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Three peanut-allergic/sensitized phenotypes with gender difference

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HAL Authorization

1 **Three peanut allergic/sensitized phenotypes with gender difference**

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3 **Short title: peanut allergic/sensitized phenotypes**

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32 Jocelyne JUST: involvement in the conception, hypotheses delineation, writing the article and
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34 Chabi Fabrice ELEGBEDE: acquisition, analysis and interpretation of the data, and
35 substantial involvement in its revision prior to submission

36 Antoine DESCHILDRE: involvement in the conception, hypotheses delineation, acquisition,
37 analysis and interpretation of the data, and substantial involvement in its revision prior to
38 submission

39 Denise Anne MONERET-VAUTRIN: involvement in the conception, hypotheses delineation,
40 acquisition, analysis and interpretation of the data, and substantial involvement in its revision
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42 Jean BOUSQUET: interpretation of the data, and substantial involvement in its revision prior
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44 Amélie CREPET: involvement in the conception, hypotheses delineation, acquisition,
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51 **Abstract 293 (300)**

52 **Background:** Peanut allergic reactions are heterogeneous ranging from mild symptoms to
53 anaphylaxis. **Objective:** Identify peanut allergic/sensitized phenotypes to personalize patient
54 management. **Methods:** A combined factor and cluster analysis was used to study the
55 phenotypes of 696 patients diagnosed with peanut sensitization and enrolled in the MIRABEL
56 survey. The method was first applied to the 247 patients with an Oral Food Challenge (OFC).
57 It was then applied to the 449 patients without OFC to confirm the findings in an independent
58 population. **Results:** Three independent clusters emerged from the OFC subgroup. Cluster 1,
59 “*Severe peanut allergy with little allergic multimorbidity*” (123 subjects), had the highest
60 proportion of patients with positive OFC (92%), a medium level of peanut protein inducing a
61 positive OFC (235 mg), lower percentage of allergic multimorbidity (2% asthma plus atopic
62 dermatitis (A+AD), no cases of A+AD + multiple food allergies (MFA)). Cluster 2, “*Severe*
63 *peanut allergy with frequent allergic multimorbidity*” (62 subjects), had a high proportion of
64 patients with positive OFC (85%) with the lowest level of peanut protein inducing a positive
65 OFC (112mg), 89% allergic subjects, 100% with allergic multimorbidity (A+AD) and 84%
66 with A+AD+MFA. Cluster 3, “*Mild peanut allergic/sensitized phenotype*” (62 subjects), had
67 the lowest mean age, the lowest proportion of patients with positive OFC (53%) with a high
68 level of peanut protein inducing a positive OFC (770 mg), a low percentage of allergic
69 multimorbidity (48% A+AD+MFA). The two severe peanut allergy phenotypes were more
70 frequent in girls. The same clusters were found in the subgroup of patients without OFC.
71 **Conclusion & Clinical Relevance:** Besides the classic markers associated with lower
72 threshold doses of OFC (such as SPT and rAra h2), allergic multimorbidity and female gender
73 should also be taken into account to better adapt the progressive dosage of provocation tests.

74

75 **Key words:** asthma, atopic dermatitis, cluster analysis, gender, peanut allergy,
76 multimorbidity.

77 **Abbreviations**

78 Specific immunoglobulin E: sIgE

79 Skin prick test: SPT

80 Atopic dermatitis: AD

81 Asthma: A

82 Allergic rhinitis: AR

83 Multiple Food Allergies: MFA

84 Oral food challenge: OFC

85 **Number of words: 3573 (5000)**

86 **Introduction**

87 Peanut allergy is a common food allergy affecting up to 1.3% of children in Europe¹. Its
88 prevalence is on the increase and this is reflected in an increased prevalence of hospitalization
89 for peanut-induced anaphylaxis in the United States². However, the severity of systemic
90 allergic reactions to peanut is variable and fatal peanut-induced anaphylaxis is rare³.
91 Moreover, a considerable number of children with positive specific immunoglobulin E (sIgE)
92 and positive skin prick test (SPT) are asymptomatic or present a milder clinical picture^{4,5,6,7}.
93 Thus, it is crucial to better detect patients with a severe food allergy phenotype for appropriate
94 follow-up care and management.

95 The diagnosis of peanut allergy in comparison to peanut sensitization is not always easy.
96 The most relevant features to diagnose peanut allergy would appear to be clinical in real life
97 or in provocation tests. Moreover, a small proportion of children with peanut allergy can
98 outgrow their allergy⁸. On the other hand, the severity of the disease can also increase over
99 time. This is illustrated by contradictory results in studies, some of which have previously
100 suggested a relationship between a history of anaphylaxis or severe symptoms and the risk of
101 anaphylaxis upon subsequent exposure and others the opposite^{9,10,11}.

102 Nicolaou et al.¹² found a high rate of false-positive SPT and irrelevant sIgE results for peanut.
103 The threshold level of peanut sIgE or SPT to predict a positive provocation test is unclear^{13,14}.
104 These discrepancies in the current approach to peanut allergy testing could be improved by
105 component-resolved diagnosis which has been extensively explored in this area. In 2004,
106 Koppelman et al.¹⁵ first suggested the importance of the peanut component rAra h 2 in
107 predicting reactivity or tolerance to peanut. More recently, other components of peanut such
108 as rAra h 6, have been found to be associated with the risk of anaphylaxis¹⁶. However, to date,
109 a provocation test remains necessary not only to confirm diagnosis but also to assess the
110 severity of peanut allergy (related to the threshold reactive dose).

111 These features underline the necessity to perform provocation tests to distinguish between
112 peanut sensitized and allergic patients, but this test is at risk of anaphylaxis and time
113 consuming.

114 A novel approach to distinguish patients who present peanut allergic or sensitized phenotypes
115 with different clinical and biological characteristics, is to identify different disease phenotypes
116 by cluster analysis. This statistical approach has never been performed to identify
117 allergic/sensitized phenotypes.

118 The MIRABEL survey is a multicentre survey based on the voluntary participation of peanut-
119 allergic/sensitized patients from Metropolitan France, Belgium and Luxembourg to evaluate
120 the allergic risk in patients with well-characterized peanut allergy or sensitization ¹⁷. It is thus
121 an ideal cohort in which to test the hypothesis that peanut allergic/sensitized phenotypes exist.

122 We set out to define allergic/sensitized phenotypes by unsupervised analysis in a subgroup of
123 patients of the MIRABEL survey who had undergone oral food challenges (OFC) taking into
124 account informative parameters such as clinical symptoms, SPT, sIgE to native and
125 informative epitopes (rAra h 2). To generalize these phenotypes to the entire allergic
126 population, the same analysis was performed in an independent population of patients without
127 OFC.

128 **Material and Methods**

129 *MIRABEL design and inclusion of patients*

130 Between April 2012 and December 2013, allergists were asked to include consecutive
131 patients with suspected peanut allergy. Patients were then classified as “sensitized” on the
132 basis of positive SPT performed with commercial extracts (mean wheal diameter ≥ 3 mm) and
133 sIgE to rAra h 2 (≥ 0.35 kUA/L; ImmunoCAP, Thermofisher, Sweden)¹⁸ without any clinical
134 reaction, or “allergic” based on sensitization (as previously defined) with an allergic reaction
135 to peanut exposure.

136 *Ethics*

137 The study was approved by the French Data Protection Authority (CNIL) (Authorization no.
138 DE-2011-048). All patients or parents signed an informed consent.

139 *Medical questionnaire and oral food challenge*

140 Data were collected by a questionnaire filled in by the allergist after medical diagnosis of
141 peanut allergy and included the following variables (as previously published¹⁹). Briefly:

142 The age at diagnosis of peanut allergy.

143 Symptom severity during real-life exposure was classified into two categories: *mild to*
144 *moderate reactions* (urticaria or angioedema without respiratory symptoms, rash/dermatitis,
145 isolated and mild to moderate gastro intestinal symptoms); or *severe reactions* (anaphylactic
146 shock, laryngeal angioedema, acute asthma, systemic serious reaction (involving two or more
147 organs)²⁰.

148

149 Active allergic comorbidities over [the past year](#), including asthma (A), atopic dermatitis (AD),
150 allergic rhinitis (AR) and multiple food allergies (MFA) [were diagnosed by an experienced](#)
151 [allergist from the patient's medical records](#).

152 SPT were performed using different peanut and food extracts (mainly from Stallergènes,
153 Antony, France). As the MIRABEL survey is observational, the patients were administered
154 the OFC according to the physician's practice either by a single-blind or double-blind
155 placebo-controlled challenge or as an open OFC. For positive OFCs, the reactive cumulated
156 dose, based on objective symptoms only, was expressed in mg of peanut protein equivalent.
157 The OFC was considered negative in the absence of an objective sign for a cumulative dose \geq
158 7 g of peanut.

159 Dietary advice provided by the allergist was recorded as: "strict eviction " if the patient was
160 advised to avoid all products containing peanuts and products with PAL; compared with a
161 combined category of "lax" if the patient was merely advised to avoid products containing
162 peanuts but that PAL products were allowed; and "absent" if the patient was advised that no
163 avoidance was necessary.

164 ***Variable selection for cluster analysis***

165 The variables for statistical analysis were those that reflected physiologic parameters (age at
166 diagnosis and age at time of OFC, gender) and those related to the clinical presentation of
167 peanut allergy such as the allergic/sensitized status, route of exposure that induced reaction
168 (ingestion and/or inhalation and/or contact), the test results (SPT, rAra h 2, OFC) and allergic
169 comorbidities. In case of two highly correlated variables, only the one considered as the most
170 relevant was retained in the analysis. The variables selected for analysis are marked in Table 1

171 by a ‡. Composite variables were used to distinguish patients with one, two or three
172 multimorbidity symptoms: one variable for patients with both A and AD (A+AD), and one for
173 patients with both A+AD and MFA (A+AD+MFA).

174 *Variable reduction and cluster analysis*

175 Phenotype clusters were identified by coupling a factor analysis with a cluster analysis as
176 previously reported by Just et al .¹⁹. A factor analysis for mixed data (categorical and
177 continuous) was first applied to the selected variables to study their associations and identify
178 which variables contributed the most to explaining the variability of the dataset²¹. Factor
179 analysis also makes it possible to reduce the dimension of the dataset to a few principal
180 components. A hierarchical cluster analysis was then applied to these principal components to
181 classify the population into homogeneous groups of peanut allergy severity. The method is
182 based on Ward's minimum variance criterion which minimizes the total within-cluster
183 variance. The distance between individuals was calculated using the Euclidian distance. Thus,
184 variables between the different groups were compared using the one-way ANOVA test for
185 continuous variables and the Chi-squared test for categorical variables. The Kruskal-Wallis
186 and the Fisher's exact tests were respectively used when the required conditions were not
187 respected to perform the ANOVA and the Chi-squared tests. Statistical analyses were
188 performed with the FactoMineR package of R version 3.1.1.

189 **Results**

190 *Description of the population*

191 785 patients were recruited by 70 allergists. Complete information was available for 696
192 patients, and 247 of these had complete OFC results. The variables have been fully described
193 in a previous article about the MIRABEL survey¹⁷.

194 *Variable associations*

195 Factor analysis applied to the OFC subgroup using all selected variables resulted in three
196 principal components explaining 46% of the total variance. The first component was
197 composed of allergic multimorbidity variables. The second component was composed of the
198 age at which the OFC was conducted and the time between diagnosis and the OFC. The third
199 component included SPT, sIgE to rAra h 2 and OFC results. A similar structure was obtained
200 when applying factor analysis to the population without OFC, except that the
201 allergic/sensitized status was also part of the second component and associated with age at
202 diagnosis.

203 *Peanut allergic/sensitized phenotypes of the 247 patients with OFC*

204 Three independent clusters emerged from the application of a hierarchical classification on
205 the three principal components selected from the previous factor analysis.

206 Cluster 1, “*Severe peanut allergy with little allergic multimorbidity*” (123 subjects), had the
207 highest proportion of patients with positive OFC (92%), the highest proportion of severe
208 reactions upon exposure via ingestion (84%), a medium level of peanut protein equivalent
209 inducing a positive OFC (235 mg) associated with a high mean level of rAra h 2 (34kUA/l),
210 and finally a lower percentage of allergic multimorbidity (2% asthma plus atopic dermatitis
211 (A+AD), no cases of A+AD + MFA) (Table 1).

212 Cluster 2, “*Severe peanut allergy with frequent allergic multimorbidity*” (62 subjects), had a

213 high proportion of patients with positive OFC (85%) with the lowest level of peanut protein
214 inducing a positive OFC (112mg) associated with the highest mean level of SPT wheal size
215 (13mm), the highest mean level of rAra h 2 (43 kUA/l) and the highest proportion of severe
216 reactions upon exposure via inhalation. This cluster was characterized by the highest
217 percentage of allergic multimorbidity compared to the two other clusters, 100% (A+AD) and
218 84% A+AD+MFA (Table 1).

219 Cluster 3, “*Mild peanut allergic/sensitized phenotype*” (62 subjects), had the lowest mean
220 disease duration (3.5 years), the lowest proportion of patients with positive OFC (53%) with
221 the highest level of peanut protein inducing a positive OFC (770 mg), a low percentage of
222 allergic multimorbidity (48% A+AD+MFA) and AD only found in a high percentage of cases
223 (95%) (Table 1).

224 ***Peanut allergic/sensitized phenotypes in subgroup of patients without OFC***

225 Clusters of the subgroup without OFC (n=449) are similar to those of the OFC subgroup
226 (n=247), for most parameters and especially for allergic comorbidities (Table 2). The results
227 were consistent even though the statistical significance of some variables decreased slightly.

228 ***Analysis based on gender***

229 Separate cluster analyses were carried out for boys and girls with OFC. These analyses
230 identified the same three clusters as the previous analysis for the boys (Table 3) but only two
231 clusters for the girls (Table 4) i.e. the severe peanut allergic phenotypes called the “*Severe*
232 *peanut allergy with frequent allergic multimorbidity*” and the “*Severe peanut allergy with*
233 *little allergic multimorbidity*”.

234

235 **Discussion**

236 Cluster analysis of the MIRABEL data showed that peanut allergy is a heterogeneous disease.
237 The clustering approach divided the population into two subgroups of severe peanut
238 phenotypes “*Severe peanut allergy with little allergic multimorbidity*” and “*Severe peanut*
239 *allergy with frequent allergic multimorbidity*” and one non-severe subgroup “*Mild peanut*
240 *allergic/sensitized phenotype*”. The severe peanut allergy phenotypes were more frequently
241 encountered in girls.

242 ***Strengths and weaknesses***

243 One strength of this study is that it is a multicenter study performed in large population of 696
244 peanut allergic/sensitized patients recruited by allergists. Moreover, for a large part of this
245 population (almost 250), peanut allergy was diagnosed by OFC, although the reasons for
246 undergoing an OFC or not are not known in this real-life survey. Another strength is that the
247 statistical analyses to identify different phenotypes were conducted by an unsupervised
248 approach with a large range of variables and in a large cohort of patients with severe allergy.
249 The factor analysis was conducted in several steps. A first analysis was performed including
250 all available variables; a second analysis was then conducted excluding variables that were
251 too highly correlated, variables that did not play a large role in explaining the variance, and in
252 combining some variables frequently encountered in patients with multiple food
253 allergies/sensitization. The phenotypes described here remain stable in all the analyses.
254 Moreover, this concordance of three phenotypes (established in patients with and without
255 OFC) highlights the one message of our article, i.e. the importance of multiple comorbidities
256 (especially A+AD or A+AD+MFA) to define a particular phenotype of severe peanut-allergy.
257 One limitation of the study is the different ways in which the OFC was carried out. However,
258 this actually reflects physicians’ daily practices and the OFCs selected for analysis were
259 supported by objective symptoms (for positive OFC) and a high dosage of peanut ingested

260 during OFC (> 7 g of peanut) for the negative test. Similarly, SPTs were not standardized.
261 Another limitation of our study is the heterogeneity of the population, in which patients were
262 probably at different disease stage (for instance, initial diagnosis vs. resolution of peanut
263 allergy). This explains cluster 3 which has the lowest mean disease duration (3.5 years) with
264 the highest proportion of sensitized children. This result is in accordance with the natural
265 history of the disease in which sensitization (more than allergy) is associated with a smaller
266 diameter of the SPT and lower levels of rAra h 2⁸. The clustering algorithms are different
267 when working on the group with OFC and the group without. We consequently analyzed the
268 group with OFC as follows: first using the variables related to the OFC (as presented), and
269 then without the variables related to OFC. Three similar phenotypes were obtained with both
270 methods (data not shown). Therefore, we can conclude that we do not need to have
271 information about OFC to correctly classify a patient into the right cluster. Finally, by our
272 analysis, it was not possible to distinguish at individual level, sensitized or allergic patient,
273 but parameters associated to severe allergic phenotypes (in our cluster analysis) will be taking
274 into account to adapt the schedule of provocation tests.

275

276 ***“Severe peanut allergy with frequent allergic multimorbidity”***

277 This result underlines that allergic multimorbidity (asthma with AD and/or MFA) is
278 associated with a higher reported severity of peanut-induced allergic reactions. Colver et al.
279 showed that asthma was a strongly significant risk factor for severe allergic reactions to food,
280 specifically with peanut²². Bock et al. reported similar findings among 32 fatal cases; all of
281 those for whom medical records were available had a history of asthma²³. Summers et al.²⁴, in
282 a study of 1,094 patients with tree nut and peanut allergies demonstrated that, as well as
283 severe asthma being associated with life-threatening bronchospasm, severe pharyngeal edema
284 was more common in patients with severe AR. They also found that having severe AD was

285 associated with a 3-fold increased risk of becoming unconscious during an acute allergic
286 reaction, thus further highlighting the link between the severity of acute allergic reactions and
287 the severity of co-existing atopic disease. We recently described²⁵, a “*Multiple Allergies and*
288 *Severe Asthma phenotype*” in which 100% of the children had AD and multiple sensitizations.
289 This is very close to the “*Severe peanut allergy with frequent allergic multimorbidity*”
290 phenotype we present here. This phenotype could correspond to the previously described
291 phenotype of AD associated with filaggrin loss-of-function mutations associated to a greater
292 risk of severe asthma²⁶.

293 ***“Severe peanut allergy with little allergic multimorbidity” or the high proportion of patients***
294 ***with severe reaction during OFC had a high level of rAra h 2***

295 This severe phenotype underlines the axis of recombinant rAra h 2 in predicting clinical
296 severity of peanut allergy. rAra h 2 is a heat-stable seed-storage protein and is considered to
297 be the major peanut allergen contributing to peanut sensitization. Peeters et al. looked at
298 whether sensitization to rAra h 1, 2, 3, or 6 can predict the severity of allergic reactions to
299 peanut in a group of 30 patients. They found that patients with severe reactions had a greater
300 SPT response to rAra h 2 and rAra h 6 at low concentrations and to rAra h 1 and rAra h 3 at
301 higher concentrations. They also found that patients with more severe symptoms recognized a
302 greater number of allergens. Sensitization to rAra h 2 plus sensitization to rAra h 1 and/or
303 rAra h 3 was associated with greater severity of reactions²⁷. Peptide microarray
304 immunoassays in a group of 77 patients similarly showed that those with wide epitope
305 diversity were associated with a history of more severe allergic reactions²⁸.

306 ***“Mild peanut allergic/sensitized phenotype” or mild severity of peanut allergy was***
307 ***explained by a high proportion of sensitized patients compared to the other clusters***

308 The subjects in this phenotype were younger at diagnosis, more likely to be sensitized
309 (41.9%), had the lowest positive allergic reaction during OFC, the smallest SPT wheal size,
310 the lowest mean levels of rAra h 2 and a higher percentage of AD (95% of cases). This
311 phenotype could correspond to the current hypothesis that allergic sensitization to food occurs
312 through low-dose cutaneous sensitization²⁹. Many studies suggest^{30,31,32} that late introduction
313 of potential food allergens and cutaneous exposure³³ might be associated with allergy while
314 early oral exposure might contribute to tolerance. It is thus possible that the young children in
315 our mild peanut phenotype could be in the process of developing real peanut allergy in the
316 case of delayed oral exposure.

317 *More females have the severe phenotypes of peanut allergy: a possible gender effect*

318 The food allergy register has already shown an age-dependent gender distribution, with a M/F
319 sex ratio of 0.67 from early adulthood, in contrast to children where the ratio is 1.50³⁴. Similar
320 differences in gender have emerged from several questionnaire-based studies in other
321 countries^{35,36}. This observed age-related gender difference is similar to that reported for
322 asthma, hay fever and atopic disease, suggesting that puberty and the influence of sex
323 hormones may have an important impact on the prevalence of atopic diseases in general³⁷. In
324 the same vein, a survey reporting on severe allergic reactions defined by the necessity of
325 medical care, showed a higher incidence of food allergy in females. Finally, an Australian
326 study has also reported that females outnumbered males in both acute allergic reactions and
327 anaphylaxis³⁸.

328 *Conclusions*

329 Our results underline that, beside the classic markers associated with lower **threshold doses of**
330 **OFC** (such as SPT or rAra h2), allergic multimorbidity and female gender should also be
331 taken into account to better adapt the progressive dosage of provocation tests.

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362 **Conflicts of interest**

363 A Deschildre reports personal consultancy and lecture fees from GSK, MSD, Aerocrine,
364 MEDA, ALK, Novartis, Stallergènes, Chiesi, outside the submitted work.

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367 E Beaudoin reports personal fees from ALK abello SA, MSD, Novartis, outside the submitted
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371 **References**

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- ¹ Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:992-1007.
- ² Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006. *Ann Allergy Asthma Immunol* 2008;101:387-93.
- ³ Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016 ; S0091-6749(15)02991-7.
- ⁴ Burks AW: Peanut allergy. *Lancet* 2008;371: 1538-46.
- ⁵ Wood RA: The natural history of food allergy. *Pediatrics* 2003;111:1631-37.
- ⁶ Patriarca G, Schiavino D, Pecora V, Lombardo C, Pollastrini E, Aruanno A et al. Food allergy and food intolerance. *Intern Emerg Med* 2009;4:11-24.
- ⁷ Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanuts: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125: 191-7.
- ⁸ **Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol* 2015;135:1257-66.**
- ⁹ Summers CW1, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 2008;121:632-8.
- ¹⁰ Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F et al. Italian Society of Pediatric Allergy and Immunology Anaphylaxis' Study Group. Risk factors for severe

pediatric food anaphylaxis in Italy. *Pediatr Allergy Immunol* 2011;22:813-9.

¹¹ Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006;118:466-72.

¹² Nicolaou N1, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-7.

¹³ Nicolaou N, Custovic A. Molecular diagnosis of peanut and legume allergy. *Curr Opin Allergy Clin Immunol* 2011;11:222-8.

¹⁴ Dang TD, Tang M, Choo S, Licciardi PV, Koplin JJ, Martin PE et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol* 2012;129:1056-63.

¹⁵ Koppelman SJ1, Wensing M, Ertmann M, Knulst AC, Knol EF. Relevance of Ara h1, Ara h2 and Ara h3 in peanut-allergic patients, as determined by immunoglobulin E Western blotting, basophil-histamine release and intracutaneous testing: Ara h2 is the most important peanut allergen. *Clin Exp Allergy* 2004;34:583-90.

¹⁶ Otsu K, Guo R, Dreskin SC. Epitope analysis of Ara h 2 and Ara h 6: characteristic patterns of IgE-binding fingerprints among individuals with similar clinical histories. *Clin Exp Allergy* 2015;45:471-84.

¹⁷ Crépet A, Papadopoulos A, Elegbede CF, Loynet C, Ait-Dahmane S, Millet G, et al. MIRABEL: an integrated framework for risk and cost/benefit analysis of peanut allergen. *Regul Toxicol and Pharmacol* 2015;71:178-83.

¹⁸ Astier C, Morisset M, Roitel O, Codreanu F, Jacquenet S, Franck P, et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol*. 2006;118:250-6.

-
- ¹⁹ Deschildre A, Elégbédé CF, Just J, Bruyère O, Van der Brempt X, Papadopoulos A et al. Peanut allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. *Clin Exp Allergy* 2015 Nov 20.
- ²⁰ Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 2001;357:111-5.
- ²¹ Pagès J. Factorial Analysis of Mixed Data. In: Pagès J. *Multiple Factor Analysis by Example Using R*. Boca Raton: CRC Press, 2014; 67-78.
- ²² Colver AF, Nevantaus H, Macdougall CF, Cant AJ. Severe food- allergic reactions in children across the UK and Ireland, 1998– 2000. *Acta Paediatr* 2005;94:689-95.
- ²³ Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
- ²⁴ Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 2008;121:632-8.
- ²⁵ Just J, Saint-Pierre P, Gouvis-Echraghi R, Laoudi Y, Roufai L, Momas I and al. Allergic Asthma Is Not a Single Phenotype. *J Pediatr* 2014;164:815-20.
- ²⁶ Marenholz I, Kerscher T, Bauerfeind A, Esparza-Gordillo J, Nickel R, Keil T, et al. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol* 2009;123:911-6.
- ²⁷ Peeters KA, Koppelman SJ, van Hoffen E, van der Tas CW, den Hartog Jager CF, Penninks AH et al. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin Exp Allergy* 2007;37:108-15.
- ²⁸ Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;113:776-82.

-
- ²⁹ Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
- ³⁰ Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417-23.
- ³¹ Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-91.
- ³² Nwaru BI, Erkkola M, Ahonen S, Kaila M, Haapala AM, Kronberg-Kippilä C et al. Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* 2010;125:50-9.
- ³³ Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348:977-85.
- ³⁴ Namork E1, Fæste CK, Stensby BA, Egaas E, Løvik M. Severe allergic reactions to food in Norway: a ten year survey of cases reported to the food allergy register. *Int J Environ Res Public Health* 2011;8:3144-55.
- ³⁵ Makinen-Kiljunen S, Haathela T. Eight years of severe allergic reactions in Finland; A register-based report *WAO J* 2008;1:184-9.
- ³⁶ Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;63:1418-27.
- ³⁷ Uekert SJ, Akan G, Evans MD, Li Z, Roberg K, Tisler C et al. Sex-related differences in immune development and the expression of atopy in early childhood. *J Allergy Clin Immunol* 2006;118:1375-81.
- ³⁸ Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: A review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;108:861-6.