental history of
195 atopy.

196 **Biological markers**

197 **Blood eosinophilia.** Increased levels of blood eosinophilia were observed in 26.2 %
198 (59/225) with an average value of $356.2 \pm 548.7/\text{mm}^3$ (mean \pm SD).

199 **Total IgE.** Increased total IgE was observed in 36.9 % (83/225) with an average
200 value of 111.2 ± 316.1 KU/L (mean \pm SD).

201 **Specific IgE.** 58% (132/229) of the children had sensitization to food allergens and
202 37 % (86/229) multiple sensitizations. Hen's egg, cow's milk, peanut represented
203 95% (125/132) of sensitization to food allergens (hen's egg 44%, cow's milk 26%,
204 peanut 25%, fish 4%, wheat 3%, soy 2.2%). Seventeen percent (40/229) of the
205 children were sensitized to at least one inhaled allergen. Cat dander represented

206 52% (21/40) of sensitization to inhaled allergens, HDM and dog dander 17 % (7/40),
207 all the pollens 12% (5/40) and cockroaches 2.5 % (1/40).

208 **Descriptive atopic biological markers during the follow-up period**

209 **Changes in blood eosinophilia.** Analysis by a linear mixed model taking the level of
210 blood eosinophilia at baseline variable as an interaction with time showed that levels
211 of eosinophilia remained on average significantly higher in children with an increased
212 level of blood eosinophilia at baseline, compared to those with a low level at baseline
213 ($+705/\text{mm}^3$ vs $+76.1/\text{mm}^3$ over the follow-up period, respectively, $p<0.001$).

214 **Changes in total IgE.** Analysis based on a linear mixed model of the total IgE level
215 variable considered as an interaction with time showed that children with an
216 increased total IgE at baseline had significantly higher average values throughout
217 follow-up than the children in whom the initial total IgE value was normal ($+284.6$
218 kU/L vs $+39.2 \text{ kU/L}$ over the follow-up period, $p<0.001$) (Figure 2).

219 **Changes in specific IgEs.**

220 Overall, sensitization to food allergens decreased from 58% (132/229) at inclusion to
221 34% (66/195) at the end of the follow-up period. In contrast, the percentage of
222 children sensitized to inhaled allergens increased over time from 17% (39/229) at
223 inclusion to 67% (130/195) at the end of follow up. 46% (90/195) of the children were
224 sensitized to both food and inhaled allergens at the end of the follow-up compared to
225 17% (39/229) at baseline. More precisely, at the end of the follow-up period
226 sensitization to inhaled allergens consisted of timothy grass pollens (30%), HDM
227 (28%) while sensitization to cat dander decreased to 18%. Sensitization to dog
228 dander remained stable at around 5%, as well as birch pollen that represented 18%
229 of sensitizations. Hen's egg, cow's milk and peanut together represented 86% of

230 sensitizations to food allergens, with 35%, 29% and 22% for peanut, egg and cow's
231 milk respectively (Figure 3).

232

233 **Factors associated with the risk of sensitization to inhaled allergens at the end**
234 **of the follow-up period**

235 *In univariate analysis*, clinical and biological markers were evaluated as risk factors
236 for developing inhaled sensitization (Table 1). No clinical parameters (such as
237 severity of atopic dermatitis or food allergy) were found to be risk factors. In contrast,
238 elevated total IgE at baseline emerged as a risk factor for developing sensitization to
239 inhaled allergens at the end of follow up (OR 2.94 {1.58-5.47} $p < 0.001$). One
240 hundred infants (76.9%) sensitized to food allergens were sensitized to inhaled
241 allergens at 6 years (OR 3.32 {1.90-5.84} $p < 0.001$). More precisely, infants with
242 multiple sensitizations to food allergens were more likely to be sensitized to inhaled
243 allergens (OR 4.32 {2.22-8.40} $p < 0.001$) than infants with a single food sensitization
244 (OR 2.20 {1.05-4.60} $p = 0.035$).

245 *In multivariate analysis*, only sensitization to food allergen remained a determinant
246 and multiple food sensitizations were the most predictive marker associated with the
247 risk of developing sensitization to inhaled allergens at school age (OR 3.72 {1.68-8.30}
248 $p < 0.001$). This was almost double than that for children with one food sensitization
249 (OR 2.20 {1.01- 4.72} $p = 0.05$) (Table 2).

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256 **Discussion**

257 The main result of this study is that multiple sensitizations to food allergens as
258 opposed to a single sensitization, could be a predictor of sensitization to inhaled
259 allergens in children suffering from early-onset AD. This finding leads to the
260 emergence of a particular phenotype of sensitizations in early-onset AD.

261

262 **High T-helper cell 2 (Th2) dominant lymphocyte pattern exists in early-life and**
263 **persists during preschool age**

264 We have shown that both elevated blood eosinophilia and elevated total IgE seem to
265 follow a track during childhood for infants with a particular phenotype of AD. This
266 corresponds to what is known as the extrinsic form of AD as opposed to the intrinsic
267 form. While both forms are clinically identical, the former is characterized by high
268 levels of specific IgEs. Yamamoto *et al.* {12} reported significant differences in terms
269 of heterogeneity of the interleukin 5 gene between AD with high and low blood
270 eosinophil levels. Thus AD can present different clinical phenotypes-genotypes.
271 There is considerable evidence that some individuals with AD present immune
272 dysregulation, including increased serum IgE and allergen sensitization, and
273 increased Th2 cytokine expression in eczematous lesions {13}. Genetic factors
274 predispose atopic subjects to mount exaggerated Th2 responses {14} and to
275 exaggerated abnormality of the epidermal barrier {15}, which may favor allergic
276 sensitization. Recently, Suárez-Fariñas *et al.* {16} demonstrated a significant
277 correlation between IgE levels and SCORAD scores ($r=0.76$, $p<10^{-5}$) only in patients
278 with extrinsic AD.

279

280 **Sensitizations to food allergens move towards sensitizations to inhaled**
281 **allergens in some children suffering from early-onset AD** Extrinsic AD implies
282 the presence of a Th2 lymphocyte pattern with a cytokine profile facilitating an IgE
283 response to environmental antigens. It is therefore hardly surprising that early
284 expression of IgE-mediated sensitization to food is accompanied by a high risk of
285 sensitization to inhaled allergens. This fact is in accordance to results published from
286 the DARC cohort, in which predominately sensitization to foods, however shifting
287 toward inhalant allergens with age (Eller E, Kjaer HF, Høst A, Andersen KE,
288 Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort.
289 *Pediatr Allergy Immunol.* 2010 Mar;21(2 Pt 1):307-14.)

290 In the case of early-onset eczema, IgE sensitization often occurs weeks or months
291 after the eczema lesions first appear, suggesting the allergens are first introduced
292 through the skin. Once allergens have penetrated the skin barrier, they interface with
293 antigen-presenting cells, which can then initiate a Th2 response by dendritic cells
294 {17}. The ensuing cascade can result in a long-lasting response with sensitization of
295 the host. Subsequent exposures can then lead to allergic rhinitis and asthma {18}.

296 A recent larger birth cohort study demonstrated a strong association between food
297 allergen sensitization, especially hen's egg, and asthma development by age 6 years
298 {19}. Our study therefore confirms that early-onset AD is often associated with
299 sensitization to food allergens and more precisely multiple food sensitizations.

300

301 **Multiple food sensitizations are the most predictive biomarker of early**
302 **sensitization to inhaled allergens**

303 These results validate our previous findings that there are multiple atopic phenotypes
304 {20}. In the same way, Lazic *et al.* {21} recently validated his previous study

305 suggesting that allergic phenotypes change little over time, and that one phenotype
306 with sensitization to a wide variety of allergens was much more likely to give rise to
307 asthma during childhood. This class is relatively unfrequent, comprising
308 approximately one third of the children who would be considered atopic by
309 conventional criteria. In the same manner, in a particular phenotype with early-onset
310 AD, we have shown here that sensitization to food allergens conveys a high risk of
311 sensitization to inhaled allergens rather when multiple than when unique. This finding
312 supports the hypothesis that the clinical expression of allergic diseases does not
313 merely depend on the presence of specific IgE antibodies, but rather on patterns of
314 IgE responses over time.

315

316 ***Strength and limitations of our study***

317 The strength of the study resides in the fact that it was a longitudinal prospective
318 cohort in a highly selected population of infants with early-onset AD explored
319 annually in a standardized manner. However, one limitation could be the rather small
320 size of the cohort and the absence of a control group. However, as mentioned in the
321 introduction, we selected a rare but potentially severe phenotype i.e., early-onset AD.
322 In this context, the size of this selected population was greater than the number of
323 patients suffering from this phenotype if selected from a large birth cohort. It would
324 have been of interest to know if multiple food sensitizations could predict not only
325 sensitization to inhaled allergens but also to severe allergic diseases such as
326 persistent AD and mainly asthma. Nevertheless, inhaled sensitization has been
327 found to be a strong predictor of asthma development and airway
328 hyperresponsiveness up to school age, which is a strong risk factor for respiratory
329 allergies [22]. In the same manner, Kjaer HF et al showed that children with atopic

330 dermatitis, asthma, or rhinoconjunctivitis, and sensitization at 6 yr, were sensitized to
331 food allergens to a large extent (53%, 42%, and 47%, respectively) already at 6
332 months. This relationship will constitute our future research on this cohort.

333

334 ***In conclusion,*** Our data have showed longitudinal changes in sensitization patterns
335 of children with early-onset AD and more precisely that multiple food sensitizations,
336 rather than single food sensitization, conveys a high risk of sensitization to inhaled
337 allergens at school age. It is thus important to identify this phenotype during infancy
338 to optimize patient management.

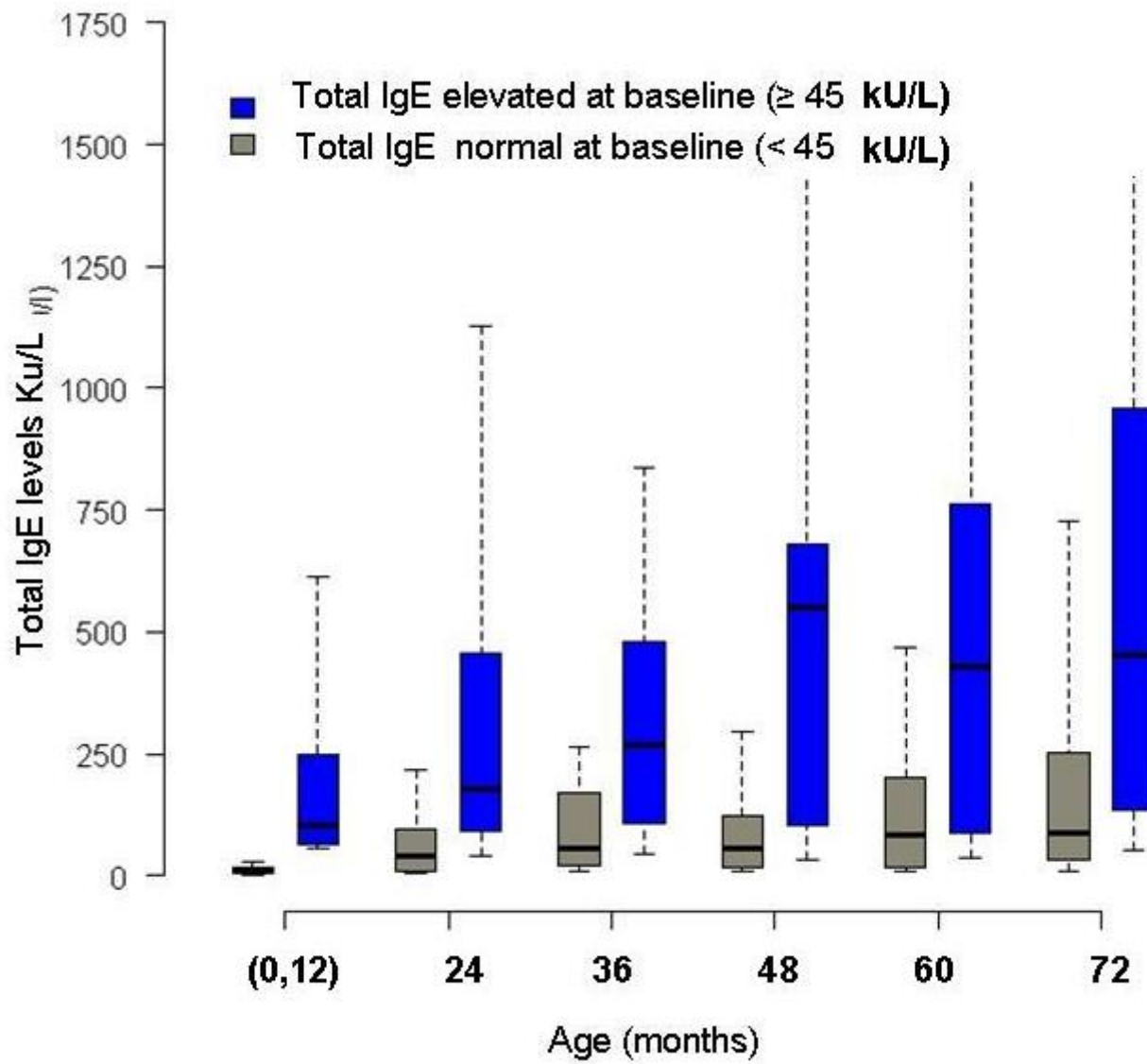
339 **Acknowledgements**

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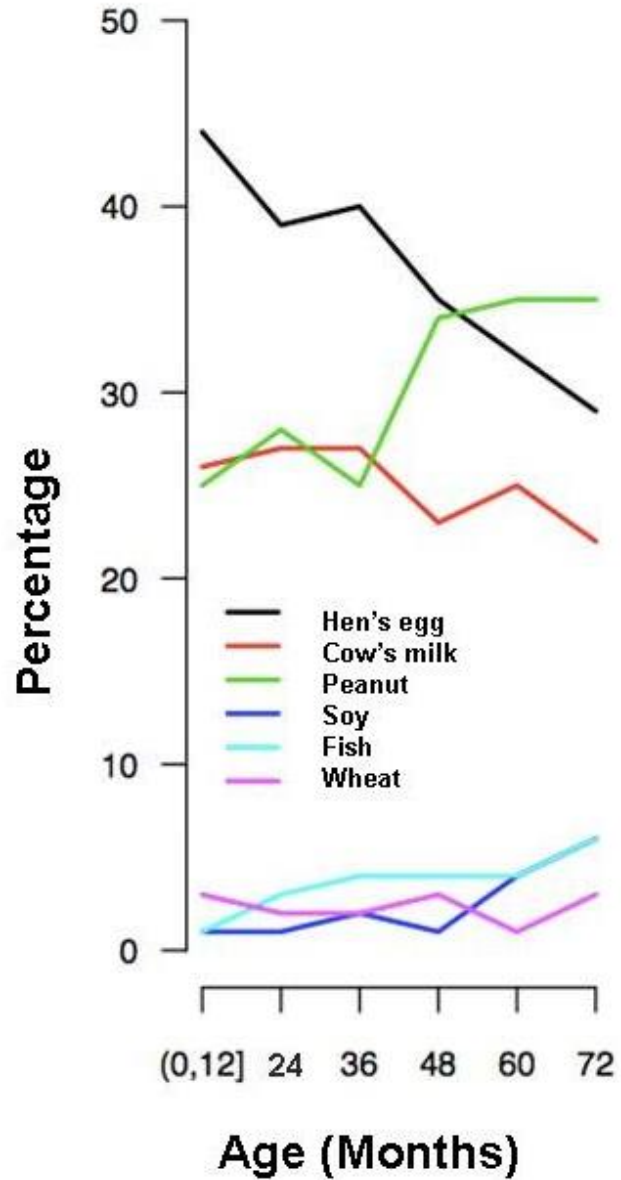
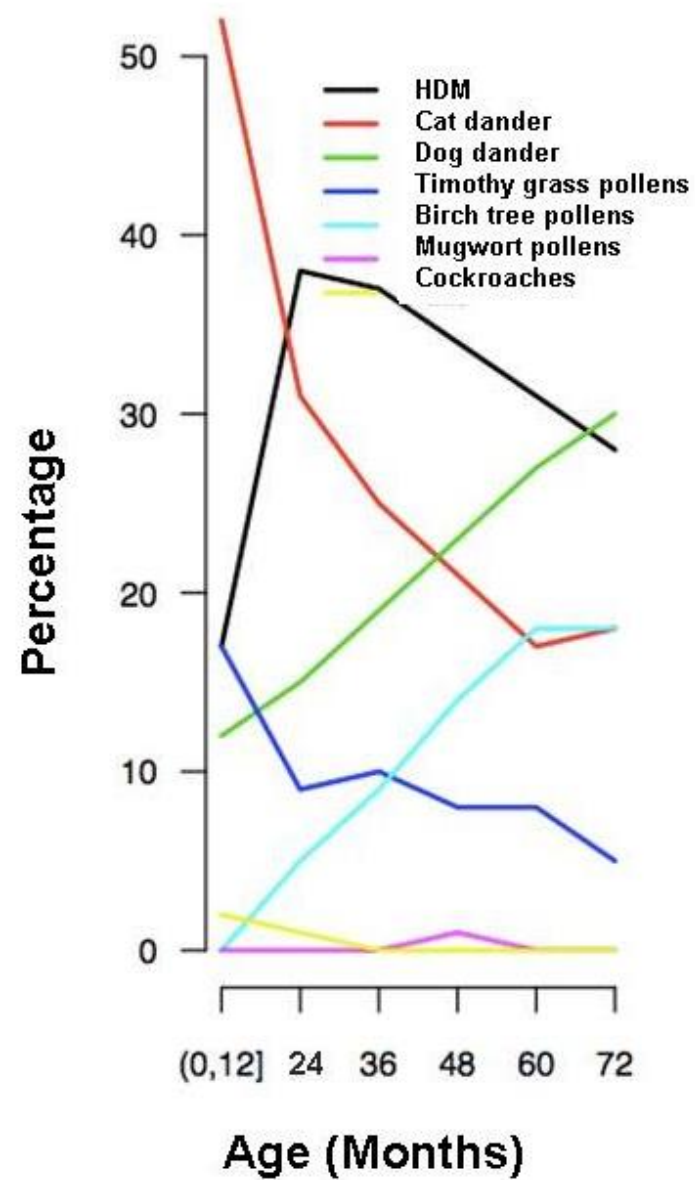
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342 **Figure 1. Flow-chart of the study.**

343 Legend: AD atopic dermatitis, n number of patients, mean age at each visit is under brackets.



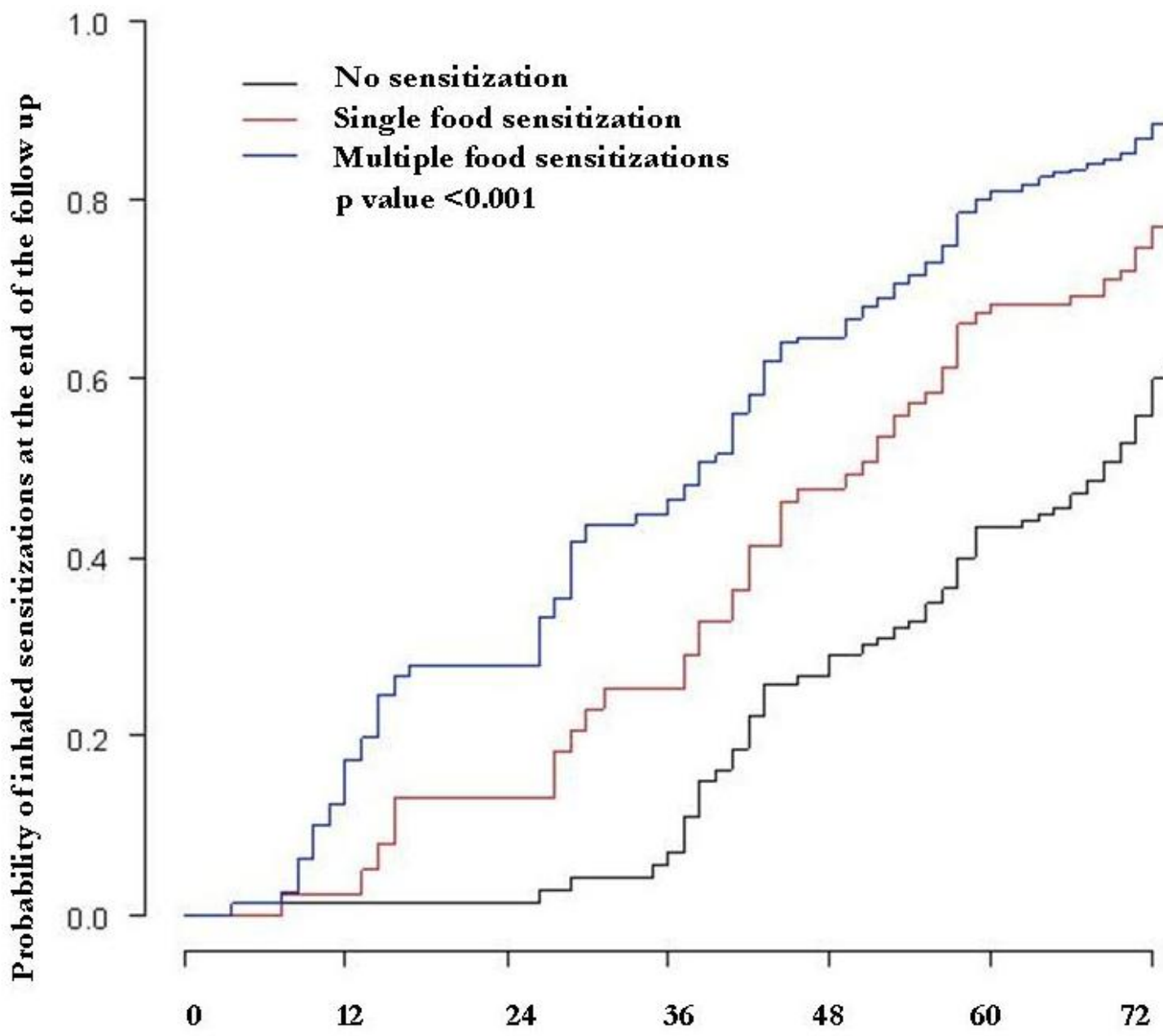
345 **Figure 2: Phenotypes of total IgE levels during the 72 months of follow up: changes in the low (<45 kU/L) and high (≥45**
346 **kU/L) total IgE levels at inclusion.** The horizontal lines of the box represent the lower, median and upper quartile, the hatched
347 traits represent the values outside of the whiskers (the ends of the whiskers represent the lowest datum still within 1.5 interquartile
348 range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile).

A**B**

350 **Figure 3: Changes in each sensitization to food (A) and inhaled allergen (B) during the 72 months of the follow-up**

351 Changes are expressed in percentage of sensitized children. HDM house dust mite

352



354 **Table 1: Estimated univariate OR of variables at baseline associated to sensitization to inhaled allergens at the end of**
 355 **follow up**

Covariables at baseline	Univariate models		
	Sensitization to inhaled allergens at 5 or 6 years N / N total	OR (CI 95%)	p-value
Eosinophilia level			
Low	94/150	1.00	
High	39/59	1.16 (0.62; 2.18)	0.64
Total IgE level			
Low	75/136	1.00	
High	65/83	2.94 (1.58; 5.47)	0.0007
Atopic Dermatitis score			
SCORAD \leq 15	24/45	1.00	
15<SCORAD \leq 40	69/104	1.72 (0.84; 3.51)	0.13
SCORAD >40	54/80	1.82 (0.86; 3.84)	0.12
Food allergy			
No	123/196	1.00	
Yes	10/13	1.98 (0.53; 7.42)	0.31
Sensitization to food allergens			
No	47/97	1.00	
Yes	100/132	3.32 (1.90; 5.84)	<0.001
Sensitization to food allergens			
No	47/97	1.00	
Single food sentization	31/46	2.20 (1.05; 4.60)	0.035
Multiple food sensitizations	69/86	4.32 (2.22; 8.40)	< 0.001
Sensitization to inhaled allergens			
No	117/189	1.00	
Yes	30/40	1.85 (0.85; 4.00)	0.12

356 Specifying those for the first group awareness / those for all patients. Boldfaced text indicates statistical significance.
 357 Allergen sensitization: specific IgE \geq 0.35kU/L. multiple sensitizations to food allergen is defined as two or more specific allergen sensitizations.
 358

359 **Table 2: Estimated multivariate OR of variables at baseline associated to sensitization to inhaled allergens at the end of**
 360 **follow up**
 361

Covariables at baseline	Multivariate models	
	OR (CI 95%)	p-value
Total IgE level		
Low	1.00	0.27
High	1.52 (0.72; 3.21)	
Sensitization to food allergens		
No	1.00	
Single food sensitization	2.20 (1.01; 4.72)	0.05
Multiple food sensitizations	3.72 (1.68; 8.30)	0.0012

362

363 Allergen sensitization: specific IgE \geq 0.35kU/L. Multiple sensitization to food allergen is defined as sensitization to two or more
 364 specific allergens. Risk factors associated with allergic sensitization to inhaled allergens in the univariate analysis ($p < 0.2$) are
 365 included in the multivariate analysis. Boldface values indicate statistical significance.
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 367
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