High-dose oral immunotherapy

in children with anaphylaxis to peanut

by

Tonje Reier-Nilsen

University of Oslo, Institute of Clinical Medicine

&

Oslo University Hospital, Division of Paediatrics

&

ORAACLE

Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment

2019

TABLE OF CONTENTS

1 PREFACE

1.1 Acknowledgements

I would like to express my special thanks to all the participating children, their siblings and parents: I am deeply impressed by your courage and perseverance through the time-consuming oral immunotherapy, eating distasteful daily doses of peanut. In addition, the children participating in the control group and the children who were defined as ineligible for the oral immunotherapy have contributed invaluably. This project would not have been possible without each and every one you.

Special thanks go to my main supervisor, Geir Håland. I admire your academic approach and experience, and I am grateful that you found time in a busy schedule to share some of your competence with me. I am very grateful for the personal conversations we have shared, which helped me the most throughout these years. To my co-supervisors, professor Karin Cecilie Lødrup Carlsen and professor emeritus Kai-Håkon Carlsen: I am deeply impressed by your academic achievements and really admire your ever-lasting enthusiasm in science as well as in your PhD-students. I am forever grateful for your academic advices throughout these years. And to all co-authors: Please receive my sincere gratitude for all your contributions.

1.2   Summary of the thesis

Introduction

Peanut allergy is common and the main cause of life-threatening allergic reactions. There is no available treatment, except vigilant dietary avoidance with the additional use of rescue medication like adrenaline auto injectors when needed. Accidental exposure is frequent, followed by possible life-threatening allergic reactions. Social restrictions and emotional distress result in reduced quality of life among affected children and their families.

The diagnosis of food allergy is usually based on a convincing history of an allergic reaction after exposure to the culprit allergen. The diagnosis is supported by clinical and/or immunological investigations, usually skin prick testing (SPT) and/or demonstration of specific immunoglobulin E (s-IgE). However, the oral food challenge (OFC), or preferably the double-blinded placebo-controlled food challenge (DBPCFC), is considered gold standard to determine the clinical diagnosis of allergy.

During OFC, the amount of allergen that elicits an allergic reaction can be determined and is referred to as the reactivity threshold. Determining the reactivity threshold is important for at least two reasons: Firstly, to determine the eligibility for oral immunotherapy (OIT) and secondly, to identify the level of management for the individual patient. In order to avoid the costs and the risk of systemic reactions by OFC, s-IgE to peanut and the peanut component Ara h 2, peanut SPT and basophil activation have been evaluated for prediction of the reactivity threshold. In previously published studies, an association between reactivity threshold and peanut SPT, s-IgE to peanut, s-IgE to Ara h 2 and basophil activation has been reported. However, there is little information of such associations in populations consisting solely of children highly sensitized to peanut. The lack of such information is explained by these children often being excluded from OFCs due to the risk of severe allergic reactions.

Trials with OIT have shown promising results for desensitization with acceptable safety profiles in populations of varying severity of peanut allergy. Desensitization, meaning no allergic reaction after exposure to the culprit allergen while on treatment, is the first step to sustained unresponsiveness (SU), meaning no reaction after cessation of treatment. Children with severe peanut allergy are expected to benefit the most from a successful OIT. However, it remains unclear if the promising results of desensitization and safety are transferable to this sub-group of children.

Treatment effectiveness should, in addition to biological outcomes, include patient-reported outcomes (PROs). The PROs include standardized quality of life (QoL) questionnaires and one-dimensional reports of treatment burden. The QoL has been reported to improve in children allergic to peanut after desensitization by OIT. However, previously published studies are based on parental proxy-reports and not on child self-reports, except for one study which was conducted without a control group. For one-dimensional reports of patient-perceived burden through OIT, there is little information.

The main objective of the present thesis was to determine the feasibility and effect of two years OIT in children highly allergic to peanut.

The specific research aims were:

1. To identify baseline characteristics that predicts the possibility of entering a peanut OIT and completing an up-dosing phase.

2. To determine the feasibility and identify factors associated with achieving a high maintenance dose in peanut OIT.

3. To identify patient perspective burden of peanut OIT.

4. To determine the effect of 2-years of OIT by desensitization to peanut and PROs.

Methods

The present thesis reports the results from the ongoing 4-year peanut OIT project: Take away food allergy: Inducing tolerance in children allergic to peanut trial (the TAKE-AWAY trial). The TAKE-AWAY trial is a prospective, open labelled, randomized, controlled trial with the primary aim to assess SU one year after cessation of 4 years of OIT in children with primary peanut allergy. The trial consists of four phases: a screening phase (three days of eligibility screening); an up-dosing phase (50-78 weeks); a maintenance phase (36 months) and a follow-up phase after stopping maintenance treatment (12 months). The presented results span from the screening for eligibility to participate and until two years of OIT (one year of maintenance treatment). The results obtained were categorized into three time-points: screening (Y_0); one year of OIT (the end of up-dosing phase) (Y_1) and two years of OIT (one year of maintenance treatment) (Y_2).

At $Y_{0,}$ a DBPCFC with defatted peanut flour was performed in 100 5-15-year-old children with a history of systemic allergic reactions to peanut and/or sensitization to peanut (SPT $\geq$ 3 mm or s-IgE $\geq$ 0.35 kUA/L). Investigations preceding the DBPCFC included a general clinical examination, a structured interview, standardized QoL questionnaires (Pediatric Quality of Life Inventory Version 4.0 child self-reports and parental proxy-reports, and the Food Allergy Quality of Life – Parental Burden), SPT, lung function measurements (spirometry with reversibility testing), serological immunology assessment (IgE, IgG and IgG_4), basophil activation test (BAT) and conjunctival allergen provocation test (CAPT). International standards were used to define anaphylaxis and grade the allergic reaction during OFC.

Children randomized to OIT attended a bi-weekly up-dosing protocol until reaching the pre-defined maximum maintenance dose (MMD) of 5000 mg peanut protein or the individual maintenance dose (IMD). Adverse events (AEs) were registered and characterized by the

involved organ(s) as well as classified into subjective and mild objective, moderate or severe including anaphylaxis in line with the modified Bock's criteria. An open OFC was performed at Y_2 to determine the level of desensitization. The QoL assessments as well as all tests from screening were repeated in all enrolled children at Y_1 and Y_2. Only children who received OIT were asked to complete a visual analogue scale (VAS) form for perceived treatment burden at Y_1 and Y_2, presented by the mean VAS-score from each of three domains: GI-related AEs, taste/amount of peanuts and time spent on OIT.

Results

Among all children referred for screening (n = 213), 36.2 % (n = 77) were enrolled in the TAKE-AWAY trial. Concern for AEs was reported by 46.5 % as the main reason for unwillingness to participate, while 17.4 % were excluded by the exclusion criteria. At the pre-trial DBPCFC, four children had no allergic reactions, while 19 children in addition to the 77 enrolled had a positive DBPCFC and reacted with anaphylaxis having objective symptoms from at least two organ systems. In the 19 children, a very low reactivity threshold ≤ 3 mg of peanut protein was determined, defining them ineligible for OIT. The included 77 (median (range)) 9.6 (5.1, 15.2) year-old children were randomized to OIT (n=57) or observation only (controls) (n=20). All 77 enrolled children had primary sensitization to peanut with a s-IgE to Ara h 2 of geometric mean (min, max) 40.6 (27.5, 60.3) kUA/L and 81.2 % reported a history of anaphylaxis to peanut prior to enrolment. In 71.4 % of the 77 included children, the parents had a combined annual income above 850.000 NOK, and 84.4 % of the mothers and 75.3 % of the fathers had an education attainment level of at least three years of college/university. Basophil activation (CD63+ basophils ≥ 15 %), peanut SPT and the ratio of peanut s-IgE/total IgE were significantly associated with reactivity threshold and lowest observed adverse events level (LOAEL) (all $p < 0.04$). The basophil activation performed best in predicting very low

reactivity threshold (< 3 mg of peanut protein), with an optimal cut-off of 75.8 % giving a 93.5 % negative and a 36.8 % positive predictive value.

During OIT up-dosing, 21.1 % (n = 12) of the children reached the MMD of 5000 mg peanut protein, while 54.4 % reached the lower IMD and 24.5 % discontinued the treatment. The main reason for not reaching MMD was distaste for peanuts as reported by 66.7 % (n = 28 within IMD and 2 discontinued), followed by AEs reported by 26.7 % (n = 3 within IMD and 9 discontinued) and social reasons reported by 6.7 % (n = 3 discontinued, two found the treatment too time-consuming, while one discontinued due to family reasons). Compared with the 78.9 % children who did not reach the MMD, children who reached the MMD were significantly older, had a significantly lower s-IgE to peanut and Ara h 2, a significantly lower ratio of peanut s-IgE/total IgE, and a significantly higher ratio of peanut $s-IgG_4$/s-IgE. In both bivariate and multivariate regression analyses, the ratio of peanut $s-IgG_4$/s-IgE was the only identified factor significantly associated with achieving MMD.

Mild OIT-related AEs were reported in 13.9 % of the OIT doses, whereas moderate AEs were reported in 0.6 % of the AEs, and anaphylaxis was reported in 0.06 % of the AEs by 19.3 % of the children. The AEs were mostly related to the gastro-intestinal tract (86 %), occurred most often in the first two days of each up-dosing period (p = 0.001), as well as in the first dose-interval step (1-65 mg peanut protein) as compared with the second (66-800 mg) and the third (801-5000 mg peanut protein) dose-interval steps (overall p = 0.03).

The VAS-reported perceived treatment burden was significantly reduced from Y_1 to Y_2 for the GI-domain from (mean (95 % CI)) 2.6 (1.9, 3.3) to 1.4 (1.0, 1.8) (p = 0.001), and for the taste-/amount-domain from 6.5 (5.5, 7.3) to 5.3 (4.3, 6.3) (p = 0.02)). The perceived burden of time spent on treatment was equal at Y_1 and Y_2 (2.9 (2.1, 3.7) to 2.2 (1.5, 2.9) (p = 0.06)).

The OFC at Y_2 was completed by 37 of the 39 children still receiving OIT, and demonstrated that 35/37 challenged children were desensitized to 7500 mg peanut protein independently of

maintenance doses ranging from 350 - 5000 mg with a mean (SD) dose of 3322 (1376) mg peanut protein.

In the child self-reports, the improved QoL in OIT children from Y_0 to Y_2 (mean change (95% confidence intervals (C.I.) (4.4 (0.5, 8.3)) was half of that observed in the parental proxy-reports (9.3 (4.3, 14.3) (both p<0.0001)). Controls reported no significant improvement. In contrast to the child self-report's, the two-fold larger mean change (95% CI) in QoL observed in the parental proxy-reports of the OIT group (9.3 (4.3, 14.3)) was significantly different from that of the controls (0.4 (-7.1, 8.0)) (p = 0.02). Neither perceived treatment burden, level of desensitization, maintenance dose nor AEs significantly predicted changes in QoL.

Discussion

In a homogenous population of children highly sensitized to peanut, a large proportion refused participation prior to screening. Concern for AEs was reported as the main reason for unwillingness for participation. Furthermore, pre-trial information of a time-consuming and perhaps challenging treatment may have biased the study population towards dedicated and resourceful parents and children.

The significant associations between reactivity threshold, and basophil activation, peanut SPT and Ara h 2, are consistent with previous reports, with basophil activation being the best predictor for very low reactivity threshold and thereby eligibility for OIT. The latter may be explained by the BAT being an "in vitro OFC", which may provide associations over a wider spectrum of reactions in the basophils, not limited to stop at a positive OFC.

The finding that no baseline characteristics were significantly associated with completion of the up-dosing phase may be explained by the non-biological finding of distaste for peanuts as the main reason for withdrawal.

11

The up-dosing phase was completed by 75.5 % (n = 43) of the enrolled children, while 21.1 % only reached the MMD. Distaste for peanuts was the main reason for not achieving MMD. There is little of information of peanut distaste in previous reports, which may be explained by the MMD being higher than in most other OIT trials. The high MMD was chosen based on subcutaneous immunotherapy trials of inhalant allergens reporting association between SU and maintenance dose. Nevertheless, a maintenance dose of at least 300 mg peanut protein was achieved by 73.7 % of our children in line with the previously reported 63.6 % to 86.9 % in other peanut OIT studies.

The 13.9 % prevalence of mild GI-related AEs in our children are in line with previous reports. In contrast, anaphylactic OIT-related events in 19.3 % of our children during up-dosing were higher than in most previously published reports, but in consent with the recently reported AR101 peanut OIT. In the AR101 study, 14 % of the 372 OIT children reported at least 76 anaphylactic events, a higher frequency of anaphylactic events per dose-days as compared with the TAKE-AWAY children. The high proportion of anaphylactic events may reflect a highly peanut allergic population, or maybe the high MMD. In the AR101 study, however, the maintenance dose was 300 mg of peanut protein. These observations question the safety of OIT in highly allergic patients.

The desensitization level after two years of OIT was independent of maintenance dose, similar to a recent report. The improved QoL in children after OIT as reported by the parents are consistent with previous reports mostly including such parental proxy-reports. However, the parents reported a two-fold larger improvement in child QoL as compared to their children. This parentally reported QoL score, but not the children's, was significantly associated with OIT. The discrepancy may in part reflect the parents' own improved QoL.

Conclusions

In conclusion, the present thesis brings important insight to the feasibility and effect of high-dose OIT in a homogeneous population of children reacting with anaphylaxis following exposure peanut. None of the baseline clinical or immunological markers were sufficient to substitute OFC in determining a reactivity threshold necessary to define eligibility for entering OIT. Nor could baseline characteristics predict the possibility to complete the up-dosing phase.

Even though the majority of the children completed up-dosing and reached a maintenance dose, high-dose oral immunotherapy was feasible only for a small proportion. Distaste for peanuts were the main limitation of reaching MMD, followed by AEs.

Mild AEs were similar in number and character with previous studies, but the proportion of OIT-related anaphylaxis was higher in this population of children exclusively highly allergic to peanut as compared with previously published studies including less sensitized peanut allergic children. This finding questions the feasibility and safety of high-dose OIT in these children.

The observed discrepancy between the extent of change in child QoL score reported by parents and children following OIT, suggests that parents may over-estimate the effect of the treatment. Hence, it may be more appropriate to use child self-reported rather than parental proxy-reported QoL when assessing patient-related outcome of OIT.

1.3   Abbreviations

AEs – adverse events

ASIT – allergen specific immunotherapy

AUC – area under curve

BAT – basophil activation test

CAPT – conjunctival allergen provocation test

% CD63+ – percentage of CD63 positive basophils – proportion of activated basophils as a measure of allergen induced basophil reactivity

CD-sens – basophil allergen sensitivity, the allergen concentration eliciting half of the maximum basophil activation

CRD – component-resolved diagnostics

DBPCFC – double-blind placebo-controlled food challenge

EAACI – the European Academy of Allergology and Clinical Immunology

EoE – eosinophil esophagitis

EPIT – epicutaneous immunotherapy

FA – food allergy

FAQL-PB – Food Allergy Quality of Life – Parental Burden

FC – food challenge

GI – gastro-intestinal

IgE-mediated – involvement of Ig-E antibodies in the pathogenesis of allergy

IMD – individual maintenance dose

LOAEL – lowest observed adverse effect level

MMD – maximum maintenance dose

NOAEL – no observed adverse effect level

OFC – oral food challenge

OAS – oral allergy syndrome

OIT – oral immunotherapy

PedsQL 4.0 – Paediatric Quality of Life Inventory Version 4.0

PPI – proton pump inhibitor

PPV – positive predictive value

PRO – patient related outcome

RCT – randomized controlled trial

SCIT – subcutaneous immunotherapy

s-IgE/G/G_4 – specific immunoglobulin E/G/G_4

ROC – receiver operating characteristic

SLIT – sublingual immunotherapy

SPT – skin prick test

SU – sustained unresponsiveness

TAKE-AWAY trial – Take away food allergy: Inducing tolerance in children allergic to peanut

Y_0 – at screening (enrolment)

Y_1 – at completed up-dosing, approximately 1 year of treatment, 1 year for controls

Y_2 – at one year of maintenance treatment, approximately 2 years of treatment

QoL – quality of life

1.4   List of papers

Paper #1:

Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, Namork E, Borres MP, Haland G.

Predicting reactivity threshold in children with anaphylaxis to peanut

Clin Exp Allergy. 2018 Apr; 48(4):415-423. doi: 10.1111/cea.13078. Epub 2018 Jan 25.

Paper #2:

Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, Namork E, Borres MP, Haland G.

Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy

Allergy 2018 Oct doi: 10.1111/all.13604. Epub 2018 Sep 17.

Paper #3:

Reier-Nilsen T, Lodrup Carlsen KC, Michelsen MM, Drottning S, Carlsen KH, Chi Zhang, Borres MP, Haland G.

The child's perspective of quality of life in a randomized controlled peanut oral immunotherapy trial.

Submitted to PAI Dec 3.

2 GENERAL INTRODUCTION

2.1 Definitions and mechanisms

2.1.1 Definitions

Allergy is defined by the European Academy of Allergology and Clinical Immunology (EAACI) nomenclature task force as a type of a hypersensitivity reaction initiated by immunologic mechanisms (1). Hypersensitivity reactions are reproducible with objective symptoms or signs following exposure to a defined stimulus at a dose tolerated by normal subjects, and may be either allergic or non-allergic (1). Allergic reactions are classified as immunoglobulin E (IgE) mediated or the rarer non-IgE mediated type, based on the involvement of IgE antibodies in the pathogenesis of reactions. The IgE-mediated allergy results from a type I hypersensitivity reaction (2). If the binding of antigen to IgE antibodies causes an allergic reaction, it is defined as an allergen.

Allergic reactions are categorized into four categories: Type I-IV, depending on the underlying immunologic mechanism. The type I hypersensitivity reaction is responsible for the immediate allergic reaction and the most common mechanism underlying food allergies. The type II-IV hypersensitivity reactions will therefore not be discussed in any further detail in this thesis and the term allergy will be used to equate type I hypersensitivity reaction in the remaining of the thesis.

2.1.2 Mechanisms of type I hypersensitivity reaction

To become sensitized to a food allergen, the culprit allergen that is presented to T cells must be followed by an immune response skewed towards the Th2 pathway, allowing B cells to produce s-IgE antibodies (3). Subsequently, the s-IgE antibodies bind to specific IgE-receptors ($F_{c\varepsilon}RI$) on the surface of basophils in the circulating blood and mast cells in the

tissues (Figure 1). Sensitization refers to this production of allergen specific IgE antibodies

only, and is not synonymous with an allergic reaction.
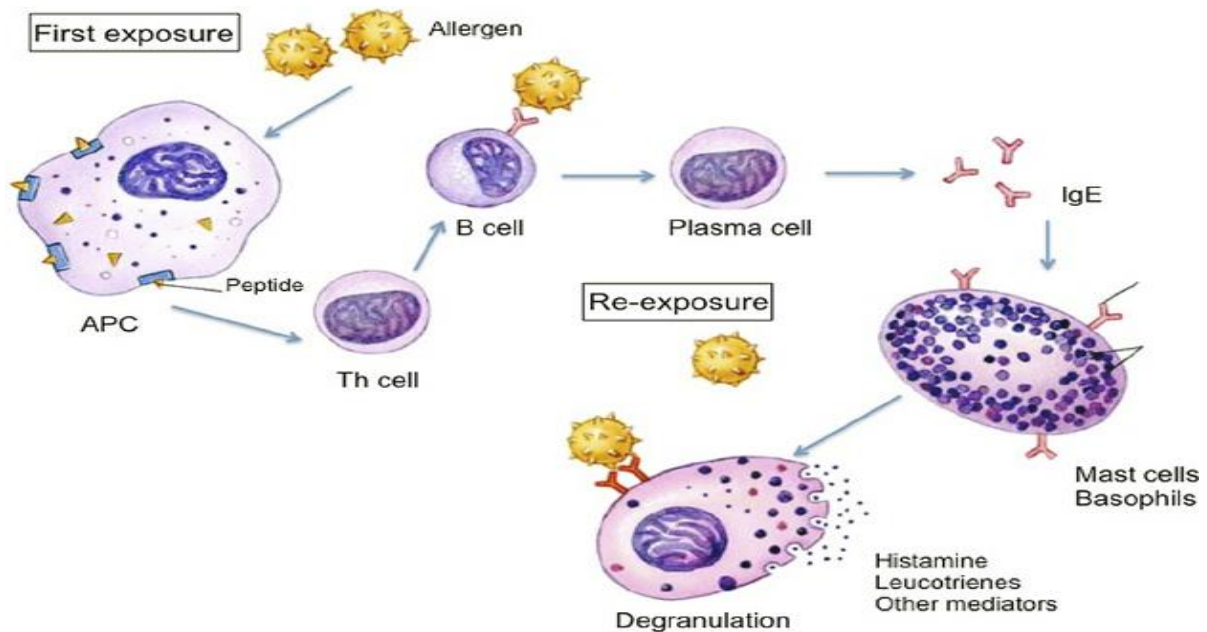
Figure 1. *Type I hypersensitivity reaction. The first exposure causes sensitization with the production of antibodies, while the re-exposure demonstrates the mechanism for an allergic reaction. Reprinted from "onlinebiologynotes.com", with permission Mr. Gaurab Karki.*

After initial sensitization, development of a clinical allergy requires re-exposure of the culprit

allergen (Figure 1). The allergen must be able to bind to the s-IgE antibodies on the surface of

basophils and mast cells in sufficient numbers to cause cross-linking of the IgE antibodies.

Such cross-linking causes basophils and mast cells to release mediators (cytokines and

leukotrienes) contributing to the allergic reaction (3). Hence, individuals may be sensitized as

determined by clinical and/or immunological sensitization tests, but without allergic

symptoms at exposure to the allergen (i.e. sensitized, but tolerant patient) (3), explaining why

allergy is considered a clinical diagnosis. In tolerant individuals, higher levels of s-IgG

antibodies have been observed compared with that of allergic individuals, and several studies

support the hypothesis that s-IgG antibodies compete with s-IgE antibodies in allergen binding to basophils and mast cells (4-6).

2.1.3   Allergic reactions

2.1.3.1   *Primary sensitization*

A type I hypersensitive reaction mostly occurs within minutes of exposure, and the allergic symptoms depend on the location of allergen exposure. In primary sensitization, it is the allergen itself that causes an allergic reaction, or a primary allergy. Primary allergy may result in a life-threatening systemic hypersensitivity reaction, known as anaphylaxis (1). The European Academy of Allergy and Clinical Immunology (EAACI) task force papers use the Sampson's clinical criteria for anaphylaxis (7) and define anaphylaxis by the occurrence of moderate allergic symptoms from at least two organ systems (8, 9) (Table 1).

Table 1. *Clinical criteria for the diagnosis of anaphylaxis.*

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

   And at least one of the following:

   a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).

   b. Cardiovascular compromise (e.g. hypotension, collapse).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin or mucosal tissue (e.g. generalized hives, itch, flushing, swelling).

   b. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).

   c. Cardiovascular compromise (e.g. hypotension, collapse).

   d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).

3. Hypotension after exposure to known allergen for that patient (minutes to several hours)

Hypotension for children is defined as systolic blood pressure <70 mmHg from 1 month to 1 year, (<70 mmHg + (2 × Age)) from 1 to 10 years, and <90 mmHg from 11 to 17 years

Reprinted from Allergy. 2007;62(8):857-71; Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al.:"The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology.", with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/17590200

When diagnosing anaphylaxis, the EAACI task force suggests classifying the anaphylactic reaction. Based on the Sampson's Grading of Food-Induced Anaphylaxis According to the Severity of Clinical Symptoms (Table 2) with a clinical severity scale ranging from one to five (10), the EAACI task force recommends using the simplified scoring system Severity of anaphylaxis (8, 9) scoring from 1-3 (mild-moderate-severe), which later has been modified for children by Vetander et al. (11) (Table 3).

In a comprehensive review article of food-induced anaphylaxis (12), the first signs of anaphylaxis were most commonly gastro-intestinal (GI); abdominal pain and vomiting. This is probably explained by the GI-system being the location for food allergen exposure. Skin reactions were involved in 70 % to 98 % of the cases. Respiratory symptoms were the primary cause of death, especially in asthmatic patients. Cardiovascular symptoms were rare, and seldom seen in isolation from respiratory arrest, particularly in small children.

Table 2. *Sampson's Grading of Food-Induced Anaphylaxis.*

Grade	Skin	GI Tract	Respiratory Tract	Cardiovascular	Neurological
1	Localized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral "tingling," mild lip swelling			
2	Generalized pruritus, flushing, urticaria, angioedema	Any of the above, nausea and/or emesis x's 1	Nasal congestion and/or sneezing		Change in activity level
3	Any of the above	Any of the above plus repetitive vomiting	Rhinorrhea, marked congestion, **sensation of throat pruritus or tightness**	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
4	Any of the above	Any of the above plus diarrhea	Any of the above, hoarseness, "barky" cough, difficulty swallowing, dyspnea, wheezing, cyanosis	Any of the above, dysrhythmia and/or mild hypotension	"Light headedness," feeling of "pending doom"
5	Any of the above	Any of the above, loss of bowel control	Any of the above, **respiratory arrest**	**Severe bradycardia and/or hypotension or cardiac arrest**	**Loss of consciousness**

All symptoms are not mandatory. The severity score should be based on the organ system most affected, eg, if grade 3 respiratory symptoms are present but only grade 1 GI symptoms, then the anaphylaxis severity score would be "grade 3." **Boldface symptoms** are absolute indications for the use of epinephrine; use of epinephrine with other symptoms will depend on patient's history.

Reprinted from Pediatrics. 2003;111(6 Pt 3):1601-8; Sampson HA: "Anaphylaxis and emergency treatment.", with permission from Elsevier.
http://www.ncbi.nlm.nih.gov/pubmed/12777599

Table 3. *EAACI grading of anaphylaxis.*

Grade	Skin	GI-tract	Respiratory	Cardiovascular	Neurological
1 Mild	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral 'tingling', mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, mild wheezing, **chest tightness**	Tachycardia (increase >15 beats/min)	Change in activity level, anxiety, **tiredness**
2 Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhoea, recurrent vomiting	Any of the above, hoarseness, **cough,** barky cough, swallowing or **speaking difficulties, muffled voice,** stridor, dyspnoea, moderate wheezing	As above	'Light headedness', feeling of 'pending doom', **somnolence**
3 Severe	Any of the above	Any of the above, loss of bowel control	Any of the above, cyanosis or saturation <92%, respiratory arrest	Hypotension* and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest	Confusion, loss of consciousness

Reprinted from Pediatr Allergy Immunol. 2011;22(4):369-73; Vetander M, Helander D, Lindquist C, Hedlin G, Alfvén T, Ostblom E, et al.: «Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. ", with permission from Elsevier. http://www.ncbi.nlm.nih.gov/pubmed/21535177

2.1.3.2 Cross-reactivity

In cross-reactivity, it is proteins similar to allergens (homologues) that cause the allergic reaction. These homologues often come from closely related species or from the same protein family, are often heat-labile and often highly homologues with pollen allergens (3). The pollen-food syndrome or the oral allergy syndrome (OAS) is the most typical example of cross-reactivity. In OAS, the proteins found in fruits and vegetables are homologues to the proteins in pollen. The OAS typically results in harmless oral itching and/or swelling and sometimes a perioral rash. In rare cases, the symptoms may progress to severe throat swelling and very uncommonly, to anaphylaxis.

2.2 Epidemiology

Food allergies (FA) are common (13), affecting more than 1-2 % but less than 10 % of the population as reported in a systematic review of studies published from January 1988 to September 2009 (14). The variations between reported prevalence in the reviewed studies might be explained by lack of consistent diagnostic criteria between studies, the age of study participants or geographical variations. A North-American study (15) demonstrated that relying on self-reported FA resulted in 10 times as high prevalence compared with those who based FA on positive sensitization or challenge-proven FA. The prevalence in FA should be adjusted for age, as they generally tend to resolve before school age. In a study from the United States (16), the prevalence of doctor-diagnosed FAs decreased from 4.7 % in the first two years of life to 1.2 % in pre-school children. Food allergies also vary between geographic areas, suggesting lower prevalence in non-Westernized countries (17). Despite adjusting for age, geographic variations and different methodologies, the prevalence of FAs has been increasing in the last two to three decades (13, 18, 19) (Figure 2). In 2011, the Australian HealthNuts study reported that more than 10 % of 1-year-old children had challenge-proven IgE-mediated allergy (20).
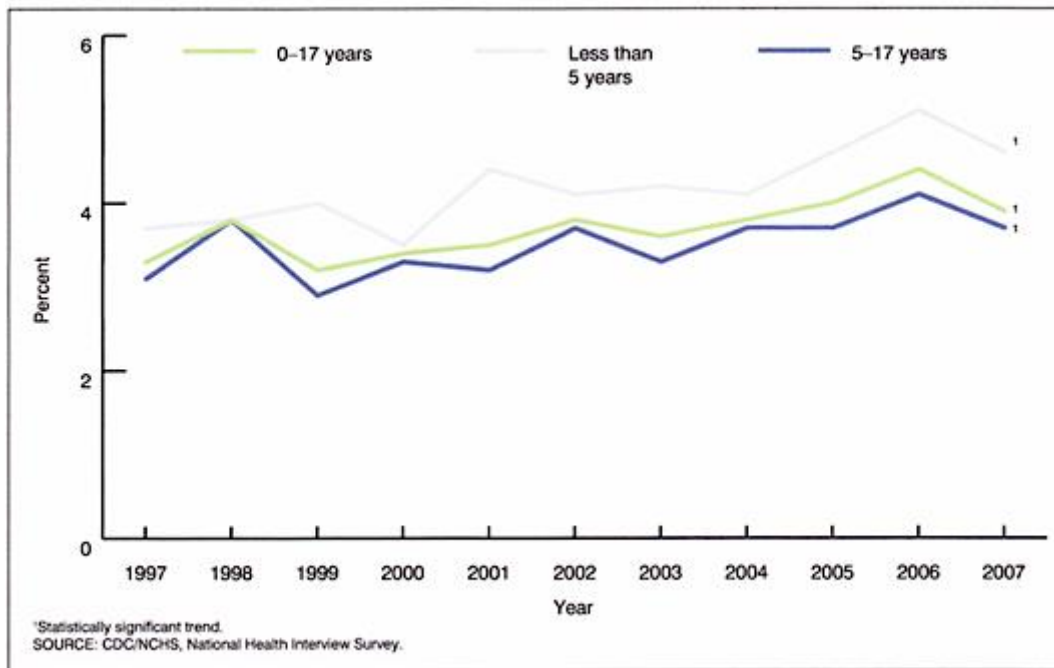
Figure 2. *Percentage of children under 18 years of age who had reported food or digestive allergy in the past 12 months, by age group: United States 1997-2007.*
Reprinted from NCHS Data Brief. 2008(10):1-8; Branum AM, et al.: "Food allergy among U.S. children: trends in prevalence and hospitalizations", which appears within the public domain without further need for permission to reprint.

In children, the most commonly reported allergens are cow's milk protein (2.2 %), peanut (1.8 %) and tree-nuts (1.7 %) are, whereas shell-fish (1.9 %), fruit (1.6 %) and vegetables (1.3 %) are most commonly reported in adults (18). However, much research has been performed on peanut allergy, as it is the main cause of life-threatening allergic reactions in the Western world (21, 22) (Figure 3). In the comprehensive review article (12), food induced anaphylaxis accounted for up to 81 % of the anaphylactic reactions in children, with nuts being the provoking food in the most severe episodes.
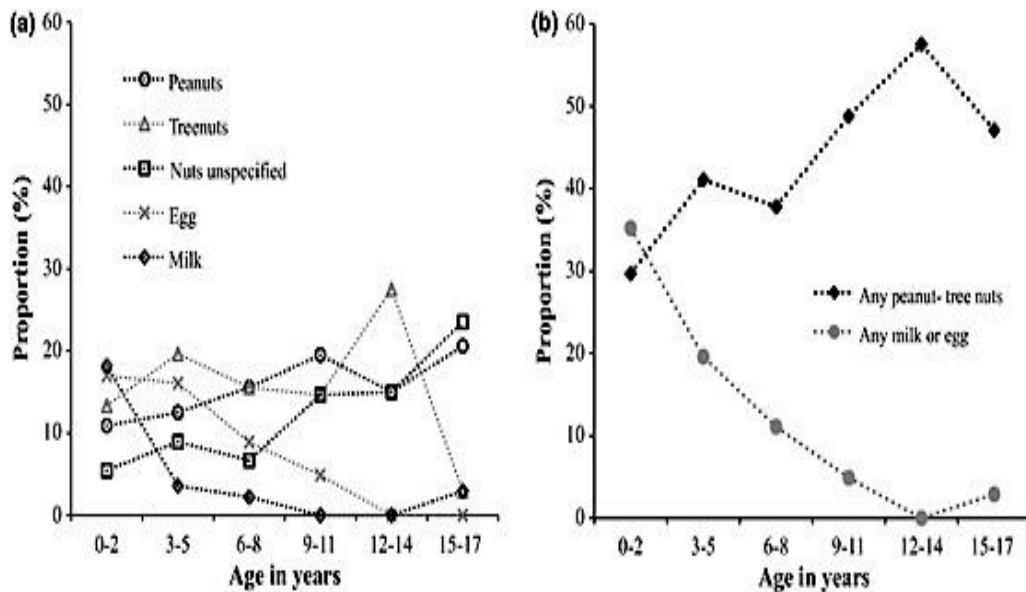
Figure 3. *Eliciting foods in relation to age among 371 children with 381 emergency department visits due to acute reactions to foods in Stockholm, Sweden, during 2007. In (a) the five most common eliciting food items are displayed and in (b) the proportions of reactions to peanuts, specified and unspecified nuts are summated as well as the proportions of reactions to cow's milk and hen's egg.*
Reprinted from Clin Exp Allergy. 2012;42(4):568-77; Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH, et al.: «Anaphylaxis and reactions to foods in children--a population-based case study of emergency department visits.", with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/22417215

Peanut allergy affects 1-2 % of the paediatric population (23), and is increasing (15, 17). In a study including three cohorts of 3- to 4-year-old children from the same geographical area in the UK, the prevalence of peanut sensitization and clinical peanut allergy increased from 1989 to 2002. In contrast to allergies to basic foods like cow's milk, hen's egg and soy protein, spontaneous resolution of peanut allergy is uncommon (24). A spontaneous remission rate of 20 % has been reported for clinical peanut allergy from the first two years of life to pre-school age (24, 25).

2.3 Diagnosing IgE-mediated food allergy

2.3.1 Clinical and immunological investigations

The cornerstone of diagnosing FA includes a convincing history of allergic reaction related to exposure to the culprit allergen, supported by positive relevant allergic sensitization, identified through allergy testing (26). Allergy testing includes immunological investigations by s-IgE antibodies and total IgE and more rarely the basophil activation test (BAT), as well as clinical investigations including SPT and more rarely the recently reported conjunctival allergen provocation test (CAPT) (27). Allergy testing reflects different aspects of the type I hypersensitivity mechanism, as shown in Figure 4.
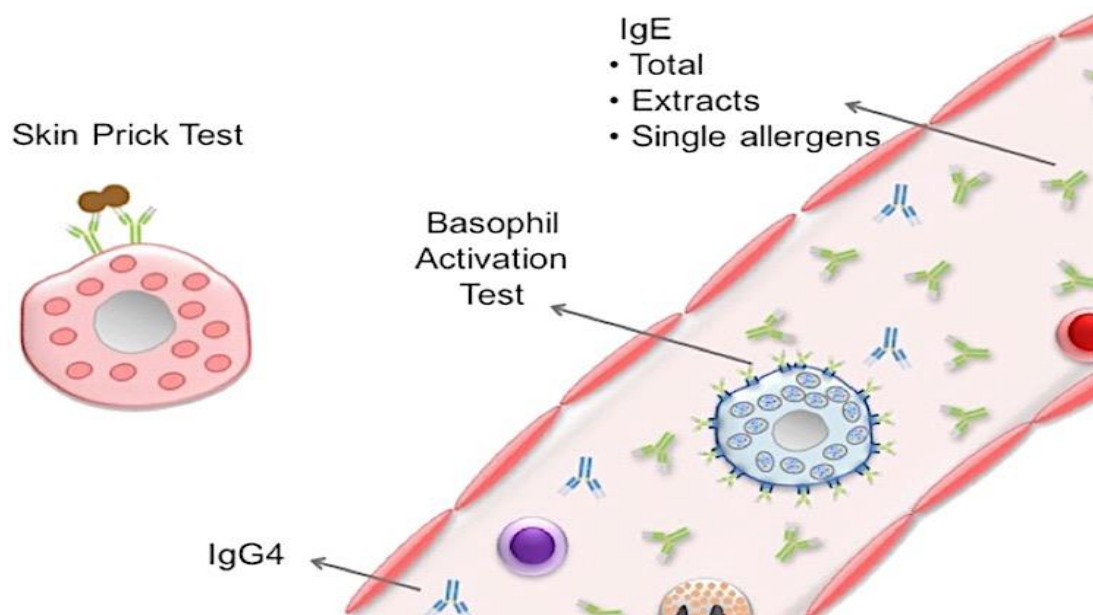
Figure 4. *Tests used to determine sensitization reflecting different aspects of the underlying mechanism. The skin prick test - response of skin mast cells to allergen; the basophil activation test - the response of circulating basophils to allergen; IgE tests - the concentration of circulating IgE, either total IgE or s-IgE to allergen extracts or to individual allergen components.*
Reprinted from The journal of allergy and clinical immunology In practice 2017;5(2):237-48; Santos AF, Brough HA.: "Making the Most of In Vitro Tests to Diagnose Food Allergy.", with permission from Creative Commons Distributions License.
https://www.ncbi.nlm.nih.gov/pubmed/28283150

The SPT reflects the response of mast cells in the skin using allergen extracts or component allergens, whereas the IgE analysis reflects the s-IgE concentration in serum samples (28). Through allergen exposure, the circulating concentration of either total IgE antibodies or s-IgE antibodies to allergen extracts or allergen components may be measured in serum samples (Figure 5). Allergen extracts contain the natural mix of allergenic and non-allergenic proteins that constitutes the allergen source (28). Sensitization given by use of allergen extracts is, therefore, considered crude and cannot distinguish between primary allergy and cross-over reactivity. Another disadvantage is the natural variation in protein composition despite using the same allergen source, as well as the variation in allergen concentration as a consequence of e.g. heating during the preparation process (28). Hence, allergen extracts may vary in composition and concentration, and the use of different allergen producers may therefore lead to different results of s-IgE levels. Four decades ago, there was a call for standardization of allergen extracts with subsequent large production of purified allergens (29). The allergen components consisting of pure allergen proteins however, are produced by purification from natural allergen sources or recombinant expression of allergen-encoding complementary DNA. Using component-resolved diagnostics (CRD) may provide more precise information about the likelihood of clinical allergy in sensitized individuals (28). Hence, CRD can give information of primary sensitization associated with primary allergy and/or cross-sensitization associated with cross-reactivity.

If a clinical history of allergic reaction together with SPT and/or s-IgE is not sufficient for a clear diagnosis of FA, further allergy testing may be warranted.

Some studies suggest using ratios of s-IgE/total IgE (30) and $s\text{-}IgG_4$/s-IgE (4) when diagnosing FAs. However, there are discrepancies in the findings regarding utility of the ratio of s-IgE/total IgE for different FAs. In a study of persistent FAs (e.g. peanut, tree-nuts, shellfish) the ratio of peanut s-IgE/total IgE improved the diagnostic outcome of an oral food
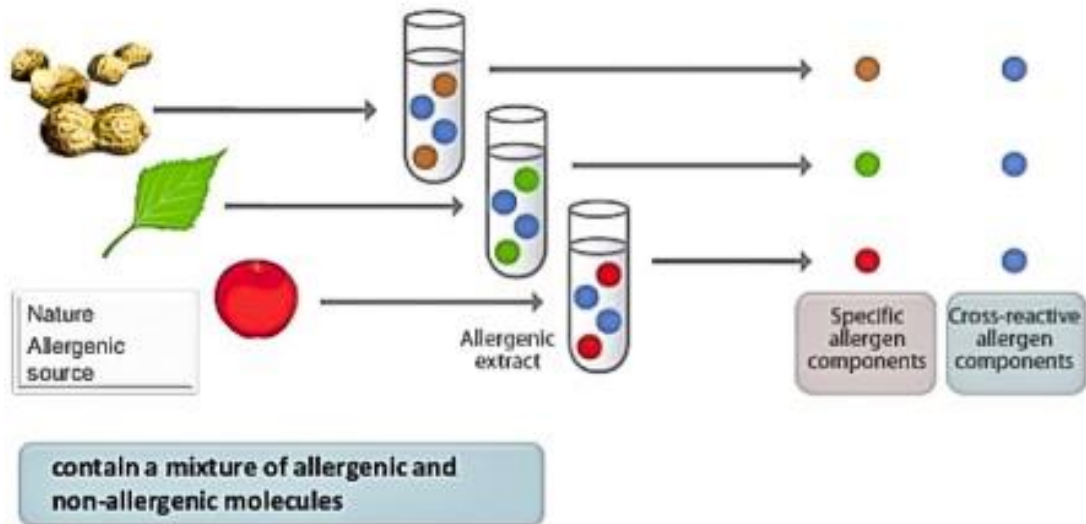
Figure 5. *The allergenic extract contains a mix of allergenic and non-allergenic proteins, while the component-resolved diagnostics uses the allergenic protein only.*
Reprinted wih free permission from Boonmee, S., slideshare.net

challenge (OFC) when compared to s-IgE (30), while similar findings were not reported in a study focusing on transient FAs (e.g. cow's milk, hen's egg, wheat) (31).

For the ratio of s-IgG$_4$/s-IgE to peanut the diagnostic utility has not yet been established, but an association between s-IgG$_4$/s-IgE to peanut and the diagnostic outcome of an OFC has been reported (4).

The BAT may provide added value in allergy testing with its enhanced specificity and often conserved sensitivity as compared with the SPT and s-IgE (26). The BAT has been considered an OFC in a test tube (32), as it measures the response of basophils exposed to food allergens in a test tube. Compared with an OFC, the exposure of food allergen can continue to higher doses.

The CAPT reflects the response of mast cells in the conjunctiva (not shown in Figure 4). In the Oslo Peanut Study (27), the CAPT was able to distinguish peanut sensitized allergic vs. peanut sensitized tolerant individuals with food allergy, and in a study of immunotherapy to

cat dander (26), the CAPT reactivity threshold increased after treatment (33). Whereas SPT and CAPT are both in vivo tests, analysis of s-IgE and BAT represent vitro tests.

Up to date, the OFC is considered gold standard and the conclusive test in diagnosing FA.

2.3.2 Double-blind placebo-controlled food challenge

For the last four decades, the double-blinded placebo-controlled food challenge (DBPCFC) has been considered gold standard in the accurate diagnosis of FA (26). However, in clinical practice an open OFC may be sufficient, as food challenges are mostly used as a diagnostic tool to confirm clinical allergy. The DBPCFC is particularly useful when subjective or mild objective symptoms are considered as signs of an allergic reaction, according to the modified Bock's criteria (Table 4) (34). The DBPCFC is also preferable to determine the reactivity threshold for allergic symptoms, i.e. the expected amount of the offending food that will elicit allergic reactions.

The starting dose of an OFC should be lower than the expected reactivity threshold and a 20 - 30 minutes interval has been recommended between each challenge dose in the PRACTALL consensus report for standardizing food challenges (34). In the absence of allergic reactions, the next challenge dose is given until the OFC is considered positive. However, there is no consensus as to when to define the food challenge as positive. In line with the PRACTALL guidelines (34), some studies record the DBPCFC positive if subjective symptoms occur in consecutive doses (35), while other studies require objective symptoms to occur (36). It has, however, been demonstrated that subjective symptoms may occur at doses 20-fold lower than the lowest dose eliciting objective symptoms (37), while some patients do not experience subjective symptoms at all prior to the occurrence of objective symptoms (38). As a solution to this problem, the PRACTALL guidelines (34) recommend observation of an objective symptom to determine a food challenge as positive, even though subjective

Table 4. *The modified Bock's criteria for classification of adverse events.*

I. SKIN
  A. Erythematous Rash- % area involved_____

  B. Pruritus
  0 = Absent
  1 = Mild, occasional scratching
  2 = Moderate -scratching continuously for > 2 minutes at a time
  3 = Severe – hard continuous scratching – excoriations

  C. Urticaria/Angioedema
  0 = Absent
  1 = Mild – < 3 hives, or mild lip edema
  2 = Moderate - < 10 hives but >3, or significant lip or face edema
  3 = Severe – generalized involvement

  D. Rash
  0 = Absent
  1 = Mild – few areas of faint erythema
  2 = Moderate – areas of erythema
  3 = Severe – generalized marked erythema (>50%)

II. UPPER RESPIRATORY
  A. Sneezing/Itching
  0 = Absent
  1 = Mild – rare bursts, occasional sniffing
  2 = Moderate – bursts < 10, intermittent rubbing of nose, and/or eyes or frequent
    sniffing
  3 = Severe – continuous rubbing of nose and/or eyes, periocular swelling and/or long
    bursts of sneezing, persistent rhinorrhea

III. LOWER RESPIRATORY
  A. Wheezing
  0= Absent
  1 = Mild – expiratory wheezing to auscultation
  2 = Moderate – inspiratory and expiratory wheezing
  3 = Severe – use of accessory muscles, audible wheezing

  B. Laryngeal
  0= Absent
  1 = Mild – >3 discrete episodes of throat clearing or cough, or persistent throat
    tightness/pain
  2 = Moderate – hoarseness, frequent dry cough
  3 = Severe – stridor

IV. GASTROINTESTINAL
  A. Subjective Complaints
  0 = Absent
  1 = Mild–complaints of nausea or abdominal pain, itchy mouth/throat
  2 = Moderate – frequent c/o nausea or pain with normal activity
  3 = Severe - notably distressed due to GI symptoms with decreased activity

  B. Objective Complaints
  0 = Absent
  1 = Mild – 1 episode of emesis or diarrhea
  2 = Moderate – 2-3 episodes of emesis or diarrhea or 1 of each
  3 = Severe – >3 episodes of emesis or diarrhea or 2 of each

V. CARDIOVASCULAR/NEUROLOGIC
  0 = normal heart rate or BP for age/baseline
  1 = mild-subjective response (weak, dizzy), or tachycardia
  2 = moderate-drop in blood pressure and/or >20% from baseline, or significant
    change in mental status.
  3 = severe-cardiovascular collapse, signs of impaired circulation (unconscious)

TABLE LEGEND:

GREEN:
- Not usually an indication to alter dosing.
- Not generally sufficient to consider a challenge positive.

Orange (scores increasing to orange):
- Caution, dosing could proceed, be delayed, have a dose repeated rather than escalated.
- If clinically indicated, dosing is stopped.
- Symptoms that recur on 3 doses, or persist (e.g., 40 minutes) are more likely indicative
  of a reaction than when such symptoms are transient and not reproducible.
- 3 or more scoring areas in orange more likely represent a true response.

RED:
- Objective symptoms likely to indicate a true reaction
- Usually an indication to stop dosing.

symptoms in consecutive doses also are accepted. For children in particular, it is suggested that change in activity level should be considered as a very sensitive sign of a beginning clinical reaction (39).

Concerns have been raised of the possibility of evolving a rush desensitization which increases the amount of allergen required to elicit an allergic reaction during the OFC by using low starting doses, semi-logarithmic dose increases, and prolonged dose intervals (40). Even though these concerns have been contradicted by other studies (41), a final determination of a negative OFC should ideally be followed by giving a single dose with the cumulated amount of the challenged food (40).

2.3.3 Diagnosing peanut allergy

Several attempts have been made to establish highly predictive cut-off values to distinguish patients with allergic reactions from tolerant patients among sensitized subjects, in particular for the commonly used s-IgE to peanut and peanut SPT (42-44). Studies have reported that a wheal size ≥ 8 mm (42) or s-IgE to peanut ≥ 15 kUA/L (44) gives a 95 % positive predictive value for clinical peanut allergy. These values are now the basis of many of the currently accepted predictive cut-offs in use (45). In one retrospective study of food challenges in peanut sensitized children (46), however, a history of an allergic reaction and a s-IgE to peanut ≥ 5 kUA/L always resulted in a positive food challenge, whereas 77 % with similar s-IgE without a previous allergic reaction had a negative food challenge. Hence, validated cut-off values may vary not only between populations, as well as age. For cow's milk and hen's egg allergies, it has been shown that the cut-off levels for a positive food challenge are lower in younger children (< 2 years old) (47).

The s-IgE to Ara h 2 are superior in predicting diagnostic outcome of an OFC (48), while the ratio of peanut s-IgE/total IgE (30) and s-IgG$_4$/s-IgE to peanut (4) are less sensitive. The

peanut component allergen Ara h 2 has been demonstrated best in predicting severe allergic reactions (45, 49, 50). In one multicentre European study, s-IgE to Ara h 2 > 1.00 kUA/L conferred a 97 % probability of a systemic reaction (51). However, it seems like the Ara h 2 cut-off value for a 100 % positive predictive value (PPV) in predicting peanut allergy may be somewhat higher the younger the age. In adults, the Ara h 2 cut-off value with a 100 % PPV in predicting primary peanut allergy has been shown to be 1.75 kUA/L (52), whereas the 100 % PPV cut-off value in children with a median age of 6 years was 5.17 kUA/L (49).

The BAT (32, 53, 54) as well as the recently reported CAPT (27) may be valuable contributors when diagnosing peanut allergy, but are until now mainly used in experimental settings.

2.3.3.1 *Predicting severity of allergic reactions*

Once a diagnosis of peanut allergy is made, predicting allergy severity may contribute to optimal management, including prescription of appropriate treatment.

Allergy severity has been associated with basophil activation (55), and with peanut SPT and s-IgE in some (53, 56, 57), but not all (38, 58) studies. In one study of 71 patients with a median age of 16 years and various FAs (53), the allergy severity grade during a DBPCFC correlated significantly although weakly with peanut SPT ($r_s = 0.24$) and s-IgE to Ara h 2 ($r_s = 0.31$). In another study of 175 patients, with an age range of $1 - 26$ years and a clinical history of allergic reaction to peanut, an even stronger correlation of $r_s = 0.60$ was reported between s-IgE to Ara h 2 and allergy severity (57).

In a study of 21 children (mean age of 60 months) with peanut allergy and 34 controls (28 tolerant and 6 non-anaphylactic reaction) (56), a peanut SPT of 11.25 mm was 33 % sensitive and 97 % specific, and a s-IgE to peanut of 7.7 kUA/L was 70 % sensitive and 97 % specific in predicting anaphylaxis. A titrated SPT (SPT_t) differentiated between Sampson severity

grade of anaphylaxis grade 3-5, grade 1-2 and negative food challenge in a study of hen's egg allergy (59), while similar results have not been shown for peanut allergy.

In a study including SPT, s-IgE to peanut and Ara h 2, the ratio of s-IgG$_4$/s-IgE to peanut and BAT in multivariate analyses to assess association with peanut allergy severity (55), basophil activation (% CD63+) was the marker strongest associated with severity.

2.3.3.2   *Reactivity thresholds*

The reactivity threshold is defined as the amount of peanut ingested at the time of a positive food challenge (60). There remains some disagreement however, as to what constitutes a positive food challenge (34). The consensus protocol for determination of threshold doses (60), however, suggested standardized threshold levels, such as the lowest observed adverse effect level (LOAEL). The LOAEL is defined as the lowest amount of food ingested eliciting mild, objective symptoms (mild urticaria, erythema, oral angioedema) according to the modified Bock's criteria (Table 4) (34).

Determination of the reactivity threshold may be helpful to individualize treatment strategies related to peanut exposure. Previously, allergists gave precautionary advice assuming that the threshold dose of the offending food was zero (60). However, a zero-tolerance policy created huge practical problems, and increased the precautionary labelling of food by the food industry. As a consequence of the significant reduction of "allergen safe food", the distribution model for expected LOAELs was published in 2014 (61). This distribution model was based on peanut OFCs in more than 200 peanut sensitized individuals (Figure 6) (61). The ED$_{01}$ for peanut, i.e. the predicted eliciting dose for the most sensitive 1 % of the population, was 0.2 mg peanut protein. The distribution model provided the basis of the revised Voluntary Incidental Trace Allergen Labelling (VITAL) 2.0 thresholds in Australia, and manufacturers were enabled to apply more appropriate precautionary labelling (61).
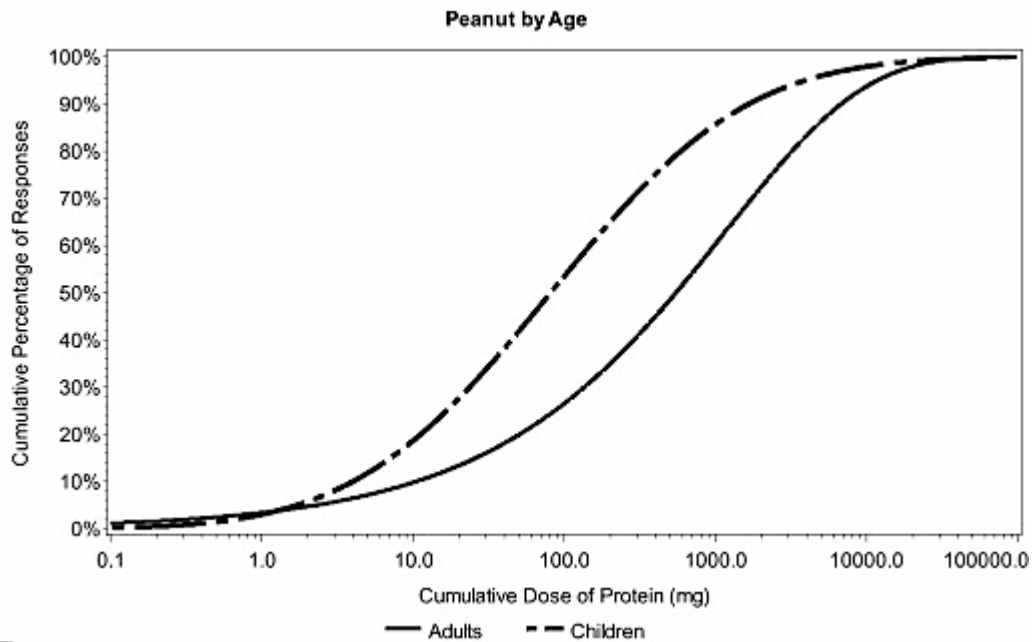
Figure 6. *Probability distribution model for individual thresholds (expressed as milligrams of protein) based on age of the allergic patient at challenge.*
Reprinted from J Allergy Clin Immunol. 2014 Jan;133(1):156-64; Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. "Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications.», with permission from Elsevier.
https://www.sciencedirect.com/science/article/pii/S009167491301059

Determining reactivity thresholds has been complicated by reports of inconsistent reactivity thresholds, varying between different individuals with the same FA (62), as well as within the individual as demonstrated in two OFCs performed median 14 (range 7 – 126) days apart (63). Intra-individual variations may be unexplained, but augmenting factors like exercise, impaired compliance to asthma treatment, excessive tiredness, ongoing infection or menstruation are identified (35). Furthermore, different allergenic foods have been reported to have different threshold doses (60).

Determining reactivity thresholds by food challenge is resource intensive, expensive and carries the risk of a systemic reaction. Hence, attempts have been made to identify clinical or biological markers which can predict low threshold doses in individuals. In study populations heterogeneous with respect to the severity of peanut allergy, reactivity threshold has been

shown to be associated with s-IgE with Ara h 2 (57), as well as with the s-IgE to peanut, peanut SPT and basophil activation (38) in some (38, 57), but not all studies (63). However, the associations of the reactivity threshold were not sufficient to replace food challenge. The ability of these markers to predict reactivity threshold in a homogeneous population of children with severe peanut allergy is still unclear.

Despite the unique ability of CRD in predicting the diagnosis of peanut allergy, OFC, and preferably a DBPCFC, is still considered gold standard to determine the severity of allergic reactions as well as the reactivity threshold (60).

2.4   Treatment strategies

2.4.1   Previous and current treatment for food allergy

Once diagnosed with primary food allergy, the doctor's advice is to avoid the offending food. Despite vigilant dietary restrictions, accidental exposure occurs, and for peanuts, an annual accidental incidence rate of 14.3 % is reported (64). There is a need, therefore, for patients susceptible of severe allergic reactions always to carry rescue medication like adrenaline auto-injectors. Adrenaline is, however, under-used. Only one third of the children in a recent study received adrenaline (65), either before arrival or as part of the treatment at the emergency department (65). Hence, the constant risk of a potentially fatal allergic reaction results in a call for more efficacious treatment strategies.

2.4.2   Allergen specific immunotherapies

Allergen specific immunotherapy (ASIT) modifies the immune system by multiple mechanisms including desensitization of basophils and mast cells, induction of Treg and Breg cells and suppression of Th2 and Th1 cells (Figure 7) (66).
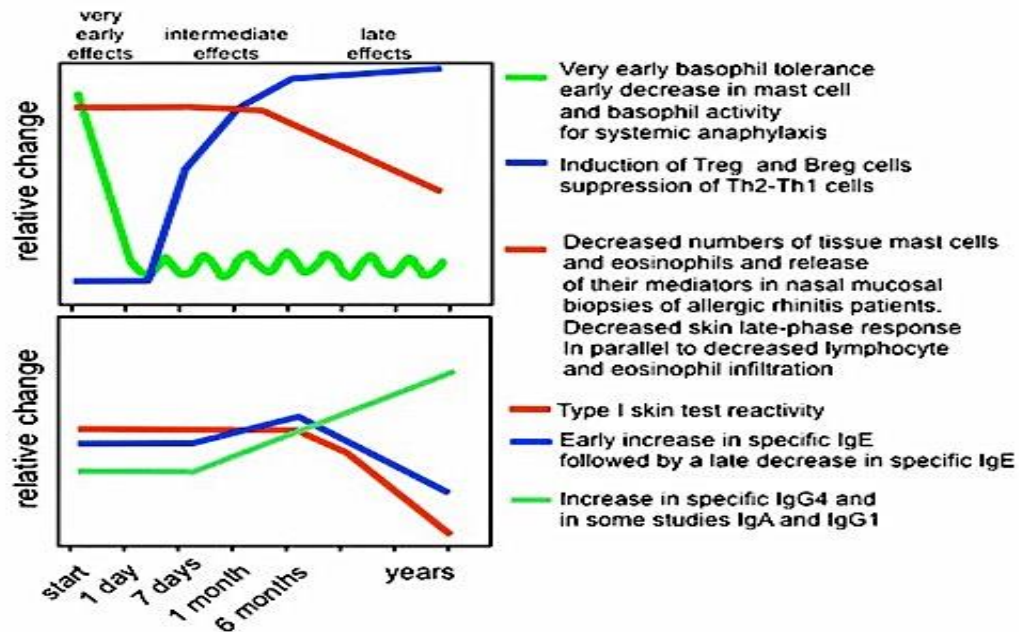
Figure 7. *Immunologic changes during the course of ASIT. Within the first hours of the first dose, the activity of basophils and mast cells as well as the ability of degranulation are reduced. Subsequently, allergen-specific Treg and Breg cells are produced and the Th1 and Th2 cells are suppressed. Levels of s-IgE increase in early treatment followed by a late decrease, while s-IgG₄ levels increase. The ratio of s-IgE/s-IgG₄ decreases after several months.*

Reprinted from World Allergy Organ J. 2015; 8(1): 1-12: Akdis C. "Mechanisms of allergen-specific immunotherapy amd immune tolerance to allergens.", with permission through the Creative Commons Attributions License.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4430874/

To date, ASIT is the only therapy that has been shown closest to cure allergy. In clinical practice, ASIT has been used for more than hundred years, and the first study of ASIT was published in 1911 by Noon (67). The principle of ASIT is gradually exposure to increasing doses of a specific allergen through the oral, sublingual or subcutaneous routes until a maintenance dose is reached (68). The ASIT protocols typically consist of an up-dosing phase and a maintenance phase which is continued mostly for 3 – 5 years. The up-dosing phase is scheduled either as a conventional build-up of gradually incrementing doses administered weekly or biweekly, or as a cluster, rush or ultra-rush build-up which accelerates the schedule and shortens the up-dosing phase. The goal is to achieve post-discontinuation effectiveness

known as sustained unresponsiveness (SU) or tolerance. The first step to achieve SU is desensitization with no allergic reaction while regularly exposed to the allergen, given by the increasing threshold of allergen exposure required to elicit an allergic reaction. Desensitization and SU are the desired biological outcomes of a successful OIT.

Today, subcutaneous immunotherapy (SCIT) is established as a conventional treatment for allergies to pollen, venom, mite and furry animals (69). For pollen induced allergic rhinitis, SU has been shown after three years of SCIT (70, 71). Venom SCIT has been reported to reduce life-threatening reactions (72). Higher maintenance doses have been associated with higher likelihood of SU in SCITs for inhalant and venom allergies (73, 74).

2.4.3   Allergen specific immunotherapies for food allergies including peanut

In the beginning of the 1990s, two separate studies of SCIT for peanut allergy were performed with good efficacy, but were stopped due to a high level of systemic AEs ranging from a rate of 13.3 % to 39 % (75, 76). Sublingual immunotherapies (SLITs) for food allergies have, however, reported more favorable safety profiles, but have modest success in desensitization and poor success in SU (68), as have peanut SLITs (77, 78). In one study of peanut SLIT (79), 14 of 20 patients completed 44 weeks of treatment and 60 % reported no AEs while threshold level increased from 3.5 mg to 496 mg.

Nowadays, epicutaneous immunotherapy (EPIT) for peanut is under growing investigation (80). To date, studies on EPIT report high adherence rates above 94 % with no persistent GI-symptoms and seldom AEs outside of the local patch site (81, 82). The major AEs are well-tolerated, localized patch-site reactions (80). The effect measured in increasing reactivity thresholds at OFC is associated with younger children under 11 years of age and duration of the treatment (82). The reactivity threshold is reported to increase from median 30 mg to 400 mg after one year of treatment in one study (81) and from 44 mg to 1440 mg in another (82)

sufficient to reduce allergic reactions after accidental exposure by at least 95 % on a population level (83).

The last three decades, an increasing amount of oral immunotherapies (OITs) have been commenced. Studies of OIT for cow's milk (84) and hen's egg (85) showed promising results for desensitization with acceptable safety profiles. Most studies, however, have been initiated for peanut OIT. The principle of OIT is outlined in Figure 8.
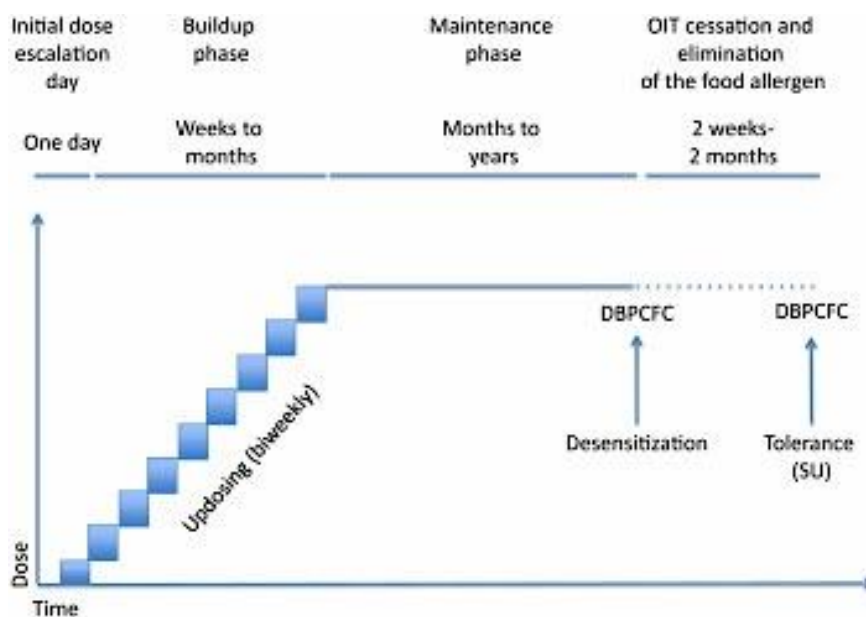
Figure 8. *Typical protocol of OIT in clinical trials. The starting dose is lower than the threshold dose. During an initial rush build-up, doses are rapidly increased every 30 minutes to identify the highest tolerated dose. During the slow build-up phase, the daily OIT dose is increased every other week until a maintenance dose is reached. The maintenance dose is typically continued for 3- 5 years. An oral food challenge to the food is performed to assess desensitization while still receiving OIT. Sustained unresponsiveness is typically assessed 4 to 12 weeks after cessation of OIT.*
Reprinted from J Allergy Clin Immunol Pract 2017; 5: 250-72: Gernez Y et al.: "Immunotherapy for Food Allergy: Are We There Yet?" with permission from Elsevier.
https://www.sciencedirect.com/science/article/pii/S2213219816306675?via%3Dihub#fig2

The starting dose must be lower than the reactivity threshold, preferably determined by a DBPCFC. The up-dosing phase consists of a rush build-up, a conventional build-up, or often a combination of biweekly up-dosing proceeded by a one-day escalation day. The protocol is finalized by a maintenance phase which is continued for some time. Desensitization and SU are determined by OFCs, most preferably DBPCFCs. Furthermore, the use of non-biological patient-reported outcomes (PROs) when assessing treatment effect is recommended (86). The PROs are any patient-reported health data including one-dimensional reports of AEs and multidimensional assessment of at least physical, emotional (or psychological) and social domains using standardized assessments of QoL, either generic or health-related.

Peanut OIT trials have shown promising results for desensitization with a 63.6 % to 86.9 % success rate as previously reported, with maintenance doses varying from 125 mg to 4000 mg of peanut protein (87-94). The safety profiles have been acceptable with AEs reported in up to 20 % of the dose-days (68, 87-91, 95). Evidence of SU after OIT is, however, scarce (87, 90), but two studies with maintenance doses of 4000 mg peanut protein reported SU in 50 % of the participants after four weeks cessation of treatment (87), decreasing to 15 % after six months cessation (90). Hence, the effect of OIT on SU is much smaller as compared to effect on desensitization (77). The most successful SU reported by peanut OIT, is the 78 % of 37 children (age range 9 – 36 months) who achieved a 4-weeks SU regardless of maintenance dose of 300 mg or 3000 mg peanut protein (96). However, published studies vary in design when it comes to inclusion criteria, maintenance dose, time of treatment and definition of desensitization and SU.

Adverse events reduce the feasibility of peanut OITs reflected by the relatively high drop-out rate ranging from 10 % to 32 % in studies (97). The most frequently reported AEs are GI-related (oral itching and stomach ache) (92-94, 97), while the worrying observation of OIT-related eosinophil oesophagitis (EoE) (92, 98) is estimated to develop in 2.7 % of patients

undergoing OIT (97, 98). Anaphylactic events rarely occurred (≤ 1) in studies with maintenance doses ranging from 300 mg to 1400 mg peanut protein (88, 91, 94), except from the 14 percent of the children in the recently published AR101 who experienced anaphylaxis with the need of adrenaline. The AR101 study included children and adolescents with a reactivity threshold < 100 mg peanut protein who were treated with maintenance doses of 300 mg peanut protein (99).

A fixed starting dose and a gradual up-dosing protocol have been associated with fewer AEs and a higher rate completing the treatment (88, 100) as compared to a rush-protocol. Using anti-IgE treatment has been reported to reduce AEs in rush protocols (101). To date, it is not clear which starting dose and maintenance dose are the most appropriate with respect to efficacy by desensitization and SU, balanced against the safety of OIT. In participants with severe allergic reactions, a very low OIT starting dose may be preferable, based on the associations reported between very low reactivity thresholds and severe reactions (36, 53, 55, 102, 103).

Peanut OIT are reported to improve QoL in children (91, 104-108) despite challenging and sometimes severe AEs (92, 109). Most of these reports, however, were based on parental reports of the child's QoL (91, 104-107), sometimes referred to as parental proxy-reports (110, 111), and rarely on the children's self-reports (108). One study included both parental proxy-reports and child self-reports and reported improved QoL after OIT (108). However, this study did not include a control group, making it unclear whether the improvement in QoL was caused by the OIT (108). In a report of 122 children with different food allergies, parents assessed QoL in their children higher than the children themselves (112). Hence, only relying on parents' assessment of child QoL, may be misleading. Furthermore, previous peanut OIT studies contain no information of one-dimensional patient perspectives of treatment burden including AEs, reported by, for example a visual analogue scale (VAS).

Previously published peanut OIT trials have included populations with large variations of allergy severity (87, 89-91). In one study of 23 children (88), anaphylaxis was diagnosed based solely on a peanut specific (s-) IgE of median (range) 95.6 (3 – 2071) kU_A/L, but clinical anaphylaxis was not verified in all by a DBPCFC. It is unclear, therefore, if the promising results of OIT desensitization are transferable to a sub-group of children with anaphylaxis to peanut, expected to benefit the most from a successful OIT (35, 89, 100).

3   OBJECTIVE AND SPECIFIC AIMS OF THE THESIS

Oral immunotherapy is promising for inducing allergen desensitization, whereas evidence that successful OIT will induce sustained unresponsiveness (SU) is scarce. Theoretically, a high allergen maintenance dose in OIT may increase the likelihood of SU. Even though children highly allergic to peanut probably would benefit the most from a successful OIT (35, 68, 89, 100), there is limited documentation of feasibility and safety of high-dose OIT in this group of patients.

Therefore, the present thesis tests the hypothesis that children who are highly allergic to peanut will benefit from a high-dose peanut OIT.

The objective of the present thesis was to determine the feasibility and effect of two-years OIT in children highly allergic to peanut.

The specific research aims of the present thesis are visualized in Figure 9 and were:

1. To identify baseline characteristics that predicts the possibility of entering (1A) and completing (1B) an up-dosing phase of peanut OIT (papers #1 and #2).

2. To determine the feasibility and identify factors associated with achieving a high maintenance dose in peanut OIT (papers #1 and #2).

3. To identify patient perceived burden of peanut OIT (papers #2 and #3).

4. To determine the effect of 2-years of OIT by desensitization to peanut and PROs (paper #3).
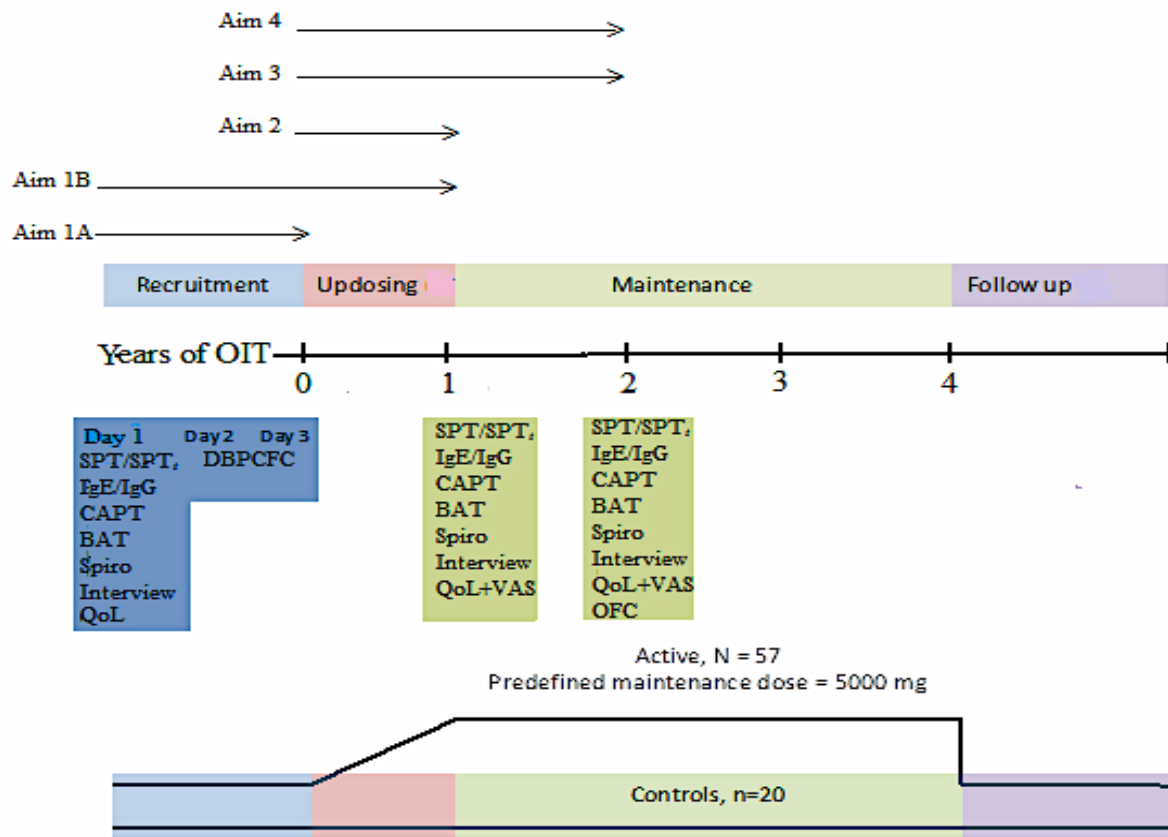
BAT – basophil activation test; CAPT – conjunctival allergen provocation test; DBPCFC – double-blind placebo-controlled food challenge; OFC – oral food challenge; Spiro – spirometry with reversibility testing; SPT – skin prick test; SPT_t – titrated skin prick test; VAS*; visual analogue scale form of perceived treatment burden; QoL – standardized quality of life questionnaires
*only in the OIT children

Figure 9. *End-points related to the various aims. Aim 1A is related to characteristics at baseline and outcome at Y_0, whereas aim 1B is related to characteristics at baseline and outcome at Y_1. Aim 2 is related to characteristics at baseline (Y_0) and the up-dosing phase, Y_0 to Y_1. Aims 3 and 4 are related to the two years of OIT, Y_0 to Y_2.*

4 METHODS AND SUBJECTS

4.1 Study design

The present thesis reports results from the first two years of the ongoing "Take away food allergy: Inducing tolerance in children allergic to peanut" trial (TAKE-AWAY trial), designed to assess one-year SU after four years of OIT in children with primary peanut allergy.

The TAKE-AWAY trial is a prospective, open labelled, randomized, controlled peanut OIT trial (RCT), consisting of four phases:

- screening phase (three days of eligibility screening)

- up-dosing phase (50-78 weeks)

- maintenance phase (36 months)

- follow-up phase (12 months)

Results were categorized into three time-points:

- screening (Y_0)

- one year of OIT (the end of up-dosing phase) (Y_1)

- two years of OIT (one year of maintenance treatment) (Y_2)

Children who discontinued the treatment were not assessed at subsequent time-points.

The TAKE-AWAY trial was conducted as a single centre trial at the Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Norway. Children were recruited for screening investigations by referral from the in-house clinic, other paediatric allergy clinics in Oslo and the surrounding area, as well as from the Oslo Peanut Allergy Study (27).

Screening and subsequent enrolment were performed from February 2014 to June 2015 and all participants reached Y_2 by September 2017.

Time-points for the investigations are shown in Figure 9. Prior to screening, a telephone interview with families of referred children was performed to assess the inclusion and exclusion criteria. The 3-day investigation program included a general clinical examination, a structured interview and standardized QoL questionnaires, blood samples for serological and immunological analyses, lung function measurements (predicted forced expiratory volume in one second ($FEV_1\%$) (113)), SPT and titrated SPT (SPT_t), CAPT and BAT, followed by a DBPCFC.

The QoL assessments as well as all tests from screening were repeated in all children who attended Y_1 and Y_2. Children who received OIT filled in a visual analogue scale (VAS) form of perceived treatment burden at Y_1 and Y_2. Children who were defined ineligible for OIT had their QoL reassessed at Y_1 only. An OFC for peanut was performed at Y_2 in children undergoing OIT.

Written informed consent was obtained from both parents after detailed oral and written information. The TAKE-AWAY trial was approved by the Regional Committee for Medical and Health Research Ethics and monitored by a safety board with regular communications in case of severe or unexpected adverse events. The study was registered with ClinicalTrials.gov (number NCT02457416).

4.1.1 Inclusion and exclusion criteria and eligibility for enrolment

Inclusion criteria for screening were: Age 5-15 years with either a history of systemic allergic reactions to peanut or sensitization to peanut by a peanut skin prick test (SPT) ≥ 3 mm or s-IgE to peanut ≥ 0.35 kUA/L; living within acceptable distance from the Oslo University Hospital and willingness to participate in the peanut OIT study. Exclusion criteria were: Poorly controlled asthma; allergy or intolerance to any other ingredients of the peanut DBPCFC vehicle (ginger bread); current or previous allergen specific immunotherapy;

cardiac disease; severe atopic skin disease; diabetes mellitus or other severe diseases that might interfere with adherence to the study protocol. Participants who, during the screening visit, had a positive DBPCFC defined by at least two objective symptoms in one or more organ systems at a reactivity threshold > 3 mg peanut protein, were enrolled in the TAKE-AWAY trial.

4.1.2 Randomization

Allocation to OIT vs. observation only, followed an initial 2:1 block-size. The OIT starting dose was initially 5 mg of peanut protein based on previously published studies (27, 88, 100), but was reduced to 1 mg of peanut protein after enrolment of 26 children (17 active vs. 9 controls) due to low reactivity threshold in the referred patients.

4.2 Study population

The present thesis includes 96 children (5-15 years of age) who all had a positive DBPCFC with moderate objective symptoms in at least two organ systems, and thereby fulfilled the EAACI criteria for anaphylaxis (8, 9). None had an EAACI score of 3 or a Sampson score of 5, i.e. severe anaphylaxis. For more than half of the children, the reactivity threshold corresponded to the LOAEL.

Of the 213 children referred for screening, 95 did not wish to enter screening explained by concern for severe AEs, but also due to insufficient available time to adhere to the protocol. Another 14 children were excluded by the exclusion criteria, four withdrew during screening and four had a negative DBPCFC (Figure 10).

Fifty-seven children were randomized to OIT, 20 to observation only (controls), whereas 19 children were found ineligible for OIT due to a reactivity threshold ≤ 3 mg peanut protein (Figure 10).
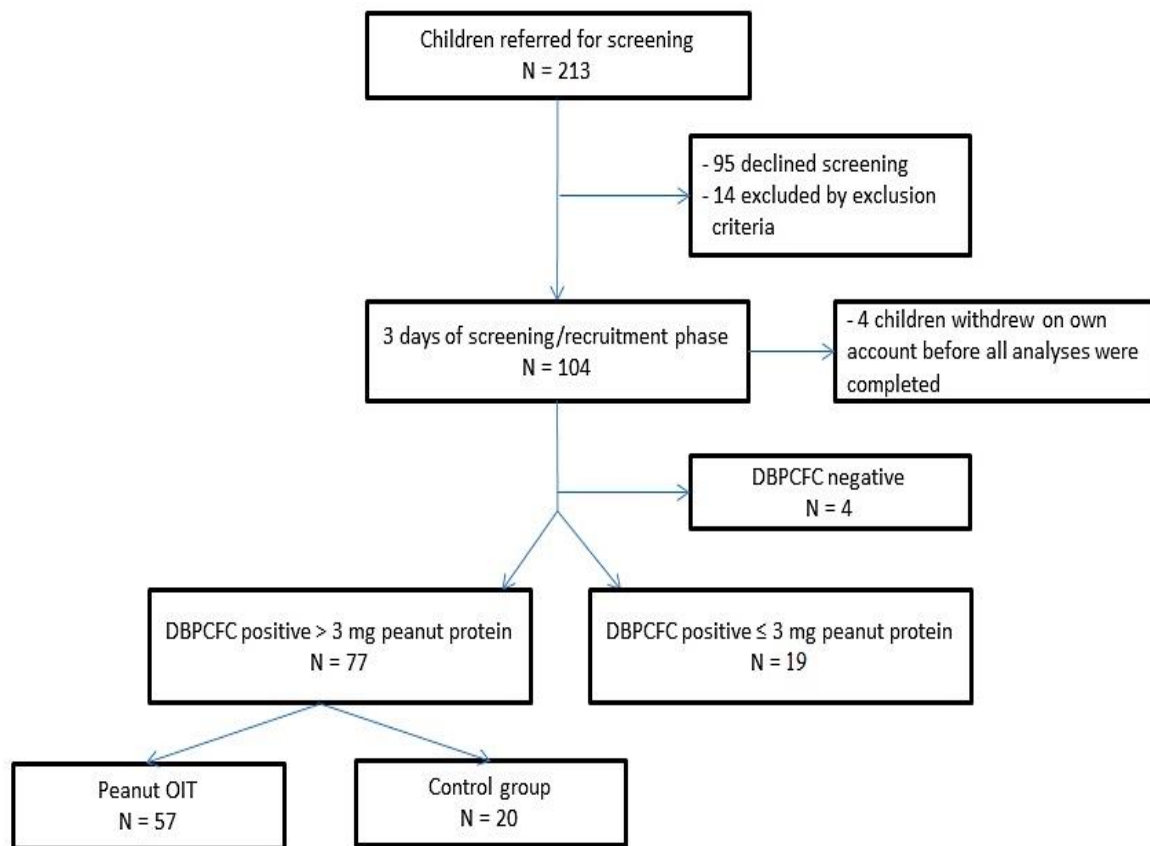
Figure 10. *Flow chart of the recruitment phase in the TAKE-AWAY trial.*

Baseline characteristics were not significantly different between the OIT children, the controls and those defined ineligible for OIT (Table 5).

The baseline characteristics for children with an OIT starting dose of 5 mg and 1 mg of peanut protein (n = 17 vs. 40, respectively) were not significantly different with the exception of parental atopic disease, allowing them to be assigned as one intervention group (Table 6).

Table 5. *Baseline characteristics of children randomized to peanut OIT in the TAKE-AWAY trial and children ineligible for enrolment.*

	Active (n = 57)	Controls (n = 20)	Ineligible (n = 19)	Overall p-value
Age	9.3 (5.2, 15.2)	9.3 (5.1, 13.3)	10.3 (5.6, 14.6)	0.08
Male	31 (54.4)	13 (65.0)	6 (31.6)	0.10
Current asthma	24 (42.1)	9 (45.0)	11 (57.9)	0.46
Allergic rhinitis	15 (26.3)	8 (40.0)	5 (26.3)	0.73
Atopic dermatitis ever	47 (82.5)	14 (73.9)	13 (68.4)	0.40
Allergy to tree-nuts	20 (35.1)	7 (36.8)	9 (53.0)	0.35
Allergy to other food than nuts	27 (47.4)	11 (57.9)	11 (61.1)	0.64
Parental atopic disease*	50 (87.7)	16 (80.0)	17 (89.5)	0.63
Parental food allergy**	21 (36.8)	6 (30.0)	11 (57.9)	0.16
FEV1% predicted	102.1 (98.7, 105.4)	99.3 (90.7, 107.9)	96.3 (88.8, 103.8)	0.15
Pos s-IgE (≥ 0.35 kUA/L):				
tree-nuts***	52 (91.2)	16 (80.0)	19 (100.0)	0.07
other food****	54 (94.7)	19 (95.0)	19 (100.0)	0.47
Peanut SPT (mm)	10.7 (9.3, 12.2)	10.7 (8.3, 13.0)	10.4 (8.3, 12.5)	0.56
S-IgE (kUA/L) peanut	265.1 (164.9, 365.3)	146.8 (63.3, 230.4)	157.3 (83.6, 231.1)	0.34
Ara h 2	118.2 (83.3, 154.1)	59.8 (31.0, 88.6)	69.5 (38.8, 100.3)	0.13
Peanut s-IgE/total IgE (kUA/L)	0.4 (0.3, 0.5)	0.7 (0.3, 1.8)	0.3 (0.2, 0.4)	0.39
Peanut s-IgG$_4$/ s-IgE (ng/ml)	23.1 (10.0, 36.1)	62.0 (16.1, 140.1)	148.7 (106.1, 403.5)	0.12
Pre-OIT DBPCFC:				
Anaphylaxis severity grade:				
modified EAACI	1.7 (1.6, 2.0)	1.8 (1.6, 2.0)	1.8 (1.6, 2.0)	0.50
Sampson	2.7 (2.5, 2.9)	2.9 (2.6, 3.2)	2.5 (2.2, 2.9)	0.25
Use of adrenaline	30 (52.6)	5 (25.0)	8 (42.1)	0.10
LOAEL(mg peanut prot (ppt))	105.9 (28.9, 182.8)	96.1 (53.3, 245.4)	NA	0.34
Reactivity threshold (mg ppt)	177.3 (86.7, 268.0)	375.5 (40.1, 791.1)	4.4 (1.6, 7.3)	0.06

Variables are given as mean (95 % CI) or n (%), except age which is given with (min, max). One-way ANOVA was applied to determine statistically significant differences between group means.
Chi-square test was applied to determine statistically differences between categorical data.
*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis.
**All food allergy including peanut and tree-nut allergy.

***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut.
****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat.

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers (8, 9) ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) (10) ranging from 1 to 5. Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC.

SPT, skin prick test; Ig - immunoglobulin; LOAEL - lowest observed adverse effect level; OIT – oral immunotherapy; DBPCFC – double-blind placebo controlled food challenge; LOAEL – lowest observed adverse effect level (amount of peanut eliciting mild, objective symptoms)

Table 6. *Baseline characteristic of the 57 children randomized to peanut OIT based upon their starting dose.*

	OIT starting dose 1 mg peanut protein (n = 40)	OIT starting dose 5 mg peanut protein (n = 17)	p-value
Age	9.7 (5.4, 15.0)	10.4 (6.3, 15.1)	0.26
Male sex	23 (57.5)	8 (47,5)	0.47
Ever had eczema	32 (80.0)	15 (88.2)	0.46
Current asthma	20 (50.0)	11 (64.7)	0.56
Allergic rhinitis	10 (25.0)	5 (29.4)	0.77
Parental atopic disease*	38 (90.5)	12 (70.6)	**0.01**
Parental food allergy**	15 (37.5)	6 (35.3)	0.87
Peanut SPT (mm)	9.8 (4.0, 36.3)	9.4 (4.0, 22.9)	0.88
Positive SPT other nuts ($\geq$ 3 mm)***	22 (55.0)	6 (35.3)	0.17
S-IgE (kUA/L) peanut	92.8 (9.8, 2290.9)	102.3 (3.1, 955.0)	0.86
Ara h 2	46.8 (9.9, 489.8)	61.7 (2.5, 457.1)	0.60
Positive s-IgE (kUA/L)			
other nuts***	38 (95.0)	14 (87.5)	0.33
other food****	38 (95.0)	16 (100.0)	0.36
Peanut s-IgE/total IgE (kUA/L)	9.5 (8.0, 10.0)	9.5 (9.1, 9.9)	0.46
Peanut s-IgG$_4$/s-IgE (ng/ml)	4.7 (9.2, 288.4)	4.7 (9.9, 42.7)	0.72
BAT (%CD63+), pos ******	63.1 (16.2, 93.3)	64.6 (37.2, 91.2)	0.80
CAPT positive (dilution) *****			
1/160	5 (12.5)	2 (11.8)	0.59
1/80	11 (27.5)	2 (11.8)	
1/40	12 (30.0)	9 (52.9)	
1/20	11 (27.5)	2 (11.8)	
1/10	11 (27.5)	2 (11.8)	
Pre-OIT DBPCFC			
Use of adrenaline	23 (57.5)	7 (41.2)	0.26
Anaphylaxis severity modified EAACI	1.7 (1.0, 2.0)	1.4 (1.0, 2.0)	0.10
Reactivity threshold	42.8 (3.0, 933.3)	93.7 (12.9, 1584.9)	0.12

*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis

**All food allergy including peanut and tree-nut allergy

***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut

****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat

***** The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

****** N = 50. The BAT was not performed in 7 children due to technical causes (n = 5) and non-reponders were excluded from the analyses (n = 2).

Anaphylaxis severity was graded according to the modified EAACI position papers (8, 9) ranging from 1 to 3.

Reprinted from Allergy 2018; Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al.: «Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy.”, with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/30225844

4.3 Methods

4.3.1 The screening interview

The structured parental interview included information about history of allergic reactions including anaphylaxis, allergic co-morbidities (current asthma, allergic rhinitis, previous or current atopic dermatitis and allergy to other foods or nuts), medical history including medicine use and socio-demographic data.

4.3.2 Lung function measurements

Lung function was measured using SensorMedics to obtain maximal expiratory flow volume loops according to international standards (114), expressed as percent predicted forced expiratory volume in one second ($FEV_1\%$) using the reference values of Zapletal et al. (113).

4.3.3 Skin prick test

Skin prick tests were performed according to international guidelines (115). The allergen extracts used included hazelnut, almond, soybean, birch, grass (timothy), mugwort, cat, dog, mite and mold (cladosporium herbarium) (ALK SQ extracts, ALK Abello (Hørsholm, Denmark)), pea and positive and negative controls (Allergopharma (Reinbek, Germany)). *A titrated SPT (SPT_t)* to peanut was performed with dilutions of 1:20, 1:200, 1:2000 and 1:20000 of the peanut allergen extract (ALK SQ extracts, ALK Abello (Hørsholm, Denmark)). Wheal size was recorded after 15 minutes, and regarded positive if $\geq$ 3 mm larger than negative control.

4.3.4 The conjunctival allergen provocation test

Conjunctival allergen provocation test (CAPT) was performed double-blinded and placebo-controlled. Randomization was performed using Statistical Analysis System (SAS, Version

9.3, SAS Institute Inc., Chapel Hill, NC, USA), and all tests were un-blinded only after the last child had completed all investigations. A commercially available peanut extract (Greer laboratories, Lenoir, NE, USA) was diluted with NaCl 0.9 % to make test solutions of 1:160, 1:80, 1:40, 1:20, 1:10 and 1:1, as previously described by Lindvik et al. (27). The 0.9 % NaCl was used as placebo. The incremental concentrations of peanut extract and placebo were applied every 30 minutes with two independent observers recording redness, itching, chemosis and/or lacrimation. The CAPT was defined positive with the occurrence of ≥ 2 recorded symptoms (27). Photos were taken before and after the CAPT for documentation.

4.3.5   Immunological investigations

Analyses of total IgE and s-IgE to peanut and peanut component allergens (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9) as well as other common allergens including hazelnut and hazelnut allergen components (Cor a 1, Cor a 8, Cor a 9, Cor a 14), almond, cashew nut, pistachio, walnut, pecan nut, brazil nut, macadamia nut, fenugreek, soy bean, lupine seed, wheat, latex, common silver birch, timothy and mugwort were performed in fresh serum sampled in EDTA tubes. The serum was sent the same day to the Fürst Medical Laboratory (Oslo, Norway) using the Phadia CAP-System FEIA (ThermoFisher, Uppsala, Sweden) and the analyses were performed according to the manufacturer's instruction. Specific IgE ≥ 0.35 kUA/L was considered positive.

Analyses of s-IgG and s-IgG$_4$ to peanut and Ara h 2 were performed in collected sera stored at - 86°C using the Phadia CAP-System FEIA (ThermoFisher, Uppsala, Sweden). Levels of IgG > 2.0 mg$_A$/L and IgG4 of > 0.07 mg$_A$/L were considered positive, according to the manufacturer's instructions.

The BAT was performed in fresh EDTA blood sampled prior to the food challenge and stored at room temperature (usually 1-3 hours, maximum 24 hours). The proportion of activated blood basophils (basophil activation - CD63+ basophils) was determined in whole blood aliquots incubated for 15 minutes at 37 °C. The negative control was incubated with stimulation buffer containing IL-3, calcium and heparin, and the positive control with n-Formyl-methionyl-leucyl-phenylalanine (anti-FcεR1 or fMLP). Further blood aliquots were incubated with 2.5, 5 and 10 ng/ml peanut extract (all reagents from the FlowCAST kit and CAST-allergen peanut BAG-F13, both from Buhlmann Laboratories AG, Schönenbuch, Switzerland). All aliquots were incubated with 20 μl staining solution containing a mix of anti-CD63 FITC and anti-CCR3-PE (Buhlmann), in addition to 5 μl anti-CD203c-APC monoclonal antibody (BioLegend, San Diego, CA USA). After red blood cell lysis, centrifugation and resuspension in wash buffer (Buhlman), the cells were analysed on a LSRII flow cytometer with BD FACSDIVA software (all from BD Biosciences, New Jersey, USA). Basophils were gated as side-scatter (SSC) low and CCR3+ cells, and for the present thesis, basophil activation is expressed as the % CD63 positive basophils (% CD63+) after stimulation of 5 ng/ml of the peanut extract. Because all children had strong basophil activation already to the lowest allergen concentration of 2.5 ng/ml peanut extract, the basophil allergen sensitivity (CD-sens) expressing the allergen concentration eliciting half of the maximum basophil activation could not be determined. Non-responders were defined as children responding with basophil activation < 5 % (116). In the present thesis, participants with a basophil activation of 5 − 15 % were classified as low-responders, whereas a basophil activation > 15 % was defined as positive, as suggested by Glaumann et al. (117) and the kit provider (Buhlmann Laboratories AG). In ten children, BAT was not performed due to missed sampling (n = 5) or technical causes (n = 5) (technical failure of equipment (n = 1), incorrect handling of the blood sample (n = 1) or no available allergen extract (n = 3)).

4.3.6 Double-blind placebo-controlled food challenge to peanut

The DBPCFC was performed in line with international standardized procedure (34, 41).

Peanut flour (Golden Peanut Company, Alpharetta, GA, USA) was used as the active

challenge ingredient. Gingerbread was used as matrix, baked according to a recipe by Vlieg-

Boestra et al. (118), allocated and blinded by the cook.

The first challenge dose contained 3 mg of peanut protein. The maximal cumulated dose of

6443 mg peanut protein was given as 7 incremental steps (3 mg, 10 mg, 30 mg, 100 mg, 300

mg, 1 000 mg, 5 000 mg of peanut protein) with 30 minute interval. In the case of persistent

subjective or mild objective symptoms in line with the modified Bock's criteria (Table 4)

(34), interval was increased up to 60 minutes, in which case the next step repeated the

previous dose in consent with recommendations from international work groups (119, 120).

The DBPCFC was defined positive with the occurrence of two or more moderate objective

symptoms (34, 39), and the DBPCFC was stopped if scored positive, even though only part of

the current dose was eaten. The cumulated peanut protein (mg) intake at the time of positive

DBPCFC was recorded and regarded as the reactivity threshold. The lowest amount of peanut

protein that elicited the first mild, objective symptom during food challenge was recorded

post hoc and is defined as the lowest observed adverse effect level (LOAEL).

The order of active vs. placebo days and block-size were unknown to all study personnel

present at the challenge, provided by the statistician using Statistical Analysis System (SAS,

Version 9.3, SAS Institute Inc., Chapel Hill, NC, USA), and un-blinded first at the end of the

recruitment phase.

4.3.7 Oral food challenge at two-years of oral immunotherapy

An open oral food challenge at Y_2 was performed to determine the level of desensitization,

defined as the highest cumulated amount of peanut protein ingested without eliciting allergic

reactions corresponding to a positive Y_2 OFC.

The goal of the Y_2 food challenge was ingestion of a cumulated dose of 7500 mg peanut

protein without allergic reactions. The first challenge dose was individualized in reflection to

the patient's maintenance dose, the second and third dose were each 25 % of the maintenance

dose. The cumulated dose of 7500 mg peanut protein was reached after a maximum of six

doses with 30 minutes' intervals (Table 7), in line with international standards (119, 120).

Table 7. *Protocol for the open oral food challenge performed after two years of oral immunotherapy (Y_2) in children highly allergic to peanut.*

1. dose: peanut protein (mg)	2. dose	3. dose	4.dose	5. dose	6. dose	Cumulated dose
350	87	87	919	3000	3057	7500
450	112	112	769	3000	3057	7500
600	150	150	543	3000	3057	7500
800	200	200	243	3000	3057	7500
1000	250	250	2943	3057		7500
1250	312	312	2569	3057		7500
1500	375	375	2193	3057		7500
1800	450	450	1743	3057		7500
2200	550	550	1143	3057		7500
2700	675	675	393	3057		7500
3300	825	825	2550			7500
4000	1000	1000	1500			7500
5000	1250	1250				7500

The 1_{st} dose is individualized and relates to the individual maintenance dose. The 2_{nd} and 3_{rd} dose combined constitutes 50 % of the individual maintenance dose. The last dose was equal for all individuals.

4.3.8 Up-dosing protocol of the oral immunotherapy

The biweekly step-up protocol for the peanut OIT in the TAKE-AWAY trial had a fixed

starting and a high pre-defined maximum maintenance dose (MMD) of 5000 mg peanut

protein (Table 8). A 50 - 100 % increase for every dose was used initially with a subsequent

20 - 44 % increase per dose.

Table 8. *Long-term step-up protocol with a fixed starting dose for oral immunotherapy in the TAKE-AWAY trial.*

Dose-step	Peanut (mg)
1	1
2	3
3	5
4	10
5	20
6	30
7	45
8	65
9	90
10	125
11	175
12	250
13	350
14	450
15	600
16	800
17	1000
18	1250
19	1500
20	1800
21	2200
22	2700
23	3300
24	4000
25	5000

The allergen source for the lowest doses was peanut flour (Golden Peanut Company, Alpharetta, GA, USA). However, most children reported distaste for larger amounts of peanut flour, and all but one child switched to roasted peanuts at OIT doses of 65 - 500 mg peanut protein. Each up-dosing period with an increased dose-step was discussed with the patient and their parents. An up-dosing period started with an incremented OIT dose ingested under observation at the hospital with subsequent daily intake of this OIT dose at home for 14 days. Increasing the OIT dose required absence of ongoing infections, bronchial obstruction and OIT-related AEs during the five previous days. A clinical examination and peak expiratory flow rate were performed prior to, and 1-2 hours after, the ingestion of the OIT dose. If no AEs occurred, the child started a new up-dosing period with the increased OIT dose. In case of subjective or mild to moderate symptoms, participants were advised to use oral antihistamines, but if moderate objective symptoms occurred, up-dosing was postponed for one week. If the child was unwilling to increase the OIT dose or if AEs resulted in three consecutive unsuccessful attempts to increase the OIT dose, the current dose would represent the participant's individual maintenance dose (IMD).

The child was strongly advised to avoid exercise within two hours after ingesting the OIT dose. Ingestion of other dietary peanut sources was also strongly discouraged. Menstruating girls were asked to closely monitor possible OIT-related symptoms during menstrual cycle. During the daily intake of OIT doses at home, children were advised to postpone the OIT dose to the next day in case of ongoing infections, asthma exacerbations, excessive tiredness or vaccinations. If the OIT dose was not eaten for three or fewer consecutive days, the OIT was resumed at home. However, if more than three consecutive days went by without daily ingestion of the OIT dose, the OIT was resumed under observation at the hospital.

If moderate objective symptoms occurred after ingesting the OIT dose at home for > 2 - 3 consecutive days, the OIT dose was reduced to the previous dose-step in the up-dosing

protocol. In case of anaphylaxis, the OIT dose was reduced by two dose-steps for 1-2 weeks before resuming the up-dosing protocol.

The child was withdrawn from the OIT and discontinued treatment if unwilling to continue OIT, if severe or troublesome AEs occurred, or if more than two anaphylactic reactions occurred in one child. Unexpected severe AEs were reported to the independent safety board. The peanut intake, AEs, use of medication and accidental exposure to peanut were recorded in a daily symptom diary. Grading of AEs was in line with the modified Bock's criteria (34, 120).

All participants were prescribed adrenaline auto-injectors and antihistamines, received a written treatment plan for OIT-related AEs, and had around-the-clock access to the study paediatricians.

4.3.9 Classification of allergic reactions/adverse events

Adverse events during food challenge and related to OIT were classified as mild, moderate or severe (including anaphylaxis) according to the Bock's criteria modified by Sampson et al. (Table 4) (34, 120).

Skin symptoms classified as mild include occasional scratching, less than three hives, mild lip oedema, or a few areas of erythema, whereas moderate include scratching for more than two continuous minutes, more than three but less than ten hives, significant face oedema or areas of erythema, conjunctivitis, periocular swelling and severe symptoms include excoriations or generalised erythema or urticaria. Mild respiratory symptoms include rare bursts or mild congestion, expiratory wheezing by auscultation or less than three episodes of throat clearing, whereas moderate include less than ten bursts, frequent sniffing, inspiratory and expiratory wheezing by auscultation or hoarseness, and severe include persistent rhinorrhoea, use of accessory muscles or audible wheezing or stridor.

Mild GI-symptoms include complaints of nausea or stomach ache or one episode of emesis or diarrhoea, whereas moderate include frequent complaints of nausea and stomach ache with normal activity and two to three episodes of emesis or diarrhoea or one of each, and severe include complaints of nausea or stomach ache with change of activity level or more than three episodes of emesis or diarrhoea or two of each.

Mild cardiovascular symptoms include subjective weakness or tachycardia, whereas moderate include more than 20 % drop in baseline blood pressure, and severe include signs of impaired circulation.

Anaphylaxis was defined as objective symptoms from at least two organ systems according to the task force position papers of European Academy of Allergy and Clinical Immunology (EAACI) (8, 9), modified for children by Vetander et al. (11). The EAACI position papers (8, 9) also established a severity grading of anaphylaxis scoring from 1 - 3 (mild-moderate-severe). Additionally, anaphylaxis was graded by the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) ranging from 1 - 5 (extremely severe reaction) (10).

4.3.10 Measurements of quality of life

The quality of life in participating children was assessed using the generic Paediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0), which is age-adapted (age 5-7, 8-12 and 13-18 years), validated for clinical trials (110, 121) and consists of 13 items within the following four functioning domains; physical, emotional, social and school. A 5-point Likert scale (0 = never, 4 = almost always) is applied for the 8-12 and 13-18 years reports, while a simplified 3-point scale is applied for the 5-7 years child reports. Results are classified by Physical Health Score (Physical Functioning) and Psychosocial Health Summary Score (Emotional,

Social and School Functioning). Both children and parents assessed child QoL using PedsQL 4.0 self- and proxy-reports, respectively.

The quality of life in parents of participating children was assessed using the health-related Food Allergy Quality of Life – Parental Burden (FAQL-PB) Questionnaire (122). The FAQL-PB consists of 17 items including family/social activities (restaurant meals, social activities, child care and vacation), school, time spent for meal preparation, health concerns, and emotional issues. The FAQL-PB has a 7-point Likert scale (1 = not troubled, 7 = extremely troubled), with summated scores ranging from 17-119. The minimal important difference (MID) (the smallest change that the patient perceive as important) on a 7-point Likert scale is defined as 0.5 (123).

Translation into Norwegian has been validated for PedsQL 4.0 (124), whereas the FAQL-PB was translated into Norwegian in the OPAS-study (27) with permission from The Food Allergy and Anaphylaxis Network.

4.3.11 Measurement of perceived treatment burden

A visual analogue scales (VAS) form was developed to obtain one-dimensional perception of treatment burden during the last 12 months. The VAS form including eight VAS items ranging from $0 – 10$ (0 = no burden, 10 = massive burden), and was completed by children receiving OIT together with their parents at time-points Y_1 and Y_2. One item referred to overall perception of treatment burden, whereas seven items referred to treatment burden within three domains: Gastro-intestinal (GI) related AEs (stomach ache, nausea/vomiting and oral itching) (3), taste and amount of daily peanut OIT (2), and time spent on OIT (up-dosing at hospital and ingestion of OIT doses at home) (2). Results were classified per domain and reported with mean score per domain.

4.4   Definitions, outcomes and explanatory factors

The reactivity threshold (paper #1) was defined as the cumulated peanut protein (mg) intake at positive DBPCFC.

Very low reactivity threshold (paper #1) was defined as DBPCFC reactivity threshold of ≤ 3 mg of peanut protein.

The LOAEL (60) was set post hoc and the threshold value representing the amount of peanut protein eaten at the occurrence of the first mild objective symptom. The LOAEL was set to 3 mg for children with a positive DBPCFC at the first challenge dose (paper #1).

The feasibility of desensitization (paper #2) was defined as the proportion of children who reached the pre-defined maximum maintenance dose (MMD) of 5000 mg peanut protein.

The level of desensitization (paper #3) was defined as the highest cumulated dose of peanut protein ingested without eliciting allergic reactions corresponding to a positive Y_2 food challenge.

For aim #1 of the present thesis, the primary outcome was the proportion of children being enrolled in the TAKE-AWAY trial, whereas the secondary outcome was the proportion of children who still received OIT at the end of up-dosing phase (after one year of treatment). Possible explanatory factors for enrolment and continuation of the OIT in the TAKE-AWAY trial included baseline sociodemographic characteristics, as well as immunological and clinical characteristics associated with reactivity thresholds, as reactivity threshold determined eligibility.

For aim #2, the primary outcome was the proportion of children who reached the pre-defined MMD of 5000 mg peanut protein, whereas the secondary outcome was the proportion of children who reached a lower individual maintenance dose (IMD) (< 5000 mg peanut protein). Potential explanatory factors of reaching the MMD or the lower IMDs were baseline characteristics, the treatment burden including AEs, medication for AEs and protocol

deviations (dose reduction or postponed up-dosing due to social events, AEs or infections), as well as the ability to be compliant to the OIT.

For aim #3, the primary outcome was the number AEs in the up-dosing phase, characterized by the involved organ(s) and classified into subjective and mild objective, moderate or severe (including anaphylaxis) in line with the modified Bock's criteria (34). The secondary outcome was the reported patient perceived burden of treatment. Potential explanatory factors of treatment burden were factors known to augment AEs including exercise within two hours of a dose, ongoing infection, excessive tiredness, impaired compliance to OIT or asthma treatment, taste/amount of peanuts and time spent on OIT.

For aim #4, the primary outcome was the desensitization given by reactivity threshold at the Y_2 OFC, whereas the secondary outcomes were change in QoL scores from Y_0 to Y_2 obtained from the PedsQL 4.0 child self-reports and the corresponding parental proxy-reports. The third outcome was the parental QoL reported by the FAQL-PB. Potential factors influencing change in QoL were OIT-related AEs, level of desensitization determined by the OFC at Y_2, the maintenance dose and the child's perception of treatment burden at Y_1 and Y_2 presented by the mean VAS-score from each of three domains: GI-related AEs, taste/amount of peanuts and time spent on OIT. Sub-analysis including change in QoL from Y_0 to Y_1 rather than Y_0 to Y_2 was used to determine if ineligibility for OIT influenced change in QoL.

4.5   Statistical analyses

Statistical power analyses was based upon studies reporting that a step-up peanut OIT desensitized up to 80 % of children with less severe peanut allergy (89, 95) and tolerance (lasting SU) that spontaneously develops in 20 % (24). A somewhat lower proportion of children with severe peanut allergy is expected to achieve desensitization, and was set to 57

%. Consequently, a treatment group of 40 and a control group of 20 subjects would provide a statistical power of 80 % at a five percent significance level.

Due to non-normal distribution, continuous baseline characteristics are presented by geometric mean (95 % CI) and median (range), while categorical data are presented as number of cases (n) with percentage (%). To assess possible differences, the Mann-Whitney U test was used for continuous data and the Pearson's chi-square test for categorical data. One-way ANOVA was used to analyse the overall difference in continuous data between the three groups of children who reached the MMD, the IMD and those who discontinued OIT with the latter group as reference (paper #2). One-way ANOVA was also used to analyse the overall difference in continuous data between the three groups of children who were randomized to OIT or controls, or defined as ineligible for OIT, with controls as the reference (paper #3). Finally, one-way ANOVA was used to analyse the overall difference between AEs occurring in the three dose-intervals of the up-dosing phase (1-65, 66-800 and 801-5000 mg peanut protein) (paper #2). In the case of a significant overall p-value, the Dunnett's post hoc test was used to confirm between which groups the statistically significant difference had occurred.

As recommended for analyses of PedsQL 4.0 (121), the items were reverse-scored (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) with the mean sum of each item reported (paper #3). Basophil activation was measured as a continuous variable (paper #1 and #2).

A paired samples t-test was used to determine if a statistically significant desensitization had occurred in the individual (paper #2), comparing the maintenance dose with the reactivity threshold at screening food challenge. Paired samples t-test was also used to determine the difference in the individual's QoL scores at Y_0 and Y2 as well as to determine the difference in VAS from Y_1 to Y_2 (paper #3).

Change in QoL scores from Y_0 to Y_2 were assessed using generalized repeated-measures in linear mixed models including QoL score at Y_0, age, gender, randomization group, and Y_1 and Y_2 as independent variables. The Scheffe's test was used to determine group differences (paper #3). Unpaired t-test was also used to determine significant differences in change in QoL from Y_0 to Y_1 between the ineligible children and the controls.

Bivariate unadjusted analyses were performed with Spearman correlation analyses ($r_s =$ Spearman correlation coefficient) (paper #1 and #3).

Bivariate logistic regression analyses were used to assess the associations between explanatory factors and feasibility of desensitization (paper #2) with the proportion of children who reached the MMD (as independent variable) versus the proportion of children who reached IMD or discontinued OIT (as dependent variable). The analyses were duplicated with the proportion of children who reached MMD or IMD as the dependent variable versus the proportion who discontinued OIT.

As the underlying assumptions for the multiple linear regression analysis were not fulfilled, multivariate robust regression analyses with Huber's M-estimator were used to assess associations between immunological parameters (as independent variables) and reactivity threshold, LOAEL as well as severity of the allergic reaction (as the dependent variables) (paper #1). Multivariate robust regression analyses were also used to assess the associations between possible factors influencing QoL (as independent variables), and change in QoL from Y_0 to Y_2 in the PedsQL child or parental reports, and the FAQL-PB (as dependent variables) (paper #3). For sub-group analyses to determine if ineligibility to OIT influenced change in QoL from Y_0 to Y_1 (paper #3), change in QoL from Y_0 to Y_1 was used as the dependent variable. Hosmer's step down multivariate analysis (125), a priori retaining age and gender in the analysis, included all variables statistically significant at the 0.35 level in the bivariate analyses. The final model was tested for confounding with all excluded variables.

Confounding was considered significant if including the variable led to a minimum of a 25 % change in the result (125).

P-value of ≤ 0.05 was considered statistically significant.

Statistical analyses were performed using Statistical Analysis System (SAS, Version 9.3, SAS Institute Inc., Chapel Hill, NC, USA) and the IBM Statistical Package for Social Sciences (IBM SPSS Statistics, Version 21.0.1. Armonk, NY: IBM Corp).

4.6   Ethical issues

The TAKE-AWAY trial was approved by the Regional Committee for Medical and Health Research Ethics and registered in the ClinicalTrials.gov (number NCT02457416). As OIT is considered an experimental treatment, the child and both parents were given thorough oral and written information prior to obtaining a written informed consent from both parents. The information was age-adjusted and included the uncertainty and probability of achieving sustained unresponsiveness, as well as the potential challenge of time expected spent on treatment as well as AEs including severe reactions (92). Severe or unexpected AEs were reported to, and consulted with, a safety board.

The prospective, open labelled, randomized controlled study design rather than placebo controlled was a result of discussions with the ethical committee, concluding that four years of blinded placebo treatment were ethically inappropriate.

5   RESULTS

5.1   Baseline characteristics predicting the possibility of entering and completing an up-dosing phase of peanut oral immunotherapy (paper #1 and #2)

5.1.1   Baseline characteristics predicting the possibility of entering peanut oral immunotherapy (paper #1)

As outlined in Figure 10, 36.2 % of the 213 children referred for screening were included in the TAKE-AWAY trial. In 71.4 % of the enrolled children, parents had a combined annual income above 850.000 NOK, whereas 84.4 % of the mothers and 75.3 % of the fathers had education attainment level of three or more years of college/university.

In unadjusted bivariate analyses, the reactivity threshold as well as the LOAEL correlated significantly with basophil activation only, with a correlation coefficient (r_s) for reactivity threshold of - 0.30 (p = 0.004) and an r_s for LOAEL of - 0.02 (p = 0.032). Neither reactivity threshold nor LOAEL correlated significantly with any of the following: Age, gender, allergic co-morbidities, FEV_1%, peanut SPT or s-IgE to peanut, Ara h 2, the ratios of peanut s-IgE/total Ig-E and s-IgG_4/s-IgE to peanut or the severity of the allergic reaction during pre-OIT DBPCFC (data not shown).

In multiple robust regression analysis including peanut SPT, s-IgE to peanut and Ara h 2, the ratios of peanut s-IgE/total IgE and s- IgG_4/s-IgE, and BAT, both the reactivity threshold and LOAEL were significantly associated with basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE (all p < 0.04) (Table 9). Furthermore, the reactivity threshold was associated with s-IgE to Ara h 2 and the ratio of s- IgG_4/s-IgE to peanut, while LOAEL was associated with s-IgE to peanut (Table 9). Neither reactivity threshold nor LOAEL was significantly associated with age, gender, allergic co-morbidities or lung function. Similar results were observed in subgroup analyses excluding the 23 children with a basophil activation ≤ 15 % CD63+ (non-responders (n = 6) and the low responders (n = 17)) (data not shown).

Table 9. *Multivariate robust regression analyses for significant associations between peanut reactivity threshold and the lowest observed adverse event level (LOAEL) in children anaphylactic to peanut.*

	Reactivity threshold		LOAEL	
	ß –value (95 % CI)	p-value	ß –value (95 % CI)	p-value
Peanut SPT (mm)	1.45 (0.08, 2.83)	0.04	0.87 (0.43, 1.31)	0.0001
Peanut s-IgE (kUA/L)	-		0.01 (0.002, 0.018)	0.01
Ara h 2 s-IgE (kUA/L)	0.09 (0.02, 0.17)	0.01	-	
Ratio peanut s-IgE/ total IgE (kUA/L)	29.20 (22.57, 35.82)	< 0.0001	3.58 (1.44, 5.71)	0.001
Ratio s-IgG$_4$/s-IgE to peanut (ng/ml)	1.69 (1.61, 1.78)	< 0.0001	-	
BAT all children (%)*	-0.45 (-0.73, - 0.17)	0.002	-0.09 (-0.17, -0.002)	0.04

Associations are given as the relative change (ß) related to each mg increase in peanut threshold.
N = 86, BAT was not performed in 10 children due to missed sampling (n = 5) or technical causes (n = 5).
*included all children with a positive basophil activation (% CD63+ basophils)
- no significant association

SPT - skin prick test; Ig - immunoglobulin; BAT - basophil activation given as per cent activated CD63 cells test

In a receiver operating characteristic (ROC) curve to predict ineligibility for peanut OIT by a very low reactivity threshold ≤ 3 mg of peanut protein, variables associated to both reactivity threshold and LOAEL were included. Among basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE, basophil activation best predicted ineligibility for peanut OIT with an area under the curve (AUC) (95% C.I) of 0.71 (0.53, 0.82), compared with the AUC for peanut s-IgE/total Ig-E of 0.55 (0.39, 0.67)) and peanut SPT of 0.53 (0.36, 0.66) (Figure 11). The optimal basophil activation cut-off level of 75.8 % gave a 93.5 % negative and a 36.8 % positive predictive value for predicting very low reactivity threshold.
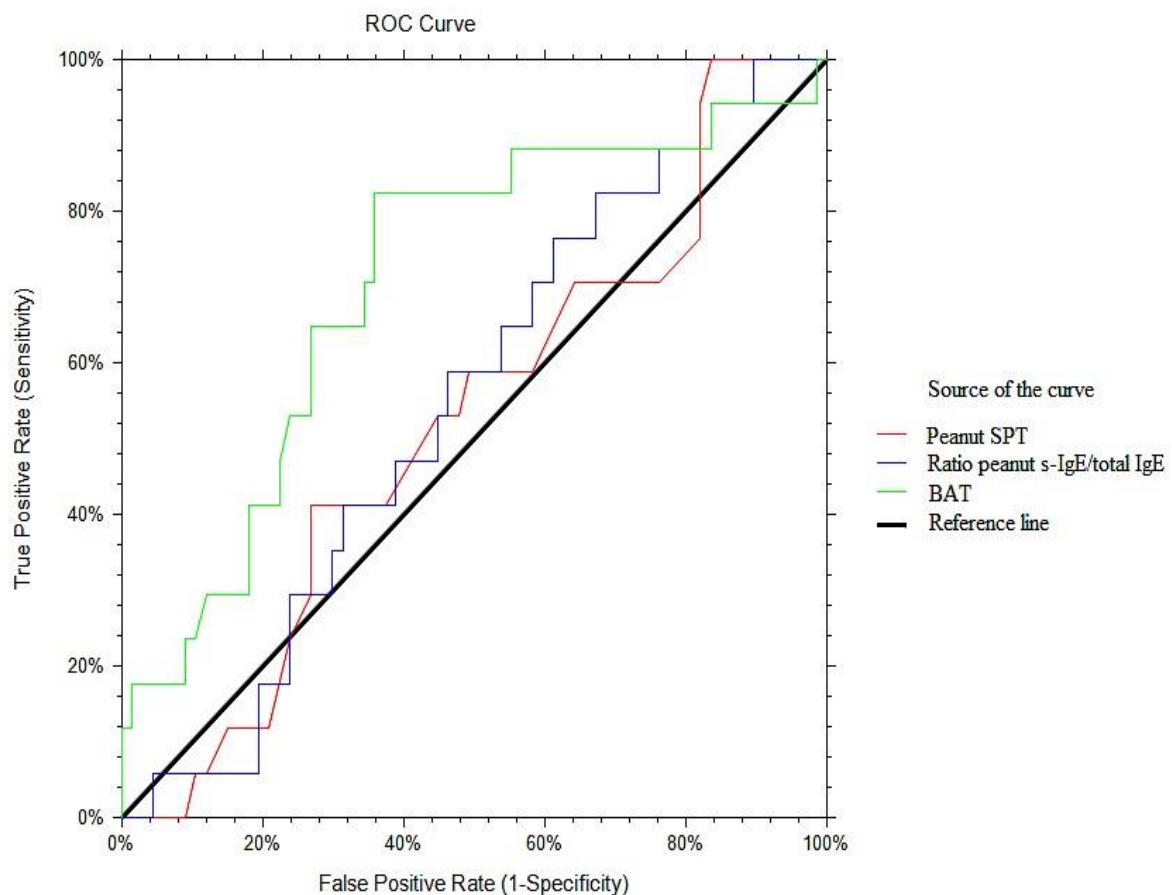
Figure 11. *Receiver operating characteristic curves predicting very low threshold (< 3 mg of peanut protein). The BAT used 5 ng/mL of allergen.*
Reprinted from Clin Exp Allergy 2018; Apr;48(4):415-423; Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al.: « Predicting reactivity threshold in children with anaphylaxis to peanut.", with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/29284183

5.1.2 Baseline characteristics predicting the possibility of completing an up-dosing phase of peanut oral immunotherapy (paper #2)

The up-dosing phase was completed by 75.5 % (n = 43) of the 57 included children, while 14 children discontinued the OIT. As shown in Table 10, children who completed the up-dosing phase had significantly lower ratio of peanut s-IgE/total IgE (p = 0.009), more often allergy to tree-nuts (p = 0.002) and to other foods (p = 0.003) and more often a positive SPT to tree-nuts (p = 0.02) compared to the children who discontinued OIT.

Table 10. *Baseline characteristics of children completing or discontinuing the up-dosing phase of the peanut OIT TAKE-AWAY trial.*

	Completing (n = 43)	Discontinuing (n = 14)	p-value
Age (median, min-max)	9.0 (5.2, 15.2)	11.1 (5.4, 15.1)	0.13
Male	21 (48.8)	10 (71.4)	0.14
History of anaphylaxis to peanut	32 (74.4)	13 (92.8)	0.41
Current asthma	16 (69.6)	8 (57.1)	0.26
Allergic rhinitis	13 (30.2)	2 (14.3)	0.53
Atopic dermatitis	36 (83.7)	11 (78.6)	0.64
Allergy to tree-nuts	20 (48.8)	0 (0.0)	**0.002**
Allergy to other food than nuts	25 (59.5)	2 (14.3)	**0.003**
Parental atopic disease*	36 (83.7)	14 (100.0)	0.16
Parental food allergy**	14 (32.6)	7 (50.0)	0.51
FEV1% predicted	102.7 (98.6, 106.7)	99.7 (94.0, 105.8)	0.58
SPT tree-nuts ≥ 3 mm	25 (58.1)	3 (21.4)	**0.02**
S-IgE (≥ 0.35 kUA/L):			
tree-nuts***	40 (95.2)	12 (85.7)	0.08
other food****	41 (95.3)	13 (92.9)	0.63
Peanut SPT (mm)	10.3 (8.7, 11.9)	12.1 (8.3, 15.8)	0.48
Total IgE (kUA/L)	570.6 (405.1, 736.2)	713.9 (314.1, 1113.6)	0.51
S-IgE peanut (kUA/L)	197.5 (12.8, 270.1)	472.8 (120.2, 825.3)	0.09
S-IgE Ara h2 (kUA/L)	99.0 (62.7, 135.2)	177.1 (85.9, 268.4)	0.05
Peanut s-IgE/ total IgE (kUA/L)	0.3 (0.3,0.4)	0.5 (0.4, 0.7)	**0.009**
Peanut s-IgG$_4$/ s-IgE (ng/ml)	27.4 (10.5, 44.4)	9.7 (1.9, 21.3)	0.22
CAPT pos level*****	3.0 (2.6, 3.3)	2.6 (2.0, 3.2)	0.31
BAT (%CD63+)	59.5 (50.5, 68.5)	69.7 (54.6, 84.7)	0.17

At baseline DBPCFC:			
Number of anaphylaxis:	43 (100.0)	14 (100.0)	C
Anaphylaxis severity grade:			
modified EAACI	1.7 (1.6, 1.8)	1.6 (1.4, 1.9)	0.70
Sampson	2.7 (2.3, 2.9)	2.7 (2.3, 3.1)	0.94
Use of adrenaline	22 (51.2)	8 (57.1)	0.70
LOAEL(mg peanut prot)	113.3 (12.4, 214.3)	82.9 (16.3, 149.5)	0.11
Reactivity threshold (mg peanut protein)	155.4 (48.9, 261.9)	250.1(60.9, 439.3)	0.07

Variables are given as mean (95 % CI) or n (%), except age which is given as median (min, max).
Bold values are statistically significant (p < 0.05).
C Not able to compute – anaphylaxis at DBPCFC is a constant.
*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis
**All food allergy including peanut and tree-nut allergy
***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut
****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat
*****The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers (8, 9) ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) (10) ranging from 1 to 5. LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective symptoms
Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC, with at least two moderate objective symptoms in one or more organ systems symptoms according to Bock's criteria (34, 120).

SPT, skin prick test; Ig - immunoglobulin; BAT - basophil activation test; CAPT – conjunctival allergen provocation test; LOAEL - lowest observed adverse effect level; OIT – oral immunotherapy; DBPCFC – double-blind placebo-controlled food challenge

None of the baseline characteristics were significant predictors for completing the OIT up-dosing phase until a maintenance dose was reached in bivariate (Table 11) and multivariate logistic regression analyses (not shown). Non-significant trends were, however, observed for s-IgE to peanut, s-IgE to Ara h 2, the peanut s-IgE/total IgE ratio and AEs (p = 0.06 to 0.07) (TableTable 11).

Table 11. *Possible factors that could explain reaching any maintenance dose ($\leq$ 5000 mg peanut protein, eq. MMD + IMD) compared to children who discontinued OIT and the pre-defined maximum maintenance dose (MMD) of 5000 mg peanut protein compared to children not reaching MMD (eq. IMD + discontinued) using bivariate logistic regression analyses.*

	Reached MMD or IMD (n = 43)	p-value	Reached MMD (n = 12)	p-value
Parent education (graded 1(low) - 5(high))	1.25 (0.95, 1.66)	0.12	0.95 (0.70, 1.30)	0.77
Siblings	1.04 (0.43, 2.53)	0.94	0.83 (0.32, 2.12)	0.69
Male sex	2.55 (0.72, 9.10)	0.15	0.80 (0.23, 2.82)	0.73
Current asthma	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Allergic rhinitis	2.14 (0.46, 10.03)	0.33	2.55 (0.67, 9.63)	0.17
Peanut SPT (mm)	0.95 (0.86, 1.05)	0.31	0.94 (0.82, 1.08)	0.40
S-IgE (kUA/L):				
peanut	1.00 (1.00, 1.00)	0.07	1.00 (1.00, 1.00)	0.42
Ara h 2	1.00 (0.99, 1.00)	0.07	1.00 (0.99, 1.00)	0.57
Peanut s-IgE/total IgE (kUA/L)	0.10 (0.01, 1.08)	0.06	0.44 (0.03, 5.87)	0.53
Peanut s-IgG$_4$/s-IgE (ng/ml)	1.01 (0.99, 1.03)	0.45	1.02 (1.00, 1.04)	**0.02**
BAT (%CD63+)*	0.99 (0.96, 1.03)	0.98	0.99 (0.96, 1.03)	0.66
CAPT positive (dilution)	1.36 (0.76, 2.40)	0.30	1.55 (0.83, 2.89)	0.17
Anaphylaxis severity: modified EAACI	1.35 (0.38, 4.74)	0.64	0.36 (0.10, 1.32)	0.12
LOAEL (mg)	1.00 (1.00, 1.00)	0.99	1.00 (1.00, 1.01)	0.08
During up-dosing: AEs**				
(days/period/child)	0.80 (0.64, 1.01)	0.06	0.69 (0.39, 1.20)	0.18
Anaphylaxis (days/period/child)	1.83 (0.42, 79.71)	0.75	1.86 (0.25, 136.35)	0.78
Asthma medication (yes/no)	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Postponements (total)	1.46 (0.88, 2.42)	0.14	0.87 (0.55, 1.38)	0.55
Dose reductions (total)	3.00 (0.34, 26.60)	0.32	1.40 (0.17, 11.24)	0.75

Associations are given as odds ratio (OR) (95 % CI).
Bold values are statistically significant (p < 0.05).

N = 57 children randomized to active peanut OIT in the TAKE-AWAY trial.
* N = 50. The BAT was not performed in 5 children due to technical causes (n = 5) and non-responders were excluded from the analyses (n = 2).

SPT, skin prick test; IgE/G/G₄/ - immunoglobulin E/G/G₄; BA - basophil activation, CAPT – conjunctival allergen provocation test; OIT – oral immunotherapy; DBPCFC – double blind placebo-controlled food challenge; LOAEL - lowest observed adverse effect level; AEs – adverse events

5.2   The feasibility of achieving a high maintenance dose in peanut oral immunotherapy (papers #1 and #2)

At end of up-dosing (Y_1), 21.1% (n = 12) reached the pre-defined MMD of 5000 mg peanut protein, while 54.4 % (n = 31) reached a lower IMD and 24.5 % had discontinued OIT. The median (min, max) maintenance dose reached for the IMD children was 2700 (250, 4000) mg peanut protein.

As shown in Table 12, children who reached MMD were older, had lesser allergy to other food and higher reactivity thresholds as compared with the IMD children, and had lower s-IgEs to peanut and Ara h 2, lower ratio of peanut s-IgE/total IgE and higher ratio of peanut s-IgG₄/s-IgE compared with children who discontinued OIT.

Table 12. *Baseline characteristics of children randomized to peanut OIT in the TAKE-AWAY trial.*

	Total study population (n = 57)	MMD (n = 12)	IMD (n = 31)	Dis-continued (n = 14)	Overall p-value
Age (median, min-max)	10.1 (5.2, 15.2)	10.7 (7.2, 15.2)	8.5 (5.2, 14.4)	10.2 (5.4, 15.1)	**0.02##**
Male	31 (54.4)	7 (58.3)	14 (45.2)	10 (71.4)	0.26
History of anaphylaxis to peanut	45 (78.9)	9 (75.0)	23 (74.2)	13 (92.8)	0.82
Current asthma	24 (42.1)	5 (83.3)	11 (64.7)	8 (88.9)	0.37
Allergic rhinitis	15 (26.3)	5 (41.7)	8 (25.8)	2 (14.3)	0.53
Atopic dermatitis ever	47 (82.5)	11 (91.7)	25 (80.6)	11 (78.6)	0.64
Allergy to tree-nuts	20 (35.1)	5 (41.7)	15 (48.4)	0 (0.0)	0.15
Allergy to other food than nuts	27 (47.4)	6 (50.0)	19 (61.3)	2 (14.3)	**0.02#**
Parental atopic disease*	50 (87.7)	9 (75.0)	27 (87.1)	14 (100.0)	0.16
Parental food allergy**	21 (36.8)	4 (33.3)	10 (32.3)	7 (50.0)	0.51
FEV1% predicted	101.2 (97.6, 105.0)	101.0 (91.2, 112.2)	101.9 (97.7, 104.7)	99.7 (94.0, 105.8)	0.86
Pos s-IgE ($\geq$ 0.35 kUA/L):					
tree-nuts***	52 (91.2)	10 (83.3)	30 (96.7)	12 (85.7)	0.08
other food****	54 (94.7)	12 (100.0)	29 (96.7)	13 (92.9)	0.63
Peanut SPT (mm)	9.8 (8.6, 11.0)	8.7 (7.0, 10.9)	9.7 (8.4, 11.3)	10.3 (7.3, 14.6)	0.64
S-IgE (kUA/L):					
Peanut	110.6 (70.4, 173.8)	21.9 (4.9, 97.8)	129.3 (88.9, 188.0)	175.7 (55.0, 561.6)	**0.003#**
Ara h2	56.2 (37.2, 87.1)	13.5 (3.1, 59.1)	67.0 (47.8, 94.0)	89.6 (33.9, 235.9)	**0.004#**
Peanut s-IgE/ total IgE (kUA/L)	0.4 (0.0, 1.5)	0.3 (0.1, 0.6)	0.3 (0.1, 0.6)	0.5 (0.4, 0.7)	**0.002#**
Peanut s-IgG$_4$/ s-IgE (ng/ml)	5.7 (3.7, 8.9)	15.5 (3.4, 60.3)	4.9 (2.9, 8.3)	3.3 (1.4, 7.8)	**0.04#**
CAPT pos level*****	2.6 (2.3, 3.0)	3.0 (2.2, 4.1)	2.6 (2.3, 3.1)	2.3 (1.7, 3.1)	0.41
BAT (%CD63+)	68.0 (61.6, 75.1)	34.4 (15.5, 75.9)	49.6 (34.7, 70.8)	63.7 (46.0, 88.2)	0.28

To be continued on the next page.

	Total study population (n = 57)	MMD (n = 12)	IMD (n = 31)	Dis-continued (n = 14)	Overall p-value
At baseline DBPCFC:					
Number of anaphylaxis:	57 (100.0)	12 (100.0)	31 (100.0)	14 (100.0)	0.11
Anaphylaxis severity grade:					
modified EAACI	1.6 (1.4, 1.7)	1.4 (1.1, 1.8)	1.7 (1.5, 1.9)	1.6 (1.3, 1.9)	0.22
Sampson	2.6 (2.4, 2.8)	2.8 (2.4, 3.4)	2.5 (2.3, 2.8)	2.6 (2.3, 3.1)	0.49
Use of adrenaline	30 (52.6)	5 (41.7)	17 (54.8)	8 (57.1)	0.70
LOAEL (mg peanut protein)	18.4 (11.8, 28.6)	45.9 (10.2, 207.1)	15.1 (10.3, 22.1)	36.2 (15.4, 84.4)	0.05
Reactivity threshold (mg peanut protein)	46.2 (29.7, 72.0)	108.7 (29.3, 402.9)	32.1 (22.0, 46.9)	93.3 (40.0, 222.4)	**0.01##**

Variables are given as geometric mean (95 % CI) or n (%), except age which is given as median (min, max).
Bold values are statistically significant (p < 0.05).
One-way ANOVA was applied to determine statistically significant differences between group means and the Dunnett's post hoc test to confirm which groups differed.
 # Statistically significant difference between MMD and discontinued.
Statistically significant difference between MMD and IMD.
*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis
**All food allergy including peanut and tree-nut allergy
***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut
****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat
*****The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers (8, 9) ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) (10) ranging from 1 to 5.
LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective symptoms
Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC, with at least two moderate objective symptoms in one or more organ systems symptoms according to Bock's criteria (34, 120).

MMD – subjects who reached the maximum maintenance dose; IMD – subjects who reached the individual maintenance dose; SPT, skin prick test; Ig - immunoglobulin; BAT - basophil activation test; CAPT – conjunctival allergen provocation test; LOAEL - lowest observed adverse effect level; OIT – oral immunotherapy; DBPCFC – double blind placebo-controlled food challenge

Reprinted from Allergy 2018; Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al.: «Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy.", with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/30225844

Failure to reach MMD was explained by distaste for peanuts in 66.7 % of the children (IMD (n) = 28 and discontinued (n) = 2), followed by AEs in 26.7 % (IMD (n) = 3 and discontinued (n) = 9) and social reasons in 6.7 % (discontinued (n) = 3, two found the treatment too time-consuming, while one discontinued due to family reasons). In 77.2 % of the children, distaste for peanuts was reported as a daily challenge. Detailed characteristics of the children who discontinued OIT are reported in Table 13.

In the bivariate (Table11) and the multivariate logistic regression model (not shown), the ratio of peanut s-IgG$_4$/s-IgE was the only identified factor significantly associated with reaching MMD.

Table 13. *Characteristics of children who discontinued oral immunotherapy without reaching a maintenance dose.*

Patient no.	Age years	Peanut s-IgE kUA/L	Ara h 2 s-IgE kUA/L	LOAEL mg peanut protein	Reactivity threshold mg peanut protein	Dose at dis-continuation mg peanut protein	Reason for dis-continuation mg peanut protein
1	8.8	93.2	82.7	110.8	110.8	5	Social
2	11.3	493.0	221.0	35.8	35.0	5	AEs
3	14.3	26.2	14.6	110.8	243.0	450	AEs
4	15.1	179.0	77.0	13.0	13.0	10	AEs
5	14.8	951.0	457.0	443.0	943.0	45	AEs
6	6.5	63.9	32.4	43.0	43.0	20	Distaste
7	10.9	271.0	158.0	43.0	43.0	350	AEs
8	13.8	2311.0	475.0	43.0	43.0	45	AEs
9	11.7	114.0	87.4	3.0	43.0	1000	Distaste
10	10.1	629.0	179.0	3.0	13.0	20	AEs
11	9.8	352.0	210.0	13.0	143.0	1	Social
12	5.4	0.6	0.8	143.0	443.0	1	Social
13	7.3	92.8	61.6	143.0	943.0	65	AEs
14	11.6	285.0	131.0	13.0	443.0	5	AEs

5.3 The patient perspective burden of peanut oral immunotherapy (papers #2 and #3)

5.3.1 Adverse events (paper #2)

All but one child reported AEs. Mild AEs were reported in 13.9 % of the OIT doses, while moderate AEs were reported in 0.6 % and moderate anaphylaxis in 0.06 % of the dose-days with AEs. The 11 anaphylactic events occurred in 11 children (Table 14).

Table 14. *Adverse events (AEs) related to oral immunotherapy in children highly allergic to peanut.*

	Overall OIT (n = 57) (doses = 18470)	MMD (n = 12) (doses = 5292)	IMD (n = 31) (doses = 11536)	Discontinued (n=14) (doses =1642)
Total AEs				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2560 (13.9)	290 (5.5)	1957 (17.0)	313 (19.1)
Mild AEs, total				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2473 (13.4)	290 (5.5)	1725 (15.0)	515 (31.4)
Moderate AEs				
Patients, n (%)	22 (38.6)	4 (33.3)	14 (45.2)	4 (28.6)
Events, n (%)	116 (0.6)	21 (0.4)	81 (0.7)	14 (0.9)
Oral itching				
Patients, n (%)	49 (86.0)	10 (83.3)	28 (90.3)	11 (78.6)
Events, n (%)	1096 (5.9)	173 (3.3)	822 (7.1)	79 (4.8)
GI related AEs*				
Patients, n (%)	48 (84.2)	7 (58.3)	27 (87.1)	13 (92.9)
Events, n (%)	1100 (6.0)	31 (0.6)	959 (8.3)	110 (6.7)
Skin related AEs				
Patients, n (%)	43 (75.4)	9 (75.0)	27 (87.1)	7 (50.0)
Events, n (%)	140 (0.8)	26 (0.5)	95 (0.8)	71 (4.3)
Respiratory related AEs				
Patients, n (%)	37 (64.9)	10 (83.3)	19 (61.3)	8 (57.1)
Events, n (%)	59 (0.3)	10 (0.2)	31 (0.3)	18 (1.0)
Anaphylaxis				
Patients, n (%)	11 (19.3)	2 (16.7)	5 (16.1)	4 (28.6)
Events, n (%)	11 (0.06)	2 (0.04)	5 (0.04)	4 (0.24)
Sampson severity grade median (min, max)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
Used epinephrine				
Patients, n (%)	6 (10.5)	2 (16.7)	2 (6.5)	2 (14.3)
Events, n (%)	6 (0.03)	2 (0.04)	2 (0.02)	2 (0.12)
Used acute salbutamol**				
Patients, n (%)	5 (8.8)	1 (8.3)	2 (6.5)	2 (7.1)
Events, n (%)	5 (0.03)	1 (0.02)	3 (0.03)	2 (0.1)

The AEs were mostly characterized as oral itching (43.5 %) or other gastro-intestinal (GI) related symptoms (42.5 %) (Figure 12). Dyspeptic symptoms were reported by eight children who either discontinued treatment (n = 2), or had symptom relief related to spontaneous resolution (n = 2) or treatment with proton pump inhibitor (PPI) (n = 4) and completed the up-dosing phase.

The 11 moderate anaphylactic events occurred in 11 different children and adrenaline was administered in six of the episodes. All but two anaphylactic reactions were preceded by known risk factors; exercise within two hours after a dose (5), ongoing infection (1), excessive tiredness (1), impaired compliance to OIT (1) or asthma treatment (1). The control group did not experience any anaphylactic events to peanut during the same time-span.

Children who discontinued OIT reported median (min, max) 2.5 (0.3, 10.5) dose-days of OIT-related AEs per dose-step, which is significantly more frequent as compared with the reported 1.0 (0.0, 12.9) (p = 0.01) as reported by children who completed the OIT up-dosing phase. On the other hand, reported dose-days of moderately graded AEs including anaphylactic events were similar in these two groups of children (p = 0.61).

The AEs occurred more often during the first two, compared with the remaining days in each up-dosing period (p = 0.001) as shown in Figure 12. Also, the AEs were more frequent in the first dose-interval step (1-65 mg peanut protein), as compared with the second (66-800 mg) and the third (801-5000 mg peanut protein) dose-interval steps (overall p = 0.03) (Figure 12).
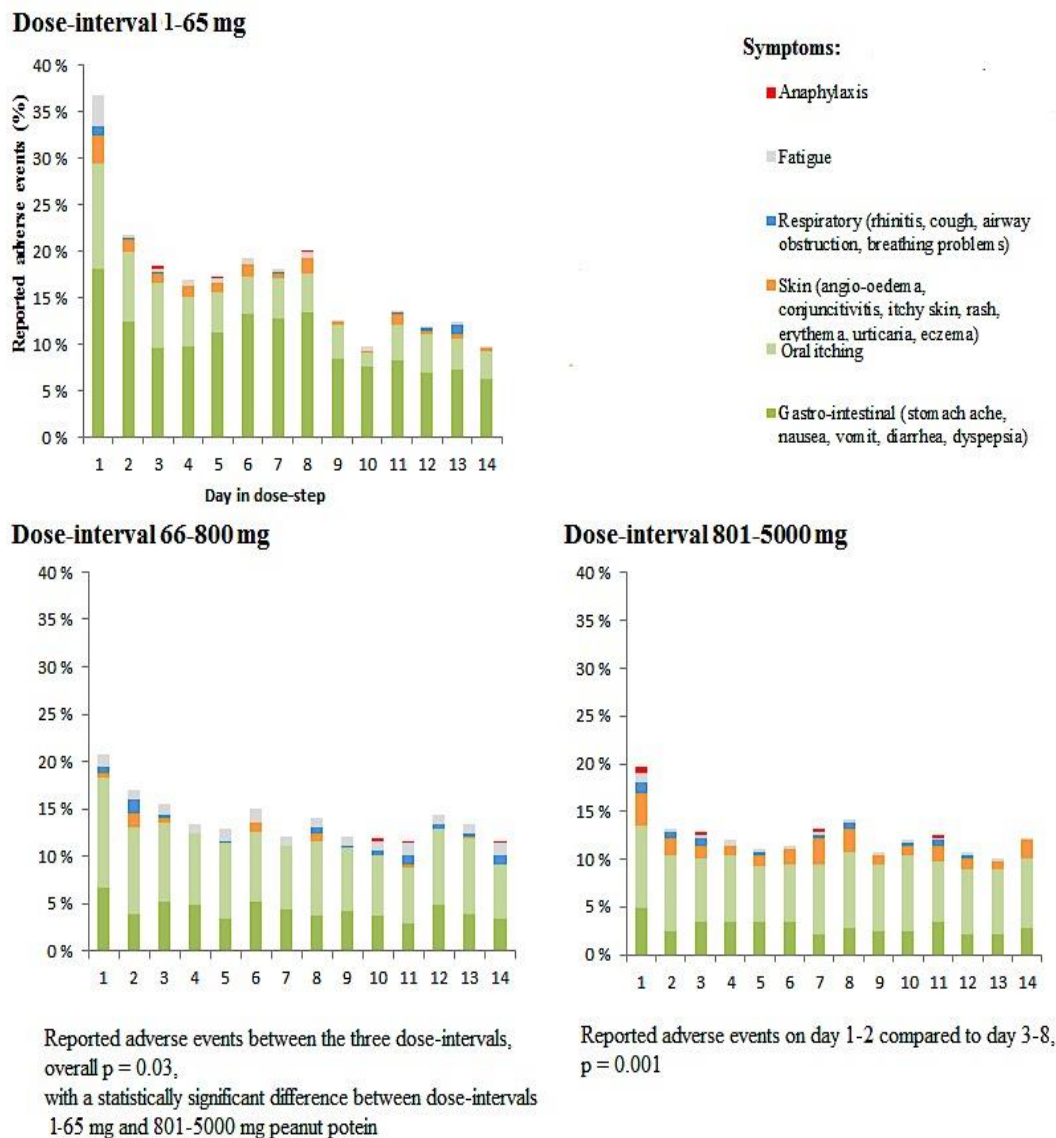
Figure 12. *Reported doses with adverse events (AEs) per dose-day (%) in the three dose-intervals of the up-dosing phase. If there were another cycle of 14 days of the same dose-step due to AEs or vacations in the same dose-interval, this cycle would also be a part of the same dose-interval, and the Y-axis would still represent reported doses with AEs per dose-day (%). One-way ANOVA was applied to determine statistically significant differences between the intervals and the Dunnett's post hoc test to confirm which groups differed.*
Reprinted from Allergy 2018; Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al.: «Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy.", with permission from Elsevier.
https://www.ncbi.nlm.nih.gov/pubmed/30225844

5.3.2 The patient perceived treatment burden (paper #3)

Children who completed the OIT up-dosing phase attended a median of (min, max) 25 (17, 32) hospital attendances until a maintenance dose was reached. In addition, they attended another 11 pre-set protocol-based visits until one year of maintenance treatment (Y_2); at recruitment, three months, one year and two years' of treatment including the three-monthly visits during maintenance phase.

As shown in table 15, the treatment burden was perceived highest related to the taste-domain among children who completed the up-dosing phase as well as one year of maintenance treatment, followed by time spent related to the treatment and GI-related AEs. Although the overall score was similar at Y_1 and Y_2, the time spent on treatment remained relatively unchanged, whereas the mean (95 % CI) taste-domain burden decreased significantly from 6.5 (5.5, 7.3) to 5.3 (4.3, 6.3) (p = 0.02) and the GI-related symptom burden decreased from 2.6 (1.9, 3.3) in the up-dosing phase to 1.4 (1.0, 1.8) at Y_2 (p = 0.001) (Table 15). The four children who discontinued OIT from Y_1 to Y_2, had VAS reports at Y_1 which was not significantly different from the children who reached Y_2; for the GI-domain 2.3 (1.2, 3.5) (p = 0.64), the taste-/amount-domain 8.0 (5.8, 10.0) (p = 0.11) and the time spent-domain 3.5 (1.9, 5.0) (p = 0.29).

Table 15. *The perceived treatment burden is given at Y_1 (after up-dosing) and Y_2 (after one year of maintenance treatment) as mean values with 95% confidence intervals among all children randomized to OIT.*

	One year of treatment (Y_1) (N = 43)	Two years of treatment (Y_2) (N = 37)	p-value
Overall	3.9 (3.1, 4.8)	3.7 (2.9, 4.6)	0.84
GI-domain	2.6 (1.9, 3.3)	1.4 (1.0, 1.8)	0.001
Oral itching	3.4 (2.5, 4.4)	2.1 (1.3, 2.9)	0.02
Stomach ache	2.6 (1.7, 3.5)	1.4 (0.8, 2.0)	0.008
Nausea or vomiting	1.6 (0.8, 2.5)	0.6 (0.3, 0.9)	0.02
Taste-/amount-domain	6.5 (5.5, 7.3)	5.3 (4.3, 6.3)	0.02
Taste	7.0 (5.9, 8.0)	6.1 (4.9, 7.3)	0.10
Amount	5.8 (4.8, 6.7)	4.3 (3.3, 5.2)	0.01
Time spent-domain	2.9 (2.1, 3.7)	2.2 (1.5, 2.9)	0.06
at home	2.5 (1.6, 3.4)	2.5 (1.5, 3.6)	0.94
at hospital (up-dosing/visits)	3.0 (2.2, 3.)	1.7 (1.2, 2.3)	0.005

Unpaired t-test was applied to determine statistically significant difference between means at Y_1 and Y_2.

The GI-domain represents average of how AEs like stomach ache, nausea/vomiting and oral itching are perceived.
The taste-/amount-domain represents average of perceived taste and amount of peanut eaten.
The time spent-domain represents perceived average of time spent on eating OIT doses at hospital for up-dosing visits and at ingesting OIT doses at home.

A negative correlation was observed between treatment burden at Y_1 and change in perceived

treatment (range of correlation coefficient (r_s) (– 0.82, – 0.44)) (p < 0.001) (Figure 13).
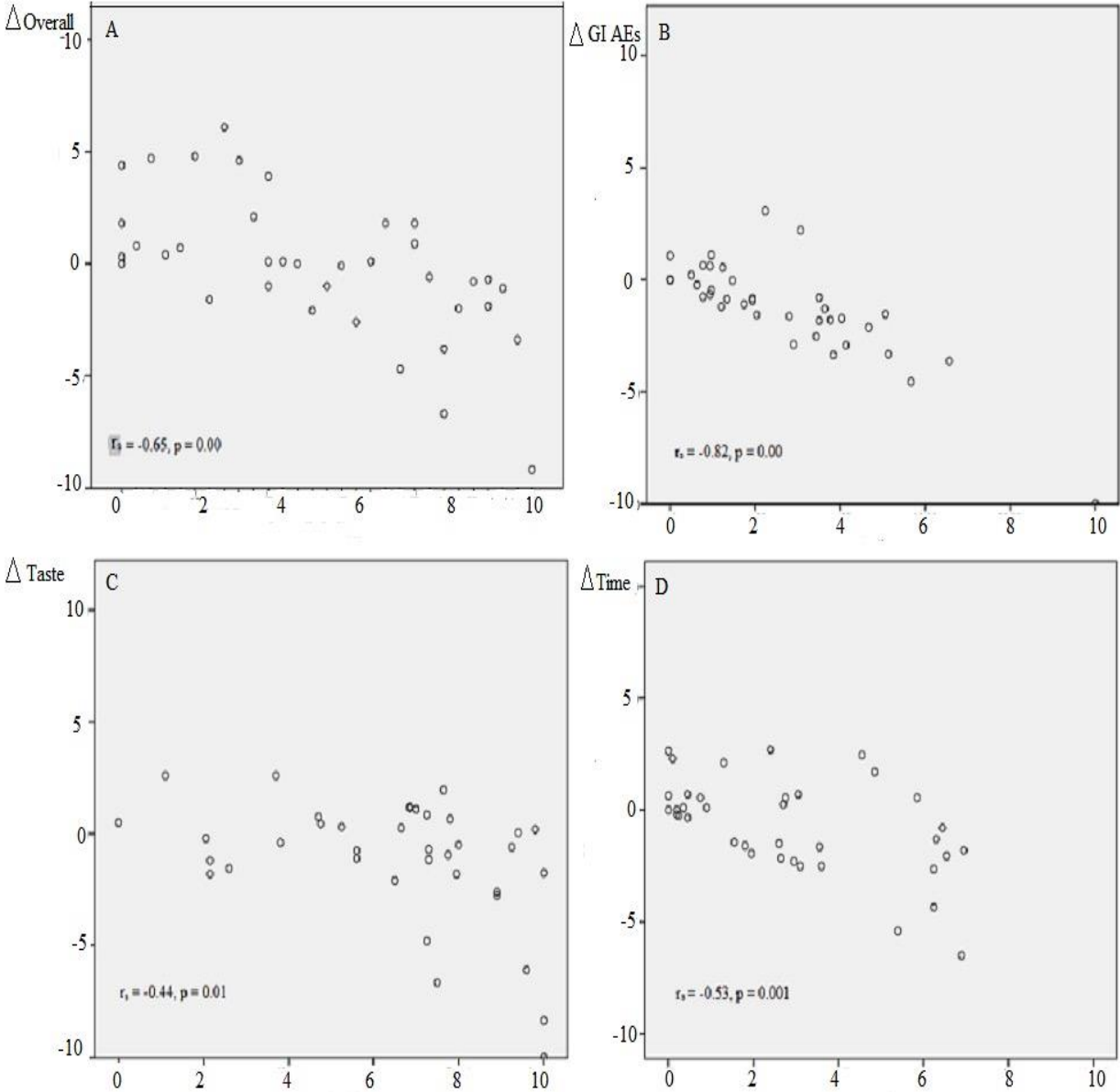
Figure 13. *Correlation between change in perceived treatment burden from end of up-dosing (Y_1) to second year of treatment (one year of maintenance) (Y_2) and perceived burden at Y_1. Perceived treatment burden is reported as overall burden (A), and within three domains: Adverse events (stomach ache, nausea/vomiting and oral itching) (B), taste and amount of daily peanut oral immunotherapy (OIT) (C) and time spent on OIT (D).*

5.4   The effect of 2-years peanut oral immunotherapy (paper #3)

After two years of OIT, 18 children had discontinued treatment, while the mean (SD) daily maintenance dose among the 39 children who still received OIT was 3322 (1376) mg peanut protein, ranging from 350 - 5000 mg. Two of the 39 refused OFC at Y_2 out of concern for allergic reactions.

Desensitization to 7500 mg peanut protein was confirmed in 35/37 of the challenged children (94.6 %). Two children developed objective allergic reactions before reaching 7500 mg peanut protein; one child with a maintenance dose of 1500 mg reacted with conjunctivitis and urticaria at 7500 mg peanut protein; the other child had self-discontinued the maintenance dose of 1250 mg for three months and just resumed the OIT for the last three months prior to OFC. The latter child reacted with moderate anaphylaxis (erythema, urticaria and wheezing) at a cumulated dose of 4444 mg peanut protein.

As shown in Figure 14, the child-reported QoL was significantly higher (improved) after two years of OIT as compared baseline, with mean (95 % CI) QoL scores increasing from Y_0 (82.1 (79.1, 85.2)) to Y_2 (86.7 (83.6, 89.7)) (p < 0.0001). The controls reported no significant difference in QoL scores from Y_0 (83.4 (75.4, 91.4) to Y_2 (82.2 (76.0, 88.4)) (p = 0.80)). However, the mean change (95 % CI) in QoL scores from Y_0 to Y_2 between the OIT group (4.4 (0.5, 8.3)) and the controls (-0.9 (-7.9, 6.11)) was not significantly different (p = 0.12) (Figure 14).

In the corresponding parental proxy-reports, parents of the OIT group reported significantly higher mean (95 % CI) QoL scores at Y_2 as compared with Y_0 with mean (95 % CI) QoL scores improving from Y_0 (78.7 (73.6, 83.7)) to Y_2 (88.0 (85.2, 90.8)) (p < 0.0001), with no significant difference in QoL scores for parents of the controls between Y_0 (81.7 (74.6, 88.8)) and Y_2 (82.1 (75.8, 88.4)) (p = 0.90) (Figure 14). However, parents of the OIT group reported a two-fold larger improvement in mean change (95 % CI) QoL scores in their child's QoL

(9.3 (4.3, 14.3)) as compared with the children themselves (4.4 (0.5, 8.3)), and which, became

significantly different from that of the controls (0.4 (-7.1, 8.0)) (p = 0.02) (Figure 14).

Figure 14. *The absolute quality of life scores in children who receive oral immunotherapy (OIT) and the controls at screening (Y_0), at one year of up-dosing (Y_1) and at second year of treatment (Y_2), as reported by the child self-reports and the parental proxy-reports. Statistically significant group differences were assessed by mixed models for repeated measures. Increased value reflects improved QoL*

In unadjusted bivariate analyses, the number of AEs did not correlate significantly with change in QoL from Y_0 to Y_2, neither as reported by the children (p = 0.76) nor the parents (p = 0.90). The change in QoL from Y_0 to Y_2 was not influenced by the level of desensitization, maintenance dose or perceived treatment burden in any of the three domains at Y_1 or Y_2 (Table 16). The results did not change if children who discontinued OIT or perceived burden of time spent on OIT were included in the analyses (data not shown). During step-down procedures, the effect size of burden of peanut (dis-)taste/amount decreased by more than 25 % when maintenance dose was excluded from the multivariate regression analyses model.

Table 16. *Multivariate robust regression analyses for associations between factors that may influence change in quality of life from screening (Y_0) to second year of treatment (Y_2).*

	PedsQL 4.0 child	p-value	PedsQL 4.0 parents	p-value	FAQLPB (parents)	p-value
Age	-0.49 (-2.17, 1.19)	0.56	1.50 (0.24, 3.23)	0.09	0.02 (-0.06, 0.10)	0.63
Gender	-8.90 (-18.55, 0.76)	0.07	-5.90 (-16.29, 4.50)	0.26	0.23 (-0.25, 0.71)	0.34
Maintenance dose (mg)	-0.00 (-0.01, 0.00)	0.48	-	-	-	-
Perceived <u>burden of:</u>						
Adverse events	*-0.22 (-0.59, 0.15)*	0.23	0.19 (-0.17, 0.56)	0.29	-0.02 (-0.04, 0.00)	0.10
Taste/amount of peanuts	0.15 (-0.02, 0.32)	0.09	-	-	0.01 (-2.02, -0.13)	0.09

Associations are given as the relative change (ß) related to each unit increase by the in QoL score.
N=37, including only children still receiving OIT at Y_2 with no missing data.
- no significant association
Change in QoL is given by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) child self-report and parental proxy-report, or the food allergy quality of life – parental burden (FAQLPB). Decreasing values of PedsQL and increasing values of FAQLPB reflects poorer QoL.
Perceived treatment burden was reported by VAS (range 0–10 (0=no burden, 10=massive burden) within the domains: Adverse events (stomach ache, nausea/vomiting and oral itching) and taste and amount of daily peanut OIT.

The parents' QoL improved significantly (decreased score) as reported by the FAQL-PB from Y_0 to Y_2 for both the OIT group and the controls, as shown in Figure 15.
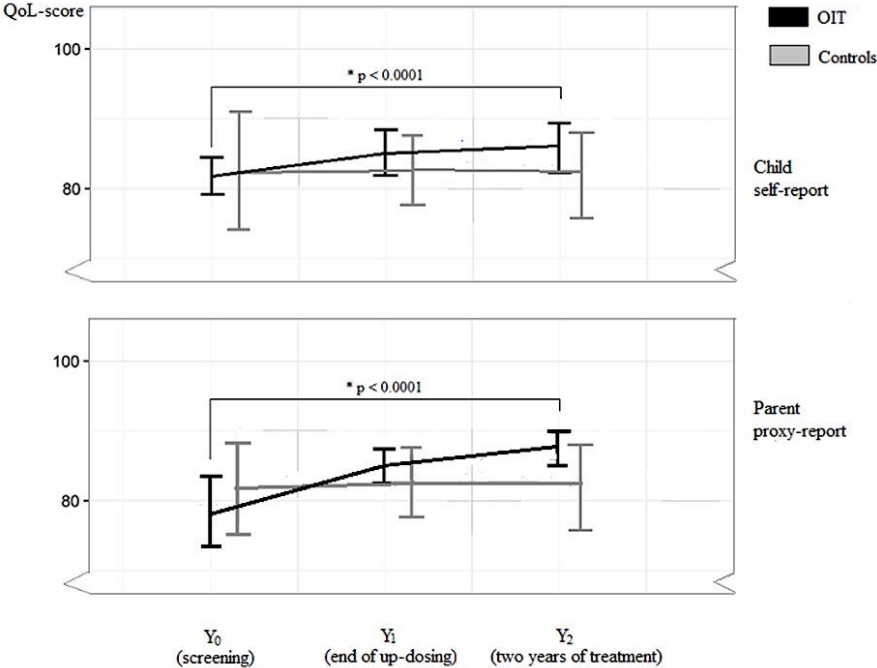

Figure 15. *The absolute quality of life (QoL) scores in parents of children receiving oral immunotherapy (OIT) and the controls at screening (Y_0), at one year of up-dosing (Y_1) and at second year of treatment (Y_2). Decreased value reflects improved QoL.*

The QoL reported by the children who were defined ineligible for OIT was similar to that of controls at Y_0 and Y_1, with the mean change (95 % CI) in QoL scores of 2.5 (-3.6, 8.6)) compared with the corresponding (-1.0 (-7-7, 5.6)) (p = 0.37) among the controls. Similar findings were observed for the parental proxy-reports (7.3 (0.4, 14.0) vs. 0.4 (-8.1, 9.0) (p=0.18)) (Figure 16).
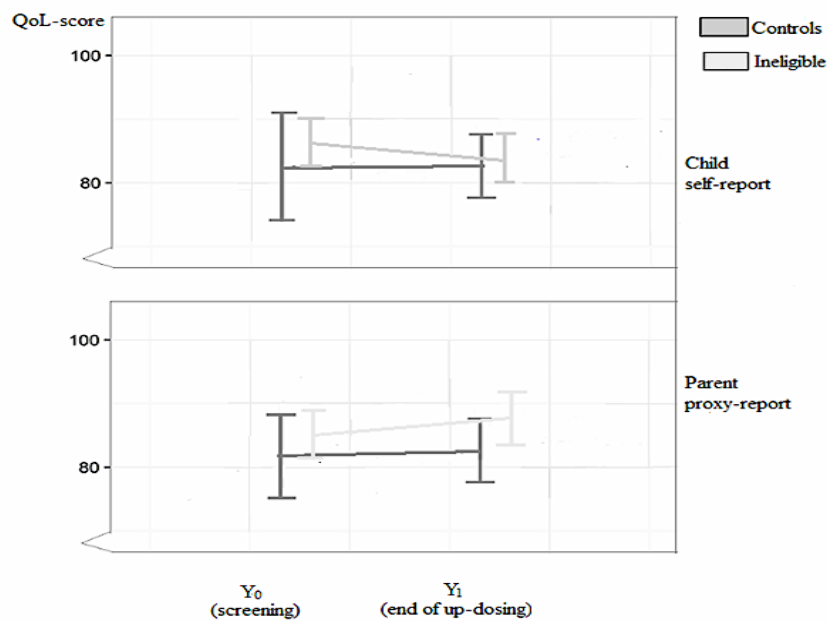
Figure 16. *The absolute quality of life (QoL) scores in children who receive oral immunotherapy (OIT) and the controls at screening (Y_0) and at one year of up-dosing (Y_1), as reported by the child self-reports and the parental proxy-reports. Increased score reflects improved QoL.*

In contrast, the QoL decreased significantly in the parents of ineligible children compared to control parents (p=0.048) one year after screening for study participation (Figure 17).
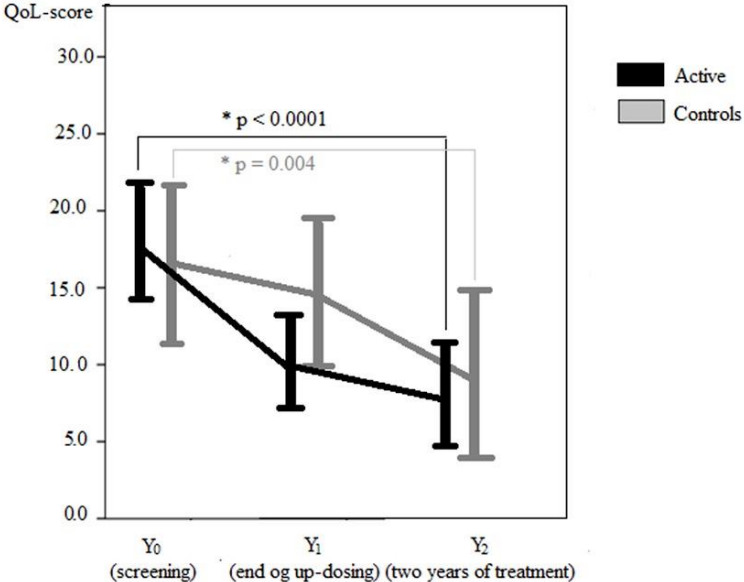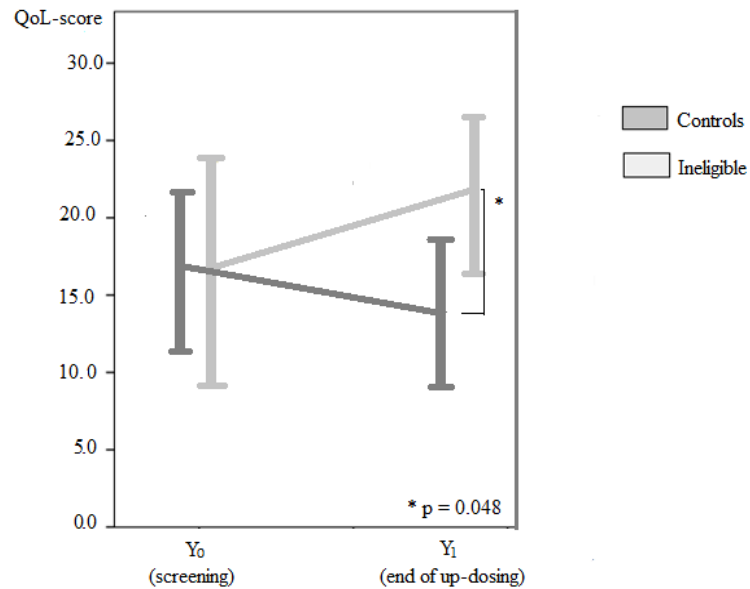

Figure 17. *The absolute quality of life (QoL) scores in parents of children receiving oral immunotherapy (OIT) and the controls at screening (Y_0) and at one year of up-dosing (Y_1). Decreased score reflects improved QoL.*

6   GENERAL DISCUSSION

6.1   Baseline characteristics predicting the possibility of entering and completing an up-dosing phase of peanut oral immunotherapy (papers #1 and #2)

6.1.1   Baseline characteristics predicting the possibility of entering peanut oral immunotherapy (paper #1)

All of the 96 children with a positive DBPCFC during screening for the TAKE-AWAY trial were primary sensitized to peanut and reacted with anaphylaxis. A very low reactivity threshold of less than 3 mg peanut protein was determined in 20 percent of the subjects, rendering them ineligible for peanut OIT according to our protocol.

The finding that reactivity threshold as well as LOAEL was significantly associated with basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE are in line with previously published studies (38, 55, 57). The association between reactivity threshold and basophil activation given by % CD 63+, is consistent with previous reports including children with varying severity of peanut allergy (38, 55). In 52 peanut allergic children with a median age of 5.4 years, Santos et al. observed that basophil activation given by CD-sens in addition to peanut SPT, s-IgE to peanut, Ara h 2 and the ratio of s-IgG$_4$/s-IgE to peanut, were significantly associated with reactivity threshold (55). Basophil activation given by % CD63+ however, best predicted allergy severity grade (55). This is in contrast to the basophil activation given by % CD63+ in the TAKE-AWAY trial, which best predicted very low threshold level (< 3 mg of peanut protein). The lack of results for CD-sens in the TAKE-AWAY trial is that CD-sens could not be assessed since strong basophil activation occurred even at the lowest concentration of 2.5 ng/ml allergen extract. This probably reflects and supports the very low reactivity thresholds determined in the TAKE-AWAY cohort.

The additional significant associations observed between reactivity threshold and Ara h 2, and LOAEL and s-IgE to peanut, are consistent with previous reports (38, 55, 57). Reactivity threshold has been reported to correlate with s-IgE to Ara h 2 ($r_s = 0.30$) (57), and LOAEL

with basophil activation, peanut SPT and s-IgE to peanut and Ara h 2 (r_s = - 0.20 to - 0.40) (38).

The finding of a discrepancy between the associations of baseline immunologic characteristics with reactivity threshold and LOAEL may have several explanations. The larger variation observed in reactivity threshold compared with LOAEL may increase the likelihood of observing correlations. Also, LOAEL and reactivity thresholds reflect different threshold entities since reactivity threshold requires moderate objective symptoms, while LOAEL appears to be more sensitive as it reflects the lowest dose that elicits a mild objective symptom. The LOAEL was determined post-hoc to facilitate comparisons across studies with different stopping-criteria of OFC (34, 39, 41). Hence, the discrepancies may also have been caused by the LOAEL being estimated rather than exactly determined for the lowest thresholds.

The very low reactivity thresholds found in 34.4 % of our study population exceeded the expected 10 % with a LOAEL ≤ 3 mg of peanut protein obtained from a data-set of OFCs in more than 200 subjects (61). This is a much higher proportion of children with low reactivity thresholds than the 4.7 % reported in a study by Blumchen et al. of 63 peanut allergic children using a modified food challenge expected to result in a lower LOAEL (38). The finding that reactivity threshold was associated with baseline characteristics also reported to predict allergy severity (53, 55-57), supports the previously suggested association between allergy severity and reactivity (p = 0.027) (102). The may also be supported by the finding that the LOAELs were lower and the s-IgEs to peanut were higher in the homogenous cohort of highly allergic children in TAKE-AWAY trial, as compared with previous published peanut OIT trials (87-94, 99). The suggestion of an association between severity and threshold is in keeping with the previously reported correlation between LOAEL and basophil activation in

63 peanut allergic children for both % CD 63+ (r_s = - 0.32) and CD-sens (r_s = - 0.36) (38), since basophil activation is suggested to reflect reactivity thresholds (55).

The time-consuming protocol, with slow dose escalation to a high maintenance dose in children highly allergic to peanut required a good understanding of the study protocol and huge commitment from the participants.

6.1.2 Baseline characteristics predicting the possibility of completing an up-dosing phase of peanut oral immunotherapy (paper #2)

Among all 57 children commencing peanut OIT, 75.5 % completed the up-dosing phase and reached some level of a maintenance dose. Even though the MMD was only attained by one fifth of the children, 73.7 % reached a maintenance dose of at least 300 mg, similar to previous studies, reporting 63.6 % to 86.9 % for peanut OITs (87-94, 99, 126).

The findings of non-significant trends and associations between AEs, s-IgEs to peanut and Ara h 2, peanut s-IgE/total IgE, and completion of the OIT up-dosing phase, may be explained by the non-biological factor "distaste for peanuts" as well as by the limited sample size. Distaste for peanuts was the main reason for not reaching MMD (paper #2), which may have influenced the association between biological baseline characteristics and reaching a maintenance dose. The s-IgE to peanut (43, 44), and even more the s-IgE to Ara h 2 (45, 49, 50), have been reported to predict allergic reactions to peanut with an Ara h 2 > 1.00 kUA/L conferring a 97 % probability of a systemic reaction (51). Among the children who discontinued OIT, 64.3 % reported unacceptable AEs as the main reason for discontinuation (paper #2), in line with previously published peanut OIT trials (92).

90

6.2 The feasibility of achieving a high maintenance dose in peanut oral immunotherapy (papers #1 and #2)

The high pre-defined MMD was reached by 21.1 % of the children only, which is lower than the 63.6 % to 86.9 % reported for other peanut OITs (87-94, 99, 126) with lower maintenance doses ranging from 125 mg – 4000 mg peanut protein. A lower IMD was reached by 54.4 % of the children. At the onset of the TAKE-AWAY trial, there was little knowledge of what the optimal MMD was with regard to efficacy and safety. A high MMD of 5000 mg peanut protein was chosen for the TAKE-AWAY trial to reach the overall aim of SU after four years of OIT. This dosage was based upon findings from several published studies. Firstly, theoretical considerations from SCIT trials of inhalant and venom allergies suggested that a high maintenance dose were more likely to induce SU (73, 74): Secondly, an OIT study which used a bi-weekly step-up protocol to 4000 mg peanut protein reported no AEs requiring epinephrine (89).

The main reason for not reaching MMD was distaste for peanuts, followed by AEs and social reasons. An amount of 5000 mg peanut protein represents approximately 25 whole peanuts kernels, which turned out to be too challenging to eat for many of our children. Distaste for peanuts was reported as a daily challenge in almost three out of four children, a finding further discussed in an Editorial Article of paper #2 (127) in the present thesis. As suggested in the Editorial Article by Bluemchen and Eiwegger (127), distaste for peanuts may be a serious challenge when a large amount is needed, and may result in decreasing safety due to reduced compliance. Little information is found about distaste in previous reports, but in one study of 23 children (88), distaste for peanuts resulted in withdrawal of one patient and reduction of maintenance dose in two others.

Adverse events were reported by 64.3 % of the drop-out children as the main reason for withdrawal, and were second most common reason for not reaching MMD. This finding is in line with the 65.0 % reported by drop-out children in pooled data of 104 children undergoing

peanut OIT (92). Despite that our cohort included solely children with anaphylaxis to peanut, our 24.5 % drop-out rate is in line with previously published peanut OIT studies, including mainly less severe peanut allergic children, with a drop-out rate ranging from $10 - 32$ % (97). The ratio of peanut $s\text{-IgG}_4$/s-IgE was a limited predictor of reaching MMD, as the odds ratio (OR) was almost similar to the non-significant OR for reaching any maintenance dose. This is consistent with the high ratio of peanut $s\text{-IgG}_4$/s-IgE reported in sensitized children who were asymptomatic on peanut exposure (128). The high ratio of peanut $s\text{-IgG}_4$/s-IgE (102) as well as the low s-IgE to peanut (38) and Ara h 2 (57) at Y_0, have all been reported to indicate a higher reactivity threshold. A high reactivity threshold was also determined at baseline in the MMD vs. IMD children. Furthermore, a high ratio of peanut $s\text{-IgG}_4$/s-IgE was associated with a higher reactivity threshold and reduced basophil activation as reported in the first paper from the TAKE-AWAY trial (paper #1). Finally, the MMD children were older than the IMD children, which may contribute to a deeper understanding of the purpose of the treatment, result in a higher degree of compliance despite troublesome AEs, and possibly facilitate the intake of a large amount of peanuts.

6.3   The patient perspective burden of peanut oral immunotherapy (papers #2 and #3)

In children with anaphylaxis to peanut, mild AEs were reported in 13.9 % of the OIT doses, 0.6 % of the AEs were reported as moderate and 0.06 % (n = 11) OIT-related moderate anaphylactic episodes occurred. The mild AE rates were higher in children who discontinued OIT, while moderate AEs plus anaphylactic events were similar in children who discontinued OIT and children who completed the up-dosing phase.

The finding of 13.9 % mild OIT-related AEs is consistent with the 13.5 % AEs in the STOP II study by Anagnostou et al. including 99 children to peanut OIT, with severities of allergic reactions ranging from mild reactions in one organ system (24.2 %) to severe respiratory

symptoms (5.1 %) (91). The reported 0.6 % moderate AEs in the TAKE-AWAY trial was, however, lower than the 2.6 % objective AEs reported by 23 highly peanut sensitized children undergoing a rush peanut OIT in another study by Blumchen et al. (88). This discrepancy may be explained by the use of a rush OIT protocol with a tailored starting in these 23 children, reported to be associated with more AEs (88, 100).

The most frequently reported AEs in the TAKE-AWAY trial were GI-related including oral itching and stomach ache, which responded well to oral antihistamines in the absence of dyspeptic symptoms. These findings are in line with previously published studies of the most common OIT-related AEs (92-94, 97), as well as reports of effectiveness of oral antihistamines in OIT (91). Eight (14 %) of our children reported dyspepsia which may represent eosinophil oesophagitis (EoE) (92, 98), a much debated AE reported in 2.7 % undergoing OIT (97, 98). Four of the eight children were treated with a proton pump inhibitor (PPI) with three becoming asymptomatic whereas the fourth reported a decrease in symptoms. Dyspepsia caused two children to withdraw from the study, while two children reported spontaneous symptom relief.

Anaphylactic events occurred in almost 20 % of the TAKE-AWAY children, which is significantly higher than previously reported for peanut OIT studies, including study populations heterogeneous in peanut allergy severity (88, 91, 94) with AEs reported from no systemic reactions (88), only one anaphylactic episode (91) or once the use of epinephrine (94). In the TAKE-AWAY trial, 19.4 % of the children experienced anaphylactic events in 11 dose-days (paper #2), most of them occurred at OIT doses above 300 mg of peanut protein. Similarly, in the AR101 study, 14 % of the 372 participants with reactivity thresholds < 100 mg peanut protein and maintenance doses of 300 mg peanut protein reported anaphylactic events treated with adrenaline in at least 76 anaphylactic events (99). Hence, children highly allergic to peanut seem to run a high risk of anaphylaxis even at low-dose OIT, with possibly

increasing the risk by increasing the OIT doses. Determining the optimal maintenance dose in OIT studies are thus urgently needed, both from a safety as well as an efficacy point of view. It might be that high maintenance doses are necessary to achieve SU, and thus will outweigh the risk of anaphylaxis. However, if long term SU is achievable remains to be assessed in the TAKE-AWAY trial and other follow-up studies. For now, desensitization by low-dose peanut OIT increasing the reactivity threshold from 100 to 300 mg has been calculated shown to reduce the risk of allergic reactions from accidental exposure on a population level by 95 % (83). If SU is achievable, remains to be assessed in the TAKE-AWAY trial and other follow-up studies. If higher OIT doses prove necessary to achieve SU, the risk of potential anaphylaxis will have to be weighed up against the potential benefits of the treatment.

The finding that the number of AEs decreased as the treatment proceeded is consistent with previous reports (91), suggested resulting from a beginning desensitization (91). Mild AEs occurred significantly more often during the first two days of each up-dosing period and in the first third of the dose-steps, as previously reported (91). In contrast to the mild AEs, anaphylactic events were equally distributed between the first and second years of OIT and between children completing and not completing the OIT. Moderate AEs as well as anaphylactic episodes were similar in these two groups, suggesting that the completers and those who discontinued OIT perceived AEs differently. This is supported by the lack of association between QoL and number of AEs in the TAKE-AWAY children (paper #3), as well as in previously published OIT studies (107, 112, 129). However, the lack of association observed in the TAKE-AWAY trrial, may also be explained by a potential bias caused by missing assessments of QoL and perceived treatment burden in children withdrawing from the treatment, especially if withdrawal was related to increased treatment burden.

Children who completed two years of OIT reported reduced treatment burden related to GI-symptoms and taste-/amount of the OIT-dose from the first to the second year of treatment.

We observed a negative correlation between perceived treatment burden at Y_1 and change in treatment burden from Y_1 to Y_2, as previously described for QoL at baseline and change in QoL (107) suggesting that patients with a high level of treatment burden during up-dosing experienced less AEs as they achieved maintenance dose. For children reporting increased burden, it might be that their motivation to maintain treatment and accept the related challenges decreased. Even though similar negative correlation has been reported between QoL at baseline and change in QoL after OIT (107), we could not find that perception of treatment burden influenced change in QoL (paper #3).

6.4   The effect of 2-years peanut oral immunotherapy (paper #3)

After two years of OIT, 18 children had discontinued treatment. Desensitization to 7500 mg peanut protein was confirmed in 94.6 % of the children continuing treatment. Desensitization was not associated with maintenance dose, in line with a peanut OIT report comparing the effect of maintenance doses of 300 vs. 3000 mg peanut (96).

The finding that child QoL significantly improved among OIT treated children from inclusion and until two years of OIT but not among the controls, is consistent with previously published studies mostly based on parental proxy-reports only (91, 104, 107, 126). Although child QoL improved from baseline to Y_2 as reported by both the children themselves as well as by their parents, the parents reported a two-fold larger improvement than the children. This is likely to explain why an OIT-related improvement in child QoL was observed for the parental reports and not for the children's self-reports. The larger improvement in child QoL as reported by the parents may be explained by an influence of the improvement in parents' own QoL, which improved similarly in the OIT group and the controls. The improvement in parental QoL for both the OIT group and the controls may result from general study participation including the pre-OIT DBPCFC (104, 107, 108, 130). Additionally, less social restrictions are reported to

have a greater impact on parents' QoL than on children's QoL (112), and may explain the larger improvement in child QoL as reported by the parents. For the child self-reports, the lack of significant difference in improved QoL between the OIT children and the controls may be explained by the larger variation observed in the QoL scores, as well as the limited sample size. The larger variation may indicate a more complex explanation for factors influencing change in QoL as perceived by the children themselves, like the treatment burden including distaste for peanuts and AEs (131). The limited sample size was comparable with previous studies of QoL in peanut OIT (104-107) and sufficient to identify the larger improvement in child QoL reported by parents as well as a significant difference in change in QoL for the parental proxy-reports.

The finding that QoL improved after OIT in children with anaphylaxis to peanut is in line with previously published studies of varying severities of peanut allergy (91, 104, 106, 108). In a study of 156 peanut with similar allergy severity to the TAKE-AWAY cohort, the QoL was not influenced by severity of allergic reactions allergic children (112).

Neither perception of treatment burden, level of desensitization, maintenance dose nor AEs influenced change in QoL, in line with previous studies reporting no association between change in QoL and AEs (107, 112, 129). This suggests that perceived treatment burden is disassociated from the number and severity of AEs during OIT (107, 112). The observation of maintenance dose and distaste for peanuts being confounding factors in influencing change in QoL, is probably explained by distaste for peanuts being the main reason for not reaching MMD, as it was reported as a daily challenge to 77.2 % of the children (paper #2). The negative correlation observed between perceived treatment burden at Y_1 and change in treatment burden from Y_1 to Y_2 is in line with the previously reported negative correlation between change in QoL and QoL at baseline (107) and might be explained by regression towards the mean.

Desensitization to 7500 mg peanut protein was achieved in almost all challenged children. As the level of desensitization was constant, it was less likely to influence change in QoL. Our finding that maintenance dose did not influence change in QoL has also recently been described (107).

The exploratory finding that QoL deteriorated in parents of children determined ineligible for OIT after OFC, is in contrast to the improved QoL reported by parents of children undergoing OFC (130). This may be explained by the determination of a very low reactivity threshold, which may increase social restrictions and deemed the children ineligible to OIT.

6.5 Strengths and limitations

6.5.1 Strengths

To the best of our knowledge, the TAKE-AWAY trial is the first OIT study consisting of a study population in which all participants have a challenge proven anaphylaxis to peanut. The vast majority also had a previous history of anaphylaxis to peanut. Peanut OIT is currently an experimental treatment which may be implemented in clinical practice (127). The TAKE-AWAY trial provides important knowledge of OIT in children with severe peanut allergy, as there still are concerns about who will benefit the most from such treatment and what maintenance dose to apply (127). It is also unclear whether the promising results from previous published peanut OITs performed in study populations heterogeneous in peanut allergy severity, are transferable to children highly allergic to peanut (127), the subgroup of children thought to benefit the most from such treatment (35, 89, 100).

The strict definitions of a positive DBPCFC in all children prior to enrolment requiring the occurrence of at least two moderate objective symptoms, confirmed the peanut allergy severity and reactivity threshold in this homogenous study population.

In line with the PRACTALL guidelines (34), some studies define a food challenge positive by milder symptoms, sometimes already by the occurrence of reproducible subjective symptoms (91). This approach may be misleading, as subjective symptoms have been demonstrated to occur at doses 20-fold lower than the LOAEL (37) one cannot rule out that an anaphylaxis would have occurred if another dose was given. However, the TAKE-AWAY children seem to have higher s-IgEs to peanut and lower LOAELs than in previously published OIT trials (87-94, 99), supporting that these children are highly allergic to peanut. Nevertheless, there is a need for a consensus of when to define a food challenge positive. While waiting for such a consensus, calculating the objective LOAEL enables comparison between studies (36). Although not feasible for the present thesis, the TAKE-AWAY trial has been designed to assess SU one year after cessation of four years' treatment in a group of children who are highly allergic to peanuts. Hence, the TAKE-AWAY trial may fill an important knowledge gap in terms of long term effects of OIT in children highly allergic to peanut. Immunological and clinical investigations including the novel CAPT to peanut (27) were performed at study entry as well as after one and two years of study participation. At the same time-points, PROs including standardized QoL questionnaires were also obtained and the novel VAS reports of perceived treatment burden were obtained after one and two years of treatment. Close monitoring through repeated tests at several time-points increase the ability of correct assessment of treatment efficacy. An OFC was performed after two years of treatment to determine the achieved desensitization. Hence, the combination of biological outcomes and PROs enabled complete determination of the effect of two years' peanut OIT. The QoL assessments included two perspectives of child QoL; the child's self-report and the parental proxy-report. These two aspects enable comparison of the assessment of QoL between children and parents in OIT. Including children ineligible for OIT in the QoL

assessment provided important insight into the effect of an unforeseen outcome of a food challenge, such as ineligibility for OIT.

The use of VAS for reporting perceived treatment burden is novel and may improve our understanding of patient perception of the burden of OIT. Although the newly developed VAS was not pre-validated for the TAKE-AWAY trial, VAS forms have previously been validated for measuring subjective psychosocial phenomena like pain and nausea and correlated strongly with numeric rating score and verbal rating scale (132).

6.5.2 Limitations

The TAKE-AWAY cohort including highly sensitized children in which 94.8 % had a s-IgE to Ara h 2 > 1.75 kUA/L, demonstrated to have a 100 % positive predictive value of a systemic allergic reaction (52), and a low-dose challenge would be preferred according to the consensus protocol for OFCs (60). A low-dose challenge would have enabled a more accurately determination of LOAEL for the entire study population.

Our homogeneous population of highly peanut allergic children may have limited the possibility to identify correlations between immunological and clinical characteristics on one hand, and reactivity thresholds and severity reactions on the other hand.

For the BAT, there is no consensus of diagnostic cut-off values for a positive BAT (32), and non-responding basophils (116) represent an additional limitation.

As distaste for peanuts was the main reason for not reaching the MMD, a placebo arm could theoretically have strengthened the study. However, this was not approved by the regional medical ethical committee due to the unfavourable ratio of treatment burden to expected patient benefit by placebo intervention. Furthermore, a blinded vehicle to our study's high-dose peanut OIT appeared not feasible. Switching ingestion of defatted flour to whole roasted peanuts may have influenced efficacy of the OIT, as whole peanuts may include additional

properties and do involve larger amounts to be ingested than flour. Anyway, whole peanuts were more easily tolerated.

The allocation for observation only may represent a bias as these participants do not have an expectation for a better QoL caused by a placebo treatment, resulting in a larger difference between OIT children and the controls.

Despite a long-term step-up protocol with a fixed starting dose, and around-the-clock access to study paediatricians to increase the likelihood of a high retention rate of the OIT, every fourth child dropped out of study intervention. A small study population decreases the possibility of finding significant differences due to a type 2 statistical error. Mixed models were used to correct for the relatively high proportion of missing data following children dropping out of OIT. Nevertheless, the small study population was sufficiently large for several significant findings. These results are important, as peanut OIT still is considered to be an experimental treatment.

7   MAIN CONCLUSIONS

In a cohort of children with anaphylaxis to peanut, we found:

The reactivity threshold together with the objective LOAEL were associated with basophil activation, SPT and the ratio of peanut s-IgE/total IgE. Basophil activation best predicted very low reactivity threshold and thereby eligibility for OIT. None of the baseline clinical or immunological markers were sufficient to substitute OFC in determining a reactivity threshold necessary to define eligibility for entering OIT.

One fourth of the children commencing peanut OIT discontinued treatment during up-dosing. We found no significant baseline predictor for completing the up-dosing phase.

In children who were confirmed to be highly allergic to peanut, 75.5 % were able to reach a level of a maintenance dose ranging from 250 mg – 5000 mg, while 21 % only reached the pre-defined MMD of 5000 mg of peanut protein. The main reason for not reaching the MMD was distaste for peanuts, followed by AEs. The ratio of peanut s-IgG$_4$/s-IgE only, was significantly associated with reaching MMD.

Mild AEs occurred in 13.9 % of the dose-days most commonly reported as GI-related in line with previously published studies. In contrast, the proportion of OIT-related anaphylaxis was mostly higher in this study population, probably related to all children being highly allergic to peanut. This finding questions the feasibility and safety of high-dose OIT in these children.

Almost all children who completed two years of OIT were desensitized to 7500 mg of peanut protein. The significant improvement in child QoL with two years of OIT reported by parental proxy reports and not by the children, suggests that parents may over-estimate the effect of the treatment. Conclusively, it may be more appropriate to use child self-reported rather than the parental proxy-reported QoL when assessing patient-related outcome of OIT.

8 FUTURE PERSPECTIVES

Oral immunotherapy is promising for inducing desensitization in the majority of patients. Although still regarded an experimental treatment, it is offered in clinical practice by some allergy clinics. There are, however, several unanswered questions related to this treatment. Assessment of OIT eligibility includes determination of the reactivity threshold of the offended food by an OFC. There is, however, no consensus of when to score a food challenge positive. Although the PRACTALL guidelines (34) recommend using objective symptom(s), many OIT-studies accept recurrent subjective symptoms to define a positive food challenge. Determining the objective LOAEL may be preferable to determine reactivity threshold, enabling comparison between studies. Additionally, assessing severity of allergic reactions is a matter of current international debate (133). The need for a consensus of which scoring system to use, was recently demonstrated as severe allergy is reached more quickly in some scoring systems (134), making comparison of allergy severity between studies difficult.

The present thesis presents results from the first two years of high-dose OIT in the TAKE-AWAY trial. The study includes a homogeneous population of children with challenge proven anaphylaxis to peanut and low LOAELs as compared with previous peanut OIT trials heterogeneous in allergy severity (87-94), i.e. the patients expected to benefit the most from a successful OIT (35, 89, 100). The study raises questions and concerns about safety of peanut OIT in this group of patients, as systemic reactions occurred much more frequently than in previous published studies including children with less severe allergy (89, 95). It may be argued that this is explained by the high maintenance dose. In the large recently published AR101 study (99), low-dose OIT was commenced in a study population including mostly patients with previous anaphylaxis to peanut, and the prevalence of OIT-related anaphylaxis with use of adrenaline was similar to the TAKE-AWAY trial. Therefore, new studies optimizing the treatment with respect to starting dose, up-dosing speed, maintenance dose and

possible use of protective drugs like omalizumab are needed to improve safety of OIT in these patients. A very low starting dose with a conventional slow, gradual up-dosing may be beneficial. The maintenance dose may also be crucial, as well as the duration of the treatment. In the study of Vickery et al. (96), maintenance doses of 300 mg and 3000 mg of peanut protein were compared, with no difference in desensitization or SU four weeks after cessation of the OIT. Hence, it might be that SU depends more on the duration of the treatment. On the other hand, the Vickery study included only preschool children 9 - 36 months of age. Young children are likely to have a more "plastic" immune system, easier to modulate than in older children and adults. This is partly supported by the AR101 study reporting effect of OIT in older children and adolescents but not in adults (99).

Finally, there is a need to conclude if OIT has the potential to induce long lasting SU or only desensitization. The few studies addressing these questions report conflicting results (87, 90, 96), and the observation time is in general short, often four weeks only. Studies with longer observational time are needed to assess the potential of OIT to "cure allergy". Assessment of potential effect should also include the child's perspective on QoL as well as the costs for the health care system. The experience from the TAKE-AWAY trial gives the impression that these patients, understandably, need frequent contact with health personnel, suggesting that a patient coordinator is essential.

To conclude, assessing long time SU is especially important for patients highly allergic to peanut, as it is likely that one have to make a decision where the potential effect must be balanced up against safety for the patient and costs for the health care system. For some patients highly allergic to peanut, perhaps an OFC including theoretical information, practical training and subsequent follow-up, may provide similar efficacy measured in PROs as an OIT?

9 REFERENCES

1.   Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001;56(9):813-24.
2.   Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S73-80.
3.   Stokes J. C, T.B. The relationship between IgE and allergic disease. UpToDate. 2018.
4.   Santos AF, James LK, Bahnson HT, Shamji MH, Couto-Francisco NC, Islam S, et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. J Allergy Clin Immunol. 2015;135(5):1249-56.
5.   Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol. 2004;113(6):1025-34; quiz 35.
6.   Savilahti EM, Rantanen V, Lin JS, Karinen S, Saarinen KM, Goldis M, et al. Early recovery from cow's milk allergy is associated with decreasing IgE and increasing IgG4 binding to cow's milk epitopes. J Allergy Clin Immunol. 2010;125(6):1315-21 e9.
7.   Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373-80.
8.   Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy. 2007;62(8):857-71.
9.   Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-25.
10.   Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601-8.
11.   Vetander M, Helander D, Lindquist C, Hedlin G, Alfvén T, Ostblom E, et al. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. Pediatr Allergy Immunol. 2011;22(4):369-73.
12.   Cianferoni A, Muraro A. Food-induced anaphylaxis. Immunol Allergy Clin North Am. 2012;32(1):165-95.
13.   Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58.
14.   Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010;303(18):1848-56.
15.   Venter C, Arshad SH. Epidemiology of food allergy. Pediatric clinics of North America. 2011;58(2):327-49, ix.
16.   Schnabel E, Sausenthaler S, Schaaf B, Schafer T, Lehmann I, Behrendt H, et al. Prospective association between food sensitization and food allergy: results of the LISA birth cohort study. Clin Exp Allergy. 2010;40(3):450-7.
17.   Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol. 2015;15(5):409-16.
18.   Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291-307; quiz 8.
19.   Branum AM, Lukacs SL. Food allergy among U.S. children: trends in prevalence and hospitalizations. NCHS Data Brief. 2008(10):1-8.
20.   Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668-76 e1-2.

21.   Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001;107:191-3.

22.   Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH, et al. Anaphylaxis and reactions to foods in children--a population-based case study of emergency department visits. Clin Exp Allergy. 2012;42(4):568-77.

23.   Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. Allergy. 2010;65(1):103-8.

24.   Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. J Allergy Clin Immunol. 2015;135(5):1257-66 e1-2.

25.   Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. J Allergy Clin Immunol. 2008;121(3):731-6.

26.   Santos AF, Brough HA. Making the Most of In Vitro Tests to Diagnose Food Allergy. The journal of allergy and clinical immunology In practice. 2017;5(2):237-48.

27.   Lindvik H, Lodrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. Clin Exp Allergy. 2017.

28.   M. B. Mäta IgE-antikroppar mot allergenextrakt eller allergena komponenter – vad är den kliniska nyttan? . Allergi i Praksis. 2018; 1: 30–2.

29.   Aas K. Clinical and experimental aspects of standardization and purification of allergen. Int Arch Allergy Appl Immunol. 1975;49(1-2):44-54.

30.   Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. The journal of allergy and clinical immunology In practice. 2014;2(3):300-5.

31.   Mehl A, Verstege A, Staden U, Kulig M, Nocon M, Beyer K, et al. Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children. Allergy. 2005;60(8):1034-9.

32.   Santos AF, Lack G. Basophil activation test: food challenge in a test tube or specialist research tool? Clin Transl Allergy. 2016;6:10.

33.   Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy. 1997;27(8):860-7.

34.   Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.

35.   Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy. 2011;41(9):1273-81.

36.   Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al. Predicting reactivity threshold in children with anaphylaxis to peanut. Clin Exp Allergy. 2017.

37.   Chen L, Lucas JS, Hourihane JO, Lindemann J, Taylor SL, Goodman RE. Evaluation of IgE binding to proteins of hardy (Actinidia arguta), gold (Actinidia chinensis) and green (Actinidia deliciosa) kiwifruits and processed hardy kiwifruit concentrate, using sera of individuals with food allergies to green kiwifruit. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2006;44(7):1100-7.

38.   Blumchen K, Beder A, Beschorner J, Ahrens F, Gruebl A, Hamelmann E, 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(2):390-8.

39.   Niggemann B. When is an oral food challenge positive? Allergy. 2010;65(1):2-6.

40.   Niggemann B, Lange L, Finger A, Ziegert M, Muller V, Beyer K. Accurate oral food challenge requires a cumulative dose on a subsequent day. J Allergy Clin Immunol. 2012;130(1):261-3.

41.   Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 2004;59(7):690-7.
42.   Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Allergy. 2000;30(11):1540-6.
43.   Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. J Allergy Clin Immunol. 2005;115(6):1291-6.
44.   Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997;100(4):444-51.
45.   Chokshi NY, Sicherer SH. Interpreting IgE sensitization tests in food allergy. Expert Rev Clin Immunol. 2016;12(4):389-403.
46.   Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004;114(1):144-9.
47.   Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. J Allergy Clin Immunol. 2007;119(5):1272-4.
48.   Grabenhenrich L, Lange L, Hartl M, Kalb B, Ziegert M, Finger A, et al. The component-specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses. J Allergy Clin Immunol. 2016;137(6):1751-60 e8.
49.   Klemans RJ, Otte D, Knol M, Knol EF, Meijer Y, Gmelig-Meyling FH, et al. The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. J Allergy Clin Immunol. 2013;131(1):157-63.
50.   Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol. 2010;125(1):191-7 e1-13.
51.   Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, Seneviratne S, Hanschmann KM, Vogel L, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. Allergy. 2015;70(4):391-407.
52.   Klemans RJ, Broekman HC, Knol EF, Bruijnzeel-Koomen CA, Otten HG, Pasmans SG, et al. Ara h 2 is the best predictor for peanut allergy in adults. The journal of allergy and clinical immunology In practice. 2013;1(6):632-8 e1.
53.   Song Y, Wang J, Leung N, Wang LX, Lisann L, Sicherer SH, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. Ann Allergy Asthma Immunol. 2015;114(4):319-26.
54.   Ocmant A, Mulier S, Hanssens L, Goldman M, Casimir G, Mascart F, et al. Basophil activation tests for the diagnosis of food allergy in children. Clin Exp Allergy. 2009;39(8):1234-45.
55.   Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol. 2015;135(1):179-86.
56.   Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. Pediatr Allergy Immunol. 2010;21(4 Pt 1):603-11.
57.   Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. Allergy. 2013;68(2):190-4.
58.   Ta V, Weldon B, Yu G, Humblet O, Neale-May S, Nadeau K. Use of Specific IgE and Skin Prick Test to Determine Clinical Reaction Severity. British journal of medicine and medical research. 2011;1(4):410-29.
59.   Tripodi S, Businco AD, Alessandri C, Panetta V, Restani P, Matricardi PM. Predicting the outcome of oral food challenges with hen's egg through skin test end-point titration. Clin Exp Allergy. 2009;39(8):1225-33.

60.   Taylor SL, Hefle SL, Bindslev-Jensen C, Atkins FM, Andre C, Bruijnzeel-Koomen C, et al. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clin Exp Allergy. 2004;34(5):689-95.
61.   Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. J Allergy Clin Immunol. 2014;133(1):156-64.
62.   Hourihane JB, Kilburn SA, Nordlee JA, Hefle SL, Taylor SL, Warner JO. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. J Allergy Clin Immunol. 1997;100(5):596-600.
63.   Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. PloS one. 2013;8(1):e53465.
64.   Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, et al. Accidental ingestions in children with peanut allergy. J Allergy Clin Immunol. 2006;118(2):466-72.
65.   Dubus JC, Le MS, Vitte J, Minodier P, Boutin A, Carsin A, et al. Use of epinephrine in emergency department depends on anaphylaxis severity in children. Eur J Pediatr. 2018.
66.   Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J. 2015;8(1):17.
67.   L. N. Prophylactic inoculations against hay fever. Lancet. 1911;1:1572-1573.
68.   Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799-815.
69.   Dreborg S. Immunterapins historia. Allergi i Praxis. 2017; 1: 52-62.
70.   Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. The Cochrane database of systematic reviews. 2007(1):CD001936.
71.   Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999;341(7):468-75.
72.   Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of hymenoptera venom hypersensitivity: a meta-analysis. Clin Ther. 2000;22(3):351-8.
73.   Incorvaia C, Frati F, Puccinelli P, Riario-Sforza GG, Dal Bo S. Dose dependence of efficacy and safety of subcutaneous immunotherapy. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace. 2006;65(1):41-3.
74.   Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. Allergy. 2011;66(10):1345-59.
75.   Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. The Journal of allergy and clinical immunology. 1997;99(SCIT peanøtt god effekt, men altfor mange systemiske reaksjoner, selv i vedlikeholdsfase.):744-51.
76.   Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90(2):256-62.
77.   Anagnostou K. Recent advances in immunotherapy and vaccine development for peanut allergy. Ther Adv Vaccines. 2015;3:55-65.
78.   Parrish CP, Har D, Andrew Bird J. Current Status of Potential Therapies for IgE-Mediated Food Allergy. Current allergy and asthma reports. 2018;18(3):18.
79.   Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119-27 e1-7.
80.   Wang J, Sampson HA. Safety and efficacy of epicutaneous immunotherapy for food allergy. Pediatr Allergy Immunol. 2018;29(4):341-9.
81.   Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol. 2017;139(4):1242-52 e9.

82.	Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity: A Randomized Clinical Trial. JAMA. 2017;318(18):1798-809.

83.	Baumert JL, Taylor SL, Koppelman SJ. Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy. The journal of allergy and clinical immunology In practice. 2018;6(2):457-65 e4.

84.	Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343-7.

85.	Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233-43.

86.	Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspect Clin Res. 2011;2(4):137-44.

87.	Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014;133(2):468-75.

88.	Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126(1):83-91 e1.

89.	Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654-60.

90.	Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133(2):500-10.

91.	Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-304.

92.	Virkud YV, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol. 2017;139(3):882-8 e5.

93.	Kukkonen AK, Uotila R, Malmberg LP, Pelkonen AS, Makela MJ. Double-blind placebo-controlled challenge showed that peanut oral immunotherapy was effective for severe allergy without negative effects on airway inflammation. Acta Paediatr. 2017;106(2):274-81.

94.	Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, et al. Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial. The journal of allergy and clinical immunology In practice. 2017.

95.	Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(2):292-300, .e1-97.

96.	Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173-81 e8.

97.	Anagnostou K. Recent advances in immunotherapy and vaccine development for peanut allergy. Ther Adv Vaccines. 2015;3(3):55-65.

98.	Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113(6):624-9.

99.	Investigators PGoC. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018;379(21):1991-2001.

100.   Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009;64(8):1218-20.
101.   Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2018;3(2):85-94.
102.   Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CA, Knulst AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. J Allergy Clin Immunol. 2002;110(6):915-20.
103.   Turner PJ, Campbell DE. Epidemiology of severe anaphylaxis: can we use population-based data to understand anaphylaxis? Curr Opin Allergy Clin Immunol. 2016;16(5):441-50.
104.   Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK, team Ps. The longitudinal impact of Probiotic and Peanut Oral Immunotherapy (PPOIT) on health related quality of life (HRQL). Allergy. 2017.
105.   Kamilaris JS SP, Kulis MD, Edie AH, Vicekry PB, Burks AW. Participation in peanut oral immunotherapy improves quality of life. J Allergy Clin Immunol. 2012;129(Abs):AB29-110.
106.   Otani IM, Begin P, Kearney C, Dominguez TL, Mehrotra A, Bacal LR, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. Allergy Asthma Clin Immunol. 2014;10(1):25.
107.   Rigbi NE, Goldberg MR, Levy MB, Nachshon L, Golobov K, Elizur A. Changes in patient quality of life during oral immunotherapy for food allergy. Allergy. 2017.
108.   Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol. 2012;109(5):348-52 e2.
109.   Bindslev-Jensen C, Briggs D, Osterballe M. Can we determine a threshold level for allergenic foods by statistical analysis of published data in the literature? Allergy. 2002;57(8):741-6.
110.   Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambulatory pediatrics : the official journal of the Ambulatory Pediatric Association. 2003;3(6):329-41.
111.   Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy. 2000;30(8):1135-43.
112.   Stensgaard A, Bindslev-Jensen C, Nielsen D, Munch M, DunnGalvin A. Quality of life in childhood, adolescence and adult food allergy: Patient and parent perspectives. Clin Exp Allergy. 2017;47(4):530-9.
113.   Alois Z. Lung function in children and adolescents; methods, reference values. 1987.
114.   Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. Thorax. 2006;61(9):744-6.
115.   Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. Allergy. 1993;48(14 Suppl):48-82.
116.   Santos AF, Douiri A, Becares N, Wu SY, Stephens A, Radulovic S, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol. 2014;134(3):645-52.
117.   Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. Allergy. 2012;67(2):242-7.
118.   Vlieg-Boerstra BJ, Herpertz I, Pasker L, van der Heide S, Kukler J, Jansink C, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. Allergy. 2011;66(7):948-54.
119.   Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl):S365-83.
120.   Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol. 1988;82(6):986-97.

121.   Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care. 2001;39(8):800-12.

122.   Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol. 2004;114(5):1159-63.

123.   Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.

124.   Reinfjell T, Diseth TH, Veenstra M, Vikan A. Measuring health-related quality of life in young adolescents: reliability and validity in the Norwegian version of the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2006;4:61.

125.   Hosmer DWaL, S. . Applied logistic regression , 2.ed., John Wiley & sons New York, USA. 2000

126.   Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G, et al. Efficacy, safety, and quality of life in a multi-center, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in peanut allergic children. The journal of allergy and clinical immunology In practice. 2018.

127.   Bluemchen K, Eiwegger T. Oral peanut immunotherapy - How much is too much? How much is enough? Allergy. 2018.

128.   Tomicic S, Norrman G, Falth-Magnusson K, Jenmalm MC, Devenney I, Bottcher MF. High levels of IgG4 antibodies to foods during infancy are associated with tolerance to corresponding foods later in life. Pediatr Allergy Immunol. 2009;20(1):35-41.

129.   Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006;96(3):415-21.

130.   DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy. 2010;40(3):476-85.

131.   Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et al. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy. Allergy. 2018.

132.   Lara-Munoz C, De Leon SP, Feinstein AR, Puente A, Wells CK. Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli. Arch Med Res. 2004;35(1):43-8.

133.   Muraro A, Fernandez-Rivas M, Beyer K, Cardona V, Clark A, Eller E, et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. Allergy. 2018;73(9):1792-800.

134.   Pettersson ME, Koppelman GH, Flokstra-de Blok BMJ, Kollen BJ, Dubois AEJ. Prediction of the severity of allergic reactions to foods. Allergy. 2018;73(7):1532-40.

PAPERS

Paper #1

WILEY

Predicting reactivity threshold in children with anaphylaxis to peanut

T. Reier-Nilsen[1,2] | M. M. Michelsen[1,2] | K. C. Lødrup Carlsen[1,2] | K.-H. Carlsen[1,2] | P. Mowinckel[1,2] | U. C. Nygaard[3] | E. Namork[3] | M. P. Borres[4,5] | G. Håland[1,2]

[1]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

[4]Thermo-Fisher Scientific, Uppsala, Sweden

[5]Institute of Maternal & Child Health, Uppsala University, Uppsala, Sweden

Correspondence
Tonje Reier-Nilsen, Division of Paediatrics and Adolescent Medicine Ullevål, Oslo University Hospital, Oslo, Norway.
Emails: tonjre@ous-hf.no; tonje.nilsen@medisin.uio.no

Funding information
Extra Foundation; Kloster Foundation; South-Eastern Norway Regional Health Authority; Norwegian Asthma and Allergy Association

Summary

Background: Peanut allergy necessitates dietary restrictions, preferably individualized by determining reactivity threshold through an oral food challenge (OFC). However, risk of systemic reactions often precludes OFC in children with severe peanut allergy.

Objective: We aimed to determine whether clinical and/or immunological characteristics were associated with reactivity threshold in children with anaphylaxis to peanut and secondarily, to investigate whether these characteristics were associated with severity of the allergic reaction during OFC.

Methods: A double-blinded placebo-controlled food challenge (DBPCFC) with peanut was performed in 96 5- to 15-year-old children with a history of severe allergic reactions to peanut and/or sensitization to peanut (skin prick test [SPT] $\geq$3 mm or specific immunoglobulin E [s-IgE] $\geq$0.35 kUA/L). Investigations preceding the DBPCFC included a structured interview, SPT, lung function measurements, serological immunology assessment (IgE, IgG and IgG_4), basophil activation test (BAT) and conjunctival allergen provocation test (CAPT). International standards were used to define anaphylaxis and grade the allergic reaction during OFC.

Results: During DBPCFC, all 96 children (median age 9.3, range 5.1-15.2) reacted with anaphylaxis (moderate objective symptoms from at least two organ systems). Basophil activation ($CD63^+$ basophils $\geq$15%), peanut SPT and the ratio of peanut s-IgE/total IgE were significantly associated with reactivity threshold and lowest observed adverse events level (LOAEL) (all $P < .04$). Basophil activation best predicted very low threshold level (<3 mg of peanut protein), with an optimal cut-off of 75.8% giving a 93.5% negative predictive value. None of the characteristics were significantly associated with the severity of allergic reaction.

Conclusion and Clinical Relevance: In children with anaphylaxis to peanut, basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE were associated with reactivity threshold and LOAEL, but not with allergy reaction severity.

KEYWORDS
anaphylaxis, basophil, double-blinded placebo-controlled food challenge, food allergy, immunoglobulin E, immunologic tests, peanut allergy, threshold levels

1 | INTRODUCTION

Peanut allergy, the most common cause of severe and fatal allergic reactions in children in the western world,[1] has increased in prevalence over the last two decades[2,3] currently affecting 1%-2% of the paediatric population.[4] Once established, peanut allergy is likely to last a lifetime.[5,6] The only established therapy is peanut avoidance and rescue medication, including intramuscular epinephrine auto injectors in case of severe systemic reactions. Nevertheless, accidental exposures frequently occur due to poorly labelled foods, manufacturing errors and peanut contamination.[7] Consequently, quality of life is reduced in peanut-allergic children and their families.[8-10]

Diagnosing peanut allergy requires a convincing history of allergic reaction related to peanut exposure, supported by clinical and immunological investigations and/or an oral food challenge (OFC) to peanut. Clinical investigations include skin prick tests (SPT) and possibly the recently reported clinical conjunctival allergen provocation test (CAPT),[11] whereas immunological investigations include specific Immunoglobulin E (s-IgE) to peanut and its allergen components as well as the basophil activation test (BAT).[12-14]

Clinical reactions to peanut have been associated with weal size of SPT and s-IgE levels to peanut,[15,16] while s-IgE to the peanut component allergen Ara h 2 has been shown to be the best predictor of allergic reactions[17-19] with levels exceeding 1.00 kUA/L conferring a 97% probability of a systemic reaction.[20] Allergy reaction severity has been associated with basophil activation,[21] and with peanut SPT and s-IgE in some[13,22,23] but not all[24,25] studies, whereas the ratio of s-IgG$_4$/s-IgE to peanut[26] and peanut s-IgE/total IgE[27] has been associated with diagnostic outcome of OFC. Finally, reactivity threshold has been associated with peanut SPT and s-IgE to peanut, Ara h 2 and basophil activation.[23,24]

Reactivity threshold is necessary to personalize precautions related to peanut exposure, preferably determined by a double-blinded placebo-controlled food challenge (DBPCFC) and reported as the cumulated amount of peanut intake at the time of a positive OFC[28] or as the lowest amount of peanut protein that elicited mild, objective symptoms, that is the lowest observed adverse effect level (LOAEL).[28] However, children with the greatest likelihood of severe and life-threatening reactions are often excluded from DBPCFC and oral immunotherapy (OIT) due to the risk of systemic reactions.[29]

Screening children with peanut allergy for enrolment in the open randomised controlled (RCT) peanut OIT trial; "Take-Away food allergy; inducing tolerance in children allergic to peanut" (the Take-Away trial), included clinical and immunological investigations as well a DBPCFC to determine reactivity threshold and severity grade of allergic reaction.

The primary aim of this study was to determine whether clinical and/or immunological characteristics were associated with reactivity threshold in children with anaphylaxis to peanut, and secondarily to investigate whether these characteristics were associated with severity of the allergic reaction.

2 | METHODS

2.1 | Study design

This study setting was a 3-day investigation programme for children screened for eligibility for enrolment into the ongoing Take-Away trial, performed from February 2014 to June 2015 at the Department of Paediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Norway.

Children were recruited for screening investigations from the Oslo Peanut Allergy Study[11] as well as by referral from in-house and other paediatric allergy clinics in Oslo and the surrounding area.

Eligibility for enrolment in the Take-Away trial was determined by screening, consisting of a telephone interview to assess screening inclusion and exclusion criteria followed by a 3-day investigation programme. On day one, a structured interview, blood samples for cellular and immunology analyses, lung function measurements, SPT and titrated SPT (SPT$_t$), CAPT and BAT were performed, followed by a DBPCFC. Enrolment required a positive DBPCFC, whereas a positive food challenge at a level of ≤3 mg peanut protein precluded participation in the OIT.

Inclusion criteria for screening were age of 5-15 years, a history of systemic reactions to peanut or sensitization to peanut by a peanut SPT ≥3 mm or a s-IgE to peanut ≥0.35 kUA/L, living within acceptable distance from the Oslo University Hospital and willingness to participate in the peanut OIT study. Exclusion criteria were non-controlled asthma, allergy or intolerance to any other ingredients in the peanut DBPCFC vehicle (ginger bread), current or previous allergen-specific immunotherapy, cardiac disease, severe atopic skin disease, diabetes mellitus or other severe diseases that might interfere with adherence to the study protocol.

Written informed consent was obtained from both parents after detailed oral and written information. The Take-Away trial was approved by the Regional Committee for Medical and Health Research Ethics and monitored by a safety board with regular communications in case of severe or unexpected adverse events, and registered in the ClinicalTrials.gov (number NCT02457416).

2.2 | Study population

This study included 96 children with a positive DBPCFC. Of the 213 children referred for screening, 113 did not wish to enter the study, did not fulfil the inclusion and exclusion criteria or withdrew during screening and 4 had a negative DBPCFC (Figure 1).

2.3 | Methods

A structured parental interview including history of allergic reactions, allergic comorbidities and medical history of the child, use of medication and sociodemographic data was performed on day one.

Lung function was measured by maximal expiratory flow volume loops in accordance with international standards,[30] and reported by
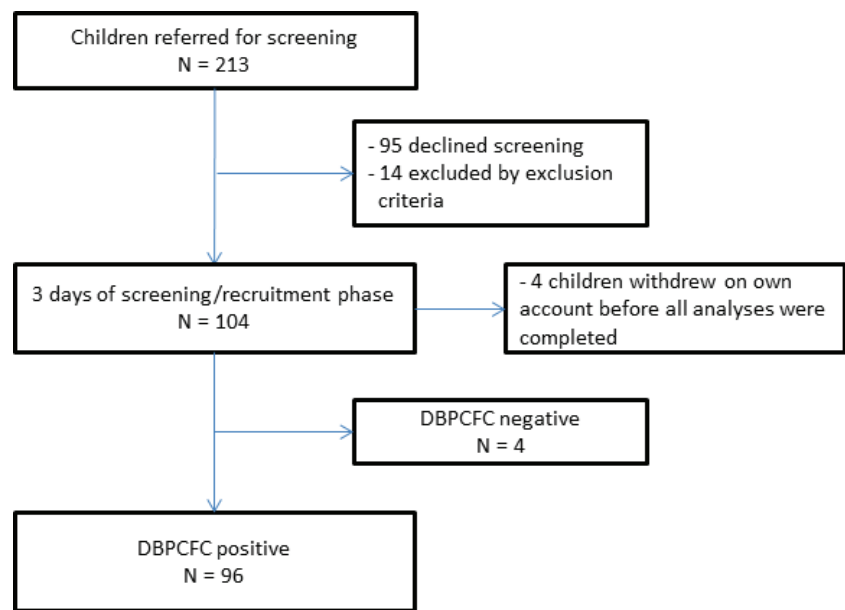
FIGURE 1 Flow chart of the recruitment phase in the Take-Away trial

percentage predicted forced expiratory volume in one-second (FEV$_1$%) using the reference values of Zapletal.[31]

Skin prick tests were performed using peanut and 11 other common food and inhalant allergens (see online supplement) according to international guidelines.[32]

Titrated SPT (SPT$_t$) to peanut was performed with dilutions of 1:20, 1:200, 1:2000 and 1:20 000 of the peanut allergen extract. Weal size was recorded after 15 minutes, and regarded positive if ≥3 mm greater than negative control.

Total IgE and s-IgE to peanut and peanut component allergens (Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9) as well as other common allergens (see online supplement) were analysed in whole blood sampled in EDTA tubes and sent the same day to Furst Medical Laboratory using the Phadia CAP-System FEIA (ThermoFisher, Uppsala, Sweden). Specific IgE ≥0.35 kUA/L was considered positive.

Specific IgG (s-IgG) and IgG$_4$ (s-IgG$_4$) to peanut and to Ara h 2 were analysed in sampled frozen sera stored at −86°C using the Phadia CAP-System FEIA (ThermoFisher). According to the manufacturer's instructions, a positive test was defined as IgG >2.0 mg$_A$/L and IgG4 of >0.07 mg$_A$/L.

Conjunctival allergen provocation test (CAPT) was performed double-blinded and placebo-controlled with commercially available extract of peanut (Greer laboratories, Lenoir, NE, USA) as described by Lindvik et al.[11] The NaCl 0.9% was used as placebo and as dilution fluid to make test solutions of 1:160, 1:80, 1:40, 1:20, 1:10 and 1:1[11] (further details in online supplement).

The BAT was performed in fresh EDTA blood stored at room temperature (usually 1-3 hours, maximum 24 hours). Whole blood aliquots were incubated with 20 μL staining solution as negative control, positive control, or with 2.5, 5 and 10 ng/mL peanut extract (further details in online supplement). For this study, basophil activation was only expressed as the % CD63-positive basophils (% CD63$^+$) after stimulation of 5 ng/mL of the peanut extract, as all children had a strong basophil activation already to the lowest allergen concentration of 2.5 ng/mL peanut extract, thus CD-sens (basophil allergen sensitivity—the allergen concentration eliciting half of the maximum basophil activation) could not be determined. Non-responders were defined as children responding with 0%-5% basophil activation.[33] In addition to analysing basophil activation as a continuous variable, the cut-off value for positive basophil activation in this study was set to >15% CD63$^+$ basophils, whereas children with basophil activation of 5%-15% were classified as low responders, as suggested by Glaumann et al[34] and the kit provider (Buhlmann Laboratories AG). In 10 children, BAT was not performed due to missed sampling (n = 5) or technical causes (n = 5) (technical failure of equipment [n = 1], incorrect handling of the blood sample [n = 1] or no available allergen extract [n = 3]).

The DBPCFC was performed according to international standardized procedure[35,36] using peanut flour (Golden Peanut Company, Alpharetta, GA, USA) as active challenge ingredient in baked gingerbread according to a recipe by Vlieg-Boestra et al[37] (further details in online supplement). The first challenge dose was chosen to 3 mg peanut protein, and the maximal cumulated dose was 6443 mg, distributed by 7 incremental steps (3, 10, 30, 100, 300, 1000, 5000 mg of peanut protein) of 30 minutes interval. In case of persistent subjective or mild objective symptoms, the interval was increased up to 60 minutes, in line with the modified Bock's criteria by Sampson et al,[38,39] in which case the next step repeated the previous dose. The DBPCFC was regarded positive with the occurrence of moderate objective symptoms[35,40] even if only part of the current dose had been eaten. Cumulated peanut protein (mg) intake at the time of positive DBPCFC was recorded. The LOAEL was recorded post hoc as the lowest cumulated amount of peanut protein that elicited the first mild, objective adverse reaction during food challenge was observed, according to the modified Bock's criteria.

Anaphylaxis was defined as moderate symptoms from at least two organ systems in line with European Academy of Allergy and Clinical Immunology (EAACI) task force position papers[41,42] (Table S2), modified for children by Vetander et al.[43] Severity of anaphylaxis was also graded in line with the EAACI position papers[41,42] scoring from 1 to 3 (mild-moderate-severe) in addition to the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms) ranging from one to five (extremely severe reaction).[44]

2.4 | Outcomes and predictors

The primary outcome was reactivity threshold, defined as the cumulated peanut protein (mg) intake at positive DBPCFC. The LOAEL[28] was used as an additional threshold value and set to 3 mg for children with a positive DBPCFC at the first challenge dose.

Very low reactivity threshold was defined as a DBPCFC reactivity threshold of ≤3 mg of peanut protein.

The secondary outcome was severity of the allergic reaction during DBPCFC.

Potential predictors were baseline characteristics (age and gender, medical history including previous history of anaphylaxis, and parental atopic disease or food allergy) allergic comorbidities (current asthma, allergic rhinitis, previous or current atopic dermatitis and allergy to other foods or nuts), $FEV_1\%$, clinical test results (SPT and SPT_t to peanut, peanut CAPT) and immunological test results (s-IgE, s-IgG and s-IgG_4 to peanut and Ara h 2), the ratios of peanut (s-IgE/total IgE and s-IgG_4/s-IgE to peanut), as well as basophil activation.

2.5 | Statistical analyses

Due to non-normal distribution, continuous baseline characteristics are presented by geometric mean (95% CI) and median (range), and categorical data are presented as number of cases (n) with percentage (%). Furthermore, bivariate unadjusted analyses were performed with Spearman correlation analyses (r_s = Spearman correlation coefficient). As the underlying assumptions for the standard mean regression analysis were not fulfilled, multivariate robust regression analyses with Huber's M-estimator were used to further assess associations between immunological parameters as the independent variables and both reactivity threshold and LOAEL as the dependent variables. Multivariate robust linear regression was used to assess the association between immunological parameters and severity of the allergic reaction.

A Hosmer step down multivariate analysis[45] included all variables significant at the 0.35 level in the bivariate analyses, and the final model was tested for confounding with all excluded variables.

Statistical analyses were performed using Statistical Analysis System (SAS, Version 9.3; SAS Institute Inc., Chapel Hill, NC, USA) and the IBM Statistical Package for Social Sciences (IBM SPSS Statistics, Version 21.0.1; IBM Corp., Armonk, NY, USA).

The level of significance was set to .05.

3 | RESULTS

All included 96 children (median [range] age of 9.3 [5.1, 15.2] years) were sensitized to peanut with s-IgE to Ara h 2 above 1.0 kUA/L in all but 4 patients (Table 1) who had levels of 0.96, 0.82 (two children) and 0.38 kUA/L, respectively. A prior history of anaphylaxis was reported by 83.0% with unknown time interval because the last anaphylactic event, whereas all children had anaphylaxis during the DBPCFC (Table 1). None of the children had an EAACI score of 3 or a Sampson score of 5 (Table 1).

The geometric mean (95% CI) for reactivity threshold and LOAEL was 33 (22.9, 48.4) and 13.8 (9.9, 19.5) mg of peanut protein, respectively (Table 1). Reactivity threshold level was <3 mg in five children, 3 mg in 14 children and >3 mg in 77 children. As anaphylaxis occurred at the first challenge dose in 19 children, their LOAEL was set equal to reactivity threshold. In 14 children with reactivity threshold >3 mg, the first objective symptom occurred at the first challenge dose, yet without a positive DBPCFC, resulting in a LOAEL of 3 mg. Consequently, five children were classified with a LOAEL <3 mg, 28 had the LOAEL set to 3 mg, and 64 had a LOAEL >3 mg.

In unadjusted bivariate analyses, basophil activation correlated significantly with reactivity threshold (correlation coefficient [r_s] = −.30, P = .004) and with LOAEL (r_s = −.02, P = .032). No significant correlations were found for reactivity threshold or LOAEL with peanut SPT or s-IgE to peanut, Ara h 2 or with the ratios of peanut s-IgE/total IgE and s- IgG_4/s-IgE to peanut (data not shown). Neither age, gender, allergic comorbidities nor $FEV_1\%$ were significantly associated with reactivity threshold, LOAEL or severity of allergic reaction in the bivariate regression analyses (data not shown).

In multiple robust regression analyses, reactivity threshold was significantly associated with basophil activation, peanut SPT, Ara h 2 and the ratios of peanut s-IgE/total IgE and s- IgG_4/s-IgE to peanut (Table 2). Neither peanut CAPT nor s-IgE or SPT_t to peanut was significantly associated with reactivity threshold. Repeating the analyses for LOAEL, significant association was found with peanut SPT, s-IgE to peanut, the ratio of peanut s-IgE/total IgE and basophil activation, but not with Ara h 2, the ratio s- IgG_4/s-IgE to peanut, peanut SPT_t and peanut CAPT (Table 2).

Subgroup analyses after excluding 23 children with a basophil activation ≤15% CD63+ (non-responders [n = 6] and the low responders [n = 17]) from the model gave similar results for reactivity threshold and for LOAEL (data not shown).

Basophil activation was significantly associated with immunological and clinical test results with closest association with peanut CAPT (β = −7.60, P = .02) (Table 3) and with age among girls (r_s = .31, P = .04), but not among boys (r_s = −.009, P = .95). Additionally, basophil activation was the best predictor of very low reactivity threshold (<3 mg of peanut protein) (Figure 2), with an optimal cut-off of 75.8% giving a 93.5% negative predictive value (Table S1).

Neither peanut SPT or SPT_t nor CAPT to peanut nor any of the immunological parameters was significantly associated with severity of allergic reaction in the Hosmer step down multivariate robust regression analysis (data not shown).

TABLE 1 Baseline characteristics from screening in the Take-Away trial

	n (%)	Geometric mean (95% CI)	Median (min, max)
Age		9.3 (5.1, 15.2)	9.7 (5.6, 14.6)
Male sex	50 (52.1)		
Current asthma	52 (54.2)		
Allergic rhinitis	28 (29.2)		
Ever had eczema	74 (77.1)		
Allergy to other nuts than peanut	36 (37.5)		
Allergy to other food than nuts	49 (51.0)		
Parental atopic disease[a]	83 (86.5)		
Parental food allergy[b]	38 (39.6)		
History of anaphylaxis	80 (83.3)		
Mild	18 (18.8)		
Moderate	36 (37.5)		
Severe	26 (27.1)		
FEV1% predicted		97.1 (94.8, 102.1)	100 (42, 137)
Peanut SPT (mm)		9.8 (9.0, 10.7)	9.5 (4.0, 36.0)
S-IgE (kUA/L)			
Peanut		88.1 (62.4,124.5)	108.5 (0.6, 2311.0)
Ara h2		44.6 (32.1, 61.9)	61.8 (0.38, 492.0)
Pos s-IgE (≥0.35 kUA/L)			
Other nuts[c]	87 (91.6)		
Other food[d]	92 (96.8)		
Ratio peanut s-IgE/total IgE (kUA/L)		4.0 (3.1, 5.3)	0.3 (0.0, 10.0)
Peanut s-IgG (mgA/L)		13.8 (11.5, 16.6)	13.9 (2.4, 80.9)
Peanut s-IgG$_4$ (mgA/L)		2.1 (1.6, 2.6)	0.5 (0.1, 18.7)
Ara h 2 s-IgG (mgA/L)		6.3 (5.4, 7.3)	5.2 (0.0, 41.1)
Ara h 2 s-IgG$_4$ (mgA/L)		8.9 (12.0, 6.6)	0.1 (0.0, 1.7)
Ratio s-IgG$_4$/s-IgE to peanut (ng/mL)		5.5 (3.9, 7.7)	5.0 (0.2, 564.6)
BA (%CD63$^+$) pos[e]		69.5 (64.0, 75.4)	76.9 (16.1, 94.4)
BA (%CD63$^+$) all children		44.9 (35.0, 57.5)	74.3 (0.5, 94.4)
CAPT positive (dilution)			
1/160	9 (9.4)		
1/80	24 (25)		
1/40	38 (39.6)		
1/20	20 (20.8)		
1/10	5 (5.2)		
Pre-OIT DBPCFC			
Use of adrenaline	42 (43.8)		
Anaphylaxis severity grade			
Modified EAACI[43]		1.7 (1.6, 1.8)	2 (1, 2)
Sampson[44]		2.6 (2.5, 2.8)	3 (2, 4)
LOAEL (mg)		13.8 (9.9, 19.5)	13.0 (0.8, 1610.0)
Reactivity threshold (DBPCFC positive) (mg)		32.4 (22.1, 47.5)	35.0 (1.0, 3943.0)

SPT, skin prick test; Ig, immunoglobulin; BAT, basophil activation test, CAPT, conjunctival allergen provocation test; OIT, oral immunotherapy; LOAEL, lowest observed adverse effect level; reactivity threshold—cumulated peanut protein eaten at positive DBPCFC.

[a]Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis.

[b]Food allergy includes all food allergy including peanut and tree nut allergy.

[c]IgE to other nuts ≥0.35 kUA/L includes hazelnut, almond, cashew nut, pistachio nut, walnut, pecan nut, Brazil nut and macadamia nut.

[d]IgE to other food includes fenugreek, soya bean, pea, red kidney bean, lupin seed and wheat.

[e]BAT results with basophil activation ≥15% CD63$^+$ basophils (positive).

TABLE 2 Multivariate robust regression analyses for significant associations between peanut reactivity threshold and the lowest observed adverse event level (LOAEL) in children anaphylactic to peanut

	Reactivity threshold		LOAEL	
	ß-value (95% CI)	P-value	ß-value (95% CI)	P-value
Peanut SPT (mm)	1.45 (0.08, 2.83)	.04	0.87 (0.43, 1.31)	.0001
Peanut s-IgE (kUA/L)	-		0.01 (0.002, 0.018)	.01
Ara h 2 s-IgE (kUA/L)	0.09 (0.02, 0.17)	.01	-	
Ratio peanut s-IgE/total IgE (kUA/L)	29.20 (22.57, 35.82)	<.0001	3.58 (1.44, 5.71)	.001
Ratio s-IgG$_4$/s-IgE to peanut (ng/mL)	1.69 (1.61, 1.78)	<.0001	-	
BAT all children (%)[a]	−0.45 (−0.73, −0.17)	.002	−0.09 (−0.17, −0.002)	.04

SPT, skin prick test; Ig, immunoglobulin; BAT, basophil activation given as percentage-activated CD63 cells test; -, no significant association.
Associations are given as the relative change (ß) related to each mg increase in peanut threshold.
N = 86, BAT was not performed in 10 children due to missed sampling (n = 5) or technical causes (n = 5).
[a]Included all children with a positive basophil activation (% CD63$^+$ basophils).

4 | DISCUSSION

In this novel study including 96 children who all had primary sensitization to peanut and anaphylaxis during the DBPCFC, reactivity threshold as well as LOAEL was significantly associated with basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE. Reactivity threshold was further significantly associated with Ara h 2 and the ratio of s-IgG$_4$/peanut s-IgE to peanut, while LOAEL was significantly associated with s-IgE to peanut. Neither reactivity threshold nor LOAEL was significantly associated with age, gender, medical history, allergic comorbidities or lung function. None of the investigated clinical or immunological characteristics were significantly associated with severity of the allergic reaction during food challenge.

The significant association between reactivity threshold as well as LOAEL with basophil activation given by % CD63$^+$ in our children with anaphylaxis to peanut is in line with previous reports[21,24] in children

TABLE 3 Robust regression analyses for the associations between basophil activation and immunological and clinical parameters

	Bivariate	
	Coeff (95% CI)	P-value
SPT to peanut (mm)	0.60 (−0.34, 1.54)	.21
Peanut s-IgE (kUA/L)	0.04 (0.02, 0.06)	<.01
S-IgE Ara h 2 (kUA/L)	0.08 (0.02, 0.13)	<.01
Ratio peanut s-IgE/total IgE (kUA/L)	58.2 (34.8, 81.7)	<.01
Ratio s-IgG$_4$/s-IgE to peanut (ng/mL)	− 0.14 (−0.19, −0.09)	<.01
CAPT positivity level[a]	−7.60 (−14.06, −1.15)	.02

SPT, skin prick test; Ig, immunoglobulin; BAT, basophil activation test, CAPT, conjunctival allergen provocation test.
The coefficient represents the relative change related to percentage increase in activated basophils.
N = 80, BAT was not performed in 10 children due to missed sampling (n = 5) or technical causes (n = 5), non-responders are excluded (n = 6).
[a]Dilution steps at which the test was considered positive.
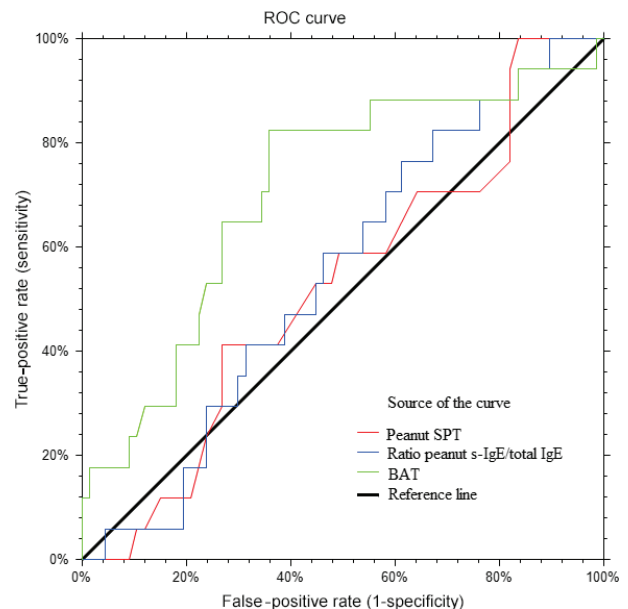
FIGURE 2 Receiver operating characteristic curves predicting very low threshold (<3 mg of peanut protein). The basophil activation test used 5 ng/mL of allergen

with varying severity of peanut allergy. In 52 of 124 children with a median age of 5.4 years with a positive peanut challenge, Santos et al[21] reported that basophil activation given by CD-sens as well as peanut SPT, s-IgE to peanut, Ara h 2 and the ratio of s-IgG$_4$/s-IgE to peanut was significantly associated with reactivity threshold, whereas basophil activation given by % CD63$^+$ was the best predictor of allergy severity grade. In 63 peanut-allergic children with a median age of 6.5 years, Blumchen et al[24] found similar correlation between LOAEL and basophil activation for both % CD63$^+$ (r_s = −.32) and CD-sens (r_s = −.36), which is also in line with other reports of correlation between CD-sens and % CD63$^+$ (r_s = .60, P = <.01)[21] and a 100% concordance has been shown between CD-sens and a positive DBPCFC.[34] In the present study, basophil activation expressed as % CD63$^+$ best predicted very low threshold level (<3 mg of peanut

protein), whereas CD-sens could not be assessed due to strong basophil activation even at the lowest concentration of 2.5 ng/mL allergen extract, reflecting a study population with very low reactivity threshold.

Our finding of significant associations between reactivity threshold and peanut SPT and Ara h 2 is in line with previous reports in children[21,24] and young adults.[23] In addition to correlation with basophil activation, Blumchen et al[24] found LOAEL also to correlate with peanut SPT, s-IgE to peanut and Ara h 2 (r_s = −.20 to −.40), in line with a Danish study[23] reporting correlation between reactivity threshold and Ara h 2 (r_s = .30) in 205 subjects 1-26 years of age, of whom 175 had a positive peanut challenge.

The associations between immunological and clinical test results and LOAEL were largely similar to those with reactivity threshold in the present study, with basophil activation, peanut SPT and peanut s-IgE/total IgE being significantly associated with both, although Ara h 2 was associated with reactivity threshold only, and peanut s-IgE with LOAEL only. The reasons for the different associations for reactivity threshold and LOAEL may be related to the observed larger variation in reactivity threshold compared to the LOAEL, or they may reflect different threshold entities with reactivity threshold requiring moderate objective symptoms while LOAEL appears more sensitive reflecting the lowest cumulated dose at which a mild objective symptom was noted. Additionally, the discrepancies may be due to the estimated rather than measured LOAEL in our study, with the first challenge dose of 3 mg. The estimated LOAEL may also explain why basophil activation was less strongly correlated to LOAEL than reactivity threshold and why the correlation is weak (r_s = −.02). On the other side, such a low correlation may also be irrelevant. It has been suggested that ideally, the highest dose that does not elicit objective symptoms (NOAEL = no observed adverse effect level) should be determined for defining the exact LOAEL,[35] but this was not possible in our study. The post hoc decision to also determine LOAEL was made to facilitate comparisons across studies with different stopping criteria of OFC.[35,36,40] Some studies use only subjective symptoms that occur in consecutive doses as a sign of a positive OFC,[17,46] although subjective symptoms may occur at doses 20-fold lower than the LOAEL[47] and some patients report no subjective symptoms prior to the objective symptoms.[24] Determining LOAEL might also be helpful in identifying the peanut exposure amount that elicited the first symptom or sign related to the importance of food labelling.[28]

The severity of allergic reactions was not associated with any of the clinical or immunological characteristics in the present study, in line with the study of Blumchen et al,[24] but in contrast to the MIRABEL study,[48] in which baseline characteristics like age (teenagers and adults), asthma and not having atopic dermatitis were associated with more severe allergic reactions. Also, peanut SPT,[13] s-IgE to peanut and Ara h 2,[22,23] peanut SPT$_t$[49] and basophil activation (% CD63$^+$)[21] have been found to correlate to severity grades of allergic reactions. Song et al[13] performed DBPCFC for different foods (42 of 44 positive with peanut DBPCFC) in 71 sensitized patients with a median age of 16, and found SPT (r_s = .24) and Ara h 2 (r_s = .31) to correlate with severity grade, in line with the correlation between Ara h 2 and allergy severity (r_s = .60) in 175 patients age of 1-26 years with a clinical history of allergic reaction.[23] In 21 children (mean age of 60 months) with peanut allergy and 34 controls (28 tolerant and 6 non-anaphylactic reaction), Wainstein et al[22] found both peanut SPT and s-IgE to peanut to predict anaphylaxis, whereas Tripodi et al[49] reported that the end-point titration in SPT$_t$ differentiated between Sampson severity grades 3-5, grades 1-2 and negative food challenge in 20 of 47 children with OFC-proven hen's egg allergy. Methodological differences may explain some of the differences, including our reading of the SPT$_t$ after 15 minutes vs 30 minutes in the Tripodi study. Finally, after multivariate analyses, Santos et al[21] found that only basophil activation (% CD63$^+$) and not SPT or other immunological test results was retained as the one marker closest associated with severity grade of allergic reaction. The lack of significant associations between biological markers and severity of allergy reaction in the present study is likely to reflect our relatively homogenous study population; all with primary peanut allergy and anaphylaxis[42,44] during DBPCFC and 34.4% of the children with a LOAEL ≤ 3 mg of peanut protein, which exceeded the expected 10% with a very low reactivity threshold.[50] It also exceeded the 4.7% of the 63 peanut-allergic children with LOAEL at 3 mg of peanut protein reported by Blumchen et al,[24] although they suggested that their modified food challenge would result in a lower LOAEL.

Also, the DBPCFC was stopped when it was defined positive, which may have prohibited more severe reactions. Basophil activation on the other hand can be regarded as an "in vitro challenge"[12] that can proceed to higher doses. In the present study, it was associated with immunological and clinical test results shown to predict severity grade of allergic reaction,[13,21-23] which may suggest a relationship between allergy severity and reactivity. This finding is in line with the previously reported association between severity of allergic reaction and reactivity threshold (P = .027).[51] To our knowledge, the association between basophil activation in the present study with the peanut CAPT dilution at which subjects experienced allergy symptoms and signs[11] has not been shown previously, but is supported by the study of Varney et al[52] where conjunctival provocation threshold increased significantly after specific immunotherapy to cat dander. Finally, we found basophil activation also to correlate with female gender, a finding we are not aware has been shown previously. The clinical relevance of the latter finding is not clear.

4.1 | Strengths and limitations

All 96 children had confirmed primary peanut allergy by DBPCFC, with moderate objective signs from at least two organ systems, excluding only skin symptoms and very mild symptoms as anaphylaxis[41,42] in line with international standards, and the study included a novel CAPT to peanut to assess potential biological correlates. However, as all children had anaphylaxis this may limit the possibility to identify correlations across a wider variation of reactivity thresholds and severity reactions. Although we found immunological and clinical test results to correlate to reactivity thresholds and LOAEL within our study population, the generalizability of our study may be limited to children with similar peanut allergy severity. Further, to be

able to address biomarkers associated with very low reactivity threshold and LOAEL, the study would have benefited from setting a lower starting dose than was chosen for the study. Finally, a potential limitation to interpretation of the results may be that thresholds determined by OFC are not completely reproducible.[53,54]

5 | CONCLUSION

In children with anaphylaxis to peanut, basophil activation, peanut SPT and the ratio of peanut s-IgE/total IgE were associated with reactivity threshold and LOAEL. None of the clinical or immunological markers appeared sufficient to substitute oral peanut challenge to determine reactivity threshold, and none were associated with severity of the allergic reactions.

CONFLICT OF INTEREST

Magnus P. Borres is employed by Thermo Fisher Scientific, and the other authors declare no conflict of interest for the present study.

ORCID

T. Reier-Nilsen http://orcid.org/0000-0001-8184-0607

REFERENCES

1. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191-193.
2. Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? *Curr Opin Allergy Clin Immunol*. 2015;15:409-416.
3. Venter C, Arshad SH. Epidemiology of food allergy. *Pediatric Clin North Am*. 2011;58:327-349, ix.
4. Venter C, Hasan Arshad S, Grundy J, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy*. 2010;65:103-108.
5. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol*. 2008;121:731-736.
6. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol*. 2015;135:1257-1266.
7. Yu JW, Kagan R, Verreault N, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol*. 2006;118:466-472.
8. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol*. 2003;14:378-382.
9. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy*. 2000;30:1135-1143.
10. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65:238-244.
11. Lindvik H, Lodrup CK, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy*. 2017;47:785-794.
12. Santos AF, Lack G. Basophil activation test: food challenge in a test tube or specialist research tool? *Clin Transl Allergy*. 2016;6:10.
13. Song Y, Wang J, Leung N, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol*. 2015;114:319-326.
14. Ocmant A, Mulier S, Hanssens L, et al. Basophil activation tests for the diagnosis of food allergy in children. *Clin Exp Allergy*. 2009;39:1234-1245.
15. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol*. 2005;115:1291-1296.
16. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997;100:444-451.
17. Klemans RJ, Otte D, Knol M, et al. The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. *J Allergy Clin Immunol*. 2013;131:157-163.
18. Chokshi NY, Sicherer SH. Interpreting IgE sensitization tests in food allergy. *Expert Rev Clin Immunol*. 2016;12:389-403.
19. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol*. 2010;125:191-197 e1-13.
20. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy*. 2015;70:391-407.
21. Santos AF, Du Toit G, Douiri A, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol*. 2015;135:179-186.
22. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol*. 2010;21(4 Pt 1):603-611.
23. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy*. 2013;68:190-194.
24. 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;134:390-398.
25. Ta V, Weldon B, Yu G, Humblet O, Neale-May S, Nadeau K. Use of specific IgE and skin prick test to determine clinical reaction severity. *Br J Med Med Res*. 2011;1:410-429.
26. Santos AF, James LK, Bahnson HT, et al. IgG4 inhibits peanut-induced basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens. *J Allergy Clin Immunol*. 2015;135:1249-1256.

27. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. *J Allergy Clin Immunol Pract*. 2014;2:300-305.

28. Taylor SL, Hefle SL, Bindslev-Jensen C, et al. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? *Clin Exp Allergy*. 2004;34:689-695.

29. Bindslev-Jensen C, Briggs D, Osterballe M. Can we determine a threshold level for allergenic foods by statistical analysis of published data in the literature? *Allergy*. 2002;57:741-746.

30. Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. *Thorax*. 2006;61:744-746.

31. Zapletal A, Paul T, Samanek M. Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl). *Zeitschrift fur Erkrankungen der Atmungsorgane*. 1977;149(3):343-71.

32. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. *Clin Transl Allergy*. 2013;3(1):3.

33. Santos AF, Douiri A, Becares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. *J Allergy Clin Immunol*. 2014;134:645-652.

34. Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy*. 2012;67: 242-247.

35. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260-1274.

36. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. *Allergy*. 2004;59:690-697.

37. Vlieg-Boerstra BJ, Herpertz I, Pasker L, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. *Allergy*. 2011;66:948-954.

38. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol*. 2009;6(Suppl): S365-S383.

39. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol*. 1988;82:986-997.

40. Niggemann B. When is an oral food challenge positive? *Allergy*. 2010;65:2-6.

41. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62:857-871.

42. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025.

43. Vetander M, Helander D, Lindquist C, et al. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol*. 2011;22:369-373.

44. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111(6 Pt 3):1601-1608.

45. Hosmer DW, Lemeshow S. *Applied Logistic Regression*, 2 edn. New York, NY: John Wiley & Sons; 2000.

46. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet*. 2014;383:1297-1304.

47. Chen L, Lucas JS, Hourihane JO, Lindemann J, Taylor SL, Goodman RE. Evaluation of IgE binding to proteins of hardy (*Actinidia arguta*), gold (*Actinidia chinensis*) and green (*Actinidia deliciosa*) kiwifruits and processed hardy kiwifruit concentrate, using sera of individuals with food allergies to green kiwifruit. *Food Chem Toxicol*. 2006;44:1100-1107.

48. Deschildre A, Elegbede CF, Just J, et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. *Clin Exp Allergy*. 2016;46:610-620.

49. Tripodi S, Businco AD, Alessandri C, Panetta V, Restani P, Matricardi PM. Predicting the outcome of oral food challenges with hen's egg through skin test end-point titration. *Clin Exp Allergy*. 2009;39:1225-1233.

50. Allen KJ, Remington BC, Baumert JL, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol*. 2014;133:156-164.

51. Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CA, Knulst AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J Allergy Clin Immunol*. 2002;110:915-920.

52. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy*. 1997;27:860-867.

53. Obh J. The threshold concept in food safety and its applicability to food allergy. *Allergy*. 2001;56(Suppl 67):86-90.

54. Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. *PLoS One*. 2013;8:e53465.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Paper #2

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy

Tonje Reier-Nilsen[1,2] (ID) | Merethe Melbye Michelsen[1,2] | Karin C. Lødrup Carlsen[1,2] (ID) |
Kai-Håkon Carlsen[1,2] | Petter Mowinckel[1] | Unni C. Nygaard[3] | Ellen Namork[3] |
Magnus P. Borres[4,5] | Geir Håland[1,2]

[1]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Norwegian Institute of Public Health, Division for Infection Control and Environmental Health, Oslo, Norway

[4]Thermo Fisher Scientific, Uppsala, Sweden

[5]Institute of Maternal & Child Health, Uppsala University, Uppsala, Sweden

Correspondence
Dr. Tonje Reier-Nilsen, Oslo University Hospital, Division of Paediatric and Adolescent Medicine Ullevål, Oslo, Norway.
E-mails: tonjre@ous-hf.no; tonje.nilsen@medisin.uio.no

Abstract

Background: There are limited data on the feasibility, efficacy and safety of high-dose oral immunotherapy (OIT) in children highly allergic to peanuts.

Objective: In children highly allergic to peanut, we primarily aimed to determine the feasibility of reaching the maximum maintenance dose (MMD) of 5000 mg peanut protein or, alternatively, a lower individual maintenance dose (IMD), by OIT up-dosing. Secondarily, we aimed to identify adverse events (AEs) and determine factors associated with reaching a maintenance dose.

Methods: The TAKE-AWAY peanut OIT trial enrolled 77 children 5-15 years old, with a positive oral peanut challenge. Fifty-seven were randomized to OIT with biweekly dose step-up until reaching MMD or IMD and 20 to observation only. Demographic and biological characteristics, AEs, medication and protocol deviations were explored for associations with reaching maintenance dose.

Results: All children had anaphylaxis defined by objective symptoms in minimum two organ systems during baseline challenge. The MMD was reached by 21.1%, while 54.4% reached an IMD of median (minimum, maximum) 2700 (250, 4000) mg peanut protein, whereas 24.5% discontinued OIT. During up-dosing, 19.4% experienced anaphylaxis. Not reaching the MMD was caused by distaste for peanuts (66.7%), unacceptable AEs (26.7%) and social reasons (6.7%). Increased peanut s-IgG$_4$/s-IgE ratio (OR [95% CI]: 1.02 [1.00, 1.04]) was associated with reaching MMD.

Conclusion: Although 75.5% of children with peanut anaphylaxis reached a maintenance dose of 0.25-5 g, only 21.1% reached the MMD. Distaste for peanuts and AEs, including high risk of anaphylaxis, limited the feasibility of reaching MMD.

KEYWORDS
adverse events, desensitization, feasibility, oral immunotherapy, peanut allergy

1 | INTRODUCTION

Peanut allergy affects 1%-2% of the paediatric population,[1] is seldom resolved[2] and is the main cause of life-threatening allergic reactions in the Western World.[3] The only established treatment is dietary restrictions and rescue medication including epinephrine auto-injectors. However, the possibility of accidental exposure[4] causes anxiety and reduced quality of life.[5–7]

Peanut oral immunotherapy (OIT) trials are promising for inducing desensitization with acceptable safety profiles,[8–14] but evidence of sustained unresponsiveness (SU) after OIT discontinuation is limited.[8,14] The optimal starting dose of peanut OIT is not clear, and there is limited documentation of what maintenance dose would be safe and provide the greatest likelihood of inducing sustained unresponsiveness (SU). The ongoing "Take-Away food allergy; inducing tolerance in children allergic to peanut" trial (the TAKE-AWAY trial) is an open randomized controlled trial which primarily aims to assess SU after 4 years of peanut OIT. At the onset of the TAKE-AWAY trial, peanut OIT trials reported maintenance doses ranging from 125 to 4000 mg peanut protein,[9,12,13] with no adverse events (AEs) requiring epinephrine reported during a biweekly step-up protocol to 4000 mg peanut protein.[13] A high maintenance dose confers an increased likelihood of SU in subcutaneous immunotherapy (SCIT) trials for inhalant and venom allergies,[15,16] while this issue has not been adequately addressed for OIT. However, in a recent peanut OIT study,[17] maintenance dose was not decisive for SU 4 weeks after cessation of OIT. A fixed starting dose and a long-term step-up protocol have been associated with fewer AEs and higher retention rate.[9,18] Even though a recent workshop concluded that severe reactions occur unpredictably at any dose,[19] a possible relationship between allergen dose and the occurrence of anaphylaxis[20] may suggest a low OIT starting dose.

The feasibility of OIT is likely to be influenced by AEs,[21] while other factors are less well known. A low starting dose with a high maintenance dose increases the number of dose steps in an already time-consuming long-term protocol,[9,18] thereby excluding patients with less time resources.[22]

Therefore, the primary aim of the present study was to determine the feasibility of reaching the predefined maximum maintenance dose (MMD) of 5000 mg peanut protein or, alternatively, a lower individual maintenance dose (IMD), by OIT up-dosing in children highly allergic to peanut. Secondarily, we aimed to identify AEs and determine factors associated with reaching a maintenance dose, and in particular the MMD.

2 | METHODS

2.1 | Study design

The TAKE-AWAY trial, conducted at the Department of Paediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Norway, consists of four phases: the screening phase (3 days of eligibility

What is known on this subject

Peanut oral immunotherapy (OIT) is promising for inducing desensitization with acceptable safety profiles, but children highly allergic to peanuts and susceptible of severe systemic reactions to peanut are often excluded from OIT trials. Hence, there is limited information on the feasibility of performing OIT in this group of patients.

This study adds

The present peanut OIT study in children proven highly allergic to peanut during food challenge demonstrates that only 21% reached the predefined maintenance dose of 5000 mg peanut protein, mostly due to reported distaste for peanuts or adverse events. However, 75% of the children were able to reach an individual maintenance dose. Anaphylaxis occurred in 19.4% during up-dosing, causing discontinuation of OIT in 36.3% of these children.

Impact on current management guidelines

High-dose peanut OIT may be initiated in children highly allergic to peanut, but distaste for peanuts and adverse events may limit the likelihood of successful OIT. The high risk of anaphylaxis during treatment questions the safety of OIT in these children.

screening), up-dosing phase (50-78 weeks), maintenance phase (36 months) and follow-up phase (12 months). The present study explored the up-dosing phase.

Children were recruited from February 2014 to June 2015 from the Oslo Peanut Allergy Study[23] and from in-house or other paediatric allergy clinics in Oslo and the surrounding area.

Inclusion criteria for screening were age 5-15 years, with a history of systemic reactions to peanut and/or sensitization to peanut by a peanut skin prick test (SPT) $\geq$ 3 mm or a peanut sIgE $\geq$ 0.35 kUA/L. Exclusion criteria were noncontrolled asthma or severe chronic disease (further details in Appendix S1).

Screening included a structured interview, blood samples for serological and immunological analyses, lung function measurements, SPT, conjunctival allergen provocation test (CAPT) and basophil activation test (BAT), followed by a DBPCFC. The DBPCFC was defined positive with at least two moderate objective symptoms in one or more organ systems according to Bock's criteria.[24–26] Cumulated peanut protein (mg) intake at positive DBPCFC was recorded as the reactivity threshold, whereas the lowest observed adverse effect level (LOAEL) was calculated post hoc and defined as the amount of peanut protein ingested eliciting mild, objective symptoms.[22] Enrolment in the TAKE-AWAY trial required a positive DBPCFC with a reactivity threshold > 3 mg peanut protein.[22] Of the 213 children referred for screening, 113 did not wish to enter the study, did not fulfil the screening inclusion and exclusion criteria, withdrew during

screening, and had a negative DBPCFC or a positive DBPCFC but with a reactivity threshold ≤3 mg peanut protein.[22]

Randomization to OIT vs observation followed an initial 2:1 block size, and restarted by approval from the Regional Committee for Medical and Health Research Ethics (the ethical committee) when the OIT starting dose was lowered (further details in Table S1).

Written informed consent was obtained from both parents after oral and written study information.

TAKE-AWAY was approved by the ethical committee (number 2013/430) with regular communications in case of severe or unexpected AEs, and registered at ClinicalTrials.gov (number NCT02457416).

2.2 | Study population

The present study includes the 57 children (5-15 years of age) randomized to peanut OIT. Anaphylaxis was defined as objective symptoms from at least two organ systems in line with European Academy of Allergy and Clinical Immunology (EAACI) task force position papers,[27,28] modified for children by Vetander et al[29]

2.3 | Immunological investigations

Specific IgE, IgG and IgG$_4$ were analysed using the Phadia CAP System FEIA (Thermo Fisher, Uppsala, Sweden), with positive tests defined as sIgE ≥ 0.35 kUA/L, IgG > 2.0 mg$_A$/L and IgG4 > 0.07 mg$_A$/L. The BAT is described in the Appendix S1.

2.4 | Up-dosing protocol of the oral immunotherapy

The peanut OIT followed a biweekly step-up long-term protocol with a fixed starting dose and a predefined MMD of 5000 mg peanut protein (details in the Appendix S1 and Table S2). The OIT starting dose was initially 5 mg peanut protein based on previously published studies[9,18] and results from the OPAS trial,[23] but lowered to 1 mg due to low reactivity thresholds in the referred patients.[22] For the lowest doses, the allergen source was peanut flour (Golden Peanut Company, Alpharetta, GA, USA). Because larger amounts of peanut flour mixed with other food became too sticky to eat, all but one patient switched to roasted peanuts at OIT doses of 65-500 mg peanut protein. Each increasing OIT dose was discussed with the patient and their guardian and ingested under observation at the hospital, followed by daily intake of this dose at home for 14 days.

In case of intolerable distaste or AEs, or if AEs resulted in three consecutive unsuccessful attempts to dose step-up, the IMD was considered reached (further details in Appendix S1). Withdrawal followed self-discontinuation of OIT, intolerable or severe AEs or more than two anaphylactic reactions. All unexpected severe AEs were reported to an independent safety board. In case of ongoing infections, asthma exacerbations, excessive tiredness or vaccinations, children were advised to postpone the daily OIT dose to the next day. The OIT was resumed at home if less than three consecutive doses

were missing, and in hospital if three or more doses were missed. Exercise within 2 hours after the OIT dose was discouraged.

Registration of peanut intake, AEs, use of medication and accidental exposure to peanut were based upon daily symptom diary recordings. Grading AEs followed the modified Bock's criteria,[24,25] as described in the Appendix S1.

All participants received prescriptions of epinephrine auto-injectors and antihistamines and a written treatment plan for AEs and had around-the-clock access to the study paediatricians.

2.5 | Outcomes and explanatory factors

The primary outcome was the feasibility of reaching MMD, defined by the proportion of children who reached the predefined MMD of 5000 mg peanut protein. The secondary outcome was the proportion of children who reached the IMD (<5000 mg peanut protein).

Potential explanatory factors of reaching the MMD or the lower IMDs were AEs characterized by the involved organ(s) and classified into either subjective and mild objective, moderate or severe (including anaphylaxis) in line with the modified Bock's criteria,[25] baseline characteristics, biological markers, LOAEL, severity grade of anaphylaxis at screening DBPCFC, medication for AEs and protocol deviations (dose reduction or postponed up-dosing due to social events, AEs or infections).

2.6 | Statistical analyses

The statistical power analyses at study onset were based upon studies reporting that up to 80% of peanut-allergic children were desensitized using a step-up peanut OIT[12,13] and development of spontaneous tolerance in 20%.[2] In children with severe peanut allergy, we expected desensitization in 57%. A treatment group of 40 and a control group of 20 subjects would provide a statistical power of 80% at a five per cent significance level.

Due to nonnormal distribution, continuous baseline characteristics are presented by geometric mean with 95% confidence intervals (CI) and categorical data as number of cases (n) with percentage (%), while potential differences between groups were analysed using the Mann-Whitney U test for continuous data and the Pearson's chi-square test for categorical data.

To determine the statistical significance of desensitization based upon the individual difference in peanut daily maintenance dose to the reactivity threshold and LOAEL at baseline, we used a paired-sample t test. The associations between explanatory factors and feasibility of desensitization were assessed using bivariate logistic regression analyses with the proportion of children who reached the MMD versus the proportion who reached either IMD or discontinued OIT as the dependent variable. The analyses were duplicated with the proportion of children who reached either MMD or IMD as the dependent variable versus the proportion who discontinued OIT.

A one-way ANOVA was used to analyse the overall difference between the three groups of children who reached the MMD, those

who reached the IMD and those who discontinued OIT with the latter group as reference. One-way ANOVA was also used to analyse the overall difference between AEs occurring in the three dose intervals of the up-dosing phase (1-65, 66-800 and 801-5000 mg peanut protein). In the case of a significant overall P-value, the Dunnett's post hoc test was used to confirm between which groups the statistically significant difference had occurred.

Statistical analyses were performed using the Statistical Analysis System (SAS, version 9.3; SAS Institute Inc., Chapel Hill, NC, USA) and IBM Statistical Package for the Social Sciences (IBM SPSS Statistics, version 21.0.1.; IBM Corp, Armonk, NY, USA).

A 2-tailed P-value of ≤0.05 was considered statistically significant.

3 | RESULTS

All 57 children randomized to active peanut OIT were primary sensitized to peanut with geometric mean (min, max) sIgE to Ara h 2 of 56.2 (0.82, 492.0) kUA/L and had a LOAEL of 18.4 (11.8, 28.6) mg peanut protein, and 78.9% had a history of a anaphylaxis to peanut. During baseline DBPCFC, all children randomized to OIT, as well as the control children in the TAKE-AWAY trial, reacted with anaphylaxis.[22] The baseline characteristics including grading of anaphylaxis are reported in Table 1 for children reaching MMD or IMD or those who discontinued peanut OIT, as well as for the controls.

The predefined MMD of 5000 mg peanut protein was reached by 21.1% (n = 12) of the children, while 54.4% (n = 31) reached a lower IMD and 24.5% (n = 14) discontinued (Table 2). The median (min, max) IMD reached was 2700 (250, 4000) mg of peanut protein, which was 207 (3.1, 1666.7) (P < 0.001 for both) times higher than LOAEL at screening.

The most common reasons for not reaching the MMD were distaste for peanuts in 66.7% (n = 28 within IMD and 2 discontinued) of the children and AEs in 26.7% (n = 3 within IMD and 9 discontinued) and social reasons in 6.7% (n = 3 discontinued; two found the treatment too time-consuming, while one discontinued due to parents' divorce). Distaste for peanuts was reported as a daily challenge in 77.2% of the children.

Mild AEs were reported in relation to 13.9% of the OIT doses. One child only did not report any AEs. The AEs occurred more often in the first (1-65 mg peanut protein), compared with the second (66-800 mg) and third (801-5000 mg peanut protein) dose interval steps (overall P = 0.03), with a statistically significant difference between the first and the last dose intervals (Figure 1). The AEs, mostly oral itching (43.5%) or other gastrointestinal (GI)-related (42.5%) symptoms, occurred more frequently during the first two, compared with the remaining days in each up-dosing period (P = 0.001; Figure 1). Dyspeptic symptoms were reported as the main reason for discontinuation in two children, while six children with dyspeptic symptoms had spontaneous (n = 2) or proton pump inhibitor (PPI)-related (n = 4) symptom relief and continued treatment throughout the up-dosing phase.

Moderately graded AEs constituted 0.6% of all AEs (Table 3), and 11 anaphylactic events classified as moderate occurred in 11 children (0.06% of the doses), with epinephrine administered in six of the episodes (Table S3). All but two anaphylactic reactions were preceded by known augmenting factors: exercise within two hours of a dose,[5] ongoing infection,[1] excessive tiredness,[1] impaired compliance to OIT[1] or asthma treatment.[1] In comparison, the control group did not experience any anaphylactic events to peanut.

Children discontinuing OIT reported significantly more AEs per dose step per child than children who reached any maintenance dose (MMD or IMD) median (min, max) 2.45 (0.27, 10.50) vs 1.04 (0, 12.90), respectively (P = 0.01), whereas moderately graded AEs were similarly reported in these two groups (P = 0.61).

The only identified significant predictor of reaching a maintenance dose was the peanut sIgG$_4$/sIgE ratio ratio that was associated with MMD in the bivariate (Table 4) and the multivariate logistic regression model (not shown). Including Sampson's anaphylaxis severity grading did not influence the results (not shown). We found nonsignificant trends for associations between LOAEL and MMD, and between sIgE to peanut, sIgE to Ara h 2, the peanut sIgE/total IgE ratio and AEs and any maintenance dose (MMD + IMD) (P = 0.06–0.08) (Table 4).

4 | DISCUSSION

In the randomized controlled peanut OIT TAKE-AWAY trial, desensitization to peanut was feasible for most children highly allergic to peanut and reacting with anaphylaxis at baseline food challenge. The high predefined MMD of 5000 mg peanut protein was reached by 21.1%, whereas 54.4% reached the lower IMD. Failure to reach the MMD was most often due to distaste for peanuts, whereas AEs were the main reason for discontinuation. Anaphylaxis occurred in 19.3% of the children during the up-dosing phase. Peanut sIgG$_4$/sIgE ratio was the only significant predictor of reaching MMD, while AEs, baseline sIgE to peanut or Ara h 2 and LOAEL showed a nonsignificant tendency to be associated with the maintenance dose reached.

Desensitizing children with anaphylaxis to peanut by reaching the MMD of 5000 mg peanut protein was feasible in 21.1% only, while 73.7% reached a maintenance dose of at least 500 mg, in line with the 63.6% to 86.9% previously reported.[8–11,13,21,30,31] Based upon the limited experience with peanut OIT and MMD varying from 125 mg to 4000 mg of peanut protein trial,[8–11,13,21,30,31] our high MMD was chosen to increase the likelihood of SU in children with severe peanut allergy. However, 5000 mg peanut protein represents approximately 25 whole peanuts, a quantity that was challenging for many children as they developed distaste for peanuts. Few reports have addressed this issue previously, except one study[9] reporting distaste for peanuts as the reason for withdrawal of one patient and reduction of maintenance dose in two patients.

The 24.5% discontinuation of OIT in our cohort of children highly allergic to peanut is in line with previously published peanut OIT studies, ranging from 10% to 32%.[32] Experiencing AEs

TABLE 1 Baseline characteristics of children randomized to peanut OIT and controls in the TAKE-AWAY trial

	Total patients receiving OIT (n = 57)	Patients reaching MMD (n = 12)	Patients reaching IMD (n = 31)	Patients discontinued OIT (n = 14)	Overall P-value between MMD, IMD and dis-continued	Controls (n = 20)	P-value between OIT patients and controls
Age (median, min-max)	10.1 (5.2, 15.2)	10.7 (7.2, 15.2)	8.5 (5.2, 14.4)	10.2 (5.4, 15.1)	0.02[##]	8.9 (5.1, 13.3)	0.28
Male	31 (54.4)	7 (58.3)	14 (45.2)	10 (71.4)	0.26	13 (65.0)	0.41
History of anaphylaxis to peanut	45 (78.9)	9 (75.0)	23 (74.2)	13 (92.8)	0.82	18 (90.0)	0.63
Current asthma	24 (42.1)	5 (41.2)	11 (35.4)	8 (57.1)	0.37	9 (45.0)	0.78
Allergic rhinitis	15 (26.3)	5 (41.7)	8 (25.8)	2 (14.3)	0.53	8 (40.0)	0.83
Atopic dermatitis	47 (82.5)	11 (91.7)	25 (80.6)	11 (78.6)	0.64	14 (73.9)	0.41
Allergy to tree-nuts	20 (35.1)	5 (41.7)	15 (48.4)	0 (0.0)	0.15	7 (36.8)	0.99
Allergy to other food than nuts	27 (47.4)	6 (50.0)	19 (61.3)	2 (14.3)	0.02[#]	11 (57.9)	0.65
Parental atopic disease[a]	50 (87.7)	9 (75.0)	27 (87.1)	14 (100.0)	0.16	16 (80.0)	0.40
Parental food allergy[b]	21 (36.8)	4 (33.3)	10 (32.3)	7 (50.0)	0.51	6 (30.0)	0.58
FEV1% predicted	101.2 (97.6, 105.0)	101.0 (91.2, 112.2)	101.9 (97.7, 104.7)	99.7 (94.0, 105.8)	0.86	95.5 (88.3, 107.2)	0.22
Pos sIgE ($\geq$0.35 kUA/L)							
Tree-nuts[c]	52 (91.2)	10 (83.3)	30 (96.7)	12 (85.7)	0.08	16 (80.0)	0.11
Other food[d]	54 (94.7)	12 (100.0)	29 (96.7)	13 (92.9)	0.63	19 (95.0)	0.50
Peanut SPT (mm)	9.8 (8.6, 11.0)	8.7 (7.0, 10.9)	9.7 (8.4, 11.3)	10.3 (7.3, 14.6)	0.64	9.3 (7.4, 11.7)	0.94
sIgE (kUA/L)							
Peanut	110.6 (70.4, 173.8)	21.9 (4.9, 97.8)	129.3 (88.9, 188.0)	175.7 (55.0, 561.6)	0.003[#]	52.2 (20.3, 134.4)	0.12
Ara h2	56.2 (37.2, 87.1)	13.5 (3.1, 59.1)	67.0 (47.8, 94.0)	89.6 (33.9, 235.9)	0.004[#]	22.4 (8.4, 58.9)	0.09
Peanut sIgE/total IgE (kUA/L)	0.4 (0.0, 1.5)	0.3 (0.1, 0.6)	0.3 (0.1, 0.6)	0.5 (0.4, 0.7)	0.002[#]	0.2 (0.1, 0.6)	0.12
Peanut sIgG$_4$/sIgE (ng/mL)	5.7 (3.7, 8.9)	15.5 (3.4, 60.3)	4.9 (2.9, 8.3)	3.3 (1.4, 7.8)	0.04[#]	5.3 (2.6, 10.9)	0.46
CAPT pos level[e]	2.6 (2.3, 3.0)	3.0 (2.2, 4.1)	2.6 (2.3, 3.1)	2.3 (1.7, 3.1)	0.41	3.1 (2.7, 3.4)	0.19
BAT (%CD63$^+$)	68.0 (61.6, 75.1)	34.4 (15.5, 75.9)	49.6 (34.7, 70.8)	63.7 (46.0, 88.2)	0.28	51.2 (32.0, 85.4)	0.48
At baseline DBPCFC							
Number of anaphylaxis	57 (100.0)	12 (100.0)	31 (100.0)	14 (100.0)	0.11	20 (100.0)	0.51
Anaphylaxis severity grade							
Modified EAACI	1.6 (1.4, 1.7)	1.4 (1.1, 1.8)	1.7 (1.5, 1.9)	1.6 (1.3, 1.9)	0.22	1.7 (1.5, 2.0)	0.33
Sampson	2.6 (2.4, 2.8)	2.8 (2.4, 3.4)	2.5 (2.3, 2.8)	2.6 (2.3, 3.1)	0.49	2.8 (2.5, 3.2)	0.23

(Continues)

TABLE 1 (Continued)

	Total patients receiving OIT (n = 57)	Patients reaching MMD (n = 12)	Patients reaching IMD (n = 31)	Patients discontinued OIT (n = 14)	Overall P-value between MMD, IMD and dis-continued	Controls (n = 20)	P-value between OIT patients and controls
Use of adrenaline	30 (52.6)	5 (41.7)	17 (54.8)	8 (57.1)	0.70	5 (25.0)	**0.03**
LOAEL (mg peanut protein)	18.4 (11.8, 28.6)	45.9 (10.2, 207.1)	15.1 (10.3, 22.1)	36.2 (15.4, 84.4)	0.05	5 (25.0)	0.19
Reactivity threshold (mg peanut protein)	46.2 (29.7, 72.0)	108.7 (29.3, 402.9)	32.1 (22.0, 46.9)	93.3 (40.0, 222.4)	**0.01**[##]	75.9 (33.1, 173.8)	0.63

MMD, subjects who reached the maximum maintenance dose; IMD, subjects who reached the individual maintenance dose; SPT, skin prick test; Ig, immunoglobulin; BAT, basophil activation test; CAPT, conjunctival allergen provocation test; LOAEL, lowest observed adverse effect level; OIT, oral immunotherapy; DBPCFC, double-blind placebo-controlled food challenge.

Variables are given as geometric mean (95% CI) or n (%), except age which is given as median (min, max).

Bold values are statistically significant (P < 0.05).

One-way ANOVA was applied to determine statistically significant differences between group means and the Dunnett's post hoc test to confirm which groups differed.

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers[27,28] ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms)[42] ranging from 1 to 5.

LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective symptoms.

Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC, with at least two moderate objective symptoms in one or more organ systems according to Bock's criteria.[24–26]

[a]Atopic disease includes asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis.

[b]All food allergy including peanut and tree nut allergy.

[c]Hazelnut, almond, cashew nut, pistachio nut, walnut, pecan nut, brazil nut and macadamia nut.

[d]Fenugreek, soya bean, pea, red kidney bean, lupin seed and wheat.

[e]The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

#Statistically significant difference between MMD and discontinued.

##Statistically significant difference between MMD and IMD.

TABLE 2 Characteristics of children who discontinued oral immunotherapy without reaching a maintenance dose

Patient no.	Age years	Peanut sIgE kUA/L	Ara h 2 sIgE kUA/L	LOAEL mg peanut protein	Reactivity threshold mg peanut protein	Dose at discontinuation mg peanut protein	Reason for discontinuation mg peanut protein
1	8.8	93.2	82.7	110.8	110.8	5	Social
2	11.3	493.0	221.0	35.8	35.0	5	AEs
3	14.3	26.2	14.6	110.8	243.0	450	AEs
4	15.1	179.0	77.0	13.0	13.0	10	AEs
5	14.8	951.0	457.0	443.0	943.0	45	AEs
6	6.5	63.9	32.4	43.0	43.0	20	Distaste
7	10.9	271.0	158.0	43.0	43.0	350	AEs
8	13.8	2311.0	475.0	43.0	43.0	45	AEs
9	11.7	114.0	87.4	3.0	43.0	1000	Distaste
10	10.1	629.0	179.0	3.0	13.0	20	AEs
11	9.8	352.0	210.0	13.0	143.0	1	Social
12	5.4	0.6	0.8	143.0	443.0	1	Social
13	7.3	92.8	61.6	143.0	943.0	65	AEs
14	11.6	285.0	131.0	13.0	443.0	5	AEs

AEs, adverse events; LOAEL, lowest observed adverse effect level.

were the cause of OIT discontinuation in 55% of our children (three with anaphylaxis and two with dyspeptic symptoms), in line with pooled data of three OIT studies including 104 children in which 20% discontinued treatment mostly due to AEs (65%) and logistic reasons (35%).[21]

Our finding that 13.9% of the doses elicited mild AEs is in line with previously published OIT studies,[10,32] including the 13.5% AEs reported in the STOP II study[10] of 99 children with allergy severity ranging from a mild allergic reaction in one organ system (24.2%) to severe respiratory symptoms (5.1%). Our children most frequently reported GI-related AEs including oral itching and stomach ache in line with previous studies,[21,30–32] as well as effect of oral antihistamines if simultaneous dyspeptic symptoms were absent.[10] Dyspepsia, reported by eight (14%) of our children, may be a symptom of OIT-related eosinophilic oesophagitis (EoE),[21,33] estimated to develop in 2.7% undergoing OIT.[32,33] In two children, OIT was discontinued due to dyspepsia, while three of the four children treated with PPI became asymptomatic and the fourth reported decreasing symptoms. Mild AEs occurred significantly more often during the first two days of each up-dosing period and in the first third of the dose steps, as previously described.[10]

The reported 0.6% of moderate AEs is somewhat lower than the 2.6% objective AEs reported in a German study of 23 children highly sensitized to peanut.[9] This may be explained by the German study's use of a rush OIT protocol with a tailored starting dose reported to be associated with more AEs.[9,18] In contrast, anaphylactic events occurred in every fifth child in our study, which is significantly higher than in comparable peanut OIT studies with MMDs (range) 300-1400 mg peanut protein,[9,10,31] reporting no systemic reactions,[9] one anaphylactic event[10] or use of epinephrine once only.[31] Although the high proportion of children

who reacted with anaphylaxis throughout up-dosing was equally distributed by OIT dose, most anaphylactic reactions occurred at OIT doses above 300 mg of peanut protein and none among the controls. Recently, Baumert et al[34] showed that increasing the reactivity threshold from 100 to 300 mg reduced the risk of allergic reactions from accidental exposure by 95%. Hence, a high-dose OIT may not be clinically meaningful, but it remains unclear if a higher treatment dose is required to achieve SU. The patients in the TAKE-AWAY trial will be analysed for SU in follow-up studies. Nevertheless, even if children with anaphylaxis to peanut would benefit the most from a successful OIT,[13,14,18,35] it might be that the risk of severe systemic reactions outweighs the potential benefit of the treatment.[36,37]

Peanut sIgG$_4$/sIgE was significantly associated with reaching MMD with an absolute OR value almost similar to the nonsignificant OR for reaching any maintenance dose. Hence, the clinical value of this biological marker in predicting MMD versus any maintenance dose is limited. The lack of a significant association between AEs, LOAEL, peanut sIgE/total IgE ratio and the sIgE to peanut and Ara h 2, and reaching maintenance dose may be explained by distaste for peanuts being the main reason for not reaching MMD as well as the limited sample size.

4.1 | Strengths and limitations

To our knowledge, the TAKE-AWAY children had sIgE to peanut higher and LOAELs lower than in previous OIT trials[8–11,13,21,30,31] with more than half of them experiencing anaphylaxis already at the LOAEL. These findings are in line with previously published reports that suggest an association with high sIgE to peanut and low LOAEL, and severity of allergic reactions.[38–41] All our children, older than in
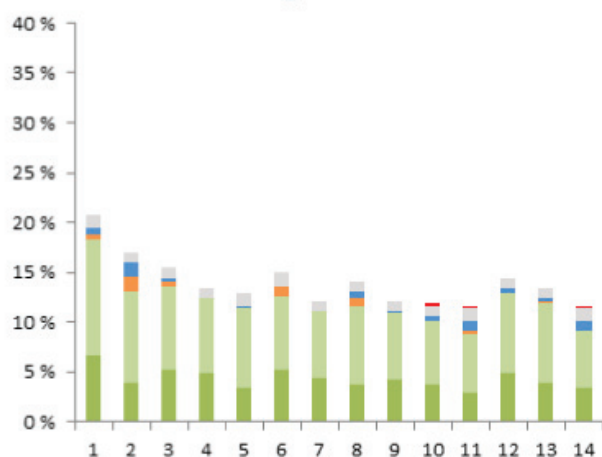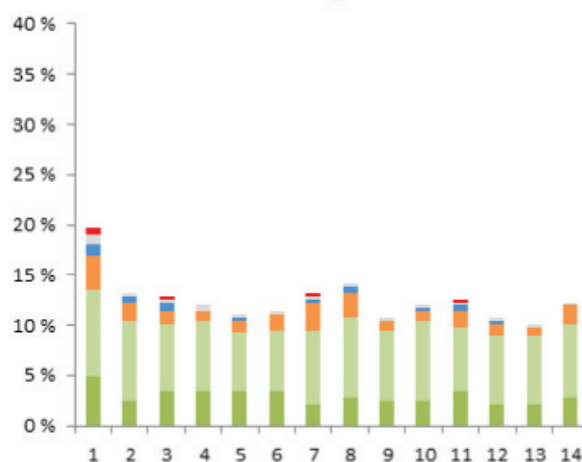
Dose-interval 1-65 mg
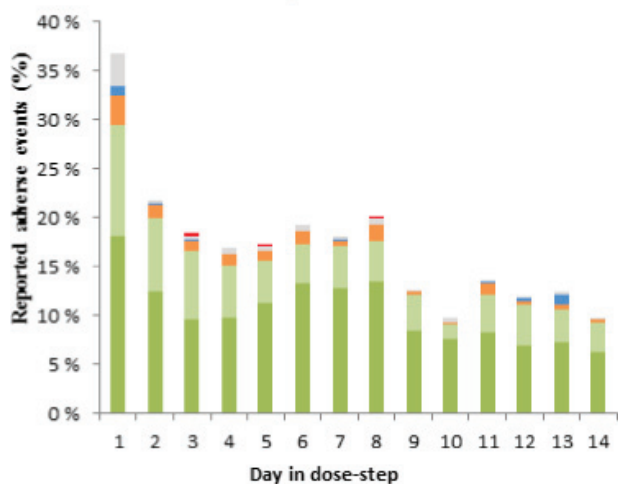
Dose-interval 66-800 mg

Reported adverse events between the three dose-intervals, overall $P = 0.03$,
with a statistically significant difference between dose-intervals 1-65 mg and 801-5000 mg peanut potein

Dose-interval 801-5000 mg

Reported adverse events on day 1-2 compared to day 3-8, $P = 0.001$

FIGURE 1 Reported doses with adverse events (AEs) per dose day (%) in the three dose intervals of the up-dosing phase. If there were another cycle of 14 days of the same dose step due to AEs or vacations in the same dose interval, this cycle would also be a part of the same dose interval, and the Y-axis would still represent reported doses with AEs per dose day (%). One-way ANOVA was applied to determine statistically significant differences between the intervals and the Dunnett's post hoc test to confirm which groups differed.

some,[9,13,17,30,31] but younger than in other[10,11] studies, reacted with anaphylaxis during the pre-OIT DBPCFC, which may be explained by most of our children having a history of anaphylaxis to peanut as well as not defining the food challenge positive until the occurrence of two objective symptoms. Some studies[10] define a food challenge positive already by the occurrence of reproducible subjective symptoms as suggested in the PRACTALL guidelines,[25] and one cannot rule out that an anaphylaxis would occur if another dose was given. Calculating the objective LOAEL enables comparison between studies.[22]

Switching ingestion of defatted flour to whole roasted peanuts at a wide range of doses (65-500 mg) may influence the efficacy of the OIT, as whole peanuts are more aromatic and were disliked. A placebo arm could have strengthened the study as distaste was the main reason for not reaching the MMD. However, this was regarded un-ethical based on the unfavourable ratio of treatment burden to expected benefit in the placebo group. A blinded vehicle to our high-dose peanut OIT also seemed unfeasible.

An OFC after up-dosing phase would have been preferable, but was not repeated for ethical reasons.

TABLE 3 Adverse events (AEs) related to oral immunotherapy in children highly allergic to peanut

	Total patients receiving OIT (n = 57) (doses = 18 470)	Patients reaching MMD (n = 12) (doses = 5292)	Patients reaching IMD (n = 31) (doses = 11 536)	Patients discontinuedOIT (n = 14) (doses = 1642)
Total AEs				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2560 (13.9)	290 (5.5)	1957 (17.0)	313 (19.1)
Mild AEs, total				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2473 (13.4)	290 (5.5)	1725 (15.0)	515 (31.4)
Moderate AEs				
Patients, n (%)	22 (38.6)	4 (33.3)	14 (45.2)	4 (28.6
Events, n (%)	116 (0.6)	21 (0.4)	81 (0.7)	14 (0.9)
Oral itching				
Patients, n (%)	49 (86.0)	10 (83.3)	28 (90.3)	11 (78.6)
Events, n (%)	1096 (5.9)	173 (3.3)	822 (7.1)	79 (4.8)
GI-related AEs[a]				
Patients, n (%)	48 (84.2)	7 (58.3)	27 (87.1)	13 (92.9)
Events, n (%)	1100 (6.0)	31 (0.6)	959 (8.3)	110 (6.7)
Skin-related AEs				
Patients, n (%)	43 (75.4)	9 (75.0)	27 (87.1)	7 (50.0)
Events, n (%)	140 (0.8)	26 (0.5)	95 (0.8)	71 (4.3)
Respiratory-related AEs				
Patients, n (%)	37 (64.9)	10 (83.3)	19 (61.3)	8 (57.1)
Events, n (%)	59 (0.3)	10 (0.2)	31 (0.3)	18 (1.0)
Anaphylaxis				
Patients, n (%)	11 (19.3)	2 (16.7)	5 (16.1)	4 (28.6)
Events, n (%)	11 (0.06)	2 (0.04)	5 (0.04)	4 (0.24)
Anaphylaxis severity grade: Sampson, median (min, max)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
Used epinephrine				
Patients, n (%)	6 (10.5)	2 (16.7)	2 (6.5)	2 (14.3)
Events, n (%)	6 (0.03)	2 (0.04)	2 (0.02)	2 (0.12)
Used acute salbutamol[b]				
Patients, n (%)	5 (8.8)	1 (8.3)	2 (6.5)	2 (7.1)
Events, n (%)	5 (0.03)	1 (0.02)	3 (0.03)	2 (0.1)

AEs, adverse events; MMD, subjects who reached the maximum maintenance dose; IMD, subjects who reached the individual maintenance dose.
Percentages were based on the number of patients in each group, stratified by reaching maximum maintenance dose (MMD), a lower individual maintenance dose (IMD) or discontinuing treatment. Patients were counted once per category.
Grading of OIT-related AEs was in line with the modified Bock's criteria by Sampson et al[24,25,43]
[a]Except oral itching.
[b]In relation to OIT AEs.

5 | CONCLUSION

In children highly allergic to peanut and reacting with anaphylaxis at baseline food challenge, reaching a high MMD of 5000 mg peanut protein was feasible for every fifth child. More than half of the children rather stopped at the lower IMD, mainly due to distaste for peanuts. Every fifth child experienced an anaphylactic adverse event, which questions the safety of OIT for these patients.

TABLE 4 Possible factors that could explain the feasibility of reaching maintenance dose using bivariate logistic regression analyses

	Reached MMD or IMD (n = 43)	P-value	Reached MMD (n = 12)	P-value
Parent education (graded 1 (low)-5 (high))	1.25 (0.95, 1.66)	0.12	0.95 (0.70, 1.30)	0.77
Siblings	1.04 (0.43, 2.53)	0.94	0.83 (0.32, 2.12)	0.69
Male sex	2.55 (0.72, 9.10)	0.15	0.80 (0.23, 2.82)	0.73
Current asthma	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Allergic rhinitis	2.14 (0.46, 10.03)	0.33	2.55 (0.67, 9.63)	0.17
Peanut SPT (mm)	0.95 (0.86, 1.05)	0.31	0.94 (0.82, 1.08)	0.40
sIgE (kUA/L)				
Peanut	1.00 (1.00, 1.00)	0.07	1.00 (1.00, 1.00)	0.42
Ara h 2	1.00 (0.99, 1.00)	0.07	1.00 (0.99, 1.00)	0.57
Peanut sIgE/total IgE (kUA/L)	0.10 (0.01, 1.08)	0.06	0.44 (0.03, 5.87)	0.53
Peanut $sIgG_4$/sIgE (ng/mL)	1.01 (0.99, 1.03)	0.45	1.02 (1.00, 1.04)	**0.02**
BAT ($\%CD63^+$)[a]	0.99 (0.96, 1.03)	0.98	0.99 (0.96, 1.03)	0.66
CAPT positive (dilution)	1.36 (0.76, 2.40)	0.30	1.55 (0.83, 2.89)	0.17
Anaphylaxis severity				
Modified EAACI	1.35 (0.38, 4.74)	0.64	0.36 (0.10, 1.32)	0.12
LOAEL (mg)	1.00 (1.00, 1.00)	0.99	1.00 (1.00, 1.01)	0.08
During up-dosing				
AEs[a] (days/period/child)	0.80 (0.64, 1.01)	0.06	0.69 (0.39, 1.20)	0.18
Anaphylaxis (days/period/child)	1.83 (0.42, 79.71)	0.75	1.86 (0.25, 136.35)	0.78
Asthma medication (yes/no)	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Postponements (total)	1.46 (0.88, 2.42)	0.14	0.87 (0.55, 1.38)	0.55
Dose reductions (total)	3.00 (0.34, 26.60)	0.32	1.40 (0.17, 11.24)	0.75

SPT, skin prick test; IgE/G/G_4, immunoglobulin E/G/G_4; BA, basophil activation; CAPT, conjunctival allergen provocation test; OIT, oral immunotherapy; DBPCFC, double-blind placebo-controlled food challenge; LOAEL, lowest observed adverse effect level; AEs, adverse events.
Associations are given as odds ratio (OR) (95% CI).
Bold values are statistically significant ($P < 0.05$).
Parent education: 1 – primary school; 2 – secondary school; 3 – high school; 4 – college/university ≤ 3 years; 5 – college/university > 3 years N = 57 children randomized to active peanut OIT in the TAKE-AWAY trial.
The right column presents reaching any maintenance dose (MMD (5000 mg peanut protein) + IMD (<5000 mg)) compared with children who discontinued OIT. The left column presents reaching the MMD compared with children not reaching MMD (eq. IMD + discontinued).
[a]N = 50. The BAT was not performed in five children due to technical causes (n = 5), and nonresponders were excluded from the analyses (n = 2).

CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

ORCID

Tonje Reier-Nilsen http://orcid.org/0000-0001-8184-0607
Karin C. Lødrup Carlsen http://orcid.org/0000-0002-9257-1198

REFERENCES

1. Venter C, Hasan Arshad S, Grundy J, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy*. 2010;65:103-108.

2. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol*. 2015;135:1257-1266.

3. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191-193.

4. Yu JW, Kagan R, Verreault N, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol*. 2006;118:466-472.

5. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol*. 2003;14:378-382.

6. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65:238-244.

7. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy*. 2000;30:1135-1143.

8. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133:468-475.

9. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol*. 2010;126:83-91.

10. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet*. 2014;383 (9925):1297-1304.

11. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol*. 2014;133:500-510.

12. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol*. 2009;124:292-300.

13. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127:654-660.

14. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73:799-815.

15. Incorvaia C, Frati F, Puccinelli P, Riario-Sforza GG, Dal Bo S. Dose dependence of efficacy and safety of subcutaneous immunotherapy. *Monaldi Arch Chest Dis*. 2006;65:41-43.

16. Calderon MA, Larenas D, Kleine-Tebbe J, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. *Allergy*. 2011;66:1345-1359.

17. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173-181.

18. Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. *Allergy*. 2009;64:1218-1220.

19. Dubois AEJ, Turner PJ, Hourihane J, et al. How does dose impact on the severity of food-induced allergic reactions, and can this improve risk assessment for allergenic foods?: Report from an ILSI Europe Food Allergy Task Force Expert Group and Workshop. *Allergy*. 2018;73:1383-1392.

20. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71:1241-1255.

21. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol*. 2017;139:882-888.

22. Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, et al. Predicting reactivity threshold in children with anaphylaxis to peanut. *Clin Exp Allergy*. 2017;48:415-423.

23. Lindvik H, Lodrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy*. 2017;47:785-794.

24. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol*. 1988;82:986-997.

25. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260-1274.

26. Niggemann B. When is an oral food challenge positive? *Allergy*. 2010;65:2-6.

27. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62:857-871.

28. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025.

29. Vetander M, Helander D, Lindquist C, et al. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol*. 2011;22:369-373.

30. Kukkonen AK, Uotila R, Malmberg LP, Pelkonen AS, Makela MJ. Double-blind placebo-controlled challenge showed that peanut oral immunotherapy was effective for severe allergy without negative effects on airway inflammation. *Acta Paediatr*. 2017;106:274-281.

31. Bird JA, Spergel JM, Jones SM, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. *J Allergy Clin Immunol Pract*. 2017;6:476-485.

32. Anagnostou K. Recent advances in immunotherapy and vaccine development for peanut allergy. *Ther Adv Vaccines*. 2015;3:55-65.

33. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014;113:624-629.

34. Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. *J Allergy Clin Immunol Pract*. 2018;6:457-465.

35. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy*. 2011;41:1273-1281.

36. Bindslev-Jensen C, Briggs D, Osterballe M. Can we determine a threshold level for allergenic foods by statistical analysis of published data in the literature? *Allergy*. 2002;57:741-746.

37. Nowak-Węgrzyn A, Sampson HA. Future therapies for food allergies. *J Allergy Clin Immunol*. 2011;127:558-573.

38. Santos AF, Du Toit G, Douiri A, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol*. 2015;135:179-186.

39. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy*. 2013;68:190-194.

40. Song Y, Wang J, Leung N, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of

oral food challenges. *Ann Allergy Asthma Immunol.* 2015;114:319-326.

41. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol.* 2010;21(4 Pt 1):603-611.

42. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics.* 2003;111(6 Pt 3):1601-1608.

43. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol.* 2009;6(Suppl):S365-S383.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Reier-Nilsen T, Michelsen MM, Lødrup Carlsen KC, et al. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy. *Allergy*. 2018;00:1–12. https://doi.org/10.1111/all.13604

Paper #3

1 **Parent and child perspective of quality of life in a randomized controlled peanut oral**
2 **immunotherapy trial.**

3

4 Tonje Reier-Nilsen[1,2], Karin C. Lødrup Carlsen[1,2], Merethe Melbye Michelsen[1,2], Sebastian

5 Drottning[1], Kai-Håkon Carlsen[1,2], Chi Zhang[3], Magnus P. Borres[4,5] and Geir Håland[1,2].

6 **Affiliations**: [1]Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo,

7 Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of

8 Biostatistics, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo,

9 [4]Thermo-Fisher Scientific, Uppsala, Sweden, [5]Department of Women's and Children's

10 Health, Uppsala University, Uppsala, Sweden.

11 The study was performed within the ORAACLE (Oslo Research group of Asthma and

12 Allergy in Children; the Lung and Environment), Oslo University Hospital and the University

13 of Oslo.

14 **Correspondence to**: Dr Tonje Reier-Nilsen, Address: Oslo University Hospital, Division of

15 Pediatrics and Adolescent Medicine Ullevål, Postboks 4956 Nydalen, 0424 Oslo, Norway,

16 Tel: + 47 99 70 90 50, Fax: + 47 22 11 86 63, E-mail: tonjre@ous-hf.no,

17 tonje.nilsen@medisin.uio.no

18 **Short title**: Quality of life at Y_2 in the TAKE-AWAY trial

19 **Word count summary**: 247

20 **Word count manuscript body excluding tables/figures**: 2496

21 **Numbers of tables/figures**: 5

22 **Key words:**

23 Child, Desensitization, Double-blind placebo controlled food challenge, Oral Immunotherapy,

24 Peanut allergy, Perceived treatment burden, Self- and proxy-reports, Quality of life, Visual

25 analogue scale

33 **What is already known about this topic?**

34 The improved quality of life (QoL) observed in children with peanut allergy are

35 predominantly based on parents' assessment. Discrepancies between the children's and the

36 parents' assessments of the children's QoL may impact the use of patient-reported outcomes

37 (PROs) in oral immune therapy (OIT).

38 **What does this article add to our knowledge?**

39 The present randomized controlled peanut OIT study includes child self-reports and parental

40 proxy-reports to assess QoL. Compared with the children's reports, parents reported a two-

41 fold increase in their children's QoL from before to after two years of OIT, and the improved

42 QoL was significantly associated with OIT for these parental proxy-reports only.

43 **How does this study impact on current management guidelines?**

44 Evaluation of OIT efficacy based upon PROs may be more appropriate using the child-

45 reported rather than the parents' proxy-reported QoL which may over-estimate improvement

46 in QoL with this treatment.

47 **Abbreviations**:

48 AEs – adverse events

49 BAT – basophil activation test

50 CAPT – conjunctival allergen provocation test

51 %CD63+ - allergen induced basophil reactivity (proportion of activated basophils)

52 CI – confidence interval

53 DBPCFC – double blind placebo controlled food challenge

54 FAQL-PB - Food Allergy Quality of Life – Parental Burden

55 GI – gastro-intestinal

56 s-IgE/s-IgG/s-IgG$_4$ – specific Immunoglobulin E, G, G$_4$

57 OFC – oral food challenge

58 OIT - oral immunotherapy

59 PedsQL 4.0 - Pediatric Quality of Life Inventory Version 4.0

60 PRO – Patient-related outcome

61 QoL – quality of life

62 SPT – skin prick test

63 SU – sustained unresponsiveness

64 TAKE-AWAY trial – The "Take-Away food allergy; inducing tolerance in children allergic

65 to peanut" trial

66   VAS – visual analogue scale

67   Y_0 – at screening (enrolment)

68   Y_1 – at completed up-dosing, approximately after 1 year of treatment, 1 year for controls

69   Y_2 – at one year of maintenance treatment/after 2 years of treatment

70

71 **SUMMARY**

72 **Background**

73 Improved quality of life (QoL) after oral immunotherapy (OIT) in peanut allergic children is

74 often reported by their parents, while the child's perspective is less clear.

75 **Objective**

76 We aimed to explore if two years of OIT improved QoL in children with peanut allergy and to

77 identify factors influencing change in QoL.

78 **Methods**

79 In the open labelled randomized controlled TAKE-AWAY peanut OIT trial, QoL was

80 assessed in 77 5-15 year-olds with anaphylaxis to peanuts. The children and their parents

81 fulfilled the Pediatric Quality of Life Inventory Version 4.0 at enrolment (Y_0) after one year

82 (end of up-dosing) (Y_1) and after two years (Y_2) of OIT (n=57) or observation only (n=20).

83 Perceived treatment burden was recorded by visual analogue scales, including adverse events

84 (AEs). An open food challenge (OFC) was performed at Y_2.

85 **Results**

86 At Y_2, 18 children had discontinued OIT, 2/39 OIT children refused OFC, while 35/37 were

87 desensitized to 7500 mg peanut protein. From Y_0 to Y_2, the child's mean change (95%

88 confidence intervals) in QoL was 4.4 (0.5, 8.3) by child self-report and twice as large by

89 parental proxy-report (9.3 (4.3, 14.3)) (both p<0.0001), with no significant improvement in

90 the 20 controls. The change in QoL was significantly associated with OIT for the parental

91 proxy-reports only (p=0.002). Neither treatment burden nor AEs significantly predicted

92 changes in QoL.

93 **Conclusion**

94   Two years of OIT improved child QoL as reported by parents, but not by the children,

95   suggesting that parents may over-estimate improvement in child QoL by OIT.

96 **INTRODUCTION**

97 Peanut oral immunotherapy (OIT) appears promising for inducing desensitization (no allergic

98 reaction while regularly exposed to the allergen) (1-5), which is the first step to sustained

99 unresponsiveness (SU) after OIT discontinuation. In line with recommendations,

100 measurements of treatment effect should include patient-reported outcomes (PROs) (6) such

101 as QoL assessments including physical, emotional (or psychological) and social domains.

102 Improved QoL has been reported in children after OIT (1, 7-12) despite adverse events (AEs)

103 (13). Most studies on QoL during OIT are based on parents' assessments of their child's QoL

104 (1, 7-10), sometimes referred to as proxy-reports (14, 15), while a recent study showed that

105 parents of 122 0–18 years old children with peanut, hazelnut or egg allergy assessed their

106 children's QoL better than did the children themselves (16), questioning the appropriateness

107 of relying on parental proxy-reports alone. While one study demonstrated improved QoL after

108 OIT by both parental proxy-reports and child self-reports, the lack of a control group limited

109 the possibility to assess if this was due to the OIT (11). Information on one-dimensional PROs

110 using e.g. a visual analogue scale (VAS) of treatment burden is largely lacking.

111 Peanut OIT is projected soon to become available as a treatment for peanut allergy. However,

112 a recent editorial (17) raised concerns regarding OITs in children highly sensitized to peanuts

113 due to high risk of systemic AEs and distaste for peanuts and low feasibility of reaching a

114 high maintenance dose, based upon our ongoing 4-year peanut OIT; "Take-Away food

115 allergy: Inducing tolerance in children allergic to peanut" trial (the TAKE-AWAY trial) (18).

116 This open labelled randomized controlled trial has an overall objective to assess if four years

117 of OIT followed by one year without regular peanut exposure can induce SU in children with

118 primary peanut allergy. In the present study, we explored the effect of OIT on desensitization

119 and PROs reported by the children and their guardians. Our primary aim was to explore if

120 peanut OIT improved child QoL as reported by the parents and/or the children themselves.

121   Secondarily, we aimed to explore if factors including perceived treatment burden influenced

122   change in QoL from pre-treatment to second year of treatment. Finally, we aimed to explore if

123   ineligibility to OIT affected QoL one year later.

124   **METHODS**

125   *Study design*

126   As shown in supplement Figure 1, the TAKE-AWAY trial (5, 18) has four phases; screening

127   for eligibility (Y_0), the OIT up-dosing phase ending after 50-78 weeks (Y_1), 36 months

128   maintenance therapy with desensitization assessed after two years OIT (Y_2) and the follow-up

129   of 12 months with SU assessed at Y_5 (to be completed in 2020).

130   The present study reports QoL assessed at Y_0, Y_1 and Y_2. Children who discontinued

131   treatment were not assessed at subsequent time-points, while QoL was reassessed at Y_1 in the

132   19 OIT-ineligible children.

133   Children 5-15 years old with sensitization to peanut by a peanut skin prick test (SPT) ≥3 mm

134   and/or a specific IgE (s-IgE) to peanut ≥0.35 kUA/L or with a history of systemic reactions to

135   peanut were screened for study enrolment at the Department of Pediatric and Adolescent

136   Medicine, Oslo University Hospital, Ullevål, Norway from February 2014 to June 2015, as

137   previously described (18).

138   Enrolment further required a positive double-blind placebo-controlled food challenge

139   (DBPCFC) defined by at least two objective symptoms in one or more organ systems and a

140   reactivity threshold >3 mg peanut protein (18). Anaphylaxis was defined according to the

141   European Academy of Allergy and Clinical Immunology criteria (19). Children with a

142   reactivity threshold≤3 mg peanut protein were defined ineligible for randomization. Exclusion

143   criteria were non-controlled asthma or severe chronic disease including severe atopic eczema

144   and diabetes mellitus.

145   The screening investigations, described in detail in the online supplements included a

146   structured interview, standardized QoL questionnaires, serological and immunological

147   analyses, lung function measurements (predicted forced expiratory volume in one second

148   (FEV$_1$%) (20)), SPT and conjunctival allergen provocation test (CAPT) (21), followed by the

149   DBPCFC.

150   Randomization to active peanut OIT or controls (observation only) had a block-size of 2:1,

151   which restarted when the OIT starting dose was decreased (5) as described in the online

152   supplements and Supplement Table 1.

153   The OIT started with 1 mg or 5 mg followed by bi-weekly up-dosing up to the predefined

154   high maintenance dose of 5000 mg, as described in the online supplements (5).

155   The QoL assessments and all tests from the screening except the DBPCFC, were repeated in

156   all children at Y$_1$ and Y$_2$. Children undergoing OIT recorded perceived treatment burden in a

157   VAS form at Y$_1$ and Y$_2$.

158   At Y$_2$, desensitization was assessed by an open food challenge (OFC) with a maximum

159   cumulated dose of 7500 mg peanut protein, as described in details in the online supplement.

160   Written parental informed consent was obtained after detailed oral and written study

161   information.

162   The TAKE-AWAY trial was approved by the Regional Committee for Medical and Health

163   Research Ethics (number 2013/430) with regular communications in case of severe or

164   unexpected AEs, and registered at ClinicalTrials.gov (number NCT02457416).

165   *Study population*

166   As previously reported (5), 96 children (5-15 years of age) had a positive DBPCFC at Y$_0$ with

167   moderate objective symptoms in minimum two organ systems, and fulfilled the EAACI

168   criteria for anaphylaxis. Fifty-seven children were randomized to OIT and 20 to controls,

169   whereas 19 were defined ineligible for enrolment (Figure 1). The 77 children enrolled had

170   primary sensitization to peanut with a mean (95% CI) s-IgE to Ara h 2 of 103.0 (75.8, 130.3)

171   kUA/L. Baseline characteristics were not significantly different between children randomized

172   to OIT (n=57) or controls (n=20), except from significantly more children randomized to OIT

173   (p=0.03) needed adrenaline during DBPCFC (Table 1) (5). Of the 57 children randomized to

174   OIT, 43 completed Y_1 and 39 Y_2, while all 20 controls attended investigations at both Y_1 and

175   Y_2.

Quality of life measurements

177   Children completed the validated (14, 22) age-adapted (age 5-7, 8-12 and 13-18 years)

178   generic Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) consisting of 13 items

179   within four domains of functioning; physical, emotional, social and school. The PedsQL 4.0

180   applies a 5-point Likert scale (0=never, 4=almost always) for the 8-12 and 13-18 years

181   reports, and a simplified 3-point scale for the 5-7 years child reports.

182   Parents completed both the PedsQL 4.0 proxy-report as well as the Food Allergy Quality of

183   Life–Parental Burden (FAQL-PB) Questionnaire (23, 24) for parents' own QoL, both

184   described in online supplements.

Measurement of perceived treatment burden

186   A VAS-form was developed to obtain one-dimensional reports of perceived treatment burden

187   during the last 12 months within three domains: Gastro-intestinal (GI) related AEs (stomach

188   ache, nausea/vomiting and oral itching), taste and amount of daily peanut dose, and time spent

189   on OIT (up-dosing at hospital and ingestion of OIT doses at home) with details in the

190   supplementary material.

Outcomes and explanatory factors

192   The primary outcome was change in child-QoL scores from Y_0 to Y_2 reported by the children

193   themselves, the secondary outcome was the corresponding parental proxy-reported child QoL.

194   The level of desensitization was defined as the highest cumulated dose of peanut protein eaten

195   without eliciting allergic reactions corresponding to a positive Y_2 OFC.

196   Factors that potentially could influence the change in QoL included level of desensitization,

197   AEs, maintenance dose at Y_1 and personal perception of treatment burden (mean of the three

198   domains: GI-related AEs, taste/amount of peanuts and time spent on OIT) at Y_1 and Y_2.

Statistical analyses

200   Baseline characteristics are reported as geometric means with 95% confidence interval (95%

201   CI) or means (95% CI) for non-normal and normal distribution for continuous data,

202   respectively. Potential differences between groups were explored using the Mann-Whitney U

203   test for continuous data, and the chi-square test for categorical data.

204   Analyses in the present study were explorative, while the TAKE-AWAY study population

205   size was determined by statistical power analysis outlined in the online supplements,

206   indicating that a treatment group of 40 and a control group of 20 subjects would provide a

207   statistical power of 80% to observe a difference in SU at a five percent significance level

208   between the two groups.

209   The items in the PedsQL 4.0 were reverse-scored (0=100, 1=75, 2=50, 3=25, 4=0), as

210   recommended (22), reporting the mean sum of each item. To assess changes in QoL scores

211   from Y_0 to Y_2, we applied generalized repeated-measures linear mixed models with QoL score

212   at Y_0, age, gender, randomisation group, and Y_1 and Y_2 as independent variables, while

213   significant differences and changes between groups were assessed by Scheffe's test.

214   The changes in VAS from Y_1 to Y_2 were assessed using paired t-test.

215   As the normality assumptions for the multiple linear regression analysis not were fulfilled,

216   multivariate robust regression analyses with Huber's M-estimator and further description in

217   online supplements was used to assess associations between possible factors influencing QoL,

218   and change in QoL from Y_0 to Y_2.

219   Bivariate unadjusted analyses were performed with Spearman correlation analyses

220   (r_s=Spearman correlation coefficient).

221   P-value of ≤0.05 was considered statistically significant.

222   Randomization to OIT or controls was performed using Statistical Analysis System (SAS,

223   Version 9.3, SAS Institute Inc., Chapel Hill, NC, USA) and statistical analyses were

224   performed with the IBM Statistical Package for Social Sciences (IBM SPSS Statistics,

225   Version 23. Armonk, NY: IBM Corp).

226

227   **RESULTS**

228   By Y_2, 18/57 children had withdrawn from OIT (31.6%), with their baseline characteristics

229   given in Supplement Table 2, while all 20 controls attended Y_0, Y_1 and Y_2. The mean (SD)

230   daily maintenance dose of peanut protein was 3322 (1376) mg, ranging from 350-5000 mg.

231   The Y_2 OFC was refused by 2 of the remaining 39 OIT children due to fear of allergic

232   reactions. Among the 37 challenged children, tolerance to 7500 mg peanut protein was

233   confirmed in 35 (94.6%), as described further in the online supplements.

234   As shown in Figure 2, the children's self-reported mean (95% CI) QoL scores improved

235   significantly from Y_0 (82.1 (79.1, 85.2)) to Y_2 (86.7 (83.6, 89.7)) within the OIT group

236   (p<0.0001), whereas the QoL scores among controls did not change significantly from the

237   83.4 (75.4, 91.4) at Y_0 to 82.2 (76.0, 88.4) at Y_2 (p=0.80). However, the mean (95% CI) QoL

238   change of 4.4 (0.5, 8.3) from Y_0 to Y_2 in the OIT group was not significantly different from

239   the -0.9 (-7.9, 6.11) change observed among the controls (p=0.12) (Figure 2).

240   The parental proxy-reported mean (95% CI) QoL score of 88.0 (85.2, 90.8) at Y_2 was

241   significantly higher than the QoL score at Y_0 (78.7 (73.6, 83.7) (p<0.0001) in the OIT group,

242   while the corresponding QoL at Y_2 of 82.1 (75.8, 88.4) was similar to the QoL at Y_0 of 81.7

243   (74.6, 88.8) (p=0.90) among controls, as shown in Figure 2.

244   In contrast to the child-reports, the two-fold larger mean (95% CI) change in parents' proxy-

245   reported QoL of 9.3 (4.3, 14.3) in the OIT group was significantly different from the parental

246   proxy-reported change (0.4 (-7.1, 8.0)) (p=0.02) among the controls (Figure 2).

247   For OIT children, the change in QoL from Y_0 to Y_2 was not significantly associated with the

248   number of AEs in bivariate analyses, nor maintenance dose, any of the three perceived

249   treatment burden domains at Y_1 or Y_2 (Table 2). Nor was the level of desensitization

250   significantly associated with change in QoL in the final regression model (Table 3), as

251   outlined in details in the online supplements.

252   The parents' QoL reported by the FAQL-PB improved significantly among both the OIT

253   group and controls from Y_0 to Y_2 (Supplement Figure 3).

254   The QoL was similar among OIT ineligible children and controls at Y_0 and Y_1 (Supplement

255   Figure 4A), while the QoL of parents was significantly (p=0.048) poorer among parents of

256   ineligible compared with parents of control children at Y_1, despite being similar at Y_0

257   (Supplement Figure 4B).

258 **DISCUSSION**

259 By two years of OIT, 18 children had discontinued treatment, while most children with two

260 years of OIT were desensitized to 7500 mg peanut regardless of maintenance dose. The child-

261 reported QoL improvement after two years OIT was not significantly different between OIT

262 children and the controls, while the corresponding two-fold larger improvement in child-QoL

263 reported by the parents of OIT children was significantly larger than that reported by control

264 parents. Neither AEs nor perception of treatment burden reported by the children, level of

265 desensitization or maintenance dose significantly influenced the change in QoL. The QoL of

266 OIT ineligible children was similar to that of controls at enrolment and Y_1 while the QoL of

267 their parents was poorer after one year compared with control parents.

268 Our finding that parental proxy-reported, but not child self-reported QoL improved

269 significantly with two years of OIT compared to that of controls, is to the best of our

270 knowledge novel. In line with studies mostly based on parental proxy-reports (1, 7, 10, 12),

271 we observed significant improvement in child QoL with two years of treatment in both

272 parental proxy-report and the child self-report. However, the significant difference in child

273 QoL improvement reported by parents only in the OIT compared with control group, is likely

274 due to the two-fold larger improvement compared with child self-reports. In line with

275 discrepancies shown between child self-reported and parental proxy-reported QoL in children

276 with food allergies (16) and children undergoing OFCs (25), the QoL of our OIT parents

277 improved more than that of controls. Parents may thus respond more positively than their

278 children to lesser social restrictions (16) in line with improved desensitization. The larger

279 variation observed among the child-reports as well as the limited sample size may also

280 contribute to the non-significant differences in change in QoL between OIT children and

281 controls. However, our study size is comparable to previous studies on QoL in peanut OIT

282 (7-10, 12) and sufficiently large to identify significant larger improvement in the parental

283 proxy-reports of the OIT children compared with controls.

284 Neither perception of treatment burden, level of desensitization, maintenance dose nor AEs

285 influenced change in QoL from baseline to two years OIT, supported by the lack of

286 association between change in QoL and AEs shown previously (10, 16, 26). This suggests that

287 perceived treatment burden may be, at least partly disassociated from the number and severity

288 of AEs during OIT (10, 16).

289 ***Strength and limitations***

290 The study strengths include the standardized QoL assessments completed by children and

291 parents of both the OIT group and the controls, close follow-up and detailed information of

292 AEs and a VAS scale for child-assessment of treatment burden after one and two years of

293 OIT. Using VAS to report perceived treatment burden may improve our understanding of

294 patient perceived burden of OIT. The VAS was not pre-validated for the TAKE-AWAY trial,

295 but has previously been validated for pain and nausea (27).

296 Our results may be biased towards an overestimation of the positive effect on QoL by OIT, as

297 we unfortunately did not have the QoL assessment of the 23% of the OIT children

298 discontinued treatment, supporting our interpretation that peanut OIT did not significantly

299 improve child-reported QoL.

300

301   **CONCLUSION**

302   Among the two-thirds of children who completed two years of peanut OIT, QoL improved

303   compared with controls as reported by the parents, but not by the children themselves,

304   indicating that parents may over-estimate improvement in QoL by OIT.

305 **AUTHOR CONTRIBUTIONS**

313

314 **ACKNOWLEDGEMENTS**

324 **REFERENCES**

325 1.   Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral
326 immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised
327 controlled trial. Lancet. 2014;383(9925):1297-304.
328 2.   Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral
329 peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126(1):83-
330 91 e1.
331 3.   Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized
332 controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the
333 allergic response. J Allergy Clin Immunol. 2011;127(3):654-60.
334 4.   Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and
335 immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124(2):292-300,
336 .e1-97.
337 5.   Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et
338 al. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy.
339 Allergy. 2018.
340 6.   Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era
341 in clinical research. Perspect Clin Res. 2011;2(4):137-44.
342 7.   Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK, team Ps. The longitudinal
343 impact of Probiotic and Peanut Oral Immunotherapy (PPOIT) on health related quality of life (HRQL).
344 Allergy. 2017.
345 8.   Kamilaris JS SP, Kulis MD, Edie AH, Vicekry PB, Burks AW. Participation in peanut oral
346 immunotherapy improves quality of life. J Allergy Clin Immunol. 2012;129(Abs):AB29-110.
347 9.   Otani IM, Begin P, Kearney C, Dominguez TL, Mehrotra A, Bacal LR, et al. Multiple-allergen
348 oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. Allergy
349 Asthma Clin Immunol. 2014;10(1):25.
350 10.   Rigbi NE, Goldberg MR, Levy MB, Nachshon L, Golobov K, Elizur A. Changes in patient quality
351 of life during oral immunotherapy for food allergy. Allergy. 2017.
352 11.   Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to
353 peanut on food-specific quality of life. Ann Allergy Asthma Immunol. 2012;109(5):348-52 e2.
354 12.   Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G, et al. Efficacy,
355 safety, and quality of life in a multi-center, randomized, placebo-controlled trial of low-dose peanut
356 oral immunotherapy in peanut allergic children. The journal of allergy and clinical immunology In
357 practice. 2018.
358 13.   Virkud YV, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline
359 predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin
360 Immunol. 2017;139(3):882-8 e5.
361 14.   Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health
362 measure: feasibility, reliability, and validity. Ambulatory pediatrics : the official journal of the
363 Ambulatory Pediatric Association. 2003;3(6):329-41.
364 15.   Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden
365 of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic
366 children. Clin Exp Allergy. 2000;30(8):1135-43.
367 16.   Stensgaard A, Bindslev-Jensen C, Nielsen D, Munch M, DunnGalvin A. Quality of life in
368 childhood, adolescence and adult food allergy: Patient and parent perspectives. Clin Exp Allergy.
369 2017;47(4):530-9.
370 17.   Bluemchen K. ET. Oral peanut immunotherapy - How much is too much? How much is
371 enough? Allergy. 2018.
372 18.   Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen KH, Mowinckel P, Nygaard UC, et
373 al. Predicting reactivity threshold in children with anaphylaxis to peanut. Clin Exp Allergy. 2017.

374   19.   Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al.
375 EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy.
376 2014;69(8):1008-25.
377   20.   Alois Z. Lung function in children and adolescents; methods, reference values. 1987.
378   21.   Lindvik H, Lodrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH.
379 Conjunctival provocation test in diagnosis of peanut allergy in children. Clin Exp Allergy. 2017.
380   22.   Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life
381 Inventory version 4.0 generic core scales in healthy and patient populations. Medical care.
382 2001;39(8):800-12.
383   23.   Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to
384 measure quality of life in families with a child with food allergy. J Allergy Clin Immunol.
385 2004;114(5):1159-63.
386   24.   Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G, et al. Validation of the
387 Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). Pediatr Allergy Immunol.
388 2013;24(3):288-92.
389   25.   Kansen HM, Le TM, Meijer Y, Flokstra-de Blok BMJ, Welsing PMJ, van der Ent CK, et al. The
390 impact of oral food challenges for food allergy on quality of life: A systematic review. Pediatr Allergy
391 Immunol. 2018;29(5):527-37.
392   26.   Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food
393 allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol.
394 2006;96(3):415-21.
395   27.   Lara-Munoz C, De Leon SP, Feinstein AR, Puente A, Wells CK. Comparison of three rating
396 scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled
397 auditory stimuli. Arch Med Res. 2004;35(1):43-8.
398   28.   Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of
399 anaphylaxis in childhood: position paper of the European academy of allergology and clinical
400 immunology. Allergy. 2007;62(8):857-71.
401   29.   Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601-8.
402   30.   Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance
403 induction in severe peanut allergy. Allergy. 2009;64(8):1218-20.
404   31.   Position paper: Allergen standardization and skin tests. The European Academy of
405 Allergology and Clinical Immunology. Allergy. 1993;48(14 Suppl):48-82.
406   32.   Vetander M, Helander D, Lindquist C, Hedlin G, Alfvén T, Ostblom E, et al. Classification of
407 anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. Pediatr
408 Allergy Immunol. 2011;22(4):369-73.
409   33.   Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-
410 controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol.
411 1988;82(6):986-97.
412   34.   Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al.
413 Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy,
414 Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus
415 report. J Allergy Clin Immunol. 2012;130(6):1260-74.
416   35.   Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work Group
417 report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl):S365-83.
418   36.   Reinfjell T, Diseth TH, Veenstra M, Vikan A. Measuring health-related quality of life in young
419 adolescents: reliability and validity in the Norwegian version of the Pediatric Quality of Life Inventory
420 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2006;4:61.
421   37.   Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal
422 clinically important difference. Control Clin Trials. 1989;10(4):407-15.
423   38.   Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of
424 peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment.
425 J Allergy Clin Immunol. 2015;135(5):1257-66 e1-2.

426   39.   Hosmer DWaL, S. . Applied logistic regression , 2.ed., John Wiley & sons New York, USA. 2000

427   40.   Niggemann B. When is an oral food challenge positive? Allergy. 2010;65(1):2-6.

428

429   **Table 1.** Baseline characteristics of children randomized to peanut OIT or controls, and

430   children ineligible for enrolment.

	Active (n = 57)	Controls (n = 20)	Ineligible (n = 19)	Overall p-value
Age	9.3 (5.2, 15.2)	9.3 (5.1, 13.3)	10.9 (5.6, 14.6)	0.08
Male	31 (54.4)	13 (65.0)	6 (31.6)	0.10
History of systemic reaction to peanut	45 (8.9)	18 (90.0)	17 (89.5)	0.55
Current asthma	24 (42.1)	9 (45.0)	11 (57.9)	0.47
Allergic rhinitis	15 (26.3)	8 (40.0)	5 (26.3)	0.83
Atopic dermatitis	47 (82.5)	14 (73.9)	13 (68.4)	0.40
Allergy to tree-nuts	20 (35.1)	7 (36.8)	9 (53.0)	0.37
Allergy to other food than nuts	27 (47.4)	11 (57.9)	11 (61.1)	0.57
Parental atopic disease*	50 (87.7)	16 (80.0)	17 (89.5)	0.84
Parental food allergy**	21 (36.8)	6 (30.0)	11 (57.9)	0.17
FEV1% predicted	101.2 (97.6, 105.0)	95.5 (88.3, 107.2)	93.3 (85.8, 102.3)	0.15
Pos s-IgE ($\geq$ 0.35 kUA/L):				
tree-nuts***	52 (91.2)	16 (80.0)	19 (100.0)	0.07
other food****	54 (94.7)	19 (95.0)	19 (100.0)	0.65
Peanut SPT (mm)	9.8 (8.6, 11.0)	9.3 (7.4, 11.7)	9.8 (8.2, 12.1)	0.97
S-IgE (kUA/L):				
Peanut	110.6 (70.4, 173.8)	52.2 (20.3, 134.4)	128.8 (74.1, 218.8)	0.34
Ara h 2	56.2 (37.2, 87.1)	22.4 (8.4, 58.9)	63.6 (38.0, 102.3)	0.13
Peanut s-IgE/total IgE (kUA/L)	0.3 (0.2, 0.4)	0.2 (0.1, 0.4)	0.3 (0.2, 0.5)	0.39
Peanut s-IgG$_4$/s-IgE (ng/ml)	117.5 (82.9, 165.9)	97.7 (46.3, 208.8)	104.7 (42.4, 263.0)	0.39
QoL child self-report	82.1 (79.1, 85.2)	83.4 (75.4, 91.4)	81.8 (75.8, 87.7)	0.81
QoL parental proxy-report	79.8 (76.3, 83.3)	80.7 (73.6, 87.7)	80.0 (69.6, 90.4)	0.62
Baseline DBPCFC: Anaphylaxis severity grade:				
modified EAACI	1.6 (1.4, 1.7)	1.7 (1.5, 2.0)	1.7 (1.5, 1.7)	0.50
Sampson	2.6 (2.4, 2.8)	2.8 (2.5, 3.2)	1.8 (1.5, 2.0)	0.25
Use of adrenaline	30 (52.6)	5 (25.0)	8 (42.1)	0.10

LOAEL (mg peanut prot (ppt))	18.4 (11.8, 28.6)	16.6 (6.2, 44.7)	NA	0.34
Reactivity threshold (mg ppt)	46.2 (29.7, 72.0)	75.9 (33.1, 173.8)	NA	0.06

431 Continuous variables are given as geometric mean (95 % CI) or n (%), except age which is
432 given as median (min, max) and QoL which is given as mean (95 % CI).
433 One-way ANOVA was applied to determine statistically significant differences between
434 group means.
435 Chi-square test was applied to determine statistically differences between categorical data.
436 Significant differences are shown in bold.
437 *Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic
438 conjunctivitis.
439 **All food allergy including peanut and treenut allergy.
440 ***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and
441 macadamianut.
442 ****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat.
443
444 Ineligible children had a reactivity threshold of 3 mg peanut protein or less.
445
446 Anaphylaxis severity was graded by two grading systems according to the modified EAACI
447 position papers (19, 28) ranging from 1 to 3 and the method of Sampson (Grading of Food-
448 Induced Anaphylaxis According to Severity of Clinical Symptoms) (29) ranging from 1 to 5.
449 Reactivity threshold was defined as the cumulated peanut protein (mg) ingested at positive
450 DBPCFC.
451
452 Quality of life scores was given by the generic Pediatric Quality of Life Inventory Version 4.0
453 (PedsQL 4.0) (14, 22).
454
455 SPT, skin prick test; Ig - immunoglobulin; LOAEL - lowest observed adverse effect level;
456 OIT – oral immunotherapy; DBPCFC – double blind placebo controlled food challenge;
457 LOAEL - lowest observed adverse effect level (amount of peanut eliciting mild, objective
458 symptoms); QoL – quality of life
459

Table 2. The perceived treatment burden is given at Y_1 (after up-dosing) and Y_2 (after one year of maintenance treatment) as mean values with 95% confidence intervals among all children randomised to OIT.

	One year of treatment (Y_1) (N=43)	Two years of treatment (Y_2) (N=37)	p-value
Overall	3.9 (3.1, 4.8)	3.7 (2.9, 4.6)	0.84
GI-domain	2.6 (1.9, 3.3)	1.4 (1.0, 1.8)	0.001
Oral itching	3.4 (2.5, 4.4)	2.1 (1.3, 2.9)	0.02
Stomach ache	2.6 (1.7, 3.5)	1.4 (0.8, 2.0)	0.008
Nausea or vomiting	1.6 (0.8, 2.5)	0.6 (0.3, 0.9)	0.02
Taste-/amount-domain	6.5 (5.5, 7.3)	5.3 (4.3, 6.3)	0.02
Taste	7.0 (5.9, 8.0)	6.1 (4.9, 7.3)	0.10
Amount	5.8 (4.8, 6.7)	4.3 (3.3, 5.2)	0.01
Time spent-domain	2.9 (2.1, 3.7)	2.2 (1.5, 2.9)	0.06
at home	2.5 (1.6, 3.4)	2.5 (1.5, 3.6)	0.94
at hospital (up-dosing/visits)	3.0 (2.2, 3.)	1.7 (1.2, 2.3)	0.005

Unpaired t-test was applied to determine statistically significant difference between means at Y_1 and Y_2.

The GI-domain represents average of how AEs like stomach ache, nausea/vomiting and oral itching are perceived.
The taste-/amount-domain represents average of perceived taste and amount of peanut eaten.
The time spent-domain represents perceived average of time spent on eating OIT doses at hospital for up-dosing visits and at ingesting OIT doses at home.

472 **Table 3.** Multivariate robust regression analyses for associations between factors that may

473 influence change in quality of life from screening (Y_0) to second year of treatment (Y_2).

474

	PedsQL 4.0 child	p-value	PedsQL 4.0 parents	p-value	FAQLPB (parents)	p-value
Age	-0.49 (-2.17, 1.19)	0.56	1.50 (0.24, 3.23)	0.09	0.02 (-0.06, 0.10)	0.63
Gender	-8.90 (-18.55, 0.76)	0.07	-5.90 (-16.29, 4.50)	0.26	0.23 (-0.25, 0.71)	0.34
Maintenance dose (mg)	-0.00 (-0.01, 0.00)	0.48	-	-	-	-
Perceived <u>burden of:</u>						
Adverse events	*-0.22 (-0.59, 0.15)*	0.23	0.19 (-0.17, 0.56)	0.29	-0.02 (-0.04, 0.00)	0.10
Taste/amount of peanuts	0.15 (-0.02, 0.32)	0.09	-	-	0.01 (-2.02, -0.13)	0.09

475
476
477 Associations are given as the relative change (ß) related to each unit increase by the in QoL
478 score.
479 N=37, including only children still receiving OIT at Y_2 with no missing data.
480 - no significant association
481 Change in QoL is given by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0)
482 child self-report and parental proxy-report, or the food allergy quality of life – parental burden
483 (FAQLPB). Decreasing values of PedsQL and increasing values of FAQLPB reflects poorer
484 QoL.
485 Perceived treatment burden was reported by VAS (range 0–10 (0=no burden, 10=massive
486 burden) within the domains: Adverse events (stomach ache, nausea/vomiting and oral itching)
487 and taste and amount of daily peanut OIT.

488   **FIGURE LEGENDS**

489   **Figure 1**

490   Flow chart from screening to second year of oral immunotherapy in the TAKE-AWAY trial.

491   **Figure 2**

492   The absolute quality of life (QoL) scores in children who receive oral immunotherapy (OIT)

493   and the controls at screening (Y_0), at one year of up-dosing (Y_1) and at second year of
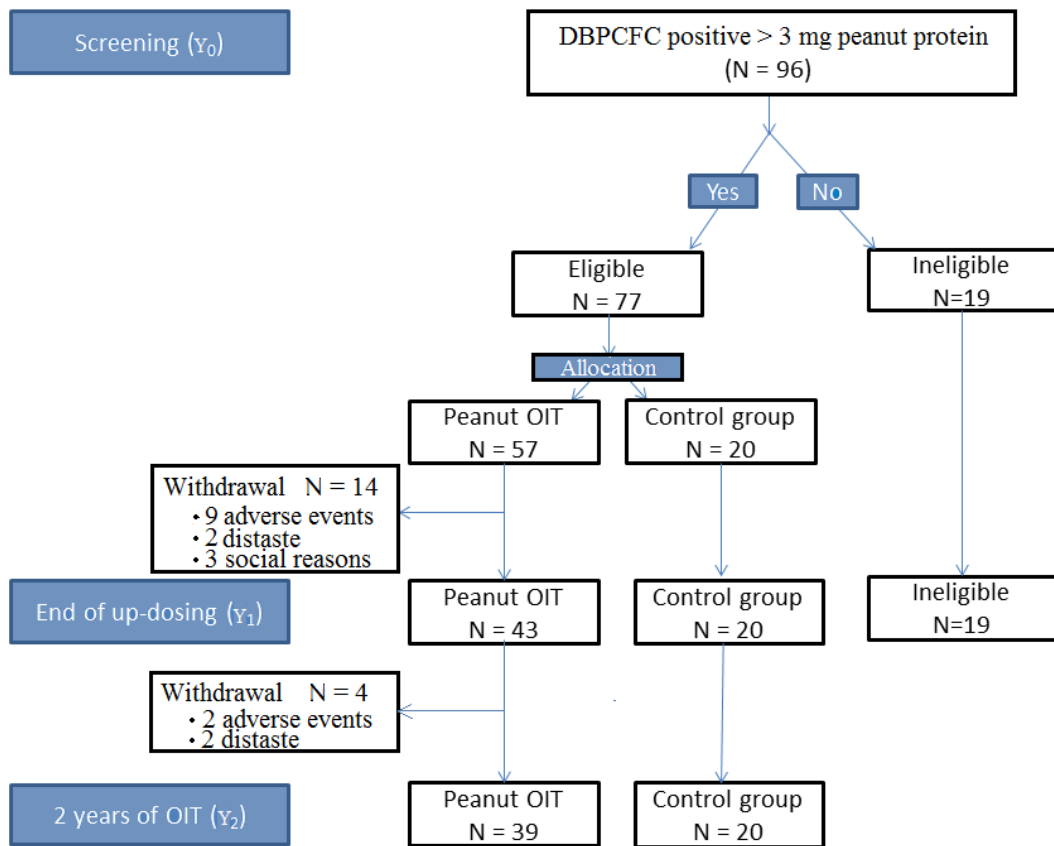
494   treatment (Y_2), as reported by the child self-reports and the parental proxy-reports.

495   Statistically significant group differences were assessed by mixed models for repeated

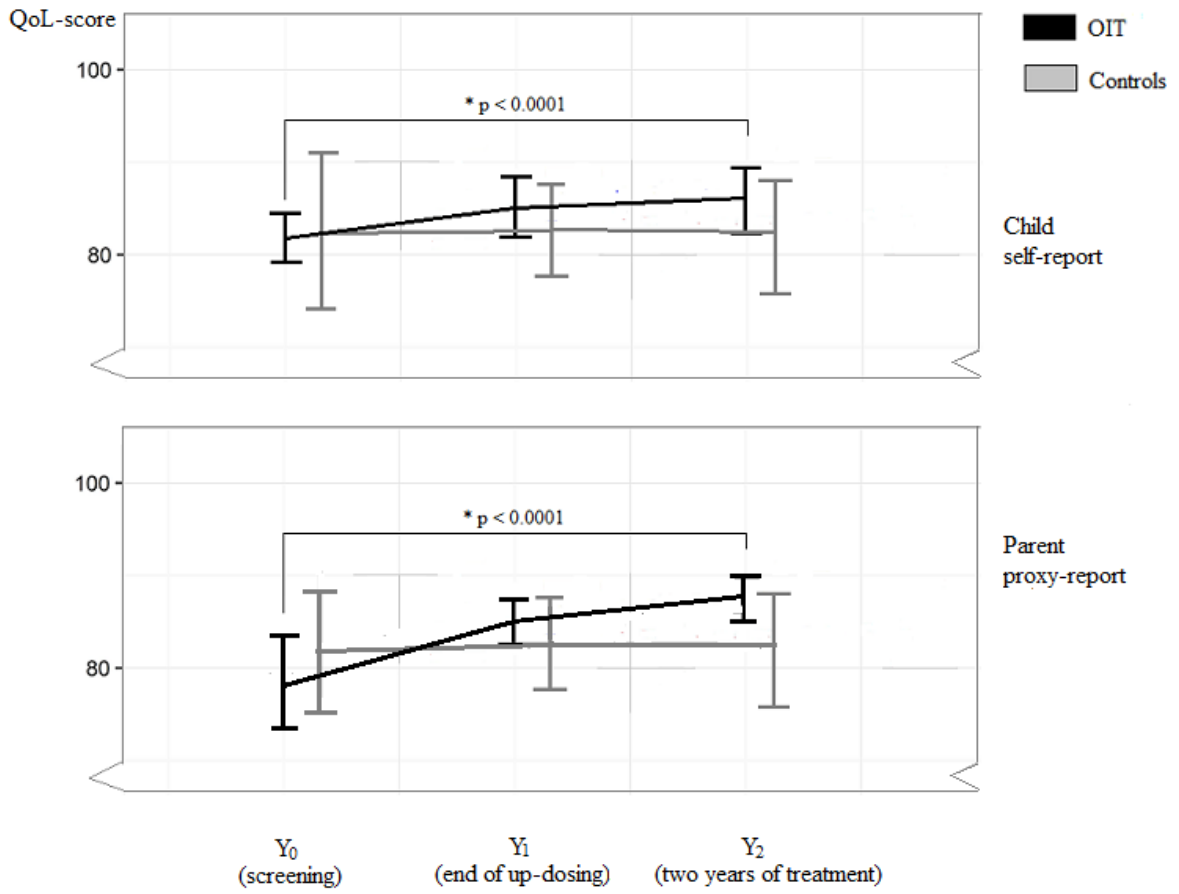496   measures. Increased value reflects improved QoL.

497

498 **Figure 1**

499

500   **Figure 2**

QoL at Y2 in the TAKE-AWAY trial 03.12.18

502 **SUPPLEMENTARY MATERIAL**

503 **METHODS**

504 *Study design*

505 Inclusion criteria for screening in the Take-Away trial were age 5-15 years, a history of

506 systemic reactions to peanut or sensitization to peanut by a peanut specific skin prick test

507 (SPT) ≥3 mm or a specific immunoglobulin E to peanut (s-IgE) ≥0.35 kUA/L, and living

508 within acceptable distance from the Oslo University Hospital to ensure feasibility of a

509 possible OIT. Exclusion criteria were non-controlled asthma, allergy or intolerance to any

510 other ingredients in the peanut DBPCFC vehicle (ginger bread), current or previous allergen

511 specific immunotherapy, cardiac disease, severe atopic skin disease, diabetes mellitus or other

512 severe diseases that might interfere with adherence to study protocol.

513 The OIT starting dose was initially 5 mg of peanut protein based on previously published

514 studies (2, 21, 30), but lowered to 1 mg of peanut protein after including 26 children (17

515 active vs 9 controls) due to low reactivity threshold in the referred patients (18). Lowering the

516 starting dose was approved by the ethical committee, and results from statistical analyses

517 comparing children with a different OIT starting dose of 5 mg vs 1 mg of peanut protein (n =

518 17 vs 40), allowed that all children on active OIT could be assigned as one intervention group

519 *Immunoglobulin assessments and skin prick test*

520 Specific IgE was analyzed for peanut and peanut allergen components (Ara h1, Ara h2, Ara

521 h3, Ara h8, Ara h9), hazelnut and hazelnut allergen components (Cor a 1, Cor a 8, Cor a 9,

522 Cor a 14), almond, cashew nut, pistachio, walnut, pecan nut, brazil nut, macadamian nut,

523 fenugreek, soy bean, lupine seed, wheat, latex, common silver birch, timothy and mugwort

524 with positive tests defined as s-IgE≥0.35 kUA/L. Specific IgG and IgG_4 were analyzed for

525 peanut and Ara h 2 with positive tests defined as IgG>2.0 mg_A/L and IgG4 of>0.07 mg_A/L.

526 Immunoglobulins were analyzed using the Phadia CAP-System FEIA (ThermoFisher,

527 Uppsala, Sweden).

528 The SPT was performed according to European guidelines (31) and included common food

529 and inhalant allergens including peanut, hazelnut, almond, soy, birch, grass (timothy),

530 mugwort, cat, dog, mite and mold (cladosporium herbarium) (ALK SQ extracts from ALK

531 Abello (Hørsholm, Denmark), pea positive control (histamine) and negative control

532 (Allergopharma (Reinbek, Germany).

533 ***Anaphylaxis definition and grading***

534 Anaphylaxis was defined as moderate symptoms from at least two organ systems in line with

535 European Academy of Allergy and Clinical Immunology (EAACI) task force position papers

536 (19, 28), modified for children by Vetander et al. (32). Severity of anaphylaxis was also

537 graded in line with the EAACI position papers (19, 28) scoring from 1-3 (mild-moderate-

538 severe) in addition to the method of Sampson (Grading of Food-Induced Anaphylaxis

539 According to Severity of Clinical Symptoms) ranging from one to five (extremely severe

540 reaction) (29).

541 ***Up-dosing protocol of the oral immunotherapy***

542 For the lowest doses, the allergen source was peanut flour (Golden Peanut Company,

543 Alpharetta, GA, USA). Since larger amounts of flour was found hard to eat, all but one child

544 switched to roasted peanuts at OIT doses of 65-500 mg peanut protein. Each up-dosing period

545 started with the incremented OIT dose ingested under observation at the hospital, followed by

546 daily intake of a specific peanut dose at home for 14 days. In case of ongoing infections,

547 asthma exacerbations, excessive tiredness or vaccinations we advised to postpone the daily

548 OIT dose to the next day. The OIT was resumed at home if less than three consecutive doses

549 were missing, and in hospital if three or more doses were missed. Exercise within two hours

550 after ingesting the OIT dose was strongly discouraged.

QoL at Y2 in the TAKE-AWAY trial 03.12.18

551   Registration of peanut intake, AEs, use of medication and accidental exposure to peanut were

552   based upon daily symptom diary recordings. An independent safety board was contacted if

553   unexpected severe AEs occurred. All participants received prescriptions of adrenaline auto-

554   injectors and antihistamines, a written treatment plan for AEs, and had around-the-clock

555   access to the private cell-phone numbers of the study personnel.

556   The AEs were classified as mild, moderate and severe (including anaphylaxis) according to

557   the modified Bock's criteria (33, 34). Mild skin symptoms include occasional scratching, less

558   than three hives, mild lip oedema, or a few areas of erythema, whereas moderate include

559   scratching for more than two continuous minutes, more than three but less than ten hives,

560   significant face oedema or areas of erythema, and severe skin symptoms include excoriations

561   or generalized erythema or urticaria. Mild respiratory symptoms include rare bursts or

562   sniffing, expiratory wheezing by auscultation or less than three episodes of throat clearing,

563   whereas moderate include less than ten bursts, frequent sniffing, conjunctivitis, inspiratory

564   and expiratory wheezing by auscultation or hoarseness, and severe respiratory symptoms

565   include persistent rhinorrhea, use of accessory muscles or audible wheezing or stridor. Mild

566   GI-symptoms include complaints of nausea or stomach ache or one episode of emesis or

567   diarrhea, whereas moderate include frequent complaints of nausea and stomach ache with

568   normal activity and two to three episodes of emesis or diarrhea or one of each, and severe GI-

569   symptoms include complaints of nausea or stomach ache with change of activity level or more

570   than three episodes of emesis or diarrhea or two of each. Mild cardiovascular include

571   subjective weakness or tachycardia, whereas moderate include more than 20 % drop in

572   baseline blood pressure, and severe cardiovascular symptoms include signs of impaired

573   circulation.

574   ***The oral immunotherapy protocol***

575   The peanut OIT followed a biweekly step-up protocol with a fixed starting dose and a pre-

576   defined maximum maintenance dose (MMD) of 5000 mg peanut protein as previously

577   reported (18). Each increment of peanut dose was based upon an agreement between the

578   participating child, parents and the study pediatrician. In case of distaste for peanuts,

579   intolerable AEs or three consecutive unsuccessful up-dosing attempts due to AEs, the current

580   dose would represent the individual maintenance dose. Withdrawal was initiated by self-

581   discontinuation, severe AEs or more than two anaphylactic reactions.

582   Grading of AEs was in line with the modified Bock's criteria (33-35) (further described in

583   online supplements).

584   *Quality of life measurements*

585   For the PedsQL 4.0, results are classified by Physical Health Score (Physical Functioning)

586   and Psychosocial Health Summary Score (Emotional, Social and School Functioning).

587   Translation into Norwegian has been validated for PedsQL 4.0 (36).

588   In addition to fulfilling the PedsQL 4.0 parental proxy-report, parents completed the health-

589   related Food Allergy Quality of Life – Parental Burden (FAQL-PB) Questionnaire (23, 24).

590   The FAQL-PB (23, 24) consists of 17 items including family/social activities (restaurant

591   meals, social activities, child care and vacation), school, time spent for meal preparation,

592   health concerns, and emotional issues. The FAQL-PB has a 7-point Likert scale (1 = not

593   troubled, 7 = extremely troubled), with summated scores ranging from 17-119. The minimal

594   important difference (MID) (the smallest change that the patient perceive as important) on a

595   7-point Likert scale was defined as 0.5 (37). The FAQL-PB was translated into Norwegian for

596   use in the Oslo Peanut Allergy Study (21) with permission from The Food Allergy and

597   Anaphylaxis Network.

598   *Measurement of perceived treatment burden*

599   The VAS developed to obtain one-dimensional reports of perceived treatment burden during

600   the last 12 months included eight individual VAS items and was completed by OIT children

601   together with their parents at Y_1 and Y_2. One item referred to overall perception of treatment

602   burden, whereas seven items referred to treatment burden within three domains: Gastro-

603   intestinal (GI) related AEs (stomach ache, nausea/vomiting and oral itching), taste and

604   amount of daily peanut dose, and time spent on OIT (up-dosing at hospital and ingestion of

605   OIT doses at home). Each VAS item ranged from 0–10 (0=no burden, 10=massive burden),

606   reporting the mean score per domain.

607   *Oral food challenge at Y_2*

608   The first challenge dose equaled the maintenance dose. A cumulated dose of 7500 mg peanut

609   protein was reached after maximum six doses, ingested with a 30 minutes interval.

610   *Statistical analyses*

611   The statistical power analysis at onset of the TAKE-AWAY trial was based upon reports

612   desensitization of up to 80% of peanut allergic children using a step-up peanut OIT (3, 4) and

613   spontaneous tolerance development in up to 20% (38). Assuming that desensitization would

614   be less successful in children with severe peanut allergy, we estimated that with a

615   desensitization rate of 57%, a treatment group of 40 and a control group of 20 subjects would

616   provide a statistical power of 80% at a five percent significance level.

617   As the underlying assumptions for the multiple linear regression analysis were not fulfilled,

618   multivariate robust regression analyses with Huber's M-estimator was used to assess

619   associations between possible factors influencing QoL (as independent variables), and change

620   in QoL from Y_0 to Y_2 in the PedsQL 4.0 or the FAQL-PB (as dependent variables). Hosmer's

621   step down multivariate analysis (39) retaining age and gender in the analysis included all

622   variables significant at the 0.35 level in the bivariate analyses and the final model was tested

623   for confounding with all excluded variables. Confounding was considered significant if

624   including the variable caused a minimum of a 25% change in the result (39).

625

626   **RESULTS**

627   At Y_2 OFC, two children had allergic reactions during challenge. One child reacted with

628   conjunctivitis and urticaria at 7500 mg peanut protein (maintenance dose 1500 mg), and the

629   other child (maintenance dose 1250 mg) with a 3-month treatment discontinuation before

630   resuming OIT the last three months before OFC had moderate anaphylaxis (erythema,

631   urticaria and wheezing) at 4444 mg peanut protein.

632   The change in QoL from Y_0 to Y_2 was not significantly associated with the number of AEs in

633   unadjusted bivariate analyses, neither as reported by the children (p=0.76) nor by the parental

634   proxy-reports (p=0.90). Among the OIT-children, perceived treatment burden was

635   significantly lower at Y_2 compared with Y_1 for the GI-domain and the taste-/amount-domain,

636   but not for the time spent-domain from Y_1 to Y_2 (Table 2). The associations between changes

637   in perceived treatment burden from Y_1 to Y_2 vs baseline VAS reports at Y_1 are shown in

638   Supplement Figure 2). Although maintenance dose altered the effect size of the burden of

639   peanut taste/amount >25 % in step-down analyses, neither maintenance dose, any of the three

640   perceived treatment burden domains at Y_1 and Y_2, nor the level of desensitization were

641   significantly associated with change in QoL in the final regression model (Table 3). The

642   results were similar including children who discontinued OIT and burden of time spent on

643   OIT into the analyses (data not shown).

644   The change in perceived treatment correlated significantly with the VAS reported burden at

645   Y_1 with mean correlation coefficients ranging from –0.82 to –0.44) (p<0.001) (Supplement

646   Figure 2).

QoL at Y2 in the TAKE-AWAY trial 03.12.18

647   The parents' QoL improved significantly (decreased score) from Y_0 to Y_2 in both groups as

648   shown in Supplement Figure 3, with a FAQL-PB score decreasing from 2.1 (1.8, 2.3) to 1.5

649   (1.3, 1.7) (p<0.0001) among the OIT parents and from 1.9 (1.7, 2.3) to 1.4 (1.2, 1.7) (p =

650   0.004) among the control parents. No significant difference in mean change (95% CI) among

651   parents' QoL was observed from Y_0 to Y_2 between the OIT group (-9.9 (-14.6, -5.3)) and the

652   controls (-9.4 (-15.3, -3.6)) (p = 0.57) (Supplement Figure 3).

653

SUPPLEMENTARY REFERENCES

27.   Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy. 2007;62(8):857-71.

28.   Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601-8.

29.   Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009;64(8):1218-20.

30.   Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. Allergy. 1993;48(14 Suppl):48-82.

31.   Vetander M, Helander D, Lindquist C, Hedlin G, Alfvén T, Ostblom E, et al. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. Pediatr Allergy Immunol. 2011;22(4):369-73.

32.   Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol. 1988;82(6):986-97.

33.   Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.

34.   Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, et al. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009;123(6 Suppl):S365-83.

35.   Reinfjell T, Diseth TH, Veenstra M, Vikan A. Measuring health-related quality of life in young adolescents: reliability and validity in the Norwegian version of the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2006;4:61.

36.   Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.

37.   Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. J Allergy Clin Immunol. 2015;135(5):1257-66 e1-2.

38.   Hosmer DWaL, S. . Applied logistic regression , 2.ed., John Wiley & sons New York, USA. 2000

39.   Niggemann B. When is an oral food challenge positive? Allergy. 2010;65(1):2-6.

SUPPLEMENTARY TABLES

Supplement Table 1. Baseline characteristics in children with peanut OIT starting dose 1 mg and 5 mg peanut protein.

	OIT starting dose 1 mg peanut protein (n = 40)	OIT starting dose 5 mg peanut protein (n = 17)	p-value
Age	9.7 (5.4, 15.0)	10.4 (6.3, 15.1)	0.26
Male sex	23 (57.5)	8 (47,5)	0.47
Ever had eczema	32 (80.0)	15 (88.2)	0.46
Current asthma	20 (50.0)	11 (64.7)	0.56
Allergic rhinitis	10 (25.0)	5 (29.4)	0.77
Parental atopic disease*	38 (90.5)	12 (70.6)	**0.01**
Parental food allergy**	15 (37.5)	6 (35.3)	0.87
Peanut SPT (mm)	9.8 (4.0, 36.3)	9.4 (4.0, 22.9)	0.88
Positive SPT other nuts ($\geq$ 3 mm)***	22 (55.0)	6 (35.3)	0.17
S-IgE (kUA/L)			
Peanut	92.8 (9.8, 2290.9)	102.3 (3.1, 955.0)	0.86
Ara h 2	46.8 (9.9, 489.8)	61.7 (2.5, 457.1)	0.60
Positive s-IgE (kUA/L)			
other nuts***	38 (95.0)	14 (87.5)	0.33
other food****	38 (95.0)	16 (100.0)	0.36
Peanut s-IgE/total IgE (kUA/L)	9.5 (8.0, 10.0)	9.5 (9.1, 9.9)	0.46
Peanut s-IgG$_4$/s-IgE (ng/ml)	4.7 (9.2, 288.4)	4.7 (9.9, 42.7)	0.72
BAT (%CD63+), pos ******	63.1 (16.2, 93.3)	64.6 (37.2, 91.2)	0.80
CAPT positive (dilution) *****			
1/160	5 (12.5)	2 (11.8)	0.59
1/80	11 (27.5)	2 (11.8)	
1/40	12 (30.0)	9 (52.9)	
1/20	11 (27.5)	2 (11.8)	
1/10	11 (27.5)	2 (11.8)	
Pre-OIT DBPCFC			
Use of adrenaline	23 (57.5)	7 (41.2)	0.26
Anaphylaxis severity modified EAACI	1.7 (1.0, 2.0)	1.4 (1.0, 2.0)	0.10
Reactivity threshold	42.8 (3.0, 933.3)	93.7 (12.9, 1584.9)	0.12

*Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis

**All food allergy including peanut and treenut allergy

***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and macadamianut

****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat

***** The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

****** N=50. The BAT was not performed in 7 children due to technical causes (n=5) and non-reponders were excluded from the analyses (n=2).

698   Anaphylaxis severity was graded according to the modified EAACI position papers (19, 28)
699   ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis
700   According to Severity of Clinical Symptoms) (29) ranging from 1 to 5.
701

702   SPT, skin prick test; BAT, basophil activation test; CAPT, conjunctival provoacation test;
703   Ig - immunoglobulin; LOAEL - lowest observed adverse effect level; OIT – oral
704   immunotherapy; DBPCFC – double blind placebo controlled food challenge; LOAEL -
705   lowest observed adverse effect level (amount of peanut eliciting mild, objective symptoms)

706 **Supplement Table 2.**

	Patients completing OIT up-dosing (n = 43)	Patients dis-continuing OIT (n = 14)	p-value		
Age (median, min-max)	9.0 (5.2, 15.2)	11.1 (5.4, 15.1)	0.13		
Male	21 (48.8)	10 (71.4)	0.14		
History of anaphylaxis to peanu	32 (74.4)	13 (92.8)	0.41	6 (42.9)	0.82
				8 (57.1)	0.37
Current asthma	16 (69.6)	8 (57.1)	0.26		
Allergic rhinitis	13 (30.2)	2 (14.3)	0.53		
Atopic dermatitis	36 (83.7)	11 (78.6)	0.64		
Allergy to tree-nuts	20 (48.8)	0 (0.0)	**0.002**		
Allergy to other food than nuts	25 (59.5)	2 (14.3)	**0.003**		
Parental atopic disease*	36 (83.7)	14 (100.0)	0.16		
Parental food allergy**	14 (32.6)	7 (50.0)	0.51		
FEV1% predicted	102.7 (98.6, 106.7)	99.7 (94.0, 105.8)	0.58		
SPT tree-nuts ≥ 3 mm	25 (58.1)	3 (21.4)	**0.02**		
Pos s-IgE (≥ 0.35 kUA/L):					
tree-nuts***	40 (95.2)	12 (85.7)	0.08		
other food****	41 (95.3)	13 (92.9)	0.63		
Peanut SPT (mm)	10.3 (8.7, 11.9)	12.1 (8.3, 15.8)	0.48		
Total IgE (kUA/L)	570.6 (405.1, 736.2)	713.9 (314.1, 1113.6)	0.51		
S-IgE (kUA/L):					
Peanut	197.5 (12.8, 270.1)	472.8 (120.2, 825.3)	0.09		
Ara h2	99.0 (62.7, 135.2)	177.1 (85.9, 268.4)	0.05		
Peanut s-IgE/ total IgE (kUA/L)	0.3 (0.3,0.4)	0.5 (0.4, 0.7)	**0.009**		
Peanut s-IgG$_4$/ s-IgE (ng/ml)	27.4 (10.5, 44.4)	9.7 (1.9, 21.3)	0.22		
QoL child self-report	78.6	81.7	0.80		

QoL at Y2 in the TAKE-AWAY trial 03.12.18

	(75.6, 81.7)	(77.6, 86.3)	
QoL parental proxy-report	82.7 (80.0, 85.4)	82.1 (75.5, 88.8)	0.71
At baseline DBPCFC:			
Number of anaphylaxis:	43 (100.0)	14 (100.0)	*C*
Anaphylaxis severity grade: modified EAACI	1.7 (1.6, 1.8)	1.6 (1.4, 1.9)	0.70
Sampson	2.7 (2.3, 2.9)	2.7 (2.3, 3.1)	0.94
Use of adrenaline	22 (51.2)	8 (57.1)	0.70
LOAEL (mg peanut protein)	113.3 (12.4, 214.3)	82.9 (16.3, 149.5)	0.11
Reactivity threshold (mg peanut protein)	155.4 (48.9, 261.9)	250.1 (60.9, 439.3)	0.07

707 Variables are given as mean (95% CI) or n (%), except age which is given as median (min,
708 max).
709 Bold values are statistically significant (p<0.05).
710 C Not able to compute – anaphylaxis at DBPCFC is a constant.
711 *Atopic disease includes asthma, allergic rhinitis, atopic dermatitis, allergic
712 conjunctivitis
713 **All food allergy including peanut and treenut allergy
714 ***Hazelnut, almond, cashewnut, pistachionut, walnut, pecannut, brazilnut and
715 macadamianut
716 ****Fenugreek, soybean, pea, red kidney bean, lupin seed and wheat
717 *****The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).
718
719 Anaphylaxis severity was graded by two grading systems according to the modified EAACI
720 position papers (19, 28) ranging from 1 to 3 and the method of Sampson (Grading of Food-
721 Induced Anaphylaxis According to Severity of Clinical Symptoms) (29) ranging from 1 to 5.
722 LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective
723 symptoms
724 Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive
725 DBPCFC, with at least two moderate objective symptoms in one or more organ systems
726 symptoms according to Bock's criteria (33, 34, 40).
727
728 Quality of life scores was given by the generic Pediatric Quality of Life Inventory Version 4.0
729 (PedsQL 4.0) (14, 22).
730
731 SPT, skin prick test; Ig - immunoglobulin; LOAEL - lowest observed adverse effect level;
732 OIT – oral immunotherapy; DBPCFC – double blind placebo controlled food challenge;
733 LOAEL - lowest observed adverse effect level (amount of peanut eliciting mild, objective
734 symptoms); QoL – quality of life

735   **SUPPLEMENTAL FIGURE LEGENDS**

736   **Supplement Figure 1**

737   Overall study design. The "Take away food allergy; inducing tolerance in children allergic to

738   peanut" trial (TAKE-AWAY trial) established in 2012 consists of four phases; the screening

739   phase (three days of eligibility screening), up-dosing phase (50-78 weeks), maintenance phase

740   (36 months) and follow-up phase (12 months). Defined time-points in the study was Y_0 – at

741   screening, Y_1 - after one year of OIT (the end of up-dosing phase), Y_2, Y_3, Y_4 after two, three

742   and four years of OIT (one, two and three years of maintenance treatment), respectively, and

743   Y_5 - one year after cessation of 4 years of OIT, with assessments expected to be completed in

744   2020.

745   **Supplement Figure 2**

746   Correlation between change in perceived treatment burden from end of up-dosing (Y_1) to

747   second year of treatment (one year of maintenance) (Y_2) and perceived burden at Y_1.

748   Perceived treatment burden is reported as overall burden (A), and within three domains:

749   Adverse events (stomach ache, nausea/vomiting and oral itching) (B), taste and amount of

750   daily peanut oral immunotherapy (OIT) (C) and time spent on OIT (D).

751   **Supplement Figure 3**

752   The absolute quality of life (QoL) scores in parents of children receiving oral immunotherapy

753   (OIT) and the controls at screening (Y_0), at one year of up-dosing (Y_1) and at second year of

754   treatment (Y_2). Decreased value reflects improved QoL.
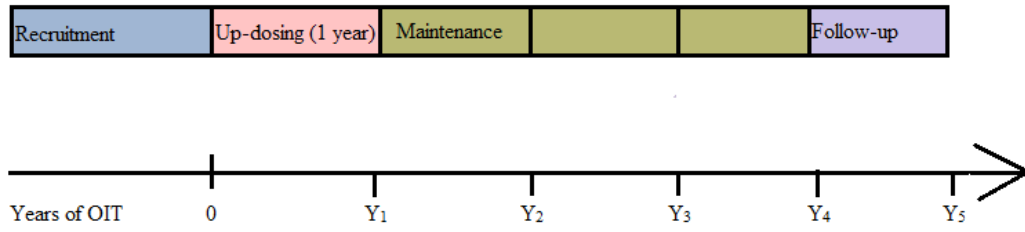
755   **Supplement Figure 4**

756   **A.** The absolute quality of life (QoL) scores in children who receive oral immunotherapy

757   (OIT) and the controls at screening (Y_0) and at one year of up-dosing (Y_1), as reported by the

758   child self-reports and the parental proxy-reports. Increased score reflects improved QoL.

759   **B**. The absolute quality of life (QoL) scores in parents of children receiving oral

760   immunotherapy (OIT) and the controls at screening (Y_0) and at one year of up-dosing (Y_1).

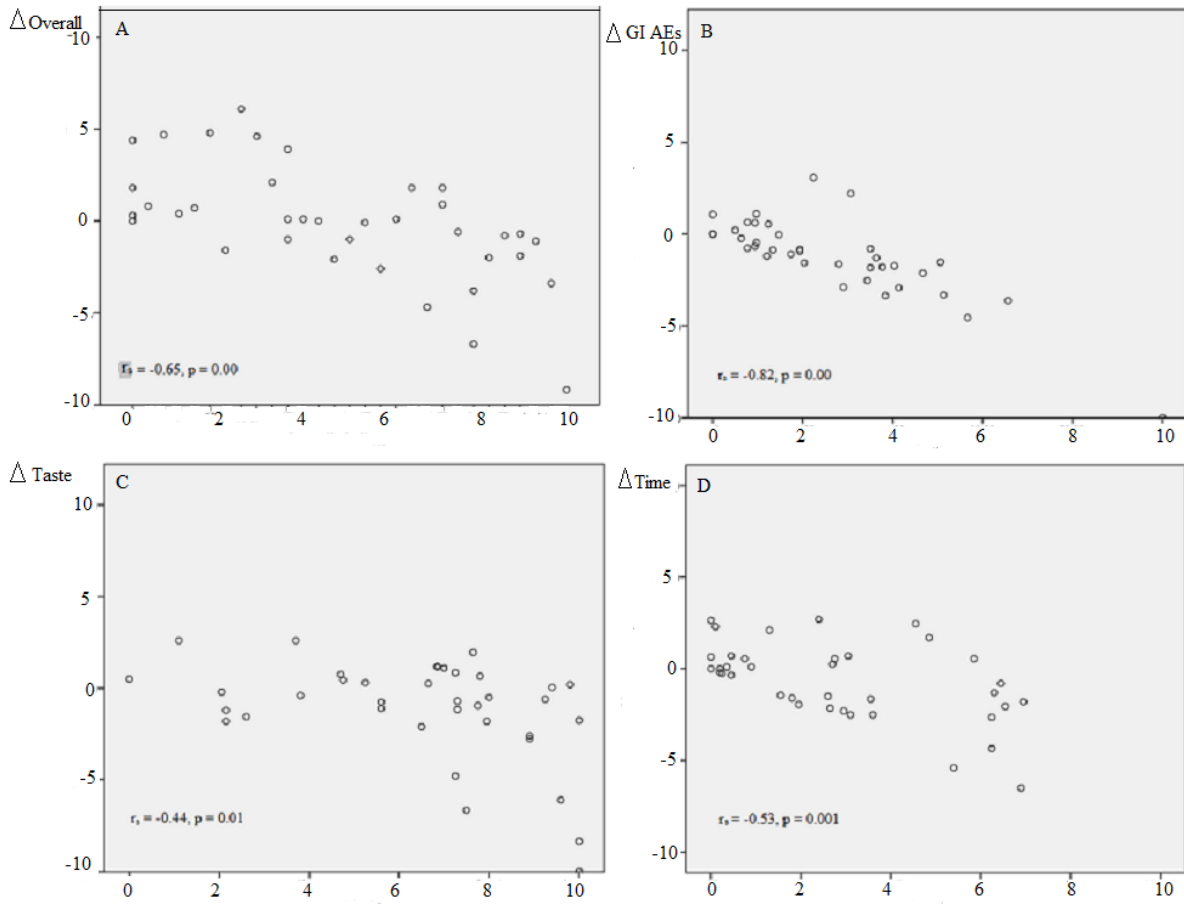761   Decreased score reflects improved QoL.

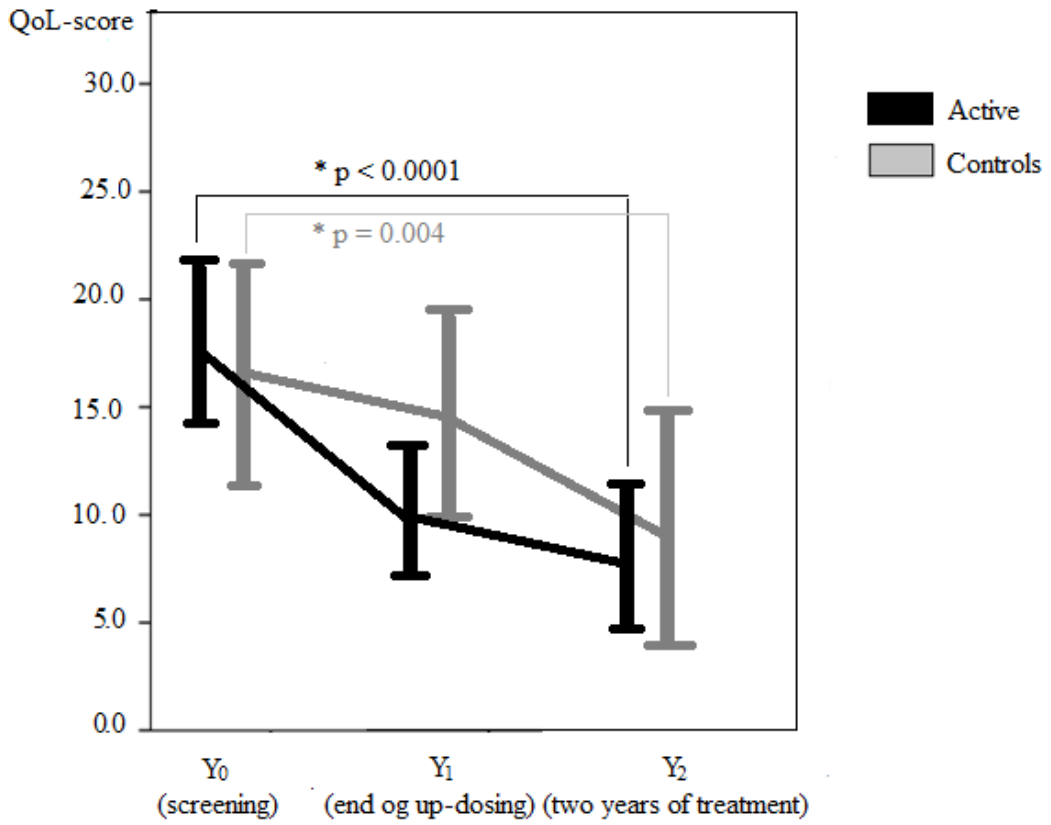762

763

764   **Supplement Figure 1**

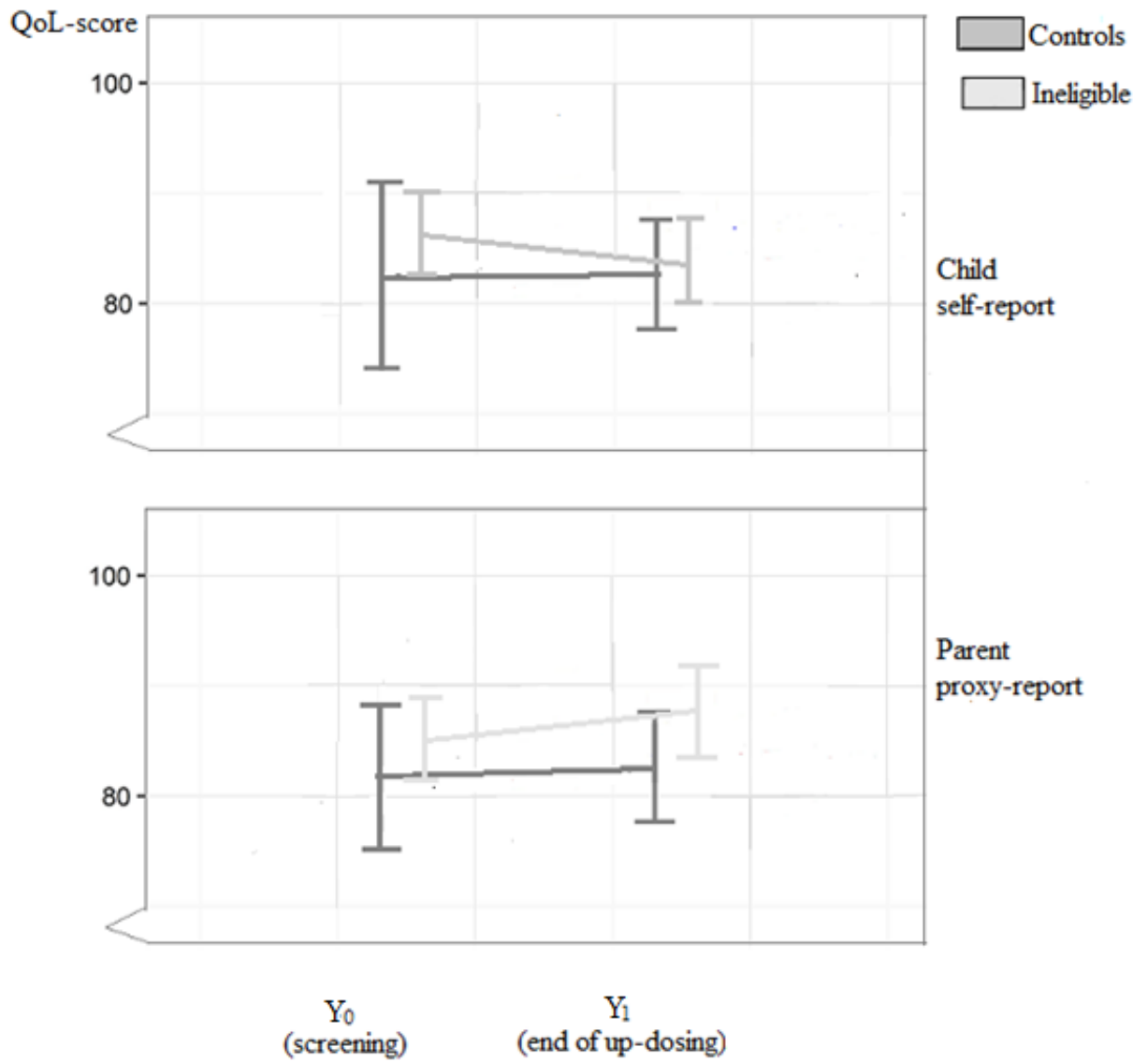| Recruitment | Up-dosing (1 year) | Maintenance | | | Follow-up |

Years of OIT   0 Y_1 Y_2 Y_3 Y_4 Y_5

765

QoL at Y2 in the TAKE-AWAY trial 03.12.18

766 **Supplement Figure 2**

767

QoL at Y2 in the TAKE-AWAY trial 03.12.18

768   **Supplement Figure 3**

769

770

QoL at Y2 in the TAKE-AWAY trial 03.12.18

771   **Supplement Figure 4A**

772

773

QoL at Y2 in the TAKE-AWAY trial 03.12.18

774   **Supplement Figure 4B**

QoL at Y2 in the TAKE-AWAY trial 03.12.18
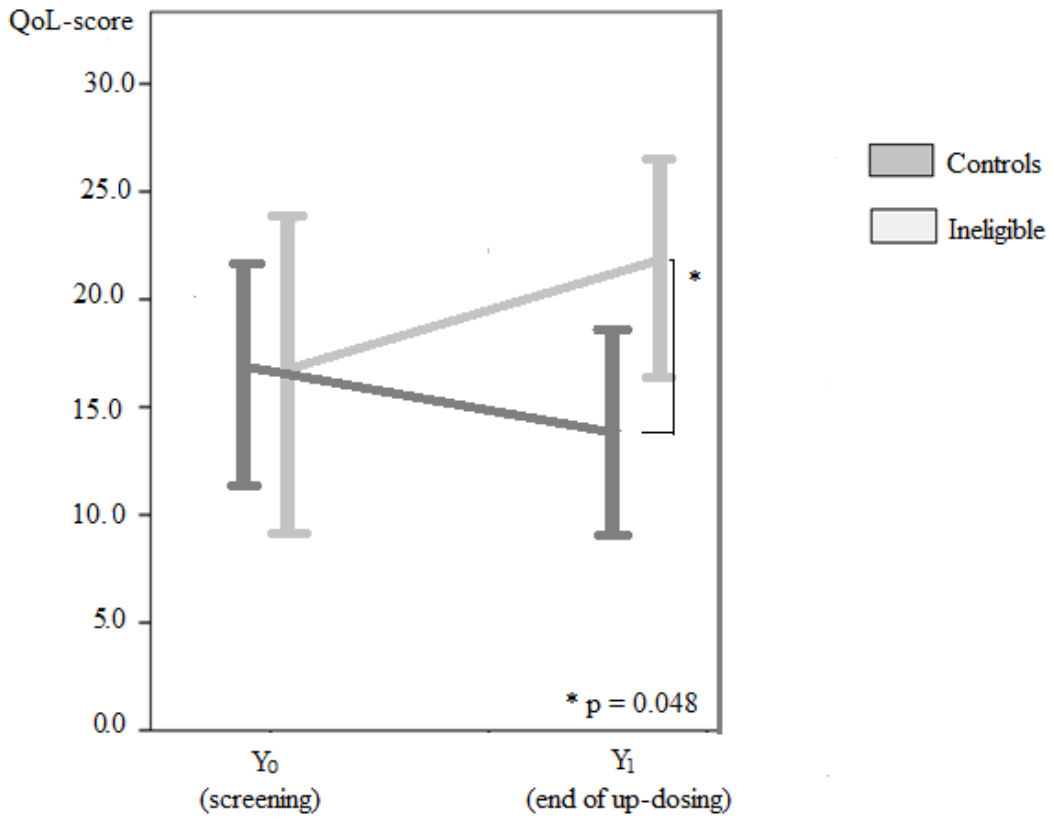
775

776

APPENDIX

216

Take-away studien: Intervjuskjema

1.Kode ☐☐☐

2. Fødselsdato ☐☐ . ☐☐ . ☐☐☐☐
dd   mm   åååå

3. Kjønn: ☐
1.Gutt
2.Jente

4. Dato for intervju ☐☐ . ☐☐ . ☐☐☐☐
dd   mm   åååå

5. Alder ☐☐ år ☐☐ mnd

6. Hvem følger: ☐
1. Mor
2. Far
3. Mor og far
4. Andre

7. Hvem svarer: ☐
1. Mor
2. Far
3. Mor og far
4. Andre

Familie:

8. Hvor mange søsken har barnet: ☐☐

9. Helsøsken: ☐☐   **10. Halvsøsken:** ☐☐

11(a-e). Alder søsken

☐☐ år   ☐☐ år   Andre.................................
☐☐ år   ☐☐ år ......
☐☐ år   ☐☐ år
☐☐ år

12. Hvem bor deltager sammen med:

☐ Hos mor og far   ☐ Hos far   ☐ Andre ....

☐ Hos mor   ☐ Vekselsvis hos mor og far

13. Hvor mange søsken bor hjemme? ☐☐

14 Foreldrenes utdanning:

14a. Mors utdanning:

☐ Grunnskole
☐ Videregående
☐ Høyskole/universitet inntil 3 år
☐ Høyskole/universitet 4 år eller mer
☐ Informasjon ikke tilgjengelig

14b. Fars utdanning:

☐ Grunnskole
☐ Videregående
☐ Høyskole/universitet inntil 3 år
☐ Høyskole/universitet 4 år eller mer
☐ Informasjon ikke tilgjengelig

15 Økonomi- familiens totale brutto yrkesinntekt siste år:

15a Samlet husstand:

☐ 0-400.000
☐ 400.001-550.000
☐ 550.001-700.000
☐ 700.001-850.000
☐ Over 850.000
☐ Informasjon ikke tilgjengelig

15b.Mors husstand:

☐ 0-400.000
☐ 400.001-550.000
☐ 550.001-700.000
☐ 700.001-850.000
☐ Over 850.000
☐ Informasjon ikke tilgjengelig

15c. Fars husstand:

☐ 0-400.000
☐ 400.001-550.000
☐ 550.001-700.000
☐ 700.001-850.000
☐ Over 850.000
☐ Informasjon ikke tilgjengelig

1.Kode ☐☐☐☐

Sykdom familie

16. Har mor, far eller søsken hatt, eller har de i dag noen av følgende sykdommer; astma, høysnue, matallergi, atopisk eksem, eller anafylaktisk reaksjon?:

☐ 0. Nei
1. Ja
2. Vet ikke

17. Hvis ja på sp 16:

	Mor 1. Ja 2. Usikker	Far 1. Ja 2. Usikker	Søsken Ja, antall	Søsken Usikker, antall
Astma	a ☐	h ☐	o ☐	v ☐
Rhinitt	b ☐	i ☐	p ☐	w ☐
Konjunktivitt	c ☐	j ☐	q ☐	x ☐
Matareallergier, unntatt peanøtter og nøtter	d ☐	k ☐	r ☐	y ☐
Peanøttallergi	e ☐	l ☐	s ☐	z ☐
Allergi mot nøtter	f ☐	m ☐	t ☐	æ ☐
Atopisk eksem	g ☐	n ☐	u ☐	ø ☐

18. Andre kroniske sykdommer
....

Mor ☐ 0. Nei 1. Ja 2. Vet ikke

Far ☐ 0. Nei 1. Ja 2. Vet ikke

Søsken ☐ 0. Nei 1. Ja 2. Vet ikke

Røyk/Snus

19. Røyker noen i husstanden? ☐
0. Nei
1. Ja, nå
2. Ja, tidligere
3. Vet ikke

20. Hvis ja, hvem: ☐
1. Mor   2. Far
3. Mor og far
4. Deltager
5. Andre
6. Flere av de over

21a. Hvis nå, hvor hyppig?:

Mor ☐ Deltager ☐ ☐
1. Daglig
2. Ukentlig, men ikke daglig
3. Av og til, men ikke ukentlig

Far ☐ Andre ☐

21b. Hvis tidligere, hvor hyppig?:

Mor ☐ Deltager ☐ ☐
1. Daglig
2. Ukentlig, men ikke daglig
3. Av og til, men ikke ukentlig

Far ☐ Andre ☐

22. Hvor lenge er det siden noen i husstanden røkte hjemme, dersom det ble røykt i husstanden tidligere? (år) ☐☐

23. Bruker deltager snus? ☐
0. Nei
1. Daglig
2. Ukentlig, men ikke daglig
3. Av og til, men ikke ukentlig

24. Bruker mor eller far snus? ☐
0. Nei
1. Mor
2. Far
3. Mor og far

25. Røkte mor under svangerskapet? ☐
0. Nei
1. Ja, under deler
2. Ja, under hele
3. Vet ikke/husker ikke

26. Brukte mor snus under svangerskapet? ☐
0. Nei
1. Ja, under deler
2. Ja, under hele
3. Vet ikke/husker ikke

Svangerskap

1.Kode □ □ □

Brukte mor noe av dette under svangerskapet?

27. Kosttilskudd □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

Hvis ja, hvilke..
Hvor ble de kjøpt?.......................................

28. Tran □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

29. Vitamin D □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

30. Folat □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

31. Paracetamol □
- 0. Nei
- 1. Ja
- 3. Vet ikke/husker ikke

32. Dispril, globoid eller aspirin □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

33. Andre medikamenter □
- 0. Nei
- 1. Ja
- 3. Vet ikke/husker ikke

Hvis ja, hvilke..

----

34. Hadde mor diett under svangerskapet? Hvis nei, gå rett til sp. 36. □
- 0. Nei
- 1. Ja
- 3. Vet ikke/husker ikke

35. Hvis ja, hvilke matvarer ble unngått?

a. □ Melk og melkeprodukter

e. □ Hvete/gluten

b. □ Egg

f. □ Fisk

c. □ Peanøtter

g. □ Jordbær

d. □ Nøtter

h. □ Andre matvarer ....

36. Hvis nei på sp. 34. Hvor ofte spiste mor peanøtter under svangerskapet? □
- 1. Daglig
- 2. Ukentlig
- 3. Av og til, men ikke ukentlig

Fødsel og amming

37. Forløsningsmetode □
- 1. Vaginal
- 2. Sectio
- 3. Ukjent

38. Komplikasjoner i svangerskapet □
- 0. Nei
- 1. Ja, under deler
- 2. Ja, under hele
- 3. Vet ikke/husker ikke

Hvilke...

39. Gestasjonsalder ved fødsel (hele uker)? □ □

40. Fødselsvekt (g): □ □ □ □

41. Fødselslengde (cm): □ □

42. Ble barnet ammet? □
- 0. Nei
- 1. Ja
- 3. Husker ikke/vet ikke

43. Hvor lenge ble barnet fullammet (mnd)? □ □

44. Hvor lenge ble barnet ammet (mnd)? □ □

1.Kode

45. Unngikk mor peanøtter under amming?
- 0. Nei
- 1. Ja
- 3. Husker ikke/vet ikke

46. Hvor ofte spiste mor peanøtter under ammingen?
- 1. Daglig
- 2. Ukentlig
- 3. Av og til, men ikke ukentlig

47. Unngikk mor andre matvarer under amming?
- 0. Nei
- 1. Ja
- 3. Husker ikke/vet ikke

Hvilke matvarer ble evt. unngått: ....

Vaksiner

48. Har barnet fulgt vanlig vaksinasjonsprogram?
- 0. Nei
- 1. Ja
- 3. Husker ikke/vet ikke

Hvilke vaksiner har barnet ikke fått? ....

Introduksjon av matvarer

49. Alder ved introdukasjon av matvarer:

- 0. Husker ikke/vet ikke
- 1. 0-6 mnd.
- 2. 7-12 mnd
- 3. 13-18 mnd.
- 4. 19-24 mnd.
- 5. 2-3 år
- 6. >3 år
- 7. Aldri

Melk ☐   Hvete ☐   Peanøtt ☐

Egg ☐   Fisk ☐   Morsmelktillegg ☐

Mineral/vitamintilskudd til barnet

50. Brukte barnet mineral/vitamintilskudd 1. leveår:
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

51. Hvis ja, hvilket tilskudd:

a. ☐ Vitamin C   b. ☐ Sanasol   c. ☐ Biovit   d. ☐ Tran   e. ☐ Vitamin D   f. ☐ Jern   g. ☐ Annet

52. Brukte barnet mineral/vitamintilskudd etter 1. leveår og frem til siste år:
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

Hvilke(t):......................................

53. Hvis ja, hvilket tilskudd:

a. ☐ Vitamin C   b. ☐ Sanasol   c. ☐ Biovit   d. ☐ Tran   e. ☐ Vitamin D   f. ☐ Jern   g. ☐ Annet

Hvilke(t):......................................

54. Bruker barnet mineral/vitamintilskudd nå:
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

55. Hvis ja, hvilket tilskudd:

a. ☐ Vitamin C   b. ☐ Sanasol   c. ☐ Biovit   d. ☐ Tran   e. ☐ Vitamin D   f. ☐ Jern   g. ☐ Annet

Hvilke(t):......................................

216

Pubertet

56. Vekstspurt [ ]
- 0. Husker ikke/vet ikke
- 1. Har ikke startet
- 2. Har så vidt startet
- 3. Er definitivt i gang
- 4. avsluttet

57. Hårvekst(armhuler/kjønnshår) [ ]
- 0. Husker ikke/vet ikke
- 1. Har ikke startet
- 2. Har så smått begynt å vokse
- 3. Er definitivt i gang
- 4. Behåringen øker ikke lenger

58. Hudforandringer? Kviser spesielt?: [ ]
- 0. Nei
- 1. Ja, så vidt
- 2. Ja, definitivt
- 3. Avsluttet

Pubertet- Gutter

59. Dypere stemme? [ ]
- 0. Nei
- 1. Ja, så vidt
- 2. Ja, definitivt
- 3. Avsluttet

60. Skjeggvekst? [ ]
- 0. Nei
- 1. Ja, så vidt
- 2. Ja, definitivt
- 3. for fullt

Pubertet- Jenter

61. Har hatt første menstruasjon? [ ]
- 0. Nei
- 1. Ja

62. Alder ved første menstruasjon [ ][ ] år

63. Regelmessig menstruasjon? [ ]
- 0. Nei
- 1. Ja

64. Antall dager i syklus? [ ][ ] dager

65. Hvor er du i syklusen nå? (Dager siden 1.dag?) [ ][ ] dager

66. Er du plaget med PMS? [ ]
- 0. Nei
- 1. Ja, litt
- 2. Ja, mye

Sykehistorie peanøttallergi

67. Ble det oppbevart peanøtt i huset i.l.a 1.leveår? [ ]
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

68. Ble det oppbevart peanøtt i huset etter 1.leveår? [ ]
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

69. Ble det oppbevart peanøtt i huset siste år [ ]
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

70. Har barnet spist peanøtt? [ ]
- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

71. I hvilken form spiste barnet peanøtt: [ ]
- 0. Ren peanøtt
- 1. Peanøttsmør
- 2. Bakt
- 3. Annet...............................

72. Barnets alder ved første kjente eksponering overfor peanøtt (mnd): [ ][ ] år [ ][ ] mnd

73. Alder ved første allergiske reaksjon på peanøtt (mnd): [ ][ ] år [ ][ ] mnd

1.Kode ☐ ☐ ☐ ☐

74. Ved første allergiske reaksjon. Hvilken form av peanøtt spiste barnet? ☐

- 0. Ren peanøtt
- 1. Peanøttsmør
- 2. Bakt
- 3. Annet..............................

75. Var første allergiske reaksjon på peanøtt i forbindelse med første kjente eksponering? ☐

- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

76. Hvilke symptomer fikk barnet ved første allergiske reaksjon på peanøtt:

☐ Elveblest/urticaria
☐ Angioødem
☐ Eksem   ☐ Erythem
☐ Annet utslett
☐ Kløe i huden
☐ Rhinitt
☐ Konjunktivitt
☐ Astma
☐ Annet pustebesvær/andre luftveissympt

☐ Kløe i munn/svelg
☐ Kvalme/oppkast
☐ Magesmerter
☐ Diare
☐ Uro/adferdsendring
☐ Anafylaksi
☐ Bevissthetstap
☐ Blekhet
☐ Annet

77. Hvor alvorlig var den første allergiske reaksjonen? ☐

- 0. lett
- 1. Moderat
- 2. Alvorlig
- 3. Svært alvorlig

78. Mengde peanøtt inntatt ved første allergiske reaksjon ☐

- 0. Spor
- 1. Litt
- 2. Mye
- 3. Vet ikke/ukjent

79. Ble lege kontaktet ved 1. reaksjon? ☐

- 0. Nei
- 1. Ja
- 3. Vet ikke

80. Ble det gitt medikamentell behandling? ☐

- 0. Nei
- 1. Ja
- 3. Vet ikke

81. Hvis ja, hvilke medikamenter:

☐ Adrenalin
☐ Steroider inj
☐ Steroider p.o.

☐ Antihistamin inj
☐ Antihistamin p.o.
☐ Andre medikamenter

☐ Husker ikke hvilke medikamenter

82. Hvor raskt oppsto symptomene ved 1. reaksjon? ☐

- 1. innen 10 min
- 2. 10-30 min
- 3. 30 min - 2 timer
- 4. 2-4 timer
- 5. 4-8 timer
- 6. over 8 timer
- 7. husker ikke/vet ikke

83. Har barnet hatt flere allergiske reaksjoner på peanøtt?
Hvis nei gå til spm **93** ☐

- 0. Nei
- 1. Ja
- 2. Husker ikke/vet ikke

84. Hvis ja, oppgi antall allergiske reaksjoner på peanøtt: ☐ ☐

85. Hvis ja, var siste reaksjon-- enn første reaksjon: ☐

- 1. kraftigere   4. varierende
- 2. lettere   5. vet ikke
- 3. uendret

86. Hvilke symptomer hadde barnet ved den siste allergiske reaksjonen på peanøtt:

☐ Elveblest/urticaria
☐ Angioødem
☐ Eksem   ☐ Erythem
☐ Annet utslett
☐ Kløe i huden
☐ Rhinitt
☐ Konjunktivitt
☐ Astma
☐ Annet pustebesvær/andre luftveissympt

☐ Kløe i munn/svelg
☐ Kvalme/oppkast
☐ Magesmerter
☐ Diare
☐ Uro/adferdsendring
☐ Anafylaksi
☐ Bevissthetstap
☐ Blekhet
☐ Annet

1.Kode ☐ ☐ ☐ ☐

87. Hvor alvorlig var den siste allergiske reaksjonen?
☐
0. Lett
1. Moderat
2. Alvorlig
3. Svært alvorlig

88. Mengde peanøtt inntatt ved siste allergiske reaksjon
☐
0. Spor
1. Litt
2. Mye
3. Vet ikke/ukjent

89. Ble lege kontaktet ved siste reaksjon?
☐
0. Nei
1. Ja
3. Vet ikke

90. Ble det gitt medikamentell behandling ved siste reaksjon?
☐
0. Nei
1. Ja
3. Vet ikke

91. Hvis ja, hvilke medikamenter:
☐ Adrenalin   ☐ Antihistamin inj
☐ Steroider inj   ☐ Antihistamin p.o.
☐ Steroider p.o.   ☐ Andre medikamenter

92. Hvor raskt oppsto symptomene ved siste reaksjon?
☐
1. innen 10 min
2. 10-30 min
3. 30 min - 2 timer
4. 2-4 timer
5. 4-8 timer
6. over 8 timer
7. husker ikke/vet ikke

93. Unngår dere å ha peanøtter hjemme?
☐
0. Nei
1. Ja
3. Vet ikke

94. Hvis nei, hvor ofte spises det peanøtter i hjemmet?
☐
0. Aldri
1. Daglig
2. Ukentlig
3. Av og til, men ikke ukentlig

95. Har dere peanøttsmør hjemme?
☐
0. Nei
1. Ja
3. Vet ikke

96. Hvis ja, hvor ofte spises det peanøttsmør i hjemmet?
☐
0. Aldri
1. Daglig
2. Ukentlig
3. Av og til, men ikke ukentlig

97. Unngår barnet å være på steder hvor det serveres peanøtter?
☐
0. Nei
1. Ja
3. Vet ikke

98. Hvilke tiltak er iverksatt hjemme?
☐
0. Totalforbud
1. Har peanøtter hjemme, barnet unngår selv.
3. Kan smake på matvarer med spor av peanøtter

99. Hvilke tiltak er iverksatt ved skolen/barnehage?
☐
0. Totalforbud
1. Andre barn kan ha med peanøtter, barnet unngår selv.
3. Kan smake på matvarer med spor av peanøtter

100. Unngår dere andre nøtter, enn peanøtter, hjemme?
☐
0. Nei
1. Ja
3. Vet ikke

Hvis ja, hvilke:...

101. Unngår barnet matvarer som inneholder spor av nøtter?
☐
0. Nei
1. Ja
3. Vet ikke

102. Er det andre matvarer (enn peanøtter og nøtter) som dere unngår hjemme?
☐
0. Nei
1. Ja
3. Vet ikke

103. Hvis ja, hvilke:
☐ Melk   ☐ Hvete
☐ Egg   ☐ Annet
☐ Fisk   :...................................

Pga barnet eller andre i familien? :...................................

104. Hvordan forholder barnet seg til peanøtt, og hvordan påvirker det hverdagen?

☐ Unngår å besøke andre

☐ Unngår å spise hos andre

☐ Spiser hos andre, men har med egen mat

☐ Spiser hos andre, men tar forholdsregler

☐ Unngår å gå på kafe/restaurant

☐ Går på kafe/restaurant, men tar forholdsregler

☐ Unngår ferieturer en ellers ville tatt

☐ Drar på ferieturer, men tar forholdsregler

105. Hvor engstelig er foreldrene for at barnet skal få i seg peanøtt? ☐
0. Ikke engstelig
1. Litt engstelig
2. Veldig engstelig

106. Hvor engstelig er du for å få i seg peanøtt? Her spør en barnet! ☐
0. Ikke engstelig
1. Litt engstelig
2. Veldig engstelig
3. Barnet i en slik alder at spørsmålet ikke er relevant

107. Har barnet opplevd allergisk reaksjon mot andre nøtter: ☐
0. Nei
1. Ja
3. Vet ikke

108. Hvis ja, hvilke(n) nøtt(er)?
☐ Hasselnøtt ☐ Cashew ☐ Paranøtt ☐ Pistasj
☐ Mandel ☐ Pecannøtt ☐ Valnøtt ☐ Andre nøtter

Reaksjon på andre matvarer enn peanøtter og nøtter:

111. Har barnet reagert allergisk mot noen andre matvarer enn peanøtter og nøtter, hvis nei-gå til spm 118 ☐
0. Nei
1. Ja
3. Vet ikke

109. Hvis ja, hvilke matvarer har dere opplevd at barnet noen gang har reagert allergisk mot?
☐ Melk ☐ Stenfrukt
☐ Egg ☐ Sitrus
☐ Hvete
☐ Bakevarer ☐ Tomat
☐ Fisk
☐ Soya ☐ Annet

I tilfelle hva:.........................

110. Hvis ja, hvilke matvarer er barnet allergisk mot i dag?
☐ Melk ☐ Stenfrukt
☐ Egg ☐ Sitrus
☐ Hvete
☐ Bakevarer ☐ Tomat
☐ Fisk
☐ Soya ☐ Annet

I tilfelle hva:.........................

Hvilke symptomer fikk barnet etter å ha spist matvaren(e):

112. Melk:
☐ Elveblest/urticaria ☐ Kløe i munn/svelg
☐ Angioødem ☐ Kvalme/oppkast
☐ Eksem ☐ Magesmerter
☐ Annet utslett ☐ Diare
☐ Kløe i huden ☐ Uro/adferdsendring
☐ Rhinitt ☐ Anafylaksi
☐ Konjunktivitt ☐ Bevissthetstap
☐ Astma ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt ☐ Annet

113. Egg:
☐ Elveblest/urticaria ☐ Kløe i munn/svelg
☐ Angioødem ☐ Kvalme/oppkast
☐ Eksem ☐ Magesmerter
☐ Annet utslett ☐ Diare
☐ Kløe i huden ☐ Uro/adferdsendring
☐ Rhinitt ☐ Anafylaksi
☐ Konjunktivitt ☐ Bevissthetstap
☐ Astma ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt ☐ Annet

1.Kode ☐☐☐☐

114. Hvete:

☐ Elveblest/urticaria | ☐ Kløe i munn/svelg
☐ Angioødem | ☐ Kvalme/oppkast
☐ Eksem | ☐ Magesmerter
☐ Annet utslett | ☐ Diare
☐ Kløe i huden | ☐ Uro/adferdsendring
☐ Rhinitt | ☐ Anafylaksi
☐ Konjunktivitt | ☐ Bevissthetstap
☐ Astma | ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt | ☐ Annet

115. Fisk:

☐ Elveblest/urticaria | ☐ Kløe i munn/svelg
☐ Angioødem | ☐ Kvalme/oppkast
☐ Eksem | ☐ Magesmerter
☐ Annet utslett | ☐ Diare
☐ Kløe i huden | ☐ Uro/adferdsendring
☐ Rhinitt | ☐ Anafylaksi
☐ Konjunktivitt | ☐ Bevissthetstap
☐ Astma | ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt | ☐ Annet

116. Soya:

☐ Elveblest/urticaria | ☐ Kløe i munn/svelg
☐ Angioødem | ☐ Kvalme/oppkast
☐ Eksem | ☐ Magesmerter
☐ Annet utslett | ☐ Diare
☐ Kløe i huden | ☐ Uro/adferdsendring
☐ Rhinitt | ☐ Anafylaksi
☐ Konjunktivitt | ☐ Bevissthetstap
☐ Astma | ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt | ☐ Annet

117. Andre matvarer:...

☐ Elveblest/urticaria | ☐ Kløe i munn/svelg
☐ Angioødem | ☐ Kvalme/oppkast
☐ Eksem | ☐ Magesmerter
☐ Annet utslett | ☐ Diare
☐ Kløe i huden | ☐ Uro/adferdsendring
☐ Rhinitt | ☐ Anafylaksi
☐ Konjunktivitt | ☐ Bevissthetstap
☐ Astma | ☐ Blekhet
☐ Annet pustebesvær/ luftveissympt | ☐ Annet

Anafylaksi

118. Har barnet hatt alvorlig allergisk reaksjon med påvirkning av flere organsystemer samtidig, eller med påvirket bevissthet for andre matvarer enn peanøtt? Hvis nei eller vet ikke så gå rett til spørsmål nr. **124**.

☐ 0. Nei
1. Ja
3. Vet ikke

119. Hvis ja, antall ganger: ☐

1. En gang
2. 2-4 ganger
3. 5-10 ganger
4. Mer enn 10 ganger
5. Vet ikke

120. Hvis ja, hvilke(n) matvare(r) ga anafylaktisk reaksjon:

☐ Hassenøtt ☐ Melk ☐ Hvete ☐ Soya
☐ Annen nøtt ☐ Egg ☐ Fisk ☐ Annet

Hva:...

Type nøtt: ....

121. Hvis ja, kom reaksjonen i forbindelse med fysisk aktivitet eller 2-6 timer etter fysisk aktivitet? ☐

0. Nei
1. Ja
3. Vet ikke

122. Hvis ja, ble barnet innlagt på sykehus? ☐

0. Nei
1. Ja
3. Vet ikke

123. Hvis ja, barnet behandlet med adrenalin? ☐

0. Nei
1. Ja
3. Vet ikke

Behandling ved akutt allergisk reaksjon

1.Kode ☐☐☐☐

124. Har barnet EpiPen/ adrenalinpenn?
Hvis nei, gå til spm **138**

☐ 0. Nei
1. Ja
3. Vet ikke

125. Hvis ja, alder ved første gangs utskrivelse (år): ☐☐

126. Har dere fått opplæring i bruk av EpiPen?

☐ 0. Nei
1. Ja
3. Vet ikke

Hvor?:...
..

127. Hvis ja, hvor ofte anskaffes ny EpiPen?

☐ 1. Før den er gått ut på dato
2. Årlig
3. Hvert annet år
4. Annet

128. Hvis ja, hvor mange EpiPen'er har barnet? ☐

129. Hvis ja, hvor ofte har barnet den med seg?

☐ 0. Aldri
1. Av og til
2. Alltid

130. Hvis ja, har foresatte eller barnet satt EpiPen i forbindelse med akutt allergisk reaksjon?

☐ 0. Nei
1. Ja
3. Vet ikke

131. Hvis ja, antall ganger: ☐☐

133. Har barnet EpiPen med i barnehage/på skole?

☐ 0. Nei
1. Ja
3. Vet ikke

134. Har barnehage/skole fått opplæring??

☐ 0. Nei
1. Ja
3. Vet ikke

135. Har barnet andre medikamenter hjemme til bruk ved allergiske reaksjoner?

☐ 0. Nei
1. Ja
3. Vet ikke

136. Hvis ja, hvilke?

a. ☐ Antihistamin

b. ☐ Steroider

c. ☐ Adrenalin

d. ☐ Annen behandling

137. Har barnet behandlingsskjema for akutt allergisk reaksjon?

☐ 0. Nei
1. Ja
3. Vet ikke

....

Rhinitt

138.Har du fått diagnosen høysnue, allergisk rhinitt?

a ☐ 0.Nei
1.Ja

Hvis ja, alder: ☐☐ **b**

139.Har du hatt nesetetthet, rennende nese eller nysing uavhengig av forkjølelse?

a ☐ 0.Nei
1.Ja

Hvis ja, alder ved debut: **b** ☐☐ hvilke

c ☐ Rennende nese
d ☐ Nesetetthet
e ☐ Nysing

Har du hatt kløende/ rennende øyne uavhengig av forkjølelse?

f ☐ 0.Nei
1.Ja

g Hvis ja, alder ved debut: ☐☐

140.Har du noen gang iløpet av de siste 12 mnd hatt nese symptomer (se over) uavhengig av forkjølelse?

a ☐ 0.Nei
1.Ja

Hvis ja, hvilke:
b ☐ Rennende nese
c ☐ Nesetetthet
d ☐ Nysing

e Har du i løpet av de siste 12 mnd hatt kløende/ rennende øyne?

☐ 0.Nei
1.Ja

Hvis nei på begge gå til spm 143.

f Hvis ja, når har du **nese**- symptomer? ☐

g **Øye**-symptomer? ☐

1.Hele året
2.Vår/sommerhalvåret
3.Høst/vinterhalvåret

1.Kode ☐☐☐☐

141.Hva er det som utløser disse øye/nese symptomer?

a. ☐ vet ikke   g. ☐ Bjørk   m. ☐ Temperaturforandring/fysisk aktivitet

b. ☐ katt   h. ☐ Gress (timotei)   n. ☐ Fødemidler

c. ☐ Hund   i. ☐ Burot   o. ☐ Annet   ....

d. ☐ Kanin   j. ☐ Andre pollen   Hvilke pollen:........................

e. ☐ Hest   k. ☐ Midd

f. ☐ Andre dyr   l. ☐ Muggsopp

Hvilke dyr:........................

142.I hvor stor grad har disse øye/nese symptomene innvirket på de daglige aktivitetene? ☐

1.Ikke i det hele tatt
2.Litt
3.Moderat
4.Mye

143.Har du gjennomført en allergiologisk luftveis utredning?   **a** ☐   0.Nei 1.Ja   Alder **b** ☐☐

Hvis ja. hvordan?

c ☐ Prikktest   **g** ☐ Røntgen/CT/MR (Øvre LV)
d ☐ Provokasjon   Hva: _____
e ☐ Sykehistorie alene   **h** ☐ Røntgen/CT/MR (Nedre LV)
f ☐ Blodprøver(Spesifikk IgE)   Hva: _____

144.Hva slags behandling har du fått for dine øye/nese symptomer?   a.Har/hatt behandling ☐

0.Nei
1.Ja
3. Vet ikke

b. Lokale antihistaminer ☐   f.Leukotrienantagonister ☐

c. Systemiske antihistaminer ☐   g.Immunoterapi/allergivaksine ☐

NB sett nummer!   d.Lokale steroider ☐   h.IgE antagonist(Omalizumab) ☐

e.Natriumkromglikat ☐   i.Annet ☐   ....

1:Tidligere, ikke siste 12 mnd
2:Siste 12mnd
3:Siste 14 dager
4:Kontinuerlig

Atopisk eksem

145. Har barnet/har barnet hatt atopisk eksem, d.v.s. rødt, tørt og kløende eksem?   ☐   0. Nei 1. Ja 3. Vet ikke   146.Hvis ja, alder ved symptomstart (mnd): ☐☐

Hvis nei, gå til spm **152**

147. Hvis ja, har barnet fortsatt atopisk eksem? ☐   0. Nei 1. Ja 3. Vet ikke   148. Hvis nei (147), alder ved symptomslutt (mnd): ☐☐☐

149. Faktorer som forværrer eksemet:

a. ☐ Melk og melkeprodukter   e. ☐ Sitrus   i. ☐ Pollen

b. ☐ Egg   f. ☐ Tomat   j. ☐ Dyr

c. ☐ Peanøtter   g. ☐ Jordbær   k. ☐ Annet ....

d. ☐ Nøtter   h. ☐ Andre matvarer   ....

150. Når er eksemet tilstede: ☐   1. Hele året 2. Kun i vinterhalvåret 3. Vet ikke/husker ikke   4. Annet.........................

151. Hva slags behandling har barnet fått for eksemet: a. ☐ Kun fuktighetskrem   d. ☐ KP-bad/krystallfiolett/alsol

b. ☐ Steroidsalve/krem gruppe 1-2   e. ☐ Lokal immunmodulator (protopic/elidel)

c. ☐ Steroidsalve/krem gruppe 3-4   f. ☐ Annet ....

Elveblest

152. Har barnet/har barnet hatt elveblest?
Hvis nei, gå til spm **156**

☐ 0. Nei
1. Ja
3. Vet ikke

153. Faktorer som forværrer/utløser elveblesten:

a. ☐ Melk og melkeprodukter e. ☐ Sitrus i. ☐ Pollen l. ☐ fysikalske stimuli n. ☐ Vet ikke

b. ☐ Egg f. ☐ Tomat j. ☐ Dyr m. ☐ Infeksjoner

c. ☐ Peanøtter g. ☐ Jordbær k. ☐ Annet ....

d. ☐ Nøtter h. ☐ Andre matvarer ....

154. Hva slags behandling har barnet fått for elveblest:

a. ☐ Antihistamin d. ☐ Annen behandling

b. ☐ Steroider e. ☐ Ingen behandling

c. ☐ Adrenalin

155. Har barnet hatt pustevansker i
forbindelse med episoder med elveblest:

☐ 0. Nei
1. Ja
3. Vet ikke

Astma

Hvis ja,når?   Hvor gammel var du sist gang du hadde...?

156.Har du noen ganghatt tung pust,
tetthet eller piping/vesing i brystet?

a. ☐ 0.Nei 1.Ja b. ☐ 1.Ikke siste år
2.Siste 12 mndr
3.Siste 14 dager

c.tungpust ☐ ☐ år

157.Har du hatt tørr hoste om natten
uten å være forkjølet eller ha andre
luftveisinfeksjoner?
Hvis nei, gå til spm **163**

a. ☐ 0.Nei 1.Ja b. ☐

c.tørrhoste ☐ ☐ år

158.Hvor mange perioder
med tung pust, tetthet eller
piping/vesing i brystet har du
hatt siste 12 måneder?

☐ 0. Ingen
1. 1-3
2. 4-12
3. mer enn 12

159.Hvor mange dager med
tung pust, tetthet eller
piping/vesing i brystet har
du hatt siste 14 dagene?

☐ 0. Ingen
1. 1-3
2. 4-12
3. mer enn 12

160.Er/var det årstids- variasjon i
symptomer?

☐ 0.Nei
1.Ja

161.Hvis ja 160, hvilken/hvilke årstider er verst?

a. ☐ Vår c. ☐ Høst

b. ☐ Sommer d. ☐ Vinter

162.Hva er/var det som utløser/forverrer
symptomene?

	>12 mnd siden	<12mnd
Anstrengelse	a. ☐	k. ☐
Sigarettrøyk	b. ☐	l. ☐
Pollen	c. ☐	m. ☐
Mat/drikke	d. ☐	n. ☐
Tåke/fuktig luft	e. ☐	o. ☐
Infeksjoner	f. ☐	p. ☐
Sterke lukter	g. ☐	q. ☐
Pelsdyr	h. ☐	r. ☐
Kald luft	i. ☐	s. ☐
Annet,	j. ☐	t. ☐

163.Har du fått diagnosen
astma noen gang?

a. ☐ 0.Nei 1.Ja

Hvis ja, hvilken alder?

b. ☐ ☐ år

Hvis ja, har du etter din
mening fortsatt astma?

c. ☐ 0.Nei 1.Ja

Hvis nei, alder ved symptomslutt:

d. ☐ ☐ år

164.Har du noen gang brukt
medisin for luftveiene?
Hvis nei, gå til spm**175**

☐ 0.Nei 1.Ja

165.Hvis ja, kun hostesaft/efedrin?

☐ 0.Nei 1.Ja

1.Kode [ ][ ][ ][ ]

1.Ikke siste år
2.Siste 12 mndr
3.Siste 14 dager

166.Har du noen gang brukt (1-3): (som hjemme behandling)

β -2 agonist på forstøver a. [ ]

β -2 agonist som spray b [ ]

β -2 agonist som spray m/kammer c. [ ]

β -2 agonist som pulver d [ ]

β -2 agonist som mikstur e. [ ]

Langtidsvirkende e -2 agonist f. [ ]

Lomudal som spray g. [ ]

Lomudal som pulver h. [ ]

Lomudal på forstøver i. [ ]

Inhalasjons steroider som spray j. [ ]

Inhalasjonssteroider som spray m/kammer k. [ ]

Inhalasjonssteroider som pulver l. [ ]

Inhalasjonssteroider på forstøver m. [ ]

Leukotrienantagonist n. [ ]

Ipratropiumbromid (Atrovent) o. [ ]

Adrenalin på forstøver p. [ ]

Aminophyllin klyster q. [ ]

Aminophyllin p.o. r. [ ]

Hyposensibilisering s. [ ]

Systemiske steroider t. [ ]

Anti IgE u. [ ]

167.Hvis du har brukt β -2 agonist siste 12 mnd/14 dager, hvor stort har forbruket i gjennomsnitt vært pr. brukeruke?

1. Daglig
2. 4-6 dager/uke
3. 1-3 dager/uke

Siste 12 mnd
a. [ ]
Antall puff/dag b. [ ][ ]
Hvor mange uker c. [ ][ ]

Siste 14 dager
d. [ ]
e. [ ][ ]
Dager f. [ ][ ]

168.Har du brukt β -2 agonist (hurtigvirkende astmamedisin) i forbindelse med fysisk aktivitet de siste 12 måneder? [ ] 0.Nei 1.Ja

169.Hvis du har brukt inhalasjonssteroider, hva var alder ved behandlingsstart? a. [ ][ ] år

Bruker du fortsatt inhalasjonssteroider? b [ ] 0.Nei 1.Ja

Hvis nei, alder ved seponering: c. [ ][ ] år

170.Hvis du har brukt inhalasjonsteroider siste 12 mnd/14 dager, hvilken type og hvor stor dose?

1. Flutide
2.Pulmicort/Becotide/ Aerobec
3. Annen.................................

Siste 12 mnd a. [ ]
b. [ ][ ][ ][ ]

Siste 14 dager c [ ]
Dose (ug/dag) d. [ ][ ][ ][ ]

171.Hvis du bruker inhalasjonssteroider, bruker du det hele året? [ ] 0.Nei 1.Ja

172.Hvis ja, hvor mange måneder, siste år? [ ][ ]

173.Hvis nei, hvilken/hvilke deler av året bruker du inhalasjonssteroider?

a. ☐ Vår   c. ☐ Høst
b. ☐ Sommer   d. ☐ Vinter

174.Hvis du bruker inhalasjonssteroider, bruker du det kun ved forverrelser? a. [ ] 0.Nei 1.Ja

Hvis ja, hvor mange perioder brukte du inhalasjonssteroider siste år? b. [ ][ ]

1.Kode ☐☐☐☐

175.Har du noen gang brukt systemiske steroidkurer ? a. ☐☐   0.Nei
1.Ja

Hvis ja, hva var alder ved første kur?   b. ☐☐   Antall systemiske steroidkurer siste 12 mnd?   c. ☐☐

176.Hvordan vil du karakterisere din helse i forhold til astma/astmalignende symptomer?

Tidligere, ikke siste 12 mnd
a. ☐

0. Ikke syk i det hele tatt

1.Svært lite syk

Siste 12 mnd   Siste 14 dager
b. ☐   c. ☐

2. Endel syk, men ikke særlig plagsomt

3. Mye syk, men tolerabelt for familien

4. Svært mye syk, går utover familien

177.Hvor mye har du vært borte fra skolen pga astma?   a. siste 12 mnd ☐   b. siste 14 dager ☐

1. Intet fravær
2. < 5 dager
3. 5-10 dager
4. > 10 dager

178.Føler du at astmaen hemmer din fysiske aktivitet?   a.tidligere ☐   0.Nei
1.Ja

b. siste 12 mnd ☐

Andre sykdommer

182. Har barnet annen kronisk sykdom: ☐   0. Nei
1. Ja

183.Hvis ja, hvilke(n):   a ☐ hjertesykdom   d ☐ epilepsi

b ☐ diabetes   e ☐ Annet ....

c ☐ revmatisk sykdom

184. Faste medikamenter (med unntak av med. for atopisk sykdom):   ☐   0. Nei
1. Ja

Hvis ja, hvilke:..