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Safety of oral immunotherapy for cashew nut and peanut allergy in children – a retrospective single-centre study

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Summary

AIM OF THE STUDY: Oral immunotherapy (OIT) is increasingly used for the treatment of childhood food allergies, with limited data available on cashew nut OIT. This real-life study investigated the safety and feasibility of cashew nut OIT, comparing it with peanut OIT, with a focus on the up-dosing process.

METHODS: We analysed cashew nut (n = 24) and peanut (n = 38) OIT cases with treatment initiated between 2018 and 2022 at the University Children's Hospital Basel. All patients who commenced therapy within this time frame were enrolled without prior selection. Two different starting protocols were used. Within the up-dosing protocol, the nut intake was incrementally increased by 20–30% every 2 weeks until reaching a maintenance dose of 1 g of nut protein. After consuming the maintenance dose regularly for 18–24 months, a second oral food challenge was performed. Patients who passed this challenge were considered desensitised. The safety of the therapy was evaluated based on the severity of adverse reactions during the up-dosing phase. Symptom severity was evaluated using the validated ordinal food allergy severity scale (o-FASS-5).

RESULTS: Over the study period, 33% of cashew nut-allergic and 63% of peanut-allergic patients experienced mild to moderate allergic reactions. Severe allergic reactions occurred in five peanut-allergic children with high baseline allergen-specific IgE levels. Six patients with peanut, and none with cashew nut OIT, discontinued the therapy due to adverse reactions. The mean duration to reach the maintenance phase was longer for children with asthma or another food allergy. Among children who already underwent the second oral food challenge, desensitisation was achieved in 91% (11 out of 12) of cashew nut- and 73% (11 out of 15) of peanut-allergic patients.

CONCLUSION: Cashew nut OIT had a low severity of adverse reactions and was generally well-tolerated. However, patient characteristics influenced side effect risk and treatment duration, emphasising the need for individualised OIT strategies.

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Introduction

Cashew nuts are a common cause of food allergies worldwide [1–3], often triggering more severe reactions than other foods [4, 5]. The prevalence of cashew nut allergy is on the rise [6], possibly due its increasing use in the Western diet. In Europe, peanuts are the primary cause of anaphylaxis in children under the age of 18 years, but cashew nuts rank first in Switzerland [7, 8]. Even a small amount (less than 1 teaspoon) of cashew nuts or peanuts can induce an allergic reaction [8]. Notably, in only about 9% of all tree nut allergies and 29% of peanut allergies, natural tolerance occurs [9, 10]. Therefore, it is imperative to explore strategies to enhance reaction threshold and minimise the risk of severe reactions [11].

In recent years, oral immunotherapy (OIT) has emerged as a promising therapeutic option for children with food allergies and is supported by encouraging data [12–15]. In 2018, the European Academy of Allergy and Clinical Immunology (EAACI) officially recommended allergen immunotherapy for peanut, milk, and egg allergies in children older than 4 years with persistent Immunoglobulin E (IgE)-mediated food allergies [16]. Furthermore, subsequent work has shown more favourable outcomes and safety for younger age groups [15, 17, 18]. Nevertheless, several studies have demonstrated that OIT increases the likelihood of allergic reactions that are mostly mild in nature, though severe reactions are possible [12, 19]. While OIT for tree nuts lacks official endorsement, it is frequently employed, yet data on its efficacy and safety remain scarce. The NUT CRACKER (Nut Co-Reactivity-Acquiring Knowledge for Elimination Recommendations) study, a prospective cohort study involving 50 patients undergoing cashew nut OIT, showed promising results with a high rate of desensitisation and moderate incidence of adverse reactions [20]. Another real-life analysis of preschool children who underwent OIT for tree nuts, including cashew nuts, demonstrated adverse reactions of varying degree in 70% of participants [21].

This retrospective single-centre study aimed to evaluate the safety and feasibility of real-world cashew nut OIT, comparing it with peanut OIT, as well as to identify factors

influencing adverse reactions and treatment duration with a focus on the up-dosing process.

Methods

Study design and population

We conducted a retrospective analysis of OIT for cashew nut or peanut allergies initiated between October 2018 and April 2022 at the University Children's Hospital Basel, Switzerland. The option for OIT was offered to all paediatric patients with peanut or cashew nut allergy, except those with contraindications (uncontrolled asthma, eosinophilic oesophagitis, non-compliance or relevant language barriers, active autoimmune diseases, or malignancies). Allergy diagnoses were established based on a clear history of a systemic immediate-type allergic reaction or an observed reaction during an open oral food challenge (OFC), and either positive results from a skin prick test (SPT) or specific immunoglobulin E levels (sIgE) exceeding 0.35 kU/l for the respective allergen, or both. All patients who commenced therapy were included in our study without prior selection, thereby presenting a real-life investigation.

Oral immunotherapy protocol

Two different strategies were used to start the OIT (see figure S1 in the appendix). In the peanut allergy group, based on the history of their previous reactions and laboratory results, patients were either considered low-risk or high-risk. Low-risk peanut-allergic patients and all cashew nut-allergic patients initiated OIT with an open OFC. The OFC protocol, following international guidelines, was stopped when symptoms appeared, in line with the PRACTALL consensus report [22]. The dosage at symptom onset was considered the individual reactive dose. For these patients, OIT began with the highest tolerated OFC dose. High-risk peanut allergy patients were started with an initial seven-step dose escalation from 0.0001 g to 0.0064 g of nut protein (figure S1, protocol slightly adapted from [23]), the dose with which they began their OIT.

The daily intake portions were provided to the families in pre-weighed doses, each containing the corresponding ground fresh nut. The portions were prepared by the nursing staff within the allergy department. Families were given the following general instructions [24]: Patients were advised to consume the daily dose with a meal and avoid physical activity for 2 hours after intake. In case of an infection or intake of anti-inflammatory medication, families were instructed to reduce or temporarily pause the daily intake after consulting with their doctor.

During the up-dosing protocol, the nut intake was increased by 20–30% every 2 weeks, aiming for a daily maintenance dose of 1 g protein. The decision to select 1 g protein as the maintenance dose was based on various considerations, including our clinical experience, observations of OFC outcomes in our patient population, and practicality for daily dietary inclusion. While recent data may suggest the effectiveness of low-dose OIT, there is still limited evidence to support its widespread adoption as a standard practice beyond treatment with commercially available peanut powder. OIT up-dosing was avoided during pollen season in case of seasonal symptoms to reduce adverse reactions in patients, or when reactions occurred. After reaching the maintenance dose of 1 g nut protein per day, patients continued this regimen for 4 weeks and then were allowed to reduce the intake to 1 g protein at least every other day for 18 to 24 months. In patients who underwent multiple nut OIT, there was an interval of at least 3 months between starting the first OIT and commencing the second nut OIT. During overlapping up-dosing periods, the two doses were administered together.

Following the maintenance period of 18 to 24 months, another OFC was conducted, aiming for the consumption of a total of 4.4 g nut protein. The quantity of individual OFC doses, including the cumulative amount of 4.4 g nut protein, corresponds to the international PRACTALL guidelines [22]. Patients who tolerated this second OFC without experiencing any allergic reactions were considered desensitised and were allowed to eat the nut without limitations but were instructed to continue consuming ≥1 g nut protein at least twice per week. For those patients without other food allergies, the adrenaline auto-injector was then removed from their emergency medication kit, provided they consumed the allergen regularly, independent of their sIgE levels. They continued to have yearly follow-up appointments. In case of an allergic reaction during this second OFC, patients returned to their previous maintenance regimen.

Immunological parameters

Specific IgE levels to the storage proteins were assessed at three time points: before OIT start, upon reaching the maintenance dose, and before the second OFC. Skin prick tests were considered positive if the wheal was more than 3 mm larger than the negative control and were typically only conducted during the initial diagnosis of nut allergy. We opted to analyse the specific IgE to the storage protein rather than the specific IgE to the allergen extract due to its higher sensitivity and specificity [25]. Additional immunological data (e.g., specific IgG4 levels) were not included in our data collection.

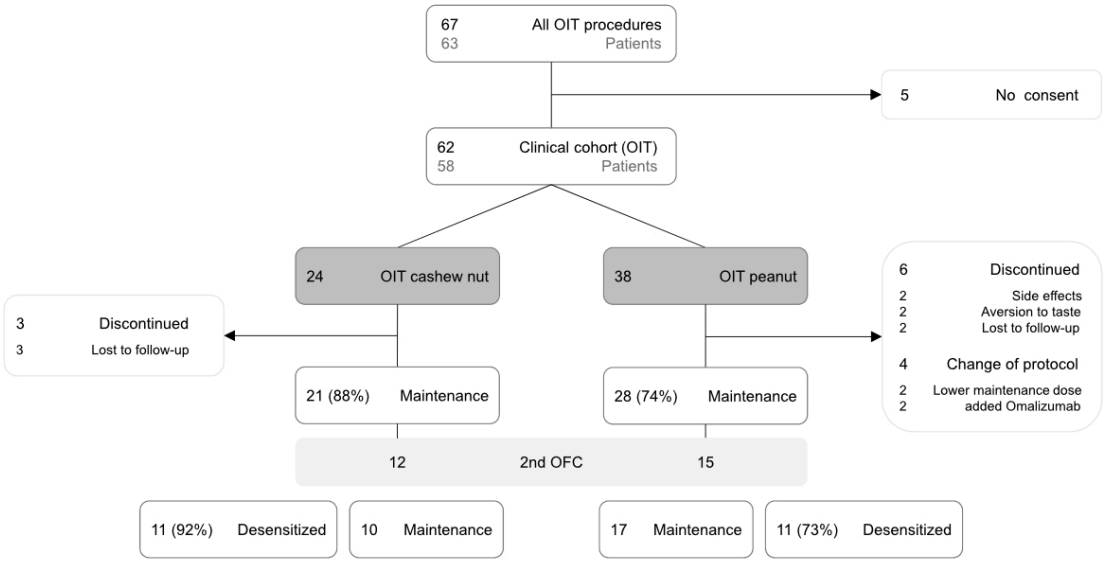
Outcomes

The safety of OIT was assessed by comparing the percentage of patients experiencing adverse effects during the up-dosing phase, as documented at each appointment. Symptoms severity was evaluated using the validated ordinal food allergy severity scale (o-FASS-5) [26]. Grade 1 reactions involved only the oral cavity and were categorised as mild. Grade 2 reactions included one, while grade 3 reactions involved two of the following organ systems: skin, nose, eye, digestive, or uterine, both considered moderate. Grade 4 reactions affected the larynx or bronchi, while grade 5 reactions involved the cardiovascular or nervous system, both categorised as severe reactions.

Statistics

Statistical analysis was performed using R (version 4.2.2) with packages ggsurvfit, ggthemes, tidycmprsk, tidyverse [27]. Categorical variables were compared using Fisher's exact test and continuous variables using the Mann-Whitney U-test. A p-value <0.05 was considered significant.

Figure 1: Patient flow through the study. Approximately half of the patients on maintenance treatment underwent a second oral food challenge (2nd OFC). Among these, 92% cashew nut oral immunotherapy (OIT) patients and 73% peanut oral immunotherapy patients passed the challenge and were considered desensitised. The remaining patients either stayed on or reverted to maintenance treatment.



Time to reach maintenance in subgroups was compared using the cumulative incidence function and Gray's test. Reaching maintenance was considered to be the event of interest, stopping therapy was considered a competing event, and the patients who either paused the up-dosing or were lost to follow-up were right censored on their last clinical follow-up.

Ethics

General consent policy was applied for further use of patient data, and data from patients whose parents or guardians had denied general consent were not further analysed. Approval of this study was granted by the ethics committee of the Canton of Basel (BASEC-Nr. 2023-00524). All aspects of the study were conducted in accordance with the ethical principles of the Declaration of Helsinki. The privacy and confidentiality of all study participants were strictly upheld, and all data were coded prior to analysis to ensure the protection of their personal information.

Results

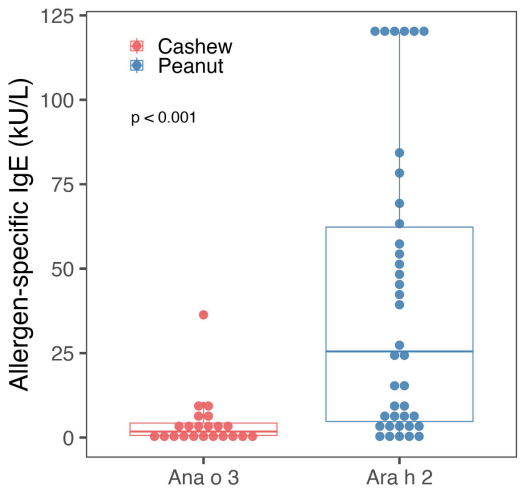
Patient characteristics

During the study period, 67 cashew nut or peanut OIT cases were initiated. Five patients (or their legal guardians) who did not provide consent were excluded. The final analysis included data from 24 cashew nut and 38 peanut OIT cases (figure 1), with four patients undergoing treatment for both nuts; 18 peanut allergy patients (47%) had been considered high-risk.

Both groups displayed a similar sex distribution, median age at initiation of the therapy, and prevalence of other atopic diseases upon starting OIT (table 1). However, children with peanut allergy had significantly higher specific IgE concentrations against storage protein compared to those with cashew nut allergy (median, 25.5 kU/l *vs* 1.78 kU/l; p <0.001) (table 1, figure 2).

During the initial OFC, individual reactive doses were comparable in both groups, with a median of 0.1 g in the cashew nut allergy group and 0.3 g protein in the low-risk peanut allergy group (i.e., peanut cases with an initial standard OFC [p = 0.97]). Most of these children had a moderate allergic reaction grade II, with similar median oFASS-5 scores (2 in both groups, p = 0.37). In contrast, the median OIT starting dose in the cashew nut allergy group was significantly higher at 0.03 g, compared to 0.0064 g protein in the entire peanut allergy group (p = 0.031). In the peanut allergy group, two patients (5%) stopped therapy due to taste aversion, while two patients relocated during the up-dosing phase and were subsequently lost to follow-up. In

Figure 2: Levels of baseline specific immunoglobulin E (sIgE) concentrations for nut-specific storage proteins Ana o3 / Ara h2 for cashew nut and peanut-allergic patients undergoing oral immunotherapy. Values >100 kU/l were set to 120 kU/l.



the cashew nut allergy group, three patients (12%) failed to come to up-dosing appointments and were lost to follow-up (figure 1).

Safety

During up-dosing phase, mild to moderate adverse reactions were observed in eight patients (33%) in the cashew nut allergy group, including mild oral pruritus and moderate reactions such as abdominal pain or acute rhino-conjunctivitis. The remaining 16 patients (66%) reported no adverse reactions. In the entire peanut allergy group, 24 patients (63%) experienced adverse effects during up-dosing. Nineteen of these 24 patients experienced mild to moderate adverse reactions such as oral pruritus and abdominal pain (figure 3A), but five children experienced severe reactions, indicated by an oFASS-5 score of ≥4. Four of these severe reactions occurred at home, and one in the outpatient clinic. A single dose of intramuscular adrenaline was administered to three of these children, and in two patients, the symptoms resolved after the intake of antihistamines. All severe reactions occurred during the up-dosing phase and involved respiratory symptoms, including wheezing and/or dyspnoea. In two of these severe reactions, an augmentation factor was present: one due to a viral infection and one due to pollen-associated symptoms.

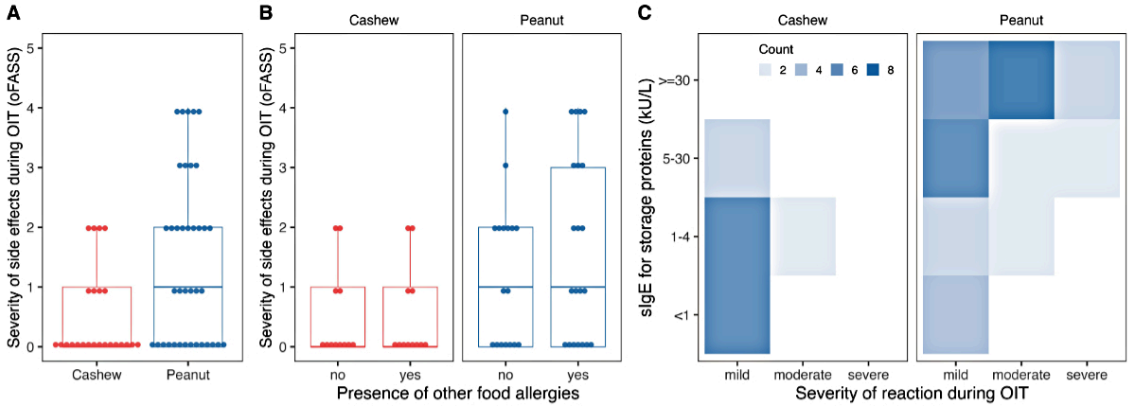
In the peanut allergy group, two patients (5%) reported symptoms consistent with eosinophilic oesophagitis (EoE). One patient discontinued treatment and declined an endoscopy. The other patient ceased therapy, but the endoscopy 4 weeks later did not meet eosinophilic oe-

Table 1:
Baseline patient characteristics.

		Cashew (n = 24)	Peanut (n = 38)	p-Value
Age in years, median (range)		6 (2, 15)	7 (3, 17)	0.69
Female, n (%)		13 (54)	18 (47)	0.79
Any atopic disease, n (%)		24 (100)	36 (95)	0.51
Bronchial asthma, n (%)		11 (46)	20 (53)	0.79
Atopic dermatitis, n (%)		17 (71)	32 (84)	0.22
Other food allergy, n (%)		12 (50)	21 (55)	0.80
Allergic rhinitis, n (%)		12 (50)	26 (68)	0.19
Specific immunoglobulin E to storage protein (Ana o3/Ara h2) in kU/l, median (range)		1.78 (0.05 to 36.9)	25.5 (0.05 to >100)	<0.001
Reactive dose in the initial oral food challenge (in g) nut protein, median (range)		0.1 (0.01 to 3)	0.3 (0.0064 to 3)	0.97
Reaction severity in the initial oral food challenge (oFASS-5), median (range)		2 (1 to 4)	2 (2 to 4)	0.37
Initial standard oral food challenge, n (%)		24 (100)	20 (52)	0.19
Reaction (oFass-5), n (%)	Grade 1	1 (4)	0 (0)	
	Grade 2	12 (50)	10 (50)	
	Grade 3	9 (38)	4 (20)	
	Grade 4	2 (8)	6 (30)	
	Grade 5	0 (0)	0 (0)	
Initial dose-escalation to 0.0064 g nut protein, n (%)		0 (0)	18 (47)	
Reaction (oFass-5), n (%)	No reaction	0	15 (83)	
	Grade 1	0	0 (0)	
	Grade 2	0	2 (11)	
	Grade 3	0	0 (0)	
	Grade 4	0	1 (5)	
	Grade 5	0	0 (0)	
Starting dose in g nut protein, median (range)		0.030 (0.001 to 1)	0.0064 (0.0032 to 1)	0.031

oFASS-5: ordinal food allergy severity scale 5.

Figure 3: (**A**) Maximum severity of allergic reactions during oral immunotherapy (OIT) by nut allergy graded by oFASS-5. (**B**) Maximum severity of adverse reactions during oral immunotherapy by nut allergy and separated by presence of other food allergies. (**C**) Heatmap of the maximum severity of reaction during oral immunotherapy (mild: oFASS 0–1; moderate: oFASS 2–3; severe: oFASS 4–5) in relation to the initial levels of specific immunoglobulin E (sIgE) against storage proteins (Ana o3, Ara h2). oFASS-5:ordinal food allergy severity scale 5.



sophagitis criteria. This patient received omalizumab treatment due to bronchial asthma. With omalizumab administered every 4 weeks, the OIT was successfully resumed. Additionally, in three (13%) peanut OIT patients, the pre-defined protocol was changed due to IgE-mediated adverse reactions: one successfully restarted OIT with omalizumab, and two continued on a lower maintenance dose. One patient opted to discontinue therapy entirely due to adverse reactions. Notably, none of the cashew nut OIT patients modified their treatment due to adverse effects or had eosinophilic oesophagitis-like symptoms.

The presence of other food allergies, atopic dermatitis, asthma/wheeze, or any allergic disease did not influence the severity of adverse reactions during OIT (figure 3B and figure S2 in the appendix). However, nearly all patients with severe reactions (oFASS ≥4) and the majority of those with moderate reactions (oFASS 2–3) had high initial specific IgE levels to the storage protein (>30 kU/l) (figure 3C). An additional analysis showed that higher age at the start of OIT was mildly associated with more severe adverse reactions during OIT ($R = 0.4$, $p = 0.001$; figure S3 in the appendix). However, there was no correlation between the severity of the index reaction during the initial OFC and the severity of adverse reactions during OIT.

Time to reach maintenance and rates of desensitisation

In the entire study population, 21 (87%) of cashew nut-allergic patients and 28 (73%) of peanut-allergic patients reached the maintenance phase. Among these patients, those in the cashew nut allergy group tended to reach maintenance faster (figure 4A). One patient in the cashew nut allergy group and two in the peanut allergy group bypassed the up-dosing phase as they tolerated the maintenance dose of 1 g and only showed an allergic reaction at the last step of 3 g protein during the initial OFC. Children with asthma (figure 4B) or another food allergy (figure 4C) needed significantly longer to reach maintenance. There was, however, no significant difference in time needed to reach the maintenance phase for patients with pre-existing allergic rhinitis or atopic dermatitis compared to those without.

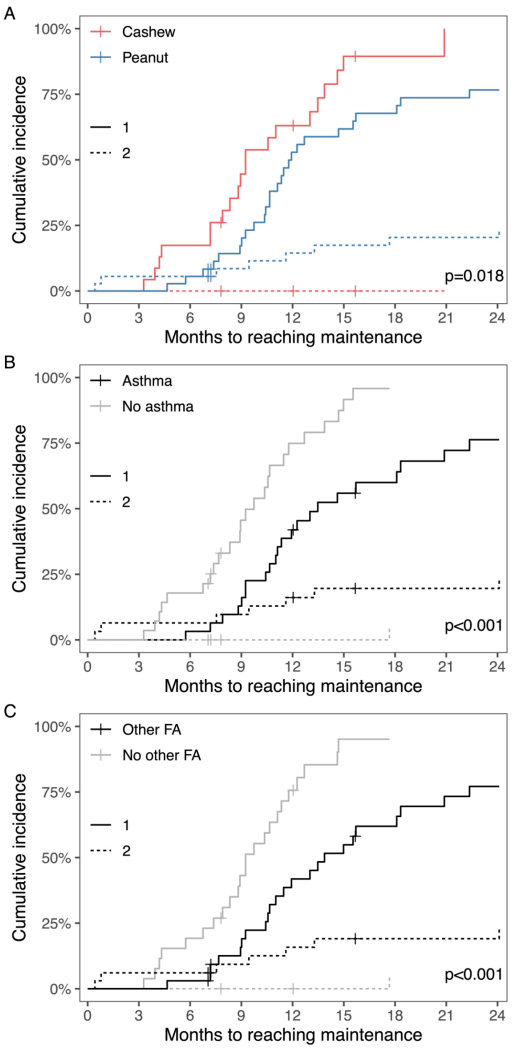
The evaluation period was extended until December 2023, with a total OIT observation period across all patients ranging from 21 to 62 months. Hence, there were patients (7 cashew nut- and 9 peanut-allergic patients) who had not yet undergone a second OFC. Additionally, six patients (4 from the peanut allergy group and 2 from the cashew nut allergy group) chose not to proceed with a second OFC for various reasons. Four patients saw no personal benefit in carrying out the second OFC due to a lack of interest in introducing a larger amount of the food allergen into their diet. Another patient, faced with a malignant tumour diagnosis, and one patient who relocated, elected to remain on the maintenance dose. Among the cashew nut allergy group, 12 patients underwent a second OFC, with 11 (91%) showing tolerance to a cumulative dose of 4.4 g nut protein, indicating desensitisation. One patient experienced a mild reaction (oral pruritus) at the last step of 3 g protein, compared to the initial OFC's 0.1 g reactive dose (generalised urticaria). In the peanut allergy group, 15 patients underwent a second OFC, with 11 of them (73%) showing tolerance to a cumulative dose of 4.4 g nut protein. Among the four patients who presented an allergic reaction during the second OFC, three experienced moderate reactions at the last step of 3 g nut protein. These three patients had a history of severe anaphylaxis (oFASS grade 4 with involvement of the lower respiratory tract). One patient had both a moderate reaction with urticaria in the initial exposure to peanut protein and a moderate reaction with vomiting in the second OFC.

Patients who did not experience an allergic reaction during the second OFC, and were thus considered desensitised, were then allowed to consume the nut freely, with a minimum intake of 1 g nut protein twice per week. To date, no allergic reactions have been reported following the second OFC.

Changes in immunological parameters

Comparing sIgE levels to the storage proteins (Ana o3/Ara h2) from before OIT to upon reaching the maintenance

Figure 4: Cumulative incidence curves for reaching maintenance dose in patients (**A**) undergoing therapy in the cashew nut (n = 24) and the peanut (n = 38) group, (**B**) with (n = 31) and without asthma (n = 31), and (**C**) with (n = 33) and without (n = 29) other food allergy (FA), (1) representing the patients who reached the maintenance dose (continuous lines), and (2) the group of patients who discontinued or changed the protocol due to adverse reactions or aversion to taste (dashed lines). Crosses representing patients who were lost to follow-up.



dose, the cashew nut allergy group (n = 19) showed a clear decreasing trend in median sIgE levels, dropping from 1.78 kU/l to 0.81 kU/l (figure 5A). In contrast, the peanut allergy group (n = 26) exhibited more variable trajectories in sIgE levels, resulting in relatively stable median values at both measurement points, from 25.5 kU/l to 18.8 kU/l.

In the analysis of 27 patients with available data who underwent a second OFC, the cashew nut allergy group showed a continued decreasing trend in median sIgE levels to the storage protein (before OIT 0.83 kU/l, at the start of maintenance phase 0.42 kU/l, before the second OFC 0.29 kU/l). Similarly, the peanut allergy group exhibited an initial increase in median sIgE levels, followed by a decrease by the time of the second OFC (before OIT, 10.6 kU/l; at the start of maintenance phase, 19.1 kU/l; before the second OFC, 6.99 kU/l) (figure 5B). No significant differences in sIgE levels against storage proteins were observed when comparing patients who tolerated the second OFC to those who did not.

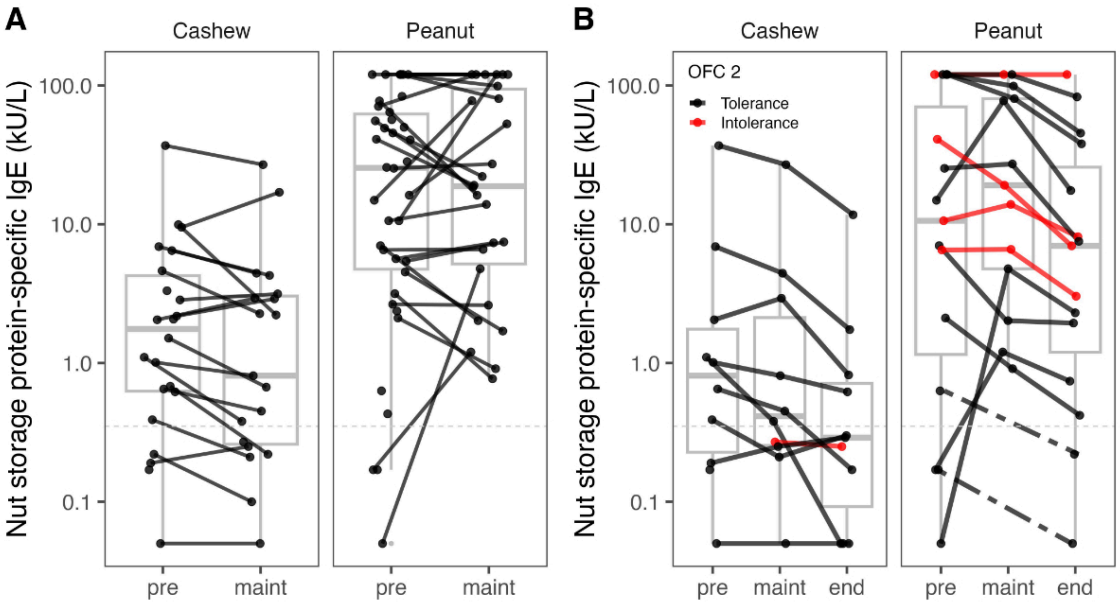
Discussion

This study offers valuable insight into the real-world application of OIT for cashew nut and peanut allergies, revealing a low incidence of adverse reactions during the up-dosing phase in the cashew nut allergy group, alongside with a high success rate in reaching maintenance. Adverse reactions were generally mild to moderate, with severe reactions primarily occurring in the peanut allergy group. Notably, a substantial proportion of patients who underwent a second OFC demonstrated desensitisation, especially in the cashew nut allergy group.

Ensuring safety during OIT is a significant concern, considering the known risk of severe adverse reactions, particularly during the up-dosing phase and especially in doses above 300 mg protein [12, 19]. In our study, we observed a low frequency and severity of allergic reactions in patients undergoing cashew nut OIT. In contrast, the NUT CRACKER study, with a cohort of 50 cashew nut-allergic patients and similar baseline immunological parameters, reported a high incidence of side effects (88%), with 18% of patients requiring adrenaline [20]. In this study, up-dosing was performed up to 4 g nut protein, with a consecutive daily consumption of 1.2 g nut protein daily during the maintenance regimen. Another real-world study on tree nut OIT in 58 cashew nut-allergic preschool children recorded no severe reactions, but 71% experienced mild to moderate reactions [21]. These patients also had baseline immunological parameters similar to those of our cashew nut allergy group, although maintenance therapy was performed with only 0.3 g protein. Our cashew nut allergy group had an even lower rate of mild to moderate adverse reactions (33%) with no episodes of anaphylaxis and no patients having eosinophilic oesophagitis-like symptoms. In contrast to the cashew nut allergy group, the peanut allergy group exhibited a significantly higher rate of adverse reactions, with 13% of patients experiencing anaphylaxis and 63% encountering any adverse reaction. The increased likelihood of severe allergic reactions during peanut OIT, compared to strict avoidance, has been reported in other studies [19, 28], underscoring the importance of thorough discussions with families to assess the risk-benefit ratio.

Previous studies reported a higher incidence and severity of reactions associated with higher sIgE levels and larger doses during OIT [29]. In one study investigating patient factors associated with clinical outcomes in 174 patients undergoing peanut OIT, the number of reactions was positively correlated with baseline sIgE levels to peanut [30].

Figure 5: (**A**) Changes in specific immunoglobulin E (sIgE) to the storage protein (Ana o3/Ara h2) from before starting the oral immunotherapy (OIT) to reaching maintenance dose. Complete data from two cashew nut and two peanut allergy patients are missing. (**B**) Progression over time of sIgE to the storage protein (Ana o3/Ara h2) for the patients who underwent a second oral food challenge (OFC) for cashew nut (n = 12) and peanut (n = 15). Black lines represent patients who had no reaction during the second oral food challenge and were classified as desensitised; red lines represent patients who failed to complete the second oral food challenge with an intolerance. Complete data from two cashew nut allergy patients and two peanut allergy patients are missing. Pre: before starting the oral immunotherapy; maint: start of the maintenance phase; end: end of the maintenance phase.



Two other studies of peanut OIT involving 75 and 653 patients reported baseline peanut-specific sIgE levels that were positively correlated with the rate and severity of allergic reactions during treatment [31, 32]. Similarly, in a sample of 270 preschoolers, higher baseline sIgE levels to peanut were found to be more likely associated with epinephrine use during OIT [18]. Taken together, for peanut OIT, higher baseline specific IgE levels appear to be associated with a higher rate and severity of allergic reactions during treatment, consistent with our study findings (figure 3C).

Our study also observed lower nut-specific IgE levels in cashew nut-allergic patients compared to those allergic to peanuts, which may contribute to the lower rate and severity of adverse reactions during cashew nut OIT. While the data supporting this observation are limited, they align with existing literature suggesting that cashew nut-allergic individuals generally exhibit lower allergen-specific IgE levels [33]. Importantly, our study included unselected patients, reflecting real-world experiences and suggesting that cashew nut OIT is generally well-tolerated. This finding underscores the potential role of specific IgE levels in influencing the safety and feasibility of OIT, highlighting the need for further investigation into the immunological factors underlying allergic reactions during OIT for different allergens. Additionally, the OFC reactive doses and reaction severity during the initial OFC were similar in both the cashew nut and peanut allergy groups, suggesting that cashew nut allergy patients were not inherently "less allergic" than peanut allergy patients despite the differences in baseline specific IgE levels. This indicates that factors beyond the initial allergic response may contribute to the differential rates and severity of allergic reactions observed during OIT for cashew nut and peanut allergies. Understanding these factors better will be crucial for improving treatment outcomes and personalising OIT protocols for different patient populations.

Of note, OIT protocols vary considerably between centres regarding the frequency and dose increments during up-dosing, as well as the maintenance dose and the duration of the maintenance phase. Furthermore, there is no clear guidance on the total protein amount required in the second food challenge to demonstrate desensitisation. We chose a maintenance dose of 1 g protein for various reasons already discussed, which resulted in good tolerability and safety. However, more research on this topic is needed, and standardising protocols in the future would be preferable in order to provide the best outcome for our patients.

In our study patients, we did not validate previous findings that associated the severity of adverse effects during OIT up-dosing with the presence of co-existing asthma or allergic rhinitis (figure S2 in the appendix) [34, 35]. However, patients with asthma or other food allergies took significantly longer to reach the maintenance phase (figure 4). It remains unclear whether this slower progress was intentional for safety reasons as 70% of asthmatic patients had seasonal symptoms, or if other factors influenced the time required to reach maintenance. This suggests the possibility that seasonal triggers may have contributed to a deceleration during the up-dosing phase, especially during pollen season. Patients undergoing cashew nut OIT reached their maintenance dose quicker, which might be attributed to the significantly lower mean starting dose in the peanut allergy group. Younger patients experienced fewer adverse reactions, consistent with existing literature [15, 17] (figure S3 in the appendix).

A small proportion (5%) of children discontinued peanut OIT due to aversion to taste, a phenomenon not observed in the cashew nut allergy group, suggesting a potentially better tolerance for the taste of cashews. The rate of desensitisation in cashew nut OIT was high (91%), in line with existing data [20, 21]. In contrast, the desensitisation rate in the peanut allergy group was lower (73%). However, all patients who did not pass the second OFC had mild to moderate reactions only, and increased their individual reactive dose, indicating partial desensitisation [11]. A review of sustained unresponsiveness through discontinuation of the therapy for a certain period followed by a third oral food challenge was deliberately omitted, as earlier data only promise limited success [15, 36, 37]. In contrast, after reaching the status of desensitisation, patients were allowed to eat the peanut or cashew nut freely but were advised to eat 1 g protein at least twice per week.

Consistent with other studies, a substantial number of patients in the peanut allergy group experienced an initial increase in sIgE levels after completion of the up-dosing phase [38, 39], with some showing persistent high levels even after years of therapy. This complexity in sIgE dynamics makes it challenging to rely on IgE levels for prognostic purposes.

This study has several limitations, including its retrospective design, which leads to potential biases. Additionally, there are missing immunological data such as specific IgG4 levels that could serve as a helpful biomarker during OIT. The heterogeneity in starting and up-dosing protocols further complicates therapy duration comparisons. But this heterogeneity in protocols mirrors the real-life setting and provides important insights into OIT handling. The open OFC format may introduce bias, and the smaller number of patients undergoing a second OFC after the maintenance phase limits statistical power and generalisability. Further evaluations, especially considering the association of low specific IgE with a higher remission rate, may offer additional insights into the study population [15, 36]. To optimise and standardise cashew nut OIT, prospective studies are needed to evaluate safety, feasibility, and long-term outcomes, enhancing the effectiveness and reliability of this treatment.

In conclusion, cashew nut OIT shows promise as a treatment option, demonstrating a low rate of severe adverse reactions and good feasibility in a real-world setting. However, careful consideration of immunological parameters and other allergic diseases is crucial when informing families and planning therapy. Further prospective studies will help enhance the safety and effectiveness of OIT as a treatment option for cashew nut-allergic children.

Acknowledgments

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: supplementary figures

Figure S1: The two starting protocols for nut oral immunotherapy (OIT) at the outpatient clinic, conducted on 1 day. Single highest tolerated dose or 6.4 mg was after eaten daily at home until first up-dosing appointment.

Figure S2: (**A**) Maximum severity of adverse reactions during oral immunotherapy (OIT) by nut allergy and separated by presence of any atopic disease. (**B**) Maximum severity of adverse reactions during oral immunotherapy by nut allergy and separated by presence of asthma. (**C**) Maximum severity of adverse reactions during oral immunotherapy by nut allergy and separated by presence of atopic dermatitis. (**D**) Maximum severity of adverse reactions during oral immunotherapy by nut allergy and separated by presence of allergic rhinitis. oFASS-5: ordinal food allergy severity scale 5.

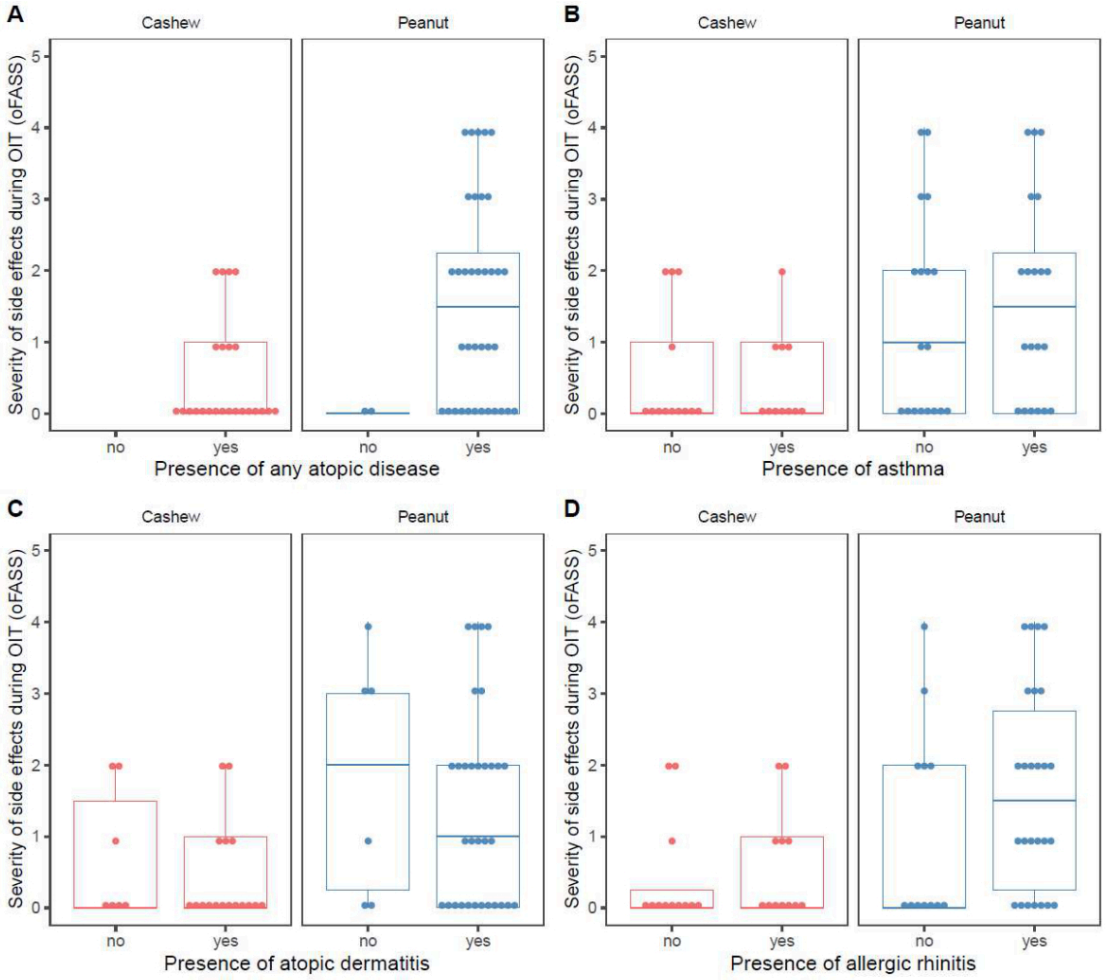

Figure S3: Maximum severity of side effects during oral immunotherapy (OIT) in relation to age at start of the oral immunotherapy. R = 0,4; p = 0.001.
oFASS-5:ordinal food allergy severity scale 5.