Improving diagnostics and quality of life in children with peanut allergy and other atopic diseases

Hannah Kansen

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PhD thesis, Utrecht University, the Netherlands

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Improving diagnostics and quality of life in children with peanut allergy and other atopic diseases

Het verbeteren van de diagnostiek en kwaliteit van leven van
kinderen met pinda allergie en andere atopische ziekten
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General introduction

Atopic diseases

The word atopy was first introduced by American allergists A.F. Coca and R.A. Cooke in 1922.¹ Atopy (Greek ατοπος, meaning out of place or unusual) refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies (sensitization) in response to common environmental proteins i.e. food allergens or inhalant allergens.² Patients with atopy can develop one or more atopic disease(s) including food allergy, asthma, allergic rhinitis and atopic dermatitis. The prevalence of atopic diseases has been on the rise over the past decades.^{3,4} The point prevalence of childhood food allergy has been estimated at approximately 6-8%^{5,6}, asthma at 8-35%³, allergic rhinitis at 7-19%³ and atopic dermatitis at 4-17%³. The progression of atopic diseases during childhood is often referred to as the 'atopic march'. Typically, the atopic march starts with atopic dermatitis, followed by food allergy, asthma and allergic rhinitis.⁷ The presence of one atopic disease increases the risk for the development of other atopic diseases and as a consequence, children often have multiple atopic diseases.⁸ As an example, the presence of atopic comorbidities in children with food allergy included in the Electronic Portal is shown in Figure 1. The Electronic Portal is a web-based application with multiple validated questionnaires administered to (parents of) children with respiratory or allergic symptoms, as previously published in detail.⁹ In this thesis, we focus mainly on improving diagnostics (part I) and quality of life (part II) in patients with (suspected) peanut allergy and in patients with asthma.

Figure 1. Presence of asthma, allergic rhinitis and atopic dermatitis in children with food allergy included in the Electronic Portal

The diagnostics of atopic diseases

'The three main tasks of the clinician are diagnosis, prognosis and treatment. Of these, diagnosis is by far the most important for upon it the success of the other two depends.'

J.A. Ryle¹⁰

Historically, diagnosis, prognosis and treatment are the cornerstones of clinical practice.¹¹ The purpose of a disease diagnosis is to categorize patients into groups with similar characteristics and thereafter, make inferences about the patients' prognosis and response to treatment (when available). An accurate diagnosis is important to adequately treat and advice patients, and to prevent unwanted events such as allergic reactions in patients with food allergy and daily symptoms or exacerbations in patients with asthma. Furthermore, an accurate diagnosis may improve health-related quality of life and reduce anxiety.^{12–14}

Peanut allergy

In the first part of this thesis, we focus on how to improve the diagnostic pathway for peanut allergy. Peanut allergy is one of the most common food allergies worldwide affecting 0.2–2.2% of children and up to 0.6% of adults.^{15–17} Patients are suspected of having a peanut allergy when allergic symptoms (i.e. skin, gastro-intestinal, respiratory, cardiovascular and/or neurological symptoms) occur immediately after ingestion of peanut together with sensitization to peanut.¹⁸ Sensitization can be detected by a positive skin prick test (SPT) or a raised level of specific IgE (sIgE) to peanut extract or peanut components in the blood. Currently, a two-day double-blind placebo-controlled food challenge (DBPCFC) is the reference standard for the definitive diagnosis of peanut allergy.¹⁸ However, a DBPCFC is time-consuming, expensive and subjective clinical symptoms can be difficult to interpret or severe systemic symptoms can occur.^{18,19}

In recent years, the diagnostic work-up for patients with a suspected peanut or hazelnut allergy has been improved with the use of component-resolved diagnostics (CRD).^{20,21} CRD measures sIgE against individual allergenic proteins utilizing purified native or recombinant allergenic molecules. Sensitization to peanut component Ara h 2 and Ara h 6 demonstrates the best association with true peanut allergy in children and adults.^{22–27} Our research group previously found that 62% of children could be classified correctly when using sIgE to Ara h 2 cutoff levels with 100% negative and positive predictive values (cutoff levels at ≤ 0.1 and ≥ 5.0 kU_A/L, respectively). When using a diagnostic flowchart based on these Ara h 2 cutoff levels, the number and days of DBPCFCs could be reduced.²⁸ Additionally,

the use of a diagnostic flowchart might result in lower costs. Previous research of a model-based economic evaluation in children with peanut allergy showed that a diagnostic flowchart using component-resolved diagnostics was more cost-effective than current clinical practice including an oral food challenge.²⁹ To date, no studies investigated the validation of previously published cutoff levels of sIgE to peanut components and the diagnostic accuracy, safety, adherence and costs of a diagnostic flowchart based on component-resolved diagnostics in daily practice. Therefore, we implemented a diagnostic flowchart for peanut allergy in one tertiary care and three secondary care centers in the Netherlands and evaluated these aspects in **chapter 2**. Furthermore, we evaluated whether we could develop a diagnostic flowchart based on component-resolved diagnostics in adults with suspected peanut allergy in **chapter 3**.

Atopic diseases and recurrent respiratory tract infections

While the prevalence of atopic diseases has been rising in the past decades, the prevalence of infectious diseases has decreased.^{5,30–34} These opposing trends in prevalence have been linked and it has been suggested that a decline in infections and thereby lower microbial exposure could contribute to the increased prevalence of atopic diseases. In support of this hypothesis, a reduced risk of allergic sensitization has been observed in children with older siblings, in children who attended day care during infancy or in children living in a rural environment (i.e. high microbial exposure).³⁵ On the contrary, an increased risk of recurrent infections has been observed in children with older siblings, in children who used a pacifier or in children who attended day care.^{36–38} Thus, (combined) environmental factors might affect the development of atopic and infectious diseases in different directions. In addition, the interaction between genetic and environmental factors is thought to be important in the pathogenesis of atopic diseases.³⁹ However, it is unknown whether these interactions are disease-specific or associated with all atopic diseases.⁴⁰ For respiratory infections, no consistent associations are observed regarding host genetic factors.⁴¹

Insight into how environmental and genetic (e.g. family history) factors are associated with atopic diseases on the one hand and infections on the other hand could improve our understanding on the pathophysiology of these diseases. We collected a large set of data on demographic, environmental and family history risk factors for atopic diseases and recurrent respiratory tract infections in children and investigated whether the associations between these risk factors with atopic diseases differed from the associations with recurrent respiratory tract infections (**chapter 5**).

The impact of atopic diseases on patients' welfare

'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.'

World Health Organization, 1948

Diagnostic modalities mainly focus on a single organ, but it is likely that diagnostic strategies have a broader impact. In this regard, outcome measures that reflect the overall wellbeing of patients are relevant. The patients' perspective on several domains of life, including physical, mental and social health, can be measured using health-related quality of life questionnaires.⁴² The concept of health-related quality of life (HRQL) is rooted in the definition of health by the World Health Organization. HRQL can be measured using generic or disease-specific questionnaires. Generic HRQL questionnaires facilitate comparison between different diseases and disease-specific HRQL questionnaires reflect disease-related impairments. Previous research using generic HRQL questionnaires showed that children with atopic diseases have impaired quality of life compared to the general population.^{43,44} Further insight into the impact of atopic diseases on patients' welfare can be gained by assessing anxiety symptoms. Previous studies indicated that anxiety symptoms are highly prevalent in children with atopic diseases, especially in children with multiple atopic diseases.^{45,46}

Peanut allergy

Food allergy is detrimental to patients' welfare due to the constant vigilance to avoid food allergens and the fear of accidental allergic reactions.⁴⁷ Children with peanut allergy experience more impairments in HRQL compared with children with other food allergies.⁴⁸ Peanut allergy may have profound impact on anxiety and HRQL as symptoms can be severe and the amount of peanut triggering an allergic reaction is often minute.^{49,50} In parents of children with peanut allergy, considerable levels of anxiety have been reported.⁵¹ Moreover, increased levels of anxiety have been reported in parents of children with suspected food allergy prior to a definitive food allergy diagnosis.⁵²

Previous research suggests that an oral food challenge may be associated with improved health-related quality of life and reduced anxiety.^{12-14,53} Children and their parents may benefit from an oral food challenge as the procedure provides insights into the absence or presence of a food allergy.⁵⁴

In **chapter 6** we systematically reviewed the current literature on the impact of diagnostic interventions on generic and disease-specific health-related quality of life. In **chapter 2** we investigated the impact of the diagnostic flowchart for peanut

allergy on patients' and parents' anxiety levels. Finally, in **chapter 4** we evaluated the long-term follow-up after a DBPCFC for peanut, including disease-specific health-related quality of life.

Asthma

Asthma is the most prevalent atopic disease and one of the most prevalent chronic diseases in children, imposing a consistent burden on the health system and on patients.^{3,55} Asthma has a significant detrimental impact on quality of life of children, especially when asthma is uncontrolled.^{56,57} Adequate asthma control is the main management goal in asthma treatment. Numerous studies have shown asthma control to be suboptimal despite the availability of effective asthma treatment.^{58–64} Several predictors of uncontrolled asthma in children have been reported including demographic characteristics (e.g. age, male gender and maternal education level), environmental characteristics (e.g. exposure to indoor smoking and pet ownership), treatment characteristics (e.g. high use of short-acting β_2 -agonists and incorrect inhaler technique) and co-existing atopic diseases (e.g. food allergy and allergic rhinitis).^{56,65–67} We investigated the prevalence and predictors of uncontrolled asthma among children who were referred for asthma or children who were referred for the evaluation of atopic diseases other than asthma to secondary care in **chapter 7**.

Uncontrolled asthma, including asthma symptoms and asthma exacerbations, often occur after exposure to allergic (e.g. pollen or animals) or non-allergic (e.g. infections or physical exercise) asthma triggers. Previous research suggests that a higher number of asthma triggers may be associated with impaired disease-specific quality of life in children with severe or difficult-to-treat asthma and in adults.^{68–70} In **chapter 8**, we examined the single and composite impact of allergic and non-allergic asthma triggers on disease-specific and generic health-related quality of life in children with asthma in secondary and tertiary care.

Aim of this thesis

This thesis focuses on improving diagnostics and quality of life in patients with atopic diseases, particularly in patients with peanut allergy and asthma.

We aimed to:

1. Improve diagnostics in patients with atopic diseases by
 - evaluating a diagnostic flowchart for peanut allergy based on sIgE to Ara h 2 in children with suspected peanut allergy in secondary and tertiary care in **chapter 2**,
 - validating a cutoff level of sIgE to Ara h 2 and developing a diagnostic flowchart in adults with suspected peanut allergy in **chapter 3**,
 - evaluating the long-term follow-up after double-blind placebo-controlled food challenges for peanut in **chapter 4**,
 - and studying risk factors for atopic diseases and recurrent respiratory infections in **chapter 5**.
2. Improve quality of life in patients with atopic diseases by
 - summarizing current literature on the impact of diagnostic testing for food allergy on quality of life in **chapter 6**,
 - evaluating the impact of a diagnostic flowchart for peanut allergy on patients' welfare in **chapter 2**,
 - evaluating the long-term impact of a double-blind placebo-controlled food challenge for peanut on quality of life in **chapter 4**,
 - investigating the prevalence and predictors of uncontrolled asthma in **chapter 7**,
 - and assessing the association between asthma triggers and quality of life in **chapter 8**.

The clinical implications of our findings are discussed in **chapter 9**.

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Chapter 2

A diagnostic flowchart for pediatric peanut allergy using Ara h 2 is accurate, safe and reduces costs

Submitted

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Geert W.J. Frederix, André C. Knulst, Cornelis K. van der Ent and Thuy My Le

Abstract

Background

Several studies showed that sIgE to Ara h 2 is a good predictor of peanut allergy and may reduce the need for double-blind placebo-controlled food challenges (DBPCFCs), yet validation and implementation in clinical practice has not been studied.

Objective

To validate previously published Ara h 2 cutoff levels and implement a diagnostic flowchart to evaluate its 1) diagnostic performance, 2) costs and 3) impact on patients.

Methods

Physicians of tertiary (n=1) and secondary (n=3) care centers were instructed to use a flowchart in 150 children with suspected peanut allergy based on the Ara h 2 level (kU_A/L): ≤ 0.1 home introduction, 0.1-5.0 DBPCFC and ≥ 5.0 open food challenge. The costs of the flowchart were calculated using financial healthcare data and were compared to the costs of a diagnosis according to the guideline. The State-Trait Anxiety Inventory was administered at baseline, after Ara h 2 was communicated and after 6 months.

Results

The diagnostic flowchart correctly classified 100% of children with Ara h 2 ≤ 0.1 kU_A/L as peanut-tolerant and 89-97% of children with Ara h 2 ≥ 5.0 kU_A/L as peanut-allergic. None of the children with Ara h 2 ≤ 0.1 kU_A/L experienced allergic symptoms during (home) introduction. Mean annual costs of the flowchart were €320-€636 per patient lower compared to the guideline. Parental state anxiety was lower after an Ara h 2 result ≤ 0.1 kU_A/L compared to baseline.

Conclusion

Ara h 2 cutoff levels are validated in secondary and tertiary care. Furthermore, the diagnostic flowchart is accurate, safe and reduces costs in children.

Introduction

Peanut allergy is one of the most common IgE-mediated food allergies, estimated to affect 0.2-2.5% of children.^{1,2} An accurate diagnosis of peanut allergy is important to adequately counsel allergic children and their parents on the elimination of peanut, the prevention and the treatment of accidental allergic reactions. In children with suspected peanut allergy who prove to be peanut-tolerant, exclusion of peanut allergy is important to guide peanut introduction and to prevent unnecessary elimination diets. In addition, an accurate diagnosis of peanut allergy is important to reduce (parental) anxiety and improve health-related quality of life.^{3,4} The oral food challenge (OFC), particularly the double-blind placebo-controlled food challenge (DBPCFC), is currently the gold standard for the diagnosis of peanut allergy according to the EAACI Food Allergy and Anaphylaxis Guidelines.⁵ However, the DBPCFC is difficult in daily practice as the procedure is time-consuming, costly to patients and health services and might be difficult to access.^{5,6} Thus, there is need for improved diagnostic strategies that could accurately predict the DBPCFC result thereby reducing the number of DBPCFCs.

Various studies, including from our own research group, have reported that sIgE to peanut specific component Ara h 2 is useful to distinguish peanut-allergic from peanut-tolerant children and is highly superior to sIgE to peanut extract and other peanut components.⁷⁻¹¹ When using the cutoff levels of sIgE to Ara h 2 with the highest negative and positive predictive value, 62% of children could be classified correctly as peanut-tolerant or peanut-allergic. The validation and implementation of scientific research into daily clinical practice is very important to validate previous findings and evaluate diagnostic accuracy, safety, costs and adherence. However, until now no studies have investigated validation of cutoff levels of sIgE to Ara h 2 and the prospective implementation of a diagnostic flowchart based on sIgE to Ara h 2 in daily practice. Thus, it is unknown whether the use of a diagnostic flowchart based on Ara h 2 in children with suspected peanut allergy is accurate and safe, whether it can be used in different clinical settings (secondary and tertiary care) and whether a diagnostic flowchart is beneficial in terms of costs and patients' welfare.

In the current study, we aimed to validate previously published sIgE to Ara h 2 cutoff levels and implement a diagnostic flowchart based on these cutoff levels to evaluate its 1) diagnostic performance, 2) direct and indirect costs and 3) impact on patients (i.e. anxiety levels).

Methods

Study population

We performed a prospective cohort study in one tertiary care center (i.e. university hospital) and three secondary care centers (i.e. general hospitals) in the Netherlands between January 2017 and July 2018. All consecutive children aged 3.5 to 18 years with suspected peanut allergy, seen by a pediatrician or an allergist, were eligible for inclusion. Suspected peanut allergy was based on a clinical history of an allergic reaction to peanut, peanut sensitization (peanut sIgE ≥ 0.35 kU_A/L or peanut skin prick test mean wheal size ≥ 3 mm) or an elimination diet for peanut for more than 1 year. The study was approved by the ethical committee of the University Medical Center Utrecht (nr. 16-1456/C). Parents and children aged 12 years and older provided written informed consent before enrolment in the study.

Study procedures

Specific IgE to Ara h 2 was determined in all children using the ImmunoCAP method (Thermo Fisher Scientific, Uppsala, Sweden). Physicians were instructed to follow the diagnostic flowchart based on previous found levels of sIgE to Ara h 2 to confirm or exclude peanut allergy as depicted in Figure 1.⁷ Children with an Ara h 2 level ≤ 0.1 kU_A/L were considered to have a very high probability of being peanut-tolerant and were instructed to introduce peanut at home. Home introduction consisted of a 7-day schedule with increasing amounts of peanuts up to 10 grams of whole peanuts on the last day. Children with an Ara h 2 level ≥ 5.0 kU_A/L were considered to have a very high probability of being peanut-allergic. The purpose of further diagnostic testing in these children was to gain insight into the severity of peanut allergy and the threshold of the peanut allergic reaction. Thus, a 1-day open oral food challenge (OFC) instead of a 2-day double-blind placebo-controlled food challenge (DBPCFC) was indicated. Children with an Ara h 2 level between 0.1 and 5.0 kU_A/L were considered inconclusive and were supposed to undergo a 2-day DBPCFC. The 2-day DBPCFCs and 1-day open OFCs were performed in a clinical setting with equipment for resuscitation. The verum day of the DBPCFC and open OFC consisted of 7 increasing doses of ginger bread containing 1 mg to 2500 mg peanut protein.¹² If no or inconclusive symptoms occurred on both days of the DBPCFC or on the day of the open OFC, a consecutive open challenge with 10 grams of whole peanuts was performed. All signs and symptoms during the challenge were scored according to the PRACTALL consensus report.¹³ Subsequently, an expert panel of 3 or 4 experienced pediatric allergologists and food allergy experts, blinded for the Ara h 2 level, individually classified children as peanut-allergic or peanut-tolerant and assessed the severity of symptoms and eliciting doses in peanut-allergic children. A food challenge was considered positive when objective or severe long-lasting or repetitive subjective symptoms occurred.

The severity of symptoms was graded according to the Sampson classification of anaphylaxis as grade 1 to 5.¹⁴ Any discrepancies between the experts were discussed in a panel discussion meeting until agreement among all experts was reached.

Demographic and clinical information regarding history of peanut allergy and other atopic diseases was obtained by standardized questionnaires. Asthma, allergic rhinitis, atopic dermatitis and other food allergies were defined as having a doctor's diagnosis.

Figure 1. Design of the diagnostic flowchart

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; OFC, oral food challenge; sIgE, specific IgE.

Validation of Ara h 2 cutoff levels

The validity of the sIgE to Ara h 2 cutoff levels was evaluated by calculating the corresponding sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). Furthermore, the percentage of patients diagnosed correctly using the sIgE to Ara h 2 cutoff levels was calculated.

Diagnostic performance of the diagnostic flowchart

The diagnostic accuracy of the diagnostic flowchart was evaluated using the area under the curve (AUC) of the receiver operating characteristic. These analyses were stratified by secondary and tertiary care. The safety of the diagnostic flowchart was assessed by calculating the number of allergic reactions during home introduction of peanut. The adherence to the diagnostic flowchart was evaluated by calculating the number of children diagnosed according to the diagnostic flowchart and

identifying reasons for non-adherence. By exception and with argumentation, physicians could choose a different diagnostic strategy than the diagnostic flowchart based on their expert opinion.

Cost assessment

The cost assessment was conducted from a societal perspective and included relevant costs borne by the healthcare system (i.e. consultations and diagnostic tests), costs borne by patients and families (i.e. travel expenses) and costs borne by other sectors (i.e. productivity losses) in 12 months after the baseline visit. Costs were based on national guidelines (i.e. Dutch Healthcare Authority and the National Health Care Institute in the Netherlands) and were corrected for inflation using the consumer price index for 2018.^{15,16} The costs were calculated per patient per year by multiplying the volume by the costs per item. The direct medical costs included allergy consultations (i.e. outpatient visits and telephonic consultations) and allergy diagnostic tests (i.e. laboratory tests, skin prick tests, pulmonary function tests and oral food challenges). The data on healthcare use were extracted from the financial healthcare data of the participating centers. Missing data regarding oral food challenges were complemented using electronic patients files. In addition, direct out-of-pocket costs borne by patients and families were included and comprised of travel expenses arising out of the outpatient visits and oral food challenges. Travel expenses were calculated by determining the geographical distance between the families' residence and the hospital using Google Maps and costs for transportation were taken from the national guideline.¹⁶ The indirect costs comprised of productivity losses due to work absenteeism. The total costs of productivity losses were estimated by multiplying the number of visits to the outpatient clinic and oral food challenges by the time spent for each item, respectively 1 and 8 hours. The lost time of work was then valued according to the Dutch average hourly wage (€38.21).¹⁶

Mean costs were calculated per patient per year for three scenarios. Scenario A reflected the mean costs of the diagnostic flowchart in daily practice (including children who were diagnosed according to the trajectory of the diagnostic flowchart and children who were diagnosed with other strategies). Scenario B reflected the mean costs of the diagnostic flowchart in theory: only the subset of children who followed the trajectory of the diagnostic flowchart were included in this scenario. Scenario C reflected the mean costs of the diagnostic pathway for peanut allergy according to the current Dutch national guideline.¹⁷ In scenario C, all children with sensitization to peanut (sIgE peanut extract ≥ 0.35 kU_A/L or skin prick test ≥ 3 mm) were supposed to undergo a DBPCFC and all children without peanut sensitization were supposed to start eating peanut at home. The costs for scenario C were derived from the costs in scenario B.

Impact on patients

Anxiety was measured at baseline, after the telephonic consultation communicating the sIgE to Ara h 2 level and discussing the subsequent diagnostic strategy with parents and patients and after 6 months follow-up. Anxiety was measured using the Spielburger State-Trait Anxiety Inventory (STAI) for parents and the State-Trait Anxiety Inventory for Children (STAIC) for children aged 8 years and older.^{18,19} To assess State-Anxiety (anxiety as an emotional state), parents were instructed to imagine how they would feel if their child was offered peanuts and children to imagine how they would feel if they were offered peanuts.⁴ The items were scored on a 4-point scale with a cumulative score ranging between 20 (low anxiety) and 80 points (high anxiety) for the STAI and between 20 and 60 for the STAIC. The difference in scores was considered clinically relevant when the minimal clinically important difference (MCID) of 10 points was exceeded.²⁰

Statistical analysis

Descriptive statistics were expressed as numbers (percentages) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables with a normal or skewed distribution, respectively. Differences in baseline characteristics between children across different sIgE to Ara h 2 levels (≤ 0.1 , 0.1 - 5.0 and ≥ 5.0 kU_A/L) were statistically evaluated by the chi-square test for categorical variables and the one-way analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate, with correction for multiple testing using the Benjamini-Hochberg procedure. Statistical analyses were performed using SPSS for Windows (version 25.0. Armonk, NY: IMB Corp) and R (packages data.table v. 1.12.2 and dplyr v. 0.8.3). A *P*-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 150 children with suspected peanut allergy were included in secondary care (65%) and tertiary care (35%). Children were grouped based on the level of sIgE to Ara h 2: ≤ 0.1 kU_A/L in 29 (19%) children, 0.1 to 5.0 kU_A/L in 68 (45%) children and ≥ 5.0 kU_A/L in 53 (35%) children. Overall, children had a median (interquartile range) age of 7.9 (5.4 to 13.0) years (Table 1).

Children were suspected of peanut allergy because of a previous reaction to peanut (71%), sensitization without previous ingestion (16%) or an elimination diet for more than 1 year (13%). Children with a sIgE to Ara h 2 level ≤ 0.1 kU_A/L were significantly older (median age 12.1 years) compared to children with an Ara h 2 level of 0.1 to 5.0 kU_A/L or ≥ 5 kU_A/L (median age 7.6 and 7.1 years, respectively) ($p=0.014$) and were more often suspected of peanut allergy based on an

elimination diet for at least 1 year (31%) compared to children with an Ara h 2 level of 0.1 to 5 or ≥ 5 (12% and 6%, respectively) ($p=0.014$).

Table 1. Baseline characteristics

	All children	sIgE to Ara h 2 category (kU _A /L)			P-value [†]
		≤ 0.1	0.1-5.0	≥ 5.0	
Number (%)	150	29 (19)	68 (45)	53 (35)	
Age in years, median (IQR)	7.9 (5.4-13)	12.1 (8-15.7)	7.6 (5.2-11.5)	7.1 (5.3-10.5)	0.014
Gender: male	88 (59)	11 (38)	44 (65)	33 (62)	0.090
Setting					0.860
Secondary care	97 (65)	20 (69)	43 (63)	34 (64)	
Tertiary care	53 (35)	9 (31)	25 (37)	19 (36)	
Suspected peanut allergy					0.014
Previous reaction	106 (71)	17 (59)	53 (78)	36 (68)	
Sensitization	24 (16)	3 (10)	7 (10)	14 (26)	
Elimination diet >1 year	20 (13)	9 (31)	8 (12)	3 (6)	
Previous reaction [‡]					0.453
No reaction	44 (29)	12 (41)	15 (22)	17 (32)	
Grade 1	31 (21)	6 (21)	15 (22)	10 (19)	
Grade 2	32 (21)	3 (10)	20 (29)	9 (17)	
Grade 3	18 (12)	2 (7)	8 (12)	8 (15)	
Grade 4	21 (14)	4 (14)	9 (13)	8 (15)	
Grade 5	0	0	0	0	
Missing data	4 (3)	2 (7)	1 (1)	1 (2)	
Elimination other food allergens					0.266
No	42 (28)	9 (31)	22 (32)	11 (21)	
1 or 2	43 (29)	5 (17)	20 (29)	18 (34)	
3 or 4	30 (20)	5 (17)	17 (25)	8 (15)	
5 or 6	27 (18)	7 (24)	8 (12)	12 (23)	
7 or more	8 (5)	3 (10)	1 (1)	4 (8)	
Atopic comorbidities					
Atopic dermatitis	118 (79)	21 (72)	57 (84)	40 (75)	0.453
Allergic rhinitis	70 (47)	17 (59)	37 (54)	16 (30)	0.042
Asthma	48 (32)	5 (17)	22 (32)	21 (40)	0.207

Value are numbers (%), unless otherwise indicated.

[†] Benjamini-Hochberg adjusted *P*-values for comparison of differences among 3 groups.

[‡] Missing data n=4. Most severe reaction according to the Sampson classification of anaphylaxis.

Abbreviations: IQR, interquartile range; sIgE, specific IgE.

Validation of Ara h 2 and diagnostic accuracy and safety of the flowchart

Figure 2 shows the results of the diagnostic flowchart. All children with a sIgE to Ara h 2 level ≤ 0.1 kU_A/L were classified as peanut-tolerant after home introduction or diagnostic testing (i.e. food challenge or clinical introduction). Fifty-eight percent of children with a sIgE to Ara h 2 level between 0.1 and 5.0 kU_A/L were classified as peanut-allergic and 42% as peanut-tolerant. Eighty-nine percent of children with a sIgE to Ara h 2 level ≥ 5 kU_A/L were classified as peanut-allergic, 3% ($n = 1$) as peanut-tolerant (Ara h 2 level 7.1 kU_A/L) and 8% ($n = 3$) as inconclusive. Children with an inconclusive result did not complete the open OFC due to aversion ($n=1$),

mild abdominal pain (n=1) or mild abdominal pain and nausea (n=1). Thus, we could classify 100% of children with a sIgE to Ara h 2 level ≤ 0.1 kU_A/L correctly as peanut-tolerant (i.e. 100% negative predictive value). Furthermore, we could classify 89% of children with a sIgE to Ara h 2 level ≥ 5.0 kU_A/L correctly as peanut-allergic if all children with an inconclusive outcome would be peanut-tolerant or 97% of children if all these children would be peanut-allergic (i.e. 89-97% positive predictive value). The sensitivity, specificity and predictive values of the sIgE to Ara h 2 cutoff levels are depicted in Supplemental Table 1.

Figure 2. Results of the diagnostic flowchart

Values are numbers (%).

Abbreviations: FC, food challenge, Inc, inconclusive; sIgE, specific IgE.

Specific IgE to Ara h 2 was a strong predictor of peanut allergy and showed high discriminative capacity (AUC 0.94; 95% confidence interval [CI] 0.90-0.98) (Figure 3). A stratified analysis by health care line showed high discriminative capacity in children in tertiary care (AUC 0.99; 0.98-1.00) and in secondary care (AUC 0.92; 0.86-0.98). Finally, the diagnostic flowchart was safe as none of the children with an Ara h 2 level ≤ 0.1 kU_A/L experienced allergic symptoms during peanut introduction.

Figure 3. ROC-curves of sIgE to Ara h 2

Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; sIgE, specific IgE.

Adherence to the diagnostic flowchart

Overall, 92 of 150 (61%) children followed the trajectory of the diagnostic flowchart. Thirty-four (23%) children were not further evaluated after Ara h 2 determination and in 24 (16%) children, a different diagnostic strategy was chosen (Supplemental Figure 1). The most common reason to choose a different diagnostic strategy in children with an Ara h 2 level ≤ 0.1 and 0.1 to 5.0 kU_A/L was patients' preference due to anxiety of the child and/or parent(s). However, baseline state anxiety in parents who reported anxiety as reason to choose a different diagnostic strategy was comparable to state anxiety in parents who did not report anxiety (state anxiety 50 and 52, respectively). The most frequent reason to choose a different diagnostic strategy in children with an Ara h 2 level ≥ 5.0 kU_A/L was the physician's preference not to perform an oral food challenge due to a suggestive clinical history of previous reaction to peanut and/or anaphylaxis (Supplemental Figure 2).

Cost assessment

Mean (95% CI) cumulative costs of the diagnostic flowchart in daily practice (scenario A) and the diagnostic flowchart in theory (scenario B) were € 2120 (€1924 - € 2317) and € 2437 (€ 2189 - € 2685) per patient per year, respectively (Table 2; Figure 4). Mean costs of the diagnostic flowchart in practice were lower because 34 children did not undergo an oral food challenge. Mean cumulative costs of the diagnostic pathway according to the current national guideline were € 2757 (€ 2441 - € 3072) per patient per year. Thus, the use of the diagnostic flowchart may reduce direct and indirect food-allergy related costs by € 320 (i.e. flowchart in theory) to €636 (i.e. flowchart in daily practice) per patient per year compared to the current national guideline.

Table 2. Mean costs per patient per year

	A Flowchart in practice	B Flowchart in theory	C Guideline
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Number	150	92	134
Total costs	€ 2120 (1924-2317)	€ 2437 (2189- 2685)	€ 2757 (2441- 3072)
Direct costs			
<i>Consultations</i>			
Outpatient clinic	€ 319 (270-369)	€ 269 (227-311)	€ 246 (179-314)
Telephone	€ 67 (58-77)	€ 72 (59-84)	€ 62 (44-80)
<i>Diagnostic testing</i>			
Food challenges	€ 937 (809-1,064)	€ 1204 (1,041-1,367)	€ 1,433 (1,233-1,634)
Laboratory testing	€ 112 (95-129)	€ 103 (81-126)	€ 116 (77-155)
Skin prick testing	€ 48 (34-61)	€ 44 (28-60)	€ 47 (20-73)
Lung function	€ 44 (26-61)	€ 26 (13-40)	€ 29 (5-53)
<i>Travel expenses</i>	€ 54 (45-63)	€ 54 (44-64)	€ 60 (44-75)
Indirect costs			
Productivity loss	€ 540 (477-602)	€ 666 (584-47)	€ 763 (664-86)

Including all children (A), children diagnosed according to the diagnostic flowchart (B) and a scenario analysis on the costs for children diagnosed according to the guideline (C).

Abbreviations: CI, confidence interval.

Figure 4. Mean costs per patient per year

Including all children (A), children diagnosed according to the diagnostic flowchart (B) and a scenario analysis on the costs for children diagnosed according to the guideline (C).

Abbreviations: n, number.

Impact on patients

Parental state anxiety was high at baseline in all Ara h 2 groups with a mean (standard error [SE]) score of 57.7 (2). Parental state anxiety reduced clinically relevant after the telephonic consultation discussing the Ara h 2 result if the Ara h 2 level was ≤ 0.1 kU_A/L (mean difference, MD 17; SE 4.1) (Figure 5). In parents of children with an Ara h 2 level > 0.1 kU_A/L, state anxiety reduced after 6-months follow-up if the child underwent an oral food challenge (MD 17.9; SE 3.2) and not if the child did not undergo an oral food challenge (MD 5; SE 2.9). Parental state anxiety reduced clinically relevant both after a positive and negative oral food challenge result with a mean (SE) difference of 16.6 (3.6) and 19.6 (6) respectively. Child-reported state anxiety did not improve clinically relevant during follow-up.

Figure 5. State anxiety of parents and children across groups with different Ara h 2 levels
The cumulative score for the state anxiety of parents ranged between 20 (low anxiety) and 80 points (high anxiety) and for state anxiety of children between 20 and 60.
Abbreviations: n, number; SE, standard error.

Discussion

This is the first study investigating the validation of sIgE to Ara h 2 cutoff levels and the implementation of a diagnostic flowchart based on sIgE to Ara h 2 in children with suspected peanut allergy. Our previously published sIgE to Ara h 2 cutoff levels were validated in children in secondary and tertiary care.⁷ The implemented diagnostic flowchart accurately classified children as peanut-tolerant and peanut-allergic with a negative and positive predictive value of 100% and 89-97%, respectively. Furthermore, the diagnostic flowchart was safe to use in daily clinical practice and could reduce direct and indirect costs of diagnosing peanut allergy by € 320 to € 636 per patient per year compared to diagnosing peanut allergy according to the current national guideline.

All children in our cohort who were not sensitized to Ara h 2 were peanut-tolerant, even when the child reported a severe allergic reaction to peanut in clinical history. It should be kept in mind that rare cases of (severe) peanut allergy have been described in literature in children who were not sensitized to Ara h 2.²¹⁻²⁵ These children might be sensitized to other peanut components than Ara h 2, for example Ara h 6 or Ara h 7.^{26,27} However, we believe our diagnostic flowchart is safe to use as the probability of an allergic reaction in children with an Ara h 2 level ≤ 0.1 kU_A/L is very low (0% in this and in our previous study) and children are instructed to introduce peanut according to an introduction schedule starting at a very small amount of peanut. The adherence to the diagnostic flowchart for children with an Ara h 2 level ≤ 0.1 kU_A/L was low. The majority of children with an Ara h 2 level ≤ 0.1 kU_A/L in our cohort introduced peanut in the hospital and not at home because children, parents or physicians (unfairly afterwards) feared an allergic reaction to peanut. In this regard, physicians may consider introducing peanut at the outpatient clinic instead of in the hospital to further reduce costs.

We also conclude that total direct and indirect costs seemed to be lower when children were diagnosed according to the diagnostic flowchart compared to the current national guideline. With an estimated 2400 referrals per year in the Netherlands this implicates a reduction in societal costs of € 767,101 per year when all children adhere to the diagnostic flowchart up to € 1,526,688 per year in daily practice.^{1,28} A model-based cost-effectiveness analysis has been performed in a Norwegian cohort of children with suspected peanut allergy.²⁹ In support of our findings, the authors reported that a diagnostic flowchart based on peanut components (i.e. Ara h 1, 2, 3, 8 and 9) appeared to be more cost-effective than current clinical practice based on sIgE to peanut extract, skin prick testing and oral food challenges.

We showed that parental state anxiety is largely reduced after a negative Ara h 2 result and after oral food challenges, irrespective of the oral food challenge result. Parental state anxiety remained high during 6-months follow-up if children (were) declined further diagnostic testing after a positive Ara h 2 outcome (i.e. > 0.1 kU_A/L). One of the main reasons to decline further diagnostic testing was anxiety. These results further underline the beneficial impact of a clear diagnosis of food allergy on parental state anxiety and quality of life as previously reported.^{3,4} Further research is needed to investigate how to handle and/or reduce food-related anxiety in children, especially when anxiety is the reason to decline further diagnostic testing.

To appreciate the results of our study, several limitations should be taken into account. First, our study lacked a control group limiting the ability to compare the diagnostic flowchart to current daily clinical practice according to the guideline.

However, by comparing the flowchart in theory, in practice and a guideline-scenario we are able to draw valid conclusions regarding the costs of the diagnostic flowchart. Second, we may have underestimated the direct out-of-pocket costs borne by patients and families as we included only the costs of travel to the hospital. A recent systematic review assessed the economic burden of food allergy and showed that food allergy is associated with substantial out-of-pocket costs, for instance the costs of special allergen-free foods, costs of safe child care and copayments for medications.^{30,31} In addition, there is a risk of registration error as direct costs were based on financial healthcare data and indirect costs were based on the average hourly wage. However, our results on the difference in costs between the diagnostic flowchart and the current guideline is not likely influenced by these limitations as the data collection methods were comparable between the analyzed scenarios. Finally, one fourth of children were not included in the analysis on the validation of Ara h 2 cutoff levels and the diagnostic accuracy and safety of the diagnostic flowchart as these children did not undergo further diagnostic testing after the Ara h 2 result. However, the denoted reasons to decline further testing provide meaningful insight into psychosocial barriers and practical implications of the implementation of a new diagnostic strategy in daily practice.

The results of our study are strengthened by the prospective recruitment of all children with a suspected peanut allergy in four centers representing a large area in the Netherlands. In addition, this is the first study that evaluated the validation of Ara h 2 cutoff levels and the prospective implementation of a diagnostic flowchart based on sensitization to peanut component Ara h 2 in daily practices in secondary and tertiary care. Our study assessed a broad range of relevant outcomes, including validation, diagnostic accuracy, safety, adherence, direct and indirect costs and impact on patients.

In conclusion, previously published cutoff levels of sIgE to Ara h 2 were validated in children with suspected peanut allergy in secondary and tertiary care. The diagnostic flowchart based on these Ara h 2 cutoff levels was accurate, safe and beneficial in terms of costs and parental anxiety levels. Our results support the continued use of the diagnostic flowchart and implementation of the diagnostic flowchart in our national guideline. Furthermore, an (adapted) diagnostic flowchart may be used in other countries after international validation studies.

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Supplemental figures

Supplemental Figure 1. Diagnostic pathway of included children

[†] All children were peanut-tolerant.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; FC, food challenge; OFC, oral food challenge.

Supplemental Figure 2. Reasons to choose a diagnostic strategy other than the diagnostic flowchart per Ara h 2 category

Supplemental tables

Supplemental Table 1. Diagnostic value of sIgE to Ara h 2 cutoff levels to predict peanut allergy

Patients	N	Cutoff level	Sensitivity	Specificity	PPV	NPV
		kU _A /L	%	%	%	%
All children	113	0.1	100	53	74	100
		5.0	53	98	97	62
Secondary care	77	0.1	100	59	78	100
		5.0	49	97	96	57
Tertiary care	36	0.1	100	41	66	100
		5.0	63	100	100	71

Abbreviations: n, number; NPV, negative predictive value; PPV, positive predictive value.

Chapter 3

**Accurate prediction of peanut allergy in
one third of adults using a validated
Ara h 2 cutoff**

Submitted

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Abstract

Background

The diagnostic value of peanut components is extensively studied in children, but to a lesser extent in adults with suspected peanut allergy. The use of peanut components in daily practice may reduce the need for double-blind placebo-controlled food challenges (DBPCFCs), however validation studies are currently lacking.

Objective

To 1) evaluate the diagnostic value of (combined) peanut components and 2) validate a previous found Ara h 2 cutoff level with 100% positive predictive value (PPV) in adults with suspected peanut allergy.

Methods

Adults who underwent a peanut DBPCFC were included: 84 patients from a previous study (2002 to 2012) and 70 new patients (2012 to 2019). sIgE to peanut extract, Ara h 1, 2, 3, 6 and 8 was measured using ImmunoCAP. Diagnostic value was assessed with an area under the curve (AUC) analysis.

Results

In total, 95 (62%) patients were peanut-allergic. sIgE to Ara h 2 and Ara h 6 were the best predictors with an AUC (95% CI) of 0.85 (0.79-0.91) and 0.85 (0.79-0.92), respectively. The Ara h 2 cutoff level with 100% PPV (≥ 1.75 kU_A/L) was validated in the 70 new patients. Thirty percent of all included patients could be classified correctly as peanut-allergic using this validated cutoff level.

Conclusion

Specific IgE to Ara h 2 and Ara h 6 have equally high discriminative ability. Peanut allergy can be predicted accurately in one third of adults using a validated cutoff level of sIgE to Ara h 2.

Introduction

Peanut allergy affects up to 0.60% of adults in Europe.^{1–3} The reference standard to diagnose or exclude peanut allergy is a double-blind placebo-controlled food challenge (DBPCFC).⁴ However, a DBPCFC is time-consuming, labor-intensive, costly and not without risks because of the potential for severe allergic reactions including anaphylaxis.⁵ Given these limitations, new diagnostic strategies have been evaluated that could reduce the number of DBPCFCs.⁶

Serology tests may be used to reduce the number of DBPCFCs when validated cutoff levels are used.^{7–9} Sensitization to peanut component allergens (e.g. component-resolved diagnostics) has emerged as a useful tool to diagnose peanut allergy with increased diagnostic accuracy compared to sensitization to crude peanut extract or skin prick testing.^{8,10–16} Currently, 17 peanut allergens have been described by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee.¹⁷ Ara h 2 and Ara h 6 are seed storage proteins and 2S albumins with highly similar protein structure¹⁸, and have been recognized as the most important allergens associated with peanut allergy.^{8,10,15} Ara h 7 is a third 2S albumin and is gaining attention as predictor for peanut allergy.¹¹ Ara h 1 and Ara h 3 are also seed storage proteins and, together with Ara h 2, have been designated as the major peanut allergens.^{19,20} Ara h 8 is a Bet v 1 homologous pathogenesis-related (PR)-10 protein which cross-sensitizes with major-birch pollen allergen Bet v 1 in adults.²¹ Isolated sensitization to Ara h 8 is associated with mild or no symptoms, although the role of Ara h 8 in multiple sensitized patients remains unclear.²² Finally, Ara h 9 is a lipid transfer protein, and a major allergen in the Mediterranean area.²³

Current evidence on cutoff levels for peanut components in adults is limited, as the majority of research has been conducted in children. Furthermore, validation studies of the diagnostic value of peanut components are currently lacking. Validation studies are warranted to implement research findings into daily practice. A previous study performed in our center included 84 adults, and showed that peanut allergy can be predicted with 100% positive predictive value (PPV) using a sIgE to Ara h 2 cutoff level of ≥ 1.75 kU_A/L.¹⁶ Other recent studies have shown that the discriminative ability of sIgE to Ara h 6 is comparable to sIgE to Ara h 2.^{8,15,24} Peanut component Ara h 6 has mainly been studied using a multiplex assay as opposed to a singleplex assay.^{14,15,24,25} The results of a multiplex assay are semi-quantitative and therefore, these results cannot be used to determine cutoff levels.²⁶

In the current study, we aimed to evaluate the diagnostic value of sIgE to peanut extract, Ara h 1, 2, 3, 6 and 8, and combinations, using a singleplex assay in adults with suspected peanut allergy. Furthermore, we aimed to validate the previously published cutoff level of sIgE to Ara h 2 with 100% positive predictive value (i.e. ≥ 1.75 kU_A/L).

Methods

Study population

All 84 adult patients who participated in the previous diagnostic study and underwent a double-blind placebo-controlled food challenge (DBPCFC) for peanut at the University Medical Centre Utrecht between 2002 and June 2012 were eligible for inclusion.¹⁶ Furthermore, we expanded the cohort with patients who underwent a DBPCFC for peanut between June 2012 and May 2019 (n=120). The DBPCFC was performed because of a suspected peanut allergy based on clinical history or sensitization. Patients with an inconclusive DBPCFC result (n=18) or without leftover serum (n=32) were excluded from the analysis. Included and excluded patients were comparable in age, gender, presence of allergic rhinitis, severity of peanut allergy and levels of sIgE to peanut extract and components (Supplemental Table 1). The current study was approved by the ethical committee of the University Medical Center Utrecht (no. 18-428).

Oral food challenges

DBPCFCs were performed in a clinical setting equipped for resuscitation in accordance with the international consensus protocol as previously described.^{27–29} The DBPCFC result was discussed among food allergy experts and was considered positive when objective symptoms occurred ('positive objective'), or when subjective symptoms lasted for at least 45 minutes, or occurred to at least 3 subsequent doses ('positive subjective'). The severity of the DBPCFC was based on the adapted Mueller score: 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.^{16,30}

Sensitization (sIgE) measurements

Specific IgE (sIgE) values to peanut extract and peanut components Ara h 1, 2, 3, 6 and 8 were determined using the ImmunoCAP platform (Thermo Fisher Scientific Uppsala, Sweden). In the previous diagnostic study, sIgE to peanut extract, Ara h 1, 2, 3 and 8 was already measured in all patients (n=84). In these patients Ara h 6 was determined as part of the current study in those with available leftover serum (n=48). In all newly included (n = 70) patients, we determined Ara h 1, 2, 3, 6 and 8.

In peanut-allergic patients without sensitization to peanut components or peanut extract as measured using the ImmunoCAP platform, sensitization to Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15 was assessed using a line blot (EUROLINE, EUROIMMUN, Lübeck, Germany) as described elsewhere.¹¹

Statistical analyses

The differences between patients with a positive and a negative DBPCFC result were analyzed using the chi-square test and Mann-Whitney U test, when appropriate. The diagnostic value of sIgE to peanut extract and peanut components was assessed by the area under the curve (AUC) of the receiver-operating characteristic (ROC). The AUC values were compared using DeLong's test for correlated ROC curves.³¹ To evaluate the diagnostic value of all serology tests combined (i.e. sIgE to peanut extract, Ara h 1, 2, 3, 6 and 8), logistic least absolute shrinkage and selection operator (LASSO) regression analysis was performed. The LASSO regression method is based on the regular least-squares method, but includes an additional parameter λ to prevent overfitting and automatically deletes unnecessary covariates.³² We used cross-validation to select λ .

The previously published cutoff level of sIgE to Ara h 2 with 100% positive predictive value (PPV) was validated by calculating the PPV of this cutoff level (≥ 1.75 kU_A/L) in the newly included patients (43 peanut-allergic and 27 peanut-tolerant patients). The sample size needed to have 95% confidence and 80% power to detect a difference of 5% from a presumed PPV of 98% was 31 cases.³³ In addition, the cutoff levels with optimal positive and negative predictive values with corresponding sensitivities and specificities were calculated for peanut extract and all peanut components. Statistical analyses were performed in SPSS for Windows (version 25.0. Armonk, NY: IBM Corp) and R (pROC package v 1.15.3, randomForest package v 4.6-14, OptimalCutpoints package v 1.1-4).

Results

In total, 154 adults were included after a positive (n=95) or a negative (n=59) DBPCFC result. A positive DBPCFC result was based on objective symptoms in 69 (73%) patients and on subjective symptoms in 26 (27%) patients. Patients with a positive DBPCFC result were significantly younger compared to patients with a negative DBPCFC result (median age 25 and 34 years, respectively) and had higher levels of sIgE to peanut extract, Ara h 1, 2, 3 and 6 (Table 1). The level of sIgE to Ara h 8 was comparable between patients with a positive and a negative DBPCFC result.

Table 1. Characteristics of participating patients and details of DBPCFCs

	Total	Positive DBPCFC result	Negative DBPCFC result	P-value
n (%)	154	95 (62)	59 (38)	
Age, median (IQR)	27 (22-38)	25 (21-31)	34 (24-43)	<0.001
Male gender	52 (34)	35 (37)	17 (29)	0.306
Allergic rhinitis [†]	69 (45)	30 (32)	22 (37)	0.236
Sensitization, median (IQR)				
sIgE peanut extract	1.65 (0.35-11.05)	6.20 (0.72-23.70)	0.44 (0.16-1.65)	<0.001
sIgE Ara h 1	0.02 (0.00-0.61)	0.10 (0.01-7.58)	0.00 (0.00-0.03)	<0.001
sIgE Ara h 2	0.16 (0.03-3.50)	2.20 (1.14-10.00)	0.03 (0.00-0.08)	<0.001
sIgE Ara h 3	0.03 (0.01-0.18)	0.07 (0.01-0.92)	0.01 (0.00-0.03)	<0.001
sIgE Ara h 6 [‡]	0.07 (0.00-3.14)	1.37 (0.08-9.50)	0.00 (0.00-0.03)	<0.001
sIgE Ara h 8	2.02 (0.11-8.57)	2.05 (0.24-8.70)	1.50 (0.03-8.53)	0.198
DBPCFC period				0.952
2003-2012	84 (55)	52 (55)	32 (54)	
2012-2019	70 (45)	43 (45)	27 (46)	
DBPCFC result				NA
Positive objective	69 (45)	69 (73)	NA	
Positive subjective	26 (17)	26 (27)	NA	
Negative	59 (38)	NA	59 (100)	
Severity positive DBPCFC [§]				NA
Mueller 0	15 (16)	15 (16)	NA	
Mueller 1	16 (17)	16 (17)	NA	
Mueller 2	32 (34)	32 (34)	NA	
Mueller 3	28 (29)	28 (29)	NA	
Mueller 4	2 (2)	2 (2)	NA	

Value are n (%) unless otherwise indicated.

[†] Missing data n=85

[‡] Missing data n=36

[§] Missing data n=1. Severity of symptoms during the oral food challenge based on the Mueller score with 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.^{16,30}

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; IQR, interquartile range; NA, not applicable; sIgE, specific IgE.

Specific IgE to Ara h 2 and Ara h 6 are the best predictors of peanut allergy

The levels of sIgE to peanut extract, Ara h 1, 2, 3 and 8 were available in all 154 patients and the level of sIgE to Ara h 6 in 118 patients. The diagnostic value of sIgE to peanut extract, Ara h 1, 2, 3 and 8 were comparable in the cohort of 118 and 154 patients (Supplemental Table 2).

The discriminative abilities of sIgE to Ara h 2 and sIgE to Ara h 6 for predicting peanut allergy were high and comparable, with an AUC (95% CI) of 0.85 (0.79-0.91) and 0.85 (0.79-0.92), respectively (Figure 1a). The AUC values of sIgE to Ara h 2 and Ara h 6 were significantly higher than the AUC values of sIgE to peanut extract, Ara h 1, Ara h 3 and Ara h 8 (Supplemental Table 3). When serology tests were used to

predict peanut allergy with objective symptoms, the AUC values of sIgE to Ara h 2 and Ara h 6 increased slightly to respectively 0.90 (0.85-0.95) and 0.90 (0.84-0.96) (Figure 1b). The concentrations of sIgE to Ara h 2 and Ara h 6 were strongly correlated (Pearson Correlation coefficient 0.83).

The final covariates included in the LASSO model for predicting peanut allergy were sIgE to Ara h 1 and Ara h 6, with Ara h 6 as the most influential predictor. The AUC-value of the LASSO model was 0.85 (0.78-0.92).

Figure 1a. ROC-curves of serology tests to predict a positive DBPCFC result
The Lasso model included sIgE to Ara h 1 and Ara h 6.
Data are AUC values with 95% confidence interval.
Abbreviations: AUC, area under the curve; DBPCFC, double-blind placebo-controlled food challenge; ROC, receiver-operating characteristic.

Figure 1b. ROC-curves of serology tests to predict positive DBPCFC result with objective symptoms

The Lasso model included sIgE to peanut extract, Ara h 1, Ara h 6 and Ara h 8.

Data are AUC values with 95% confidence interval.

Abbreviations: AUC, area under the curve; DBPCFC, double-blind placebo-controlled food challenge; n, number; ROC, receiver-operating characteristic.

The Ara h 2 cutoff level with 100% positive predictive value is validated

A previous study performed in our center, including 84 adults, showed that peanut allergy can be diagnosed in 28% of patients by using a sIgE to Ara h 2 cutoff level with 100% positive predictive value (PPV) of ≥ 1.75 kU_A/L.¹⁶ In the expanded cohort, including 84 adults from the previous study and 70 adults who were challenged after the first study, this cutoff level has again 100% positive predictive value (Table 2). Thus, we were able to confirm the previously published cutoff level of Ara h 2 in a larger group of adult patients. Thirty-two percent of patients had an Ara h 2 value above the validated cutoff level and could be predicted correctly as peanut-allergic. Eighty-eight percent of patients above the Ara h 2 cutoff level had a positive DBPCFC result with objective symptoms. The optimal Ara h 2 cutoff level with 100% PPV in patients who were not part of the previous diagnostic study (n=70) was ≥ 0.43 kU_A/L. Six patients had an Ara h 2 level between 0.43 kU_A/L and 1.74 kU_A/L and were all peanut-allergic (4 with objective symptoms and 2 with subjective symptoms).

Cutoff levels for Ara h 6 and other peanut components

The Ara h 6 cutoff level with 100% PPV was ≥ 1.80 kU_A/L, comparable to the Ara h 2 cutoff level (Table 2). Twenty-eight percent of patients had an Ara h 6 value above this cutoff level and could be predicted correctly as peanut-allergic. The highest NPVs were observed for Ara h 6 and Ara h 8 at a cutoff of 0.1 kU_A/L and were 81% and 88%, respectively. The NPVs for sIgE to peanut extract, Ara h 1, Ara h 2 and Ara h 3 (at a cut off of 0.1 kU_A/L) were 78%, 58%, 79% and 62%, respectively.

Table 2. Validation of sIgE to Ara h 2 cutoff level and cutoff levels with optimal positive and negative predictive values

	n	Cutoff kUA/L	PPV %	NPV %	Sens %	Spec %
Validation						
sIgE to Ara h 2	70	1.75	100	60	58	100
Optimal PPV cutoff levels						
sIgE to Ara h 2	154	1.75	100	56	52	100
sIgE to Ara h 6	118	1.80	100	55	46	100
sIgE to Ara h 1	154	2.47	100	49	36	100
sIgE to Ara h 3	154	0.88	100	46	26	100
sIgE to Ara h 8	154	100	100	39	1	100
sIgE to peanut extract	154	15.10	100	48	34	100
Optimal NPV cutoff levels						
sIgE to Ara h 2	154	0.02	71	79	94	37
sIgE to Ara h 6	118	0.04	88	81	88	81
sIgE to Ara h 1	154	0.05	89	58	60	88
sIgE to Ara h 3	154	0.01	67	62	88	31
sIgE to Ara h 8	154	0.01	64	88	99	12
sIgE to peanut extract	154	0.11	67	78	96	24

Abbreviations: n, number of patients included; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; sIgE, specific IgE; Spec, specificity.

Higher titers in patients with objective symptoms

Figure 2 shows the percentage of patients with and without sensitization (cutoff 0.10 kU_A/L) to peanut components and peanut extract per DBPCFC result (i.e. positive with objective symptoms, positive with subjective symptoms and negative) and the titers of sensitization. Patients with a positive DBPCFC result with objective symptoms recognized Ara h 1, 2, 3 and 6 more often and had a higher titer compared to patients with subjective symptoms or a negative DBPCFC result. A large proportion of patients recognized Ara h 8 (75%) and peanut extract (89%), irrespective of the DBPCFC result.

Figure 2. Percentage of patients with sensitization to peanut extract or peanut components and titers of sensitization, per DBPCFC result

Sensitization is defined as a value of ≥ 0.10 kU_A/L. Median (interquartile range) titers of sIgE are displayed on logarithmic scales (base 10).

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; sIgE, specific IgE.

Peanut-allergic patients without sensitization to Ara h 1, 2, 3 and 6

In 16 (17%) patients with a positive DBPCFC result we did not detect sensitization to Ara h 1, 2, 3 and 6 (Figure 3). Five of 16 patients had objective symptoms Mueller grade 3 during the DBPCFC. Peanut-allergic patients with undetectable sensitization to Ara h 1, 2, 3 and 6 were sensitized to Ara h 8 and peanut extract (n=8), to Ara h 8 only (n=2), to peanut extract only (n=2) or were not sensitized to peanut extract or any of the peanut components (n=4).

Additional diagnostic testing on a line blot (EUROLINE) was performed, measuring Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15, in 14 of 16 patients with leftover serum available after the ImmunoCAP measurements. Again, no sensitization to Ara h 1, 2, 3 or 6 was measured on the line blot. Furthermore, all patients were tested negative to Ara h 5, 7, 10, 11, 14 and 15. Two patients were sensitized to Ara h 9 (patient ID 3 and ID 14 in Figure 3) on the line blot.

ID	Ara h 2	Ara h 6	Ara h 1	Ara h 3	Ara h 8	extract	Sym [†] Sev [‡]	slgE level (kU _A /L)
1	0.02	0	0	0	0	0	O 3	50.00 - 100.00
2	0	0	0	0.01	0.01	0	S 0	
3	0	0	0	0.01	0.01	1.05	S 0	17.50 - 49.90
4	0.01	0	0	0	0.01	0.19	S 0	
5	0.02	0	0	0	0.01	0	O 2	3.50 - 17.49
6	0.02	0	0	0	0.01	0.01	O 2	
7	0.03	0.01	0.01	0.01	0.50	0.01	O 3	0.70 - 3.49
8	0	0	0	0	1.39	0.03	S 2	
9	0.04	0.04	0.04	0.08	3.70	0.11	S 0	0.35 - 0.69
10	0.06	0.08	0.05	0.07	3.80	2.30	O 3	
11	0	0	0	0.01	7.20	0.16	S 0	0.10 - 0.34
12	0.04	0.01	0.01	0.01	8.11	0.15	O 3	
13	0.02	0	0	0	10.60	2.17	S 2	0 - 0.09
14	0.05	0.01	0.01	0.01	14.50	0.66	O 3	
15	0.06	0	0	0	16.80	1.08	S 0	
16	0	0	0	0.01	20.60	0.54	S 0	

Figure 3. Sensitization pattern in 16 peanut-allergic patients without sensitization to Ara h 2 and Ara h 6

[†] Symptoms during the oral food challenge: S, subjective; O, objective.

[‡] Severity of symptoms during the oral food challenge based on the Mueller score with 0. Oral symptoms, 2. Gastro-intestinal symptoms and 3. Respiratory symptoms.^{16,30}

Abbreviations: ID, patient number; O, objective; S, subjective; Sev, severity; Sym, symptoms.

Discussion

In the current study, we showed that Ara h 2 and Ara h 6 are the best predictors of peanut allergy in adults with suspected peanut allergy. Our validated Ara h 2 cutoff level with 100% positive predictive value (PPV) (cutoff ≥ 1.75 kU_A/L) can be used to accurately predict peanut allergy in one third of patients. Furthermore, we were the first to investigate the diagnostic value of sIgE to Ara h 6 using a singleplex assay in adults and were able to identify a cutoff level of Ara h 6 with 100% PPV (cutoff ≥ 1.80 kU_A/L), again applicable to almost one third of patients.

Our results are in line with previous research that identified Ara h 2 and Ara h 6 as the best predictors of peanut allergy.^{8,14,15} The AUC value of sIgE to Ara h 2 was lower in our study in adults (AUC 0.85) compared to the AUC values reported in studies in children (AUC 0.90-0.96).^{14,34} In addition, we observed a lower cutoff level of Ara h 2 with 100% PPV (cutoff ≥ 1.75 kU_A/L) compared to children (cutoff 4.0-5.0 kU_A/L).^{8,35} The Ara h 2 cutoff with 100% PPV was even lower in the subset of patients who were not part of the previous diagnostic study and underwent a DBPCFC between 2012 and 2019 (cutoff ≥ 0.43 kU_A/L). The AUC value of sIgE to Ara h 6 using a singleplex assay in our study (AUC 0.85) was comparable to the AUC value of sIgE to Ara h 6 using a multiplex assay in adults (AUC 0.82), but lower than observed in children using a multiplex assay (AUC 0.98).^{14,15} The lower diagnostic value of peanut components in adults compared to children could be explained by the higher proportion of birch pollen-related peanut allergy in adults. In patients with birch pollen allergy, cross-sensitization of Ara h 8 with major birch pollen allergen Bet v 1 occurs and these patients have mainly mild or subjective symptoms after peanut ingestion, making it more difficult to discriminate between presence and absence of allergy.^{12,14,16} As shown in the current study, adult peanut-allergic patients with subjective symptoms were less often sensitized to Ara h 2 and Ara h 6 and had lower titers, resulting in a lower diagnostic value. Further insight into the levels of IgE sensitization over time, from childhood to adulthood, could contribute to a better understanding of the differences between children and adults.

The concentrations of sIgE to Ara h 2 and Ara h 6 were highly correlated in our and previous studies.^{36,37} The extensive overlap in sIgE reactivity and comparable diagnostic accuracy, indicate that ImmunoCAP results for either Ara h 2 or Ara h 6 are sufficient in the diagnostic work-up of a suspected peanut allergy in adults. Multivariable analyses revealed that a combination of Ara h 1 and Ara h 6 had the highest diagnostic accuracy, with an AUC comparable to those of Ara h 2 and Ara h 6 alone, despite regularization (i.e. shrinkage of the coefficients) (AUC 0.85). At present, however, we recommend using sIgE reactivity to peanut component Ara h 2 in daily practice, as the cutoff level is validated in the current study,

implementation in daily practice is straightforward, and interpretation of sIgE-levels to one peanut component is more intuitive than of a clinical prediction rule based on the Lasso model.

Thirty-two percent of patients could be classified correctly as peanut-allergic when using the validated cutoff level of sIgE to Ara h 2 with 100% positive predictive value (PPV) (cutoff ≥ 1.75 kU_A/L). This cutoff level of Ara h 2 could be used in daily clinical practice to select patients for oral food challenges. In patients with an Ara h 2 level above the cutoff level, peanut allergy is diagnosed with (almost) 100% accuracy without an oral food challenge. In these patients, a 1-day oral food challenge may still be performed, in accordance with the patient and physician preference, to assess the severity of the allergic reaction and the eliciting dose. In patients with an Ara h 2 level below the cutoff level, peanut-allergic status cannot be predicted. In these patients, a 2-day double-blind placebo-controlled food challenge is needed to confirm or exclude peanut allergy.

It must be noted that sIgE to Ara h 2 and Ara h 6 cannot be used to rule out peanut allergy in adults. In 16 peanut-allergic patients (17%) in our cohort we did not detect sensitization to Ara h 2 and Ara h 6, nor for Ara h 1 or Ara h 3. In these patients, sensitization to peanut allergens might not have been detected by the ImmunoCAP platform or peanut allergy might have been caused by sensitization to other peanut components. Therefore, a different diagnostic testing modality was used to test a large number of peanut components (Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15), resulting in 2 of 16 patients recognizing Ara h 9. Ten of 16 (63%) patients were sensitized to the birch pollen related allergen Ara h 8, and 3 of these 10 patients that only recognized Ara h 8 experienced objective respiratory symptoms during the double-blind placebo-controlled food challenge (DBPCFC). However, the sensitization rate to Ara h 8 in peanut-tolerant patients was comparable (64%), thus sIgE to Ara h 8 was not predictive of clinical reactivity to peanut. A comparable frequency (18%) of allergic patients with negative serology tests, including Ara h 1, 2, 3 and 6, was reported in peanut-allergic patients in the EuroPrevall study.³⁶ The authors hypothesized that peanut oleosins may have caused allergic reactions in these patients. Interestingly, all peanut-allergic patients with negative Ara h 1, 2, 3 and 6 results in our study were tested negative to peanut oleosins (i.e. Ara h 10, 11, 14 and 15). Thus, peanut allergy in non-sensitized patients as detected in this and previous studies might be caused by sensitization to thus far unidentified peanut components.

A limitation of our study was that we only included patients from a tertiary care center with a conclusive DBPCFC result, and with leftover serum available. However, we believe our sample was a representative sample as we did not observe significant differences between included and excluded patients. Furthermore, the

percentage of positive DBPCFCs in our study (62%) was comparable to other studies (43-66%).^{16,38,39} Strengths of our study were that we included a large cohort of adult patients who all underwent a standardized DBPCFC for peanut allergy, we measured a large number of peanut components, we performed a validation of our previous results and were able to confirm these findings.¹⁶

In conclusion, we showed that specific IgE to Ara h 2 and Ara h 6 are the best predictors of peanut allergy in adults. Furthermore, we validated our previously published Ara h 2 cutoff level with 100% positive predictive value. The validated Ara h 2 cutoff level should be implemented in daily practice to reduce the need for double-blind placebo-controlled food challenges, as all adults with an Ara h 2 $\geq$ 1.75 kU_A/L were peanut-allergic.

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Supplemental tables

Supplemental Table 1. Baseline characteristics of included and excluded patients

	Included	Excluded	n available	P-value
n (%)	154 (75)	50 (25)		
Age, mean (SD)	27 (22-38)	24.5 (20.3-31)	32	0.055
Male gender	52 (34)	19 (38)	50	0.585
Allergic rhinitis [†]	52 (75)	11 (73)	15	0.869
Sensitization, median (IQR)				
sIgE peanut	1.65 (0.35-11.05)	2.35 (0.71-22.40)	23	0.377
sIgE Ara h 1	0.02 (0.00-0.61)	0.00 (0.00-0.01)	4	-
sIgE Ara h 2	0.16 (0.03-3.50)	0.38 (0.00-1.37)	19	0.424
sIgE Ara h 3	0.03 (0.01-0.18)	0.00 (0.00-0.01)	4	-
sIgE Ara h 6	0.07 (0.00-3.14)	0.02 (0.00-0.53)	6	-
sIgE Ara h 8	2.02 (0.11-8.57)	1.23 (0.01-8.75)	18	0.428
DBPCFC result [‡]			50	<0.0005
Positive	95 (62)	20 (40)		
Inconclusive	0	18 (36)		
Negative	59 (38)	12 (24)		0.213
Severity positive DBPCFC			11	
Mueller 0	15 (16)	2 (18)		
Mueller 1	16 (17)	2 (18)		
Mueller 2	32 (34)	7 (64)		
Mueller 3	28 (30)	0		
Mueller 4	2 (2)	0		

Values are numbers (%), unless otherwise indicated.

[†] Missing data included patients n=85

[‡] One of the reasons for exclusion was an inconclusive DBPCFC result. The proportion of positive and negative DBPCFC results were comparable between groups (p=0.931).

[§] Missing data included patients n=2. Severity of symptoms during the oral food challenge based on the Mueller score with 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; IQR, interquartile range; SD, standard deviation; sIgE, specific IgE.

Supplemental Table 2. Diagnostic value of peanut components in the subset of the cohort with available sIgE to Ara h 6 (n=118 of 154)

	AUC (95% CI)
sIgE extract	0.76 (0.68-0.85)
sIgE Ara h 1	0.76 (0.68-0.84)
sIgE Ara h 2	0.85 (0.78-0.92)
sIgE Ara h 3	0.75 (0.67-0.84)
sIgE Ara h 8	0.57 (0.46-0.68)

Abbreviations: AUC, area under the curve; CI, confidence interval; sIgE, specific IgE.

Supplemental Table 3. DeLong's test for comparing two correlated ROC curves

	sIgE Ara h 6	sIgE extract	sIgE Ara h 1	sIgE Ara h 3	sIgE Ara h 8
sIgE Ara h 2	0.87	0.02	<0.01	<0.01	<0.01
sIgE Ara h 6		0.02	<0.01	<0.01	<0.01
sIgE extract			0.61	0.56	<0.01
sIgE Ara h 1				0.93	<0.01
sIgE Ara h 3					<0.01
sIgE Ara h 8					

Data are *P*-values corrected for multiple testing using the Benjamini-Hochberg procedure.

Significant *P*-values are in boldface.

Abbreviations: *sIgE*, specific *IgE*.

Chapter 4

Three-year follow-up after peanut food challenges: accidental reactions in allergic children and introduction failure in tolerant children

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Abstract

Background

Long-term follow-up data after peanut double-blind placebo-controlled food challenges (DBPCFC) are limited. We sought to evaluate 1) accidental allergic reactions to peanut and health-related quality of life (HRQL) in peanut-allergic children and 2) introduction of peanut and HRQL in peanut-tolerant children 3 years after a DBPCFC.

Methods

We conducted a 3-year follow-up of 83 children who participated in a prospective study in the Netherlands and all underwent a DBPCFC for peanut. Three years after the DBPCFC, all parents and children aged 8 years or older were asked to fill out a questionnaire on accidental allergic reactions, current diet and the Food Allergy Quality of Life Questionnaire-Parent Form.

Results

In total, parents of 69 (83%) children with a mean (SD) age of 11.5 (3.5) years completed the questionnaire 3.1 (0.4) years after a peanut DBPCFC. Seventeen (41%) of 41 peanut-allergic children had a total of 68 allergic reactions during 3-year follow-up. None of 7 out of 17 children with severe lower respiratory symptoms used their epinephrine auto-injector. Nine (32%) of 28 peanut-tolerant children failed to introduce peanut. HRQL only improved significantly and clinically relevant in peanut-tolerant children after successful peanut introduction.

Conclusion

Despite adequate diagnostic procedures and guidance, living with peanut allergy remains a challenge during childhood. In peanut-tolerant children peanut introduction often fails. However, peanut introduction seems meaningful to improve HRQL.

Introduction

Peanut allergy is one of the most common food allergies among children.¹ The gold standard to diagnose peanut allergy is a double-blind placebo-controlled food challenge (DBPCFC).² Children and parents are advised to avoid peanut after a positive DBPCFC result or to introduce peanut after a negative DBPCFC result. Limited data exist on the long-term follow-up after a DBPCFC, including the frequency and treatment of accidental allergic reactions, diet and health-related quality of life (HRQL).

Children with confirmed peanut allergy have frequent accidental allergic reactions and often do not recognize and adequately treat allergic symptoms.³⁻⁶ For children with peanut allergy in Canada, the annual incidence rate of accidental reactions to peanut ranged from 10 to 15%.^{4,7} However, most children with peanut allergy participating in these studies were diagnosed based on a convincing clinical history and/or sensitization. It is unclear how often children have an allergic reaction after the explicit advice to avoid peanut following a positive DBPCFC result and how these allergic reactions are treated. On the other hand, children with a negative DBPCFC result are advised to consume peanuts regularly to maintain oral tolerance. Children who continue to avoid peanut after outgrowing a peanut allergy may be at risk for recurrence of food allergy.^{8,9} Previous studies showed that children and parents often fail to introduce peanut at home.¹⁰⁻¹³ We found that 38% of children failed to introduce peanut at home one month after a negative DBPCFC result despite guided introduction including a 7-day introduction schedule, telephonic counseling and a diary.¹⁴ Children may fail to introduce peanut into the diet due to aversion to the food that long has been eliminated, a false-negative oral food challenge result or fear of persistent allergy.^{10,14} It is unclear how often children fail to introduce peanut years after a negative DBPCFC result including standardized guided introduction.

Children and parents might benefit from a DBPCFC because our previous systematic review reported that HRQL improved up to 6 months after an oral food challenge, irrespective of the outcome.¹⁵ HRQL up to years after an oral food challenge and HRQL after peanut introduction have not been previously reported.

Limited data exist on the long-term follow-up after a DBPCFC, including the frequency and treatment of accidental allergic reactions, diet and HRQL. We sought to evaluate 1) the frequency and nature of accidental allergic reactions and HRQL in peanut-allergic children; 2) peanut introduction and HRQL in peanut-tolerant children.

Methods

Participants and procedures

The current study is a 3-year follow-up of 83 children who participated in a prospective diagnostic study performed in one tertiary care and one secondary care center in the Netherlands between January 2012 and May 2015. The previous study included children aged 3 to 18 years with a suspected peanut allergy based on a previous reaction and/or sensitization.¹⁶ All children underwent a DBPCFC for peanut. A DBPCFC was considered positive when objective or severe long-lasting subjective symptoms occurred. Children with a positive DBPCFC result (n=45; 54%) were instructed to eliminate peanut and were educated when and how to use emergency treatment. Children with a negative DBPCFC result followed by a negative or inconclusive open challenge with 10 whole peanuts (n=38; 46%) were instructed to introduce peanut at home according to a standardized, carefully monitored guided introduction during one month.¹⁴ Successful short-term introduction into the diet (n=23; 62%) was defined as parental-reported ingestion of at least 5g of whole peanuts or an equivalent at home during the introduction period and eating products containing peanuts as an ingredient on a regular basis (≥ 2 times a month). Among children with failed short-term introduction (n=14; 37%), 3 children were considered peanut-allergic because of repetitive and persistent oral itch within 5 minutes after all peanut ingestions. In conclusion, 48 children (58%) were considered peanut-allergic and 35 children (42%) were considered peanut-tolerant (Figure 1).

Three years after the DBPCFC for peanut, all parents and children aged 8 years or older were contacted by mail and were asked to fill out an electronic questionnaire on accidental allergic reactions, current diet and HRQL. Families who did not respond were reminded within 2 and/or 4 weeks of the mailing and contacted by telephone. The study was reviewed and approved by the ethical committee of the University Medical Centre Utrecht and written informed consent was obtained from parents and children before enrollment in the original study.

Figure 1. Study flowchart

Values are numbers (%).

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge.

Accidental allergic reactions in peanut-allergic children

All parents were asked whether their child has had any accidental allergic reaction to peanut since the DBPCFC for peanut. If any allergic reaction to peanut was reported, parents were asked to report on the most severe allergic reaction. Details collected on the most severe allergic reaction to peanut included the food ingested, estimated amount consumed, time interval from ingestion of the product to reaction, symptoms, duration, potential cofactors and treatment. The symptoms were categorized according to the PRACTALL consensus report.¹⁷ The severity of symptoms was categorized according to the Sampson classification of anaphylaxis as grade 1 to 5.¹⁸ Grade 1 to 3 was considered mild or moderate and grade 4 to 5 severe.

Introduction of peanut in peanut-tolerant children

Details collected on the current diet included the question whether the child consumed whole peanuts or products with visible peanut (category a), products with peanut as an ingredient (category b) or products with precautionary allergen labelling e.g. 'may contain' or 'manufactured on a shared line with products containing peanut' (category c). If children avoided one of the peanut product categories, details on the reasons for avoidance were collected. Successful long-term introduction of peanut was defined as eating category a and/or category b products at least once a month.

Health-related quality of life

Health-related quality of life (HRQL) was assessed using the Food Allergy Quality of Life Questionnaires (FAQLQ) before and 3 years after the DBPCFC for peanut. The FAQLQ is a self-reported, disease-specific instrument to evaluate the impact of food allergy on patients' HRQL. For this study, the FAQLQ parent form (FAQLQ-PF) for parents of all children, the child form (FAQLQ-CF) for children aged 8 to 13 years and the teenager form (FAQLQ-TF) for children aged 13 to 18 years were used.¹⁹⁻²¹ The FAQLQ-PF contains 30 items and 3 domains (emotional impact, food-related anxiety, social dietary limitations), the FAQLQ-CF contains 24 items and 4 domains (allergen avoidance, risk of accidental exposure, emotional impact, dietary restrictions) and the FAQLQ-TF contains 23 items and 3 domains (allergen avoidance, risk of accidental exposure, emotional impact). All items are scored on a seven-point scale ranging from 1 to 7, with 1 as the best possible score. The relevance of the change in FAQLQ-scores was evaluated using the minimal clinically important difference (MCID) of 0.50.²²

Statistical analysis

Data were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous data, and numbers (percentages) for categorical variables. Differences between responders and non-responders, between peanut-allergic and peanut-tolerant children and between children with and without allergic reactions during follow-up were statistically evaluated by the chi-square test for categorical variables and the independent samples t-test or Mann Whitney U test for continuous variables with Bonferroni correction for multiple testing. The annual incidence rate of accidental allergic reactions was expressed as the number of allergic reactions divided by the sum of the patient years (time from DBPCFC to follow-up). The difference between FAQLQ scores at baseline and follow-up were compared using the paired t-test. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows (version 25).

Results

Patient characteristics

In total, 69 (83%) of 83 children completed the questionnaire mean (SD) 3.1 (SD, 0.4) years after a positive (n=41/48) or negative (n=28/35) DBPCFC result (Figure 1). The mean (SD) age of the children at follow-up was 11.5 (3.5) years and 48 (70%) were male (Table 1). Children who completed the questionnaire and children who did not were comparable in age, gender, sensitization, HRQL, DBPCFC results and DBPCFC severity (Supplemental Table 1).

Table 1. Baseline characteristics

	All children	Peanut-allergic children	Peanut-tolerant children	P-value
n	69	41 (59)	28 (41)	
Baseline characteristics				
Age at DBPCFC, mean (SD)	8.4 (3.5)	8.6 (3.4)	8.2 (3.7)	0.624
Age at follow-up, mean (SD)	11.5 (3.5)	11.7 (3.3)	11.2 (3.7)	0.614
Male gender	48 (70)	27 (66)	21 (75)	0.417
History of atopy				
Asthma	33 (48)	23 (56)	10 (36)	0.096
Allergic rhinitis	41 (59)	27 (66)	14 (50)	0.188
Atopic dermatitis	40 (58)	23 (56)	17 (61)	0.703
Avoidance other foods than peanut				0.169
0 foods	25 (36)	13 (32)	12 (43)	
1 or 2 foods	10 (15)	6 (15)	4 (14)	
3 or 4 foods	11 (16)	4 (10)	7 (25)	
5 or 6 foods	15 (22)	12 (29)	3 (11)	
≥7 foods	8 (12)	6 (15)	2 (7)	

Values are numbers (%), unless otherwise indicated.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; n, number; SD, standard deviation.

Accidental allergic reactions in peanut-allergic children

Seventeen (41%) of 41 children with peanut allergy had 68 accidental allergic reactions during the 3-year follow-up. Three children with peanut allergy (aged < 12 years) experienced 5 or more allergic reactions during the follow-up. Children with peanut allergy and allergic reactions to peanut during follow-up were comparable to with those without accidental allergic reactions in age, gender, history of asthma, duration of elimination diet for peanut, sensitization, elimination diet for other allergens, severity of symptoms during the DBPCFC, eliciting dose of the DBPCFC and dietary advice following the DBPCFC (Supplemental Table 3). The frequency of accidental allergic reactions did not differ between children 12 years or younger and children 13 years or older. Parents of children with any allergic reaction during follow-up were asked to report the characteristics of the most

severe reaction (Table 2 and 3). All children developed symptoms within 2 hours from ingestion. Most children consumed unpacked foods (8 of 17 children) or products with peanut as an ingredient (6 of 17 children). Five of 17 children had mild or moderate symptoms and used antihistamines at home. Twelve of 17 children reported severe symptoms and used antihistamines (n=7), antihistamines and oral steroids (n=1), a bronchodilator (n=1) or used no medication at all (n=3). More than half of (parents of) children with severe symptoms did not consult a medical professional. Only two children with severe symptoms consulted a general practitioner and one child was admitted to the hospital. Seven of 17 children reported severe lower respiratory symptoms. None of these 7 children used their epinephrine auto-injector.

Table 2. Characteristics of most severe accidental allergic reactions to peanut in 17 (41%) of 41 peanut-allergic children

		n (%)
Number of reactions	1 or 2	9 (53)
	3 or 4	4 (25)
	≥5	3 (18)
	Missing data	1 (6)
Age category	Children (≤12 years)	11 (65)
	Adolescents (>12 years)	6 (35)
Contact	Ingestion	14 (82)
	In oral cavity	1 (6)
	Skin contact	2 (12)
Time from ingestion to symptoms	≤ 2 hours	17 (100)
	> 2 hours	0
Symptoms according to PRACTALL ¹⁶	Skin	10 (59)
	Gastro-intestinal	16 (94)
	Upper respiratory	8 (47)
	Lower respiratory	7 (41)
	Cardiovascular/neurologic	9 (53)
Severity of symptoms [†]	Mild or moderate	
	Grade 1	1 (6)
	Grade 2	3 (18)
	Grade 3	1 (6)
	Severe	
Treatment	Grade 4	12 (71)
	No medicines	3 (18)
	Antihistamines	12 (71)
	Antihistamines + oral steroids	1 (6)
	Epinephrine auto-injector	0
	Bronchodilators	1 (6)
Consultation with physician	No consultation	14 (82)
	GP visit	2 (12)
	Hospital/ED visit	1 (6)

[†] According to Sampson classification of anaphylaxis.¹⁸

Abbreviations: n, number.

Table 3. Characteristics of most severe allergic reaction during follow-up per patient

ID	Product	Label	All symptoms reported [†]	S [‡]	Treatment
1 [§]	Baklava	UNP	Pruritis, oral itch, feel of oral swelling, nausea, diarrhea , abdominal pain, dyspnea , feel of collapse	4	AH
2 [§]	Peanut skin contact	UNP	Pruritis, swelling eyes , diarrhea , blocked nose , wheezing	4	INH
3	Japanese rice crackers	ING	Pruritis, rash , oral itch, nausea, vomiting , diarrhea , abdominal pain, changed activity	4	None
4 [§]	Peanut	UNP	Rash , urticaria , swelling eyes , feel of oral swelling, nausea, vomiting , abdominal pain, blocked nose , dyspnea , anxiety	4	AH
5	Chocolate	UNP	Pruritis, rash , urticaria , diarrhea , blocked nose	4	None
6	Fries	UNP	Swelling eyes , oral itch, nausea, diarrhea , abdominal pain	4	AH
7	Cake	UNP	Swelling eyes , vomiting , abdominal pain	2	AH
8 [§]	Biscuit	ING	Swelling eyes , feel of oral swelling, nausea, abdominal pain, dysphagia , anxiety	4	AH + OS
9	Biscuit	ING	Oral itch, nausea, abdominal pain	2	AH
10 [§]	Pesto with cashew nut	PAL	Oral itch, feel of oral swelling, nausea, abdominal pain, sneezing , cough , anxiety	4	AH
11	Peanut butter	UNP	Oral itch, abdominal pain	1	AH
12	UNK	UNP	Nausea, diarrhea , abdominal pain	4	None
13	Potato chips	CON	Pruritis, nausea, dizziness, feel of collapse	4	AH
14	Peanut butter	ING	Pruritis, rash , swelling eyes , itching eye	2	AH
15 [§]	Biscuit	ING	Oral itch, nausea, abdominal pain, itching eyes, feel of oral swelling, hoarseness , cough , dysphagia , dyspnea , dizziness	4	AH
16 [§]	Salty sticks	ING	Pruritis, rash , urticaria , swelling eyes , itching eyes, nausea, abdominal pain, blocked nose , sneezing , dyspnea , changed activity	4	AH
17	Biscuit	PAL	Pruritis, rash , urticaria , swelling eyes , oral itch, itching eyes, blocked nose , sneezing , anxiety	3	AH

[†] Patient-reported symptoms. Objective symptoms are in boldface.

[‡] Severity of symptoms according to Sampson classification of anaphylaxis.¹⁸

[§] Severe lower respiratory symptoms requiring the use of epinephrine.

Abbreviations: AH, antihistamines; CON, contaminated with peanut by other consumers; ING, peanut mentioned as an ingredient; INH, bronchodilator; OS, oral steroids; PAL, precautionary allergen labelling for peanut; S, severity according to Sampson classification of anaphylaxis; UNP, unpacked foods; UNK, unknown.

Unchanged quality of life in peanut-allergic children after follow-up

Parent-proxy-reported HRQL remained unchanged between baseline and 3-year follow-up in children with peanut allergy (mean difference [MD], 0.05; $P=0.823$). There was no significant difference in HRQL between children with or without allergic reactions during follow-up, or between children ≤ 12 years or >12 years of age. On the individual level, HRQL improved in 29% and deteriorated in 39% of children with peanut allergy 3 years after the DBPCFC compared with before. HRQL data are presented in Figure 2 and Supplemental Table 4.

Introduction of peanut in peanut-tolerant children

Long-term introduction of peanut 3 years after the DBPCFC failed in 9 (32%) of 28 peanut-tolerant children (Figure 4). Five (28%) children with successful short-term guided introduction failed to introduce peanut on the long-term. The reported reasons for failure were aversion ($n=4$) or aversion and fear ($n=1$). Three children (33%) with failed short-term guided introduction also failed to introduce peanut on the long-term due to aversion ($n=1$), aversion and fear ($n=1$) or fear ($n=1$). One child did not start guided introduction and failed to introduce peanut on the long-term due to fear. The consumption of the different peanut product categories among children with successful and failed introduction is displayed in Figure 3. Only one child (4%) did not consume products with precautionary allergen labeling (category c) 3 years after a negative DBPCFC.

Parent-proxy-reported HRQL improved significantly between baseline and 3-year follow-up in peanut-tolerant children (MD, -0.51; $P=0.025$) (Supplemental Table 4). This change was considered clinically relevant as the minimal important difference of -0.50 was exceeded. A stratified analysis per long-term introduction outcome in peanut-tolerant children showed that HRQL improved significantly and clinically relevant after successful long-term introduction (MD -0.70; $p=0.013$) and not after failed long-term introduction (MD, -0.05; $P=0.906$). In addition, domain HRQL scores improved clinically relevant after successful long-term introduction (Supplemental Table 4). On the individual level, HRQL improved in 52% and deteriorated in 19% of peanut-tolerant children 3 years after the DBPCFC compared with before (Figure 2).

Figure 2. Percentage of children with an improved (change <-0.5), unchanged (change -0.5 to 0.5) or deteriorated (change >0.5) HRQL 3 years after a DBPCFC for peanut

Figure 3. Consumption of peanut in peanut-tolerant children with successful ($n=19$) or failed ($n=9$) long-term introduction
Products category a, whole or visible peanut; Category b, peanut as an ingredient; Category c, precautionary allergen labelling.

Figure 4. Flowchart of reintroduction to peanut after a negative or inconclusive DBPCFC for peanut. Values are numbers (%). Abbreviations: DBPCFC, double-blind placebo-controlled food challenge.

Discussion

To our knowledge, this is the first study investigating the long-term follow-up after a DBPCFC for peanut in children. In this study we have shown that almost half of peanut-allergic children have accidental reactions during 3 years after a positive DBPCFC result and that severe accidental reactions are not treated with epinephrine. In addition, peanut-tolerant children often experience failure of peanut introduction into the diet 3 years after a negative DBPCFC result. Our results indicate that HRQL improves in peanut-tolerant children after successful peanut introduction and not after failed peanut introduction or in peanut-allergic children.

The high rate of accidental allergic reactions despite the explicit advice to avoid peanut, as seen in this study, is of clinical concern. Previous studies reported that up to 60% of children with peanut allergy (diagnosed using clinical history and/or sensitization) had accidental allergic reactions to peanut over a median period of 5 to 6 years.^{23,24} Children may have frequent accidental allergic reactions because foods are often unpacked, labels are misread by children or parents, products are inadequately labelled or because of risky behavior of the child.^{25,26} Another point of concern is that none of the children with a severe accidental allergic reaction requiring epinephrine used an epinephrine auto-injector upon peanut exposure although all children were prescribed an auto-injector and were instructed on how and when to use the device. Children and parents may not have used an epinephrine auto-injector because they were not carrying the device or failed to recognize allergic reactions and anaphylaxis. A recent analysis of the European Anaphylaxis Register demonstrated that more than 85% of patients with severe anaphylaxis did not use their epinephrine auto-injectors despite clear recommendations.²⁷

Previous studies demonstrated a beneficial impact of a positive oral food challenge result on parent-proxy-reported HRQL up to 6 months after the challenge.^{22,28} In the current long-term follow-up study, we found no difference between HRQL at baseline and 3 years after a positive DBPCFC result for peanut. Although we did not measure HRQL between these two time points, our results suggest that the beneficial impact of a positive DBPCFC result on HRQL may wane over time. Psychologists may have a role to support children and their families as psychological or psychosocial interventions have been shown to improve HRQL and reduce feelings of anxiety.^{29,30} Furthermore, children with peanut allergy and their families may benefit from multidisciplinary allergy care including regular clinical consultations with an experienced physician and dietitian to evaluate any accidental ingestion of peanut, continue education on peanut avoidance and the use of emergency medications and adapt counselling to the child's age.^{31,32}

Our study showed that almost one third of peanut-tolerant children failed to introduce peanut into the diet 3 years after the DBPCFC, despite guidance after the DBPCFC. Guidance after a negative DBPCFC result may not influence introduction of the allergen as suggested by our data and by a recent retrospective study in 128 children after a negative DBPCFC result for cow's milk.³³ The rate of introduction of cow's milk did not differ between children with or without follow-up by phone or in person. Children failed to introduce peanut into the diet mainly because of aversion to peanut, although alternative products with hidden peanut were offered in the first month after the DBPCFC. Children may dislike peanuts as the taste of peanut has previously been paired with illness, they are not used to the taste and texture of peanuts or because they have long been eliminating peanut. The importance of peanut introduction in peanut-tolerant children is supported by our results that indicate that parent-proxy-reported HRQL improved only in peanut-tolerant children after successful peanut introduction and remained unchanged after failed peanut introduction. Further research and discussion with experts and patient organizations is needed to investigate whether food aversion and anxiety, which were the main reason not to introduce, may be relieved when psychological guidance is provided.

Our study is limited by a relatively small sample size limiting the possibility to evaluate predictors of accidental allergic reactions, introduction failure and HRQL. In addition, due to the small sample size we were not able to analyze child-reported HRQL per allergic status and per introduction success or failure group. It has been suggested that parents report better HRQL than children themselves.³⁴ Thus, our results on HRQL are limited to the parent perspective and further research is needed to assess the long-term impact of a DBPCFC and peanut introduction on the child's HRQL. Furthermore, we may have underestimated or overestimated the rate and severity of accidental allergic reactions due to recall bias over a 3-year time period. The study is strengthened by a prospective study design, including a well-defined patient cohort of children who all underwent a DBPCFC for peanut and a high response rate after 3-year follow-up.

In conclusion, despite adequate diagnostic procedures and guidance, living with peanut allergy remains a challenge during childhood. In peanut-tolerant children peanut introduction often fails. However, peanut introduction is meaningful to improve health-related quality of life.

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Supplemental tables

Supplemental Table 1. Comparison of children who completed the questionnaire and those who did not

	3-year follow-up	No 3-year follow-up	P-value [†]
n (%)	69 (83)	14 (17)	
Age at follow-up, mean (SD)	11.5 (3.5)	12.1 (3.6)	0.547
Male gender	48 (70)	11 (79)	0.748
sIgE to peanut, median (IQR)	4.00 (0.78-13.05)	2.15 (0.19-17.35)	0.458
sIgE to Ara h 2, median (IQR)	1.02 (0.17-8.95)	0.85 (0.05-8.63)	0.401
DBPCFC characteristics			
FAQLQ-PF score before DBPCFC, mean (SD)	2.40 (0.95)	2.80 (1.53)	0.319
Results DBPCFC			
Positive	41 (59)	7 (50)	0.563
Negative	28 (41)	7 (50)	
Positive DBPCFC			
Reaction during DBPCFC [‡]			0.236
Grade 1	5 (12)	0	
Grade 2	19 (46)	2 (29)	
Grade 3	9 (22)	1 (14)	
Grade 4	6 (15)	3 (43)	
Missing	2 (5)	1 (14)	
Negative DBPCFC			
Introduction of peanut after one month			1.000
Successful	18 (64)	5 (71)	
Failed	9 (32)	2 (29)	
Not initiated	1 (4)	0	

Values are numbers (%), unless otherwise indicated.

[†] P-values of less than 0.006 taken to be significant according to Bonferroni correction for multiple testing.

[‡] According to Sampson classification of anaphylaxis.¹⁷

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; FAQLQ-PF, Food Allergy Quality of Life Questionnaire – Parent Form; IQR, interquartile range; n, number; SD, standard deviation.

Supplemental Table 2. Comparison between peanut-allergic children with and without accidental reactions during follow-up

	Accidental reaction(s)	No accidental reaction	P-value[†]
n (%)	n (%)	n (%)	
Baseline characteristics			
Age at follow-up			1.000
4 to 13 years	11 (65)	16 (67)	
13 to 18 years	6 (35)	8 (33)	
Male gender	11 (65)	16 (67)	1.000
History of atopy			
Duration of peanut elimination diet			0.972
3 to 8 years	6 (35)	9 (38)	
8 to 13 years	7 (41)	9 (38)	
Lifelong	4 (24)	6 (25)	
Previous reaction to peanut [‡]			0.615
Never ingested peanut	3 (18)	7 (29)	
Contact	3 (18)	2 (8)	
Grade 1-3	5 (29)	9 (38)	
Grade 4-5	6 (35)	6 (25)	
Elimination diet >1 other allergen	12 (71)	16 (67)	1.000
History of asthma	8 (47)	15 (63)	0.358
Sensitization before DBPCFC			
sIgE to peanut, median (IQR)	8.3 (2.7 to 21.45)	7.1 (1.54 to 43.50)	0.853
sIgE to Ara h 2, median (IQR)	6.4 (2.36 to 23.85)	3.45 (0.93 to 32.50)	0.662
DBPCFC			
FAQLQ-PF score before DBPCFC, mean (SD)	2.37 (1.00)	2.35 (1.01)	0.950
Reaction during DBPCFC [‡]			0.565
Grade 1-3	12 (71)	20 (83)	
Grade 4-5	3 (18)	3 (13)	
Missing	2 (12)	1 (4)	
LOAEL DBPCFC, median (IQR)			
Subjective	65 (1 to 1950)	100 (20 to 1000)	0.609
Objective	1000 (0 to 2500)	1000 (38 to 1000)	0.939
Dietary advice: no products with PAL	7 (41)	6 (25)	0.322

[†] P-values of less than 0.003 taken to be significant according to Bonferroni correction for multiple testing.

[‡] According to Sampson classification of anaphylaxis.¹⁷

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; FAQLQ-PF, Food Allergy Quality of Life Questionnaire – Parent Form; IQR, interquartile range; LOAEL, lowest-observed-adverse-effect level; n, number; PAL, precautionary allergen labelling; SD, standard deviation.

Supplemental Table 3. Domain scores of parent-proxy reported health-related quality of life using the FAQLQ-PF

		Before DBPCFC (T1)	3 years after DBPCFC (T2)	Delta score [†]	P- value [‡]
	Domain	Mean (SD)	Mean (SD)	Mean	
Parent-proxy reported HRQL					
All children (n=44)	Overall	2.38 (0.97)	2.17 (1.00)	-0.22	0.187
	FRA	2.66 (1.17)	2.53 (1.18)	-0.14	
	SDL	2.41 (1.08)	2.02 (0.96)	-0.38	
	EI	2.19 (1.17)	2.05 (1.04)	-0.14	
Peanut-allergic children (n=23)	Overall	2.29 (1.02)	2.35 (0.80)	0.05	0.823
	FRA	2.50 (1.22)	2.66 (0.80)	0.16	
	SDL	2.31 (1.17)	2.22 (0.85)	-0.10	
	EI	2.13 (1.08)	2.24 (0.90)	0.11	
Peanut-tolerant children (n=21)	Overall	2.48 (0.94)	1.97 (1.18)	-0.51	0.025
	FRA	2.84 (1.25)	2.38 (1.50)	-0.46	
	SDL	2.50 (1.00)	1.80 (1.05)	-0.69	
	EI	2.25 (1.29)	1.84 (1.15)	-0.40	
Successful introduction (n=15)	Overall	2.59 (1.06)	1.90 (1.20)	-0.70	0.013
	FRA	2.89 (1.38)	2.22 (1.35)	-0.67	
	SDL	2.65 (1.12)	1.80 (1.19)	-0.85	
	EI	2.37 (1.47)	1.76 (1.17)	-0.61	
Failed introduction (n=6)	Overall	2.21 (0.52)	2.16 (1.20)	-0.05	0.906
	FRA	2.71 (0.94)	2.77 (1.89)	0.06	
	SDL	2.11 (0.51)	1.81 (0.71)	-0.30	
	EI	1.94 (0.72)	2.04 (1.18)	0.10	
Child-reported HRQL					
Child Form (n=6)	Overall	3.72 (1.82)	3.29 (1.72)	-0.42	0.648
Teen Form (n=3)	Overall	4.54 (1.15)	3.85 (1.26)	-0.69	0.270
Child Form (T1) + Teen Form (T2) (n=14)	Overall	3.48 (1.26)	2.85 (1.14)	NA	NA
None (T1) + Child Form (T2) (n=18)	Overall	NA	3.40 (1.75)	NA	NA

[†] Delta scores in boldface indicate a clinically relevant difference between the two time points.

[‡] P-values in boldface indicate a significant difference between the two time points.

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; EI, emotional impact; FAQLQ-PF, Food Allergy Quality of Life Questionnaire – Parent Form; FRA, food-related anxiety; n, number; SD, standard deviation; SDL, social dietary limitations.

Chapter 5

Risk factors for atopic diseases and recurrent respiratory tract infections in children

Submitted

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Abstract

Background

The simultaneous increased prevalence of atopic diseases and decreased prevalence of infectious diseases might point to a link between the two entities. Past work mainly focused on either atopic diseases or recurrent infections. We aim to investigate whether demographic, environmental and family history risk factors for atopic diseases (i.e. asthma, allergic rhinitis, atopic dermatitis and/or food allergy) differ from risk factors for recurrent respiratory tract infections (RRTI) in children.

Methods

Cross-sectional data were used from 5517 children aged 1-18 years who participated in an Electronic Portal for children with asthma, allergies or infections between 2011 and 2019. Univariable/multivariable logistic regression analyses were performed to determine risk factors for any atopic disease and RRTI.

Results

Children aged ≥ 5 years were more likely to have any atopic disease (adjusted OR, OR, 1.50-2.77) and less likely to have RRTI (adjusted OR, 0.68-0.84) compared to children aged < 5 years. Female sex (adjusted OR 0.72; 95% CI 0.63-0.81), low birth weight (adjusted OR 0.74; 95% CI 0.57-0.97) and dog ownership (adjusted OR 0.79; 95% CI 0.66-0.95) reduced the odds of any atopic disease, but not of RRTI. Day care attendance (adjusted OR 1.22; 95% CI 1.02-1.47) was associated with RRTI, but not with atopic diseases. A family history of asthma, allergic rhinitis, atopic dermatitis and RRTI was significantly associated with the same entity in children, with an adjusted OR varying from 1.58 (95% CI 1.35-1.85) in allergic rhinitis to 2.20 (95% CI 1.85-2.61) in asthma.

Conclusion

Risk factors for atopic diseases are distinct from risk factors for RRTI, suggesting that the changing prevalence of both entities is not related to shared risk factors.

Introduction

Atopic diseases are common diseases in childhood. The prevalence of asthma, allergic rhinitis, atopic dermatitis and food allergy has been estimated at approximately 20%, 15%, 8% and 6%, respectively.^{1,2} The prevalence of atopic diseases has been steadily rising in the past decades in the Western world.³ Simultaneously, the prevalence of infectious diseases has decreased.⁴ These two trends in prevalence have been linked, leading to the hypothesis that a decline in infections or a lack of exposure to microbes could have an etiological role in the increased prevalence of atopic diseases. The known geographical variation in the prevalence of atopic diseases is in line with this hypothesis: a high prevalence in industrialized, urban environments concurrent with low microbial exposure, and a low prevalence in the developing or rural world concurrent with high microbial exposure.⁵ It is known that early, repeated exposure to infectious agents stimulates the immune system to develop regulatory T-cells, and hereby the development of atopic diseases may be prevented.⁶

Environmental factors associated with a reduced risk of atopic diseases are often described as being associated with an increased risk of infections, such as day care attendance, growing up in a rural environment, having older siblings and having pets.⁷⁻¹⁰ A large number of epidemiological studies have described that other environmental factors, such as maternal smoking during pregnancy, postnatal exposure to cigarette smoke, air pollution and a family history of atopic diseases, are associated with an increased prevalence of atopic diseases.¹¹

Although the opposing trends in the prevalence of atopic diseases and infections have been linked, studies investigating demographic, environmental and family history risk factors for both atopic diseases and recurrent infections in conjunction are lacking. Large studies investigating a broad range of risk factors for atopic diseases and recurrent infections that enable adjustment for each other may lead to a better understanding of the development of these disease entities in children. A large set of data on this topic is available in the so-called Electronic Portal developed by the UMC Utrecht. This is a standardized data collection tool used in multiple centres across the Netherlands that includes data of several validated questionnaires on atopic diseases and recurrent respiratory tract infections in childhood.¹² The primary aim of this study was to investigate how risk factors associated with any atopic disease (i.e. asthma, allergic rhinitis, atopic dermatitis and/or food allergy) are different from risk factors associated with recurrent respiratory tract infections (RRTI) in children. Our secondary aim was to investigate how these risk factors are associated with individual atopic disease entities.

Methods

Domain and data collection

We performed a cross-sectional questionnaire-based study among children aged 1 to 18 years old who participated in the Electronic Portal between June 2011 and September 2019. The Electronic Portal is a web-based application established by a nationwide collaborative network of Dutch caregivers. The details of the Electronic Portal have been previously published.¹² Children were included in the Electronic Portal as part of a first outpatient visit for respiratory or allergic symptoms in a participating secondary care (n=9) or tertiary care (n=1) centre or as part of the WHISTLER birth cohort study.¹³ No exclusion criteria were specified. Of the 9,558 children who were invited to participate in the Electronic Portal, 5517 (58%) children started the questionnaire and were evaluated in this study. Informed consent was obtained from all parents and/or children (as applicable) before enrolment. The study was reviewed and approved by the medical ethics committee of the University Medical Centre Utrecht (No. 10/348).

Outcome definitions

Information on the presence of atopic diseases and RRTI was extracted from the answers to the questionnaires in the Electronic Portal (Supplemental Table 1). The definition of asthma, allergic rhinitis and atopic dermatitis was adopted from the ISAAC questionnaires.¹⁴ Food allergy was defined as suggestive allergic symptoms within 2 hours after ingestion of the suspected food. Recurrent respiratory tract infections (RRTI) was defined as having a minimum number of upper or lower respiratory infection per year.¹⁵ The minimum number depended on the child's age (Supplemental Table 1).

Demographic, environmental and family history factors

All risk factors were selected based on prior research and clinical expertise of the authors.⁷⁻¹¹ Information on the presence of the selected risk factors was extracted from answers to the questionnaires in the Electronic Portal. Included demographic factors were age, sex, gestational age, birth weight, maternal and paternal ethnicity and education level. Included environmental factors were exclusive breastfeeding, pacifier use, having siblings, number of older siblings, day care attendance in the first year of life, living environment (i.e. rural or urban), having a dog, having a cat, maternal smoking during pregnancy, indoor smoking, adoption, vaccination status (i.e. complete age-appropriate vaccinations according to the Dutch vaccination schedule), flooring in the house and flooring in the child's bedroom (i.e. solid or carpet). Included factors on family history were having a family history (i.e. one or both parents and/or sibling(s) with the disease) of asthma, allergic rhinitis, atopic dermatitis, food allergy or recurrent respiratory tract infections.

Statistical analysis

Descriptive statistics including numbers (percentages) and medians (interquartile range) were used to describe the study population. Data on all risk factors and outcomes were complete in 55% of the children and 92% of the values. Missing values were imputed by using multiple imputations (20 iterations) using SPSS. First, the crude associations between risk factors and the disease outcome (i.e. any of the atopic diseases or RRTI) were assessed using univariable logistic regression analyses. Second, the adjusted associations between the risk factors and outcome were assessed using multivariable logistic regression analyses. The multivariable regression analyses included all risk factors (no prior selection based on p-values), the child's comorbidity and the analyses were controlled for inclusion setting (i.e. secondary care, tertiary care or birth cohort). The same analyses were performed per individual atopic disease entity. Results of the univariable and multivariable regression analyses were expressed as respectively crude odds ratios and adjusted odds ratios (OR) with 95% confidence intervals (95% CI). A p-value of < 0.05 was considered statistically significant. Data were analysed using SPSS version 25.0 for Windows (SPSS, INC, Chicago, IL, USA).

Results

Patients

The median age of the 5,517 included children was 6 years (interquartile range 3 to 10) and 43% were girls (Table 1). Children were included after referral to a secondary care centre (56%), a tertiary care centre (30%) or as part of the WHISTLER birth cohort (14%). Sixty-two percent of children had one or more atopic disease(s), 42% had recurrent respiratory tract infections (RRTI) and 23% had no atopic diseases or RRTI (Figure 1).

Table 1. Baseline characteristics of the cohort (n=5517)

		n (%)
Demographics		
Age in years, median (IQR)		6.00 (3-10)
Female sex		2370 (43)
Gestational age	< 37 weeks	607 (11)
	37-43 weeks	4807 (87)
	≥ 43 weeks	103 (2)
Low birth weight		429 (8)
Dutch maternal ethnicity		5116 (93)
Dutch paternal ethnicity		4999 (91)
Maternal education level	Low	528 (10)
	Middle	1888 (34)
	High	3101 (56)
Paternal education level	Low	612 (11)
	Middle	1944 (35)
	High	2961 (54)
Environment		
Exclusive breastfeeding	Never	3583 (65)
	< 6 months	948 (17)
	≥ 6 months	987 (18)
Pacifier use		3600 (65)
Having siblings		4349 (79)
Day care attendance		4688 (85)
Urban living environment		2360 (43)
Having a pet dog		972 (18)
Having a pet cat		971 (18)
Maternal smoking during pregnancy		221 (4)
Indoor smoking		287 (5)
Adopted		71 (1)
Vaccinated		4946 (90)
Family history		
Asthma		2230 (41)
Allergic rhinitis		3610 (65)
Atopic dermatitis		3312 (60)
Food allergy		1926 (35)
RRTI		3103 (56)
Disease outcome child		
Asthma		958 (17)
Allergic rhinitis		1919 (35)
Atopic dermatitis		2083 (38)
Food allergy		552 (10)
RRTI		2336 (42)
Combined disease outcome child		
Any atopic disease		3408 (62)
Both any atopic disease and RRTI		1523 (28)
No atopic disease or RRTI		1295 (23)

Percentages do not always add up to 100 due to rounding.

Abbreviations: IQR, interquartile range; n, number; RRTI, recurrent respiratory tract infections.

Figure 1. Venn diagram displaying the proportion of atopic diseases and respiratory tract infections in all included children

Risk factors for atopic diseases and recurrent respiratory tract infections

Table 2 and Figure 2 report the results from the multivariable regression analyses, exploring the association between demographic, environmental and family history risk factors and the presence of any atopic disease or RRTI. Table 3 reports the results from the multivariable regression analyses per individual atopic disease entity. The results of the univariable analyses are presented in Supplemental Table 2 and 3.

Demographic factors

Several demographic factors were associated with any atopic disease, while only age and gestational age were associated with RRTI (Table 2; Figure 2A). Children aged 5 years and older had a higher chance of any atopic disease (adjusted Odds Ratio, OR, 1.50 to 2.77), but a lower chance of RRTI (adjusted OR, 0.68 to 0.84), compared to children aged < 5 years. Female sex (adjusted OR, 0.72; 95% CI, 0.63-0.81) and low birth weight (adjusted OR, 0.74; 95% CI, 0.57-0.97) were associated with a reduced odds of any atopic disease. Children born between 37 and 43 weeks of gestation had a lower chance of RRTI (adjusted OR, 0.79; 95% CI, 0.62-0.99), compared to children born preterm.

In the analyses per individual atopic disease entity, children aged 5 years and older had a higher chance of asthma (adjusted OR, 3.07 to 5.21) and allergic rhinitis (adjusted OR, 2.20 to 6.65) compared to children < 5 years (Table 3). Children aged 5 years and older had a lower chance of atopic dermatitis (adjusted OR, 0.44 to 0.77) compared to children aged < 5 years. Female sex was associated with a reduced odds of asthma (adjusted OR, 0.83; 95% CI, 0.70-0.97) and allergic rhinitis (adjusted OR, 0.70; 95% CI, 0.61-0.81). Low birth weight was associated with a reduced odds of allergic rhinitis (adjusted OR, 0.72; 95% CI, 0.54-0.96) only.

Table 2. Independent risk factors for respectively any atopic disease and RRTI

	Any atopic disease		RRTI	
	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]
Demographics				
Age (in years)				
5 to 8 (vs. 1 to 4)	1.50 (1.28-1.75)	<0.001	0.84 (0.71-1.01)	0.06
9 to 12 (vs. 1 to 4)	2.04 (1.71-2.44)	<0.001	0.69 (0.57-0.83)	<0.001
13 to 17 (vs. 1 to 4)	2.77 (2.20-3.50)	<0.001	0.68 (0.53-0.86)	<0.01
Female sex	0.72 (0.63-0.81)	<0.001	1.04 (0.91-1.19)	0.54
Gestational age (weeks)				
37-43 weeks (vs. < 37)	0.98 (0.78-1.22)	0.84	0.79 (0.62-0.99)	<0.05
≥ 43 weeks (vs. < 37)	0.91 (0.54-1.54)	0.72	0.68 (0.40-1.15)	0.15
Low birth weight (vs. normal)	0.74 (0.57-0.97)	0.03	0.90 (0.69-1.17)	0.44
Non-Dutch mother (vs. Dutch)	0.93 (0.68-1.26)	0.63	0.99 (0.71-1.37)	0.95
Non-Dutch father (vs. Dutch)	1.43 (1.10-1.87)	<0.01	1.03 (0.80-1.33)	0.80
Education level mother				
Middle (vs. low)	1.35 (1.05-1.74)	0.02	0.83 (0.65-1.07)	0.16
High (vs. low)	1.27 (0.98-1.66)	0.08	0.78 (0.59-1.03)	0.08
Education level father				
Middle (vs. low)	1.02 (0.82-1.29)	0.84	0.85 (0.68-1.07)	0.16
High (vs. low)	1.03 (0.81-1.30)	0.82	0.83 (0.65-1.06)	0.14
Environment				
Exclusive breastfeeding				
< 6 months (vs. never)	1.02 (0.85-1.21)	0.87	0.86 (0.72-1.03)	0.10
≥ 6 months (vs. never)	1.08 (0.90-1.28)	0.41	0.96 (0.81-1.13)	0.61
Pacifier use	1.04 (0.91-1.19)	0.57	1.10 (0.96-1.25)	0.17
Having siblings	0.88 (0.72-1.09)	0.25	1.01 (0.79-1.29)	0.92
Number of siblings				
1 (vs. 0)	0.94 (0.80-1.11)	0.48	1.01 (0.86-1.19)	0.89
2 (vs. 0)	0.81 (0.64-1.04)	0.10	1.12 (0.88-1.43)	0.36
≥ 3 (vs. 0)	0.77 (0.40-1.45)	0.41	0.79 (0.49-1.28)	0.34
Day care attendance	1.11 (0.93-1.34)	0.24	1.22 (1.02-1.47)	<0.05
Urban living environment (vs. rural)	0.97 (0.85-1.11)	0.63	0.92 (0.81-1.05)	0.23
Having a pet dog	0.79 (0.66-0.95)	0.01	1.24 (1.04-1.48)	<0.05
Having a pet cat	0.85 (0.72-1.00)	0.05	1.09 (0.92-1.28)	0.34
Maternal smoking during pregnancy	1.01 (0.72-1.42)	0.96	1.14 (0.80-1.62)	0.47
Indoor smoking	1.27 (0.92-1.77)	0.15	1.20 (0.88-1.63)	0.26
Adopted	1.65 (0.91-3.00)	0.10	0.53 (0.28-1.01)	0.05
Vaccinated	0.94 (0.76-1.16)	0.56	1.15 (0.93-1.42)	0.19
Carpet floor house (vs. solid)	1.96 (1.10-3.48)	0.02	0.89 (0.55-1.44)	0.64
Carpet floor bedroom child (vs. solid)	0.82 (0.69-0.98)	0.03	0.95 (0.79-1.13)	0.55
Family history				
Asthma	1.24 (1.07-1.42)	<0.01	1.03 (0.90-1.18)	0.70
Allergic rhinitis	1.30 (1.13-1.50)	<0.001	0.91 (0.78-1.06)	0.23
Atopic dermatitis	1.66 (1.45-1.90)	<0.001	1.03 (0.90-1.19)	0.64
Food allergy	1.29 (1.09-1.52)	<0.01	0.91 (0.79-1.06)	0.23
RRTI	0.91 (0.80-1.04)	0.18	1.71 (1.50-1.96)	<0.001

Table 2. Independent risk factors for respectively any atopic disease and RRTI (continued)

	Any atopic disease		RRTI	
	Adjusted OR (95% CI)	<i>P</i> value [†]	Adjusted OR (95% CI)	<i>P</i> value [†]
Comorbidities				
Asthma	NA		2.01 (1.68-2.39)	<0.001
Allergic rhinitis	NA		1.39 (1.19-1.63)	<0.001
Atopic dermatitis	NA		0.70 (0.61-0.81)	<0.001
Food allergy	NA		0.62 (0.49-0.77)	<0.001
RRTI	0.94 (0.82-1.09)	0.44	NA	

Analyses were mutually adjusted within the model, for centre (secondary care, tertiary care or birth cohort) and for the child's comorbidities. Significant *P* values are in bold.

Abbreviations: *CI*, confidence interval; *OR*, odds ratio; *RRTI*, recurrent respiratory tract infections.

Figure 2A. Association between demographic risk factors and any atopic disease and RRTI
Abbreviations: GA, gestational age; mat, maternal; OR, odds ratio; pat, paternal; RRTI, recurrent respiratory tract infections.

Figure 2B. Association between environmental risk factors and any atopic disease and RRTI
Abbreviations: excl. BF, exclusive breastfeeding; mat, maternal; OR, odds ratio; RRTI, recurrent respiratory tract infections.

Figure 2C. Association between family history and comorbidity risk factors and any atopic disease and RRTI
Abbreviations: OR, odds ratio; RRTI, recurrent respiratory tract infections.

Environmental factors

Children who had a pet dog (adjusted OR, 0.79; 95% CI, 0.66-0.95) had a lower chance of any atopic disease, but a slightly higher chance of RRTI (adjusted OR, 1.24; 95% CI, 1.04-1.48). Day care attendance increased the odds of RRTI (adjusted OR, 1.22; 95% CI, 1.02-1.47), but was not associated with any atopic disease (Table 2; Figure 2B).

In the analyses per individual atopic disease entity, children who had a pet dog had a lower chance of food allergy (adjusted OR, 0.52; 95% CI, 0.38-0.72) (Table 3). Furthermore, children who had a pet cat had a lower chance of allergic rhinitis (adjusted OR, 0.71; 95% CI, 0.59-0.87). In addition, children with 1 or 2 siblings had a lower chance of allergic rhinitis (adjusted OR, 0.84; 95% CI, 0.71-0.99 and adjusted OR, 0.71; 95% CI 0.55-0.91, respectively). Children who were exclusively breastfed for

6 months or longer had a higher chance of food allergy (adjusted OR, 1.34; 95% CI, 1.04-1.72). An unexpected finding was that we observed an inverse association between maternal smoking during pregnancy and atopic dermatitis (adjusted OR 0.57; 95% CI 0.40-0.82).

Family history

The associations between family history and disease outcomes were disease-specific. Children who reported a family history of one of the atopic diseases were more likely to have any atopic disease, but were not likely to have more RRTI (Table 2; Figure 2C). Children who reported a family history of recurrent infections were more likely to have RRTI (adjusted OR, 1.71; 95% CI, 1.50-1.96), but were not more likely to have any atopic disease.

In the analyses per individual atopic disease entity, the disease-specific association between a family history and disease outcome was further confirmed for asthma, allergic rhinitis and atopic dermatitis (adjusted OR 2.20, 1.58, 1.72, respectively).

Comorbidities

A child's history of RRTI was not associated with having any atopic disease (adjusted OR, 0.94; 95% CI, 0.82-1.09) (Table 2; Figure 2C). However, children who reported a history of asthma or allergic rhinitis were more likely to have RRTI (adjusted OR, 2.01; 95% CI, 1.68-2.39, and adjusted OR, 1.39; 95% CI, 1.19-1.63, respectively). On the contrary, a history of atopic dermatitis or food allergy reduced the odds of having RRTI (adjusted OR, 0.70; 95% CI, 0.61-0.81, and adjusted OR, 0.62, 95% CI, 0.49-0.77).

In the analysis per individual atopic disease entity, a child's history of another atopic disease increased the odds of the outcome atopic disease (adjusted OR ranging between 1.34 and 2.11) (Table 3). Although a child's history of RRTI was not associated with having any atopic diseases, a history of RRTI was associated with individual atopic diseases entities. Children who reported RRTI were more likely to have asthma (adjusted OR, 1.99; 95% CI, 1.67-2.37) and allergic rhinitis (adjusted OR, 1.38; 95% CI, 1.18-1.61), but less likely to have atopic dermatitis (adjusted OR, 0.70; 95% CI, 0.61-0.81) and food allergy (adjusted OR, 0.63; 95% CI, 0.50-0.80).

Table 3. Independent risk factors for individual atopic disease entities

	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy	
	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]
Demographics								
Age (in years)								
5 to 8 (vs. 1 to 4)	3.07 (2.42-3.89)	<0.001	2.20 (1.83-2.64)	<0.001	0.77 (0.66-0.90)	<0.01	1.11 (0.86-1.44)	0.42
9 to 12 (vs. 1 to 4)	3.64 (2.83-4.66)	<0.001	4.02 (3.31-4.87)	<0.001	0.57 (0.48-0.68)	<0.001	1.13 (0.85-1.49)	0.41
13 to 17 (vs. 1 to 4)	5.21 (3.95-6.87)	<0.001	6.65 (5.25-8.43)	<0.001	0.44 (0.35-0.55)	<0.001	1.06 (0.75-1.48)	0.75
Female sex	0.83 (0.70-0.97)	0.02	0.70 (0.61-0.81)	<0.001	0.97 (0.86-1.00)	0.57	0.88 (0.72-1.07)	0.20
Gestational age								
37-43 weeks (vs. < 37)	0.84 (0.64-1.10)	0.21	0.88 (0.69-1.12)	0.29	1.03 (0.83-1.27)	0.82	1.28 (0.88-1.86)	0.19
≥ 43 weeks (vs. < 37)	1.29 (0.72-2.32)	0.39	0.82 (0.47-1.42)	0.48	0.78 (0.47-1.31)	0.35	0.98 (0.42-2.29)	0.97
Low birth weight (vs. normal)	1.04 (0.76-1.43)	0.80	0.72 (0.54-0.96)	0.02	0.79 (0.61-1.02)	0.07	1.09 (0.72-1.63)	0.69
Non-Dutch mother (vs. Dutch)	0.59 (0.37-0.93)	0.02	0.97 (0.70-1.35)	0.86	1.13 (0.84-1.52)	0.41	0.80 (0.51-1.25)	0.32
Non-Dutch father (vs. Dutch)	1.00 (0.71-1.40)	0.98	1.34 (1.03-1.74)	0.03	1.20 (0.94-1.54)	0.14	1.35 (0.92-1.98)	0.13
Maternal education level								
Middle (vs. low)	1.16 (0.87-1.55)	0.31	1.22 (0.93-1.59)	0.16	1.12 (0.87-1.44)	0.38	0.99 (0.67-1.45)	0.95
High (vs. low)	1.08 (0.79-1.48)	0.62	1.08 (0.82-1.43)	0.57	1.09 (0.84-1.42)	0.50	0.97 (0.65-1.44)	0.86
Paternal education level								
Middle (vs. low)	0.78 (0.59-1.02)	0.07	1.19 (0.94-1.52)	0.16	0.99 (0.79-1.24)	0.93	1.27 (0.88-1.85)	0.20
High (vs. low)	0.78 (0.58-1.05)	0.10	1.06 (0.82-1.37)	0.66	1.00 (0.79-1.27)	0.99	1.32 (0.90-1.95)	0.16
Environment								
Exclusive breastfeeding								
< 6 months (vs. never)	0.99 (0.79-1.24)	0.94	1.04 (0.86-1.25)	0.68	1.04 (0.88-1.22)	0.65	0.92 (0.70-1.20)	0.53
≥ 6 months (vs. never)	1.04 (0.84-1.28)	0.76	1.08 (0.90-1.30)	0.41	0.93 (0.78-1.10)	0.38	1.34 (1.04-1.72)	0.02
Pacifier use	1.28 (1.08-1.52)	<0.01	1.03 (0.89-1.19)	0.72	0.98 (0.86-1.11)	0.71	1.06 (0.87-1.30)	0.55
Having siblings	1.00 (0.73-1.36)	0.98	1.00 (0.80-1.26)	0.99	0.79 (0.65-0.95)	0.01	1.32 (0.96-1.83)	0.09
Number of siblings								
1 (vs. 0)	1.17 (0.96-1.45)	0.13	0.84 (0.71-0.99)	<0.05	1.06 (0.90-1.24)	0.48	0.86 (0.68-1.10)	0.22
2 (vs. 0)	1.14 (0.85-1.52)	0.38	0.71 (0.55-0.91)	<0.01	1.06 (0.84-1.33)	0.62	0.83 (0.59-1.18)	0.30
≥ 3 (vs. 0)	1.07 (0.54-2.14)	0.84	0.80 (0.45-1.41)	0.43	1.04 (0.71-1.52)	0.84	0.71 (0.38-1.32)	0.27
Day care attendance	1.04 (0.83-1.31)	0.71	1.16 (0.95-1.42)	0.14	0.97 (0.82-1.16)	0.74	1.19 (0.88-1.60)	0.26

Table 3. Independent risk factors for individual atopic disease entities (continued)

	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy	
	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]	Adjusted OR (95% CI)	P value [†]
Environment (continued)								
Urban living (vs. rural)	1.14 (0.96-1.36)	0.13	0.94 (0.82-1.09)	0.43	1.01 (0.89-1.15)	0.92	0.94 (0.77-1.15)	0.55
Having a pet dog	1.01 (0.81-1.26)	0.92	0.85 (0.70-1.03)	0.10	0.83 (0.69-1.00)	0.05	0.52 (0.38-0.72)	<0.001
Having a pet cat	0.91 (0.73-1.14)	0.41	0.71 (0.59-0.87)	<0.01	0.92 (0.78-1.10)	0.38	0.91 (0.69-1.21)	0.52
Maternal smoking pregnancy	1.26 (0.82-1.94)	0.29	1.16 (0.79-1.68)	0.45	0.57 (0.40-0.82)	<0.01	1.05 (0.61-1.82)	0.85
Indoor smoking	1.00 (0.69-1.45)	0.99	1.02 (0.73-1.41)	0.92	1.16 (0.85-1.57)	0.36	1.82 (1.18-2.81)	0.01
Adopted	1.58 (0.81-3.09)	0.18	1.00 (0.53-1.84)	0.98	1.62 (0.92-2.84)	0.09	0.39 (0.12-1.28)	0.12
Vaccinated	0.71 (0.56-0.91)	<0.01	0.82 (0.65-1.04)	0.10	1.11 (0.91-1.36)	0.29	1.36 (0.98-1.89)	0.07
Carpet floor house (vs. solid)	1.46 (0.83-2.57)	0.20	1.35 (0.78-2.32)	0.28	1.17 (0.74-1.85)	0.50	0.94 (0.46-1.91)	0.86
Carpet floor bedroom child	0.82 (0.65-1.05)	0.12	0.88 (0.72-1.07)	0.19	0.85 (0.72-1.01)	0.07	1.11 (0.84-1.46)	0.45
Family history								
Asthma	2.20 (1.85-2.61)	<0.001	1.07 (0.9-1.25)	0.36	1.00 (0.88-1.14)	0.99	0.93 (0.75-1.15)	0.51
Allergic rhinitis	0.94 (0.78-1.13)	0.52	1.58 (1.35-1.85)	<0.001	1.13 (0.99-1.30)	0.08	1.21 (0.96-1.54)	0.11
Atopic dermatitis	1.17 (0.98-1.41)	0.09	1.00 (0.86-1.17)	0.97	1.72 (1.50-1.98)	<0.001	1.20 (0.95-1.50)	0.13
Food allergy	0.99 (0.82-1.20)	0.92	1.14 (0.96-1.35)	0.13	1.24 (1.06-1.44)	<0.01	1.20 (0.92-1.57)	0.18
RRTI	0.88 (0.74-1.06)	0.17	1.17 (1.01-1.36)	0.04	0.89 (0.78-1.02)	0.08	0.85 (0.69-1.05)	0.13
Comorbidities								
Asthma	NA		1.77 (1.49-2.10)	<0.001	1.35 (1.14-1.59)	<0.001	1.46 (1.16-1.86)	<0.01
Allergic rhinitis	1.79 (1.51-2.13)	<0.001	NA		2.11 (1.83-2.43)	<0.001	1.63 (1.33-2.01)	<0.001
Atopic dermatitis	1.34 (1.14-1.58)	<0.01	2.11 (1.83-2.44)	<0.001	NA		1.59 (1.30-1.95)	<0.001
Food allergy	1.46 (1.15-1.86)	<0.01	1.68 (1.36-2.06)	<0.001	1.61 (1.32-1.96)	<0.001	NA	
RRTI	1.99 (1.67-2.37)	<0.001	1.38 (1.18-1.61)	<0.001	0.70 (0.61-0.81)	<0.001	0.63 (0.50-0.80)	<0.001

Analyses were mutually adjusted within the model, for centre (secondary care, tertiary care or birth cohort) and for the child's comorbidities.

[†] Significant P values are in bold.

Abbreviations: CI, confidence interval; OR, odds ratio.

Discussion

Here, we present an overview of demographic, environmental and family history risk factors for atopic diseases compared to risk factors for recurrent respiratory tract infections (RRTI) in a large cohort of Dutch children. Our data show that risk factors for atopic diseases and RRTI differ. As an example, girls, children with a low birthweight and children with a pet dog were more likely to have atopic diseases, but were not more likely to have RRTI. Furthermore, a corresponding family history was a disease-specific risk factor for atopic diseases and for RRTI.

Children aged 5 years and older had a higher chance of asthma and allergic rhinitis compared to children younger than 5 years, while older children had a lower chance of atopic dermatitis. These findings are consistent with the so called 'atopic march'.¹⁶ The atopic march is thought to start with atopic dermatitis, followed by food allergy, asthma and allergic rhinitis. Furthermore, female sex lowered the likelihood of atopic diseases as has been previously acknowledged.¹⁷ Epidemiological studies have reported a predominance of atopic diseases in males before puberty and in females after puberty, possibly explained by hormonal influences or sex-specific genetic, environmental or social factors.¹⁸ We did not observe an association between sex and RRTI, although previous studies suggest that males are more susceptible to most types of respiratory tract infections.¹⁹ The possible protective effect of low birthweight on atopic disease has been previously reported²⁰, and may be explained by differences in immune system development, gastrointestinal tract permeability and exposure to antigens between children with low and normal birthweight.

We found an increased risk of food allergy in children who were exclusively breastfed for more than 6 months. These children may have introduced allergenic foods later in life. Our data consolidate existing evidence that early introduction of allergenic foods prevents the development of food allergies.²¹ Day care attendance increased the risk of RRTI as has been acknowledged in previous research.⁹ The finding that dog ownership was associated with a reduced risk of atopic diseases confirms evidence that having a pet dog protects against atopic diseases and sensitization.⁷ The possible protective effect of pet ownership might be explained by an immunomodulatory effect of exposure to allergens, endotoxins or bacteria⁷ or by affecting DNA methylation.²² However, the protective effect of pet ownership may be partly attributed to selective avoidance of pets in households with allergic family members (reverse causality).²³

The association between family history and the child's outcome was disease-specific, i.e. children with asthma, allergic rhinitis, atopic dermatitis or RRTI were significantly more likely to have a parent and/or sibling reporting the same condition. Especially

the association between family history and RRTI is intriguing and requires further investigation, as it has not been described before. A family history of RRTI is often overlooked although it is particularly important to identify children at increased risk of RRTI and children with genetic disorders or immune deficiencies.²⁴ Given the rarity of single-gene immunodeficiency diseases²⁵, it is suggestive that this association can be more readily explained by a polygenic inheritance pattern. Host genetic factors have been implicated in respiratory infections of varying aetiology, but no consistent associations are observed.²⁶ Most likely, gene-environment interactions play a role in the pathogenesis of both atopic diseases and RRTI. Regardless of the aetiology of the observed association between family history and disease phenotype, our results do emphasize the importance of assessing the family history when confronted with a child with suspected atopic disease or RRTI.

The association between respiratory infections and atopic diseases has been studied extensively. It has been suggested that children with atopic diseases may be more susceptible to respiratory infections due to airway inflammation and impaired innate immune function.^{27,28} On the contrary, other studies have proposed that infections may stimulate a patient's protective immunity and hereby reduce the risk of atopic diseases.²⁹ In our cohort, children with a history of RRTI had a higher chance of asthma and allergic rhinitis, but a lower chance of atopic dermatitis and food allergy. Although a causal relationship cannot be demonstrated in this cross-sectional study, these data suggest that the association between RRTI and atopic diseases may be different per individual atopic disease entity.

There are a number of limitations to our study. First, this was a questionnaire-based survey. Thus, we measured the self-reported prevalence of atopic diseases and RRTI without objectively assessing clinical parameters such as lung capacity by spirometry. However, we did use validated and widely used instruments including the ISAAC questionnaires.¹⁴ A second limitation to our study is the cross-sectional study design. As we measured the prevalence rather than the incidence of diseases, it remains unknown whether the identified factors are a risk factor involved in the aetiology of the diseases. This study is strengthened by standardized data collection in a large group of children from both a birth cohort and hospital setting.

To conclude, our findings indicate that the demographic, environmental and family history risk factors for atopic diseases are distinct from the risk factors for RRTI. Thus, the changing prevalence of both disease entities might not be related to shared risk factors.

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Supplemental tables

Supplemental Table 1. Definition of asthma, allergic rhinitis, atopic dermatitis, food allergy and recurrent respiratory tract infections

Outcome	Age category	Definition based on questions in the Electronic Portal
Asthma	1-18 years	Both questions have been answered with 'yes': 1. Have you/has your child had wheezing or whistling in the chest at any time in the last 12 months? 2. Have you/has your child ever had asthma?
Allergic rhinitis	1-18 years	Both questions have been answered with 'yes': 1. Have you/has your child ever had symptoms of sneezing, running or blocked nose while not having a cold or the flu? 2. Has these symptoms in the last 12 months been accompanied by itchy-watery eyes?
Atopic dermatitis	1-18 years	Both questions have been answered with 'yes': 1. Have you/has your child ever had an itchy rash which was coming and going for at least 6 months? 2. Has this rash been present during the last 12 months?
Food allergy	1-18 years	All three criteria have been fulfilled: 1. Have you/has your child food allergy or do you think you have/your child has food allergy? 2. Have you/has your child developed symptoms within 2 hours after eating the food? 3. Did you/your child have one or more of the following symptoms? <ul style="list-style-type: none"> - Hives - Oral allergy (tingling in mouth or throat) - Angio-oedema (swelling of mouth/tongue/lips and/or eyes) - Lower respiratory symptoms (difficulty with breathing, squeaky respiration and/or shortness of breath) - Upper respiratory symptoms (swelling of throat, soreness, coughing, running nose, blocked nose, sneezing, itchy/red/tearing eyes, feeling of swollen throat) - Vomiting multiple times - Drowsiness - Anaphylaxis (loss of consciousness)
Recurrent respiratory tract infections (RRTI)	1-2 years	≥ 11 upper respiratory infections per year and/or ≥ 2 lower respiratory infections in the past year
	2-5 years	≥ 8 upper respiratory infections per year and/or ≥ 2 lower respiratory infections in the past year
	5-10 years	≥ 6 upper respiratory infections per year and/or ≥ 2 lower respiratory infections in the past year
	> 10 years	≥ 4 upper respiratory infections per year and/or ≥ 2 lower respiratory infections in the past year

Supplemental Table 2. Crude associations between risk factors and respectively any atopic disease and RRTI

	Any atopic disease		RRTI	
	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]
Demographics				
Age (in years)				
5 to 8 (vs. 1 to 4)	1.15 (1.00 – 1.32)	0.05	0.87 (0.75-1.01)	0.07
9 to 12 (vs. 1 to 4)	1.47 (1.26-1.72)	<0.001	0.78 (0.66-0.91)	<0.01
13 to 17 (vs. 1 to 4)	2.89 (2.34-3.58)	<0.001	1.15 (0.94-1.41)	0.17
Female sex	0.71 (0.63 – 0.80)	<0.001	0.92 (0.82 – 1.03)	0.15
Gestational age				
37-43 weeks (vs. < 37)	0.99 (0.82 – 1.18)	0.88	0.71 (0.59 – 0.85)	<0.001
≥ 43 weeks (vs. < 37)	1.12 (0.71 – 1.77)	0.63	0.67 (0.42 – 1.06)	0.08
Low birth weight (vs. normal)	0.86 (0.70 – 1.06)	0.15	1.24 (1.01 – 1.53)	0.04
Non-Dutch mother (vs. Dutch)	1.08 (0.85 – 1.36)	0.55	0.86 (0.66 – 1.13)	0.28
Non-Dutch father (vs. Dutch)	1.32 (1.08 – 1.62)	<0.01	0.96 (0.78 – 1.18)	0.72
Education level mother				
Middle (vs. low)	1.28 (1.03 – 1.59)	0.02	0.79 (0.64 – 0.98)	0.03
High (vs. low)	0.99 (0.80 – 1.22)	0.93	0.56 (0.46 – 0.69)	<0.001
Education level father				
Middle (vs. low)	1.00 (0.82 – 1.22)	0.98	0.70 (0.58 – 0.85)	<0.001
High (vs. low)	0.89 (0.73 – 1.07)	0.21	0.56 (0.46 – 0.68)	<0.001
Environment				
Exclusive breastfeeding				
< 6 months (vs. never)	1.02 (0.87 – 1.19)	0.83	0.79 (0.68 – 0.93)	<0.01
≥ 6 months (vs. never)	1.08 (0.92 – 1.26)	0.35	0.83 (0.71 – 0.96)	0.02
Pacifier use	1.08 (0.96 – 1.22)	0.18	1.14 (1.01 – 1.29)	0.03
Having siblings	0.93 (0.79 – 1.08)	0.32	1.05 (0.85 – 1.29)	0.65
Number of older siblings				
1 (vs. 0)	0.86 (0.76 – 0.98)	0.02	1.05 (0.92 – 1.21)	0.47
2 (vs. 0)	0.79 (0.64 – 0.96)	0.02	1.18 (0.96 – 1.45)	0.12
≥ 3 (vs. 0)	0.86 (0.54 – 1.35)	0.50	1.01 (0.56 – 1.82)	0.97
Day care attendance	1.03 (0.88 – 1.20)	0.75	1.02 (0.87 – 1.19)	0.83
Urban living environment (vs. rural)	0.75 (0.67 – 0.84)	<0.001	0.73 (0.65 – 0.82)	<0.001
Having a pet dog	0.98 (0.84 – 1.15)	0.81	1.50 (1.28 – 1.77)	<0.001
Having a pet cat	0.75 (0.65 – 0.87)	<0.001	1.02 (0.87 – 1.19)	0.83
Maternal smoking during pregnancy	0.92 (0.68 – 1.24)	0.58	1.68 (1.22 – 2.31)	<0.01
Indoor smoking	1.26 (0.95 – 1.67)	0.10	1.68 (1.28 – 2.20)	<0.001
Adopted	1.14 (0.67 – 1.91)	0.63	0.50 (0.28 – 0.90)	0.02
Vaccinated	0.79 (0.65 – 0.96)	0.02	0.96 (0.79 – 1.16)	0.64
Carpet floor house (vs. solid)	2.06 (1.24 – 3.43)	<0.01	1.01 (0.65 – 1.58)	0.95
Carpet floor bedroom child (vs. solid)	0.79 (0.68 – 0.92)	<0.01	0.85 (0.73 – 1.00)	0.06
Family history				
Asthma	1.67 (1.47 – 1.88)	<0.001	1.29 (1.15 – 1.45)	<0.001
Allergic rhinitis	1.70 (1.51 – 1.91)	<0.001	0.99 (0.87 – 1.13)	0.92
Atopic dermatitis	1.94 (1.72 – 2.19)	<0.001	1.10 (0.98 – 1.23)	0.12
Food allergy	1.74 (1.51 – 2.00)	<0.001	1.09 (0.95 – 1.24)	0.22
RRTI	1.15 (1.02 -1.30)	0.02	1.98 (1.75 – 2.24)	<0.001

Supplemental Table 2. Crude associations between risk factors and respectively any atopic disease and RRTI (continued)

	Any atopic disease		RRTI	
	Crude OR (95% CI)	<i>P</i> value [†]	Crude OR (95% CI)	<i>P</i> value [†]
Comorbidities				
Asthma	NA		2.30 (1.97-2.68)	<0.001
Allergic rhinitis	NA		1.55 (1.36-1.76)	<0.001
Atopic dermatitis	NA		0.91 (0.81-1.03)	0.14
Food allergy	NA		0.91 (0.74-1.11)	0.36
RRTI	1.29 (1.13-1.46)	<0.001	NA	

[†] Significant *P* values are in bold.Abbreviations: *CI*, confidence interval; *OR*, odds ratio.

Supplemental Table 3. Crude associations between risk factors individual atopic disease entities

	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy	
	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]
Demographics								
Age (in years)								
5 to 8 (vs. 1 to 4)	2.72 (2.20-3.36)	<0.001	1.91 (1.61-2.26)	<0.001	0.78 (0.68-0.90)	<0.001	1.40 (1.12-1.75)	<0.01
9 to 12 (vs. 1 to 4)	3.42 (2.75-4.26)	<0.001	3.15 (2.65-3.75)	<0.001	0.67 (0.58-0.78)	<0.001	1.38 (1.08-1.76)	0.01
13 to 17 (vs. 1 to 4)	6.40 (5.05-8.11)	<0.001	6.37 (5.18-7.83)	<0.001	0.71 (0.59-0.86)	<0.001	1.56 (1.17-2.09)	<0.01
Female sex	0.81 (0.70-0.94)	<0.01	0.73 (0.65-0.83)	<0.001	0.85 (0.76-0.96)	<0.01	0.83 (0.69-0.99)	0.04
Gestational age								
37-43 weeks (vs. < 37)	0.81 (0.65-1.00)	0.05	0.93 (0.77-1.12)	0.45	1.08 (0.90-1.29)	0.41	1.16 (0.85-1.59)	0.34
≥ 43 weeks (vs. < 37)	1.38 (0.83-2.27)	0.21	1.16 (0.72-1.86)	0.54	0.87 (0.55-1.38)	0.55	0.93 (0.43-2.04)	0.86
Low birth weight (vs. normal)	1.21 (0.94-1.56)	0.14	0.88 (0.71-1.10)	0.25	0.78 (0.63-0.97)	0.03	0.97 (0.69-1.35)	0.84
Non-Dutch mother (vs. Dutch)	0.66 (0.45-0.97)	0.04	1.07 (0.84-1.36)	0.61	1.22 (0.97-1.53)	0.09	0.97 (0.68-1.37)	0.85
Non-Dutch father (vs. Dutch)	0.97 (0.75-1.26)	0.81	1.25 (1.03-1.52)	0.02	1.31 (1.08-1.59)	<0.01	1.28 (0.95-1.73)	0.11
Maternal education level								
Middle (vs. low)	0.93 (0.73-1.20)	0.59	1.16 (0.93-1.45)	0.20	1.27 (1.02-1.58)	0.03	1.10 (0.77-1.56)	0.60
High (vs. low)	0.67 (0.53-0.86)	<0.01	0.86 (0.69-1.07)	0.17	1.15 (0.93-1.42)	0.20	1.07 (0.76-1.49)	0.71
Paternal education level								
Middle (vs. low)	0.70 (0.55-0.88)	<0.01	1.05 (0.85-1.29)	0.67	1.11 (0.91-1.36)	0.30	1.18 (0.84-1.65)	0.34
High (vs. low)	0.62 (0.49-0.78)	<0.001	0.88 (0.71-1.08)	0.22	1.04 (0.86-1.26)	0.70	1.20 (0.87-1.67)	0.27
Environment								
Exclusive breastfeeding								
< 6 months (vs. never)	0.92 (0.75-1.12)	0.39	1.02 (0.87-1.19)	0.83	1.06 (0.91-1.23)	0.46	0.95 (0.74-1.22)	0.67
≥ 6 months (vs. never)	1.06 (0.88-1.28)	0.56	1.13 (0.96-1.32)	0.13	0.98 (0.84-1.14)	0.76	1.36 (1.09-1.70)	<0.01
Pacifier use	1.27 (1.09-1.48)	<0.01	1.09 (0.97-1.24)	0.16	1.03 (0.92-1.16)	0.58	1.08 (0.89-1.30)	0.45
Having siblings	1.33 (0.92-1.91)	0.13	1.15 (0.94-1.40)	0.18	0.77 (0.67-0.89)	<0.001	1.30 (1.01-1.67)	0.04
Number of siblings								
1 (vs. 0)	1.05 (0.88-1.26)	0.59	0.81 (0.71-0.93)	<0.01	0.94 (0.83-1.07)	0.35	0.94 (0.76-1.16)	0.54
2 (vs. 0)	1.06 (0.81-1.38)	0.68	0.72 (0.58-0.90)	<0.01	0.94 (0.77-1.15)	0.53	0.91 (0.66-1.25)	0.56
≥ 3 (vs. 0)	1.13 (0.63-2.03)	0.67	0.86 (0.55-1.35)	0.50	1.02 (0.72-1.46)	0.90	0.80 (0.45-1.44)	0.46
Day care attendance	1.11 (0.91-1.37)	0.31	1.20 (1.01-1.43)	0.04	0.90 (0.77-1.05)	0.18	1.27 (0.97-1.67)	0.09
Urban living (vs. rural)	0.89 (0.77-1.04)	0.13	0.80 (0.71-0.91)	<0.001	0.86 (0.77-0.97)	0.01	0.91 (0.76-1.10)	0.35

Supplemental Table 3. Crude associations between risk factors individual atopic disease entities (continued)

	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy	
	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]	Crude OR (95% CI)	P value [†]
Environment (continued)								
Having a pet dog	1.24 (1.02-1.51)	0.03	1.06 (0.90-1.24)	0.49	0.79 (0.67-0.94)	<0.01	0.50 (0.37-0.68)	<0.001
Having a pet cat	0.79 (0.64-0.98)	0.03	0.65 (0.54-0.77)	<0.001	0.77 (0.66-0.91)	<0.01	0.78 (0.60-1.02)	0.07
Maternal smoking pregnancy	1.29 (0.88-1.89)	0.19	0.93 (0.67-1.28)	0.64	0.57 (0.41-0.79)	<0.01	0.93 (0.57-1.50)	0.75
Indoor smoking	1.42 (1.03-1.96)	0.03	1.18 (0.89-1.56)	0.26	0.95 (0.73-1.25)	0.73	1.38 (0.94-2.01)	0.10
Adopted	1.40 (0.79-2.47)	0.25	0.93 (0.54-1.60)	0.80	1.10 (0.66-1.84)	0.73	0.44 (0.14-1.39)	0.16
Vaccinated	0.72 (0.58-0.90)	<0.01	0.81 (0.66-0.99)	0.04	0.90 (0.75-1.08)	0.25	1.17 (0.86-1.59)	0.33
Carpet floor house (vs. solid)	1.68 (1.03-2.74)	0.04	1.64 (1.05-2.55)	0.03	1.24 (0.82-1.90)	0.31	1.13 (0.59-2.18)	0.71
Carpet floor bedroom child	0.74 (0.60-0.91)	<0.01	0.80 (0.68-0.95)	<0.01	0.83 (0.71-0.97)	0.02	0.93 (0.72-1.20)	0.58
Family history								
Asthma	2.47 (2.13-2.88)	<0.001	1.49 (1.32-1.69)	<0.001	1.35 (1.20-1.51)	<0.001	1.19 (0.98 - 1.44)	0.07
Allergic rhinitis	1.41 (1.20-1.66)	<0.001	1.92 (1.68-2.19)	<0.001	1.51 (1.34-1.71)	<0.001	1.50 (1.22-1.85)	<0.001
Atopic dermatitis	1.56 (1.32-1.83)	<0.001	1.41 (1.24-1.60)	<0.001	1.94 (1.72-2.20)	<0.001	1.48 (1.22-1.80)	<0.001
Food allergy	1.33 (1.13-1.56)	<0.01	1.45 (1.27-1.66)	<0.001	1.66 (1.44-1.90)	<0.001	1.51 (1.21-1.90)	<0.001
RRTI	1.22 (1.05-1.42)	0.01	1.29 (1.14-1.46)	<0.001	1.03 (0.92-1.16)	0.62	0.99 (0.82-1.19)	0.93
Comorbidities								
Asthma	NA		3.27 (2.82-3.80)	<0.001	1.59 (1.37-1.84)	<0.001	1.91 (1.56-2.36)	<0.001
Allergic rhinitis	3.27 (2.82-3.80)	<0.001	NA		2.25 (1.99-2.54)	<0.001	2.17 (1.81-2.60)	<0.001
Atopic dermatitis	1.59 (1.37-1.84)	<0.001	2.25 (1.99-2.54)	<0.001	NA		2.02 (1.69-2.42)	<0.001
Food allergy	1.91 (1.55-2.36)	<0.001	2.17 (1.81-2.60)	<0.001	2.02 (1.69-2.42)	<0.001	NA	
RRTI	2.30 (1.97-2.68)	<0.001	1.55 (1.36-1.76)	<0.001	0.91 (0.81-1.03)	0.14	0.91 (0.74-1.11)	0.36

[†] Significant P values are in bold.

Abbreviations: CI, confidence interval; OR, odds ratio.

Chapter 6

The impact of oral food challenges for food allergy on quality of life: a systematic review

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Abstract

Background

Food allergy significantly impairs health-related quality of life (HRQL). Currently, it is still unknown whether diagnostic interventions for food allergy improve HRQL. We aim to assess the impact of diagnostic interventions for food allergy on HRQL.

Methods

A systematic search was performed in MEDLINE, Embase, Cochrane Library and CINAHL focused on patients with a (suspected) food allergy who underwent diagnostic interventions (i.e. skin prick test, specific IgE or oral food challenges (OFC)), and in whom HRQL was assessed. The mean difference between HRQL before and after the diagnostic intervention was calculated. A minimal clinically important difference of 0.5 was considered clinically relevant for the Food Allergy Quality of Life Questionnaire.

Results

Seven of 1465 original identified publications were included in which the impact of an OFC on HRQL was investigated (total patients n=1370). No other diagnostic interventions were investigated. Food allergy specific parent-reported HRQL improved significantly after an OFC irrespective of the outcome in children with a suspected food allergy in two publications. The change was considered clinically relevant in one of two publications. In addition, parent-reported HRQL improved after an OFC to assess the eliciting dose in children with a confirmed food allergy. The parental burden was significantly reduced after an OFC to assess resolution of food allergy. A meta-analysis could not be performed due to the limited numbers of, and considerable heterogeneity between, eligible publications.

Conclusion

An OFC is associated with an improved food allergy specific HRQL and a reduced parental burden of food allergy.

Introduction

The prevalence of food allergy is thought to be increasing during recent decades.¹ Previous studies have shown that up to 35% of the population reports adverse reactions to food, while between 1% to 3% has a food allergy confirmed by an oral food challenge (OFC).^{2,3}

Currently no curative treatment for food allergy is available. Patients are advised to follow an elimination diet and to carry emergency medication to avoid or treat possible life-threatening allergic reactions.⁴ Hence, patients with a food allergy are faced with dietary and social restrictions. Due to these restrictions, and fear of an allergic reaction, patients with a food allergy have a significantly impaired food allergy specific health-related quality of life (HRQL).^{5,6} In addition, patients with a food allergy reported poorer generic HRQL than the general population and patients with diabetes mellitus type 1 but better generic HRQL than patients with rheumatoid arthritis, asthma and irritable bowel syndrome.⁷ This may be explained by the fact that patients with a food allergy live with constant vigilance and fear of an allergic reaction although they do not have daily chronic symptoms like patients with rheumatoid arthritis, asthma and irritable bowel syndrome.⁸

An accurate diagnosis of food allergy is highly important to minimize unnecessary elimination diets in non-allergic patients on the one hand and avoid allergic reactions in patients with a food allergy on the other hand. Currently the diagnostic process for food allergy consists of a careful clinical and dietary history and sensitization tests including the level of specific IgE (sIgE) to the suspected food and/or a skin prick test (SPT).⁹ However, these sensitization tests have a relatively low specificity depending on the allergen.¹⁰ The current reference standard to assess a food allergy, the threshold and the severity of the clinical reaction is an oral food challenge (OFC). In short, increasing amounts of food allergen or placebo are given with close monitoring in a hospital setting with emergency equipment.^{11,12}

The increasing prevalence of food allergy and the significant impact of food allergy on HRQL of affected patients give cause for careful consideration of current diagnostic strategies. A comprehensive assessment on the impact of diagnostic interventions for food allergy on HRQL of patients is important as these diagnostic interventions might improve HRQL. Therefore, the aim of this review is to provide a systematic synthesis of the current evidence on the impact of diagnostic interventions for food allergy on HRQL.

Methods

Search strategy

This systematic review was conducted according to a previously developed protocol registered on the international prospective register of systematic reviews (PROSPERO) and reported according to the PRISMA checklist.^{13,14}

We developed an extensive search strategy to identify all publications relevant to our research question from electronic bibliographic databases using keywords and Medical Subject Headings. The search combined keywords and synonyms for the domain (patients with a suspected or a confirmed food allergy), the determinant (diagnostic interventions for food allergy: specific IgE (sIgE), skin prick testing (SPT), oral food challenges (OFC), or component resolved diagnostics), and the outcome (food allergy specific or generic HRQL outcome measures). The search strategy was initially developed for the MEDLINE database and then adapted for use on other databases. The full search strategy is published in the supplementary material (Supplemental 1). Four databases were searched from inception until July 6th 2017: MEDLINE, EMBASE, the Cochrane Library and CINAHL. All identified citations were imported into Rayyan for de-duplication and title and abstract screening.¹⁵ All identified publications were screened by two authors (HK, FE) independently. Subsequently, all potentially relevant articles were screened full text by the same two authors independently and assessed for eligibility. The references and citations of all the publications that were screened full text were reviewed to identify any additional relevant sources. The citations were analyzed using Scopus.¹⁶ The reasons for exclusion of the publications that were screened full text are listed in the supplemental material (Supplemental Table 1). Any discrepancies between two authors were resolved by discussion and consensus, or by consulting a third reviewer (TL) if necessary.

Eligibility criteria

We included publications in English, Dutch, German, French or Spanish and did not restrict on publication year. We excluded publications if no original outcome data were reported, such as other systematic reviews, meta-analyses or editorials. We included publications of children or adults with a suspected or a confirmed food allergy if a diagnostic intervention for a food allergy was performed and HRQL scores were measured or could be calculated. In patients with a suspected food allergy the aim of the diagnostic intervention was to confirm or exclude the diagnosis of a food allergy while the aim of diagnostic interventions in patients with a confirmed food allergy was either to assess the threshold, the severity or the resolution of a food allergy. Publications were only included if a validated food allergy specific or generic HRQL instrument was used to measure a change before

and after a diagnostic intervention, or a difference in patients with or without a diagnostic intervention. We contacted the study authors of abstract publications and original publications with incomplete HRQL outcome data to obtain additional information on the study methods and the original data. When we were not able to acquire further details on abstract publications, these publications were excluded. A complete overview of inclusion and exclusion criteria is displayed in the supplemental material (Supplemental Table 2).

Quality of paper assessment

The included publications were assessed for risk of bias in duplicate (HK, FE) according to a modified version of the Quality in Prognostic Studies (QUIPS) tool (Supplemental Table 3).¹⁷ The QUIPS tool considers six domains of potential bias and every domain comprises several prompting items to consider. All items were scored (*yes, partly, no or unsure*) by two authors independently. Subsequently, the six domains of the individual publications were graded for the risk of bias and last, each publication as well as the six domains of all publications was graded for the overall risk of bias (*high, moderate or low*). Any discrepancies between two authors were again resolved by discussion and consensus, or by consulting a third reviewer (TL) if necessary.

Outcome assessment

HRQL can be measured using disease-specific or generic HRQL questionnaires. Disease-specific HRQL questionnaires are able to measure food allergy related impairments, such as the dietary and social restrictions, and the fear of allergic reactions. In contrast to disease-specific HRQL questionnaires, generic HRQL questionnaires facilitate direct comparison to other populations. We included publications that evaluated disease-specific or generic HRQL before and after a diagnostic intervention, and publications that evaluated the difference in disease-specific or generic HRQL in patients with or without a diagnostic intervention.

Disease-specific questionnaires used to evaluate HRQL in food allergic patients in the eligible publications included the self-administered Food Allergy Quality of Life Questionnaire (FAQLQ) with age-specific adaptations: the Child Form (FAQLQ-CF) for children 8 to 12 years of age, the Teenager Form (FAQLQ-TF) for adolescents 13-17 years of age, and the Adult Form (FAQLQ-AF) for adults ≥ 18 years of age. In addition, the Parent Form (FAQLQ-PF) was available to measure parent-reported HRQL of children 0-12 years of age. The FAQLQ-CF contains 24 items and 4 domains (Allergen Avoidance, Risk of Accidental Exposure, Emotional Impact, Dietary restrictions), the FAQLQ-TF contains 23 items and 3 domains (Allergen Avoidance, Risk of Accidental Exposure, Emotional Impact), the FAQLQ-AF contains 29 items and 4 domains (Allergen Avoidance, Risk of Accidental Exposure, Emotional Impact, Food Allergy-related Health), and the FAQLQ-PF contains 30

items and 3 domains (Emotional Impact, Food Anxiety, Social Dietary Limitations). The FAQLQ-items are scored on a seven-point scale. The longitudinal validity and responsiveness of the FAQLQ has been demonstrated.^{18,19} In addition, the Food Allergy Quality of Life Parental Burden Questionnaire (FAQL-PB) was used to assess the effect of a child with food allergy on caregiver HRQL. The FAQL-PB is a validated questionnaire which contains 17 items.²⁰

Generic questionnaires used to evaluate HRQL in the eligible publications were the Paediatric Quality of Life Inventory 4.0 (PedsQL™ 4.0) in children and the World Health Organization generic Quality of Life scale (WHOQOL-BREF) in parents. The PedsQL™ 4.0 is a validated generic HRQL questionnaire for children 8 to 12 years of age which contains 23 items and 4 domains (Physical, Emotional, Social, School). The WHOQOL-BREF is a validated generic HRQL questionnaire for adults which contains 26 items and 4 domains (Physical, Psychological, Social, Environmental).

Data analysis

Full details on the publications, patients, diagnostic intervention(s), and outcome (HRQL questionnaire) were gathered. Publications in patients with a suspected food allergy were analyzed separately from publications in patients with a confirmed food allergy because HRQL is associated with perceived disease severity.²¹ Furthermore, the impact of an OFC on HRQL might be profoundly different in patients with a suspected or a confirmed food allergy because the aim of an OFC in patients with a suspected food allergy is to confirm or exclude the diagnosis of a food allergy while the aim of an OFC in patients with a confirmed food allergy is either to assess the threshold, the severity or the resolution of a food allergy.

For publications using the Food Allergy Quality of Life Questionnaires (FAQLQ) we calculated the mean difference (MD) before and after the diagnostic intervention with a 95% confidence interval (95% CI). If the 95% CI of the MD was not available in the original publication and could not be provided by the study authors we computed this value using the SD of the difference scores.²² To compute the SD of the difference scores in paired data the correlation coefficient (r) between pre-scores and post-scores is required. We assumed a correlation of $r = 0.5$, and performed a sensitivity analysis to evaluate the impact of this assumption using a range of plausible correlation ($r=0.2$ and $r=0.8$). The MD score of the FAQLQ is meaningful as this change score can be interpreted using the minimal clinically important difference (MCID). The MCID is the smallest change score that is considered clinically relevant.²³ The MCID for the FAQLQ is 0.5 as estimated previously using a distribution-based method.¹⁸

For publications using other HRQL questionnaires than the FAQLQ, or if the MD of the FAQLQ could not be calculated, we estimated the standardized mean difference (SMD) before and after the diagnostic intervention with a 95% CI using Cohen's

statistics for paired data.²⁴ Again, the correlation coefficient r was imputed to calculate the SD within groups if needed. Based on Cohen's criteria, a SMD of 0.2 is considered small, 0.5 is moderate and >0.8 is large.²⁴

The MD and SMD were calculated in such a way that their direction was positive. Thus, a positive MD or SMD indicated an improved HRQL. If three or more publications reported HRQL outcomes on the same questionnaire in comparable groups of patients with comparable diagnostic interventions, the results were pooled using the random effects model.²⁵

For publications with a cross-sectional study design, a difference in mean HRQL scores between patients who underwent an OFC and those who did not undergo an OFC was evaluated using the two-sided independent t-test.

All data were extracted using standardized pre-piloted data extraction forms in Microsoft Excel 2010, and forest plots were created using GraphPad Prism 7.02 (GraphPad Software, Inc, San Diego, CA)

Results

Selection of eligible publications

The search results are summarized in a flowchart in Figure 1. We selected 31 of 1465 original identified publications for the full text eligibility screening. Seven eligible publications were included in the final systematic review. Reasons for exclusion after the full text screening were: no diagnostic intervention was investigated ($n=10$), the publication did not report original data ($n=4$), only non-allergic patients were included ($n=3$), the health-related quality of life (HRQL) questionnaire was not validated ($n=3$), no HRQL questionnaire was used ($n=2$) or no change or difference in HRQL was assessed ($n=2$). No new relevant sources were identified by checking references and analyzing citations.

Figure 1. PRISMA flowchart of study selection
Values are numbers.

Characteristics of included publications

The characteristics of the seven included publications are summarized in Table 1. Overall, 1370 patients (ranging between 54 and 420 per study) were recruited between 2007 and 2016 in tertiary care.^{18,26–30} All included publications investigated the impact of an OFC on HRQL. No publications were identified in which the impact of other diagnostic interventions on HRQL was investigated.

Four of seven included publications assessed HRQL in patients with a suspected food allergy.^{18,19,27,29} Three of these four publications compared HRQL before and after an OFC. One of the four publications compared the HRQL between patients who underwent OFC and patients who were on the waiting list for OFC or who were considered food allergic by a physician.¹⁹

Two of seven included publications assessed HRQL before and after an OFC in patients with a confirmed food allergy. The aim of the OFC was to evaluate the eliciting dose²⁶ or to assess resolution of food allergy.³⁰ In one of these two publications HRQL was also assessed in patients that did not undergo an OFC. These patients were considered food allergic by a physician.³⁰

Finally, one of seven included publications assessed HRQL in patients with a confirmed food allergy at a single point in time in both patients previously diagnosed through an OFC and in patients considered food allergic but who did not undergo an OFC.²⁸

The risk of bias was considered high in three^{28–30}, moderate in three^{18,19,26} and low in one publication²⁷ (Table 2). The complete results of the risk of bias assessment are published in the supplemental material (Supplemental Table 4).

Table 1. Characteristics of included publications

Author	Suspected food allergy Study design	Participants	Food allergen (n)	Intervention	Control	Outcome
Dunn Galvin 2010 ¹⁸	Prospective cohort study (Ireland)	82 children (≤ 12 year) with a suspected food allergy (86%) or a suspected tolerance to food (14%). No specific diagnostic criteria reported.	Peanut (26), tree nut (10), milk (24), egg (15) and fish or shellfish (7)	DBPCFC, single blind or open OFC	NA	FAQLQ-PF at: Day OFC, 2 M and 6 M after OFC
Soller 2014 ²⁹	Prospective cohort study (Ireland)	54 children (≤ 12 year) with a suspected food allergy on the waiting list for an OFC. No specific diagnostic criteria reported.	Peanut (17), tree nut (9), milk (10), egg (13), wheat (3) or soy (2)	Open OFC	NA	FAQLQ-PF at: 2 M before, day of and 2 and 6 M after OFC
van der Valk 2016 ²⁷	Prospective cohort study (Netherlands)	112 children (≤ 17 year) with a suspected cashew nut allergy and their parents. A suspected cashew nut allergy was based on 1) sensitization and a clinical history of previous reaction, or 2) unknown exposure.	Cashew nut (112)	DBPCFC	NA	FAQLQ-PF, FAQLQ-TF and FAQLQ-CF at: Before OFC and 6 M after OFC
van der Velde, 2012 ¹⁹	Prospective cohort study (Netherlands)	57 children (8-12 year), 46 adolescents (13-17 year) and 53 adults with a suspected food allergy on the waiting list for an OFC (expected waiting time < 6 months) who were challenged were compared to 20 children, 25 adolescents and 20 adults on the waiting list for an OFC (expected waiting time > 6 months) or with a confirmed food allergy based on SPT or sIgE (no cut-off values reported) who were not challenged during FU.	Peanut (68), tree nut (39), milk (17), egg (11), wheat (9), soy (8), sesame (4), or not reported (65)	DBPCFC	No DBPCFC, or other diagnostic testing	FAQLQ-AF, FAQLQ-TF and FAQLQ-CF at 1 M before OFC (or baseline), 6 M after OFC (or 7 M after baseline)

Table 1. Characteristics of included publications (continued)

Confirmed food allergy	Author	Study design	Participants	Food allergen (n)	Intervention	Control	Outcome
	Houriha ne 2017 ²⁶	Prospective cohort study (Ireland, United States and Australia)	378 children (≤18 year) with a confirmed peanut allergy based on 1) convincing clinical history < 2 years and sensitization (SPT or sIgE), or 2) a positive OFC within 2 years, or 3) no previous ingestion of peanut with sensitization to peanut > 95% PPV (sIgE ≥15 kU/L and/or peanut SPT ≥8mm within 2 months).	Peanut (378)	Single dose OFC to assess the predicted peanut eliciting dose	NA	FAQLQ-PF and FAQLQ-CF at: Before OFC and 1 M after OFC
	Franxma n 2015 ²⁸	Cross- sectional study (United States)	115 children (≤18 year) with a positive OFC during the past 11 years were compared to 305 children with a confirmed food allergy by a physician without an OFC. No specific diagnostic criteria reported.	Peanut and/or tree nut (50), milk (42), egg (23) or not reported (305)	NA. Exposure: OFC	NA. No exposure: no OFC	FAQL-PB at: 0-11 year after OFC (or after diagnosis without OFC)
	Knibb 2012 ³⁰	Prospective cohort (United Kingdom)	40 children (6-16 year) with confirmed peanut or tree nut allergy based on clinical history and sensitization (SPT and/or sIgE) were challenged to assess resolution of food allergy, and were compared to 103 children (6-16 years) with a confirmed food allergy by a physician based on sensitization whom were not challenged.	Challenged/ unchallenged: peanut (17/19), tree nut (8/8), both peanut and tree nut (15/36)	Open OFC to assess resolution of food allergy	No OFC, or other diagnostic testing	FAQL-PB, PedsQL™ 4.0, WHOQOL-BREF at: Before OFC (or post clinic), 3-6 M after OFC (or 3- 6 months after follow- up)

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: AF, Adult Form; CF, Child Form; PB, Parental Burden; PF, Parent Form); FU, follow-up; n, number; NA, not applicable; OFC, oral food challenge; sIgE, specific IgE; SPT, Skin Prick Testing; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; PPV, positive predictive value; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

Table 2. Risk of bias assessment

	Hourihane	Van der Valk	Franxman	Soller	Knibb	Van der Velde	Dunn Galvin	Overall risk of bias
	2017	2016	2015	2014	2012	2012	2010	
Study participation	L	L	H	M	M	L	L	M
Study Attrition	L	M	H	M	H	H	M	H
Diagnostic								
Intervention	L	L	M	L	M	L	H	M
Measurement								
Outcome								
Measurement	L	L	L	L	L	L	L	L
Study								
Confounding	M	L	L	H	M	L	M	M
Statistical								
Analysis and	H	L	L	M	L	L	L	M
Reporting								
Overall risk of bias	M	L	H	H	H	M	M	

Abbreviations: H, high; L, low; M, moderate.

Quality of life in patients with a suspected food allergy

In patients with a suspected food allergy who underwent an OFC with positive, negative and inconclusive outcomes combined, food allergy specific HRQL significantly improved after an OFC in four of eight groups in three publications: in both children and adults in one publication¹⁹, and in parents in two publications^{18,29} (Figure 2a). The improved HRQL was only clinically relevant in parents in one publication, with a 95% CI of the mean difference (MD) exceeding the minimal clinically important difference (MCID).²⁹

Subgroup analyses were also performed for the different OFC outcomes, i.e. positive, negative and inconclusive OFC. This showed that in patients with a positive OFC outcome (i.e. food allergic patients), parent-reported food allergy specific HRQL significantly improved after an OFC in two of three publications and this change was clinically relevant in one publication (Figure 2b).^{18,29} In patients with a negative OFC outcome (i.e. non-allergic patients), food allergy specific HRQL significantly improved after an OFC in six of eight groups in four publications: again in parents included in two publications^{18,29}, but also in adults, adolescents and children in one publication¹⁹, and in adolescents in another publication (Figure 2c).²⁷ The improved HRQL was only clinically relevant in one publication in which parent-reported HRQL was assessed.²⁹ In patients with an inconclusive OFC outcome food allergy specific HRQL did not improve after an OFC (Figure 2d).¹⁹

In two publications HRQL after the OFC was followed up in time, and was measured at 2 and 6 months after the OFC. These two publications showed that after a negative OFC the parent-reported HRQL further improved between two and six

months and this improvement was significant and clinically relevant (Supplemental Figure 1).^{18,29}

In addition to the inclusion of patients that underwent an OFC, one publication also included patients that did not undergo an OFC.¹⁹ All patients who underwent an OFC were suspected of having a food allergy, while the patients who did not undergo an OFC were either suspected of having a food allergy and were on the waiting list for OFC or were already diagnosed with a food allergy by a physician (Table 1). No significant difference was observed between food allergy specific HRQL at baseline and after 7 months in children, and adolescents (Supplemental Figure 2a). Furthermore, no significant difference was observed between the MD in HRQL in patients that underwent an OFC compared to the patients that did not undergo an OFC (Supplemental Figure 3).

Domain specific quality of life in patients with a suspected food allergy

The domain-specific parent-reported HRQL values are shown in Figure 3, and domain-specific HRQL values in children and adolescents in Supplemental Figure 4. In one publication no domain-specific HRQL values were available.¹⁹

In parents of children with all OFC outcomes combined, parent-reported HRQL significantly improved after an OFC in all three domains in two of three publications but this change was clinically relevant only in the domains of 'food anxiety' and 'social and dietary impact' in one publication (Figure 3a).^{18,29} In children and adolescents with all OFC outcomes combined, food allergy specific HRQL improved in the domain of allergen avoidance in children and in the domain of emotional impact in adolescents in one publication, although not clinically relevant (Supplemental Figure 4a).²⁷

In parents of children with a positive OFC outcome (i.e. food-allergic patients), parent-reported food allergy specific HRQL significantly improved significantly after an OFC in the domain of 'emotional impact' in two of three publications^{18,29} and this change was clinically relevant in one publication.¹⁸ In one of these two publications, food allergy specific HRQL significantly improved after an OFC in the domains of 'social and dietary impact' and 'food anxiety'.²⁹ This change in HRQL was clinically relevant in the domain of 'social and dietary impact' only. In children and adolescents with a positive OFC outcome, food allergy specific HRQL did not improve after a positive OFC outcome (Supplemental Figure 4b).

In parents of children with a negative OFC outcome (i.e. non-allergic patients), parent-reported food allergy specific HRQL significantly improved after an OFC in all three domains in two of three publications^{18,29}, and this change was clinically relevant in all domains in one publication²⁹ and in the domain of 'social and dietary

impact' in the other publication¹⁸ (Figure 3c). Furthermore, HRQL significantly improved in the domains of 'risk accidental exposure' and 'emotional impact' in adolescents included in one publication although not clinically relevant (Supplemental Figure 4c).²⁷

Figure 2. Health-related quality of life before and after an oral food challenge in patients with a suspected food allergy

Legend see Figure 3.

Figure 3. Domain-specific health-related quality of life before and after an oral food challenge in patients with a suspected food allergy

* Significant change in health-related quality of life.

** Significant and clinically relevant change in health-related quality of life.

Abbreviations: CI, confidence interval; FAQL, Food Allergy Quality of Life Questionnaire (different versions: AF, adult form; CF, child form; TF, teenager form; PF, parent form); MD, mean difference; n, number; OFC, oral food challenge.

Quality of life in patients with a confirmed food allergy

In patients with a confirmed food allergy who underwent an OFC parent-reported food allergy specific HRQL and HRQL in children significantly improved after a single dose OFC in one publication (Figure 4).²⁶ The standardized mean difference (SMD) was very large. The aim of the OFC in this publication was to assess the ED₀₅, which is the dose that elicits an allergic reaction in 5% of the allergic subjects (Table 1). The MD and domain-specific HRQL values were not available.

The parental burden was just significantly reduced after an OFC in patients with a confirmed food allergy included in one publication.³⁰ The effect size was small. Generic HRQL in both parents and children did not improve after an OFC (Figure 4). The domain-specific HRQL values were not available.

Figure 4: Health-related quality of life and the parental burden before and after an oral food challenge in patients with a confirmed food allergy

The OFC was performed to evaluate the peanut eliciting dose (Hourihane), or to assess resolution of food allergy (Knibb).

Abbreviations: CI, confidence interval; FAQL(Q), Food Allergy Quality of Life (Questionnaire) (different versions: CF, Child Form; PB, Parental Burden; PF, Parent Form); n, number; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; SMD, standardized mean difference; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

In addition to the inclusion of patients that underwent an OFC, one publication included patients that did not undergo an OFC.³⁰ All patients who underwent an OFC were suspected of resolution of their food allergy, while the patients who did not undergo an OFC were considered food allergic by a physician (Table 1). In parents of patients that did not undergo an OFC, no significant differences in the parental burden and generic HRQL were observed between baseline and after 3-6 months (Supplemental Figure 2b). Furthermore, no significant difference was observed between the SMD in the parental burden and generic HRQL in patients that underwent an OFC compared to patients that did not undergo an OFC (Supplemental Figure 5).

Finally, a lower parental burden (better HRQL) was observed in parents of children with a food allergy confirmed with an OFC compared to parents of children with a food allergy confirmed without an OFC in one publication (mean FAQL-PB after an OFC 1.5 (95% CI 1.37-1.62) and mean FAQL-PB without an OFC 1.88 (95% CI 1.79-1.95); $p < 0.0001$).²⁸

Meta-analysis

A meta-analysis was considered inappropriate due to the limited number of publications available, the profound differences between the included populations and the different outcome measurements (HRQL questionnaires) that were used in the included publications.

Discussion

We present the first systematic review that evaluates whether oral food challenges (OFC) for food allergy affect health-related quality of life (HRQL) in patients with a suspected or a confirmed food allergy. Our findings indicate that an OFC is associated with an improved food allergy specific HRQL. In the majority of included publications food allergy specific HRQL improved after an OFC^{18,19,26,29}, and not in patients that did not undergo an OFC.^{19,30} The parental burden was just significantly reduced after an OFC, and did not change in patients that did not undergo an OFC. No information was available about whether other diagnostic interventions affect HRQL.

Our results show that an OFC is associated with a significantly improved parent-reported HRQL after an OFC.^{18,26,29} An OFC might have a beneficial effect because the challenge procedure clarifies the severity of the food allergy, reduces anxiety as parents and patients experience the exposure to the food allergen in a controlled environment and learn how to handle in case of severe reaction in daily practice.³¹⁻³³ In addition, an accurate food allergy diagnosis might decrease uncertainty after an OFC which is confirmed by the lack of HRQL improvement in patients after an OFC with an inconclusive outcome. Food allergy specific HRQL continued to improve between two and six months after an OFC in parents included by DunnGalvin et al. but not in Soller et al. This difference might be explained by several modifying factors that varied between the publications, such as the maintenance of regular clinical contact, guided food reintroduction, and other differences in management strategies after the OFC.

It must be noted that, in contrast to the publications by DunnGalvin and Soller, parent-reported food allergy specific HRQL did not improve after an OFC in patients included by van der Valk et al.²⁷ This discrepant result might be explained

by differences between the populations that were studied. The children included by van der Valk et al were all suspected of having a cashew nut allergy, while the children included by DunnGalvin et al and Soller et al were suspected of other allergies like a peanut, cow's milk or hen's egg allergy. Previous research has demonstrated that the type of food allergen is associated with HRQL in children and adults.^{21,34} Children with a suspected cashew nut allergy might experience no improved HRQL after an OFC because cashew nut is probably easier to avoid than other food allergens such as peanut, cow's milk or hen's egg. This hypothesis is supported by the fact that the baseline HRQL value in patients included by van der Valk was much lower – indicating a better HRQL – compared to the baseline value in patients included by DunnGalvin et al. The baseline HRQL value in patients included by Soller et al. was not reported.

The publications by van der Velde et al. and Knibb et al. assessed food allergy specific HRQL in patients with and without an OFC, and observed a significantly improved HRQL and reduced parental burden in patients with an OFC but not in patients without an OFC.^{19,30} However, there was no significant difference between the MD in food allergy specific HRQL or the parental burden in patients that underwent an OFC compared to the patients that did not undergo an OFC. These results should be interpreted with caution because in both publications patients were not randomized to the OFC, thus confounding may have biased the results as patients in who an OFC was performed were not fully comparable to those that did not undergo an OFC (Table 1). It is not surprising that HRQL did not improve in patients on the waiting list for an OFC as these patients remain uncertain regarding their food allergic status. In the publication by Knibb et al. an OFC was only performed in patients if resolution of food allergy was considered plausible by the physician and therefore baseline HRQL was better and the parental burden was lower in patients who underwent an OFC compared to those who did not undergo an OFC. Furthermore, the patients that underwent an OFC were significantly older which might have contributed to the improvement in HRQL in this group as an older age is associated with a better HRQL.^{35,36}

We summarized the literature on the effect of diagnostic interventions on HRQL in patients with a suspected or a confirmed food allergy. The interpretation of our review is limited as no diagnostic randomized trials have been performed, which are needed to adequately assess the true effect of a diagnostic intervention on HRQL without bias.³⁷ However, such a study design is hardly feasible as an OFC is the reference standard to diagnose a food allergy. In addition, we were unable to perform a meta-analysis to summarize the results of the included publications, or to analyze subgroups of patients with different characteristics, due to the limited number of eligible publications and the differences in HRQL questionnaires that were used. Furthermore, there were a limited number of eligible publications that

satisfied inclusion criteria and the majority of the included publications were at high or moderate risk of bias. Finally, our results are based on calculations using an assumed correlation coefficient (r) of 0.5. However, a sensitivity analysis with a range of plausible r values hardly changed our results (Supplemental Table 5).

In conclusion, we found that an oral food challenge (OFC) is associated with an improved food allergy specific health-related quality of life (HRQL) and a reduced parental burden of food allergy. Further prospective HRQL research is necessary to support the findings of our review and investigate the impact of other diagnostic interventions on HRQL.

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Supplemental information

Supplemental 1: Search strategy

MEDLINE

Date search 6th of July 2017

1. foodallerg*[Title/Abstract]
2. "food allergy"[Title/Abstract]
3. "food allergies"[Title/Abstract]
4. "food hypersensitivity"[Title/Abstract]
5. "food hypersensitivities"[Title/Abstract]
6. peanut*[Title/Abstract]
7. Arachis[Title/Abstract]
8. milk*[Title/Abstract]
9. egg*[Title/Abstract]
10. fish*[Title/Abstract]
11. shellfish*[Title/Abstract]
12. "tree nut"[Title/Abstract]
13. hazelnut*[Title/Abstract]
14. walnut*[Title/Abstract]
15. macadamia*[Title/Abstract]
16. cashew*[Title/Abstract]
17. pistachio*[Title/Abstract]
18. wheat*[Title/Abstract]
19. sesame*[Title/Abstract]
20. soy*[Title/Abstract]
21. food hypersensitivity[MeSH]
22. Arachis[MeSH]
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (CRD[Title/Abstract]
25. Component*[Title/Abstract]
26. Allergen*[Title/Abstract]
27. Ara[Title/Abstract]
28. Extract[Title/Abstract]
29. IgE[Title/Abstract]
30. sIgE[Title/Abstract]
31. "skin prick test"[Title/Abstract]
32. "skin prick testing"[Title/Abstract]
33. SPT[Title/Abstract]
34. challenge[Title/Abstract]
35. DBPCFC[Title/Abstract]
36. double-blind[Title/Abstract]
37. "double blind"[Title/Abstract]
38. placebo-controlled [Title/Abstract]
39. "placebo controlled"[Title/Abstract]
40. OFC[Title/Abstract]
41. Oral[Title/Abstract]
42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. "quality of life"[Title/Abstract]
44. "quality-of-life"[Title/Abstract]
45. QoL[Title/Abstract]
46. HRQL[Title/Abstract]

47. HRQoL[Title/Abstract]
48. FAQLQ*[Title/Abstract]
49. quality of life[MeSH]
50. EQ-5D[Title/Abstract]
51. EQ5D[Title/Abstract]
52. "EQ 5D"[Title/Abstract]
53. EuroQol-5D[Title/Abstract]
54. "EuroQol 5D"[Title/Abstract]
55. HUI[Title/Abstract]
56. "Health Utilities Index"[Title/Abstract]
57. SF-6D[Title/Abstract]
58. "SF 6D"[Title/Abstract]
59. "short form-6D"[Title/Abstract]
60. SF-36[Title/Abstract]
61. "SF 36"[Title/Abstract]
62. "short form 36"[Title/Abstract]
63. SF-12[Title/Abstract]
64. "SF 12"[Title/Abstract]
65. "short form 12"[Title/Abstract]
66. "short form health survey"[Title/Abstract]
67. "State-Trait Anxiety Inventory"[Title/Abstract]
68. STAI[Title/Abstract]
69. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70. 23 and 42 and 69

EMBASE

Date search 6th of July 2017

1. foodallerg*:ab,ti
2. 'food allergy':ab,ti
3. 'food allergies':ab,ti
4. 'food hypersensitivity':ab,ti
5. 'food hypersensitivities':ab,ti
6. peanut*:ab,ti
7. Arachis:ab,ti
8. milk:ab,ti
9. egg*:ab,ti
10. fish*:ab,ti
11. shellfish*:ab,ti
12. 'tree nut':ab,ti
13. hazelnut*:ab,ti
14. walnut*:ab,ti
15. macadamia*:ab,ti
16. cashew*:ab,ti
17. pistachio*:ab,ti
18. wheat*:ab,ti
19. sesame*:ab,ti
20. soy*:ab,ti
21. 'food allergy'/exp

22. 'arachis'/exp)
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. crd:ab,ti
25. component*:ab,ti
26. allergen*:ab,ti
27. ara:ab,ti
28. extract:ab,ti
29. ige:ab,ti
30. sige:ab,ti
31. 'skin prick test':ab,ti
32. 'skin prick testing':ab,ti
33. spt:ab,ti
34. challenge:ab,ti
35. dbpcfc:ab,ti
36. 'double-blind':ab,ti
37. 'double blind':ab,ti
38. 'placebo-controlled':ab,ti
39. 'placebo controlled':ab,ti
40. ofc:ab,ti
41. oral:ab,ti
42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. 'quality of life':ab,ti
44. 'quality-of-life':ab,ti
45. qol:ab,ti
46. hrql:ab,ti
47. hrqol:ab,ti
48. faqlq*:ab,ti
49. 'quality of life'/exp
50. 'quality of life':ab,ti
51. EQ-5D:ab,ti
52. EQ5D:ab,ti
53. 'EQ 5D':ab,ti
54. EuroQol-5D:ab,ti
55. 'EuroQol 5D':ab,ti
56. HUI:ab,ti
57. 'Health Utilities Index':ab,ti
58. SF-6D:ab,ti
59. 'SF 6D':ab,ti
60. 'short form-6D':ab,ti
61. SF-36:ab,ti
62. 'SF 36':ab,ti
63. 'short form 36':ab,ti
64. SF-12:ab,ti
65. 'SF 12':ab,ti
66. 'short form 12':ab,ti
67. 'short form health survey':ab,ti
68. 'State-Trait Anxiety Inventory':ab,ti
69. STAI:ab,ti
70. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71. 23 and 42 and 70 and [embase]/lim not [medline]/lim

Cochrane Library

Date search 6th of July 2017

1. foodallerg*:ab,ti,kw
2. "food allergy":ab,ti,kw
3. "food allergies":ab,ti,kw
4. "food hypersensitivity":ab,ti,kw
5. "food hypersensitivities":ab,ti,kw
6. peanut*:ab,ti,kw
7. Arachis:ab,ti,kw
8. milk:ab,ti,kw
9. egg*:ab,ti,kw
10. fish*:ab,ti,kw
11. shellfish*:ab,ti,kw
12. "tree nut":ab,ti,kw
13. hazelnut*:ab,ti,kw
14. walnut*:ab,ti,kw
15. macadamia*:ab,ti,kw
16. cashew*:ab,ti,kw
17. pistachio*:ab,ti,kw
18. wheat*:ab,ti,kw
19. sesame*:ab,ti,kw
20. soy*:ab,ti,kw)
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. CRD:ab,ti,kw
23. Component*:ab,ti,kw
24. Allergen*:ab,ti,kw
25. Ara:ab,ti,kw
26. Extract:ab,ti,kw
27. ige:ab,ti,kw
28. sige:ab,ti,kw
29. "skin prick test":ab,ti,kw
30. "skin prick testing":ab,ti,kw
31. spt:ab,ti,kw
32. challenge:ab,ti,kw
33. dbpcfc:ab,ti,kw
34. "double-blind":ab,ti,kw
35. 'double blind':ab,ti,kw
36. "placebo-controlled":ab,ti,kw
37. "placebo controlled":ab,ti,kw
38. ofc:ab,ti,kw
39. oral:ab,ti,kw
40. 22 or 23 or 24 or 25 or 27 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. "quality of life":ti,ab,kw
42. "quality-of-life":ti,ab,kw
43. QoL:ti,ab,kw
44. HRQL:ti,ab,kw
45. HRQoL:ti,ab,kw
46. FAQLQ*:ti,ab,kw
47. EQ-5D:ti,ab,kw
48. EQ5D:ti,ab,kw
49. "EQ 5D":ti,ab,kw
50. EuroQol-5D:ti,ab,kw

51. "EuroQol 5D" :ti,ab,kw
52. HUI:ti,ab,kw
53. "Health Utilities Index" :ti,ab,kw
54. SF-6D:ti,ab,kw
55. "SF 6D" :ti,ab,kw
56. "short form-6D" :ti,ab,kw
57. SF-36:ti,ab,kw
58. "SF 36" :ti,ab,kw
59. "short form 36" :ti,ab,kw
60. SF-12:ti,ab,kw
61. "SF 12" :ti,ab,kw
62. "short form 12" :ti,ab,kw
63. "short form health survey" :ti,ab,kw
64. "State-Trait Anxiety Inventory":ti,ab,kw
65. STAI:ti,ab,kw
66. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67. 21 and 40 and 66

CINAHL

Date search 6th of July 2017

1. foodallergy
2. foodallergies
3. foodallergen
4. "food allergy"
5. "food allergies"
6. peanut
7. milk
8. egg
9. fish
10. shellfish
11. "tree nut"
12. hazelnut
13. walnut
14. macadamia
15. cashew
16. pistachio
17. wheat
18. sesame
19. soy
20. "food hypersensitivity"
21. Arachis
22. (MH "Food Hypersensitivity")
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. CRD
25. Component
26. Allergen
27. Ara
28. Extract
29. IgE
30. sIgE
31. "skin prick test"
32. "skin prick testing"
33. SPT

34. challenge
35. DBPCFC
36. double-blind
37. "double blind"
38. placebo-controlled
39. "placebo controlled"
40. OFC
41. Oral
42. 24 or 24 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. "quality of life"
44. "quality-of-life"
45. QoL OR HRQL
46. HRQoL
47. FAQLQ
48. (MH "Quality of Life+")
49. EQ-5D
50. EQ5D
51. "EQ 5D"
52. EuroQol-5D
53. "EuroQol 5D"
54. HUI
55. "Health Utilities Index"
56. SF-6D
57. "SF 6D"
58. "short form-6D"
59. SF-36
60. "SF 36"
61. "short form 36"
62. SF-12
63. "SF 12"
64. "short form 12"
65. "short form health survey"
66. "State-Trait Anxiety Inventory"
67. STAI
68. 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69. 23 and 42 and 68

Supplemental figures

Supplemental Figure 1. Health-related quality of life after an oral food challenge in patients with a suspected food allergy 2 and 6 months after an OFC

* significant change in HRQL.

** significant and clinically relevant change in HRQL.

Abbreviations: CI, confidence interval; FAQLQ-PF, Food Allergy Quality of Life Questionnaire-Parent Form; MD, mean difference; n, number; OFC, oral food challenge.

Supplemental Figure 2. Health related quality of life and parental burden in patients without an OFC at baseline and after follow-up

Abbreviations: CI, confidence interval; FAQL(Q), Food Allergy Quality of Life (Questionnaire) (different versions: AF, Adult Form; CF, Child Form; PB, Parental Burden; TF, Teen Form); MD, mean difference; n, number; SMD, standardized mean difference.

Supplemental Figure 3. Health-related quality of life with or without an oral food challenge in patients with a suspected food allergy

An OFC was performed in patients with a suspected food allergy. An OFC was not performed in patients with a suspected food allergy on the waiting list for an OFC, or in patients considered food allergic by a physician.

* significant change in HRQL.

Abbreviations: CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: AF, Adult Form; CF, Child Form; TF, Teen Form); MD, mean difference; n, number; OFC, oral food challenge.

Supplemental Figure 4. Domain specific health-related quality of life before and after an oral food challenge in children and adolescents with a suspected food allergy

* significant change in HRQL.

Abbreviations: CI, CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: CF, Child Form; TF, Teen Form); HRQL, health-related quality of life; MD, mean difference; n, number; OFC, oral food challenge.

Supplemental Figure 5. Health-related quality of life and the parental burden with or without an oral food challenge in patients with a confirmed food allergy

An OFC was performed in patients with a confirmed food allergy to evaluate resolution of food allergy. An OFC was not performed in patients considered food allergic by a physician.

Abbreviations: CI, confidence interval; FAQL-PB, Food Allergy Quality of Life-Parental Burden; MD, mean difference; n, number; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; SMD, standardized mean difference; WHOQOL-BREF, World Health Organization generic Quality of Life scale.

Supplemental tables

Supplemental Table 1. Reasons for exclusion

Reasons for exclusion of publications identified through database searching (until 06-07-2017)				
First author	Year	n	Category of exclusion	Reason for exclusion
Soller ¹	2017	1	Intervention	No diagnostic intervention investigated
Westwood ²	2016	1	Study design	Review
Uehara ³	2016	1	Outcome	Quality of life questionnaire not validated
Danchin ⁴	2016	1	Intervention	No diagnostic intervention investigated
Greenhawt ⁵	2016	1	Outcome	Quality of life questionnaire not validated
Kajornrattana ⁶	2016	1	Intervention	No diagnostic intervention investigated
Couch ⁷	2016	1	Outcome	Timing of questionnaire (not before and after intervention)
Protudjer ⁸	2015	1	Intervention	No diagnostic intervention investigated
Venter ⁹	2015	1	Intervention	No diagnostic intervention investigated
Soller ¹	2014	1	Intervention	No diagnostic intervention investigated
Howe ¹⁰	2014	1	Intervention	No diagnostic intervention investigated
Le ¹¹	2013	1	Intervention	No diagnostic intervention investigated
Zurzolo ¹²	2013	4	Study design	Study protocol
Knibb ¹³	2013	2	Intervention	No diagnostic intervention investigated
Brown ¹⁴	2012	1	Population	Tolerant patients (after negative oral food challenge)
Finger ¹⁵	2012	1	Outcome	Timing of questionnaire (not before and after intervention)
Kirste ¹⁶	2012	1	Study design	Conference abstract, no further details could be retrieved either as full text publication or after contacting study authors
Dubois ¹⁷	2011	1	Study design	Invited speaker presentation
Rotiroti ¹⁸	2011	1	Outcome	Quality of life questionnaire not validated
Paterakis ¹⁹	2011	1	Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Velde, van der ²⁰	2010	2	Outcome	Quality of life questionnaire used with informed and blind administration
Flammarion ²¹	2009	1	Population	Tolerant patients (after negative oral food challenge)
Sohi ²²	2009	1	Population	Tolerant patients (after negative oral food challenge)
Zijlstra ²³	2009	1	Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Ostblom ²⁴	2008	1	Intervention	No diagnostic intervention investigated

Supplemental Table 1. Reasons for exclusion (continued)

Reasons for exclusion of publications identified through citations analysis of all full text screened publications <i>(until 06-07-2017)</i>				
First author	Year	n	Category of exclusion	Reason for exclusion
Polloni ²⁵	2017	1	Outcome	No quality of life questionnaire (State-Trait Anxiety Inventory)
Valk, van der ²⁶	2016	1	Duplicate	Already included in systematic review
Danchin ⁴	2016	1	Duplicate	Excluded during full text screening of database search
Davis ²⁷	2015	1	Outcome	Quality of life questionnaire not validated
Venter ⁹	2015	1	Duplicate	Excluded during data analysis
Franxman ²⁸	2015	1	Duplicate	Already included in systematic review
Protudjer ⁸	2015	1	Duplicate	Excluded during full text screening of database search
Venter ⁹	2015	1	Duplicate	Already included in systematic review
Soller ²⁹	2014	1	Duplicate	Already included in systematic review
Reese	2013	1	Study design	Editorial
Herbert ³⁰	2013	1	Outcome	No quality of life questionnaire (multiple anxiety questionnaires)
Knibb ³¹	2013	1	Outcome	No quality of life questionnaire (Hospital Anxiety and Depression Scale)
Velde, van der ³²	2012	2	Duplicate	Already included in systematic review
Knibb ³³	2012	2	Duplicate	Already included in systematic review
Flammarion ²¹	2010	1	Duplicate	Excluded during full text screening of database search
Kemp ³⁴	2009	1	Outcome	Quality of life questionnaire not validated

Supplemental Table 2. Inclusion and exclusion criteria

Inclusion criteria		Exclusion criteria
Study design	<ul style="list-style-type: none">• Studies in Dutch, English, German, French or Spanish	<ul style="list-style-type: none">• Systematic reviews• Meta-analysis• Research protocols• Editorials
Population	<ul style="list-style-type: none">• All age• Suspected or confirmed food allergy• Any setting (primary, secondary and tertiary care)	<ul style="list-style-type: none">• Animal studies• Only non-allergic patients included
Intervention	<ul style="list-style-type: none">• Specific IgE using allergen extract• Skin prick testing• Oral food challenges (double blind placebo controlled food challenges and open food challenges)	
Outcome	<ul style="list-style-type: none">• Component resolved diagnostics• Changes in disease-specific or generic quality of life using a validated instrument before and after diagnostic intervention.• Difference in disease-specific or generic quality of life using a validated instrument in patients with or without diagnostic intervention	<ul style="list-style-type: none">• No validated disease-specific or generic quality of life instrument used

Supplemental Table 3a. Criteria for quality assessmentModified version of the Quality in Prognostic Studies (QUIPS) tool³⁵

Domains	Prompting items to consider
Study participation	A. Adequate participation in the study by eligible persons ($\geq 80\%$) B. Adequate methods used to identify and recruit the study population (<i>if applicable, this is graded for both cases and controls</i>) C. Adequate description of inclusion and exclusion criteria (<i>if applicable, this is graded for both cases and controls</i>)
Study attrition	D. Adequate response rate for study participants ($\geq 80\%$) E. There are no important differences between participants and non-participants on key characteristics (<i>age, criteria for suspected or confirmed food allergy, number of food allergies</i>)
Diagnostic intervention measurement	F. A clear definition or description of the diagnostic intervention is provided <i>If applicable, including a food challenge protocol.</i> G. The method and setting of the diagnostic intervention is the same for all study participants H. The diagnostic intervention of interest is not performed in the control population (<i>if applicable</i>)
Outcome measurement	I. Adequate description of the timing of the HRQL measurement J. The method and setting of the HRQL measurement is the same for all study participants
Study confounding	K. All important confounders (<i>age, number of food allergies, history of anaphylaxis and baseline HRQL scores</i>) are measured L. Important potential confounders are accounted for in the analysis
Statistical analysis and reporting	M. The statistical analysis is conducted according to a conceptual framework N. There is no selective reporting of results

Supplemental Table 3b. Grading of quality assessment

	High risk of bias	Moderate risk of bias	Low risk of bias
Total risk of bias per domain in one publication	$\geq 50\%$ of items 'no' or 'unsure', 0% 'yes', and $\leq 50\%$ of items 'partial'		$\geq 50\%$ of items 'yes', 0% 'no' or 'unsure', and $\leq 50\%$ of items 'partial'
Total risk of bias in one publication	$\geq 25\%$ of domains at high risk of bias or $\geq 66\%$ of domains at moderate or high risk	No low or high risk of bias	$\geq 66\%$ of domains considered at low risk of bias and 0% high
Total risk of bias per domain in all publications	$\geq 25\%$ of publications at high risk of bias for this domain or $\geq 66\%$ of publications at moderate or high risk		$\geq 66\%$ of publications at low risk of bias and 0% high

Supplemental Table 4. Risk of bias assessment

Houriha 2017³⁶		
Study participation		
Method used to identify population (cases)	Consecutive enrollment	L yes
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate 74%.	partial
Study attrition		
Adequate response rate ($\geq 80\%$)	The response rate is 99%.	L yes
Differences between participants and non-participants	There were no significant differences between participants and non-participants concerning age ($p=0.62$) and inclusion criteria for diagnosing peanut allergy ($p=0.17$). Single or multiple food allergies were not compared.	partial
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	A single dose peanut food challenge is performed in all cases, according to a clear described protocol. Criteria for a positive food challenge are reported.	L yes
Methods the same for all study participants	Yes, the same recipe and food challenge protocol is used for all participants.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		
Timing of quality of life measurement	The time point of the HRQL questionnaire before the OFC was not described. The follow-up questionnaire is one month after the OFC.	L partial
Methods the same for all study participants	Questionnaires were self-administered by parents (FAQLQ-PF 0-12 years) or children (FAQLQ-CF 8-17 years). It was not described which parent should fill out the questionnaire.	Yes
Study confounding		
All important confounders are measured	Yes: age. No: number of food allergies, history of anaphylaxis and baseline quality of life scores.	M partial
All important confounders are accounted for in the analyses	Yes: age. No: number of food allergies, history of anaphylaxis and baseline quality of life scores.	partial
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. The methods for model building are unclear.	H partial
Full outcome data are available	No full outcome data are reported. Mean quality of life scores before and after the diagnostic interventions or mean differences are not reported, only an effect size.	no
Overall risk of bias (publication)	Moderate	

Abbreviations: FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: PF, parent form and CF, child form); H, high; L, low; M, moderate; NA, not applicable; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

van der Valk 2016²⁶		
Study participation		
Method used to identify population (cases)	Consecutive enrollment.	L yes
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate of the initial study is around 40%.	partial
Study attrition		
Adequate response rate ($\geq 80\%$)	The response rate is 63%.	M partial
Differences between participants and non-participants	There was no significant difference in gender ($p=0.92$), age ($p=0.74$) and history of cashew nut allergy ($p=0.12$), among others. Differences in number of other food allergies were not reported.	partial
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	A DBPCFC is performed in all cases, according to a clear described protocol.	L yes
Methods the same for all study participants	Yes, all study participants were challenged according to the same DBPCFC protocol.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		
Timing of quality of life measurement	The time point of the HRQL questionnaire before the OFC was not described. The follow-up questionnaire is six months after the OFC.	L partial
Methods the same for all study participants	Yes, age appropriate questionnaires were used in all patients. No details on methods of administration or which parent should fill out the questionnaire.	yes
Study confounding		
All important confounders are measured	Yes: age, single or multiple food allergies and baseline quality of life scores. No: history of anaphylaxis.	L partial
All important confounders are accounted for in the analyses	Yes: age, single or multiple food allergies and baseline quality of life scores. No: history of anaphylaxis.	yes
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	L yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	Low	

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; HRQL, health-related quality of life; H, high; L, low; M, moderate; NA, not applicable; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

Franxman 2015 ²⁸		
Study participation		
Method used to identify population (cases)	No consecutive enrollment. Patients who had undergone an OFC were identified from a divisional database, with additional cases identified by review of International Classification of Disease coding, Current Procedural Terminology coding for an OFC, and chart review of the clinic schedules.	H Partial
Method used to identify population (controls)	Sampling and recruitment of the control cohort is not described.	no
In- and exclusion criteria are adequately described (cases)	Inclusion criteria are not adequately described, while exclusion criteria are.	partial
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria of the control population are not described.	no
Adequate participation by eligible individuals (≥80%)	The participation rate is 34%. For the control group, the participation rate is unknown.	no
Study attrition		
Adequate response rate (≥80%)	The response rate for cases is less than 50%. The response rate for controls is unknown.	H no
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	It is not described whether open or double blind challenges were performed and no food challenge protocol was provided.	M no
Methods the same for all study participants	Not described.	unsure
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an OFC.	yes
Outcome measurement		
Timing of quality of life measurement	Patients participated at a random time point ≤ 11 years after an OFC (median duration in months given), or ≤11 years after a food allergy diagnosis without an OFC.	L partial
Methods the same for all study participants	Caregivers were contacted via mail, and via follow-up telephone calls. The surveys were administered to the control group within the same time frame as for the OFC group with the same contact methodology.	yes
Study confounding		
All important confounders are measured	Yes: age, number of food allergies and history of anaphylaxis. No: baseline quality of life scores.	L partial
All important confounders are accounted for in the analyses	Yes: age, history of anaphylaxis. No: number of food allergies and baseline quality of life scores.	yes
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	L yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	High	

Abbreviations: H, high; L, low; M, moderate; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

Soller 2014²⁹		
Study participation		
Method used to identify population (cases)	No consecutive enrollment. Participants were randomly selected from the food challenge waiting list.	M partial
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion are not described.	no
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals (≥80%)	The response rate on questionnaires at all time-points is 92% of all eligible patients. Therefore also initial study participation can be considered adequate.	yes
Study attrition		
Adequate response rate (≥80%)	The response rate is 92%.	M yes
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	An open OFC is performed, without a clear described protocol. Criteria for a positive or negative food challenge are described.	L partial
Methods the same for all study participants	All food challenges were open and performed in the same allergy center.	yes
Diagnostic intervention not performed in control population	NA	
Outcome measurement		
Timing of quality of life measurement	2 months before the OFC, on the day of the OFC, and 2 months and 6 months after the OFC.	L yes
Methods the same for all study participants	The methods and setting of outcome measurement (quality of life questionnaires administered) was not described.	partial
Study confounding		
All important confounders are measured	Yes: age, baseline quality of life scores.	partial
All important confounders are accounted for in the analyses	No: number of food allergies, history of anaphylaxis.	
	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. The methods for model building are unclear.	M partial
Full outcome data are available	No full outcome data are reported, only differences in quality of life scores.	partial
Overall risk of bias (publication)		
	High	

Abbreviations: H, high; L, low; M, moderate; NA, not applicable; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

Knibb 2012³³		
Study participation		
Method used to identify population (cases)	No details described on the recruitment of the study participants.	M no
Method used to identify population (controls)	No details described on the recruitment of the study participants.	no
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria are described.	yes
Adequate participation by eligible individuals (≥80%)	The participation rate of eligible patients is 59%.	partial
Study attrition		
Adequate response rate (≥80%)	The response rate is 79%.	H partial
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	An open OFC was performed, without a clear described protocol. No criteria for positive or negative OFCs were described.	M partial
Methods the same for all study participants	All challenges were open OFCs. No further details were provided.	unsure
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an oral food chall.	yes
Outcome measurement		
Timing of quality of life measurement	Baseline (following a clinic appointment) and follow-up (3-6 months following OFC, or in the case of non-challenged families, 3-6 months following the return of baseline questionnaire)	L yes
Methods the same for all study participants	Children and mothers completed baseline and 3-6 months follow-up questionnaires at home. Questionnaires during oral food challenge were completed in the clinical setting.	yes
Study confounding		
All important confounders are measured	Yes, all important confounder data are available at baseline.	M Yes
All important confounders are accounted for in the analyses	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis is appropriate and based on a conceptual framework. No model is built.	L yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)		
	High	

Abbreviations: H, high; L, low; M, moderate; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

van der Velde 2012³²		
Study participation		
Method used to identify population (cases)	All patients visiting the clinic with suspected food allergy were placed on the waiting list for a DBPCFC on a first-come, first-served basis. Participants who were expected to have a DBPCFC within 6 months were included in the experimental group (cases).	L yes
Method used to identify population (controls)	Participants on the waiting list who were not expected to have a DBPCFC within 6 months were included in the control group. Additionally, participants recruited through Dutch food allergy support organizations were included in the control group when they reported a physician-diagnosed food allergy (skin prick test, sIgE). Methods for recruitment through the support organization are unclear.	partial
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	Inclusion and exclusion criteria are described.	yes
Adequate participation by eligible individuals ($\geq 80\%$)	The participation rate is 76%.	partial
Study attrition		
Adequate response rate ($\geq 80\%$)	The response rate is 74%.	H partial
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	A DBPCFC is performed in all cases according to a clear described protocol.	L yes
Methods the same for all study participants	The two centers collaborate on uniform methodology of DBPCFC procedures.	yes
Diagnostic intervention not performed in control population	Yes, the control population did not undergo an OFC.	yes
Outcome measurement		
Timing of quality of life measurement	Challenged cases: 1 month before (baseline) and 6 months after (follow-up) a DBPCFC. Unchallenged cases: twice with a 7-month interval without undergoing a DBPCFC.	L Yes
Methods the same for all study participants	All questionnaires were sent home and the same questionnaires were used in all study participants.	yes
Study confounding		
All important confounders are measured	Yes, all important confounder data are available.	L yes
All important confounders are accounted for in the analyses	Yes: age, number of food allergies and baseline quality of life scores. No: history of anaphylaxis.	yes
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	Statistical analysis, including model building, is appropriate and based on a conceptual framework.	L yes
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	Moderate	

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; H, high; L, low; M, moderate; NA, not applicable; OFC, oral food challenge.

Supplemental Table 4. Risk of bias assessment (continued)

Dunn Galvin 2010³⁷		
Study participation		
Method used to identify population (cases)	No consecutive enrollment, but a random sample of participants recruited during specialist pediatric allergy clinic. No recruitment details are reported.	L no
Method used to identify population (controls)	NA	
In- and exclusion criteria are adequately described (cases)	Inclusion and exclusion criteria are described.	yes
In- and exclusion criteria are adequately described (controls)	NA	
Adequate participation by eligible individuals (≥80%)	The participation rate is 94%.	yes
Study attrition		
Adequate response rate (≥80%)	The response rate is 96%.	M yes
Differences between participants and non-participants	Not described.	unsure
Diagnostic intervention measurement		
Clear definition of diagnostic intervention	Not described.	H no
Methods the same for all study participants	Not described.	no
Diagnostic intervention not performed in control population	NA	
Outcome measurement		
Timing of quality of life measurement	Before the OFC (morning of the OFC) and at 2 and 6 months after the OFC.	L yes
Methods the same for all study participants	Mothers were asked to fill-out the questionnaire in the Children's Day Unit on the morning of the OFC. Questionnaires were again completed at home 2 months and 6 months after the OFC.	yes
Study confounding		
All important confounders are measured	Yes: age, number of food allergies, history of anaphylaxis and baseline quality of life scores.	M yes
All important confounders are accounted for in the analyses	No (important) confounders were considered in the final analysis.	no
Statistical analysis and reporting		
Analysis conducted according to a conceptual framework	It is unclear what variables were taken into account in the final analysis.	L partial
Full outcome data are available	Full outcome data are reported.	yes
Overall risk of bias (publication)	Moderate	

Abbreviations: H, high; L, low; M, moderate; NA, not applicable; OFC, oral food challenge.

Supplemental Table 5a. Sensitivity analysis correlation coefficient (studies including patients with suspected food allergy)

DunnGalvin	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-2M)									
Total	0.60*	0.28	0.91	0.60*	0.20	0.99	0.60*	0.40	0.8
Positive patients	0.50*	0.08	0.92	0.50	-0.04	1.04	0.50*	0.23	0.77
Negative patients	0.70*	0.24	1.16	0.70*	0.11	1.29	0.70*	0.41	0.99
All patients (EI)	0.75*	0.46	1.05	0.75*	0.38	1.13	0.75**	0.57	0.94
All patients (FA)	0.64*	0.33	0.95	0.64*	0.25	1.04	0.64*	0.45	0.84
All patients (SDI)	0.69*	0.40	0.98	0.69*	0.33	1.06	0.69**	0.50	0.88
Positive patients (EI)	0.90**	0.51	1.29	0.90*	0.4	1.4	0.90**	0.65	1.15
Positive patients (FA)	0.40	-0.06	0.86	0.40	-0.18	0.98	0.40*	0.11	0.69
Positive patients (SDI)	0.40	-0.04	0.84	0.40	-0.14	0.94	0.40*	0.11	0.69
Negative patients (EI)	0.60*	0.15	1.05	0.60*	0.03	1.17	0.60*	0.31	0.89
Negative patients (FA)	0.90*	0.48	1.32	0.90*	0.37	1.43	0.90**	0.63	1.17
Negative patients (SDI)	1.00**	0.62	1.38	1.00**	0.52	1.48	1.00**	0.76	1.24
FAQLQ-PF (2-6M)									
Total	1.14**	0.82	1.46	1.14**	0.74	1.54	1.14**	0.94	1.34
Positive patients	0.70*	0.26	1.14	0.70*	0.14	1.26	0.70*	0.42	0.98
Negative patients	1.60**	1.14	2.06	1.60**	1.01	2.19	1.60**	1.31	1.89
All patients (EI)	1.19**	0.89	1.419	1.19**	0.81	1.57	1.19**	1.00	1.38
All patients (FA)	0.99**	0.67	1.31	0.99**	0.58	1.40	0.99**	0.78	1.19
All patients (SDI)	1.14**	0.87	1.41	1.14**	0.79	1.48	1.14**	0.96	1.31
Positive patients (EI)	0.80*	0.42	1.18	0.80*	0.32	1.28	0.80**	0.56	1.04
Positive patients (FA)	0.50*	0.02	0.98	0.50	-0.11	1.11	0.50*	0.19	0.81
Positive patients (SDI)	0.60*	0.22	0.98	0.60*	0.12	1.08	0.60*	0.36	0.84
Negative patients (EI)	1.60**	1.18	2.02	1.60**	1.07	2.13	1.60**	1.33	1.87
Negative patients (FA)	1.50**	1.03	1.92	1.50**	0.97	2.03	1.50**	1.23	1.77
Negative patients (SDI)	1.70**	1.33	2.07	1.70**	1.23	2.17	1.70**	1.46	1.94

Soller	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-2M)									
Total	0.86**	0.719	1.003	0.86**	0.68	1.04	0.86**	0.77	0.95
All patients (EI)	0.60*	0.48	0.72	0.60*	0.46	0.75	0.60**	0.51	0.70
All patients (FA)	0.95**	0.74	1.16	0.95**	0.68	1.22	0.95**	0.82	1.08
All patients (SDI)	1.05**	0.91	1.19	1.05**	0.87	1.23	1.05**	0.96	1.14
FAQLQ-PF (2-6M)									
Total	0.49	-0.01	0.99	0.49	-0.14	1.17	0.49*	0.178	0.81
All patients (EI)	0.50*	0.08	0.92	0.50	-0.04	1.04	0.50*	0.23	0.77
All patients (FA)	0.70*	0.12	1.28	0.70	-0.02	1.42	0.70*	0.32	1.08
All patients (SDI)	0.55*	0.02	1.08	0.55	-0.12	1.22	0.55*	0.21	0.89

* significant change in HRQL

** significant and clinically relevant change in HRQL

Abbreviations: CI, confidence interval; FAQLQ-PF, Food Allergy Quality of Life Questionnaire Parent Form (different domains: EI, Emotional Impact; FA, Food Anxiety; SDI, Social and Dietary Impact); M, months; MD, mean difference; r, correlation coefficient.

Supplemental Table 5a. Sensitivity analysis correlation coefficient (studies including patients with suspected food allergy) (continued)

van der Valk	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-6M)									
Total	-0.06	-0.32	0.2	-0.06	-0.38	0.26	-0.06	-0.22	0.1
Positive patients	-0.11	-0.41	0.19	-0.11	-0.48	0.26	-0.11	-0.31	0.09
Negative patients	0.1	-0.4	0.6	0.1	-0.52	0.72	0.1	-0.24	0.44
All patients (EI)	-0.09	-0.33	0.15	-0.09	-0.39	0.21	-0.09	-0.24	0.06
All patients (FA)	-0.01	-0.27	0.25	-0.01	-0.34	0.32	-0.01	-0.18	0.16
All patients (SDI)	-0.07	-0.31	0.17	-0.07	-0.37	0.23	-0.07	-0.22	0.08
Positive patients (EI)	-0.16	-0.57	0.25	-0.16	-0.59	0.27	-0.16	-0.54	0.22
Positive patients (FA)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Positive patients (SDI)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Negative patients (EI)	0.11	-0.76	0.98	0.11	-0.79	1.01	0.11	-0.71	0.93
Negative patients (FA)	0.19	-0.74	1.12	0.19	-0.77	1.15	0.19	-0.69	1.07
Negative patients (SDI)	-0.03	-1.04	0.98	-0.03	-1.07	1.01	-0.03	-0.99	0.93
FAQLQ-TF (0-6M)									
Total	0.28	-0.18	0.74	0.28	-0.3	0.86	0.28	-0.02	0.58
Positive patients	-0.06	-0.55	0.43	-0.06	-0.67	0.55	-0.06	-0.37	0.25
Negative patients	1.18*	0.18	2.18	1.18	-0.06	2.42	1.18*	0.49	1.87
All patients (AA)	0.21	-0.25	0.67	0.21	-0.37	0.79	0.21	-0.09	0.51
All patients (RAE)	0.17	-0.29	0.63	0.17	-0.41	0.75	0.17	-0.13	0.47
All patients (EI)	0.47*	0.01	0.93	0.47	-0.11	1.05	0.47*	0.17	0.77
Positive patients (AA)	0.43	-0.06	0.92	0.43	-0.18	1.04	0.43*	0.12	0.74
Positive patients (RAE)	-0.15	-0.64	0.34	-0.15	-0.76	0.46	-0.15	-0.46	0.16
Positive patients (EI)	0.26	-0.23	0.75	0.26	-0.35	0.87	0.26	-0.05	0.57
Negative patients (AA)	0.9	-0.1	1.9	0.9	-0.34	2.14	0.9*	0.21	1.59
Negative patients RAE)	1.49*	0.49	2.49	1.49*	0.25	2.73	1.49**	0.8	2.18
Negative patients RAE)	1.31*	0.31	2.31	1.31*	0.07	2.55	1.31**	0.62	2.00
FAQLQ-CF (0-6M)									
Total	-0.17	-0.65	0.31	-0.17	-0.78	0.44	-0.17	-0.48	0.14
Positive patients	-0.19	-0.74	0.36	-0.19	-0.88	0.5	-0.19	-0.54	0.16
Negative patients	-0.1	-1.08	0.88	-0.1	-1.34	1.14	-0.1	-0.72	0.52
All patients (AA)	-0.51	-0.99	-0.03	-0.51	-1.12	0.1	-0.51	-0.82	-0.2
All patients (RAE)	-0.29	-0.77	0.19	-0.29	-0.9	0.32	-0.29	-0.6	0.02
All patients (EI)	0.18	-0.3	0.66	0.18	-0.43	0.79	0.18	-0.13	0.49
All patients (DR)	0.01	-0.47	0.49	0.01	-0.6	0.62	0.01	-0.3	0.32
Positive patients (AA)	-0.53	-1.08	0.02	-0.53	-1.22	0.16	-0.53	-0.88	-0.18
Positive patients (RAE)	-0.33	-0.88	0.22	-0.33	-1.02	0.36	-0.33	-0.68	0.02
Positive patients (EI)	-0.14	-0.69	0.41	-0.14	-0.83	0.55	-0.14	-0.49	0.21
Positive patients(DR)	0.27	-0.28	0.82	0.27	-0.42	0.96	0.27	-0.08	0.62
Negative patients (AA)	-0.44	-1.42	0.54	-0.44	-1.68	0.8	-0.44	-1.06	0.18
Negative patients RAE)	-0.18	-1.16	0.8	-0.18	-1.42	1.06	-0.18	-0.8	0.44
Negative patients (EI)	0.41	-0.57	1.39	0.41	-0.83	1.65	0.41	-0.21	1.03
Negative patients (DR)	-0.56	-1.54	0.42	-0.56	-1.8	0.68	-0.56	-1.18	0.06

* significant change in HRQL

** significant and clinically relevant change in HRQL

Abbreviations: see next page.

Supplemental Table 5a. Sensitivity analysis correlation coefficient (studies including patients with suspected food allergy) (continued)

Van der Velde	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-CF (0-6M)									
Total (with OFC)	0.55*	0.18	0.92	0.55*	0.08	1.02	0.55*	0.32	0.78
Positive (with OFC)	0.39	-0.09	0.87	0.39	-0.22	1.00	0.39*	0.08	0.70
Negative (with OFC)	0.79*	0.17	1.41	0.79*	0.01	1.57	0.79*	0.40	1.18
Inconclusive (with OFC)	0.24	-1.64	2.12	0.24	-2.14	2.62	0.24	-0.95	1.43
Total (without OFC)	-0.07	-0.61	0.47	-0.07	-0.76	0.62	-0.07	-0.41	0.27
Total (with vs. without OFC)	0.62	-2.26	3.50	0.62	-2.26	3.50	0.62	-2.26	3.50
FAQLQ-TF (0-6M)									
Total (with OFC)	0.24	-0.11	0.59	0.24	-0.19	0.67	0.24*	0.01	0.47
Positive (with OFC)	0.01	-0.40	0.42	0.01	-0.51	0.53	0.01	-0.25	0.27
Negative (with OFC)	0.97*	0.35	1.59	0.97*	0.20	1.74	0.97**	0.54	1.40
Inconclusive (with OFC)	-0.4	-1.28	0.48	-0.40	-1.49	0.69	-0.40	-1.01	0.21
Total (without OFC)	0.34	-0.15	0.83	0.34	-0.27	0.95	0.34*	0.03	0.65
Total (with vs. without OFC)	-0.1	-2.84	2.64	-0.10	-2.87	2.67	-0.10	-2.74	2.54
FAQLQ-AF (0-6M)									
Total (with OFC)	0.54*	0.20	0.88	0.54*	0.11	0.97	0.54*	0.32	0.76
Positive (with OFC)	0.35	-0.09	0.79	0.35	-0.20	0.90	0.35*	0.06	0.64
Negative (with OFC)	0.88*	0.31	1.45	0.88*	0.16	1.60	0.88**	0.52	1.24
Inconclusive (with OFC)	-0.23	-1.03	0.57	-0.23	-1.23	0.77	-0.23	-0.76	0.30
Total (without OFC)	0.11	-0.56	0.78	0.11	-0.74	0.96	0.11	-0.31	0.53
Total (with vs. without OFC)	0.43	-3.43	4.29	0.43	-3.44	4.30	0.43	-3.36	4.22

* significant change in HRQL

** significant and clinically relevant change in HRQL

Abbreviations: CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: AF, Adult Form; CF, Child Form; TF, Teen Form; PF, Parent Form and different domains: AA, Allergen Avoidance; DR, Dietary Restrictions; EI, Emotional Impact; FA, Food Anxiety; RAE, Risk of Accidental Exposure; SDI, Social and Dietary Impact); M, months; MD, mean difference; OFC, oral food challenge; r, correlation coefficient.

Supplemental Table 5a. Sensitivity analysis correlation coefficient (studies including patients with suspected food allergy) (continued)

van der Valk	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-PF (0-6M)									
Total	-0.06	-0.32	0.2	-0.06	-0.38	0.26	-0.06	-0.22	0.1
Positive patients	-0.11	-0.41	0.19	-0.11	-0.48	0.26	-0.11	-0.31	0.09
Negative patients	0.1	-0.4	0.6	0.1	-0.52	0.72	0.1	-0.24	0.44
All patients (EI)	-0.09	-0.33	0.15	-0.09	-0.39	0.21	-0.09	-0.24	0.06
All patients (FA)	-0.01	-0.27	0.25	-0.01	-0.34	0.32	-0.01	-0.18	0.16
All patients (SDI)	-0.07	-0.31	0.17	-0.07	-0.37	0.23	-0.07	-0.22	0.08
Positive patients (EI)	-0.16	-0.57	0.25	-0.16	-0.59	0.27	-0.16	-0.54	0.22
Positive patients (FA)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Positive patients (SDI)	-0.08	-0.37	0.21	-0.08	-0.39	0.23	-0.08	-0.34	0.18
Negative patients (EI)	0.11	-0.76	0.98	0.11	-0.79	1.01	0.11	-0.71	0.93
Negative patients (FA)	0.19	-0.74	1.12	0.19	-0.77	1.15	0.19	-0.69	1.07
Negative patients (SDI)	-0.03	-1.04	0.98	-0.03	-1.07	1.01	-0.03	-0.99	0.93
FAQLQ-TF (0-6M)									
Total	0.28	-0.18	0.74	0.28	-0.3	0.86	0.28	-0.02	0.58
Positive patients	-0.06	-0.55	0.43	-0.06	-0.67	0.55	-0.06	-0.37	0.25
Negative patients	1.18*	0.18	2.18	1.18	-0.06	2.42	1.18*	0.49	1.87
All patients (AA)	0.21	-0.25	0.67	0.21	-0.37	0.79	0.21	-0.09	0.51
All patients (RAE)	0.17	-0.29	0.63	0.17	-0.41	0.75	0.17	-0.13	0.47
All patients (EI)	0.47*	0.01	0.93	0.47	-0.11	1.05	0.47*	0.17	0.77
Positive patients (AA)	0.43	-0.06	0.92	0.43	-0.18	1.04	0.43*	0.12	0.74
Positive patients (RAE)	-0.15	-0.64	0.34	-0.15	-0.76	0.46	-0.15	-0.46	0.16
Positive patients (EI)	0.26	-0.23	0.75	0.26	-0.35	0.87	0.26	-0.05	0.57
Negative patients (AA)	0.9	-0.1	1.9	0.9	-0.34	2.14	0.9*	0.21	1.59
Negative patients RAE)	1.49*	0.49	2.49	1.49*	0.25	2.73	1.49**	0.8	2.18
Negative patients RAE)	1.31*	0.31	2.31	1.31*	0.07	2.55	1.31**	0.62	2.00
FAQLQ-CF (0-6M)									
Total	-0.17	-0.65	0.31	-0.17	-0.78	0.44	-0.17	-0.48	0.14
Positive patients	-0.19	-0.74	0.36	-0.19	-0.88	0.5	-0.19	-0.54	0.16
Negative patients	-0.1	-1.08	0.88	-0.1	-1.34	1.14	-0.1	-0.72	0.52
All patients (AA)	-0.51	-0.99	-0.03	-0.51	-1.12	0.1	-0.51	-0.82	-0.2
All patients (RAE)	-0.29	-0.77	0.19	-0.29	-0.9	0.32	-0.29	-0.6	0.02
All patients (EI)	0.18	-0.3	0.66	0.18	-0.43	0.79	0.18	-0.13	0.49
All patients (DR)	0.01	-0.47	0.49	0.01	-0.6	0.62	0.01	-0.3	0.32
Positive patients (AA)	-0.53	-1.08	0.02	-0.53	-1.22	0.16	-0.53	-0.88	-0.18
Positive patients (RAE)	-0.33	-0.88	0.22	-0.33	-1.02	0.36	-0.33	-0.68	0.02
Positive patients (EI)	-0.14	-0.69	0.41	-0.14	-0.83	0.55	-0.14	-0.49	0.21
Positive patients (DR)	0.27	-0.28	0.82	0.27	-0.42	0.96	0.27	-0.08	0.62
Negative patients (AA)	-0.44	-1.42	0.54	-0.44	-1.68	0.8	-0.44	-1.06	0.18
Negative patients RAE)	-0.18	-1.16	0.8	-0.18	-1.42	1.06	-0.18	-0.8	0.44
Negative patients (EI)	0.41	-0.57	1.39	0.41	-0.83	1.65	0.41	-0.21	1.03
Negative patients (DR)	-0.56	-1.54	0.42	-0.56	-1.8	0.68	-0.56	-1.18	0.06

* significant change in HRQL

** significant and clinically relevant change in HRQL

Abbreviations: see next page.

Supplemental Table 5a. Sensitivity analysis correlation coefficient (studies including patients with suspected food allergy) (continued)

Van der Velde	r=0.5			r=0.2			r=0.8		
	MD	95% CI		MD	95% CI		MD	95% CI	
FAQLQ-CF (0-6M)									
Total (with OFC)	0.55*	0.18	0.92	0.55*	0.08	1.02	0.55*	0.32	0.78
Positive (with OFC)	0.39	-0.09	0.87	0.39	-0.22	1.00	0.39*	0.08	0.70
Negative (with OFC)	0.79*	0.17	1.41	0.79*	0.01	1.57	0.79*	0.40	1.18
Inconclusive (with OFC)	0.24	-1.64	2.12	0.24	-2.14	2.62	0.24	-0.95	1.43
Total (without OFC)	-0.07	-0.61	0.47	-0.07	-0.76	0.62	-0.07	-0.41	0.27
Total (with vs. without OFC)	0.62	-2.26	3.50	0.62	-2.26	3.50	0.62	-2.26	3.50
FAQLQ-TF (0-6M)									
Total (with OFC)	0.24	-0.11	0.59	0.24	-0.19	0.67	0.24*	0.01	0.47
Positive (with OFC)	0.01	-0.40	0.42	0.01	-0.51	0.53	0.01	-0.25	0.27
Negative (with OFC)	0.97*	0.35	1.59	0.97*	0.20	1.74	0.97**	0.54	1.40
Inconclusive (with OFC)	-0.4	-1.28	0.48	-0.40	-1.49	0.69	-0.40	-1.01	0.21
Total (without OFC)	0.34	-0.15	0.83	0.34	-0.27	0.95	0.34*	0.03	0.65
Total (with vs. without OFC)	-0.1	-2.84	2.64	-0.10	-2.87	2.67	-0.10	-2.74	2.54
FAQLQ-AF (0-6M)									
Total (with OFC)	0.54*	0.20	0.88	0.54*	0.11	0.97	0.54*	0.32	0.76
Positive (with OFC)	0.35	-0.09	0.79	0.35	-0.20	0.90	0.35*	0.06	0.64
Negative (with OFC)	0.88*	0.31	1.45	0.88*	0.16	1.60	0.88**	0.52	1.24
Inconclusive (with OFC)	-0.23	-1.03	0.57	-0.23	-1.23	0.77	-0.23	-0.76	0.30
Total (without OFC)	0.11	-0.56	0.78	0.11	-0.74	0.96	0.11	-0.31	0.53
Total (with vs. without OFC)	0.43	-3.43	4.29	0.43	-3.44	4.30	0.43	-3.36	4.22

* significant change in HRQL

** significant and clinically relevant change in HRQL

Abbreviations: CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire (different versions: AF, Adult Form; CF, Child Form; TF, Teen Form; PF, Parent Form and different domains: AA, Allergen Avoidance; DR, Dietary Restrictions; EI, Emotional Impact; FA, Food Anxiety; RAE, Risk of Accidental Exposure; SDI, Social and Dietary Impact); M, months; MD, mean difference; OFC, oral food challenge; r, correlation coefficient.

Supplemental Table 5b. Sensitivity analysis correlation coefficient (studies including patients with confirmed food allergy)

Hourihane	r=0.5			r=0.2			r=0.8		
	SMD	95% CI		SMD	95% CI		SMD	95% CI	
FAQLQ-PF (0-1M)									
Total	1.12*	1.00	1.25	1.12*	0.96	1.29	1.12*	1.04	1.21
FAQLQ-CF (0-1M)									
Total	2.00*	1.83	2.17	2.00*	1.78	2.22	2.00*	1.89	2.11
Knibb	r=0.5			r=0.2			r=0.8		
	SMD	95% CI		SMD	95% CI		SMD	95% CI	
FAQL-PB (0-3 to 6M)									
Total (with OFC)	0.37	0.01	0.37	-0.09	-0.09	0.83	0.37	0.14	0.60
Total (without OFC)	0.11	-0.17	0.11	-0.25	-0.25	0.46	0.11	-0.07	0.28
Total (with vs. without OFC)	0.19	-0.09	0.19	-0.16	-0.16	0.54	0.19	0.01	0.37
PedsQL™ 4.0 (0-3 to 6M)									
Total (with OFC)	0.00	-0.35	0.00	-0.45	-0.45	0.45	0.00	-0.22	0.22
Total (without OFC)	0.07	-0.20	0.07	-0.28	-0.28	0.43	0.07	-0.10	0.25
Total (with vs. without OFC)	-0.08	-0.50	-0.08	-0.61	-0.61	0.45	-0.08	-0.34	0.19
WHOQOL-BREF (0-3 to 6M)									
Total (with OFC)	-0.02	-0.38	-0.02	-0.47	-0.47	0.42	-0.02	-0.25	0.20
Total (without OFC)	0.06	-0.21	0.06	-0.29	-0.29	0.42	0.06	-0.12	0.24
Total (with vs. without OFC)	-0.09	-0.65	-0.09	-0.80	-0.80	0.62	-0.09	-0.44	0.27

* significant change in HRQL

Abbreviations: CI, confidence interval; FAQLQ, Food Allergy Quality of Life Questionnaire; PB, Parental Burden; PF, Parent Form; CF, Child Form; M, months; OFC, oral food challenge; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; r, correlation coefficient; SMD, standardized mean difference. WHOQOL-BREF, World Health Organization generic Quality of Life scale.

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Chapter 7

Prevalence and predictors of uncontrolled asthma in children referred for asthma and other atopic diseases

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Abstract

Background

Uncontrolled asthma in children is still highly prevalent despite the availability of effective asthma treatment. We investigated 1) the prevalence of uncontrolled asthma among children referred for asthma and referred for atopic diseases other than asthma (ie food allergy, allergic rhinitis, atopic dermatitis) to secondary care; 2) the predictors associated with uncontrolled asthma.

Methods

All children (4 to 18 years) referred for asthma or other atopic diseases than asthma to 8 secondary care centers in the Netherlands were invited for an Electronic Portal (EP). The EP is a web-based application with several validated questionnaires including the ISAAC questionnaires and the Asthma Control Test (ACT). Children were eligible for inclusion in this study when their parents reported in the EP that their child had asthma diagnosed by a physician. The ACT was used to assess asthma control. Multiple predictors of asthma control (patient, asthma and atopic characteristics) were evaluated by univariable and multivariable logistic regression analyses.

Results

We included 408 children: 259 children (63%) with asthma referred for asthma and 149 children (37%) with asthma referred for atopic diseases other than asthma. Thirty-nine percent of all children had uncontrolled asthma: 47% of children referred for asthma and 26% of children referred for atopic diseases other than asthma. Predictors associated with uncontrolled asthma were a family history of asthma (odds ratio [OR] 2.08; 95% confidence interval [95% CI] 1.34 to 3.24), recurrent upper and lower respiratory tract infections in the past year (OR 2.40; 95% CI 1.52 to 3.81 and OR 2.00; 95% CI 1.25 to 3.23, respectively).

Conclusions

Uncontrolled asthma is highly prevalent in children with asthma referred to secondary care, even if children are primarily referred for atopic diseases other than asthma. Thus, attention should be paid to asthma control in this population

Introduction

Asthma is one of the most common chronic inflammatory diseases in the Western world, and a notable cause of morbidity in children.¹ Good asthma control is the main management goal according to current asthma management guidelines, as this decreases the risk of asthma exacerbations and improves quality of life.² However, uncontrolled asthma is still highly prevalent despite the availability of effective asthma treatment.³ In order to achieve adequate asthma control in children with asthma it is necessary to gain insight into the current prevalence of uncontrolled asthma among children and the associated predictors.

Several predictors of uncontrolled asthma in children have been previously described such as age, male gender, maternal education level, exposure to indoor smoking, pet ownership, high use of short-acting β_2 -agonists, incorrect inhaler technique, poor adherence to asthma medication and the presence of co-existing diseases.^{2,4,5} Many children with asthma have co-existing atopic diseases - including food allergy, allergic rhinitis and atopic dermatitis – or recurrent respiratory tract infections. Food allergy has been reported in around 25% of children with asthma, allergic rhinitis in 60%, atopic dermatitis in 45% and recurrent respiratory tract infections in 60%.^{6–10} Atopic comorbidities and recurrent respiratory tract infections are associated with increased asthma morbidity. Children with asthma and food allergy have increased asthma symptoms and a significantly lower lung function compared to asthmatic children without food allergy.^{6,11} Children with asthma and allergic rhinitis have a lower level of asthma control compared to asthmatic children without allergic rhinitis.^{12,13} In addition, the presence of allergic rhinitis increases the risk of asthma exacerbations, emergency visits and hospitalizations. Furthermore, recurrent respiratory tract infections are associated with asthma exacerbations in children and a lower level of asthma control.¹⁴

Although predictors of uncontrolled asthma have been previously investigated in various studies, there are still some gaps in knowledge. The majority of research investigating asthma control is conducted among children referred for asthma^{4,15} or among children in the general population^{5,6,8,12} but not among children that are referred with atopic diseases other than asthma to secondary care. The aim of this cross-sectional study was 1) to investigate the prevalence of uncontrolled asthma among children referred for asthma and among children referred for atopic diseases other than asthma, and 2) to investigate the predictors, including atopic comorbidities, associated with uncontrolled asthma among these children.

Methods

Domain and data collection

We conducted a cross-sectional study among children aged 4 to 18 years who were referred to a participating secondary care center (n=8) in the Netherlands between June 2011 and December 2017. All children who were referred for asthma or for atopic diseases other than asthma (i.e. food allergy, allergic rhinitis, atopic dermatitis) were invited to fill in an Electronic Portal (EP) as part of their outpatient visit. There were no exclusion criteria for participation in the EP. Children were eligible for inclusion in this study when their parents reported in the EP that their child had a physician-diagnosed asthma. The structure of the EP have been published previously.¹⁶ In brief, the EP is a web-based application for children and their parents which has been developed and used by a nationwide collaborative network of Dutch caregivers in primary-, secondary- and tertiary health care. The aim of the EP is to collect information on asthma, atopic comorbidities and recurrent respiratory tract infections using validated questionnaires including the ISAAC core questionnaires for wheezing, allergic rhinitis, and atopic dermatitis, the Asthma Control Test, the Pediatric Asthma Quality of Life Questionnaire and the RAND general health questionnaire.^{17–22} The study has been approved by the Medical Ethics Committee of the University Medical Center Utrecht (No. 10/348) and all parents and/or children gave informed consent in the EP.

Outcome

Asthma control during the past month was assessed using the standardized and validated Child-Asthma Control Test (C-ACT) in children 4 to 12 years of age and the Asthma Control Test (ACT) in children ≥ 12 years of age.^{18,19} The final asthma control score is the summed score ranging from 5 through 27 (C-ACT) or 5 through 25 (ACT) with higher scores indicating better asthma control. A score of < 20 indicates uncontrolled asthma.^{18,19}

Potential predictors of asthma control

Potential predictors of asthma control were selected based on clinical knowledge and prior research: age (4 to 12 years or 12 to 18 years), gender, maternal education level (categories low, middle or high), a family history of asthma in one or both parent(s), current smoke exposure, current pet ownership, use of daily inhaled corticosteroids (categories 'no', 'yes, adherent' or 'yes, non-adherent'), food allergy, allergic rhinitis, atopic dermatitis, recurrent upper respiratory tract infections in the past year, recurrent lower respiratory tract infections in the past year and the referral reason ('referral for asthma' or 'referral for atopic diseases other than asthma'). Food allergy was defined as self-reported relevant allergic complaints (urticaria, oral allergy symptoms, angioedema, upper or lower

respiratory complaints, vomiting, a loss of consciousness or anaphylaxis) within two hours after ingestion of a food (yes or no). Allergic rhinitis was defined as having problems with sneezing, or a runny, or a blocked nose when the child did not have a cold or the flu, accompanied by itchy-watery eyes in the past 12 months (yes or no). Atopic dermatitis was defined as the presence of an itchy rash for six months or longer ever and complaints of an itchy rash in the past 12 months (yes or no). Recurrent upper respiratory tract infections included middle ear infections, croup, a cold or laryngitis and was defined as ≥ 8 episodes/year for children aged 2 to 5 years, ≥ 6 for ages 5-10 years and ≥ 4 for ages 10 years or older. Recurrent lower respiratory tract infections included severe bronchitis or pneumonia and was defined as ≥ 2 episodes/year for children of all ages. Definitions of all predictors are displayed in Supplemental Table 1.

Adherence to asthma medication was assessed among all parents of children using daily inhaled corticosteroids by the Medication Adherence Rating Scale (MARS).²³ The MARS is a 5-item questionnaire on medication use behavior. Children with a total MARS score ≥ 21 were considered adherent.²⁴

Statistical analysis

Differences between children with complete and incomplete data and differences between children referred for asthma and referred for atopic diseases other than asthma were statistically evaluated by the chi-square test for categorical variables, the unpaired t-test for normally distributed continuous variables and the Mann-Whitney U tests for non-normally distributed continuous variables with Bonferroni correction for multiple testing. Univariable and multivariable logistic regression analyses of all potential predictors as independent variables and asthma control (well-controlled versus uncontrolled) as the dependent variable were performed. We manually removed predictors one by one based on the *P*-value ($p > 0.20$ based on the likelihood ratio test) and change in model fit (Akaike information criterion).²⁵ The Odds Ratios (ORs) with 95% confidence intervals (CIs) were estimated. A *P*-value < 0.05 was considered statistically significant. In addition to backward selection, forward selection was conducted to evaluate whether the identified predictors were robust based on the sample. Both methods identified the same predictors. All analyses were performed in SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp).

Results

Patients

The study population flowchart is displayed in Figure 1. A total of 1676 children aged 4 to 18 years were invited for the Electronic Portal and 1556 (93%) completed the screening questionnaire. Parents of 579 children reported their child to have asthma diagnosed by a physician. Asthma diagnosis was established by a pediatrician in 284 (49.1%) children, by a general practitioner in 235 (40.6%) children and by a pulmonologist in 60 (10.4%) children. Complete data on the ACT and all predictors were available in 408 of 579 children (70%). These children did not differ in the level of asthma control, the frequencies of atopic comorbidities and the frequencies of other predictors (data not shown). Only children with complete data were included in the analysis of asthma control.

Asthma control in children referred for asthma or atopic diseases other than asthma

Clinical characteristics of 408 children with asthma are displayed in Table 1, stratified by the referral reason: 259 children (63%) with asthma were referred for asthma and 149 children (37%) with asthma were referred for atopic diseases other than asthma including food allergy, allergic rhinitis and atopic dermatitis. Children had a mean (SD) age of 10.6 (3.5) years and were predominantly Dutch (83%). Uncontrolled asthma (ACT score < 20) was found in 160 children (39%): in 121 of 259 children (47%) referred for asthma and in 39 of 149 children (26%) referred for atopic diseases other than asthma. Children referred for asthma were more likely to use daily inhaled corticosteroids compared to children referred for atopic diseases other than asthma (80% versus 56%, respectively), and were less likely to report at least on other atopic comorbidity (61% versus 89%, respectively). The proportion of atopic comorbidities in children in both referral groups is displayed in Figure 2. Almost 40% of children in both referral groups reported recurrent upper respiratory tract infections in the past year.

Figure 1. Study population flowchart

Abbreviations: (C-)ACT, (Child) Asthma Control Test; EP, Electronic Portal; n, number.

Table 1. Clinical characteristics of children with asthma

	All children	Referral reason		P-value [†]
		Asthma	Atopic disease other than asthma	
n (%)	408 (100)	259 (63)	149 (37)	
Demographic characteristics				
Age in years, mean (SD)	10.6 (3.5)	10.3 (3.4)	11.2 (3.6)	0.021
Male gender	238 (58)	160 (62)	78 (52)	0.076
Both parents Dutch	340 (83)	210 (81)	130 (87)	0.129
Family history of asthma	198 (49)	124 (48)	74 (50)	0.758
Family history of other atopic disease	331 (81)	205 (79)	126 (85)	0.191
Current smoke exposure	31 (8)	17 (7)	14 (9)	0.334
Current pet ownership	165 (40)	105 (41)	60 (40)	1.000
Asthma characteristics				
Wheezing at night (past year)	173 (42)	124 (48)	49 (33)	0.004
Coughing at night (past year)	196 (48)	132 (51)	64 (43)	0.124
Inhaled short-acting β_2 -agonists (past week)	228 (56)	158 (61)	70 (47)	0.007
Inhaled corticosteroids (daily) [‡]				<0.001
No	118 (29)	53 (21)	65 (44)	
Yes, adherent	213 (52)	154 (60)	59 (40)	
Yes, non-adherent	77 (19)	52 (20)	25 (16)	
(Atopic) comorbidities				
Any atopic comorbidity	291 (71)	159 (61)	132 (89)	<0.001
Food allergy	87 (21)	30 (12)	57 (38)	<0.001
Allergic rhinitis	200 (49)	100 (39)	100 (67)	<0.001
Atopic dermatitis	173 (42)	91 (35)	82 (55)	<0.001
Recurrent upper RTIs (yes)	146 (36)	89 (34)	57 (38)	0.454
Recurrent lower RTIs (yes)	116 (28)	82 (32)	34 (23)	0.068
Quality of life				
PAQLQ, median (IQR)	6.1 (5.4-6.7)	5.9 (5.0-6.6)	6.2 (5.6-6.8)	0.003
RAND, mean (SD)	21 (4.6)	21 (4.5)	21 (4.7)	0.991
Referral reason				
Asthma	259 (64)	259 (100)	0	
Food allergy	73 (18)	0	73 (49)	
Allergic rhinitis	38 (9)	0	38 (26)	
Atopic dermatitis	27 (7)	0	27 (18)	
Other, none of the above	11 (3)	0	11 (7)	

Values are numbers (%), unless otherwise stated.

[†] Statistical comparisons between referral groups with P-values of less than 0.003 taken to be significant according to Bonferroni correction for multiple testing.

[‡] Medication adherence was assessed by the Medication Adherence Rating Scale (MARS).²³ Children with a total MARS score ≥ 21 were considered adherent and a score < 21 were considered non-adherent.²⁴

Abbreviations: IQR, interquartile range; RTIs, respiratory tract infections; n, number; NA, not applicable; SD, standard deviation.

Children referred for asthma (n=259)

Children referred for atopic diseases other than asthma (n=149)

Figure 2. Venn diagram displaying the proportion of atopic comorbidities among children with asthma stratified by referral reason
Values are numbers (%).

Predictors of asthma control

Univariable logistic regression analyses showed that a family history of asthma, the use of daily inhaled corticosteroids in children who were considered non-adherent, recurrent upper and lower respiratory tract infections in the past year and a referral for asthma were associated with uncontrolled asthma (Table 2). In a multivariable logistic regression analysis, a family history of asthma (odds ratio [OR] 2.08; 95% CI 1.34 to 3.24), recurrent upper respiratory tract infections in the past year (OR 2.40; 95% CI 1.52 to 3.81), recurrent lower respiratory tract infections in the past year (OR

2.00; 95% CI 1.25 to 3.23) and a referral for asthma (OR 2.60; 95% CI 1.61 to 4.26) were independently and significantly associated with uncontrolled asthma (Table 2).

Uncontrolled asthma was observed in 47% of children with a family history of asthma versus 32% of children without a family history of asthma, in 51% of children with recurrent upper RTIs versus 32% of children without recurrent upper RTIs and in 53% of children with recurrent lower RTIs versus 34% of children without recurrent lower RTIs. The full multivariable logistic regression analysis is presented in Supplemental Table 2. Atopic comorbidities, including food allergy, allergic rhinitis and atopic dermatitis, were not associated with uncontrolled asthma.

Table 2. Univariable and fitted multivariable logistic regression analysis, with uncontrolled asthma (ACT score <20) as the outcome, in 408 children with asthma

	Univariable analysis		Fitted multivariable analysis [†]	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age category		0.616		
4 to 12 year	Ref			
12 to 18 year	0.90 (0.60 to 1.36)			
Male gender	1.45 (0.97 to 2.18)	0.074	1.50 (0.96 to 2.37)	0.073
Maternal education level		0.196		0.099
Low	Ref		Ref	
Middle	1.52 (0.81 to 2.91)		1.60 (0.81 to 3.23)	
High	1.06 (0.57 to 2.03)		0.98 (0.50 to 1.98)	
Family history of asthma	1.81 (1.21 to 2.72)	0.004	2.08 (1.34 to 3.24)	0.001
Current smoke exposure	1.73 (0.82 to 3.63)	0.146		
Current pet ownership	1.42 (0.95 to 2.13)	0.087	1.51 (0.97 to 2.36)	0.066
Inhaled corticosteroids (daily) [‡]		0.027		0.147
No	Ref		Ref	
Yes, adherent	1.54 (0.96 to 2.50)		1.05 (0.62 to 1.79)	
Yes, non-adherent	2.22 (1.23 to 4.04)		1.78 (0.93 to 3.44)	
Food allergy	0.52 (0.30 to 0.86)	0.011		
Allergic rhinitis	0.87 (0.58 to 1.29)	0.486		
Atopic dermatitis	0.85 (0.57 to 1.27)	0.430		
Recurrent upper RTIs (yes)	2.20 (1.45 to 3.34)	<0.001	2.40 (1.52 to 3.81)	<0.001
Recurrent lower RTIs (yes)	2.27 (1.47 to 3.53)	<0.001	2.00 (1.25 to 3.23)	0.004
Referral reason		<0.001		<0.001
Atopic diseases other than asthma	Ref		Ref	
Asthma	2.47 (1.60 to 3.87)		2.60 (1.61 to 4.26)	

[†] Fitted multivariable logistic regression model after backward selection.

[‡] Medication adherence was assessed by the Medication Adherence Rating Scale (MARS).²³ Children with a total MARS score ≥ 21 were considered adherent and a score <21 were considered non-adherent.²⁴ Abbreviations: ACT, Asthma Control Test; CI, confidence interval; RTIs, respiratory tract infections; n, number; OR, odds ratio; Ref, Reference category.

Discussion

Our study indicates that a high percentage of uncontrolled asthma is not only observed in children with asthma who were referred for asthma to secondary care (47%) but uncontrolled asthma is also highly prevalent in children with asthma who were referred for atopic diseases other than asthma (26%). The prevalence of uncontrolled asthma in our population of children with asthma referred for atopic diseases other than asthma is notably higher than the prevalence observed in children with asthma among the general population (15%).⁵ In addition, only 56% of children with asthma referred for atopic diseases other than asthma were prescribed daily inhaled corticosteroids suggesting these children were inappropriately treated.²⁶ Our results suggest that assessment of asthma control and optimization of asthma treatment are not only important for children referred for asthma, but also for children primarily referred for allergic complaints other than asthma.

We found a family history of asthma, recurrent upper and lower respiratory tract infections in the past year to be independently associated with uncontrolled asthma. Children with a family history of asthma might have more frequent uncontrolled asthma due to increased asthma severity, as suggested in previous research.²⁷ Furthermore, children with a family history of asthma might have more frequent uncontrolled asthma as parents with asthma may be less concerned about the asthma symptoms of their child as they are familiar with asthma symptoms themselves. Finally, recurrent upper and lower respiratory tract infections were associated with uncontrolled asthma. This observation is concordant with previous studies that showed that respiratory tract infections can have a profound effect on loss of control and asthma exacerbations in both children and adults.²⁸ Furthermore, asthma attacks are often triggered by respiratory tract infections. Another explanation for the observed association between respiratory tract infections and uncontrolled asthma might be that asthma has been misdiagnosed.²⁹ Previous studies indicate that parent-reported physician-diagnosed asthma in children is often not confirmed upon lung function testing and respiratory symptoms were due to e.g. viral illnesses.^{29,30}

Atopic comorbidities, i.e. food allergy, allergic rhinitis and atopic dermatitis, were not independently associated with asthma control in our population of children referred with respiratory or allergic complaints. Previous research in children with asthma reported an increased risk of uncontrolled asthma and increased asthma morbidity (i.e. hospitalization, use of controller medication) in children with asthma and food allergy⁶ or allergic rhinitis.^{4,5} We might not have detected an association between atopic comorbidities and asthma control because the atopic comorbidities

were self-reported. Furthermore, most studies focused on an individual comorbidity and included additional relevant predictors associated with the comorbidity in the analysis, e.g. the season of the questionnaire, the severity of the atopic comorbidity or medication use. The sample size of our study was too small to consider all these additional relevant predictors per atopic comorbidity in the regression model. This may explain why the association was not found.

The major limitation of the present study is that all data were self-reported, lacking objective data such as lung function testing or specific IgE measurement. The diagnosis of asthma was based on a parent-reported physician-diagnosis and the diagnoses of atopic comorbidities were mainly based on the ISAAC questionnaire. Therefore, the prevalence of these diseases may have been overestimated^{31,32} or underestimated.³³ In addition, we only included the children with complete data which may have caused selection bias. However, the children with complete data were comparable to the children with incomplete data in the frequencies of all predictors and the level of asthma control providing confidence that the children included in the study are a fair representation of the overall study population. Finally, we did not assess long-term asthma control and the frequency of asthma exacerbations, emergency department visits and hospitalizations. However, our study is strengthened by the inclusion of a large population of children with parent-reported physician-diagnosed asthma in eight secondary care centers in the Netherlands, rigorous data collection using several validated questionnaires in children and parents, as well as the assessment of asthma, atopic comorbidities and respiratory tract infections simultaneously.

In conclusion, this study demonstrates that assessment of asthma control is not only important for all children referred for asthma to secondary care, but also for children with asthma who are referred for atopic diseases other than asthma. Special attention should be paid to children with asthma who have a family history of asthma, or have a history of recurrent upper and/or lower respiratory tract infections in the past year, as these predictors are associated with uncontrolled asthma.

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Supplemental tables

Supplemental Table 1. Collection of clinical data using the Electronic Portal

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Physician-diagnosed asthma	Is your child diagnosed with asthma? a. Yes, by a general practitioner b. Yes, by a pediatrician c. Yes, by a pulmonologist d. No	Yes (a, b or c) or No (d)
Both parents Dutch	What ethnic group do you belong to? Mother/Father (<i>separate questions</i>) a. Dutch b. Turkish c. Moroccan d. Surinamese e. Antillean f. Other	Yes (both parents a) or No
Maternal education level	What is the highest level of education you have completed? a. Elementary school b. Lower general secondary education c. Intermediate vocational education d. Higher general secondary education e. Higher vocational education f. University	Low (a-b), Middle (c-d) or High (e-f)
Family history of asthma	Do one or more family members suffer from asthma, allergic rhinitis, food allergy or atopic dermatitis? (<i>four separate questions</i>) a. No b. Yes, the father of the child c. Yes, the mother of the child d. Yes, brother(s) of the child e. Yes, sister(s) of the child	Yes (b and/or c) or No
Family history of other atopic diseases	Do one or more family members suffer from food allergy, allergic rhinitis or atopic dermatitis? (<i>three separate questions</i>) a. No b. Yes, the father of the child c. Yes, the mother of the child d. Yes, brother(s) of the child e. Yes, sister(s) of the child	Yes (b and/or c) or No

Supplemental Table 1. Collection of clinical data using the Electronic Portal (continued)

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Current smoke exposure	<ol style="list-style-type: none"> Does the mother of the child smoke in the home? Does the father of the child smoke in the home? Do other housemates smoke in the home? 	Yes (question 1, 2 or 3 yes) or No
Current pet ownership	Do you own a pet?	Yes or no
Wheezing/coughing at night during the past year	<ol style="list-style-type: none"> In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection? 	Yes* or No * Yes if question 1 is answered with ≥ 1 , and/or question 2 answered with yes
Inhaled short-acting β_2 -agonists (past week)	<p>In the past week, how often has your child inhaled a short-acting bronchodilator (e.g. Ventolin, Salbutamol, Bricanyl) on most days</p> <ol style="list-style-type: none"> Never 1-2 inhalations on most days 3-4 inhalations on most days 5-8 inhalations on most days 9-12 inhalations on most days 13-16 inhalations on most days ≥ 16 inhalations on most days 	Yes (b-g) or No (a)
Inhaled corticosteroids (daily)	<p>Has your child used daily inhaled corticosteroids (e.g. Pulmicort, Flixotide, Seretide, Qvar)?</p> <ol style="list-style-type: none"> Yes No <p>5-item Medication Adherence Rating Scale (MARS)²³</p>	No (b), Yes adherent (a and MARS ≥ 21), Yes non-adherent (a and MARS < 21)
Food allergy	<ol style="list-style-type: none"> Has your child ever had a food allergy? Within what time period after food ingestion did your child develop symptoms? What symptoms did your child experience after food ingestion? 	Yes* or No * Yes if question 1 is answered with yes, and symptoms occurred within two hours after ingestion of the food (question 2) and food allergic symptoms were relevant (question 3): urticaria, oral allergy, angioedema, upper or lower respiratory complaints, vomiting, loss of consciousness or anaphylaxis.

Supplemental Table 1. Collection of clinical data using the Electronic Portal (continued)

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Allergic rhinitis	<ol style="list-style-type: none"> 1. In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when s/he did not have a cold or the flu? 2. If yes: In the past 12 months, has this nose problem been accompanied by itchy–watery eyes? 	Yes (both yes) or No
Atopic dermatitis	<ol style="list-style-type: none"> 1. Has your child ever had an itchy rash which was coming and going for at least 6 months? 2. Has your child had this itchy rash at any time in the past 12 months? 	Yes (both yes) or No
Recurrent upper respiratory tract infections	<ol style="list-style-type: none"> 1. In the past 12 months, how often has your child had complaints of a middle ear infection? 2. In the past 12 months, how often has your child had complaints of croup? 3. In the past 12 months, how often has your child had complaints of a cold or laryngitis? 	Yes* or No * Yes if question 1-3 is answered with ≥ 6 (age 5-10 years) or ≥ 4 (age 10 years or older)
Recurrent lower respiratory tract infections	<ol style="list-style-type: none"> 1. In the past 12 months, how often has your child had complaints of a severe bronchitis or pneumonia (= coughing, dyspnea and fever)? 	Yes* or No * If answered with ≥ 2 (all ages)

Supplemental Table 2. Full multivariable logistic regression analysis, with uncontrolled asthma (ACT score <20) as the outcome, in 408 children with asthma

	Adjusted OR (95% CI)	P-value
Age category		0.739
4 to 12 year	<i>Ref</i>	
12 to 18 year	1.09 (0.66 to 1.79)	
Male gender	1.53 (0.97 to 2.42)	0.067
Maternal education level		0.110
Low	<i>Ref</i>	
Middle	1.65 (0.82 to 3.40)	
High	1.02 (0.51 to 2.08)	
Family history of asthma	2.07 (1.33 to 3.25)	0.001
Current smoke exposure	1.53 (0.67 to 3.51)	0.313
Current pet ownership	1.43 (0.91 to 2.26)	0.123
Inhaled corticosteroids (daily) [†]		0.199
No	<i>Ref</i>	
Yes, adherent	1.09 (0.63 to 1.88)	
Yes, non-adherent	1.76 (0.90 to 3.45)	
Food allergy	0.75 (0.41 to 1.33)	0.320
Allergic rhinitis	0.94 (0.58 to 1.52)	0.856
Atopic dermatitis	1.04 (0.66 to 1.65)	0.798
Recurrent upper RTIs (yes)	2.40 (1.51 to 3.85)	<0.001
Recurrent lower RTIs (yes)	1.99 (1.23 to 3.24)	0.005
Referral reason		0.001
Atopic diseases other than asthma	<i>Ref</i>	
Asthma	2.45 (1.45 to 4.18)	

[†] Medication adherence was assessed by the Medication Adherence Rating Scale (MARS). Children with a total MARS score ≥ 21 were considered adherent and a score <21 were considered non-adherent.

Abbreviations: ACT, Asthma Control Test; CI, confidence interval; RTIs, respiratory tract infections; OR, odds ratio; Ref, Reference categories.

Chapter 8

Perceived triggers of asthma impair quality of life in children with asthma

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Abstract

Background

Data on the impact of the number and nature of perceived asthma triggers on health-related quality of life (HRQL) in children are scarce.

Objective

To investigate the impact of perceived asthma triggers on both asthma-specific and generic HRQL in children.

Methods

A cross-sectional study was conducted among children (7 to 18 years) with asthma in secondary and tertiary care. Children were screened with electronic questionnaires regarding respiratory and allergic symptoms. Asthma-specific HRQL was assessed using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (score range 1 to 7) and generic HRQL using the RAND questionnaire (score range 7 to 32). The Kruskal-Wallis test and one-way ANOVA was used to test the difference of respectively the PAQLQ and RAND score across the number of perceived asthma triggers (0, 1-2, 3-4, or ≥ 5). Univariable and multivariable linear regression analyses were performed to evaluate the association between individual triggers and HRQL.

Results

527 children with a mean (SD) age of 12.1 (2.9) years were included. Children with a higher number of perceived triggers had significantly lower PAQLQ and RAND scores (i.e. poorer HRQL). The difference in PAQLQ scores was clinically relevant between children with 0 versus 3-4 or ≥ 5 triggers and 1-2 versus ≥ 5 triggers (mean difference 0.66, 1.02 and 0.63, respectively). Especially non-allergic triggers (physical exercise, the weather, (cigarette) smoke and emotions) were significantly associated with reduced PAQLQ scores. Emotions and food/drinks were associated with reduced RAND scores.

Conclusion and Clinical relevance

A higher number of perceived triggers of asthma was associated with reduced HRQL in children with asthma. Especially non-allergic triggers were associated with reduced HRQL.

Introduction

Asthma presents as one of the most common chronic inflammatory diseases in children in the developed world, affecting up to 9% of children.¹ Asthma causes significant morbidity and has a negative impact on health-related quality of life (HRQL).² HRQL can be measured with asthma-specific and generic questionnaires. Asthma-specific HRQL reflect the perceived impact of asthma on a patient's life, while generic HRQL allow direct comparison between different diseases. Asthma-specific HRQL is especially reduced in girls, in children with uncontrolled asthma and in those with frequent or severe asthma exacerbations.^{3,4} Children with asthma report poorer generic HRQL than children in the general population and children with allergic rhinitis, food allergy, atopic dermatitis and diabetes mellitus, but better generic HRQL than children with juvenile chronic arthritis.^{5,6}

Asthma symptoms and exacerbations can be elicited by a range of allergic triggers (i.e. pollen, house dust or pets) and non-allergic triggers (i.e. physical exercise, respiratory tract infections, emotions or exposure to tobacco smoke).⁷ Only scarce data on the impact of perceived asthma triggers on HRQL in children are available. A higher number of perceived triggers of asthma can exert a toll on asthma-specific HRQL in children with severe or difficult-to-treat asthma.^{8,9} Data in children with mild or moderate asthma are lacking. Furthermore, it has been shown that asthma-specific HRQL in children was associated with grass pollen exposure and airway inflammation¹⁰ and generic HRQL in children was reduced during pollen season.¹¹ In adults, previous research has suggested that mainly non-allergic asthma triggers are associated with reduced asthma-specific HRQL.¹² The aim of this study was to investigate the single and composite impact of perceived allergic and non-allergic triggers of asthma on asthma-specific and generic HRQL in children referred to secondary or tertiary care.

Methods

Domain and data collection

A cross-sectional study was performed among children referred with respiratory or allergic complaints to 8 secondary care centers and 1 tertiary care center in the Netherlands between June 2011 and August 2018. Eligible children were aged 7 to 18 years with parent-reported physician-diagnosed asthma. All children were invited for the Electronic Portal (EP) before an outpatient visit. The details of the EP have been previously published.¹³ In short, the EP is a web-based system with electronic questionnaires for children and their parents developed to collect information on asthma, allergic rhinitis, food allergy, atopic dermatitis and recurrent respiratory tract infections. This study was approved by the Medical

Ethical Review Board of the University Medical Center in Utrecht, the Netherlands, number 10/348, and all parents and/or children gave informed consent before enrolment.

Measurements

Asthma-specific and generic HRQL

Asthma-specific HRQL in children was assessed using the child-reported Pediatric Asthma Quality of Life Questionnaire (PAQLQ).¹⁴ The PAQLQ is a validated instrument with 23 items in three domains: symptoms, activity limitation and emotional function. All PAQLQ-items are scored on a 7-point Likert response scale (i.e. 1 = extremely bothered; 7 = not bothered) with a 1-week recall period. The final overall PAQLQ score is the mean score of all 23 items and domain-scores are the means of the items in the individual domains. The mean difference (MD) in PAQLQ scores between patients can be interpreted using the minimal clinically important differences (MCID). The MCID is the smallest change score that is considered clinically relevant.¹⁵ The MCID for the PAQLQ is 0.5 as estimated previously.¹⁶

Generic HRQL in children was assessed using the parent-reported RAND questionnaire.¹⁷ The RAND is a validated general health rating index for children with 7 questions that ask parents to assess the overall health status of their child with a 1-month recall period. The final RAND score is the summed score ranging from 7 to 32 with higher scores indicating better general health. The MCID of the RAND-questionnaire is 5.3.¹⁸

Perceived triggers of asthma

Children (≥ 12 years) or parents (children 7 to 12 years) were asked if, in the last 12 months, symptoms of wheezing in the chest were worsened after exposure to one or more of the following triggers: dust, pollen, pets, physical exercise, the weather, cold or the flu, (cigarette) smoke, emotions, food or drinks, detergent, or wool clothing. Dust, pollen and pets were categorized as allergic triggers; all other triggers were categorized as non-allergic triggers.

Clinical data

Information on patients' demographic and environmental characteristics was obtained using the electronic questionnaires in the EP. Asthma control during the last month was assessed using the Asthma Control Test (ACT). The previously defined cut-off was used to classify children as having well-controlled asthma (ACT score ≥ 20) or uncontrolled asthma (< 20).^{19,20} Furthermore, the ISAAC core questionnaires for wheezing, allergic rhinitis, and atopic dermatitis were used.²¹ Comorbidities – i.e. allergic rhinitis, food allergy, atopic dermatitis and recurrent

respiratory tract infections – were defined based on a combination of questions in the EP (Supplemental Table 1).

Statistical analyses

Children with complete HRQL data, information on perceived asthma triggers and clinical data used as confounders in the multivariable analysis were included in the analysis. Differences between children with complete and incomplete data were statistically evaluated by the chi-square test for categorical variables, the unpaired t-test for normally distributed continuous variables and the Mann-Whitney U tests for non-normally distributed continuous variables with Bonferroni correction for multiple testing. Descriptive statistics were presented as number and percentages, means with standard deviations (SD) for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. The Kruskal-Wallis test was used to compare the non-normally distributed PAQLQ score and one-way analysis of variance (ANOVA) was used to compare the normally distributed RAND score across the total number of perceived asthma triggers (0, 1-2, 3-4, or ≥ 5), the number of allergic triggers (0, 1, 2 or 3) and the number of non-allergic triggers (0, 1-2, 3-4 or ≥ 5). Furthermore, the difference between the mean HRQL scores (mean difference, MD) of children in the different categories of triggers (e.g. 0 versus 1-2 triggers) was calculated along with the 95% confidence interval (95% CI) to interpret the change score using the minimal clinically important difference (MCID). In addition, the standardized mean difference (SMD) was calculated using Cohen's statistics to estimate the effect size.²² Based on Cohen's criteria, a SMD of 0.2 is considered small, 0.5 is moderate and >0.8 is large.²²

The association between the individual perceived asthma triggers and HRQL was estimated using univariable and multivariable linear regression analyses. The multivariable linear regression analyses was performed with all triggers and adjusted for age, sex, living environment, asthma control (well-controlled versus uncontrolled according to the Asthma Control Test) and the presence of allergic rhinitis, food allergy, atopic dermatitis or recurrent respiratory tract infections. The unadjusted and adjusted unstandardized regression coefficients for the difference in the outcome between patients with and without the trigger were estimated along with the 95% confidence interval and p-value. A p-value of less than 0.05 was considered statistically significant. All analyses were performed in SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp).

Results

Patients' characteristics

A total of 1869 children aged 7 to 18 years were included in the Electronic Portal in one of the participating secondary (n=8) or tertiary care (n=1) centers: 1743 children (93%) completed the screening questionnaires, and the parents of 764 children (44%) reported their child to have physician-diagnosed asthma. A total of 527 children (69%) had complete data and were included in the analysis (Figure 1). Children included in the analysis were older compared to the children with incomplete data, but did not differ in the frequency of having any perceived trigger of asthma, the level of asthma control, asthma-specific health-related quality of life (HRQL) and generic HRQL (Supplemental Table 2).

Figure 1. Study population flowchart
Abbreviations: EP, electronic portal; n, number.

Patients' characteristics are presented in Table 1. Children had a mean (SD) age of 12.1 (2.9) years, 58% were male, 88% were Dutch and 79% reported worsening of symptoms of wheezing in the chest after exposure to one or more asthma trigger in the past year. Half of the children (53%) reported both perceived allergic and non-allergic asthma triggers. Figure 2 shows the proportion of individual triggers. The three most common perceived triggers of asthma were all non-allergic: physical exercise (n=331; 63%), the weather (n=269; 51%) and a cold or the flu (n=268; 51%).

Table 1. Clinical characteristics of children with asthma

		n (%)	n available
Age in years, mean (SD)		12.1 (2.9)	527
Male sex		304 (58)	527
Both parents Dutch		458 (88)	523
Maternal education level	Low	68 (13)	524
	Middle	212 (41)	524
	High	244 (47)	524
Any asthma trigger		417 (79)	527
Both allergic and non-allergic asthma triggers		278 (53)	527
Only non-allergic asthma triggers		129 (24)	527
Only allergic asthma triggers		10 (2)	527
No asthma triggers		110 (21)	527
Family history of	Asthma	239 (45)	526
	Allergic rhinitis	353 (67)	525
	Atopic dermatitis	268 (51)	525
	Food allergy	53 (14)	379
Current living environment	Rural	318 (60)	527
	Urban	209 (40)	527
Pet ownership		234 (44)	527
Uncontrolled asthma (ACT<20)		200 (38)	527
Nocturnal wheezing/coughing in the past year		271 (51)	527
Daily inhaled corticosteroids		264 (66)	403
Inhaled short-acting β_2 -agonists in the past week		271 (51)	527
Comorbidities	Allergic rhinitis	296 (56)	527
	Atopic dermatitis	215 (41)	527
	Food allergy	153 (29)	527
	RRTI	250 (47)	527
Referred to	Secondary care	367 (70)	527
	Tertiary care	160 (30)	527
Referral reason	Asthma	209 (50)	415
	Food allergy	124 (30)	415
	Allergic rhinitis	32 (8)	415
	Atopic dermatitis	32 (8)	415
	RRTI	10 (2)	415
	Other	19 (5)	415

Abbreviations: ACT, Asthma Control Test; n, number; RRTI, recurrent respiratory tract infections; SD, standard deviation.

Figure 2. Proportion of asthma triggers in children with asthma (n=527)

The association between asthma triggers and asthma-specific HRQL

A higher number of perceived triggers of asthma was associated with reduced asthma-specific HRQL (Figure 3a). Children with a higher number of triggers had significantly lower PAQLQ scores (Table 2). The same association was observed for the domain-specific PAQLQ scores and after stratification by allergic and non-allergic triggers.

The difference of the overall PAQLQ score was considered clinically relevant between children with 0 and 3-4 triggers and 0 and ≥ 5 triggers (mean difference [MD] 0.66 and 1.02, respectively) with respectively moderate and large effect size (standardized mean difference [SMD] 0.74 and 1.10). Furthermore, the difference was clinically relevant between children with 1-2 and ≥ 5 triggers (MD 0.63) with moderate effect size (SMD 0.65) (Supplemental Table 3). In addition, clinically relevant differences of the domain-specific PAQLQ scores were observed (Supplemental Table 3). Children with only non-allergic asthma triggers had a significantly lower median (IQR) PAQLQ score (i.e. worse HRQL) (6.1 (5.2-6.7); n=129) compared to children with only allergic asthma triggers (6.7 (6.1-6.9); n=10) (p=0.029).

The association between asthma triggers and generic HRQL

A higher number of perceived triggers of asthma was associated with reduced generic HRQL as assessed with the RAND questionnaire (Figure 3b). Children with a higher number of triggers had significantly lower RAND scores (Table 2). The same association was observed if the analysis was stratified by allergic and non-allergic triggers. The difference in RAND scores were not considered clinically relevant as

the minimal clinically important difference was not exceeded. The effect size was moderate between children with 0 and ≥ 5 triggers (SMD 0.68) and between children with 1-2 and ≥ 5 triggers (SMD 0.62) (Supplemental Table 3).

The RAND score was comparable between children with only non-allergic asthma triggers (mean (SD) 21.1 (4.4)) and children with only allergic asthma triggers (22.1 (3); $n=10$) ($p=0.494$).

Table 2. The number of asthma triggers and asthma-specific (PAQLQ) and generic (RAND) quality of life scores

	n	PAQLQ score				RAND score
		Overall	Domain Symptoms	Domain Activities	Domain Emotions	
All triggers[†]						
0 triggers	110	6.47 ± 0.07	6.38 ± 0.07	6.25 ± 0.09	6.72 ± 0.07	22.74 ± 0.48
1-2 triggers	111	6.09 ± 0.08	5.83 ± 0.10	5.90 ± 0.10	6.53 ± 0.07	22.27 ± 0.40
3-4 triggers	129	5.81 ± 0.08	5.52 ± 0.11	5.48 ± 0.10	6.37 ± 0.08	20.62 ± 0.39
≥5 triggers	177	5.45 ± 0.08	5.12 ± 0.09	5.01 ± 0.09	6.16 ± 0.08	19.58 ± 0.33
<i>P</i> -value [‡]		<0.001	<0.001	<0.001	<0.001	<0.001
Allergic triggers						
0 triggers	239	6.12 ± 0.06	5.94 ± 0.07	5.87 ± 0.08	6.51 ± 0.06	21.87 ± 0.31
1 triggers	118	5.80 ± 0.09	5.49 ± 0.11	5.51 ± 0.11	6.38 ± 0.08	21.23 ± 0.42
2 triggers	91	5.71 ± 0.10	5.38 ± 0.12	5.35 ± 0.11	6.34 ± 0.09	19.77 ± 0.46
3 triggers	79	5.51 ± 0.12	5.20 ± 0.14	5.01 ± 0.14	6.20 ± 0.11	19.84 ± 0.52
<i>P</i> -value [‡]		<0.001	<0.001	<0.001	<0.001	<0.001
Non-allergic triggers						
0 triggers	120	6.48 ± 0.06	6.38 ± 0.07	6.27 ± 0.09	6.72 ± 0.06	22.68 ± 0.45
1-2 triggers	172	6.08 ± 0.07	5.83 ± 0.08	5.84 ± 0.08	6.55 ± 0.05	21.98 ± 0.32
3-4 triggers	181	5.50 ± 0.08	5.17 ± 0.09	5.11 ± 0.09	6.18 ± 0.08	19.77 ± 0.46
≥5 triggers	54	5.24 ± 0.14	4.88 ± 0.16	4.71 ± 0.17	6.12 ± 0.14	18.93 ± 0.65
<i>P</i> -value [‡]		<0.001	<0.001	<0.001	<0.001	<0.001

Values are mean $\pm$ SE, unless otherwise stated.

[†]All triggers included allergic triggers (dust, pollen, pets) and non-allergic asthma triggers (physical exercise, the weather, cold or the flu, (cigarette) smoke, emotions, food or drinks, detergent, wool clothing).

[‡]Statistical comparisons between trigger categories using Kruskal-Wallis test for the PAQLQ scores and one-way ANOVA for the RAND score with *P*-values of less than 0.004 taken to be significant according to Bonferroni correction for multiple testing.

Abbreviations: *n*, number; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; RAND, RAND general-health rating index; SE, standard error.

Figure 3. Association between the number of asthma triggers and asthma-specific (A) and generic (B) quality of life
Abbreviations: n, number; PAQLQ, Pediatric Asthma Quality of Life; RAND, RAND general health-rating index; SE, standard error.

Single and composite effects of asthma triggers on asthma-specific HRQL

In univariable linear regression analysis, all allergic asthma triggers were associated with a lower overall PAQLQ score (i.e. poorer asthma-specific HRQL) (Table 3a). In addition, all non-allergic asthma triggers except wool clothing were associated with a lower overall PAQLQ score. In the adjusted multivariable analysis, physical exercise, the weather, (cigarette) smoke and emotions were independently associated with a lower overall PAQLQ score. None of the perceived allergic triggers was independently associated with the overall PAQLQ score.

The multivariable analysis was repeated with the domain-specific PAQLQ scores as the outcome (Supplemental Table 4). Physical exercise and (cigarette) smoke were independently associated with a lower symptom domain score. Pets, physical exercise, the weather and (cigarette) smoke were independently associated with a lower activity limitations domain score. The asthma trigger emotions was independently associated with a lower emotional function domain score.

Single and composite effects of asthma triggers on generic HRQL

In univariable linear regression analysis, all allergic asthma triggers were associated with a lower RAND score (i.e. poorer generic HRQL) (Table 3b). Again, all non-allergic asthma triggers except wool clothing were associated with a lower RAND score.

In the adjusted multivariable analysis, only emotions and food or drinks were independently associated with a lower RAND score. None of the perceived allergic triggers was independently associated with the RAND score.

Table 3. Linear regression analysis for asthma-specific (a) and generic (b) quality of life

a. Overall PAQLQ score						
	Univariable analysis			Multivariable analysis		
	β	95% CI	P-value	$a\beta^{\dagger}$	95% CI	P-value
Allergic triggers						
Dust	-0.51	-0.68 to -0.34	<0.001	-0.09	-0.25 to 0.08	0.293
Pollen	-0.27	-0.45 to -0.08	0.004	0.15	-0.03 to 0.33	0.095
Pets	-0.35	-0.53 to -0.16	<0.001	-0.03	-0.19 to 0.14	0.760
Non-allergic triggers						
Physical exercise	-0.70	-0.87 to -0.53	<0.001	-0.16	-0.32 to 0.00	0.047
The weather	-0.66	-0.83 to -0.50	<0.001	-0.17	-0.33 to -0.01	0.038
Cold or the flu	-0.55	-0.71 to -0.38	<0.001	0.00	-0.16 to 0.15	0.954
(Cigarette) smoke	-0.75	-0.96 to -0.55	<0.001	-0.27	-0.47 to -0.08	0.006
Emotions	-0.75	-1.00 to -0.50	<0.001	-0.28	-0.49 to -0.08	0.007
Food or drinks	-0.29	-0.57 to -0.02	0.037	-0.14	-0.36 to 0.08	0.201
Detergent	-0.68	-0.97 to -0.38	<0.001	0.05	-0.20 to 0.31	0.670
Wool clothing	-0.31	-0.73 to 0.11	0.153	0.22	-0.10 to 0.55	0.181
b. RAND score						
	Univariable analysis			Multivariable analysis		
	β	95% CI	P-value	$a\beta^{\dagger}$	95% CI	P-value
Allergic triggers						
Dust	-2.07	-2.89 to -1.26	<0.001	-0.65	-1.55 to 0.26	0.162
Pollen	-1.24	-2.08 to -0.40	0.004	0.27	-0.71 to 1.25	0.594
Pets	-0.92	-1.79 to -0.05	0.039	0.20	-0.74 to 1.14	0.676
Non-allergic triggers						
Physical exercise	-1.46	-2.28 to -0.63	0.001	0.46	-0.41 to 1.34	0.299
The weather	-1.88	-2.67 to -1.09	<0.001	-0.17	-1.06 to 0.73	0.717
Cold or the flu	-2.21	-2.99 to -1.42	<0.001	-0.55	-1.41 to 0.31	0.212
(Cigarette) smoke	-1.79	-2.78 to -0.79	<0.001	0.00	-1.08 to 1.08	0.998
Emotions	-2.75	-3.94 to -1.56	<0.001	-1.49	-2.64 to -0.35	0.011
Food or drinks	-2.24	-3.51 to -0.96	0.001	-1.86	-3.09 to -0.63	0.003
Detergent	-2.10	-3.49 to -0.72	0.003	-0.06	-1.47 to 1.35	0.930
Wool clothing	-1.02	-2.99 to 0.96	0.312	0.85	-0.98 to 2.67	0.362

A negative β -value indicates a negative impact on HRQL-scores (i.e. poorer HRQL).

[†] Adjusted for age, gender, living environment, asthma control, allergic rhinitis, food allergy, atopic dermatitis and recurrent respiratory tract infections.

Abbreviations: (a) β , (adjusted) unstandardized regression coefficient; CI, confidence interval; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; RAND, RAND general-health rating index.

Discussion

Our cross-sectional study demonstrated that amongst a broad population of children with asthma, a higher number of perceived allergic and non-allergic asthma triggers was strongly associated with reduced asthma-specific as well as generic health-related quality of life (HRQL). The majority of children (79%) reported one or more perceived trigger(s) of asthma. Non-allergic asthma triggers were independently associated with reduced HRQL: physical exercise, the weather,

(cigarette) smoke and emotions with asthma-specific HRQL, and emotions and food/drinks with generic HRQL.

Our study is the first to indicate that not only asthma-specific HRQL was reduced in children with a higher number of asthma triggers but also generic HRQL was reduced. Previous research showed an association between a higher number of perceived triggers of asthma and reduced asthma-specific HRQL in children and adolescents with severe or difficult-to-treat asthma^{8,9}, and in children participating in an asthma education program with symptom perception interventions.²³ We were able to confirm these findings in children and adolescents with asthma of varying severity in secondary or tertiary care. The impact of asthma triggers on HRQL may be explained by the fact that asthma triggers are associated with greater severity and frequency of asthma exacerbations, emergency treatments, health care visits and hospitalization.^{12,24} In addition, a higher number of asthma triggers may result in an increased perceived burden of asthma. Furthermore, children with a higher number of asthma triggers may try to avoid asthma triggers which may have an additional negative impact on asthma-specific and generic HRQL.

Our study suggests that especially non-allergic triggers were independently associated with HRQL. It can be hypothesized that triggers that are difficult to control, i.e. the weather, (cigarette) smoke and emotions, exert a greater influence on HRQL than triggers that are more easily controlled or treated. Allergic triggers, i.e. pets, dust or pollen, might exert less influence on HRQL because adequate treatment is available to reduce the symptoms caused by these triggers. However, we might not have detected an association between allergic triggers and HRQL as data on allergen sensitization were not available. Interestingly, the asthma trigger emotions was consistently associated with both asthma-specific and generic HRQL in our study population. Strong emotions such as fear, excitement, stress, anger or laughter may cause asthma symptoms due to an abnormal breathing pattern. Furthermore, the asthma trigger emotions might indicate the presence of psychiatric comorbidities, e.g. depression and anxiety. Psychiatric comorbidities are known to be more prevalent among patients with asthma and are associated with worse asthma control, increased asthma exacerbations and emergency visits.⁷

Our results highlight the importance of trigger identification in children with asthma. Physicians should pay attention to the identification of asthma triggers and, in turn, instruct children and parents regarding avoidance strategies or treatment of the identified triggers. For instance, the impact of the trigger physical exercise on HRQL might be reduced when children are advised to use a short-acting β_2 -agonist before exercising⁷ and the impact of the trigger emotions might be reduced when children seek psychological support to reduce emotional stress. Although allergic triggers were not independently associated with HRQL in our

analysis, we showed that a higher cumulative number of allergic and non-allergic asthma triggers was associated with reduced asthma-specific and generic HRQL. Therefore, specific instructions directed at children with allergic triggers might be beneficial as well. For instance, the impact of the trigger dust on HRQL might be reduced when instructions are given on house cleaning and the impact of the trigger pollen might be reduced when adequate (pharmacological) treatment is initiated.

The major limitation of the present study is that the asthma diagnosis and asthma triggers were self-reported by parents. Furthermore, data on allergen sensitization were not available. However, patient-reported data do provide meaningful insight into the perception of allergic and non-allergic asthma triggers and HRQL among parents and children. Additionally, asthma-specific and generic HRQL cannot be directly compared as asthma-specific HRQL was assessed in children and generic HRQL in parents. Previous research reported a lack of agreement between children's self-reported and parent proxy-reported HRQL and suggested to include both perspectives in HRQL research as both are complementary to each other.^{25,26} In addition, we were not able to assess asthma severity as we did not collect data on the frequency of asthma exacerbations, emergency department visits and hospitalizations. Finally, the cross-sectional design of this study limits the assessment of possible long-term effects. Strengths of this study are the large sample size, reliable data collection in routine secondary and tertiary care using validated questionnaires in children and parents and the assessment of both asthma-specific and generic HRQL.

In summary, we demonstrated that a higher number of perceived allergic and non-allergic triggers of asthma was strongly associated with reduced asthma-specific and generic health-related quality of life (HRQL) in children with asthma. Especially non-allergic asthma triggers were independently associated with reduced HRQL. Accurate identification and, in turn, avoidance and/or treatment of triggers in children with asthma may improve health-related quality of life.

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Supplemental tables

Supplemental Table 1. Collection of clinical data using the Electronic Portal

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Physician-diagnosed asthma	Has your child been diagnosed with asthma? a. Yes, by a general practitioner b. Yes, by a pediatrician c. Yes, by a pulmonologist d. No	Yes (a, b or c) or No (d)
Both parents Dutch	What ethnic group do you belong to? Mother/Father (<i>separate questions</i>) a. Dutch b. Turkish c. Moroccan d. Surinamese e. Antillean f. Other	Yes (both parents a) or No
Maternal education level	What is the highest level of education you have completed? a. Elementary school b. Lower general secondary education c. Intermediate vocational education d. Higher general secondary education e. Higher vocational education f. University	Low (a-b), Middle (c-d) or High (e-f)
Family history of asthma, allergic rhinitis, food allergy or atopic dermatitis	Do one or more family members suffer from asthma, allergic rhinitis, food allergy or atopic dermatitis? (<i>four separate questions</i>) a. No b. Yes, the father of the child c. Yes, the mother of the child d. Yes, brother(s) of the child e. Yes, sister(s) of the child	Yes (b and/or c) or No
Current living environment	Can you describe your living environment? a. A small town b. Rural c. A city center d. Urban	Rural (a-b) or Urban (c-d)

Supplemental Table 1. Collection of clinical data using the Electronic Portal (continued)

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Nocturnal wheezing/coughing in the past year	1. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? [†] <ol style="list-style-type: none"> Never woken by wheezing Less than one night per week One or more nights per week 2. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?	Yes* or No * Yes if question 1 is answered b or c and/or question 2 answered 'yes'
Inhaled short-acting β 2-agonists in the past week	In the past week, how often has your child inhaled a short-acting bronchodilator (e.g. Ventolin, Salbutamol, Bricanyl) on most days? <ol style="list-style-type: none"> Never 1-2 inhalations on most days 3-4 inhalations on most days 5-8 inhalations on most days 9-12 inhalations on most days 13-16 inhalations on most days ≥ 16 inhalations on most days 	Yes (b-g) or No (a)
Daily inhaled corticosteroids	Has your child used daily inhaled corticosteroids (e.g. Pulmicort, Flixotide, Seretide, Qvar)? <ol style="list-style-type: none"> Yes No 	Yes (a) or No (b)
Allergic rhinitis	1. In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when s/he did not have a cold or the flu? [‡] 2. <i>If question 1 is answered "yes":</i> "In the past 12 months, has this nose problem been accompanied by itchy–watery eyes?" [‡]	Yes (both answered 'yes') or No

Supplemental Table 1. Collection of clinical data using the Electronic Portal (continued)

Variable	Question in the Electronic Portal	Variable categories (answer option questions in Electronic Portal)
Food allergy	1. Has your child ever had a food allergy? 2. Within what time period after food ingestion did your child develop symptoms? 3. What symptoms did your child experience after food ingestion?	Yes* or No * Yes if question 1 is answered 'yes', and symptoms occurred within two hours after ingestion of the food (question 2) and food allergic symptoms were relevant (question 3): urticaria, oral allergy, angioedema, upper or lower respiratory complaints, vomiting, loss of consciousness or anaphylaxis.
Atopic dermatitis	1. Has your child ever had an itchy rash which was coming and going for at least 6 months? [†] 2. Has your child had this itchy rash at any time in the past 12 months? [†]	Yes (both answered 'yes') or No
Recurrent respiratory tract infections in the past year	1. In the past 12 months, how often has your child had complaints of a middle ear infection? 2. In the past 12 months, how often has your child had complaints of croup? 3. In the past 12 months, how often has your child had complaints of a cold or laryngitis? 4. In the past 12 months, how often has your child had complaints of a severe bronchitis or pneumonia (= coughing, dyspnea and fever)?	Yes* or No * Yes if question 1 through 3 is answered ≥ 6 (age 5 to 10 years) or ≥ 4 (age 10 years or older) and/or question 4 is answered ≥ 2 (all ages).

The questions were translated from Dutch into English.

[†]ISAAC core questionnaires for wheezing

[†]ISAAC core questionnaires for allergic rhinitis

[†]ISAAC core questionnaires for atopic dermatitis

Supplemental Table 2. Differences between complete and incomplete cases

	Complete cases	Incomplete cases		P-value
			n available	
n (%)	527 (69)	237 (31)		
Age in years, mean (SD)	12.1 (2.9)	10.7 (2.7)	237	<0.001
Male sex	304 (58)	138 (58)	237	0.937
Current living environment			171	0.929
Rural	318 (60)	104 (61)		
Urban	209 (40)	67 (39)		
Any asthma trigger	417 (79)	169 (76)	223	0.334
Uncontrolled asthma	200 (38)	63 (31)	203	0.086
Allergic rhinitis,	296 (56)	121 (51)	237	0.209
Food allergy	153 (29)	64 (27)	237	0.603
Atopic dermatitis	215 (41)	107 (45)	237	0.268
Recurrent respiratory tract infections in the past year	250 (47)	93 (39)	237	0.041
PAQLQ, median (IQR)	6.1 (5.4-6.7)	6.3 (4.2-6.7)	45	0.991
RAND, mean (SD)	21.1 (4.7)	20.8 (4.7)	237	0.499

Values are numbers (%), unless otherwise indicated.

Abbreviations: IQR, interquartile range; n, number; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; RAND, RAND general-health rating index; SD, standard deviation.

Supplemental Table 3. Differences in asthma-specific (a) and generic (b) quality of life among children within different categories of asthma triggers

A. PAQLQ score				
	Overall MD (95% CI)	SMD (95% CI)	Symptoms MD (95% CI)	SMD (95% CI)
0 versus 3-4 triggers	0.66 (0.57 to 0.76)	0.74 (0.63 to 0.85)	0.86 (0.75 to 0.97)	0.82 (0.71 to 0.93)
0 versus ≥5 triggers	1.02 (0.93 to 1.10)	1.10 (1.00 to 1.21)	1.26 (1.16 to 1.36)	1.20 (1.09 to 1.31)
1-2 versus ≥5 triggers	0.63 (0.54 to 0.73)	0.65 (0.55 to 0.75)	0.71 (0.60 to 0.83)	0.62 (0.52 to 0.72)
0 versus 1-2 triggers	0.38 (0.29 to 0.47)	0.47 (0.36 to 0.59)	0.55 (0.44 to 0.65)	0.59 (0.47 to 0.70)
1-2 versus 3-4 triggers	0.28 (0.18 to 0.38)	0.29 (0.18 to 0.40)	0.31 (0.19 to 0.44)	0.27 (0.16 to 0.38)
3-4 versus ≥5 triggers	0.35 (0.25 to 0.45)	0.35 (0.25 to 0.44)	0.40 (0.28 to 0.52)	0.33 (0.23 to 0.42)
	Activities MD (95% CI)	SMD (95% CI)	Emotions MD (95% CI)	SMD (95% CI)
0 versus 3-4 triggers	0.77 (0.65 to 0.88)	0.70 (0.59 to 0.82)	0.35 (0.26 to 0.44)	0.43 (0.32 to 0.54)
0 versus ≥5 triggers	1.24 (1.13 to 1.35)	1.07 (0.96 to 1.18)	0.57 (0.48 to 0.65)	0.62 (0.52 to 0.73)
1-2 versus ≥5 triggers	0.89 (0.78 to 1.01)	0.76 (0.65 to 0.86)	0.37 (0.28 to 0.46)	0.40 (0.30 to 0.50)
0 versus 1-2 triggers	0.35 (0.23 to 0.47)	0.34 (0.23 to 0.45)	0.20 (0.11 to 0.28)	0.26 (0.15 to 0.38)
1-2 versus 3-4 triggers	0.42 (0.30 to 0.54)	0.37 (0.26 to 0.48)	0.15 (0.06 to 0.24)	0.18 (0.07 to 0.29)
3-4 versus ≥5 triggers	0.48 (0.36 to 0.59)	0.39 (0.30 to 0.49)	0.22 (0.13 to 0.31)	0.23 (0.13 to 0.32)
B. RAND score				
	MD (95% CI)	SMD (95% CI)		
0 versus 3-4 triggers	2.12 (1.60 to 2.63)	0.45 (0.34 to 0.56)		
0 versus ≥5 triggers	3.16 (2.67 to 3.65)	0.68 (0.57 to 0.78)		
1-2 versus ≥5 triggers	2.69 (2.26 to 3.13)	0.62 (0.27 to 0.72)		
0 versus 1-2 triggers	0.47 (-0.06 to 0.99)	0.10 (-0.01 to 0.21)		
1-2 versus 3-4 triggers	1.65 (1.18 to 2.12)	0.38 (0.27 to 0.49)		
3-4 versus ≥5 triggers	1.04 (0.61 to 1.48)	0.23 (0.14 to 0.33)		

A mean difference (MD) in bold font exceeds the minimal clinically important difference.

Abbreviations: CI, confidence interval; MD, mean difference; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; RAND, RAND general-health rating index; SMD, standardized mean difference.

Supplemental Table 4. Linear regression analysis for asthma-specific quality of life per domain

	Symptoms			Activities		
	$a\beta^{\dagger}$	95% CI	<i>P</i> -value	$a\beta^{\dagger}$	95% CI	<i>P</i> -value
Allergic triggers						
Dust	-0.13	-0.33 to 0.06	0.182	0.00	-0.20 to 0.20	0.991
Pollen	0.15	-0.06 to 0.36	0.173	0.20	-0.02 to 0.42	0.069
Pets	0.01	-0.20 to 0.21	0.950	-0.23	-0.44 to -0.02	0.030
Non-allergic triggers						
Physical exercise	-0.21	-0.40 to -0.02	0.027	-0.21	-0.40 to -0.01	0.038
The weather	-0.17	-0.37 to 0.02	0.078	-0.25	-0.45 to -0.05	0.015
Cold or the flu	-0.09	-0.27 to 0.10	0.349	0.01	-0.18 to 0.21	0.887
(Cigarette) smoke	-0.34	-0.58 to -0.11	0.004	-0.30	-0.54 to -0.06	0.016
Emotions	-0.21	-0.45 to 0.04	0.102	-0.23	-0.49 to 0.02	0.076
Food or drinks	-0.13	-0.39 to 0.13	0.335	-0.22	-0.50 to 0.05	0.111
Detergent	0.04	-0.27 to 0.34	0.805	-0.14	-0.45 to 0.18	0.398
Wool clothing	0.29	-0.10 to 0.68	0.150	0.25	-0.15 to 0.66	0.222
Emotions						
	$a\beta^{\dagger}$	95% CI	<i>P</i> -value			
Allergic triggers						
Dust	-0.08	-0.25 to 0.09	0.335			
Pollen	0.12	-0.06 to 0.30	0.200			
Pets	0.06	-0.11 to 0.24	0.485			
Non-allergic triggers						
Physical exercise	-0.06	-0.23 to 0.10	0.451			
The weather	-0.12	-0.28 to 0.05	0.171			
Cold or the flu	0.09	-0.07 to 0.25	0.279			
(Cigarette) smoke	-0.17	-0.37 to 0.04	0.106			
Emotions	-0.41	-0.63 to -0.20	0.000			
Food or drinks	-0.11	-0.34 to 0.12	0.344			
Detergent	0.19	-0.07 to 0.46	0.147			
Wool clothing	0.12	-0.22 to 0.46	0.483			

A negative β -value indicates a negative impact on HRQL-scores (i.e. poorer HRQL).

[†] Adjusted for age, gender, living environment, asthma control, food allergy, allergic rhinitis, atopic dermatitis and recurrent respiratory tract infections.

Abbreviations: $a\beta$, adjusted unstandardized regression coefficient of the asthma trigger in the linear regression model; CI, confidence interval; PAQLQ, Pediatric Asthma Quality of Life Questionnaire

Chapter 9

General discussion and summary

Main findings

The aim of this thesis was to improve the diagnostics and quality of life in patients with atopic diseases, particularly in patients with peanut allergy and asthma.

Part I. The diagnostics of atopic diseases

- The previously published cutoff level of specific IgE (sIgE) to peanut component Ara h 2 is validated in secondary and tertiary care (**chapter 2**).
- A diagnostic flowchart based on sIgE to Ara h 2 is accurate, safe and reduces costs in children with suspected peanut allergy in secondary and tertiary care (**chapter 2**).
- Sensitization to Ara h 2 and Ara h 6 predicts peanut allergy correctly in one third of adults with suspected peanut allergy in tertiary care (**chapter 3**).
- Despite confirmed peanut-allergy diagnosis by a double-blind placebo-controlled food challenge (DBPCFC) and careful instruction and guidance, almost half of children have peanut-allergic reactions during the 3 year follow-up after the DBPCFC. One third of children fail to introduce peanut after a negative DBPCFC result (**chapter 4**).
- Risk factors for atopic diseases are distinct from risk factors for recurrent respiratory tract infections, suggesting that the changing prevalence of both entities is not related to shared risk factors (**chapter 5**).

Part II. The impact of atopic diseases on patients' welfare

- A clear food allergy diagnosis is associated with reduced parental anxiety, improved health-related quality of life (HRQL) and reduced parental burden of food allergy (**chapter 2, 4 and 6**).
- During 3-year follow-up after a negative DBPCFC for peanut, HRQL improved in children who consumed peanut and not in children who failed to consume peanut (**chapter 4**).
- In secondary care, uncontrolled asthma is highly prevalent in children referred for asthma and in children referred for other atopic diseases than asthma (**chapter 7**).
- A higher number of perceived asthma triggers is associated with reduced HRQL in children with asthma (**chapter 8**).

The diagnostics of atopic diseases

In the first part of this thesis we focused on improving diagnostics in patients with atopic diseases, particularly in patients with suspected peanut allergy. We validated cutoff levels of specific IgE (sIgE) to Ara h 2 and implemented a diagnostic flowchart based on these cutoff levels in children in secondary and tertiary care. Furthermore, we evaluated the diagnostic value of peanut components and validated the Ara h 2 cutoff level in adults in tertiary care. Thirdly, we investigated risk factors for atopic diseases and for recurrent respiratory tract infections.

Peanut allergy diagnostics

Peanut allergy is one of the most common food allergies in childhood, affecting almost 25% of food allergic children.¹ Peanut allergy represents one of the most common elicitors of anaphylaxis², and is outgrown in less than 20% of children.³ The significant personal and societal burden of peanut allergies could be reduced to some extent by preventing overdiagnosis.⁴⁻⁶ Previous data showed that the prevalence of self-reported peanut allergy is considerably higher than the prevalence of challenge-proven peanut allergy, with an estimated point prevalence of respectively 1.67% and 0.22%.⁷

In current guidelines and in a recent review summarizing diagnostic modalities for peanut allergy, it is stated that an oral food challenge is still the reference standard for diagnosing peanut allergy.⁸⁻¹⁰ Furthermore, the implementation of component-resolved diagnostics (CRD), including sIgE to peanut component Ara h 2, is thus far not recommended as validation in daily practice has not yet been studied. In addition, most studies investigating the diagnostic performance of CRD were performed in tertiary care and the question was whether results of these studies were generalizable to other lines of care.

Accurate and safe peanut allergy diagnostics in children

With the results of this thesis, we demonstrated that cutoff levels of Ara h 2 with 100% positive and negative predictive value, as observed in previous research in our tertiary care center, are ready for implementation in daily practice in secondary and tertiary care (**chapter 2**). We showed that the diagnostic flowchart accurately confirmed (89% to 97%) and excluded (100%) peanut allergy in children aged 3.5 to 18 years with suspected peanut allergy. The diagnostic flowchart, based on Ara h 2 cutoff levels as observed in previous research conducted mainly in our tertiary care center, was accurate in both secondary and tertiary care.¹¹ These findings suggest that Ara h 2 cutoff levels as observed in tertiary care can also be used to accurately predict peanut allergy in secondary care.¹² The oral food challenge results in tertiary care were compared to the results in secondary care in a large validation

study in children in New Zealand and no differences were observed regarding patient demographics, severity and the rate of inconclusive challenges.

In line with these results, we observed no differences between children in secondary care and tertiary care in our cohort regarding age, gender, reason for suspected peanut allergy, severity of the previous reaction and severity of symptoms during the oral food challenge. These data support the generalizability of (peanut) allergy diagnostics from tertiary to secondary care.

In our implementation study as described in **chapter 2**, all children with sIgE to Ara h 2 ≤ 0.1 kU_A/L were peanut-tolerant (i.e. 100% negative predictive value). During peanut introduction, none of these children experienced any allergic symptoms. These findings endorse the safety of the diagnostic flowchart and stimulate introduction of peanut at home in children with an Ara h 2 level ≤ 0.1 kU_A/L. However, only in one third of children with an Ara h 2 level ≤ 0.1 kU_A/L the physician and/or parents initiated home introduction. The remaining two third of children introduced peanut in the hospital, mainly because the child or parent was anxious or because the physician regarded the clinical history as suggestive for peanut allergy. It must be noted that a suggestive clinical history was not associated with peanut allergy in children with an Ara h 2 level ≤ 0.1 kU_A/L. Five children reported a severe allergic reaction in clinical history, but were all tested negative (i.e. peanut-tolerant). We strongly hope that our results provide confidence to physicians to stimulate home introduction in children with an Ara h 2 level ≤ 0.1 kU_A/L. In previous research, rare cases of peanut allergy have been described in children who were not sensitized to Ara h 2.¹³⁻¹⁷ Thus, there is a small probability of peanut allergy in children with no detectable sensitization to Ara h 2, which may be explained by sensitization to other peanut components (e.g. Ara h 6 or Ara h 7) or sensitization to unidentified allergens. In this regard, careful guided introduction at home using a schedule with increasing amounts of peanut is recommended in children with negative Ara h 2 levels. As anxiety was the main reason to decline home introduction, clinicians are encouraged to identify patients with excessive anxiety and subsequently, assess the impact via anxiety and HRQL questionnaires. In children or parents with excessive anxiety who decline home introduction of peanut, a short introduction schedule of peanut at the outpatient clinic may be a good alternative. In case of persisting anxiety, psychological support should be offered.

Children with an Ara h 2 level ≥ 5.0 kU_A/L were highly likely to be peanut-allergic: the positive predictive value (PPV) ranged between 89% and 97%. Previous diagnostic studies among Dutch children report a 100% PPV for Ara h 2 ≥ 5.0 kU_A/L in tertiary care and ≥ 5.61 kU_A/L in secondary care.^{11,18} Although the PPV was not 100%, the implementation of the diagnostic flowchart did not lead to overdiagnosis of peanut allergy as all children were offered a 1-day open oral food challenge.

According to the European food allergy guideline, the design of the OFC, either open or double-blind, depends on the indication and purpose for which the food challenge is being performed.⁹ As children with an Ara h 2 level ≥ 5.0 kU_A/L have a very high probability of being peanut-allergic, the purpose of the OFC is to gain insight into the severity of peanut allergy and the threshold of the peanut-allergic reaction. Open OFCs were feasible in our cohort, as inconclusive challenges were infrequent (8%) and these inconclusive challenges were due to incomplete ingestion of the challenge material. Incomplete ingestion is equally likely, or even more likely to occur, when challenged double-blind.

It must be noted that the measures of diagnostic accuracy, including positive and negative predictive values, are dependent on the population (e.g. disease prevalence, age, setting and country).

sIgE to Ara h 2 predicts peanut allergy correctly in one third of adults

In adults with suspected peanut allergy, sensitization to peanut component Ara h 2 predicts peanut allergy correctly in one third of patients (**chapter 3**). All patients with levels of Ara h 2 ≥ 1.75 kU_A/L were peanut-allergic. These results validate the cutoff level of Ara h 2 assessed in a previous diagnostic study performed in our center.¹⁹ In addition, we were the first to determine an Ara h 6 cutoff level with a 100% PPV to confirm peanut allergy in adults (i.e. ≥ 1.80 kU_A/L). sIgE to Ara h 2 and Ara h 6 were the best individual predictors of peanut allergy in adults in our cohort. As the concentrations of sIgE to Ara h 2 and Ara h 6 were highly correlated, and Ara h 2 was validated, we developed a diagnostic flowchart for adults with suspected peanut allergy based on sIgE to Ara h 2 (Figure 1). Again, it must be noted that the measures of diagnostic accuracy as depicted in the diagnostic flowchart are dependent on the population and further studies are needed to evaluate whether the flowchart is generalizable to other countries or other settings.

In comparison to children, the same percentage of peanut-allergic patients can be identified using a cutoff level of Ara h 2 with 100% positive predictive value (PPV). However, the cutoff level to confirm peanut allergy is lower in adults (i.e. Ara h 2 ≥ 1.75 kU_A/L) compared to children (i.e. Ara h 2 ≥ 5.0 kU_A/L).¹¹ Furthermore, although sensitization to peanut components can be used to exclude peanut allergy in children, it cannot be used to exclude peanut allergy in adults. These differences between peanut allergy diagnostics in children and adults may be partly explained by the higher proportion of peanut allergy with subjective symptoms only in adults, due to birch pollen-related peanut allergy.^{19–21} Peanut allergy based on subjective symptoms only was observed in 12.5% of children (chapter 2) and 27% of adults (chapter 3). Previous research showed that sensitization to peanut storage proteins (including Ara h 1, 2 and 3) decreases with age, while sensitization to Ara h 8 and birch pollen increases.^{22,23} In our study, adults with peanut allergy based on

subjective symptoms only had lower titers of sIgE to Ara h 2 and Ara h 6, resulting in a lower diagnostic value of these components. Furthermore, we did not detect sensitization to Ara h 1, 2, 3 and 6 in 16 (17%) peanut-allergic adults included in our study. Thus, in part of the adult population, peanut allergy might be caused by sensitization to thus far unidentified peanut components. Additional insight into the reason for the difference in diagnostic performance of peanut components between children and adults may arise from evaluation of the sIgE levels over time from childhood to adulthood.

Figure 1. Diagnostic flowchart for children and adults with suspected peanut allergy

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; OFC, oral food challenge; sIgE, specific IgE.

The costs of food allergy

Food allergy is also a financial burden to patients and families, the health care system and society. Direct medical costs borne by the health care system include the costs for the diagnosis and treatment of food allergy. The total annual direct medical costs of food allergy were estimated to be mean \$2,081 per child in a recent meta-analysis.²⁴ The direct costs of food allergy are comparable to the costs of asthma²⁵ and atopic dermatitis²⁶, but higher than the costs of allergic rhinitis (\$233 to \$657 per patient).^{27,28} The indirect costs of food allergy include costs due to productivity losses and have been estimated at mean \$1,038 per patient.²⁴ These costs are comparable to the costs of atopic dermatitis²⁶, but are higher than the costs of asthma (\$207 per patient)²⁹ and allergic rhinitis (\$833 per patient).²⁷ Finally, the individual out-of-pocket costs of food allergy were estimated to be mean \$1,874 per patient.²⁴ The out-of-pocket costs of food allergy are again comparable to atopic dermatitis³⁰, but higher than the costs of asthma (\$154 per patient)³¹ and allergic rhinitis (\$50 per patient).³² However, comparing the costs between disease

entities should be done with care. The estimated costs are affected by a number of factors, including differences in healthcare and insurance system, country and year of study.

A diagnostic flowchart reduces costs of peanut allergy diagnostics

We aimed to reduce the costs of food allergy by improving peanut allergy diagnostics and reducing the number of oral food challenge days. According to the current Dutch national guideline, children with sensitization to peanut (i.e. sIgE to peanut extract ≥ 0.35 kU_A/L or skin prick test ≥ 3 mm) are supposed to undergo a double-blind placebo-controlled food challenge (DBPCFC). According to our diagnostic flowchart, no oral food challenges are needed for children with an Ara h 2 level ≤ 0.1 kU_A/L as these children have a very high probability of being peanut-tolerant. Furthermore, children with an Ara h 2 level ≥ 5.0 kU_A/L have a very high probability of being peanut-allergic and thus, the oral food challenge can be performed in one day as previously explained. Compared to the current national guideline, the diagnostic flowchart could lead to a reduction in oral food challenge days up to 60%.

In **chapter 2**, we demonstrated that the annual direct and indirect costs of peanut allergy diagnostics in children according to the diagnostic flowchart were €320 to €636 lower per child compared to the costs when following the current national guideline. With an estimated 2400 referred children per year in the Netherlands, nationwide implementation of the diagnostic flowchart could lead to a cost reduction of €767,101 to €1,526,688 per year.^{7,33,34} A previous cost-effectiveness analysis in Norway supports our findings and showed that costs of a diagnostic flowchart based on multiple peanut components, including Ara h 2, were lower compared to current clinical practice based on sIgE to peanut extract and oral food challenges.³⁵ Moreover, the implementation of a diagnostic flowchart based on sIgE to Ara h 2 in adults could even further reduce the costs of peanut allergy diagnostics. According to our diagnostic flowchart, approximately 30% of adults can be challenged in one day instead of two days. With an estimated 1800 referrals of adults with suspected peanut allergy per year in the Netherlands, nationwide implementation of the diagnostic flowchart in adults could prevent at least 540 food challenge days for peanut allergy diagnostics.^{7,33,34}

Frequent accidental reactions occur after positive peanut allergy diagnostics

In **chapter 4**, we performed a three-year follow-up of 83 children who had a confirmed or excluded peanut allergy after a DBPCFC.¹¹ The longitudinal study design enables insight into potential changes over time and long-term impact of diagnostic interventions.³⁶ We noted that almost half of peanut-allergic children experienced one or more allergic reaction(s) to peanut during the three years after their peanut DBPCFC, although all these children were advised and instructed to

avoid peanut. Other studies have shown that accidental allergic reactions to peanuts in patients on an avoidance diet are common.³⁷ Accidental allergic reactions may be caused by the consumption of products with hidden sources of peanut, by incomplete or incorrect labelling, by misreading of the labels or because of risky behavior.^{38,39} Accidental allergic reactions may be prevented by improved food allergen labelling and, when applicable, by addressing risk-taking behavior. Furthermore, children with severe allergic reactions did not use their epinephrine auto-injector despite instructions on how and when to use the auto-injector. Previous research showed underutilization of epinephrine auto-injectors by food-allergic patients.^{40,41} One of the most common reasons for not using the auto-injector is failure to recognize symptoms of anaphylaxis.⁴² Delayed administration of epinephrine in patients with anaphylaxis is associated with an increased risk of hospitalization and fatality.⁴³ The adequate use of epinephrine auto-injectors in patients with anaphylaxis may be improved by repeated practical demonstrations and training and education of both patients and health care professionals.^{44,45}

Frequent introduction failure after negative peanut allergy diagnostics

One third of peanut-tolerant children failed to introduce peanut into the diet during three years after a negative peanut DBPCFC, although all families were counseled after the DBPCFC regarding the importance and practical details of introduction (**chapter 4**). In previous studies, continued food avoidance despite negative food challenge results were reported in 25% to 38% of children.^{46–49} Children failed to consume peanut mainly because of aversion. Aversion may be partly explained by the fact that these children are not used to the taste and texture of peanuts or because the taste of peanuts has previously been paired with (severe) allergic symptoms. However, consumption of peanut may be beneficial for patients and parents as we observed an improved parent-proxy reported health-related quality of life in peanut-tolerant children after successful peanut introduction. Health-related quality of life of peanut-tolerant children who failed to introduce peanut remained unchanged. Further research should investigate how to improve the rate of peanut introduction. As an example, behavioral interventions designed for children with pediatric feeding disorders might be indicated in peanut-tolerant children with aversion to peanut.⁵⁰

Future aspects of peanut allergy diagnostics

A diagnostic flowchart based on peanut component Ara h 2 is an accurate and safe diagnostic tool in secondary and tertiary care in the Netherlands. We recommend implementation of the diagnostic flowchart in the current national guideline, both for children and adults with a suspected peanut allergy. As previously mentioned, the cutoff levels of peanut components are not fixed, but dependent on the population. International validation studies are needed to implement the (if applicable: adapted) diagnostic flowchart worldwide.

This thesis demonstrates that more than half of children and one third of adults can be classified correctly using sensitization to peanut component Ara h 2. To further increase the proportion of correctly classified patients, future studies should evaluate diagnostic tools for children and adults with 'inconclusive' levels of Ara h 2 (Ara h 2 levels between 0.1 and 5.0 kU_A/L and < 1.75 kU_A/L, respectively) and for peanut-allergic adults not showing sensitization to peanut components. A previous study demonstrated that half of children with Ara h 2 levels between 0.1 and 5.0 kU_A/L could be classified correctly when using the Basophil Activation Test (BAT) as a second step in the diagnostic process.¹¹ As the BAT is not yet used in daily practice due to practical, technical and analytical limitations⁵¹, future studies should focus on standardization, validation and automation of this procedure. Furthermore, the diagnostic value of the Mast cell Activation Test (MAT) has been evaluated.⁵² The MAT might be superior to other existing diagnostic test modalities, including sIgE to Ara h 2 and the BAT, but further research is needed to validate these findings and facilitate implementation in daily practices. In addition, patterns of IgE binding to specific regions of an allergen (i.e. allergenic epitopes) in microarray immunoassays may become a future diagnostic tool. Peanut-allergic patients showed more IgE epitope binding and broader epitope diversity compared with peanut-tolerant patients in previous studies.^{53,54} In addition, the analysis of patient-derived monoclonal antibodies may provide diagnostic insight after further development. This approach could provide information on epitope affinity and specificity.⁵⁵ Finally, understanding potentially allergy-promoting lipids may improve serum-based allergy diagnostics. Lipids may enhance the allergenicity of proteins in several ways, e.g. by enhancing an IgE dominant response or by influencing the ability of allergens to penetrate through the oral, respiratory or gastrointestinal mucosa cells.^{56,57}

It must be noted that current diagnostic IgE test modalities fail to predict the threshold of an allergic reaction and the severity of peanut allergy of individual patients. The mechanisms driving the severity of food allergic reactions remain poorly understood.^{58,59} Future research, including immunologic, genetic and epigenetic analyses, may enhance our understanding of the reaction threshold and reaction severity and identify biomarkers for severe allergic reactions. As an example, recent research observed a correlation between an expansion of peanut-specific effector T-cells and high clinical reactivity (i.e. allergic reaction at a dose less than or equal to 300 mg peanut protein) in peanut-allergic patients.⁶⁰ Another recent study identified several genes and DNA methylation sites associated with reaction severity in peanut-allergic children.⁶¹

When considering different diagnostic strategies for peanut allergy, it is vital to take into account the wishes of parents and/or patients and make shared decisions. Patients may still prefer oral food challenges to laboratory testing, as they may wish

to consume peanut in a safe environment and experience whether, when and what symptoms occur after peanut ingestion. In patients with high and conclusive Ara h 2 levels (i.e. Ara h 2 ≥ 5.0 kU_A/L in children and ≥ 1.74 kU_A/L in adults), the oral food challenge protocol may be adapted to reduce the burden and costs of food challenges.

Moreover, the future of peanut allergy diagnostics is likely changed by emerging prospects for prevention and treatment of peanut allergy.

Prevention of peanut allergy

In 2015, the Learning Early About Peanut Allergy trial clearly showed that peanut introduction early in life significantly decreased the risk of peanut allergy among infants with high-risk atopic disease(s) (i.e. severe atopic dermatitis, egg allergy or both).⁶⁴ The trial received wide publicity and new peanut allergy prevention guidelines were developed.^{65–67} The paradigm shift in the timing of food allergen introduction has implications for future peanut allergy diagnostics. Early introduction of peanut may likely lower the prevalence of peanut allergy, but may also increase the frequency of diagnostic testing at a younger age. Previous data showed that sIgE to storage proteins, including Ara h 2, is present in children below the age of 4 years.^{17,68} However, as our diagnostic flowchart is based on sIgE to Ara h 2 cutoff levels in children aged 3.5 to 18 years, further research is necessary to confirm or adapt Ara h 2 cutoff levels in younger children.

Treatment of peanut allergy

Our long-term follow-up of peanut-allergic children showed that living with a peanut allergy remains a challenge during childhood. Previous studies have observed the same in adulthood.³⁸ The current management of peanut allergy includes (instructions on) an elimination diet, instructions on and prescription of emergency medication and advice for timely administration of emergency medication when an allergic reaction occurs.⁹ In recent years, oral or epicutaneous immunotherapy for the treatment of peanut allergy has been the subject of much research.^{69,70} In January 2020, the first oral immunotherapy product has been approved by the United States Food and Drug Administration.⁷¹ Immunotherapy relies on the delivery of gradually increased doses of the allergenic food to increase the threshold of an allergic reaction during treatment (i.e. desensitization) and after treatment (i.e. sustained unresponsiveness).^{72–74} Recent studies found that the primary motivation for undergoing oral immunotherapy was to reduce the risk of fatal allergic reactions.⁷⁵ Parents who perceived their child to be at high risk of fatal food allergic reactions were more likely to enroll in peanut immunotherapy compared with routine clinical care (i.e. peanut avoidance).⁷⁶ However, a recent systematic review and meta-analysis showed that current peanut oral immunotherapy regimens increased the risk of allergic reactions, including

anaphylaxis, compared with peanut avoidance.⁷⁷ Low-dose oral or epicutaneous immunotherapy may better align with families' goals. Overall, carefully outweighing the pros versus the cons of immunotherapy for food allergy is paramount in deciding the appropriate strategy per patient.³⁷ Further research is warranted to evaluate long-term results and patients' perspectives.

Risk factors for atopic diseases differ from risk factors for recurrent infections

In this thesis, the association between risk factors and atopic diseases and between risk factors and recurrent respiratory tract infections (RRTI) was investigated in a large cohort of children aged 1 to 18 years (**chapter 5**). The results demonstrate that the demographic and environmental risk factors associated with atopic diseases largely differ from the risk factors associated with RRTI. Interestingly, family history was a disease-specific risk factor for atopic diseases and RRTI.

A family history of atopic diseases and RRTI reflects genetic susceptibility, as well as shared environmental and behavioral factors.⁷⁸ Clustering of diseases in families is typically due to multifactorial inheritance, determined by a number of genes in interaction with environmental and lifestyle factors, and not due to single genetic mutations. Strong evidence for the importance of genetic factors in the susceptibility to atopic diseases comes from studies among genetically identical twins, indicating a concordance rate of approximately 81% for food allergy, 95% for asthma, 91% for allergic rhinitis and 84% for atopic dermatitis.⁷⁹ Furthermore, atopic diseases are to a large extent genetically related.⁸⁰ However, our and previous studies indicate that some genetic risk factors are disease-specific.⁸¹ The genetic correlations between atopic diseases have been estimated <1 , suggesting that there are unique genetic influences to each atopic disease.^{82,83} In addition, the association between family history and RRTI requires further investigation, as it has not been described before. Previous literature reported an association between family history and specific genetic diseases (e.g. primary immunodeficiencies, cystic fibrosis and primary ciliary dyskinesia).^{84–86} Given the rarity of these diseases, the association between a family history and RRTI as observed in our cohort is likely explained by a multifactorial, polygenic inheritance pattern.

A family history can be easily assessed and used for the prevention, detection and management of disease.⁸⁷ Therefore, the family history of atopic diseases and recurrent respiratory tract infections should be assessed by physicians in clinical practice to identify high-risk children.

The impact of atopic diseases on patients' welfare

The evaluation of the patient's perception of their health is an important aspect of patient-centered care. The patient's perception can be evaluated using patient-reported outcome measures (PROMs).⁸⁸ An example of frequently used PROMs are standardized and validated questionnaires on anxiety and health-related quality of life (HRQL) as administered in several studies described in this thesis.

Children with food allergy have poorer HRQL than children in the general population, due to multiple disease-specific impairments such as social and dietary restrictions, the need to carry an epinephrine auto-injector and the fear of accidental allergic reactions.^{89,90} Compared to other diseases, children with food allergy showed more impairment in HRQL than children with chronic liver disease or diabetes mellitus, but less impairment in HRQL than children with asthma.^{89,91} Especially children with uncontrolled asthma have impaired HRQL.^{92,93}

In the second part of this thesis, we focused on improving the welfare of patients with atopic diseases, particularly children with peanut allergy and asthma. We studied anxiety and quality of life after peanut allergy diagnostics. Furthermore, we investigated the prevalence and predictors of uncontrolled asthma and the impact of asthma triggers on HRQL.

Anxiety and quality of life improve after a clear diagnosis

We summarized recent literature on the association between HRQL and food allergy diagnostics in **chapter 6** and showed that oral food challenges are associated with improved HRQL and reduced parental burden, regardless of the food challenge result. The greatest improvement in HRQL was observed among children who demonstrated tolerance.

In **chapter 2**, we demonstrated a large reduction of parental anxiety after the telephonic consultation discussing an Ara h 2 level ≤ 0.1 kU_A/L (i.e. peanut-tolerant) and after oral food challenges, in the latter case even irrespective of the result. Although peanut allergy diagnosis is clear in children with an Ara h 2 level ≥ 5.0 kU_A/L (i.e. peanut-allergic), parental anxiety remained unchanged after the telephonic consultation. Uncertainty regarding the severity of peanut allergy and the threshold of an allergic reaction may be associated with anxiety, as reported in previous research.⁹⁴ Uncertainty and anxiety may be reduced after an oral food challenge, as this procedure provides insight into these matters. Our and other studies have shown a reduction in food allergy-related anxiety after an oral food challenge, regardless of the result.^{94,95} These findings suggest that a clear diagnosis of food allergy may have beneficial psychosocial impact. However, the main reason to decline a food challenge or (home) introduction after the determination of sIgE

to Area 2 was anxiety of the child and/or parents. Children or parents may experience anxiety or distress about the possibility of an allergic reaction during the procedure.⁹⁴ Although some increased level of anxiety in patients with food allergy is an appropriate response, excessive anxiety should be recognized and treated. Mental health professionals may treat excessive anxiety through consultation or psychotherapy, or provide support during oral food challenges, as recommended in a recent position statement of the American Academy of Allergy, Asthma & Immunology.⁹⁶ Further work to study anxiety in food allergic children and the impact of psychological interventions needs to be done, as most studies focused on parents^{94,95,97,98} or adults.⁹⁹ The benefit of psychological interventions has been reported in mothers of food allergic children. A brief cognitive behavioral therapy session was associated with significantly reduced anxiety after one year follow-up compared to no intervention, especially in mothers with high baseline anxiety levels.⁹⁸

Uncontrolled asthma is highly prevalent in children with asthma

In **chapter 7** it was demonstrated that uncontrolled asthma is highly prevalent in children referred for asthma (47%), but also in children referred for other atopic diseases than asthma (26%) to secondary care. We found a family history of asthma, recurrent upper or lower respiratory tract infections and a referral for asthma to be independently and significantly associated with uncontrolled asthma.

The current clinical guideline emphasizes that the main goal of asthma management is to attain and to keep good asthma symptom control.¹⁰⁰ From previous studies we know that uncontrolled asthma is associated with health-related quality of life (HRQL); the better asthma control, the better HRQL.^{101,102} Patients with well-controlled asthma had similar HRQL as participants without asthma in a Swedish population-based cohort study.¹⁰³ In addition to the patient burden, uncontrolled asthma poses a substantial and growing burden on healthcare systems. A recent study in the United States estimated that around 20% of direct costs of asthma can potentially be saved if all patients would achieve adequate asthma control.¹⁰⁴ In order to reduce the patient and economic burden of uncontrolled asthma, an accurate review of the asthma control status is essential.

Our study indicates that assessment of disease control is not only important for children who are referred for asthma, but also for children who are referred for other atopic diseases than asthma. As patients and physicians tend to overestimate the level of asthma control¹⁰⁵ and differ in their perception of asthma control¹⁰⁶, standardized tools to monitor asthma control such as the Asthma Control Test are recommended at visits to the outpatient clinic.^{107,108} These tools should be used regularly, as asthma is characterized by marked fluctuations in symptoms over time.

Asthma triggers are associated with reduced health-related quality of life

Asthma control is affected by various asthma triggers. For instance, strenuous physical exercise, bad weather, strong emotions or exposure to pollen or pets can trigger asthma symptoms.¹⁰⁹ As described in **chapter 8**, more than three quarters of children with asthma report one or more perceived trigger(s) of asthma symptoms. The evaluated asthma triggers are depicted in Figure 2. Previous research identified an association between a higher number of asthma triggers and reduced asthma-specific HRQL in children with severe or difficult-to-treat asthma and in adults with asthma.^{110–113} We were able to confirm this association between asthma triggers and HRQL, both asthma-specific and generic, in children with asthma of varying severity in secondary and tertiary care. Children with a high number of asthma triggers may experience impaired HRQL due to an increased frequency of asthma exacerbations and health care visits.^{112–114} Furthermore, children may try to avoid asthma triggers which may have additional negative impact on HRQL. The asthma trigger 'emotions' was consistently associated with both asthma-specific and generic HRQL in our population. Previous work found that almost one third of asthmatic patients reported emotional triggers as the most frequent trigger of asthma symptoms.¹¹³ Examples of emotional triggers are stress, worry, feelings of loneliness or excitement and being angry. Interventions to reduce emotional distress may lower the impact of these triggers on HRQL.

The results of our study highlight the importance of asthma triggers in children with asthma. Physicians should evaluate the number and impact of asthma triggers on asthma symptoms in children with asthma. Further research is needed to evaluate the impact of identification, and subsequent avoidance and/or treatment, of asthma triggers on patient HRQL.

Figure 2. Asthma triggers

Future aspects

'Health as the ability to adapt and to self-manage, in the face of social, physical and emotional challenges.'

Machteld Huber, 2011¹¹⁵

The traditional WHO definition of health formulated in 1948, as stated in the Introduction section of this thesis, has been debated ever since.^{116,117} Particularly the absoluteness of the words 'complete wellbeing' has been criticized. This formulation of health may contribute to the medicalization of society and is no longer considered adequate in an era with increasing numbers of people living with chronic diseases. A new concept of health was introduced by Machteld Huber and colleagues in 2011.¹¹⁵ The new, dynamic concept of health, as cited above, focuses on a person's resilience and ability to cope with new situations. The support for this new health concept was evaluated among various stakeholders, including patients and physicians.¹¹⁸ Physicians considered bodily functions and quality of life as the most important dimensions of health, where patients also considered societal, mental and spiritual dimensions as important dimensions.

The changing definition of the concept of health and the discrepancy between the perception of health by patients and by physicians requires attention. Future health-related quality of life (HRQL) research in patients with atopic diseases should attempt to validate questionnaires that measure various dimensions and aspects of health, including the burden of disease, coping, resilience, patients' satisfaction and disease-specific anxiety. In addition, psychosocial interventions to reduce anxiety and improve coping and resilience should be evaluated, as these actions may improve quality of life in patients with atopic diseases and their families.

Currently, HRQL is mainly assessed in research settings, while implementation in daily clinical practice is important to improve counseling and enable identification of high-risk children who could benefit from psychosocial interventions. Health-related quality of life should be assessed in both children and parents, as they differ in their view concerning HRQL. A previous study among food allergic children aged 8 to 12 years and their parents suggest that parents report better HRQL than children.¹¹⁹ To date, child-reported food allergy specific HRQL questionnaires are available for children aged 8 years and older. Instruments to assess HRQL in younger children are needed, especially now that prevention strategies and immunotherapy target this age group.⁷³ The assessment of patient-reported outcomes before and after immunotherapy is gaining increasing importance and is critical in the evaluation of the benefits and risks of immunotherapy.⁷⁷

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Chapter 10

Nederlandse samenvatting

Voedselallergie, astma, hooikoorts en eczeem komen vaak voor bij kinderen. Deze ziekten zijn gebaseerd op een niet zinvolle en zelfs schadelijke reactie van ons afweersysteem en worden atopische ziekten genoemd.

Het begrip 'atopie' is afgeleid van het Griekse woord *atopia* en betekent 'ongewoonheid'. Atopie wijst op de aanleg van een persoon om antistoffen (van het type IgE) te maken. Deze antistoffen zijn gericht tegen 'onschuldige' eiwitten uit de omgeving, zoals de eiwitten van voedsel (bijvoorbeeld pinda of noten), huisstofmijt, pollen of gras. Wanneer deze antistoffen worden aangemaakt kan dat leiden tot verschillende atopische ziekten, namelijk voedselallergie, astma, hooikoorts en eczeem. Kinderen hebben vaak meerdere atopische ziekten.

In dit proefschrift wordt onderzocht hoe we atopische ziekten beter kunnen vaststellen (diagnostiek). De focus ligt hierbij op pinda allergie. Daarnaast richten we ons op de kwaliteit van leven van kinderen met atopische ziekten.

Diagnostiek van atopische ziekten

In de zorg voor patiënten zijn drie hoekstenen te onderscheiden. Allereerst het vaststellen van de ziekte (diagnose), vervolgens het inschatten van het vermoedelijke beloop van de ziekte (prognose) en ten derde het voorstellen van een behandeling (therapie) voor de ziekte. Het vaststellen van ziekten vindt plaats door het in kaart brengen van de klachten, lichamelijk onderzoek en, indien nodig, aanvullend diagnostisch onderzoek. Aanvullend diagnostisch onderzoek van atopische ziekten is bijvoorbeeld de bepaling van specifieke antistoffen (sIgE) in het bloed of een huidpriktest, een voedselprovoCATietest of longfunctieonderzoek. Het stellen van de juiste diagnose is belangrijk om patiënten goed te adviseren en, voor zover mogelijk, te behandelen.

Pinda allergie

Pinda allergie is één van de meest voorkomende voedselallergieën bij kinderen. Een pinda allergie is meestal blijvend en kenmerkt zich vaak door ernstige klachten. Een patiënt met een pinda allergie ontwikkelt klachten binnen enkele minuten tot twee uur na het eten van (een product met) pinda. De klachten kunnen uiteenlopen van mild, waarbij u kunt denken aan een tinteling in de mond, rode huid, galbulten, jeuk, rode ogen of niezen, tot ernstig, wat zich uit in bijvoorbeeld zwelling van de tong en keel, benauwdheid of shock.

De huidige 'gouden standaard' om een pinda allergie aan te tonen is een 2-daagse voedselprovoCATie. Deze voedselprovoCATie vindt plaats in het ziekenhuis en bestaat uit het eten van een cakeje, waarin op één dag pinda is verwerkt (verum-

dag) en op de andere dag niet (placebo-dag). Een voedselprovocatie geeft duidelijkheid over de diagnose. Als er inderdaad sprake is van een voedselallergie dan kan de voedselprovocatie ook helpen om meer te weten te komen over hoeveel pinda een allergische reactie veroorzaakt en hoe ernstig deze reactie vervolgens is. Er kleven echter ook enkele nadelen aan de test. Deze is namelijk behoorlijk belastend en de klachten van een voedselprovocatie zijn soms lastig te interpreteren. Daarnaast is de test kostbaar in financieel opzicht. Eén van de doelen van het onderzoek beschreven in dit proefschrift is om het aantal 2-daagse voedselprovocaties te verminderen bij kinderen (**hoofdstuk 2**) en bij volwassenen (**hoofdstuk 3**).

Een patiënt met een pinda allergie maakt specifieke antistoffen (sIgE) aan tegen pinda. Als de patiënt pinda eet kan het pinda-allergeen binden aan de sIgE antistoffen, waarna er stoffen vrijkomen, die klachten veroorzaken bij een patiënt met pinda allergie. De hoeveelheid sIgE tegen pinda kan gemeten worden in het bloed, zowel sIgE tegen een mix van pinda eiwitten (pinda extract) als tegen specifieke pinda eiwitten (pinda componenten). De hoeveelheid sIgE tegen pinda componenten, zoals Ara h 2, voorspelt pinda allergie beter dan de hoeveelheid sIgE tegen pinda extract. De hoogte van het sIgE tegen Ara h 2 in het bloed kan gebruikt worden om de kans op een pinda allergie in te schatten. Er wordt dan gebruik gemaakt van afkappunten. Uit eerder onderzoek in ons ziekenhuis is gebleken dat alle kinderen met een Ara h 2 waarde onder het lage afkappunt geen pinda allergie hadden en alle kinderen met een Ara h 2 waarde boven het hoge afkappunt wel. Met deze afkappunten van Ara h 2 kon de uitslag van een voedselprovocatie voor pinda bij 62% van de kinderen juist voorspeld worden.

In **hoofdstuk 2** hebben we een beslisregel op basis van deze afkappunten van sIgE tegen Ara h 2 gemaakt. We hebben de beslisregel ingevoerd in vier ziekenhuizen, één academisch ziekenhuis en drie streekziekenhuizen, bij kinderen van 3.5 tot 18 jaar met een verdenking op een pinda allergie. Kinderen met een Ara h 2 waarde onder het afkappunt waarbij zeker is dat ze niet pinda allergisch zijn, mochten thuis pinda gaan eten. De kinderen met een waarde boven het afkappunt waarbij zeker is dat ze wel pinda allergisch zijn kregen een 1-daagse open voedselprovocatie. De kinderen met een Ara h 2 waarde tussen de afkappunten (een twijfelachtige Ara h 2 waarde) kregen wel een 2-daagse voedselprovocatie.

Dit onderzoek laat zien dat de beslisregel pinda allergie goed voorspelt (89-97%) en uitsluit (100%). Daarnaast was het gebruik van de beslisregel veilig, aangezien alle kinderen die thuis pinda mochten eten geen klachten kregen. De zorg werd bij twee derde van de kinderen uitgevoerd volgens de beslisregel. De voornaamste redenen om van de beslisregel af te wijken waren angst voor een allergische reactie of een recente allergische reactie na het eten van pinda.

Naast de geringere belasting voor de patiënten, leidde de invoer van de beslisregel tevens tot lagere kosten (€320 tot €636 per patiënt per jaar) vergeleken met de diagnostiek van pinda allergie volgens de huidige Nederlandse richtlijn. Het invoeren van de beslisregel in heel Nederland zou zodoende tot een besparing van €767.101 tot €1.526.688 per jaar kunnen leiden.

Bij eerder onderzoek in ons ziekenhuis werd een afkappunt van sIgE tegen Ara h 2 gevonden waarmee pinda allergie met 100% zekerheid kon worden aangetoond bij volwassenen. In **hoofdstuk 3** is dit afkappunt gecontroleerd in een vervolgstudie. Het afkappunt klopte en voorspelde pinda allergie correct bij één derde van de volwassenen met een verdenking op pinda allergie. Daarnaast is onderzocht of andere pinda componenten (Ara h 1, 3, 6 en 8) een toevoegde waarde hebben bij het vaststellen van een pinda allergie. Van deze pinda componenten voorspelde Ara h 6 pinda allergie even goed als Ara h 2. De andere pindacomponenten speelden geen rol bij het vaststellen van een pinda allergie. Aangezien sIgE tegen Ara h 2 en Ara h 6 sterk met elkaar samenhangen, en het afkappunt van sIgE tegen Ara h 2 nu gecontroleerd is, hebben we net als bij kinderen een beslisregel op basis van sIgE tegen Ara h 2 ontwikkeld. Bij een derde van de volwassenen met een verdenking op pinda allergie en een Ara h 2 waarde boven het gecontroleerde afkappunt zou de 2-daagse dubbelblinde voedselprovocatie vervangen kunnen worden door een 1-daagse open voedselprovocatie.

We hebben 83 kinderen en ouders een vragenlijst gestuurd 3 jaar na een voedselprovocatie voor pinda om te vragen hoe het met hen gaat. Dit waren zowel kinderen bij wie een pinda allergie was aangetoond, als kinderen bij wie een pinda allergie was uitgesloten. In **hoofdstuk 4** beschrijven we de resultaten van dit onderzoek. De kinderen bij wie een pinda allergie was vastgesteld kregen na de voedselprovocatie het advies om pinda te vermijden. Ondanks deze adviezen rapporteerde toch 41% van de kinderen een allergische reactie door pinda tijdens de 3 jaar na de voedselprovocatie. Kinderen met ernstige allergische reacties gebruikten helaas geen adrenalinepen. Een derde van de kinderen bij wie een pinda allergie was uitgesloten lukte het niet om pinda te gaan of blijven eten. Deze resultaten suggereren dat het belangrijk is om kinderen na een voedselprovocatie goed te begeleiden, om allergische reacties te voorkomen of beter te behandelen (na een voedselprovocatie waarin pinda allergie is aangetoond) en om pinda niet langer te vermijden (na een voedselprovocatie waarin pinda allergie is uitgesloten).

Atopische ziekten en luchtweginfecties

De resultaten van **hoofdstuk 5** laten zien dat de factoren die samen hangen met atopische ziekten verschillen van de factoren die samen hangen met herhaaldelijke luchtweginfecties. De aanwezigheid van één of meerdere atopische ziekten was minder waarschijnlijk bij kinderen met een jonge leeftijd (≤ 4 jaar) of een laag geboortegewicht, bij meisjes en bij kinderen met een hond als huisdier. De aanwezigheid van herhaaldelijke luchtweginfecties was juist waarschijnlijker bij kinderen ≤ 4 jaar vergeleken met oudere kinderen, en als kinderen naar de crèche gingen.

Kinderen met ouders, broertjes en/of zusjes met astma hadden vaker astma. Hetzelfde gold voor hooikoorts, eczeem en herhaaldelijke luchtweginfecties. Bij kinderen die verdacht worden van een atopische ziekte of herhaaldelijke luchtweginfecties raden we dan ook aan om goed uit te vragen of familieleden ook last hebben van deze ziekten. Op deze manier kan de arts de kans op atopische ziekten en herhaaldelijke luchtweginfecties beter inschatten.

Impact van atopische ziekten op de kwaliteit van leven

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Atopische ziekten hebben een negatieve invloed op de kwaliteit van leven. Kinderen met voedselallergie moeten opletten met wat ze eten en het is dan ook vaak lastiger om bijvoorbeeld spontaan buiten de deur te eten of traktaties op school of werk aan te nemen. Daarnaast zijn kinderen en hun ouders vaak bang voor een allergische reactie. Eerder onderzoek heeft laten zien dat kinderen met astma nog meer beperkingen in hun kwaliteit van leven ervaren vergeleken met kinderen met een voedselallergie. Eén van de belangrijkste factoren die de kwaliteit van leven van kinderen met astma beïnvloedt is de mate waarin de astmaklachten gecontroleerd zijn. Kinderen met astma kunnen last hebben van een piepende ademhaling, hoesten of kortademigheid bijvoorbeeld tijdens het sporten, als ze spelen met dieren of 's nachts. Hoe meer klachten van astma (ongecontroleerd astma), des te meer beperkingen in de kwaliteit van leven kinderen ervaren.

Pinda allergie

In **hoofdstuk 6** is de literatuur samengevat over de invloed van de diagnostiek naar voedselallergie op de kwaliteit van leven. Aangetoond werd dat de kwaliteit van leven verbeterde na voedselprovocaties, zowel wanneer een voedselallergie werd aangetoond als wanneer een voedselallergie werd uitgesloten.

Vervolgens hebben we in **hoofdstuk 2** de angst van ouders van kinderen met een verdenking op een pinda allergie gemeten bij start van de studie, na een telefonische afspraak om de sIgE tegen Ara h 2 uitslag te bespreken en na 6

maanden follow-up. Het onderzoek laat zien dat de angst van ouders afnam na het horen van een negatieve Ara h 2 uitslag (geen pinda allergie) en na het bespreken van een negatieve of positieve uitslag van de voedselprovocatietest. De resultaten van hoofdstuk 2 en 6 laten zien dat een duidelijke diagnose van pinda allergie (zowel aantonen als uitsluiten) de kwaliteit van leven verbetert en de angst van ouders vermindert.

In **hoofdstuk 4** is de kwaliteit van leven van ouders van kinderen met een verdenking op een pinda allergie gemeten bij start van de studie (voor een voedselprovocatie) en na 3-jaar follow-up. De kwaliteit van leven bleek sterk te verbeteren bij ouders van kinderen met een negatieve uitslag van de voedselprovocatie (geen pinda allergie). De kwaliteit van leven bleek nog veel meer te verbeteren als deze kinderen na de test gewoon pinda gingen eten, in vergelijking tot kinderen die nog steeds geen pinda aten. Deze resultaten benadrukken het belang van het gaan eten en het niet meer vermijden van pinda na een negatieve voedselprovocatie.

Astma

Hoofdstuk 7 laat zien dat ongecontroleerd astma (veel last van hoesten en piepen) vaak voorkomt bij kinderen die al bekend zijn met astma en hiervoor naar het ziekenhuis komen, maar ook bij kinderen met astma die voor een andere atopische ziekte naar het ziekenhuis komen. Kinderen met astma in de familie (bij ouders, broertjes en/of zusjes) hadden een grotere kans om veel last te hebben van astmklachten. Ook kinderen met herhaaldelijke onderste of bovenste luchtweginfecties en astma als reden om naar het ziekenhuis te komen hadden vaker ongecontroleerd astma. Hieruit concluderen we dat het belangrijk is om te meten hoe goed astma onder controle is, zowel bij de kinderen die worden verwezen vanwege astma als bij de kinderen die worden verwezen vanwege een andere atopische ziekte.

Hoe goed astma onder controle is, wordt beïnvloed en uitgelokt door allerlei factoren. Astmklachten kunnen bijvoorbeeld uitgelokt worden door inspanning, weersomstandigheden, verkoudheid, emoties en blootstelling aan pollen of huisdieren. **Hoofdstuk 8** beschrijft dat twee derde van de kinderen met astma één of meerdere uitlokkende factoren van astma aangeeft. De meest voorkomende uitlokkende factoren waren sporten, weersomstandigheden en een verkoudheid of griep. Kinderen met meer uitlokkende factoren ervaarden ook meer beperkingen in de kwaliteit van leven, zowel in de kwaliteit van leven specifiek voor astma als in de algemene kwaliteit van leven. De uitlokkende factoren sporten, weersomstandigheden en emoties hingen samen met een lagere astma-specifieke kwaliteit van leven score. De uitlokkende factoren emoties en eten of drinken hingen samen met een lagere algemene kwaliteit van leven score. Het is aan te

bevelen om bij kinderen met astma de aanwezigheid van uitlokkende factoren van astmklachten uit te vragen om vervolgens goede voorlichting te kunnen geven over de vermijding en/of behandeling van (eventuele) uitlokkende factoren.

Aanbevelingen

Tot slot worden in **hoofdstuk 9** de belangrijkste resultaten van dit proefschrift in perspectief geplaatst en worden aanbevelingen gedaan voor toekomstig onderzoek.

Er wordt geconcludeerd dat een beslisregel op basis van sIgE tegen Ara h 2 betrouwbaar en veilig is bij kinderen in Nederland met een verdenking op een pinda allergie. De invoering van de beslisregel in de nationale richtlijn wordt aangeraden, zowel voor kinderen als volwassenen met een verdenking op een pinda allergie. Internationale studies zijn nodig om de beslisregel wereldwijd te onderzoeken en vervolgens wereldwijd in te voeren. Andere vragen die nog beantwoord moeten worden gaan in het bijzonder over het verbeteren van het voorspellen van pinda allergie bij patiënten met een twijfelachtige Ara h 2 uitslag, het voorspellen van de ernst van voedselallergie en de betrouwbaarheid van de beslisregel bij jonge kinderen (< 3.5 jaar). De laatstgenoemde vraag is toenemend relevant nu de ontwikkelingen op het gebied van het voorkomen van voedselallergie (vroeg introductie) en het behandelen van voedselallergie (immunotherapie) zich richten op deze jonge leeftijdscategorie.

Daarnaast wordt geconcludeerd dat het stellen van een duidelijke diagnose van pinda allergie bijdraagt aan het verminderen van de angst en het verbeteren van de kwaliteit van leven van ouders. Aangezien de angst van kinderen en/of ouders de belangrijkste reden was om af te zien van het eten van pinda thuis of van een voedselprovocatietest, dient vervolgonderzoek na te gaan of deze angst verminderd kan worden door bijvoorbeeld psychologische begeleiding.

Evenzeer zou meer inzicht over de kwaliteit van leven bij kinderen met atopische ziekten verkregen kunnen worden door het meten van andere aspecten, zoals weerbaarheid, hoe patiënten omgaan met hun ziekte en door de ontwikkeling van meetinstrumenten bij kinderen onder de leeftijd van 8 jaar.

Chapter 11

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List of abbreviations

ACT	Asthma control test
ANOVA	Analysis of variance
AUC	Area under the curve
BAT	Basophil activation test
C-ACT	Child asthma control test
CI	Confidence interval
CRD	Component-resolved diagnostics
DBPCFC	Double-blind placebo-controlled food challenge
ED	Eliciting dose
EP	Electronic portal
FAQL-PB	Food allergy quality of life - parental burden
FAQLQ-AF	Food allergy quality of life questionnaire - adult form
FAQLQ-CF	Food allergy quality of life questionnaire - child form
FAQLQ-TF	Food allergy quality of life questionnaire - teenager form
FAQLQ-PF	Food allergy quality of life questionnaire - parent form
FC	Food challenge
HRQL	Health-related quality of life
Inc	Inconclusive
ING	Ingredient
ISAAC	International study of asthma and allergies in childhood
IQR	Interquartile range
LOAEL	Lowest-observed-adverse-effect level
MARS	Medication adherence rating scale
MCID	Minimal clinically important difference
MD	Mean difference
N	Number
NA	Not applicable
NPV	Negative predictive value
OFC	Oral food challenge
OR	Odds ratio
PAL	Precautionary allergen labelling
PAQLQ	Pediatric asthma quality of life questionnaire
PedsQL™ 4.0	Paediatric quality of life inventory 4.0
PPV	Positive predictive value
RAND	RAND (no abbreviation) general health-rating index
ROC	Receiver operating characteristic
RRTIs	Recurrent respiratory tract infections
SD	Standard deviation
SE	Standard error

sIgE	Specific immunoglobulin E
SMD	Standardized mean difference
SPT	Skin prick testing
STAI	State-trait anxiety inventory
STAIC	State-trait anxiety inventory for children
UNK	Unknown
UNP	Unpacked foods
WHISTLER	Wheezing illnesses study Leidsche Rijn
WHOQOL-BREF	World Health Organization generic quality of life scale

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List of publications

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HM Kansen, TM Le, Y Meijer, BMJ Flokstra-de Blok, PMJ Welsing, CK van der Ent, AC Knulst, FC van Erp. The impact of oral food challenges for food allergy on quality of life: a systematic review. *Pediatr Allergy Immunol*. 2018; 29(5): 527-537.

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Hannah Kansen was born on the 20th of May 1991 in Hilversum, the Netherlands. She graduated cum laude from secondary school in 2009 (de Passie, Utrecht). In the same year she started her medical training at the University of Utrecht. During medical school, she developed her interest in pediatrics during a clinical internship at the St. Jansdal in Harderwijk and started a research project at the department of Pediatric Gastroenterology of the Wilhelmina Children's Hospital, supervised by Prof. dr. R.H.J. Houwen and dr. V.M. Wolters. In addition, she

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