

Health-related quality of life in children with objectively-diagnosed staple food allergy assessed with a disease-specific questionnaire

Protudjer JLP^{1,2}, Jansson SA^{1,3}, Östblom E^{1,4,5}, Middelveld RJM^{1,2}, Dahlén S-E^{1,2}, Ahlstedt S¹
on behalf of the Health Economics of Food Allergy (FoodHE) project group.

¹The Centre for Allergy Research, Karolinska Institutet, Stockholm

²The Institute of Environmental Medicine, Karolinska Institutet, Stockholm

³Department of Public Health and Clinical Medicine, Umeå University, Umeå

⁴Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm

⁵Dept of Clinical Research and Education, Södersjukhuset, Karolinska Institutet,

Stockholm

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Authors' emails:

JLP Protudjer jennifer.protudjer@ki.se

E Östblom eva.ostblom@ki.se

SA Jansson sven-arne.jansson@ki.se

RJM Middelveld roelinde.middelveld@ki.se

S-E Dahlén sven-erik.dahlen@ki.se

S Ahlstedt staffan.ahlstedt@ki.se

Address for correspondence:

Staffan Ahlstedt, The Centre for Allergy Research, Karolinska Institutet, P.O. Box 287, 17177
Stockholm, Sweden

E-mail: staffan.ahlstedt@ki.se

Other members of the FoodHE project group include: Heibert Arnlin M^{1,2}, Bengtsson U³,
Kallström-Bengtsson I⁴, Marklund B⁵, Rentzos G³, Sundqvist AC⁶, Åkerström J³

¹Swedish Council on Health Technology Assessment, SBU, Stockholm

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²Department of Learning, Informatics, Management and Ethics, and Medical Management Centre, Karolinska Institutet

³Allergy Unit, Sahlgrenska University Hospital, Gothenburg

⁴The Swedish Asthma and Allergy Foundation, Stockholm

⁵Department of Health and Caring Sciences, Linnaeus University, Kalmar

⁶Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm

ABSTRACT

Aims: Among Swedish children 0-12 years old, we investigated various food allergy-related exposures associated with health-related quality of life using a food allergy-specific questionnaire among children allergic to the staple foods cow's milk, hen's egg and, or wheat, and contextualised worse food allergy-associated health-related quality of life using a generic questionnaire versus controls. **Methods:** In total, 85 children with objectively-diagnosed allergy to the staple foods were included as cases, and 94 children matched for age and sex were included as controls. We administered a food allergy-specific parent-completed questionnaire originally developed by EuroPrevall to cases only, and a generic health-related quality of life questionnaire (EuroQol Health Questionnaire, 5 Dimensions; EQ 5-D); to both cases and controls. **Results:** Hen's egg was the most common offending staple food, affecting 76% of cases. Approximately 7% of cases were allergic to all three staple foods. Parent-reported respiratory and cardiovascular symptoms were associated with worse health-related quality of life. Elements of disease severity (previous anaphylaxis ($p<0.001$); epinephrine autoinjector prescription ($p<0.003$)) were negatively associated with health-related quality of life. Cases had worse health-related quality of life measured by the EQ-5D compared to controls ($p<0.01$). **Conclusions:** Use of a disease-specific questionnaire revealed that disease severity in children with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or wheat is associated with worse health-related quality of life. Use of a generic questionnaire confirmed that cases have worse health-related quality of life than controls.

Key words

Children, Food allergy, Food hypersensitivity, Health-related quality of life

Key Notes

1. Health-related quality of life of children with food allergies is incompletely understood.
2. In this study, children with objectively confirmed allergy to the staple foods cow's milk, hen's egg and, or wheat with a history of anaphylaxis had worse health-related quality of life compared to those with reports of less severe reactions.
3. Moreover, children with objectively-diagnosed allergy to staple food had worse health-related quality of life than children without allergy to staple food.

Confirmed food allergy affects 2-8% of children (1, 2). Like other allergic disorders (3, 4), food allergy has a negative impact on health-related quality of life (HRQoL). Assessed to date predominantly via generic questionnaires (3, 5-8), HRQoL differs significantly between those with food allergy and non-food allergic controls (9). Unlike generic questionnaires, disease-specific HRQoL questionnaires may provide insights into the day-to-day lives of food allergic individuals (10, 11) and disentangle the impact of comorbid conditions (11). Using the validated disease-specific questionnaire, Food Allergy Quality of Life Questionnaire, we recently reported on HRQoL in Swedish adults with allergies to the staple foods cow's milk, hen's egg and, or wheat (12). Herein, we sought to assess the disease-specific HRQoL of Swedish children 0-12 years old allergic to these foods, using the Food Allergy Quality of Life Questionnaire Parent-Form (FAQLQ-PF), which has been validated by others (13). In order to contextualise worse HRQoL due to food allergy in our population, we also used a generic HRQoL questionnaire (14) and compared the results with a control group.

Others have considered the impact of allergy to various foods on children's HRQoL using a disease-specific questionnaire (11, 15-18). However, we wanted to apply a slightly different approach. Thus, we hypothesised that objectively-diagnosed allergies to the staple foods cow's milk, hen's egg and, or wheat warrant specific consideration as these foods are difficult to avoid in a typical Western diet and thus may substantially burden HRQoL. The aims of this study were to investigate various food allergy-related exposures associated with health-related quality of life using a food allergy-specific questionnaire among children allergic to staple foods, and contextualise worse food allergy-associated health-related quality of life using a generic questionnaire versus controls.

PATIENTS AND METHODS

This study involved cases who were outpatients at the allergy clinic at Sachs' Children and Youth Hospital, Södersjukhuset, in Stockholm, Sweden. Cases were identified from medical records and recruited in 2010-2012 by a paediatric nurse specialising in allergy. Inclusion criteria were a convincing history of allergy to at least one of the staple foods cow's milk, hen's egg and, or wheat as ascertained either by a positive food challenge with evident symptoms, or by high levels of food specific Immunoglobulin E antibodies (IgE) associated with 95% probability of

having a positive result in a double-blind placebo controlled food challenge (19). All cases also had specialist's diagnosis of staple food allergy. Parent-perceived and, or doctor-diagnosed allergies to other foods were also present in most cases. Cases were excluded if they had an unclear diagnosis of allergy to staple foods, did not understand Swedish and, or if they had celiac disease, diabetes and, or a malignancy. Information on the concomitant allergic disorders asthma, allergic rhinitis, allergic conjunctivitis and eczema was also obtained. We identified 133 eligible cases who fulfilled these criteria and who were invited to participate. Parents of eligible cases were mailed a HRQoL questionnaire consisting of two instruments, the disease-specific FAQLQ-PF and the generic EuroQol Health Questionnaire, 5 Dimensions (EQ-5D; both described below), as well as with a letter containing information about the study, and a postage-paid return envelope. Parents completed both questionnaires on behalf of their children. Two movie tickets were offered upon receipt of completed questionnaires. In total, 85 children (59% boys, no significant difference versus girls) with a mean age of six years served as cases (Figure 1).

Children who neither had, nor resided with anyone allergic to cow's milk, hen's egg and, or wheat were recruited via advertisements on websites and notice boards from the same geographical area as cases. These children served as controls. No controls had any food allergies. Exclusion criteria and incentives were similar to those for cases. We identified 141 eligible controls who were sent the EQ-5D (but not the FAQLQ-PF), to be completed by their parents. In total, 94 children (57% boys, no significant difference versus girls) with a mean age of seven years served as controls. Cases and controls corresponded well according to age and sex. Age-matching was done in two-year intervals, such that controls were born in the same year plus or minus one year as cases. This study was approved by the Regional Ethical Review

Board in Stockholm, Sweden (Dnr 2009/84-31/5). Personal data were handled according to the Swedish Personal Data Act.

Questionnaires

The validated FAQLQ-PF (13) was translated into Swedish as per World Health Organization guidelines (20). The Swedish translation was piloted in 10 Swedish speaking children to ascertain comprehension. After minor linguistic adjustments, the translation was regarded as satisfactory. The FAQLQ-PF contained 30 questions (13). Each question had corresponding closed-ended answers on a 7-point scale, where 1 is the highest HRQoL and 7 is the lowest HRQoL. Floor and ceiling effects (percentages of patients with minimal and maximum scores, respectively) of the FAQLQ-PF were calculated to verify discriminative capacity. These effects were considered present if >15% of a sample of a minimum of 50 individuals achieved the highest or lowest possible scores, respectively. Absence of these effects demonstrates the efficacy of the questionnaire. The FAQLQ-PF consists of a number of questions from which three domains were formed: Emotional Impact, Food Anxiety, and Social and Dietary Limitations (Appendix A).

Questions on food allergy symptoms were included in the FAQLQ-PF and grouped according to symptoms. Consideration was also given to anaphylaxis based on the symptoms difficulty breathing, inability to stand, collapse and, or loss of consciousness representing reactions in the respiratory tract and, or cardiovascular system (21). Cases also reported whether or not they were in possession of epinephrine autoinjector (EAI). Collectively, these elements contributed to assessment of disease severity.

The EQ-5D was developed by the EuroQol Group (14) and comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three mutually exclusive responses: no problems, some problems or severe problems. Responses were converted into a single summary index by applying a formula that attaches values (preference-based weights elicited from population surveys) to each of the levels in each dimension. As there is no Swedish index tariff, we used the United Kingdom time trade-off value set based on the United Kingdom's EQ-5D index tariff (22) for this analysis. An index of 1.0 corresponds to best health (best HRQoL) and 0.0 the worst possible score (worst HRQoL). Also from the EQ-5D, disease severity was assessed by a history of anaphylaxis, EAI prescription and number of food allergies.

Statistics

HRQoL scores followed a Gaussian distribution. As such, parametric two-sample t-tests were used to test statistical significance with 95th percent confidence intervals (95% CI). The outcomes of mean domain-specific and overall HRQoL scores were calculated for the exposures of objectively-diagnosed food allergy, symptoms and severity. These scores were further analysed with consideration to the presence of parent-perceived and, or doctor-diagnosed allergy to tree nuts and, or peanuts. Linear regression was used to estimate associations between symptoms and HRQoL. The dependent variable was HRQoL and the independent variables were the different symptoms. Dummy coding was used for coding the predictors, with 1 for prevalence of a symptom and 0 for no prevalence of a symptom. Differences of $p < 0.05$ between groups were regarded as statistically significant. Statistical analyses were performed

with Statistical Package for the Social Sciences (SPSS) Statistics 20 (IBM, Somers, NY, USA).

RESULTS

Offending foods, symptoms and concomitant allergic disorders among cases

Hen's egg was the most common offending staple food, affecting 76% of cases (Table 1). Approximately 7% of cases were allergic to all three staple foods. Parent-perceived and, or doctor-diagnosed allergies to tree nuts and peanuts were also common (45% and 42%, respectively). Allergy to three or more foods including at least one staple food affected 49% of cases. Cardiovascular symptoms were the least common symptoms associated with staple food allergy. Most cases (88%) had at least one concomitant allergic disorder (Table 1).

Food allergy-associated HRQoL

Domain-specific floor and ceiling effects were below 15% (results not shown), thereby confirming the discriminant capacity of the FAQLQ-PF.

Domain-specific and total HRQoL scores are presented in Figure 2. The domain with the highest score (i.e. worst HRQoL) was Social and Dietary Limitations, while the domain with the lowest score (i.e. best HRQoL) was Food Anxiety. However, the differences between domain-specific scores did not reach statistical significance. Further analysis revealed that HRQoL was worse among cases with concomitant tree nut and, or peanut allergy, compared to cases without these concomitant allergies for the domains Emotional Impact ($p<0.02$) Social and Dietary Limitations, ($p<0.002$) and total HRQoL ($p<0.03$).

Children with four other allergic disorders had significantly worse HRQoL compared to those with three or fewer other allergic disorders (mean scores 4.07 versus 2.84, respectively; $p=0.002$).

Impact by symptoms and disease severity

Among cases, the F-test was significant, indicating a linear association between symptoms and HRQoL scores (R^2 value=0.20; adjusted $R^2=0.14$; $p=0.01$). Skin symptoms had the least impact on HRQoL, as indicated by the lowest mean score (Figure 3). The associations between symptoms and HRQoL scores were further analysed with linear regression. However, linear regression analyses revealed that skin symptoms were not a significant predictor of HRQoL for cases. HRQoL was significantly impacted by cardiovascular ($B=0.73$, 95%CI 0.00-1.46) and respiratory symptoms ($B=0.80$, 95%CI 0.08-1.52), compared to cases who did not have these symptoms.

Owing to low numbers of cases who reported 0, 1 or 2 symptoms, we grouped the number of symptoms into two categories: 0-3 versus 4-6. As indicated by higher mean scores (Figure 4), four to six symptoms compared to three or fewer symptoms was associated with worse HRQoL ($p<0.004$). A history of anaphylaxis, EAI prescription and number of food allergies were all associated with worse HRQoL, as assessed using the FAQLQ-PF (Table 2).

HRQoL in cases versus controls

Based on the EQ-5D, HRQoL was significantly worse in cases compared to controls (mean scores 0.84 versus 0.94, respectively; $p<0.01$).

DISCUSSION

Using a food allergy-specific questionnaire, we identified that EAI prescription, respiratory and cardiovascular symptoms and, or anaphylaxis, among children with allergy to the staple foods, cow's milk, hen's egg and, or wheat were negatively associated with HRQoL. Collectively, these issues can be interpreted as proxies for disease severity. Multiple concomitant allergic disorders were associated with worse HRQoL in children with allergy to staple foods. This finding parallels previous findings (5), including our report on HRQoL in Swedish adults with food allergy (12). Our results on number and type of symptoms align with previous findings that disease severity is an important risk factor in HRQoL among those with allergic disorders (23, 24). Furthermore, as assessed by the generic instrument EQ-5D, HRQoL was worse in children with allergies to staple foods compared to controls. Hen's egg was the most common offending staple food in our study population. Once previously thought to resolve by school age, it is now recognised that allergy to hen's egg may persist through later childhood, while those with the highest levels of specific IgE to

egg are unlikely to experience tolerance (25). In a recent publication, hen's egg allergy among children was associated with worse parental HRQoL than allergies to tree nuts and, or peanuts (26). Further, hen's egg is also a common adjuvant in childhood vaccinations. As such, prolonged observation following vaccination is warranted (27), which may also negatively impact on HRQoL.

In our study, 7% of cases were allergic to all three staple foods. Multiple food allergies result in a double burden of substantial food avoidances and strict dietary management to ensure that nutritional needs are being met. Much of the responsibility of this double burden is likely to be borne by the parents, thereby impacting their HRQoL (26). But, school-aged children assume some of this responsibility as they begin to understand their food allergies (28), while even very young children may recognise that the foods they are offered differ from those offered to their peers.

We further considered HRQoL in three different domains: Emotional Impact, Food Anxiety, and Social and Dietary Limitations. Calculated based on parent-responses for age-appropriate questions about the child, these domains glean better insight into specific impacts of food allergy on daily HRQoL. Interestingly, we observed no statistically significant inter-domain differences. Yet, these scores were in the midrange of possible scores, indicating that each domain independently impacted HRQoL.

Similar to a previous Swedish report (8), children with allergy to staple foods who had experienced symptoms involving the respiratory and, or cardiovascular systems had significantly worse HRQoL than children without such symptoms. This finding was observed despite the fact that respiratory and, or cardiovascular symptoms were the least common. In contrast, symptoms involving the skin, oral cavity, mucous membranes and, or gastrointestinal tract were the most common symptoms, but were not statistically significantly associated with worse HRQoL. We speculate that children may have either learned to manage these more common symptoms, or did not perceive these symptoms to be associated with acute reactions.

In keeping with our observation that respiratory and, or cardiovascular symptoms were associated with worse HRQoL, we also identified an inverse association between disease severity and HRQoL. But, after disentangling three different proxies for disease severity, we note some interesting findings. One of these proxies, number of staple food allergies, was associated with worse HRQoL. This finding parallels a previous report (29). The association between another proxy, anaphylaxis, and HRQoL has received less attention. In one study, children with allergies to milk, egg, peanuts and, or tree nuts who had caregiver-reported anaphylaxis had worse HRQoL than those with these allergies but without anaphylaxis (26). To our knowledge, we are the first to report on HRQoL and anaphylaxis among children allergic to the staple foods cow's milk, hen's egg and, or wheat. The final proxy, possession of an EAI, is most intriguing. Although a doctor-prescribed EAI highlights the potential for an acute and emergent food reaction, we had previously speculated that possession of an EAI would have reduced anxiety and thus improved HRQoL.

Our group recently reported that Swedish households with children allergic to at least one staple food had nearly €4000 higher annual costs than households without a child allergic to staple foods (30). The burden of the additional costs may impact on HRQoL among

children and their families. Moreover, as worse HRQoL predicts higher healthcare costs (31), our findings can be used to inform healthcare providers, decision makers and analysts. Our cases may not represent typical food allergy patients. All cases were allergic to at least one staple food and many had experienced severe disease. These factors may have contributed to worse HRQoL than reported in other studies. However, we used a questionnaire that has been shown to be robust over time in children with severe food allergies (16). Our results align with those of Wassenberg et al (15), suggesting that our restrictions still render the findings generalizable. We also acknowledge the relatively low number of participants. Nonetheless, we demonstrated statistically significant findings regarding different aspects of food allergy, and speculate that a larger number of participants may have permitted detection of more nuances in HRQoL. Additionally, small sample sizes precluded gender-stratified analyses of HRQoL by the number of offending foods or symptoms, or disease severity. As evidence on gender differences in HRQoL in allergic individuals is collectively inconclusive (5, 29), future research is warranted. Finally, although the severity of concomitant allergic diseases may have influenced perceptions of HRQoL, our data precluded such analyses.

We highlight three considerable strengths of this study. First, to our knowledge, we are the first group to report on HRQoL among children, in Sweden or elsewhere, allergic to the staple foods, cow's milk, hen's egg and, or wheat. Second, a disease-specific questionnaire provided insights into the impact of food allergy on HRQoL that could not have been gleaned via a generic questionnaire (11). Third, cases had objectively-diagnosed allergy to cow's milk, hen's egg and wheat, thus providing a true insight of the impact of staple food allergy on HRQoL.

In conclusion, HRQoL is negatively associated with allergy to the staple foods cow's milk, hen's egg and, or wheat in children. Children with staple food allergies and who had a previous severe reaction had worse health-related quality of life than children with staple food allergies, but less severe reactions. Use of a disease-specific questionnaire helps disentangle the impact of food allergy on HRQoL.

List of Abbreviations

EAI	Epinephrine auto-injector
EQ-5D	EuroQol Health Questionnaire, 5 Dimensions
FAQLQ-PF	Food Allergy Quality of Life Questionnaire – child form based on parental report
HRQL	Health-related quality of life
IgE	Food specific Immunoglobulin E antibodies
95% CI	95 th percent confidence interval

Competing Interests

All authors declare that they have no conflicts of interest.

Contributions

JLPP and SAJ carried out the analysis and statistical evaluation of the results.

JLPP, SAJ, EÖ, RJMM and SA drafted the manuscript.

SED and SA supervised the progress of the study.

All authors made substantial contributions to the conception and design of the study. All authors revised the manuscript for intellectual content and approved the manuscript prior to publication.

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References

1. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. *Lancet* 2013;382:1656-64.
2. Sicherer SH. Food allergy. *Lancet* 2002;360:701-10.
3. Covaciu C, Bergström A, Lind T, Svartengren M, Kull I. Childhood allergies affect health-related quality of life. *J Asthma* 2013;50:522-8.
4. Kiotseridis H, Cilio CM, Bjermer L, Tunsäter A, Jacobsson H, Dahl A. Grass pollen allergy in children and adolescents-symptoms, health related quality of life and the value of pollen prognosis. *Clin Transl Allergy* 2013;3:19.
5. Marklund B, Ahlstedt S, Nordström G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health Qual Life Outcomes* 2006;4:48.
6. Mo F, Choi BC, Li FC, Merrick J. Using Health Utility Index (HUI) for measuring the impact on health-related quality of Life (HRQL) among individuals with chronic diseases. *Scientific World J* 2004;4:746-57.
7. Roy KM, Roberts MC. Peanut allergy in children: relationships to health-related quality of life, anxiety, and parental stress. *Clin Pediatr (Phila)* 2011;50:1045-51.

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8. Östblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy* 2008;63:211-8.
 9. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, Oude Elberink JN, Raat H, DunnGalvin A, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy* 2010;65:238-44.
 10. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. *N Engl J Med* 1996;334:835-40.
 11. Salvilla SA, Dubois AE, Flokstra-de Blok BM, Panesar SS, Worth A, Patel S, et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. *Allergy* 2014;69:834-44.
 12. Jansson SE, Heibert-Arnlin M, Middelveld RJ, Bengtsson UJ, Sundqvist AC, Kallström-Bengtsson I, et al. Health-related quality of life, assessed with a disease-specific questionnaire, in Swedish adults suffering from well-diagnosed food allergy to staple foods. *Clin Transl Allergy* 2013;3:21.
 13. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008;38:977-86.
 14. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
 15. Wassenberg J, Cochard M-M, DunnGalvin A, Ballabeni P, Flokstra-de Blok BMJ, Newman CJ, et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012;23:412-19.
 16. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire – Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy* 2010;40:476-85.
 17. Liberman JA, Sicherer SH. Quality of life in food allergy. *Curr Opin Allergy Clin Immunol* 2011;11:236-42.
 18. van der Velde JL, Dubois AE, Flokstra-de Blok BM. Food allergy and quality of life: what have we learned? *Curr Allergy Asthma Rep* 2013;13:651-61.
 19. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States : report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-58.
 20. World Health Organization. Process of translation and adaptation of instruments. 2013 [04 November 2013]; Available from: http://www.who.int/substance_abuse/research_tools/translation/en/.
 21. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;47:373-80.
 22. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-108.
 23. Kimura T, Yokoyama A, Kohno N, Nakamura H, Eboshida A. Perceived stress, severity of asthma, and quality of life in young adults with asthma. *Allergol Int* 2009;58:71-9.

24. Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001;108:S45-53.
25. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120:1413-7.
26. Howe L, Franxman T, Teich E, Greenhawt M. What affects quality of life among caregivers of food-allergic children? *Ann Allergy Asthma Immunol* 2014;113:69-74.
27. Settipane RA, Siri D, Bellanti JA. Egg allergy and influenza vaccination. *Allergy Asthma Proc* 2009;30:660-5.
28. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010;65:933-45.
29. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boestra BJ, Oude Elbernik JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009;39:127-37.
30. Protudjer JLP, Jansson SA, Arnlinde Heibert M, Bengtsson U, Kallström-Bengtsson I, Marklund B, et al. Household costs associated with objectively-diagnosed allergy to staple foods in children and adolescents. *J Allergy Clin Immunol: In Practice* 2015;3:68-75.
31. Seid M, Varni JW, Segall D, Kurtin PS. Health-related quality of life as a predictor of pediatric healthcare costs: a two-year prospective cohort analysis. *Health Qual Life Outcomes* 2004;2:48.

Figure legends

Figure 1. Flow chart detailing enrolment of children with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or wheat

Figure 2. Domain-specific and overall health-related quality of life mean scores and 95th per cent confidence intervals of the FAQLQ-PF* for children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or wheat

*FAQLQ-PF subscales 1-7 where 1 corresponds to best possible HRQL and 7 corresponds to worst possible HRQL

Abbreviations: *EI* Emotional Impact, *FA* Food Anxiety, *SDL* Social and Dietary

Limitations, *HRQoL* Health-related quality of life

Figure 3. Linear regression analyses for food allergy symptoms in children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or wheat

*p<0.05, compared to children without the respective symptoms but with allergy to the staple foods cow's milk, hen's egg and, or wheat

Abbreviations: *OAS* Oral allergy syndrome; *MM* Mucous membranes; *Resp* Respiratory; *GI* Gastrointestinal; *CV* Cardiovascular

Figure 4. Health-related quality of life*, as assessed via FAQLQ-PF and number of symptoms for children (n=85) with objectively-diagnosed allergy to the staple foods, cow's milk, hen's egg and, or wheat

*FAQLQ-PF scale 1-7 where 1 corresponds to best possible HRQL and 7 corresponds

to worst possible HRQL

†p<0.04

Appendix A. Questions* included in the calculation of domain-specific scores, Food Allergy Quality of Life Questionnaire-Parent Form (FAQL-PF)

Emotional Impact (EI)	
Age of child (years)	Corresponding questions
0-3	2, 6, 7, 9, 10 and 11
4-6	2, 6, 7, 9, 10, 11, 23, 24, 25 and 26
7-12	2, 6, 7, 9, 10, 11, 23, 24, 25, 26, 27, 28 and 30

Because of food allergy my child feels...

2. Different from other children

Because of food allergy my child...

6. Experiences physical distress

7. Experiences emotional distress

Because of food allergy my child has been negatively affected by...

9. Receiving more attention more attention than other children of his/her age

10. Having to grow up more quickly than other children of his/her age

11. His/her environment being more restricted than other children of his/her age

Because of food allergy my child...

23. Is more worried in general than other children of his/her age

24. Is more cautious in general than other children of his/her age

25. Is not as confident as other children of his/her age in social situations

26. Wishes his/her food allergy would go away

Because of food allergy my child feels...

27. Worried about his/her future (opportunities, relationships)

28. Many people do not understand the serious nature of food allergy

30. Food allergy limits his/her life in general

Food Anxiety (FA)	
Age of child (years)	Corresponding questions
0-3	1, 4 and 5
4-6	1, 4, 5, 16, 17, 20 and 21
7-12	1, 4, 5, 16, 17, 20, 21 and 29

Because of food allergy my child feels...

1. Worried about food
4. Afraid to try unfamiliar foods
5. Concerned that I am worried that he/she will have a reaction to food
16. Worried when going to unfamiliar places
17. Concerned that he/she must always be cautious about food
20. Concerned about accidentally eating an ingredient to which he/she is allergic
21. Worried when eating with unfamiliar adults/children
29. Concerned by poor labelling on food products

Social and Dietary Limitations (SDL)	
Age of child (years)	Corresponding questions
0-3	3, 8, 12, 13 and 14
4-12	3, 8, 12, 13, 14, 15, 18, 19 and 22

Because of food allergy my child feels...

3. Frustrated by dietary restrictions

Because of food allergy my child...

8. Has a lack of variety in his/her diet

Because of food allergy my child's social environment is restricted because of limitations on...

12. Restaurants we can safely go to as a family
13. Holiday destinations we can safely go to as a family

Because of food allergy, my child's ability to take part has been limited...

14. In social activities in other people's houses (*sleepovers, parties, playtime*)
15. In preschool/school events involving food (*class parties/treats/lunchtime*)

Because of food allergy my child feels...

18. 'Left out' in activities involving food
19. Upset that family social outings have been restricted by the need to plan ahead
22. Frustrated by social restrictions

*All questions are answered on a 7 grade scale were 1 is "not at all" and 7 is "extremely"

Table 1. Descriptive allergy characteristics of the cases (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat

	n	(%)
<i>Offending staple foods</i>		
Cow's milk	51	60.0
Hen's egg	65	75.5
Wheat	8	9.4
<i>Number of staple food allergies</i>		
1	52	61.2
2	27	31.8
3	6	7.1
<i>Parent-perceived or doctor-diagnosed allergies to other foods</i>		
Tree nut	38	44.7
Peanut	36	42.4
Fruit	19	22.4
Vegetables	6	7.1
Fish	6	7.1
Shellfish	5	7.1
Soy	7	8.2
Sesame seed	8	9.4
<i>Number of offending foods*</i>		
1	25	29.4
2	18	21.2
3	8	9.4
>3	34	40.0
<i>Symptoms</i>		
Skin	72	84.7
Oral cavity	56	65.9
Mucous membrane	62	72.9
Respiratory	55	64.7
Gastrointestinal	61	71.8
Cardiovascular	20	23.5
<i>Number of concomitant allergic disorders†</i>		
0	10	11.8
1	17	20.0
2	26	30.6
3	14	16.5
4	15	17.6

*Includes at least 1 objectively-diagnosed staple food, as well as any parent-perceived or doctor-diagnosed allergy to other foods

†asthma, allergic rhinitis, allergic conjunctivitis, eczema

Table 2. Disease severity and health-related quality of life (HRQoL) in children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat

		EQ-5D*			FAQLQ-PF†		
		n	Mean	p-value	n	Mean	p-value
<i>History of anaphylaxis</i>	Yes	43	0.88	0.09	44	3.59	0.001
	No	40	0.79		41	2.56	
<i>Epinephrine autoinjector</i>	Yes	35	0.91	0.01	36	3.48	0.03
	No	46	0.78		47	2.76	
<i>No. of food allergies</i>	>3	37	0.84	0.89	34	3.50	0.03
	≤3	46	0.83		51	2.60	

*Generic EQ-5D questionnaire on a scale of 0.0-1.0, where 1.0 corresponds best possible HRQoL and 0.0 corresponds to worst possible HRQoL; based on parent-report

†FAQLQ-PF on a scale of 1-7, where 1 corresponds to best possible HRQoL and 7 corresponds to worst possible HRQoL; based on parent-report.

Figure 1. Flow chart detailing enrolment of children with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat

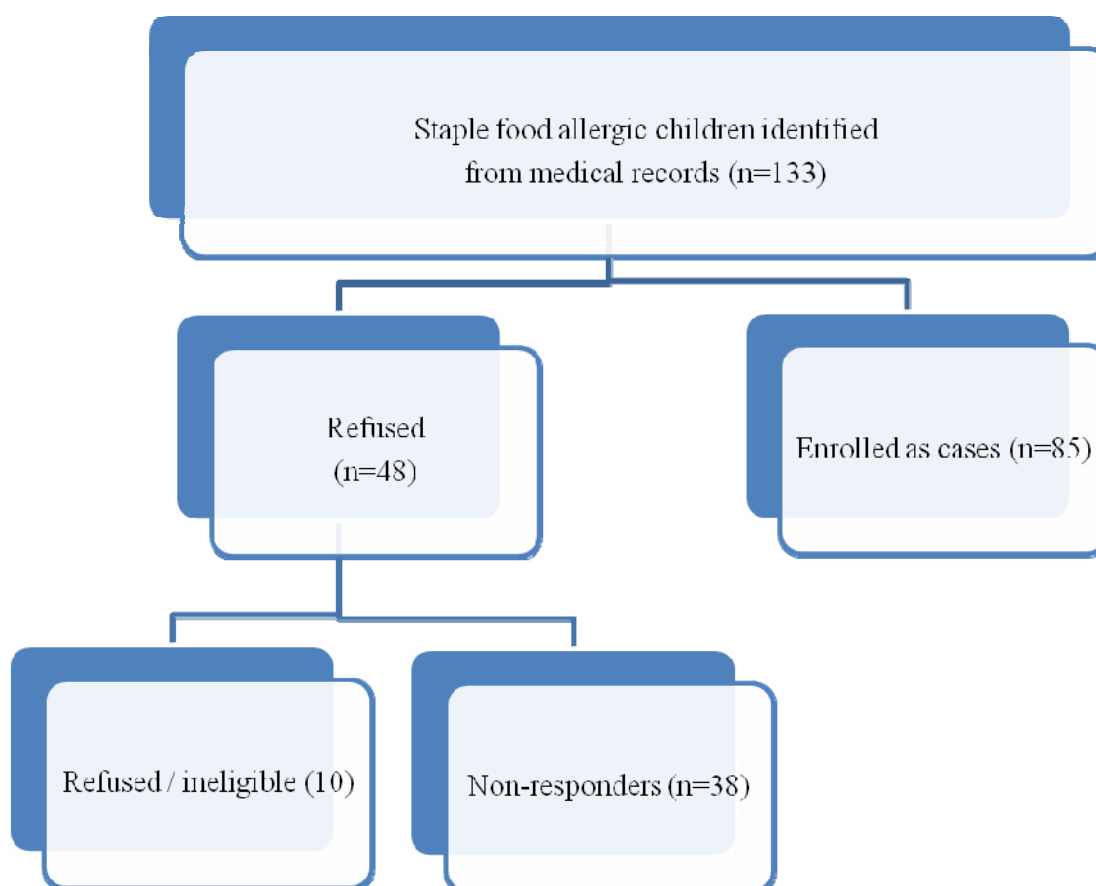
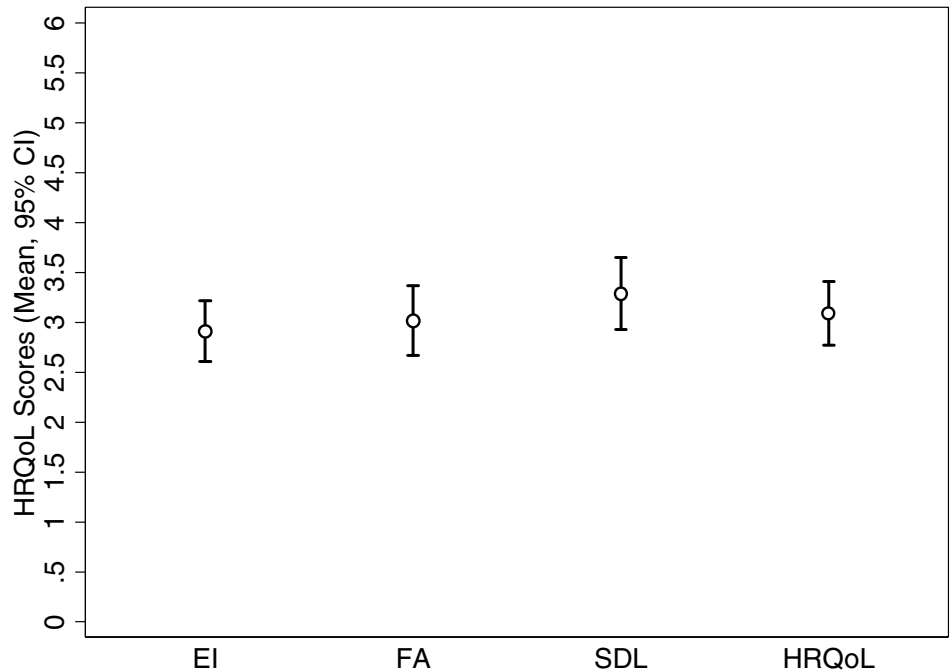


Figure 2. Domain-specific and overall HRQoL mean scores and 95th per cent confidence intervals of the FAQLQ-PF* for children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat

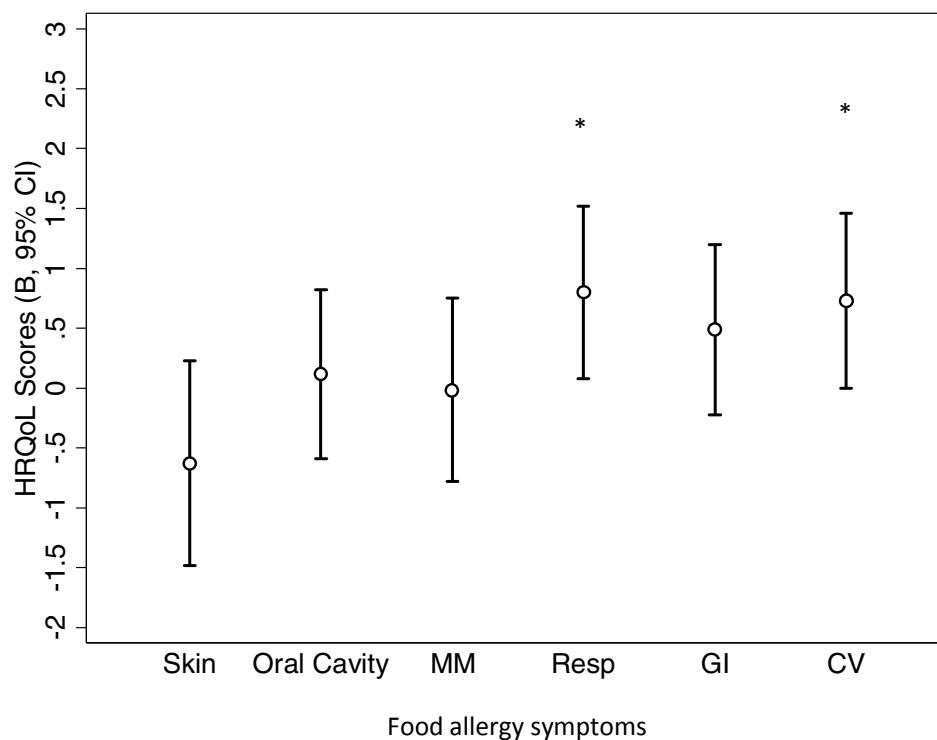


*FAQLQ-PF subscales 1-7 where 1 corresponds to best possible HRQoL and 7 corresponds to worst possible HRQoL

Abbreviations: *EI* Emotional Impact, *FA* Food Anxiety, *SDL* Social and Dietary

Limitations, *HRQoL* Health-related quality of life

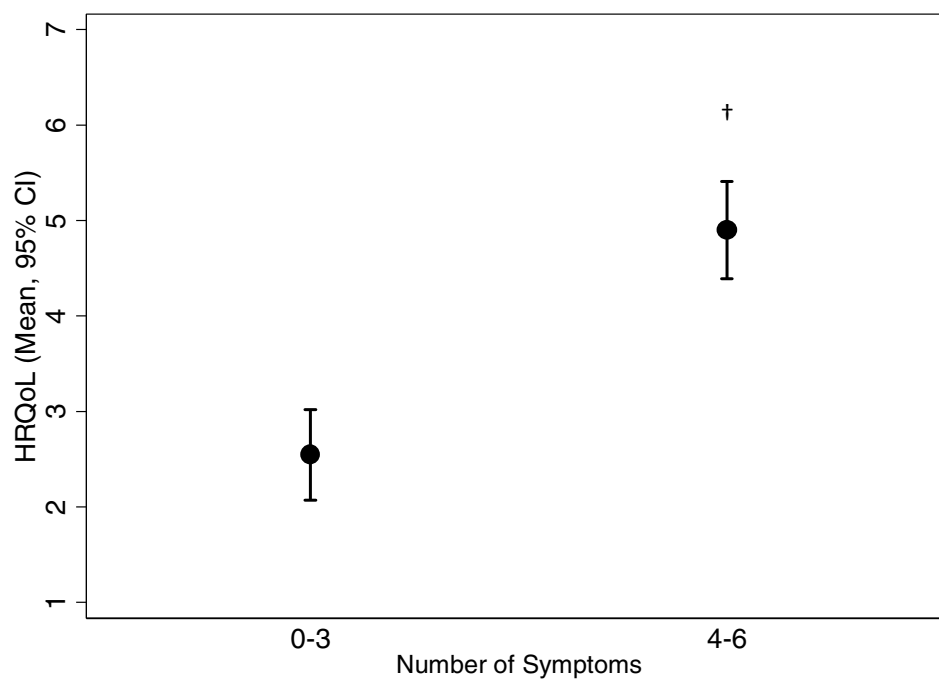
Figure 3. Linear regression analyses for food allergy symptoms in children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat



*p<0.05, compared to children without the respective symptoms but with allergy to staple foods

Abbreviations: *MM* Mucous membranes; *Resp* Respiratory; *GI* Gastrointestinal; *CV* Cardiovascular

Figure 4. Health-related quality of life*, as assessed via FAQLQ-PF and number of symptoms for children (n=85) with objectively-diagnosed allergy to the staple foods cow's milk, hen's egg and, or, wheat



*FAQLQ-PF scale 1-7 where 1 corresponds to best possible HRQoL and 7 corresponds to worst possible HRQoL

†p<0.04