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Oral Immunotherapy for Hazelnut Allergy: A Single-Center Retrospective Study on 100 Patients

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1 **Title**

2 **Oral immunotherapy for hazelnut allergy: a single-center retrospective study on 100**
3 **patients**

4

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29

30 **Conflicts of interest:**

31 There is no conflict of interest.

32 **Abstract**

33 **Background:** Oral immunotherapy (OIT) protects patients with IgE-mediated food allergies
34 from food-induced allergic reactions due to accidental exposure and may improve their
35 quality of life. This approach has never been evaluated for hazelnut, a major cause of food
36 allergy in Europe.

37 **Objective:** We sought to determine the proportion of hazelnut-desensitized patients after 6
38 months of OIT and to identify predictors of successful desensitization.

39 **Method:** In a retrospective single-center study, we included patients under 18 years of age
40 who underwent at least 6 months of hazelnut OIT for IgE-mediated allergy, defined by
41 history of hypersensitivity reaction after hazelnut ingestion, positive hazelnut skin prick test
42 (SPT) or specific IgE, and positive double-blind, placebo-controlled food challenge (DBPCFC).
43 Patients able to tolerate 1635 mg of hazelnut protein (approximately 8 hazelnuts) were
44 considered to be hazelnut desensitized. We determined the proportion of desensitized
45 patients after 6 months of OIT, searched for associations between baseline variables and
46 successful desensitization, and estimated the frequency and severity of OIT-related adverse
47 reactions.

48 **Results:** One hundred patients were included (64% male, median age 5 years). History of
49 severe reactions was noted in 7% of cases. At 6 months, the proportion of desensitized
50 patients was 34% (95%CI: 25-44). The median eliciting dose (defined as the amount of
51 hazelnut protein provoking a hypersensitivity reaction during the DBPCFC) increased from
52 106 mg [IQR: 51-249] at baseline to 523 mg [IQR: 190-1635] after 6 months of OIT
53 ($p < 0.0001$). With longer therapy, the proportion of desensitized patients increased. Using

54 multivariate analysis, successful desensitization was associated with older age (OR: 1.5,
55 95%CI: 1.2-2.2), smaller hazelnut SPT wheal diameter (OR: 0.61, 95%CI: 0.4-0.8), lower
56 hazelnut specific IgE level (OR: 0.86, 95%CI: 0.72-0.98), and absence of cashew allergy (OR:
57 0.42, 95%CI: 0.12-0.64). Adverse reactions occurred in 30% of patients; none were severe.

58 **Conclusion:** In a cohort of 100 patients aged 3-9 years, our results show for the first time
59 that hazelnut OIT is associated with hazelnut desensitization and may be safe in the majority
60 of patients undergoing this therapy.

61

62 **Highlights box :**

63 **1/ What is already known about this topic ?**

64 Oral immunotherapy raises the allergen threshold in children with IgE-mediated allergy to
65 peanut, cow's milk and eggs. However, this approach has never been evaluated for hazelnut,
66 a major cause of food allergy in Europe.

67

68 **2/ What does this article add to our knowledge ?**

69 This is the first study to show that hazelnut oral immunotherapy may lead to desensitization
70 and increase the allergen threshold safely in IgE-mediated allergic children.

71

72 **3/ How does this study impact current management guidelines ?**

73 This study provides initial evidence for the use of hazelnut immunotherapy in IgE-mediated
74 allergic children. These findings may be applied to design of a randomized controlled clinical
75 trial.

76

78 **ABBREVIATIONS**

79

DBPCFC	Double-blind, placebo-controlled food challenge
ED	Eliciting dose
EOE	Eliciting dose
FA	Food allergy
OFC	Open food challenge
OIT	Oral immunotherapy
sIgE	Specific immunoglobulin E
SPT	Skin prick test

80

81

82

83 **Introduction**

84 In Europe, the prevalence of self-reported food allergy (FA) is up to 5.9%¹, affecting 17
85 million people, of whom 3.5 million are under 25 years of age. In children, FA is a major
86 cause of anaphylaxis, a severe life-threatening allergic reaction. While hazelnut is not the
87 most common cause of FA in the United States, it is the one most frequently implicated in
88 Europe^{2,3} where it is widely consumed in food products. Indeed, hazelnut accounts for 9.3%
89 of FA cases in European adults⁴ and is the third leading cause of early food sensitization in
90 the pediatric population after cow's milk and egg³. Hazelnut could be responsible for 5% of
91 food-induced anaphylactic events, less commonly than cow's milk (29%) and hen's eggs
92 (25%), and more commonly than peanut (4%)⁵. Moreover, FA is a chronic condition with only
93 9% of patients outgrowing tree nut allergy⁶.

94 The current management of FA consists of strict avoidance of the allergenic food, provision
95 of an emergency management plan in the event of an accidental exposure or reaction, and
96 prescription of adrenaline auto-injectors in the case of anaphylaxis⁷. In some patients, the
97 fear of accidental exposure may lead to impaired health-related quality of life and food
98 neophobia, i.e. fear of unfamiliar food⁸. Despite patient education programs and
99 improvement in food labeling, the rate of accidental ingestion remains high, with 25 to 47%
100 of patients having an allergic reaction⁹⁻¹¹.

101 Quality of life and safety (protection from severe or life-threatening reactions to unintended
102 exposures) are essential goals for the treatment of patients with FA. The issues of food-
103 related anxiety, dietary restriction and social limitations must also be addressed^{12,13}. Oral
104 immunotherapy (OIT), developed as a means to achieve desensitization, involves regular
105 ingestion of small amounts of the culprit food. This strategy has been shown to be effective
106 in raising the allergen threshold dose with demonstrated safety in children with IgE-

107 mediated FA to peanut^{14,15}, cow's milk¹⁶ and eggs¹⁷. We report here the proportion of
108 hazelnut desensitized patients and predictors of successful desensitization in children who
109 have undergone an OIT program for hazelnut.

110

111 **Methods**

112 **Study population**

113 We conducted a single-center retrospective study in an academic hospital center. All
114 patients who received 6 months of hazelnut OIT were considered for inclusion. Inclusion
115 criteria were as follows: 1) age < 18 years, 2) IgE-mediated hazelnut allergy defined by
116 convincing history of hazelnut hypersensitivity, positive hazelnut skin prick test (SPT) wheal
117 diameter > 3 mm and/or specific IgE (sIgE) > 0.35 kUA/L, and a positive double-blind,
118 placebo-controlled food challenge (DBPCFC), 3) participation in at least 6 months of a
119 hazelnut OIT protocol, and 4) performance of an open food challenge (OFC) after 6 months
120 of hazelnut OIT. Exclusion criteria included: 1) age > 18 years, 2) interruption of OIT protocol
121 during first 6 months, 3) absence of OFC at 6 months, and 4) lack of consent to be included
122 in the study (Figure 1).

123 The study was approved by our institutional review board, the research and ethics
124 committee of the Catholic Institute of Lille Hospital Group and reported to the National
125 Commission of Informatics and Freedoms. Both parents and children received written
126 information and agreed to the use of their data.

127 Socio-demographic, clinical and biological data at baseline and after 6 months of OIT were
128 collected. OIT-related side effects after 6 months of OIT were gathered at the time of
129 inclusion using a standard homemade survey (Supplemental text E1).

130 **Procedures**

131 *Oral food challenge*

132 A DBPCFC was performed at the time of diagnosis and an OFC was performed after 6 months
133 of OIT. Except for placebo administration, the protocol was the same for both challenges,
134 with hazelnut or placebo given in boiled apple as a matrix. During the DBPCFC, patients

135 received ground hazelnut or placebo on two different days in randomized order. The
136 hazelnut dose escalation protocol is detailed in a supplemental data appendix (Table E1). In
137 summary, the dose started at 0.7 mg of hazelnut protein. Then, increasing doses (twice the
138 cumulative dose) were administered every 20 minutes to a maximum cumulative dose of
139 1635 mg or until the occurrence of a hypersensitivity reaction. In the event of an allergic
140 reaction, the DBPCFC was stopped and if necessary, appropriate treatment was
141 administered. The dose that triggered a hypersensitivity reaction was designated the
142 eliciting dose (ED).

143 *Hazelnut OIT*

144 As part of standard practice in our center, hazelnut OIT was offered to all patients with a
145 proven IgE-mediated hazelnut allergy, unless there was a contraindication (uncontrolled
146 asthma or inability to demonstrate compliance) or unwillingness to follow an OIT protocol.
147 Ground hazelnut was administered daily. The initial dose of hazelnut OIT was 1/10th of the
148 ED, then the doses were increased monthly without exceeding half of baseline ED. For
149 patients not desensitized at 6 months, a new dose escalation program was initiated based
150 on the ED of the 6-month OFC. The same schema was repeated every 6 months until
151 desensitization was achieved. When patients demonstrated tolerance of a cumulative dose
152 of 1635 mg hazelnut with no reaction, they were considered desensitized, and subsequently
153 continued on a maintenance dose of two whole hazelnuts (416 mg hazelnut protein) three
154 times a week. In case of acute intercurrent illness occurring during OIT, the hazelnut dose
155 was not given for 5 days to prevent adverse reactions. The OIT protocol is detailed in a
156 supplemental data appendix (Table E2). Patients and parents received a written protocol, a
157 personalized action plan, and an emergency kit containing an adrenaline auto-injector, the
158 use of which was explained during a therapeutic education session.

159 **Outcome**

160

161 The primary outcome was the proportion of desensitized patients after 6 months of OIT.

162 Desensitization was defined as no reaction during hazelnut OFC with a cumulative dose of

163 1635 mg, roughly equal to 8 hazelnuts, and an amount of hazelnut unlikely to be accidentally

164 ingested.

165 Secondary outcomes were change of ED and SPT wheal diameter after 6 months of OIT, any

166 association between successful desensitization at 6 months and baseline variables,

167 frequency and type of non-severe and severe adverse reactions, the latter being defined by

168 the need for use of adrenaline, hospitalization or death.

169 Desensitization was also recorded in subgroups of patients who continued OIT for 12, 18 or

170 24 months (Figure E1).

171 **Statistical analysis**

172 Characteristics of the study population were described using median and interquartile range

173 (IQR) for quantitative variables, and number (percentage) for qualitative variables.

174 Comparisons between baseline and 6-month values were assessed using a non-parametric

175 Wilcoxon rank sum test.

176 To assess associations between hazelnut desensitization, as the dependent variable and

177 baseline patient characteristics, univariate and multivariate logistic regression analyses were

178 performed. For multivariate analysis, baseline variables associated with desensitization at 6

179 months in univariate analysis with a p-value $\geq 0,2$ were introduced into a multivariate logistic

180 regression model. The suitability of the model was checked with both the Hosmer-

181 Lemeshow test and the model's predictive quality. Results are expressed as odds ratio (OR)

182 and 95% confidence interval (CI). The threshold for statistical significance was 0.05.

183 Statistical analyses were performed with R software (version 3.4.2.).

184 Results

185 Baseline characteristics

186 Among the 172 hazelnut-allergic patients referred to our Center between January 2012 and
187 January 2017, 168 started a hazelnut OIT program and 100 were included in the study (64%
188 male; median age 5 years [IQR: 3–9]) (Figure 1). The main reason for non-inclusion was
189 delayed 6-month OFC (n=59) due to schedule constraints (n=49), infection (n=9) and asthma
190 exacerbation (n=1). Baseline characteristics are shown in Table 1. Comorbidities included
191 asthma (56%), atopic dermatitis (64%) and allergic rhinitis (31%). Patients' hazelnut-related
192 hypersensitivity reactions included urticaria (32.6%), angioedema (35.5%), laryngeal edema
193 (4.9%), anaphylaxis (2%), or gastrointestinal symptoms with vomiting and abdominal pain
194 (4.9%). In 20% of patients, hazelnut allergy was suspected because of hazelnut sensitization
195 discovered during assessment of atopic dermatitis in patients who had never eaten hazelnut
196 and was confirmed by a positive DBPCFC. The median SPT wheal diameter was 10 mm [IQR:
197 7–12], the median sIgE for hazelnut was 5.5 kUA/l [IQR: 1.7–20.9], *Cor a 1* was 0 kUA/l [IQR:
198 0–0.5], *Cor a 9* was 1.75 kUA/l [IQR: 0.53–3.9] and *Cor a 14* was 2.53 kUA/l [IQR: 0.45–13.4].
199 The median baseline ED was 106 mg [IQR: 51–249] of hazelnut protein (equivalent to half a
200 hazelnut). According to the Sampson classification¹⁸, the severity of the allergic reaction
201 occurring during the baseline DBPCFC was grade 1 in 77%, grade 2 in 22% and grade 3 in 1%
202 of patients.

203 Aero-allergen sensitization was found in 72 of the 89 patients tested (81%) against house
204 dust mites (63%), birch pollen (19%), and other pollens (45%). A food allergen co-
205 sensitization was found in 61% of the patients including sensitizations to peanut (28%) and
206 to tree nuts with a predominance of cashew (31%) and pistachio (24%).

207

208 **Proportion of hazelnut-desensitized patients at 6 months of OIT**

209 After 6 months of OIT, the proportion of desensitized patients (absence of allergic reaction
210 after a cumulative dose of 1635 mg hazelnut protein during OFC) was 34% (95%CI: 25-44).
211 The median ED at 6 months was 523 mg [IQR: 190–1635] hazelnut protein (equivalent to 2.5
212 hazelnuts), which was an average increase of 417 mg [IQR: 139–1386] from baseline
213 ($p < 0.0001$). For the 66 non-desensitized patients at 6 months, the median ED was 259 mg
214 [IQR: 106-523] (equivalent to 1 hazelnut). The median SPT wheal diameter was 5.5 mm [IQR:
215 2–10] after 6 months of OIT, an average decrease of 5 mm [IQR: 2–7] from baseline. Data
216 from the 59 subjects who had a delayed 6-month OFC are available in a supplemental
217 appendix (Table E3).

218 **Baseline variables associated with hazelnut desensitization at 6 months**

219 In univariate analysis, desensitization to hazelnut was associated with older age, higher
220 baseline ED, smaller SPT wheal diameter, lower hazelnut and Cor a 14 sIgE, non-severe
221 hypersensitivity reaction during DBPCFC, no occurrence of side effect, and the absence of
222 allergy to cashew and pistachio. In multivariate analysis, variables associated with
223 desensitization were older age, smaller baseline SPT wheal diameter, lower hazelnut sIgE
224 level and absence of cashew allergy (Table 2).

225 **Side effects**

226 Seventy-six patients answered the survey about OIT side effects. Among them, 70% had no
227 side effects ($n=53$) and 30% had at least one non-severe side effect (urticaria 6.6%, oral
228 angioedema 1.3%, gastrointestinal symptoms including abdominal pain and nausea 23.7%).
229 No patient developed eosinophilic esophagitis (EoE) or symptoms suggestive of EoE. No
230 serious side effects were reported. The absence of side effects was associated with
231 desensitization at 6 months of OIT in univariate analysis (OR: 1.7, IC95%: 1.2–1.9) (Table E4).

232 **Discussion**

233 Our results show that in a population of young hazelnut-allergic patients, 6 months of
234 hazelnut OIT was associated with the ability to tolerate 1635mg of hazelnut protein in one-
235 third of patients. Our findings also show that baseline predictors of successful
236 desensitization were older age, smaller SPT wheal diameter, lower level of hazelnut sIgE, and
237 absence of cashew allergy. Finally, in our study, hazelnut OIT was not associated with severe
238 reactions.

239 There is currently no cure for FA, and OIT is not intended to be curative. Raising the reactive
240 threshold to the allergenic food is a key outcome of this treatment. Standard prevention of
241 allergic reactions depends upon strict avoidance of hazelnut, including hazelnut that may be
242 a hidden ingredient in foods. Avoidance is often complicated by inconsistent food labeling
243 and variable advice from food providers and manufacturers^{9,11}. Fear of accidental ingestion,
244 severe reactions and death drives down quality of life, limits social activity and contributes
245 to development of behavioral disorders⁸. There is no established threshold for OFC that
246 characterizes desensitization or true tolerance. For evaluation of hazelnut OIT efficacy, we
247 chose a cumulative challenge dose of 1635mg hazelnut protein, as this quantity is equivalent
248 to 8 whole hazelnuts, which is not an amount that is likely to be ingested inadvertently. A
249 similar definition of desensitization was previously proposed in a randomized controlled trial
250 evaluating the efficacy of OIT in peanut allergy¹⁴. In our study, more than one-third of the
251 patients tolerated a challenge with 1635mg hazelnut protein after 6 months of OIT. Patients
252 who were not considered desensitized (66%) (i.e. could not tolerate a challenge with 1635
253 mg of hazelnut protein) had at least doubled their baseline ED at 6 months (median ED: 259
254 mg (equivalent to 1 whole hazelnut) [IQR: 106-523]). This is a clinically relevant increase in
255 hazelnut tolerance, and may indicate protection from accidental exposures to small amounts

256 of hazelnut that can occur in food products. After the treatment, patients can eat quantities
257 of hazelnuts, above the levels present in contaminated meals, allowing them to eat more
258 freely and enjoy a reduction in social restrictions.

259 Stopping OIT may lead to loss of desensitization and return to the previous threshold dose
260 reactivity¹⁹. In one study of peanut allergy, 42% of patients lost the tolerance induced by
261 peanut OIT after 8 weeks of a strict elimination diet⁹. For this reason, we encourage our
262 patients to continue hazelnut consumption indefinitely. It is probable that long-term
263 hazelnut protein ingestion will be needed to provide continued protection from accidental
264 exposure. We found in a sub-group analysis that long-term hazelnut OIT increases the rate
265 of desensitization success, even in patients who were not desensitized after 6 months of OIT
266 (Figure E1).

267 Several studies have shown that age influences the acquisition of food tolerance during an
268 OIT protocol. In the STOP II study evaluating the effectiveness of peanut OIT, older age was
269 associated with failure of desensitization in a population with a median age of 12.4 years¹⁴.
270 In contrast, our results found older age to be associated with successful hazelnut OIT in a
271 younger population with a median age of 5 years. Altogether, these results suggest that the
272 ideal age range to start OIT could be between 5 and 12.4 years. This would be consistent
273 with the Burks' study showing no association between age and successful egg OIT in a
274 population with a median age of 7 years¹⁷.

275 Allergic comorbidities such as asthma and atopic dermatitis characterize a particular
276 phenotype of severe FA²⁰, but are not associated with failure of OIT. Consistently, in our
277 study, there was no association between FA comorbidities and successful desensitization,
278 provided that patients with uncontrolled asthma were not eligible for OIT²¹. Finally, a small
279 SPT wheal diameter and a low sIgE level are independent biomarkers of successful OIT, as

280 shown in our results and in accordance with results from studies of peanut²² and cow's milk
281 OIT¹⁶. It was notable that in our study, the profile of sensitization to recombinant hazelnut
282 allergens did not predict the outcome of hazelnut desensitization after 6 months of OIT. In
283 particular, a higher level of Cor a 14 IgE, which is associated with severe anaphylactic
284 reaction^{23,24}, was not associated with desensitization failure. We also found in our study that
285 cashew allergy was related to unsuccessful desensitization after 6 months of OIT. Cashew
286 has been shown to cross react with hazelnut²⁵ and to produce severe hypersensitivity
287 reactions²⁶. We therefore assume that the profile of IgE sensitization underlying the
288 hazelnut-cashew cross-allergy is associated with poorer tolerance to OIT leading to hazelnut
289 desensitization failure.

290 Finally, while a retrospective design and recall bias may have limited our ability to assess the
291 rate of adverse events, our results show that hazelnut OIT is safe. Reported side effects,
292 which occurred in less than one-third of patients, were benign and easily managed at home.
293 As in our study, long-term buildup protocol for OIT appears to be safe¹⁹. Although the
294 literature has reported contrasting data on the frequency and severity of food OIT-related
295 side effects, protocols using slow dose escalation and personalized regimens (doses adjusted
296 based on the patient's reactive threshold) are usually associated with benign side effects²⁷⁻
297 ²⁹. Furthermore, patients were carefully selected for their ability to follow the OIT protocol
298 (3 patients were excluded because of their inability to demonstrate compliance) and were
299 systematically enrolled in education programs. Some studies have highlighted the
300 occurrence of chronic gastrointestinal symptoms or EoE during OIT³⁰. In our study, there
301 were no patients who developed EoE. Educating patients undergoing OIT protocol to avoid
302 and recognize cofactors for reactions to foods, such as stress, certain medications

303 (nonsteroidal anti-inflammatory drugs, codeine), alcohol, rigorous exercise, and fever can
304 enhance the safety and tolerability of OIT^{31,32}.

305 Interpretation of these findings is limited by our single-center study population. In addition,
306 the population included in the study corresponds to 58% of the hazelnut allergic patients
307 followed in our center. These results therefore may not be generalizable. The main strength
308 of our study is that it provides the first descriptive data on 6-month hazelnut OIT in a large
309 population of children and identifies cashew sensitization as a potential predictor of
310 unsuccessful hazelnut desensitization.

311 In conclusion, our results suggest that hazelnut OIT may be effective and safe in children
312 with IgE-mediated FA to hazelnut. There is a need for randomized trials to confirm the
313 efficacy, safety, feasibility, and ideal protocol of hazelnut OIT and prospective long-term
314 tolerance monitoring studies.

315

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Figure legend

Figure 1: Flow chart

Figure 1: Flow chart

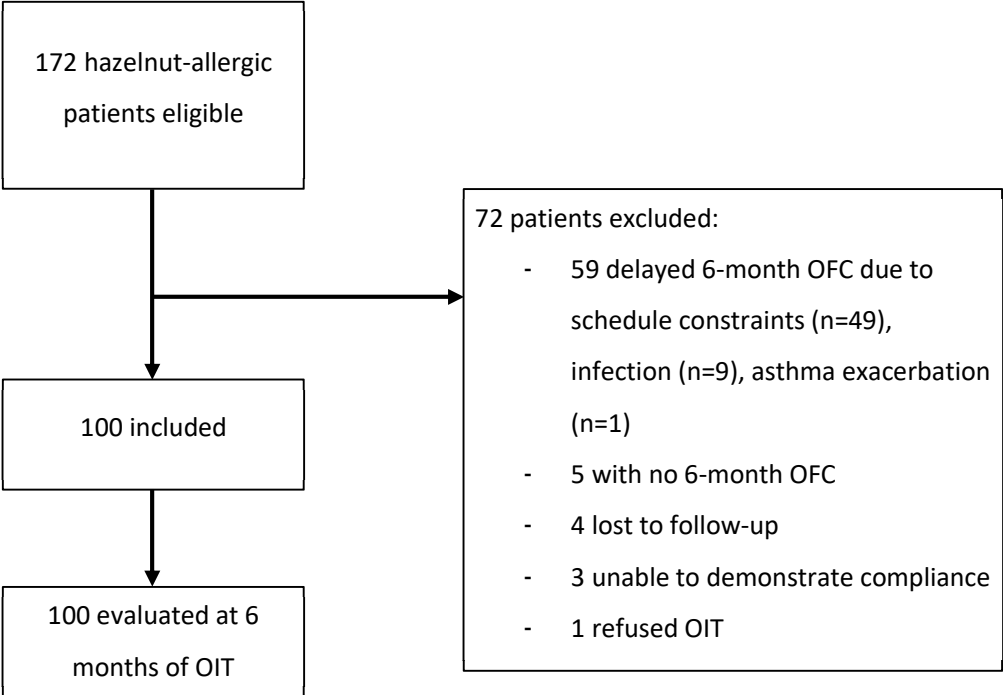


Table 1: Baseline clinical and biological characteristics

Variable	n	Value
Median age [IQR] (years)	100	5 [3-9]
Males n (%)	100	64 (64%)
Comorbidities	100	
Asthma n (%)		56 (56%)
Atopic dermatitis n (%)		64 (64%)
Allergic rhinitis n (%)		31 (31%)
History of hazelnut hypersensitivity n (%)	80	80 (80%)
Urticaria n (%)		33 (32.6%)
Gastrointestinal n (%)		5 (4.9%)
Angioedema n (%)		36 (35.5%)
Laryngeal edema n (%)		5 (4.9%)
Anaphylaxis n (%)		2 (1.97%)
Atopic Dermatitis assessment	20	20 (20%)
Sensitization to aero-allergens	89	
House dust mites n (%)		56 (62.9%)
Birch pollen n (%)		17 (19.1%)
Other pollens n (%)		40 (44.9%)
Sensitization to trophallergens	100	
Peanut n (%)		28 (28%)
Cashew n (%)		31 (31%)
Pistachio n (%)		24 (24%)
Nuts n (%)		9 (9%)
Pecan nuts n (%)		7 (7%)
Brazil nuts n (%)		3 (3%)
Macadamia nuts n (%)		3 (3%)
Egg n (%)		11 (11%)
Wheat n (%)		1 (1%)
Median wheal diameter of hazelnut SPT [IQR](mm)	94	10 [7-12]
Median hazelnut specific IgE [IQR] (kUA/L)	90	5.5 [1.7-20.9]
Median Cor.a.1 specific IgE [IQR] (kUA/L)	78	0 [0-0.5]
Patients with positive Cor.a.1 IgE (%)		29%
Median Cor.a.8 specific IgE [IQR] (kUA/L)	75	0 [0-1.52]
Patients with positive Cor.a.8 IgE (%)		32%
Median Cor.a.9 specific IgE [IQR] (kUA/L)	76	1.75 [0.53-3.9]
Patients with positive Cor.a.9 IgE (%)		83%
Median Cor.a.14 specific IgE [IQR] (kUA/L)	77	2.53 [0.45-13.4]
Patients with positive Cor.a.14 IgE (%)		83%

Median ED [IQR] (mg of hazelnut protein)	100	106 [51-249]
Stage of severity of the elicited reaction	100	
1 n (%)		77 (77%)
2 n (%)		22 (22%)
3 n (%)		1 (1%)

SPT: skin prick test; ED: eliciting dose

Table 2: Baseline variables associated with hazelnut desensitization at 6 months of OIT in univariate and multivariate analysis

Variables	Univariate analysis OR [95%CI]	Multivariate analysis OR [95%CI]
Age at diagnosis <i>n=100</i>	1.1 [1-1.2]	1.5 [1.2-2.2]
Male <i>n=100</i>	1 [0.44-2.5]	
Severity of hazelnut allergy reaction <i>n=100</i>	1 [0.6-1.9]	
Asthma <i>n=100</i>	0.69 [0.3-1.6]	
Atopic dermatitis <i>n=100</i>	1 [0.44-2.5]	
Allergic rhinitis <i>n=100</i>	1.7 [0.68-4]	
Sensitization to aero-allergens <i>n=89</i>		
House dust mites	0.85 [0.35-2.1]	
Birch pollens	1.7 [0.56-4.9]	
Other pollens	1 [0.43-2.5]	
Sensitization to trophallergens <i>n=100</i>		
Peanut	1.1 [0.43-2.7]	
Cashew	0.19 [0.053-0.56]	0.42 [0.12-0.64]
Pistachio	0.21 [0.046-0.67]	
Other nuts	0.88 [0.31-2.4]	
Baseline wheal diameter of hazelnut SPT <i>n=94</i>	0.66 [0.53-0.78]	0.61 [0.4-0.8]
Hazelnut specific IgE <i>n=90</i>	0.98 [0.97-0.99]	0.86 [0.72-0.098]
Cor a 14 IgE <i>n=77</i>	0.94 [0.87-0.99]	
ED <i>n=100</i>	2.7 [2.7-2.7]	
Grade 1 of severity during the baseline DBPCFC <i>n=100</i>	0.13 [0.021-0.5]	

SPT: skin prick test; ED: eliciting dose; DBPCFC: double blind, placebo-controlled food challenge