

Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life

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Summary

Background The MIRABEL survey is an observational study on peanut allergy in France, Belgium and Luxemburg. The objectives are to provide data on a large population, to analyse the consumer behaviour, to study the presence of peanut traces in pre-packed foods with/without precautionary allergen labelling (PAL), and to combine these data to quantify allergic risk and produce a cost/benefit analysis. This paper reports a real-life observatory of 785 patients (< 16y: 86%): medical characteristics, eliciting doses (ED) in real life and in oral food challenges (OFC), factors associated with severe reactions, allergist dietary advice and patients' anxiety regarding their allergy.

Methods Age and symptoms at diagnosis, route of exposure, comorbidities, allergy tests, ED (OFC/real life; mg peanut protein), dietary advice about PAL, and anxiety score were recorded.

Results Median age was 3 years; 85% were declared allergic. Severe/potentially severe reactions were reported in 30% of the allergic patients: serious systemic reaction (15%), laryngeal angioedema (8%), shock (4%) and acute asthma (3%); 66% had atopic dermatitis, 58% asthma. Median ara h 2 sIgE level was 11.5 kUA/L. Of the 278 OFCs, 225 were positive (median ED: 67.3 mg). Real-life ED was < 100 mg in 44.3%. Severe reactions were significantly more frequent in teenagers and adults ($P = 0.004$), asthmatic patients ($P = 0.033$), and patients who reacted to inhalation ($P < 0.001$). No significant association was found for OFC ED or ara h 2 sIgE. Factors associated with strict avoidance advice including PAL were OFC ED < 100 mg ($P < 0.001$), but not severe reaction history ($P = 0.051$) or asthma ($P = 0.34$). Anxiety was significantly associated with strict avoidance ($P < 0.001$).

Conclusion and clinical relevance Severe/potentially severe reactions, allergic comorbidities, and low EDs in real life are frequent in peanut-allergic patients. Asthma, teenage/adulthood and reaction to inhalation are associated with severe symptoms. PAL and criteria guiding dietary advice need to be improved.

Keywords diet, peanut allergy, real life, risk factor, severe reactions

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Introduction

Peanut allergy is one of the most frequent food allergies (FA), with an overall estimated prevalence of 0.4%

in Europe, and 0.3% to 0.75% in France [1, 2]. It is characterized by the risk of severe reactions, potentially fatal, which occur mainly after accidental ingestion. Factors associated with severe reactions have already

been identified [3, 4]. Mandatory allergen labelling has improved the safety of food for peanut-allergic patients. In contrast, precautionary statements relating to potential contamination during food production are not currently regulated by legislation. Only a few published reports deal with the presence of peanut traces by contamination in food, the advice provided by allergists with regard to precautionary allergen labelling (PAL), and peanut-allergic consumer behaviour [5, 6].

The MIRABEL project was conceived by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in partnership with the French National Institute for Agricultural Research (INRA) and the Allergy Vigilance Network (www.allergyvigilance.org). The objectives and the methods of the MIRABEL survey have been previously published by Crepet et al. [7]. Briefly, the aims of this observational study were: firstly, to provide medical data in real life on a large population of peanut-allergic or sensitized patients; secondly, to analyse their consumer behaviour; and finally, to study the presence of peanut traces in pre-packed foods consumed by the patients. All these data will then be combined to quantify allergic risk and produce a cost/benefit analysis.

The aim of the current paper is to report a real-life observatory of 785 peanut-allergic or sensitized patients, i.e. medical characteristics, eliciting dose in real life and in oral food challenges (OFC), factors associated with severe reactions in real life, allergist dietary advice regarding PAL and finally patients' anxiety regarding their allergy.

Methods

Study design and population

The MIRABEL study is an observational multi-centre survey based on the voluntary participation of patients from Metropolitan France, Belgium and Luxembourg, recruited from April 2012 to December 2013 during visits to their allergists (either office- and/or hospital-based). The 70 allergists who participated in the recruitment were affiliated to the Allergy Vigilance Network, had practices throughout all the regions and were representative of the medical practice of all the members of the network (76% office-based and 24% hospital-based). All the recruited patients were sensitized to peanut (wheal diameter of skin prick test (SPT) ≥ 3 mm and/or peanut-specific IgE ≥ 0.35 kUA/L). Allergic patients were those who reported a clear allergic reaction to peanut at their first visit to the allergist. Patients without any previous clinical reaction in real life at the time of the first visit and before the OFC (if performed) were considered to be sensitized. The study was approved by the French Data Protection Authority

(CNIL) (Authorization no. DE-2011-048). All patients or parents signed an informed consent.

Data collection

An anonymized standard medical questionnaire was completed by the allergists. For all the patients, the age at diagnosis of allergy or sensitization to peanut (first visit) and the age at data collection (medical questionnaire) were recorded. For allergic patients, the following data were also recorded: description of the accidental reaction reported at the first visit (the most severe reaction if the patient had a history of more than one previous reaction), exposure route, type and amount of food triggering the accidental allergic reaction in real life when known by the patient or parents; allergic comorbidities: atopic dermatitis (AD), asthma, allergic rhinitis, associated tree nut allergy/sensitization, other FAs; results of the allergy tests; and dietary advice given by the allergist.

The consumption questionnaire [7] was completed by the patient or their parents at home and comprised 11 questions about anxiety adapted from the Food Allergy Quality of Life Questionnaire (FAQLQ) [8–10]. A score summarizing this information was then calculated following a method inspired from the SF-36 health effect questionnaire [11]. To do this, an exploratory factor analysis for qualitative variables was performed and highlighted four principal components of anxiety related to: (i) outdoor consumption, (ii) PAL, (iii) inadvertent peanut consumption and risk of a severe allergic reaction and (iv) peanut allergy in general. The four types of response to each question (not worried, a little, a lot, more than a lot) were attributed a value of 0, 33, 66 and 100 respectively. We then calculated the mean score of each principal component. Finally, the overall anxiety score was calculated from the mean of the four principal component scores and ranged from 0 to 100.

Methods of analysis

For the age at the diagnosis and at the OFC, patients were divided into four groups: younger than 6 years (preschool age), 6–12 years (school age), 12–16 years (teenage), older than 16 years (adults).

Severe or potentially severe reactions were: anaphylactic shock, laryngeal angioedema, acute asthma, and serious systemic reaction (involving two or more organs). Non-severe reactions were: rash/dermatitis, urticaria, subcutaneous angioedema, oral allergy syndrome, or isolated mild gastro-intestinal symptoms.

The exposure routes were ingestion and/or inhalation and/or cutaneous contact. Reactions to inhalation were those reported by the patients without ingestion or

contact, but with the presence of peanut in the indoor environment. A patient could have reacted by more than one route.

When the amount of ingested food that elicited the accidental reaction was known (peanut, Curly®-brand snacks, sweets, snacks, others), the amount (mg) of peanut protein was estimated using the Ciqua Table on food composition [12] and considered as a proxy of the eliciting dose (ED) in real life.

The data recorded for the allergy tests were: (i) wheal diameter of the SPT for peanut, positive codeine control and negative saline control, expressed in mm; (ii) level of peanut sIgE and ara h 2 sIgE expressed in kUA/L (immunoCAP system, Thermofisher, Uppsala, Sweden). The population was classified according to the 95% positive cut-off points for peanut sIgE and SPT wheal diameter to predict allergy, ≥ 14 kUA/L and ≥ 8 mm respectively [13, 14]. The level of ara h 2 sIgE was compared to two cut-offs, both of which have been associated with the diagnosis of peanut allergy: 0.23 kUA/L validated in 166 French allergic patients (sensitivity: 93%; specificity: 96%) [15] and 0.55 kUA/L validated in 81 English school-aged children (sensitivity: 93%; specificity: 100%) [16]; (iii) OFC: date, type (single-blind, double-blind placebo-controlled, or open challenge), ED and cumulative dose if the OFC was negative [17]. The OFC was considered negative in the absence of an objective sign for a cumulative dose ≥ 7 g of peanut. OFC was considered incomplete in the absence of reaction at a cumulative dose < 7 g of peanut. The ED was defined as the lowest cumulative dose of roasted crushed peanuts causing an objective reaction, converted in mg of peanut protein.

Dietary advice provided by the allergist was recorded as: 'strict' if the patient was advised to avoid all products containing peanuts and products with PAL; 'lax' if the patient was merely advised to avoid products containing peanuts but that PAL products were allowed; and 'absent' if the patient was advised that no avoidance was necessary.

Statistical analysis

The characteristics of the MIRABEL population were expressed as percentages or median values with interquartile range (IQR). Patients were compared for the following parameters: age at the time of the first visit, and age at the time of OFC, severity of the accidental allergic reaction reported at the first visit, exposure routes, anxiety score, and dietary advice. All comparisons were tested using R version 3.1.1 (<http://www.r-project.org>) with a significance level of 0.05. For continuous variables of the different groups, medians were compared using a median test, which is a special case of the Chi-squared test. The distributions of

two continuous variables were compared using the Kolmogorov–Smirnov test (*ks.test* R function). The association between two paired continuous variables was measured and tested using one of the correlation coefficients, Spearman or Kendall (*cor.test* R function with an option indicating which correlation coefficient, Spearman or Kendall, to be used). The Chi-squared test was used to compare categorical variables between groups. When the required assumption conditions were not met for the Kolmogorov–Smirnov test and the Chi-squared test, the Cramer von Mises test and the Fisher's exact test were used respectively. The differences between the real-life ED and the ED upon OFC were compared using Wilcoxon signed rank test (*wilcox.test* R function).

Results

Medical characteristics

Data from 785 patients (French: 91%; male: 62%; < 16 years old: 86%) were collected by 70 allergists. A total of 669 (85%) patients were initially declared allergic. Characteristics at the first evaluation are given in Table 1. Allergic comorbidities were frequent (asthma: 58%; AD: 66%), with only 5% of the patients without any of them. In all, 37% of the patients had one or more tree-nut sensitizations or allergies, mainly walnut (15%), pistachio (13%), cashew (12%) and hazelnut (11%) (data not shown). The SPT wheal diameter was available in 94% of the patients and ≥ 8 mm in 62% of them. The level of peanut sIgE was available in 77% of the patients and ≥ 14 kUA/L in 56.5% of them. The level of ara h 2 sIgE was > 0.23 kUA/L and > 0.55 kUA/L in 89% and 83% respectively. Only 12 patients (1.5%) had an ara h 2 sIgE level < 0.10 kUA/L.

Foods triggering the allergic reaction were whole peanuts (51%), the peanut-based snack Curly® (36%), snacks (10%), a mix of peanuts and tree nuts (5%), and other foods such as cereal bars, chocolate or any food containing nuts (20%). Severe or potentially severe symptoms were reported in 30% of the allergic patients, with serious systemic reactions (15%) and laryngeal angioedema (8%) being the most frequent (Table 2). Ingestion was the main exposure route (89% of the patients). Patients reacted also to inhalation (6%) or cutaneous contact (19%) (Table 2). Three patients with potentially severe symptoms reacted to inhalation only: a 7-month-old boy (laryngeal and cutaneous angioedema) who did not ingest peanut, but whose parents were eating peanuts; a 2-year-old girl (urticaria and wheeze) in the presence of peanut in the room; and a 3-year-old boy (cough and palpebral oedema) in the presence of peanut consumers.

Table 1. Medical characteristics of MIRABEL patients

Variables	Total population (n = 785)	Children with Peanut sIgE ≥ 14 or SPT size ≥ 8 (n = 574)
Gender, n (%)	785 (100)	574 (100)
Males, n (%)	483 (62)	356 (62)
Age at visit (questionnaire) (year), median (IQR)	9 (6–13)	10 (6–14)
[0; 6[, n (%)	165 (21)	111 (20)
[6; 12[, n (%)	332 (42)	243 (42)
[12; 16[, n (%)	177 (23)	144 (25)
≥ 16, n (%)	111 (14)	76 (13)
Age at diagnosis (first visit) (year), median (IQR)	3 (2–5)	3 (2–4)
[0; 6[, n (%)	641 (82)	480 (84)
[6; 12[, n (%)	111 (14)	72 (12)
[12; 16[, n (%)	11 (1)	10 (2)
≥ 16, n (%)	22 (3)	12 (2)
Diagnosis (first visit)	785 (100)	574 (100)
Allergic, n (%)	669 (85)	490 (85)
Allergic comorbidities, n (%)	785 (100)	574 (100)
AD, n (%)	518 (66)	380 (66)
Asthma, n (%)	451 (58)	341 (59)
Rhinitis, n (%)	383 (49)	279 (49)
Other FA (OFA), n (%)	489 (62)	358 (62)
AD + Asthma, n (%)	311 (40)	233 (41)
AD + Asthma + OFA, n (%)	223 (28)	168 (29)
Absence of comorbidity, n (%)	43 (5)	26 (5)
Skin prick test, n (%)	739 (94)	559 (97)
Wheal size (mm), median (IQR)	9.00 (6.00–12.0)	–
Wheal size, ≥ 8 mm, n (%)	460 (59)	460 (80)
Wheal size (mm), median if ≥ 8 mm (IQR)	10.0 (9.0–15.0)	10 (9.0–15.0)
Specific IgE to peanut, n (%)	604 (77)	473 (82)
IgE (kUA/L), median (IQR)	20.1 (4.30–90.5)	–
IgE (kUA/L) ≥ 14 kUA/L, n (%)	341 (43)	341 (59)
IgE (kUA/L), median if ≥ 14 kUA/L (IQR)	82 (35.8–101)	82 (35.8–101)
Ara h 2-specific IgE (kUA/L), n (%)	747 (95)	549 (96)
Median (IQR)	11.5 (1.80–50.6)	23.3 (4.60–68.4)
> 0.23, n (%)	701 (89)	536 (93)
> 0.55, n (%)	654 (83)	513 (89)
Oral challenge, n (%)	278 (35)	208 (36)
Age at OFC (year), median (IQR)	8.00 (5.00–11.0)	8.00 (6.00–11.0)
Positive OFC, n (%)	225 (29)	177 (31)
ED at OFC (mg of peanut protein), median (IQR)	67.3 (16.4–244)	54.4 (16.4–219)
ED (mg of peanut protein) at OFC		
[0; 5[, n (%)	22 (10)	17 (10)
[5; 50[, n (%)	66 (29)	59 (33)
[50; 100[, n (%)	33 (15)	27 (15)
≥ 100, n (%)	104 (46)	74 (42)

Table 1 (continued)

Variables	Total population (n = 785)	Children with Peanut sIgE ≥ 14 or SPT size ≥ 8 (n = 574)
Dietary advice	785 (100)	574 (100)
Strict	359 (46)	286 (50)
Lax	412 (52)	283 (49)
Absent	14 (2)	5 (1)
Oral immunotherapy	35 (4)	24 (4)

IQR, interquartile range defined by the 25th and the 75th percentiles.

Eliciting dose in real life and oral food challenges

For 238 allergic patients (35.5%), the allergist could estimate the amount of food triggering the accidental reaction. The median estimated ED in real life was 125 mg (34; 177) of peanut protein. The ED was lower than 5 mg peanut protein in 0.9% of patients, between 5 and < 50 mg in 34.1%, between 50 and < 100 mg in 8.3% and ≥ 100 mg in 56.7%.

An OFC was performed in 278 patients (35%): open for 161 patients; single-blind for 68 patients; and double-blind for 49 patients. Only age (at first visit, at questionnaire visit) and asthma comorbidity showed significant differences between patients who had undergone an OFC and those who did not (Table S1, online repository). Age at time of the OFC was under 6 years for 26.5% of the patients, between 6 and 12 years for 52%, between 12 and 16 years for 16.5%, and over 16 years for 5%. The OFC was positive in 225 patients (80.9%). Forty-eight OFCs were performed in patients considered to be sensitized at the first visit and before the OFC, and 32 were positive. The distributions of the EDs according to age are described in Fig. 1. They were significantly different between the 6–12 years and 12–16 years age groups, with a lower ED in the older group patients ($P = 0.03$). Ten of the 14 OFCs performed in patients who showed reactions after inhalation were positive and the ED was between 4 and 16 mg of peanut protein in six. Finally, only four of the 16 sensitized patients and two of the 37 allergic patients who had a negative OFC had a cumulative challenge dose of peanut > 7 g, excluding allergy with certainty. For the others, the cumulative amount was too low to draw a definitive conclusion; 40 (85%) of these patients had an Ara h 2 sIgE level > 0.23 and 35 (74.5%) > 0.55 kUA/L (data not shown).

For 55 patients, the ED was quantified in real life [136 mg, (34.0; 296)] and upon OFC [67.0 mg (16.4; 253)]. The Wilcoxon test did not conclude to significant differences between real-life EDs and EDs determined upon OFC ($P = 0.44$).

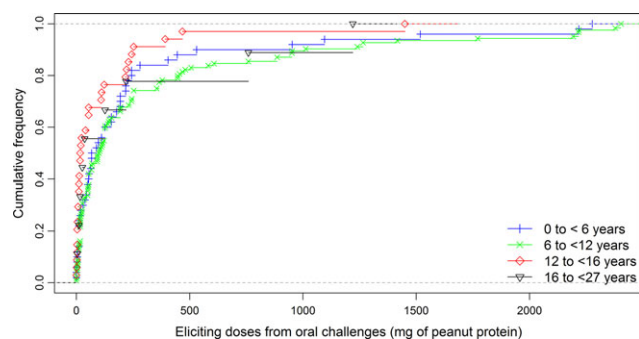
Table 2. Symptoms and exposure routes related to the reported allergic reaction, for allergic patients only ($n = 669$)

Variables	n (%)
Symptoms	669 (100)
Severe/potentially severe*	202 (30)
Anaphylactic shock	27 (4)
Laryngeal angioedema	56 (8)
Acute asthma	22 (3)
Serious systemic reaction	97 (15)
Non-severe†	467 (70)
Rash/AD	78 (12)
Urticaria or angioedema	369 (55)
Digestive symptoms	102 (15)
Other	88 (13)
Exposure routes	649 (97)
Ingestion	579 (89)
Inhalation	36 (6)
Contact	124 (19)

IQR, interquartile range defined by the 25th and the 75th percentiles.

*Severe symptoms were exclusive.

†More than one non-severe symptom could be recorded.

**Fig. 1.** Distribution of the eliciting doses upon oral challenges according to age.

Factors associated with severe or potentially severe reactions in real life

Severe or potentially severe reactions in real life were more frequent in teenagers and adults: 27% in subjects younger than 6 years at diagnosis, 39% in those between 6 and 12 years, vs. 60% in those between 12 and 16 years and 50% in those older than 16 years ($P = 0.004$) (data not shown). Severe or potentially severe symptoms were significantly more frequent in patients who reported symptoms through inhalation than ingestion or contact ($P < 0.001$) (Table 3). They were also significantly more frequent in patients with coexisting asthma ($P = 0.033$) or in patients without AD ($P = 0.036$) (Table 4). A significant difference was observed between the size of the SPT and the level of severity ($P = 0.005$, Fig 2a). No significant differences

were observed for peanut sIgE ($P = 0.73$, Fig 2b), Ara h 2 sIgE ($P = 0.81$, Fig 2c) or ED from OFCs ($P = 0.71$, Fig 2d).

Allergist dietary advice

Strict avoidance was advised by the allergists for 359 (46%) patients, lax avoidance for 412 (52%) patients and 14 (2%) patients did not receive any advice (Table 1). Strict avoidance was more frequently recommended when there was a history of severe or potentially severe reaction (53.5% vs. 45%), However, this was not significant ($P = 0.051$) (Table 5). Lax avoidance advice was significantly more frequent in patients with AD ($P = 0.012$). Dietary advice did not vary significantly with the other allergic comorbidities and was not influenced by the presence of another FA ($P = 0.78$). Strict avoidance was significantly more often advised for patients with positive OFC and EDs < 100 mg (85%) ($P < 0.001$).

Patient's anxiety

Information on peanut allergy-related anxiety was available for 401 patients (51%) (Table 6). Higher anxiety scores were obtained for patients with AD ($P = 0.003$), for those with AD and asthma ($P = 0.032$), and for those who had received strict avoidance advice ($P < 0.001$). There was no significant association between anxiety and the age at diagnosis and at visit ($P = 0.17$ and $P = 0.052$ respectively). Finally, there was no association between anxiety and the severity of the reaction ($P = 0.81$), the ED at OFC ($P = 0.13$), and the ED in real life ($P = 0.76$).

Discussion

This paper highlights some important features of peanut allergy, mainly the high frequency of coexisting allergic diseases and of the severe or potentially severe reactions, which were more frequent in asthmatic patients, teenagers and adults, and patients who react to inhalation. The real-life ED when quantifiable was not significantly different from that measured on OFC. Lastly, the study shows a large heterogeneity in dietary advice provided by allergists and confirms the anxiety of the patients and parents, especially in the case of allergic comorbidities or when advised to strictly avoid peanuts.

Clinical and biological characteristics

We confirm that peanut allergy is generally diagnosed early in childhood, before 3 years of age for half of the children and before 6 years for 80%, a rate similar to that reported in the United States, but different from

Table 3. Symptoms and exposure routes for the allergic patients (all the percentage were estimated according to the number of allergic patients $n = 669$)

Symptoms	Ingestion		Inhalation		Cutaneous		<i>P</i> -value*
	Isolated [‡]	Associated [‡]	Isolated [‡]	Associated [‡]	Isolated [‡]	Associated [‡]	
Severe/potentially severe, <i>n</i> (%)	189 (28.2)		16 (2.4)		22 (3.2)		< 0.001
Anaphylactic shock, <i>n</i> (%)	19 (2.8)	7 (1.0)	0 (0)	3 (0.4)	0 (0)	6 (0.9)	
Laryngeal angioedema, <i>n</i> (%)	49 (7.3)	3 (0.4)	1 (0.1)	2 (0.3)	1 (0.1)	3 (0.4)	
Acute asthma, <i>n</i> (%)	17 (2.5)	3 (0.4)	0 (0)	3 (0.4)	0 (0)	1 (0.1)	
Systemic serious reaction, <i>n</i> (%)	78 (11.6)	13 (1.9)	2 (0.3)	5 (0.7)	2 (0.3)	9 (1.3)	
Non-severe, <i>n</i> (%) [†]	390 (58.3)		20 (2.9)		102 (15.2)		< 0.001
	340 (51)	50 (7.5)	3 (0.4)	17 (2.5)	54 (8.1)	48 (7.2)	
Total, <i>n</i> (%)	503 (75)	76 (11)	6 (0.8)	30 (4.5)	57 (8.5)	67 (10)	

*Comparison of the different routes for severe or non-severe symptoms. χ^2 test for proportion comparisons when conditions were respected, Fisher exact test otherwise.

[†]More than one non-severe symptom could be declared.

[‡]Isolated if the exposure route was the only route recorded; associated if different exposure routes were recorded.

Bold values are not necessary in the titles of the tables

Table 4. Comorbidities and severe/potentially severe symptoms for allergic patients ($n = 669$)

Comorbidities			Severe/potentially severe symptoms				Total
			Number of patients	Anaphylactic shock	Laryngeal angioedema	Acute asthma	Serious systemic reaction
Atopic dermatitis	Absence, <i>n</i> (%)	247	15 (6)	23 (9)	8 (3)	41 (17)	87 (35)
	Presence, <i>n</i> (%)	422	12 (3)	33 (8)	14 (3)	56 (13)	115 (27)
	<i>P</i> -value*		0.065	0.56	1	0.26	0.036
Asthma	Absence, <i>n</i> (%)	288	10 (3)	20 (7)	4 (1)	40 (14)	74 (26)
	Presence, <i>n</i> (%)	381	17 (4)	36 (9)	18 (4)	57 (15)	128 (34)
	<i>P</i> -value*		0.56	0.26	0.016	0.74	0.033
Rhinitis	Absence, <i>n</i> (%)	334	16 (5)	26 (8)	10 (3)	41 (12)	93 (28)
	Presence, <i>n</i> (%)	335	11 (3)	30 (9)	12 (4)	56 (17)	109 (33)
	<i>P</i> -value*		0.33	0.68	0.83	0.12	0.21
Other food allergy	Absence, <i>n</i> (%)	273	9 (3)	25 (9)	11 (4)	40 (15)	85 (31)
	Presence, <i>n</i> (%)	396	18 (5)	31 (8)	11 (3)	57 (14)	117 (30)
	<i>P</i> -value*		0.55	0.57	0.39	1	0.67

*Comparison of symptoms between patients with and without each comorbidity. χ^2 test for proportion comparisons when conditions were respected, Fisher exact test otherwise.

that reported in southern Europe [18]. Patients declared sensitized were younger at the first visit and allergy testing was probably prescribed in the context of other atopic conditions (data not shown). In fact, these patients were often allergic, as two-thirds of the OFCs performed in this population were positive. This finding highlights the need to consider challenging sensitized patients who have never knowingly ingested peanuts [19, 20].

Our study confirms that a large majority of the patients had allergic comorbidities. The association of asthma and AD was reported in 40% of the patients, and another food allergy or sensitization in 62% of them. These associations are linked to an increased risk of severe allergic disease. Food allergy/sensitization, particularly to peanut and tree nuts, is overrepresented in severe asthmatic children [21, 22] or life-threatening acute asthma [23]. Furthermore, in patients with

filaggrin null mutations, the association of food sensitization, asthma and AD has been associated with a significant decline in lung function [24].

We observed that severe reactions or potentially severe reactions were frequent in our population (30%), mainly serious systemic reactions (50% of them). Anaphylactic shock may be underestimated because systolic blood pressure values were often missing. We observed that these reactions were more frequently recorded in teenagers and young adults, suggesting that patients are more at risk of severe reactions during this time of life [25]. Anaphylaxis is also observed in the youngest patients, with peanuts being one of the most frequent triggers [26]. Asthma was associated with severe reactions, in line with Summers et al., who found a strong link between severe allergic comorbidities and peanut- or tree nut-induced allergic reactions [4]. Uncontrolled asthma has also been associated with fatal allergic reac-

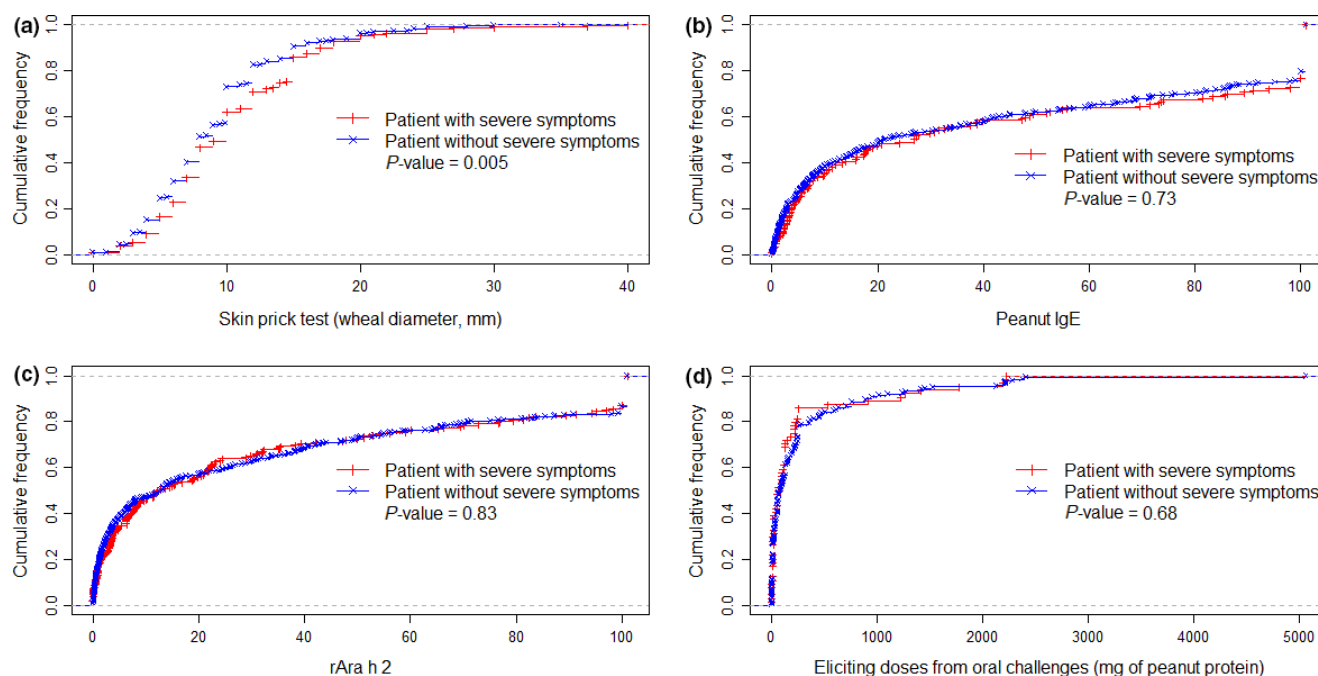


Fig. 2. Distribution of wheal size in peanut skin prick tests (a), peanut sIgE levels (b), Ara h 2 sIgE levels (c) and eliciting doses from positive oral challenge (d) in patients with and without severe/potentially severe symptoms.

Table 5. Dietary advice according to comorbidities, symptom severity, and oral food challenge results ($n = 771$)

Variables	Peanut avoidance advice		
	Strict	Lax	P -value*
Allergic comorbidities, n (%)	359 (46)	412 (52)	
Atopic dermatitis, n (%)	220 (61)	289 (70)	0.012
Asthma, n (%)	214 (60)	231 (56)	0.34
Rhinitis, n (%)	165 (46)	213 (52)	0.11
Other food allergy (OFA), n (%)	219 (61)	261 (63)	0.5
Atopic dermatitis + Asthma, n (%)	138 (38)	171 (41)	0.42
Atopic dermatitis + Asthma + OFA, n (%)	101 (28)	120 (29)	0.81
Absence of comorbidity, n (%)	27 (8)	15 (4)	0.025
Symptoms [†] , n (%)	314 (47)	346 (52)	
Severe/potentially severe, n (%)	108 (34)	94 (27)	
Non-severe, n (%)	206 (66)	252 (73)	0.051
Positive OFC [‡] , n (%)	93 (28)	127 (41)	
Eliciting dose (mg peanut protein) at OFC			
[0; 5[, n (%)	16 (17)	6 (5)	
[5; 50[, n (%)	48 (52)	18 (14)	
[50; 100[, n (%)	15 (16)	18 (14)	
≥ 100 , n (%)	14 (15)	85 (67)	< 0.001

*Comparison of patients with the different diet. χ^2 test for proportion comparisons when conditions were respected, Fisher exact test otherwise.

[†]Symptoms and anxiety score are related to allergic patients only.

[‡]Five patients with positive oral challenge had no dietary advice.

tions to food [3]. Finally, patients who react to inhalation may be a specific high-risk group, with frequent severe reactions and low EDs upon OFC. Com-

stock et al. reported on the high frequency of severe reactions to peanuts and tree nuts in 41 patients (history of asthma: 68%) during flights, 58% of which were by inhalation [27].

We also confirm that peanut allergy in France, Belgium and Luxemburg is associated with Ara h 2 sensitization. Indeed, Ara h 2 sIgE could not be detected in only 1% of the patients, a similar rate to that found in another French study [15]. Various Ara h2 sIgE cut-off points have been proposed to predict clinically relevant allergy [15, 16]. Our study supports the validity of the cut-off point of 0.23 kUA/L, suggested by Codreanu et al. [15]. However, these cut-offs have limitations and may not be applicable in other countries or populations [18, 28].

We observed a significant association between the level of severity of the reaction and the SPT size, but not with Ara h 2 sIgE levels, or ED on OFC. Previous studies have shown conflicting data. Summers et al. did not observe any correlation between peanut sIgE or SPT size and severity of acute reactions [4]. Astier et al. reported a significantly higher severity score in polysensitized (Arah 1, Ara h 2, Ara h 3) compared with monosensitized (Ara h 2) patients, but did not show any correlation with the size of SPT with Ara h 2 extract or the level of peanut sIgE [29]. At OFC, Eller and Bindslev-Jensen demonstrated a correlation between the clinical severity and peanut sIgE and Ara h 2 sIgE levels [30]. In contrast, Blumchen et al. did not observe any correlation with SPT and peanut or ara h 2

Table 6. Association of anxiety with age group, comorbidities, symptom severity, Eliciting dose (real life, OFC) and dietary advice ($n = 401$)

Variables	<i>n</i> (%)		Anxiety score median (IQR)	<i>P</i> -value*
Age at the visit (year)	401 (100)	10.0 (7.00–14.0)	54.5 (39.9–67.7)	0.052
Age at the diagnosis (year)	401 (100)	3.00 (2.00–5.00)	54.5 (39.9–67.7)	0.17
Comorbidities				
AD				
Presence	265 (66)		57.3 (41.3–68.1)	0.003
Absence	136 (34)		49.3 (38.0–66.7)	
Asthma				
Presence	228 (57)		55.9 (38.9–69.8)	0.36
Absence	173 (43)		52.4 (40.3–66.7)	
AD + Asthma				
Presence	158 (39)		58.3 (40.6–69.7)	0.032
Absence	243 (61)		51.4 (39.9–66.7)	
Other food allergy (OFA)				
Presence	256 (64)		57.1 (40.3–69.5)	0.12
Absence	145 (36)		52.4 (39.6–64.6)	
Symptoms [†]	345 (86)		52.8 (38.9–67.0)	
Severe/potentially severe	97 (28)		54.9 (39.9–69.8)	0.81
Non-severe	248 (72)		52.8 (37.9–66.7)	
Eliciting dose at OFC (Positive OFC, mg of peanut protein)	117 (29)	54.4 (16.4–243)	52.8 (40.3–66.7)	0.13
Eliciting dose in real life (mg of peanut protein)	116 (29)	125 (34.0–183)	52.6 (38.0–66.7)	0.76
Dietary advice				
Strict	211 (53)		59.0 (44.6–70.5)	< 0.001
Lax	190 (47)		47.2 (34.9–66.0)	

Bold indicates statistical significance. IQR, interquartile range defined by the 25th and the 75th percentiles.

*Association between anxiety score and each continuous variable was tested using Spearman correlations when assumptions were met, Kendall test otherwise. Comparison of anxiety scores between presence and absence of comorbidities was tested using the χ^2 test for median comparison when assumptions were met, Fisher exact test for median comparison.

[†]Symptoms: χ^2 test for median comparison was used when assumptions were met, Fisher exact test otherwise. Symptoms and anxiety score are related to allergic patients only.

sIgEs using the same Sampson scoring system [31]. There are also conflicting data about ED on OFC and severity of symptoms. Blumchen et al. demonstrated that lower EDs were associated with severe accidental reactions in contrast to van der Zee et al. and Taylor et al., who did not show this association [25, 31, 32]. However, these studies were conducted in different populations with respect to age and risk, different scoring systems were used, and the OFC protocols were different. To the best of our knowledge, there are no consistent data on the real-life threshold dose. Hourihane et al. developed a scoring system that combined peanut ED and symptoms [33]. They showed a poor correlation between low-dose double-blind, placebo-controlled OFC and community scores. Altogether, we can conclude that there are no strong criteria for predicting the severity of the accidental reaction.

Eliciting dose in real life and during OFC

We report that ED estimated from OFC may be a good proxy of ED in real life. This dose could be as low as < 5 mg of peanut protein. Allergists were asked to be as precise as possible and the peanut protein content

was calculated according to the Ciquel Table on food composition [12]. ED in real life and upon OFC were available for 55 patients and were not significantly different. The significance of the EDs observed during an OFC has been questioned, because the conditions are different from a real-life meal. This point is crucial for developing standardized food safety policies. In that regard, Blumchen et al. pointed out that 15-min time intervals may be too short and that EDs in real life may be lower than that observed during an OFC [31]. To better reflect a real-life EDs response, a modified OFC procedure with doses scheduled 2 h apart has been tested demonstrating a median latency until clinical reaction of 55 min.

Dietary advice by the allergists, patient anxiety

Finally, our data show that dietary advice was guided neither by the severity of the reactions nor by coexisting asthma, a risk factor of severe reaction. A low ED on OFC (< 100 mg) was the only criterion that significantly influenced the decision to advise strict avoidance, including PAL. We also observed that the level of avoidance, as well as comorbidities (AD $\pm$ asthma),

was linked to anxiety and consequently to the quality of life. In contrast, a history of severe reaction was surprisingly not linked to anxiety, as has previously been discussed in the literature [34, 35]. Overall, this raises the question of the criteria associated with dietary advice about PAL, which deserve to be clarified. Strict avoidance may be not necessary for a large part of the peanut-allergic population. Indeed, there are studies which report that contamination by peanut is extremely low and may also be observed in foods without PAL [36]. PAL is not a regulatory obligation. Population-based threshold levels need to be further studied, which is another issue of the MIRABEL study [7]. Reference doses based on dose-distribution modelling for different allergens are now available [37, 38]. They will help manufacturers to improve labelling, assist allergists in specifying the level of avoidance, and consequently increase patients' confidence and improve their quality of life [6, 39].

The strength of this study is linked to the size of the population, recruited by 70 allergists mainly located in France and in different parts of the country. However, while the recruitment process was rapid and inexpensive, it nevertheless suffered from some bias. For example, one limitation of the study is that we could not specify the percentage of patients who refused to be included in the study. Neither could we contact allergic individuals who do not consult allergists. Therefore, less severe allergy may be underrepresented in our study. However, patients were recruited by both office- and hospital-based allergists and should be representative of the peanut-allergic population. Another limitation of our study is linked to the fact that it was an observational study: (i) cross-sectional and some data about the diagnosis and allergy features were collected retrospectively. Because of the duration between the first visit and the visit when the questionnaire was completed, we cannot rule out bias due to recall. However, the main data were recorded in the medical charts; (ii) OFCs, mainly open, were performed in only 35% of the patients, with no details of the procedure or the titration steps. Some of them were incomplete and no firm conclusion could be drawn. Indeed, some French allergists perform OFCs to eliminate a reaction to a low dose of peanut and to further define dietary advice and personalized care projects at school; (iii) the anxiety score was constructed by extrapolation from the validated FAQLQ questionnaire [8–10], as there was no French version of the FAQLQ available when the study was designed. As a French version is now available, the questionnaire that we used will not be further validated. (iv) Finally, we are aware the eliciting dose in real life is an estimation from patient declaration with the possibility of a memory bias.

In conclusion, our analysis highlights some specific features of peanut allergy and its consequences in real life in a large population. It would seem that dietary advice could be improved with a better risk assessment approach with regard to labelling based on dose-distribution modelling. Such an approach could improve the quality of life of patients with peanut allergy by reducing their anxiety levels and increasing their confidence in making fully informed decisions about food consumption. More detailed analysis of the MIRABEL population, integrating all the outcomes related to peanut allergy, should further clarify this point.

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Author contributions

Antoine Deschildre: involvement in the acquisition, analysis and interpretation of the data, writing and revising the manuscript. Chabi Fabrice Elégbédé: involvement in statistical analysis and interpretation of the data, and substantial involvement in writing the manuscript. Jocelyne Just: involvement in the analysis and interpretation of the data and substantial involvement in revising the manuscript prior to submission. Olivier Bruyère: involvement in developing the MIRABEL project and in revising the manuscript prior to submission. Xavier Van der Brempt: involvement in the acquisition of the data and in revising the manuscript prior to submission. Etienne Beaudouin: involvement in the acquisition of the data. Jean Marie Renaudin: involvement in developing the MIRABEL project and in revising the manuscript prior to submission. Alexandra Papadopoulos: involvement in developing the MIRABEL project, and substantial involvement in revising the manuscript prior to submission. Amélie Crepet: leader in the development and design of the MIRABEL project, involvement in the formulation of hypotheses, and in the acquisition, statistical analysis and interpretation of the data and substantial involvement in writing the manuscript. Denise-Anne Moneret-Vautrin: involvement in developing the MIRABEL project, in the formulation of hypotheses, in the acquisition, analysis and interpretation of the data, and substantial involvement in revising the manuscript prior to submission. All the authors have approved the final version of the article.

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Conflict of interests

A Deschildre reports personal consultancy and lecture fees from GSK, MSD, Aerocrine, MEDA, ALK, Novartis, Stallergènes, Chiesi, outside the submitted work. J Just reports personal fees from Novartis, ALK, Stallergènes, Chiesi, Phadia, Novartis, GSK, MSD, outside the submitted work. E Beaudoin reports personal fees from ALK abello SA, MSD, Novartis, outside the submitted work. The rest of the authors declared that they have no relevant conflicts of interest.

References

- 1 Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common FA in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69**:992–1007.
- 2 Morisset M, Moneret-Vautrin DA, Kanny G, Allergo-Vigilance Network. Prevalence of peanut sensitization in a population of 4737 subjects—an Allergo-Vigilance Network enquiry carried out in 2002. *Eur Ann Allergy Clin Immunol* 2005; **37**:54–7.
- 3 Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007; **119**:1018–9.
- 4 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.
- 5 Turner PJ, Skypala IJ, Fox AT. Advice provided by health professionals regarding precautionary allergen labelling. *Pediatr Allergy Immunol* 2014; **25**:290–2.
- 6 Allen KJ, Turner PJ, Pawankar R *et al*. Precautionary labelling of foods for allergen content: are we ready for a global framework? *World Allergy Organ J* 2014; **7**:10.
- 7 Crépet A, Papadopoulos A, Elégbédé CF *et al*. MIRABEL: an integrated framework for risk and cost/benefit analysis of peanut allergen. *Regul Toxicol Pharmacol* 2015; **71**:178–83.
- 8 Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ *et al*. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol* 2008; **122**:139–44.
- 9 Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ *et al*. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009; **39**:127–37.
- 10 Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A *et al*. Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. *Allergy* 2009; **64**:1209–17.
- 11 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**:473–83.
- 12 ANSES 2013: Table de composition nutritionnelle des aliments Ciqua. Available at <https://pro.anses.fr/TableCIQUAL/>
- 13 Sampson H. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; **107**:891–6.
- 14 Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005; **115**:1291–6.
- 15 Codreanu F, Collignon O, Roitel O *et al*. A novel immunoassay using recombinant allergens simplifies peanut allergy diagnosis. *Int Arch Allergy Immunol* 2011; **154**:216–26.
- 16 Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol* 2011; **127**:684–5.

- 17 Santos C, Deschildre A, Paty E, Couderc L, Marguet C, Rancé F. Test de provocation par voie orale aux aliments chez l'enfant. Quand, pour qui et comment ? Réalisation. *Rev Fr Allergol Immunol Clin* 2006; **46**:659–69.
- 18 Vereda A, van Hage M, Ahlstedt S et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol* 2011; **127**:603–7.
- 19 Johannsen H, Nolan R, Pascoe EM et al. Skin prick testing and peanut-specific IgE can predict peanut challenge outcomes in preschoolchildren with peanut sensitization. *Clin Exp Allergy* 2011; **41**:994–1000.
- 20 Peters RL, Allen KJ, Dharmage SC et al. HealthNuts study. 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.
- 21 Deschildre A, Marguet C, Salleron J et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013; **42**:1224–33.
- 22 Just J, Saint-Pierre P, Gouvis-Echraghi R et al. Childhood allergic asthma is not a single phenotype. *J Pediatr* 2014; **164**:815–20.
- 23 Roberts G, Patel N, Levi-Schaffer F, Habibi P, Lack G. Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. *J Allergy Clin Immunol* 2003; **112**:168–74.
- 24 Marenholz I, Kerscher T, Bauerfeind A 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.
- 25 van der Zee T, Dubois A, Kerkhof M, van der Heide S, Vlieg-Boerstra B. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. *J Allergy Clin Immunol* 2011; **128**:1031–6.
- 26 Vetander M, Helander D, Flodström C et al. Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clin Exp Allergy* 2012; **42**:568–77.
- 27 Comstock SS, DeMera R, Vega LC et al. Allergic reactions to peanuts, tree nuts, and seeds aboard commercial airliners. *Ann Allergy Asthma Immunol* 2008; **101**:51–6.
- 28 Keet CA, Johnson K, Savage JH, Hamilton RG, Wood RA. Evaluation of Ara h2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. *J Allergy Clin Immunol Pract* 2013; **1**:101–3.
- 29 Astier C, Morisset M, Roitel O et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol* 2006; **118**:250–6.
- 30 Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy* 2013; **68**:190–4.
- 31 Blumchen K, Beder A, Beschorner J et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol* 2014; **134**:390–8.
- 32 Taylor SL, Moneret-Vautrin DA, Crevel RW et al. Threshold dose for peanut: risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. *Food Chem Toxicol* 2010; **48**:814–9.
- 33 Hourihane JO, Grimshaw KE, Lewis SA et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005; **35**:1227–33.
- 34 Wassenberg J, Cochard MM, DunnGalvin A et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012; **23**:412–9.
- 35 Saleh-Langenberg J, Goossens NJ, Flokstra-de Blok BM et al. Predictors of health-related quality of life of European food-allergic patients. *Allergy* 2015; **70**:616–24.
- 36 Brough HA, Turner PJ, Wright T et al. Dietary management of peanut and tree nut allergy: what exactly should patients avoid? *Clin Exp Allergy* 2015; **45**:859–71.
- 37 Taylor SL, Baumert JL, Kruizinga AG, Houben G. Establishment of reference doses for residues of allergenic foods: report of the VITAL expert panel. *Food Chem Toxicol* 2014; **63**:9–17.
- 38 Allen KJ, Remington BC, Baumert JL et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014; **133**:156–64.
- 39 DunnGalvin A, Chan CH, Crevel R et al. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy* 2015; **70**:1039–51.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of age, comorbidities, symptoms' severity and Ara h 2 sIgE levels in patients with and without OFC