

ORIGINAL ARTICLE

WILEY

Food Allergy & Anaphylaxis

Structured intervention plan including component-resolved diagnostics helps reducing the burden of food allergy among school-aged children

Johannes Savolainen¹  | Barbara Mascialino² | Elina Pensamo¹ |
K. Magnus Åberg^{2,3} | Maija Silvan⁴ | Magnus P. Borres^{2,5}  | Krista Korhonen⁴

¹Department of Pulmonary Diseases and Clinical Allergology, University of Turku and Turku University Hospital, Turku, Finland

²Thermo Fisher Scientific, Uppsala, Sweden

³Department of Environmental Science and Analytical Chemistry, Stockholm University, Stockholm, Sweden

⁴Härkätie Primary Care Center, Lieto, Finland

⁵Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Correspondence

Johannes Savolainen, Department of Pulmonary Diseases and Clinical Allergology, University of Turku and Turku University Hospital, Turku, Finland.
Email: johsav@utu.fi

Funding information

Johannes Savolainen has received grants from Allergy Research Foundation (Finland), Päivikki and Sakari Sohlberg Foundation, and State Research Funding (ERVA). Reagents and nurse salary were funded by Thermo Fisher Scientific.

Edited by: Motohiro Ebisawa

Abstract

Background: Food allergies can substantially burden patients and families by negatively affecting finances, social relationships, and personal perceptions of health. This study was performed under the Finnish Allergy Programme aimed at reducing avoidance diets to foods in schoolchildren by 50%. The main goal of this study was to investigate how many children could be freed from diet restrictions in a Finnish school district through a diagnostic algorithm including component-resolved diagnostics and food challenge. The secondary aim was to provide a crude estimate of the burden of the elimination food diets in the region, and the savings associated with the proposed intervention.

Methods: A total of 205 children on a food avoidance diet according to the school register because of food allergy were invited into the study. One hundred and fifty-seven children were interviewed, tested for IgE to extracts and allergen components and food challenged in respective order.

Results: After two years, 12 children still had an avoidance diet and three of them were treated successfully with sOTI; the rest suspended their avoidance diet (n = 134) or dropped out of the study (n = 11). The cost of the elimination diets was estimated in 172 700€ per year at start and 13 200€ per year at the end of the study; total savings were 128 400€ yearly.

Conclusions: The results demonstrate a 65% reduction of avoidance diets to foods in school-aged children, exceeding the 50% aim of the Finnish Allergy Programme. Therefore, it is possible to actively reduce the number of food allergy diagnoses that remain unmonitored in the society through a tailored diagnostic work-up.

KEYWORDS

allergen components, elimination diet, Finnish Allergy Programme, food allergy, school-aged children

Abbreviations: AD, atopic dermatitis; ANF, anaphylaxis; CRD, component-resolved diagnostics; DC, diet continue; DS, diet suspended; EAACI, European Academy of Allergy and Clinical Immunology; FA, food allergy; FAP, Finnish Allergy Programme 2008-2018; GI, gastrointestinal symptoms; IgE, Immunoglobulin E; ImmunoCAPTM ISAC, ImmunoCAP Immuno Solid-phase Allergen Chip; OAS, oral allergy syndrome; OFC, oral food challenge; SD, standard deviation; sOTI, specific oral tolerance induction.

1 | INTRODUCTION

Globally, the prevalence of food allergy in children is estimated in 4%-7%.¹ Cow's milk, egg, and wheat allergy are common among young children and may resolve by school age.² Nut allergies present more often in older children.¹

Daily activities such as the preparation of special diets can become time-consuming and expensive endeavors; allergic subjects and their families may experience anxiety and quality of life reduction.³ These concerns and fears can lead to unnecessarily restrictive environments, barriers to learning, and conflicts between families and schools. The role of the pediatric health providers is to correctly diagnose a food allergy or exclude the allergy if appropriate.⁴ With the help of molecular allergology, it is possible to more accurately diagnose, prognose, and grade allergic diseases.^{5,6}

The Finnish Allergy Programme (FAP) 2008-2018 was launched by the Finnish Government in 2007, with the purpose of reducing problems and costs incurred by allergies.^{7,8} A specific aim is to reduce special diets caused by food allergies by 50%. Erkkola et al have recently shown that the burden of allergy elimination diets in a day care setting could be decreased making simple pragmatic changes based on current allergy guidelines.⁹ A similar reduction was also possible in school-aged children where a number of avoidance diets were ascribable to peanut and nut allergy diagnoses based on cross-reactions to pollen.¹⁰ Foods causing mild symptoms as Oral Allergy Syndrome (OAS) should not require a restricted diet.¹¹

In line with the FAP, our hypothesis was that a school-based surveillance and interventional food allergy re-examination could reduce the number of school-aged children on a special diet because of a previous food allergy diagnosis. The aim of this study was to reduce the number of children with diet restrictions in the school district of Härkätie (Finland) through a diagnostic work-up including component-resolved diagnostics (CRD) and oral food challenges (OFC). The secondary aim was to provide a crude estimate of the burden of the elimination of food diets, and of the savings associated with the proposed intervention.

2 | MATERIAL AND METHODS

2.1 | Study subjects

In 2013, 2885 children attended primary or secondary schools in the Härkätie region. Two-hundred and five (7%) of these children were listed in the school diet register; the food elimination diet had been requested by their families because of supposed food allergy and was based on a physician certificate. Children listed in the register but with a certificate regarding celiac disease or lactose intolerance were not included in the study.

Eighty-one children (58% males) underwent CRD in this study; they had an age of 11.3 ± 2.6 (mean $\pm$ SD) years old, ranging from 7.2 to 17 (Table 1). According to the diet certificates, 31 children (38%)

TABLE 1 Characteristics of children with suspended diets vs children with continued avoidance diet or participating in sOTI

Description	Diet continues or sOTI	Diet suspended	P-value
Number of subjects	17	64	
Sex (male/female)	13/4	34/30	0.1 ^a
Age (median [range])	9.7 [7.2, 14.7]	11.4 [7.3, 17.0]	0.04 ^b
Birch allergy (yes/no)	6/11	22/42	1 ^a
Dietary restriction			
Egg	6	5	
Milk	3	12	
Nuts	11	17	
Fish	2	7	
Shellfish	1	5	
Peas	2	13	
Apple	7	28	
Pear	2	10	
Kiwi	2	14	
Carrot	4	15	
Citrus	1	9	
Tomato	0	11	
Other	11	35	
Symptoms related to food			
Anaphylaxis	6	0	
Asthma	1	2	
Oral allergy syndrome	7	40	
Atopic dermatitis	2	18	
Gastrointestinal	6	18	
Urticaria	0	4	
Other	3	4	

^aFisher test.

^bMann-Whitney *U* test.

had one food listed in the register, 16 children (20%) were excluding two foods, while the remaining 34 children (42%) had 3-8 different foods. The most commonly excluded foods were fruit and vegetables (*n* = 51); staple foods including milk, egg, soy, and fish (*n* = 30); and nuts (*n* = 28).

OAS was the most common self-reported symptom (*n* = 47), followed by gastrointestinal (GI) symptoms (*n* = 24), and atopic dermatitis (AD, *n* = 20). OAS was more frequent in children on a diet excluding apples (*n* = 30), nuts (*n* = 17), carrots (*n* = 15), and peas (*n* = 14), and GI symptoms were mostly common among children on a milk-free diet (*n* = 12) and egg-free diet (*n* = 7), while AD in children on a diet without fish (*n* = 7), nuts (*n* = 5), milk (*n* = 5), and citrus (*n* = 5). Five of the six children who had experienced anaphylaxis (ANF) in association with the food eliminated had nuts listed among the foods to be excluded, and all five were diagnosed as

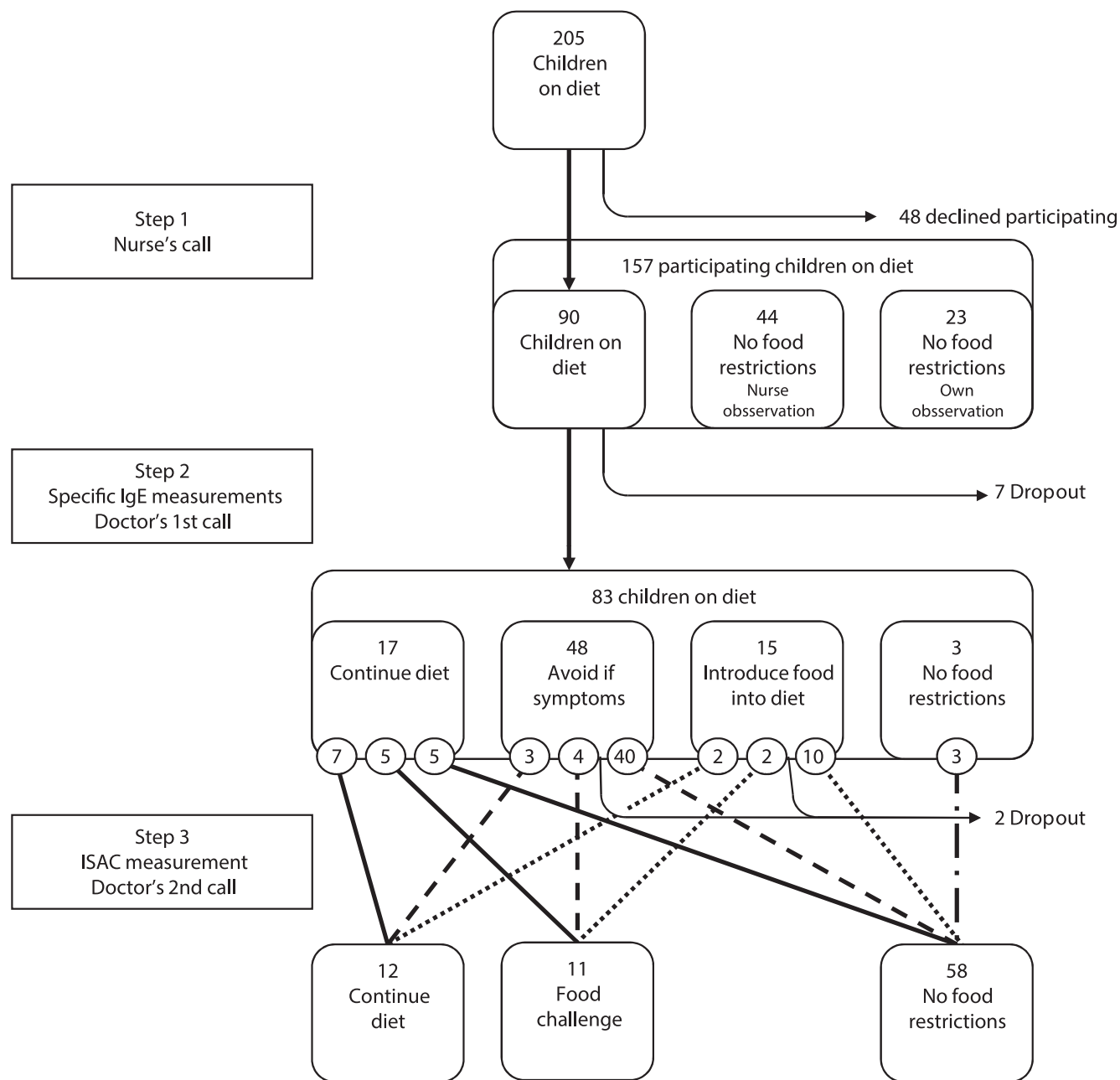


FIGURE 1 Flowchart of included subjects

nut-allergic at the end of the study. The sixth child had egg and peanut listed and was successfully treated with sOTI against egg at the end of the study.

2.2 | Diagnostic work-up

All 205 families that had requested an avoidance diet were contacted for recruitment through an information letter and a phone interview performed by a nurse dedicated to the study. Forty-eight families (23%) declined participating in the study, because of too frequent testing ($n = 11$), established contact with a physician ($n = 10$), no trust in tests ($n = 10$), busy ($n = 9$), and afraid of needles ($n = 8$). The remaining 157 children (77%) were included in the study.

The study was comprised of four intervention steps (Figure 1).

Step 1: A tailored interview was conducted by a study nurse to collect information on the diets, including demographic data, adherence to the diet both at school and at home, accidental intake, and self-reported symptoms. The interview revealed that diet restrictions were not followed by 23 children, even though they had requested an avoidance diet at school; additionally, 44 children did not need a diet. The remaining 90 children were referred for further investigations including serology.

Step 2: Forty-seven of the children were tested with ImmunoCAP™ specific allergen, whenever there was a need for quantitative

TABLE 2 Microarray test results (high/medium/low) in the two diet groups

Description	Diet continues or sOTI	Diet suspended	P-value ^a
Food components (high/medium/low)	7/12/36	0/2/15	
Food components (all negative/ ≥ 1 positive)	3/14	52/12	2×10^{-6}
Cross-reactive (high/medium/low)	21/27/47	131/138/107	
Cross-reactive (all negative/ ≥ 1 positive)	6/11	21/43	1
Airborne (high/medium/low)	20/20/23	50/70/121	
Airborne (all negative/ ≥ 1 positive)	6/11	20/44	0.78

^aFisher test.

test results. The study physician later contacted the families by phone and provided diet recommendations taking into consideration of case history, the food elimination diet as specified in the school register, the symptoms reported to the nurse, and the s-IgE test results when available. Seven children dropped out of the study.

Step 3: In this step, two more children declined being tested. The remaining 81 children were tested with the multiplex immunoassay (ImmunoCAPTM ISAC; Thermo Fisher Scientific, Uppsala, Sweden). After these results were made available to the doctor, new diet or testing recommendations were given to the families in a second phone call, and 11 children were referred for OFC (Figure 1).

Step 4: Nine children underwent OFC, while two children declined. Children who failed an egg challenge were successfully treated with specific Oral Tolerance Induction (sOTI).

2.3 | Economic estimation

An estimated 900 000 schoolchildren are daily served a free meal at school in Finland, and out of them, 70 000 (8%) require a special meal due to food allergies. The additional yearly costs per pre-school child on a diet were quantified in 1100 Euro for the geographic area of Helsinki⁹; this estimate was also considered representative for the Härmäkie region. At the beginning of the study, the yearly estimated additional costs of special school diets in the region studied were thus 225 500€.

The economic analysis included the costs in clinical procedures of the intervention proposed, and the costs associated with the food elimination diets. Costs associated with resource utilization, for example, the time the nurse and the doctors dedicated to the study, were not included in the calculations. The estimated cost (in 2017€) of one s-IgE test was 12€, ISAC was 160.5€, OFC was 160€, and sublingual sOTI was 1200€.

2.4 | Statistical analysis

Children were classified according to the diagnosis they received at the end of the study: DC-sOTI = "Diet Continues or sOTI," and DS = "Diet Suspended." To assess demographic differences between the two groups, the Fisher test¹² was used to compare gender distributions and ISAC components results, categorized as "all negative" or "at least one positive." The Mann-Whitney *U* test¹³ was used to compare age distributions. In all cases, the statistical significance level was set at 0.05.

The analysis was performed using the statistical language program R version 3.3.2.¹⁴

2.5 | Ethical approval

The study was approved by the Ethical Committee of the Hospital District of South-West Finland (ETMK: 57/1801/2013, 1355 16.04.2013).

3 | RESULTS

The number of unnecessary diets suspended was 67 out of 157 (43%) after the nurse's interview (Figure 1, Step 1). Based on negative food-specific IgE results and the doctor's first telephone call, a free diet was allowed to three more children. Fifteen children were already eating small amounts of the excluded foods in the school and were encouraged to increase the consumption of these foods. Forty-eight children were advised to perform home challenges and to eliminate the foods only if they caused symptoms. Only 17 children were advised to continue the diet. The number of unnecessary avoidance diets suspended in steps 1-2 was 85 (54% of 157 children).

The microarray analysis in Step 3 showed that 37 children had food allergies only due to Betv1 homology. The results of the DC-sOTI and DS groups differed significantly in sensitization to the food components (Table 2). A higher proportion of all-negative results was observed in the DS group (*P*-value <0.0001). For the cross-reactive components, the proportions of all-negative to at-least-one-positive results were about 50% in the DC-sOTI and the DS groups (*P*-value > 0.05). This pattern emerges clearly in Figures 2 and 3, where children are grouped based on the final diagnosis in DC-sOTI and DS.

Qualitatively, no major difference could be detected apart from the food cluster, where the children in the DC-sOTI group not only scored more frequently but also with higher degree of sensitization. The only exception was sensitization to Jugr2 (walnut 2S albumin), which were mildly positive (0.3-3.0 ISU) in 8 cases in the DS group and in 3 cases in the DC-sOTI group. Figure 3 shows a magnification of the food component results, where Jugr2 was removed from the plot for clarity of interpretation, as it has been considered as background.

In Step 3, the number of unnecessary diets suspended increased to 125 (80% of 157 children); 12 children were recommended to continue their diet at the end of Step 3. The lower part of Figure 1 compares the diet indications the study doctor gave before receiving the



FIGURE 2 The complete microarray results in the 81 children tested. The horizontal line divides the subjects into the two diet groups "diet suspended" (left) and "diet continues/sOTI" (right). Gray dots correspond to negative tests, while the darker the color (yellow, orange, red) the higher the test result

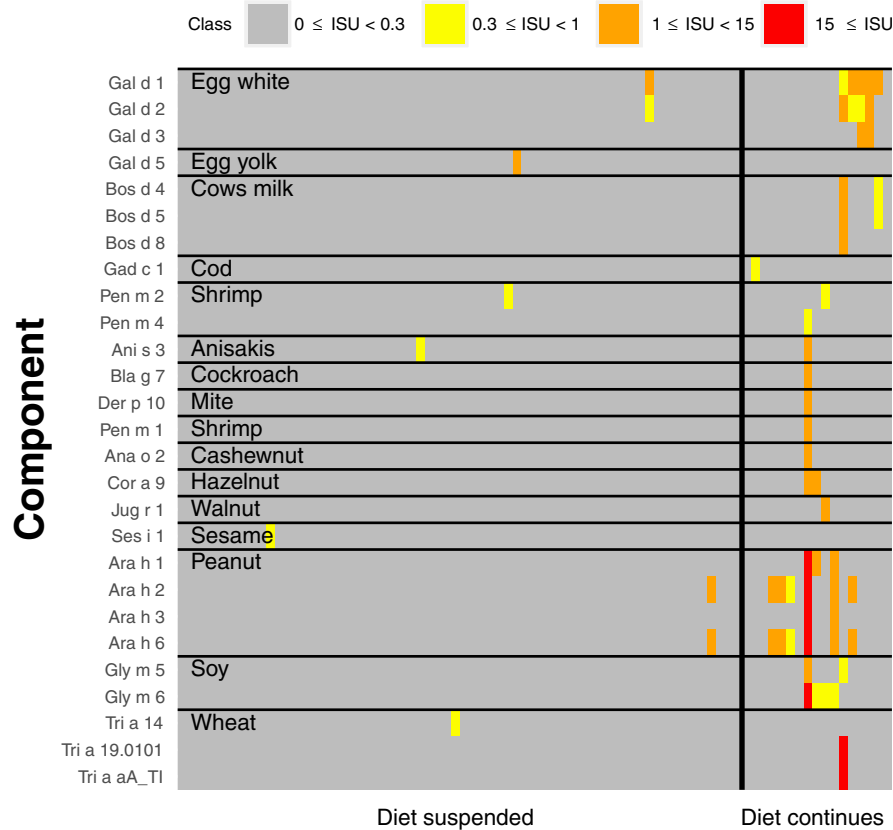


FIGURE 3 Detailed microarray results of primary sensitization of food allergens

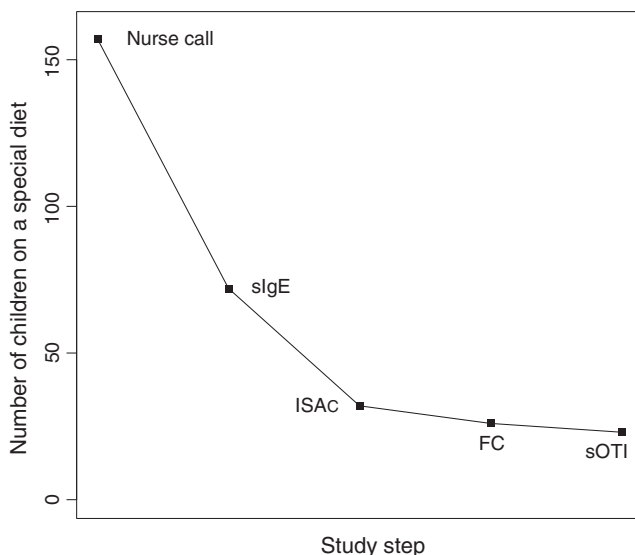


FIGURE 4 Reduction of special diets in relation to the study steps

CRD results, and the diet recommendations after seeing the results. In 10 cases (12%), CRD results did not alter the diet recommendations, but in 72% of the children ($n = 60$), they influenced the doctor's decision about the diet. Two (2%) children dropped out from the study, and the remaining eleven children (13%) were offered an OFC.

Out of the 12 children that continued their diet, nine avoided peanut, two avoided egg, and one child avoided egg and fish.

In Step 4, 11 children were referred for OFC, which was declined by two children. Four children were challenged with cow's milk, four with hen's egg, and one with wheat. Six children turned out to be negative, and their special diet was suspended. The remaining three children reacted to egg and were offered egg sOTI treatment. All of them were successfully treated, and their diet was suspended.

The number of diets at each step of the study is illustrated in Figure 4.

3.1 | Economic assessment

The cost of the clinical procedures included serology testing (960€), microarray with ISAC (13 000€), OFCs (1440€), and sOTI (3600€).

The yearly cost in elimination diets of the children who agreed participating to the study (Step 1) was 157 children $\times$ 1100€ = 172700€ per year, while this cost at the end of Step 4 was 12 children $\times$ 1100€ = 13200€; including the costs of all children that dropped out throughout the study ($n = 11$), and that they likely continued their diet, the savings ascribable to unneeded diets of 147400€.

The proposed intervention's total cost in clinical procedures was 19000€, and the savings associated with the study can be quantified in 128400€ (74% of the initial costs in food elimination diets considering 157 children).

4 | DISCUSSION

The study results confirm that it is possible to reduce avoidance diets to foods in schoolchildren by 50% in accordance with the Finnish Allergy Programme. In the studied region, there were 205 children on diets in 2013, and 71 children (35%) remained on their diet after completion of the study. Of these 71 children, 48 children did not enroll in the study. Of the 157 children that did enroll, only 23 (15%) remained on a diet after the study. Additionally, our results show that children on an elimination diet can benefit from the usage of component-resolved diagnostics in combination with tailored interviews and food challenges.

Self-reported food allergy is subjective, and in many cases inaccurate.¹⁵ Food allergy diagnosis can be challenging and complicated for the physician because *in vitro* assays and skin tests based on whole extracts have poor specificity, and therefore, misdiagnoses often occur.⁵ Once a diagnosis of food allergy has been established, the only proven therapy is strict elimination of the offending food. Therefore, we were pleased to realize that it was possible to eliminate an important number of food allergy diagnoses through a structured intervention plan.

Milk, egg, and grain allergies tend to disappear before school age,^{1,11} and many of the unnecessary diets suspended in Step 2 of the study were attributed to avoidance of milk or egg. Our results show that these diets easily remain unmonitored even after tolerance to foods is achieved, as also demonstrated in a recent surveillance work.¹⁸ The reasons behind this phenomenon are most likely habitual and slow clinical follow-up. This means that healthcare professionals need to be more active in following up individuals where tolerance to egg, milk, and wheat might have developed.

The highest number of suspended diets after ISAC results in Step 3 was because of mild food allergies due to Betv1 homology. Our findings are supported by Elizur et al who have demonstrated that tree nuts are often eliminated from the diet of multiple-food allergic patients, despite their low probability for allergy.¹⁵ Our follow-up results demonstrate that 7.6% of the diets were resumed two years after our intervention, all due to self-reported symptoms ascribable to Betv1 homology (data not shown).

Food allergies can lead to significant economic consequences on the society and the healthcare system. We could show that the cost of the elimination diet for the 157 participating children was 172700€ per year, and the cost for the 12 remaining children with diet was 13200€ per year. Considering also the 11 children that dropped out, savings could be estimated in 128400€ per year for the local community. This calculation was based on the societal cost, for example, special diet provided by the school. Including the family cost savings would of course increase the total savings. Patel et al estimated the economic burden of food-induced allergic reactions and anaphylaxis in the United States to half a billion dollars in 2007¹⁶ which is considerable much higher per patient than our study.

In the European and national guidelines,^{4,11,17} it is clearly stated that the diet for the allergic individual should be thoroughly monitored, and results evaluated to confirm diagnosis in order to prevent unnecessary food restrictions. To ensure this, we allergists need to

reform the practices for inquiring about the need of an avoidance diet. This should be done on a national and regional level and could be achieved through interventions like targeted interviews and specific IgE testing as we did in our study. To dissolve any uncertainties, an oral food challenge should be performed.

A drawback of our study is that we could not get the true regional cost estimate for the 157 elimination diets. We have used the same crude calculation as the City of Helsinki Service Center which Erkkola et al used in their study of food allergies in Finnish day care.⁸ The extra costs of special diets arise from compensatory ingredients and their storage, food waste, and extra working hours of personnel. We estimate that the same additional costs identified in day care centers in Helsinki also apply for schools in the Härkätie region.

Another drawback is that 48 families declined participating in the study.

5 | CONCLUSIONS

The main purpose of this study was to evaluate whether it was possible to reduce food elimination diets through an intervention. The reduction of the diets was possible in a large scale. There was added value in assessing allergen component diagnostics in order to select patients for food challenge and oral immunotherapy treatment.

ACKNOWLEDGEMENTS

We would like to thank Prof Raimo Isoaho, Dr Sirpa Rantanen, and Ms Lisse-Lotte Hermansson for kind contribution.

CONFLICT OF INTERESTS

B. Mascialino, KM Åberg, and MP Borres are employees of Thermo Fisher Scientific, Uppsala, Sweden. The other authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

JS, EP, and MS designed the study, made the clinical contribution, and collected the data. JS, BM, and KMÅ performed the analysis. JS drafted the manuscript and EP, MS, BM, KMÅ, and MPB critically reviewed the manuscript, and all authors approved the final version.

ORCID

Johannes Savolainen  <http://orcid.org/0000-0002-2161-7443>

Magnus P. Borres  <http://orcid.org/0000-0002-9045-2304>

REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133:291-307.

2. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract*. 2016;4:196-203.
3. Borres N, Nilsson N, Drake I, et al. Parents' perceptions are that their child's health-related quality of life is more impaired when they have a wheat rather than a grass allergy. *Acta Paediatr*. 2017;106:478-484.
4. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008-1025.
5. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol*. 2016;27(Suppl 23):1-250.
6. Borres MP, Ebisawa M, Eigenmann PA. Use of allergen components begins a new era in pediatric allergology. *Pediatr Allergy Immunol*. 2011;22(5):454-461.
7. Haahtela T, von Hertzen L, Mäkelä M, et al. Allergy Programme Working Group. Finnish Allergy Programme 2008-2018-time to act and change the course. *Allergy*. 2008;63:634-645.
8. Pelkonen AS, Kuitunen M, Dunder T, et al. Allergy in children: practical recommendations of the Finnish Allergy Programme 2008-2018 for prevention, diagnosis, and treatment. *Pediatr Allergy Immunol*. 2012;23:103-116.
9. Erkkola M, Saloheimo T, Hauta-Alus H, et al. Burden of allergy diets in Finnish day care reduced by change in practices. *Allergy*. 2016;71:1453-1460.
10. Asaranoj A, Nilsson C, Lidholm J, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol*. 2012;130:468-472.
11. Muraro A, Clark A, Beyer K, et al. The management of the allergic child at school: EAACI/GA2LEN Task Force on the allergic child at school. *Allergy*. 2010;65:681-689.
12. Fisher RA. On the interpretation of χ^2 from contingency tables, and the calculation of P. *J Roy Stat Soc*. 1922;85(1):87-94.
13. Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. New York, NY: John Wiley & Sons; 1973.
14. R Core Team. *R: A Language and Environment for Statistical Computing [Internet]*. Vienna, Austria: R Foundation for Statistical Computing; 2016.
15. Elizur A, Bollyky JB, Block WM. Elimination diet and the development of multiple tree-nut allergies. *Pediatr Res*. 2017;82:671-677.
16. Patel DA, Holdford DA, Edwards E, et al. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol*. 2011;128:110-115.
17. Borres MP, Abrahamsson G, Andersson B, et al. Asthma and allergies at school—a Swedish national position paper. *Allergy*. 2002;57:454-457.
18. Palmu S, Heikkilä P, Uski V, et al. National allergy programme had little impact on parent-reported food allergies in children aged 6–7 years. *Acta Paediatr*. 2018;107(1):121-125.

How to cite this article: Savolainen J, Mascialino B, Pensamo E, et al. Structured intervention plan including component-resolved diagnostics helps reducing the burden of food allergy among school-aged children. *Pediatr Allergy Immunol*. 2019;30:99–106. <https://doi.org/10.1111/pai.12996>