



Psychosocial Mediators of Change and Patient Selection Factors in Oral Immunotherapy Trials

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Abstract

Health-related quality of life (HRQL) is influenced by physiological, psychological, and environmental variables and can be best understood by considering the interactions of factors that cut across multiple levels. One of the most important issues relating to treatment in food allergy is to identify, describe, and define predictors that may contribute to modify HRQL outcomes. The research presented demonstrates that measures of HRQL are able to distinguish key features of known groups (e.g. relating to reaction severity, treatment, allergen type/number, expectation of outcome) and delineate impact on hitherto unknown groups (e.g. relating to personality types and coping styles). This heterogeneity may explain why HRQL or other patient-related outcomes may differ in individuals during, or following any treatment or intervention. Patient-reported outcomes are relatively poorly defined to date. Since HRQL has only been studied in relatively few oral immunotherapy trials to date, primarily looking at caregiver HRQL, it is unclear which factors, measures, or subscales are most predictive of short- and/or long-term treatment outcomes for which type of patient, and which time points for measurement are most informative. A standardised protocol that incorporates HRQL and other relevant patient-related outcome measures and agreed definitions of outcomes would allow for the comparison of efficacy of food allergy treatments between centres, trials, or countries. Further evidence-based research aimed at exploring the effects of interventions on outcomes in food allergy is needed, including the influence of patient and parent factors on protocol design. To this end, it is vital that patient-related outcomes such as improved HRQL are seen as a primary outcome and are measured at multiple intervals during the trial duration and beyond. The creative use of methods and designs (both qualitative and quantitative) to better understand the role of HRQL in immunotherapy treatment trials will enable improved modelling of the costs, risks, and benefits of any treatment. Systematic analysis and modelling of antecedent factors, mediators, and outcomes will be important to boost intervention effects and to maximise the overall benefits of treatment.

Keywords Psychosocial · Mediators of change · Patient selection factors · Oral immunotherapy trials

Introduction

Food allergy is a major public health concern affecting up to 20 million European citizens, including around 1 in 20 infants, with high costs to public health services [1–4]. Admission rates for anaphylaxis have increased approximately 3-fold between 2005 and 2012 [5–9]. In the USA, prevalence has doubled in 10 years, leading to > 300,000 annual hospital visits

with estimated costs of \$24.8 billion annually [7]. Ninety per cent of food allergy is caused by eight foods (milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish). Allergy to peanut, tree nut, fish, shellfish, and sesame seed is considered to be lifelong in 80–90% of cases, and potentially severe. Reactions can occur upon initial exposure and from minimal quantities. Symptoms range from mild (itching, swelling, hives, etc.) to more systemic involvement (gastrointestinal, cardiac, respiratory, or multi-system involvement). Allergen avoidance and self-injectable epinephrine are the current standard of treatment for food allergy, but accidental ingestion is common, causing frequent and sometimes life-threatening reactions [8–11]. Significant provider-level heterogeneity in food allergy diagnosis/management and variations in advising/counselling patients regarding individual risk and natural history of disease, together with diverse and unclear food labelling, can lead to uncertainty,

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confusion, worry, and low confidence in managing food allergy [12–18].

Patient-related outcome measures (PROMs) are increasingly being used in medical and health research. Measures of symptoms, activity limitations, health status, health-related quality of life (HRQL), and quality of life (QOL) completed by patients are all examples of PROMs [19, 20].

QOL is a broad multidimensional concept that includes subjective evaluations of both positive and negative aspects of life, including multiple life domains such as jobs, housing, and health. HRQL is a health-focused QOL concept that encompasses aspects of health that influence QOL ratings. At an individual level, HRQL includes physical and mental health perceptions and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status [13]. At an environmental level, HRQL includes resources, conditions, policies, and practices that influence a population's health perceptions and functional status. HRQL is an important concept consideration because it can contribute to evaluating the appropriateness and effectiveness of both individual- and system-level interventions and outcomes. Specifically, data on the multiple domains of HRQL can inform decisions about innovative clinical practices, new technologies, and resource allocation. HRQL measures provide critical data for selecting among alternative interventions and for guiding decision-making when there is a trade-off between treatment and HRQL [14]. HRQL measures can be generic or disease specific. The development and increased use of disease-specific HRQL measures have ensured that the impact of medical conditions and/or treatments are now being evaluated from the perspective of their impact on the specific patient's everyday life. This construct is consistent with the emphasis on 'patient-centred care' (health care responsive to the person's wants, needs, and preferences), a principle stressed in the Institute of Medicine reports on quality [21].

Clinicians and policymakers increasingly recognise the importance of measuring HRQL to inform patient management and policy decisions. Evidence shows that HRQL measures developed specifically for food allergy are more reliable indicators of the positive and negative impact of disease and treatment than clinical opinion or even some more traditional objective measures in tracking short- and long-term patient outcomes. Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) emphasise that outcome measures selected for a study should be well targeted to the specific patient population, which fundamentally rules out the use of generic PROMs [22–24]. Both bodies now consider the most widely used generic PROM, the SF-36, to be unsuitable for making claims about the value of treatments.

Research has shown that food allergy-specific measures are valid and reliable and are responsive to important

clinical changes [25–35]. Research into HRQL in food allergy has also helped to raise awareness of patient issues and provided a means of individualised assessment for a patient or parent. The Food Allergy Quality of Life Questionnaires (FAQLQ) are disease-specific developmentally appropriate measures [25–35] that have been developed to assess HRQL in food allergy for all age groups and parents and are the most frequently used HRQL tools in food allergy research and practice. These include the Parental Burden (PB), Parent Proxy Form (PF), the Child Form (CF), the Teen Form (TF), and the Adult Form (AF). The questionnaires can be used to measure cross-sectional differences in quality of life between patients at a point in time—or longitudinal changes in HRQL.

Research on HRQL in food allergy has shown a strong adverse impact of the condition on parents and patients of all ages. The central concerns relate principally to the psychological impact of living with food allergy followed by the impact of dietary and social restrictions. The most significant impairment is the persistent fear of an adverse reaction, which has more profound effects on emotional and social aspects of a patient's everyday life, than clinical reactivity induced by food intake [36, 37]. With this in mind, it appears intuitive that a treatment that induces tolerance (or sustained unresponsiveness) would improve the lives and safety of patients, particularly for peanut allergy.

Recent studies have explored the efficacy of immunotherapies such as oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) immunotherapies [38–44]. In a systematic review in 2017, the European Academy of Allergy and Clinical Immunology (EAACI) assessed evidence on the effectiveness, safety, and cost-effectiveness of allergen immunotherapy (AIT) for IgE-mediated food allergy [45]. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated SLIT, and one study evaluated EPIT. The majority of these studies were in children.

Twenty-seven studies assessed desensitisation, and eight studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitisation (risk ratio (RR) = 0.16, 95% CI 0.10, 0.26) and suggested, but did not confirm, sustained unresponsiveness (RR = 0.29, 95% CI 0.08, 1.13). Only one study reported on disease-specific HRQL, which reported no comparative results between OIT and control groups. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses. Thus, although different research groups have used

diverse protocols for the preparation of food allergens, dose escalation, maintenance dose regimens, and OFC procedures, there have been successes in desensitisation, with some mechanisms underlying immunologic changes after immunotherapy have been shown. In studies of OIT, adverse reactions were usually localised, but severe systemic reactions were observed in certain populations [43, 45, 46]. Studies of SLIT have demonstrated minimal side effects, but overall efficacy is lower than that seen with OIT [45–47].

With multiple small exploratory trials and some large randomised-controlled phase 2 trials recently published and under way, there is a clear progress and interest toward making oral immunotherapy (OIT) a treatment option for patients suffering from food allergies. The use of HRQL measures in OIT can widen the parameters of benefits and harms of these new treatments and allow for the development of process and outcome quality indicators.

However, there are particular patient-related issues to be addressed before OIT becomes an accepted option outside of the research setting, over and beyond safety, tolerability, and efficacy parameters. One of the most important questions relates to understanding what aspects (if any) of HRQL, improve for whom, and how and why does this improvement occur. To address this, we must investigate the relationships between clinical variables, outcomes, and measures of PROMs (particularly HRQL) to determine what predicts and mediates good patient outcomes. An objective evaluation of HRQL and other patient-related outcomes is needed. A clear understanding of the relationship between treatment outcomes and HRQL will facilitate the design of optimally effective interventions and treatments. We can then identify critical intervention components that influence behavioural and other mediators that in turn impact the intended therapeutic outcomes [47]. We will also be able to elicit the critical time points for administration of such measures, which can inform standardisation of treatment protocols. As therapeutic efforts focus more on improving patient function and well-being, the need to understand these relationships will increase.

This chapter will firstly examine studies of HRQL in food allergy to identify potential psychosocial mediators of change in OIT treatment, and patient selection factors. Secondly, we will investigate the impact of OIT on patient-related outcomes in studies that have used HRQL measures. Finally, in the ‘Discussion’ section, we will suggest methods and designs to better understand the role of HRQL in immunotherapy treatment trials that will enable better modelling of the costs, risks, and benefits of this promising therapy.

The chapter does not focus on selection of questionnaires, which requires consideration of several key quality standards, including the development processes, instrument scaling, psychometric properties, and cultural

translation and adaptation processes. These issues have been discussed elsewhere [48, 49].

Impact of Uncertainty and Fear of Reactions on HRQL

In one of the first studies on children in 2003, using a generic measure, the HRQL of children with peanut allergy was found to be significantly lower than that of patients with type 1 diabetes [50]. The most significant impairment was the persistent fear of an adverse reaction, which was not seen as calculable. In the course of development and validation of the FAQLQ questionnaires, participants of focus groups suggested that the anxiety associated with the risk of a potential reaction has more profound effects on emotional and social aspects of a child’s everyday life, than clinical reactivity induced by food intake [33]. Subsequently, the importance of a subscale assessing this aspect of anxiety was confirmed using clinical impact and factor analytic methodologies and was found to affect not only allergic children and adolescents but also their parents [27]. Children were also found to be ‘generally anxious’, that is the anxiety associated with food had ‘generalised’ to non-food situations. In some cases, children perceive the use of public transport, going to parties, or travelling on holiday as life-threatening [51–53].

‘Living with uncertainty’ appears as a central theme for all age groups with food allergy, including parents. One of the sources of uncertainty is reactions, that is how much allergen may trigger a reaction, how severe that reaction may be, and when and if the next reaction will occur. During the longitudinal validation of the FAQLQ-PF [14], it was found that a food challenge may alleviate this uncertainty and attendant anxiety. The FAQLQ-PF was completed by parents of children 0–12 years before the child underwent a clinically indicated food challenge, and at 2 months and 6 months post food challenge. Eighty-two children underwent a challenge in total (42 positive; 40 negative). Although significant differences were found between positive and negative groups on all subscales and total score at 6 months [$F(2,59) = 6.221$, $p < 0.003$], we found HRQL improved significantly post challenge time points (all $p < 0.05$) for both positive and negative. A possible explanation for improvement in the ‘positive’ groups concerns the impact of uncertainty on perception of HRQL.

Subjective expectation of outcome is a reliable predictor and correlate of self-reported [35, 36]. The Food Allergy Independent Measure (FAIM) measures the perceived risk of an accidental reaction to food and the potential severity of that reaction. It has 7 items answered on a 1–7 response scale with a greater score indicating a higher level of perceived risk of adverse outcome. Items include the chance that an accidental reaction will occur, that it will be severe, that the respondent

will die, and that the respondent or parent will be able to effectively manage that reaction. Subjective expectation of outcome is not only a reliable predictor and correlate of self-reported HRQL in food allergy but is related to the perception of safety and enjoyment in eating out, and the level of stress in parents (both mother and father) and in the family [13]. If the expectation of the likelihood of a reaction is strong and the likelihood of managing that reaction is weak, then there is an increased likelihood of avoiding social events and limiting the variety of foods consumed, compared to individuals who expect a less adverse outcome.

Research has found [15] that up to 40% of parents perceive that their child has a ‘very great chance’ of dying from a reaction if an allergen is accidentally ingested (Fig. 1).

Alleviating uncertainty to any degree has beneficial effects on HRQL. A food challenge (open or double blind) may be valuable, not only as an essential diagnostic tool, but as a therapeutic one [34]. HRQL improved for both children who failed or passed a food challenge, suggesting that by providing a sense of certainty and a safe context, a challenge or treatment may have a positive impact on HRQL, irrespective of outcome. The much feared event, a child having a reaction, was managed with calm and the child was well afterwards, thus decreasing uncertainty, fear, and dread in both the parent and the child. The positive impact on HRQL may also have been reinforced by specialist consultation, personalised information, and interaction with other children with food allergy during the food challenge.

The psychological mechanisms underlying this concept may also be seen in a pragmatic randomised control trial of 24-h helpline access to expert management advice for food allergy-related anaphylaxis in children, which was carried out in the Allergy Referral Centre in University College Cork in Ireland in 2010 [54]. The aim was to measure the effectiveness of providing 24-h specialist paediatric advice in improving the quality of life in children and their families with potentially life-threatening food allergy (peanut, nut, egg, and multiple),

by comparing HRQL in intervention ($N=24$) and control ($N=26$) groups, at baseline and at 1, 6, and 12 months.

The study also sought to compare the number and severity of incidents of suspected allergic reactions in both groups and to compare the clinical and health service outcomes in both groups. The protocol for the helpline was as follows: direct access helpline number to ring in the event of a suspected serious allergic reaction; phone was manned 24 h a day by a member of the paediatric allergy team (paediatric allergist, a paediatrician, a Clinical Research Fellow, and a Clinical Nurse); parents were advised to ring the helpline only in the event of a suspected allergic reaction; number could be shared with anyone acting in loco parentis of the child (teacher, family member, babysitter, etc.); older children could have access to the helpline number, if desired. One of three responses could be given to parents: The event described is likely non-allergic in nature, no treatment is needed; the event described is likely a mild allergic reaction, give antihistamine and observe; or the event described is possibly anaphylaxis, administer the adrenaline autoinjector and call an ambulance to transport your child to hospital.

Results showed that of the 24 children in the intervention group, events were only reported to the helpline for 2 children. For events in which the helpline number was contacted, the allergic reactions were mild and successfully treated with antihistamine only. For events in which the helpline number was not contacted, 5 children had minor allergic reactions which were treated successfully at home with antihistamine. HRQL improved both for those who contacted and did not contact the helpline. Significant difference in HRQL was found between control and intervention groups over the four time points ($p < 0.05$) for all age groups, with better levels of HRQL in the intervention group. These results suggest that food-allergic children and their families were successful in both avoiding the food in question and treating allergic events. In effect, 24-h access to expert guidance, and not just the actual contact and guidance given, was sufficient to have a significant impact on quality of life by providing a ‘safety net’, thus lessening uncertainty and improving confidence in management.

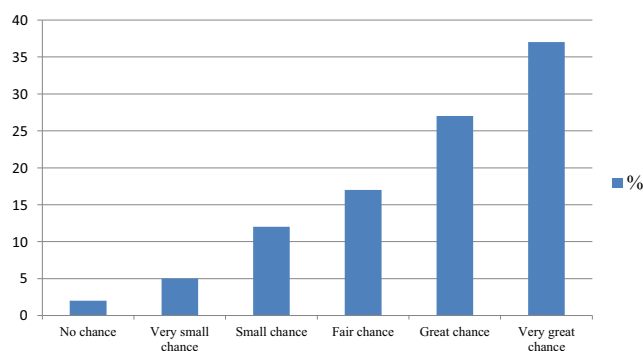


Fig. 1 Living with fear and anxiety: What is the likelihood that your child will die from an allergic reaction? From [54]

The Impact of the Development, Age, and Gender on HRQL

The developmental process programmes physical and psychological health and HRQL over the life course. Differences between age groups on HRQL have been found in many studies [25, 28, 33, 34], highlighting the importance of tracking development in order to accurately assess HRQL at any one point or over time. Using the FAQLQ-PF, age differences in impact in an American sample were compared to European samples [15]. In both Europe and the USA, significant age

differences were reported and observed, with impact increasing as the child's age increased (in each case by 1.2 points on the response scale). Figure 2 shows that developmental differences seen in FAQLQ-PF scores most likely reflect the social and emotional changes that occur around early to middle childhood and into adolescence.

Attention to subscales, in addition to overall score for HRQL, is important in order to provide a comprehensive evaluation of the impact of age and gender. The most affected HRQL domains/subscales vary according to age, gender, and country (Fig. 3). The 'social and dietary limitations' subscale is most impacted in younger children; however, a strong increase in scores indicating worse HRQL in the food anxiety subscale may be seen as the age category increases. Gender differences may also be observed since this impact is particularly pronounced for females (Fig. 3). Overall, girls are impacted more negatively on the 'emotional impact' subscale compared to males, whereas worse HRQL is found for males on the 'social and dietary limitations' subscale.

An interaction between the number of foods, severity of symptoms, number of reactions, and age has also been reported [33, 34, 37]. The impact is more pronounced in older teens and adults [31, 32]. Attention to age and gender and normed/standardised scores are thus essential to ensure measurement precision in clinical and trial settings.

The Impact of Co-morbidity and Poly-allergy on HRQL

Recent studies demonstrate not only that food allergy and asthma often co-exist but also that co-morbidity worsens prognosis. Children with food allergies and asthma are more likely to have near-fatal or fatal allergic reactions to food (among which are respiratory symptoms) and more likely to have

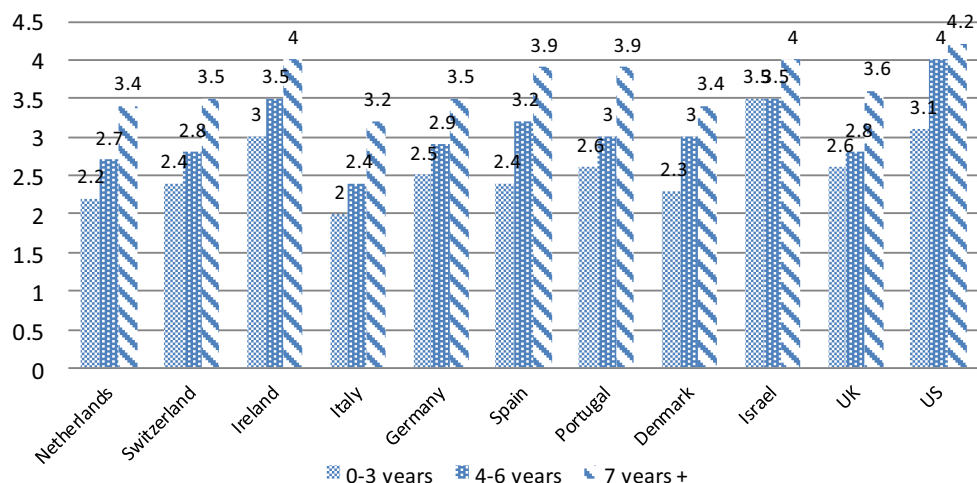
severe asthma [55] with negative impact on HRQL. Compared to patients with single food allergies, patients with multiple food allergies experience a greater decrease in HRQL, are more likely to suffer from dietary deficiencies, and are less prone to spontaneously outgrow their food allergies [55]. HRQL reduced even further in cases where children report gastrointestinal vs respiratory symptoms, and the presence of co-morbid conditions such as asthma and atopic dermatitis [55].

Cross-sectional studies show that feeding dysfunction occurs in 14 to 58.9% of children with eosinophilic gastrointestinal disorders (EGID), which may be co-exist with food allergy [56].

Since children develop feeding skills during infancy and throughout childhood, any disruption of this pattern, caused by discomfort or inflammation, can result in life changing, maladaptive eating behaviours [56–59]. Although studies to date have not focused specifically on food allergy co-morbidity, we do know that children with EGID have poorer psychological functioning, with greater internalising symptomatology and a higher degree of somatization than their healthy peers [60]. Harris et al. [61] found 69% of children with EGID experience poor psychological functioning, ranging from social and school difficulties to depression and anxiety. Parents of children with EGID experience negative changes in all of the functional domains that comprise health-related quality of life (HRQL), using generic measures [56].

Recently, disease-specific questionnaires are being developed for conditions that may co-exist with food allergy [62]. For example, during the ongoing development and validation [63] of the Food Protein-Induced Enterocolitis Syndrome (FPIES) HRQL questionnaires (parent self-report and parent proxy forms), it was found that 60% of the sample of 345 infants (aged 0–2 years) had a co-morbid condition including food allergy and asthma. The majority of parents (85%)

Fig. 2 Distribution of mean scores* for FAQLQ PF, plotted against age group for each European country and for the US. From [27]



*Higher score = worse HRQL

Fig. 3 Age and gender differences in FAQLQ-PF from 0 to 3 age group to 7–12 age group. From [27]

TABLE II. Distribution of mean scores for FAQLQ-PF subscales and total scale for US sample over 3 age groups: Comparison to European average mean score*

Subscale	0-3 y			European average mean	4-6 y			European average mean	7-12 y			European average mean
	M	F	All		M	F	All		M	F	All	
EI	2.67	2.71	2.69		3.55	4.03	3.76		3.91	4.25	4.06	
FA	2.53	2.53	2.53		3.79	4.39	4.05		4.27	4.63	4.42	
SDL	4.22	4.03	4.16		4.01	4.52	4.23		4.29	4.52	4.39	
Total	3.15	3.09	3.13	2.6	3.80	4.34	4.03	3.2	4.16	4.45	4.29	3.8

F, Female; M, male.

*Higher mean score indicates poorer HRQL.

reported that FPIES caused high levels of stress and worry. Parent issues of concern for their children included problems with nutrition, avoidance, sleep, feelings of difference, anxiety surrounding reactions, and feeding problems.

The Impact of Environmental Factors on HRQL

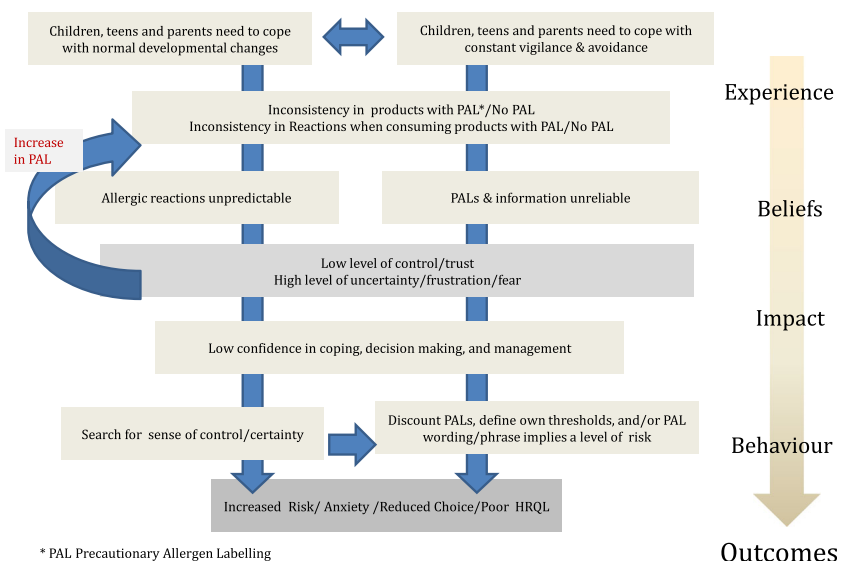
HRQL is influenced by physiological, psychological, and environmental variables and can be best understood by considering the interactions of factors that cut across multiple levels.

Strong moderators of HRQL include the number of foods avoided, the amount of activities that families and friends can take part in, and the level of enjoyment and perception of safety in eating out [62]. Social restrictions are informed by restrictions in diet, highlighting the integral role that food plays in today's world, particularly in socialising. Therefore, it is not surprising that 'avoidance' has an adverse impact on HRQL. Polloni et al. [51] found that mean state anxiety of children with food allergy was significantly higher in 'avoiders' compared with 'non-avoiders' (general population). A significant association was also found between maternal and child state anxiety.

Developmental stage and environment have a strong influence both on the type of event and on the type of food that is encountered or how that event is experienced and managed. When children are young, they rely on parents, which includes speaking and negotiating with restaurant staff, teachers, and other parents and ensuring an activity or food is safe. In cases where a product or food did not cause a reaction, and was seen as 'safe', a subsequent reaction with the same or similar product/food creates more worry and confusion. Inconsistent information from health professionals and other sources (such as from the internet) on the likelihood of reactions or level of avoidance needed, and poor-quality labelling, lowers perception of control and confidence in management. These, together with low general awareness, make diets and social events more restrictive than adolescents and young people in particular believe they need to be [53]. Figure 4 is a flow chart showing the links between poor-quality information, and beliefs, attitudes, and outcomes.

The development of autonomy is an important step in adolescence; however, this may be delayed in some food-allergic adolescents because of a high reliance on parents to ask about allergens in restaurants or remembering to carry an adrenaline autoinjector (AAI) [52, 53].

Fig. 4 'Choice under uncertainty': Flow chart showing the links between poor quality information and beliefs, attitudes, outcomes



Parents are one of the most important actors in a child's environment. Parent attitudes and beliefs have a strong impact on their children's own attitudes and beliefs and hence on HRQL. Parents report that their feeling of risk is always present. Living in a constant state of fear of an accidental food reaction can have a major impact on an individual's HRQL. Research has shown that the restrictions in daily activities are perceived as greater in families with food-allergic children than in families with children with rheumatic disease [50]. Parents face a difficult challenge to ensure children have good nutrition as well as ensuring their children are safe from reactions. Activities which take place outside the home, such as school events, school trips, overnight stays with friends, and parties, are particularly affected. Parents may avoid enjoyable activities such as dining out, travelling, and shopping. In the USA, 41.8% of parents are not comfortable going on vacation during which they spend a night away from home [7, 64, 65]. In turn, children are either excluded from social events or need to be accompanied by their parents [7]. Because of this, parents may struggle in supporting children's independence while controlling their own anxiety and genuine fears of risk. Although many parents perceive the resulting overprotectiveness as not beneficial for their child, they see no alternative [7].

Almost 30% of parents reported visiting their child's school at least once a month to discuss aspects of their child's allergy with teachers and carers. The level of stress and anxiety and the restrictions to everyday activities are greater in families with younger children than those with older children. Heightened worry is particularly noticeable at 'transition points' (such as the move from pre-school to primary school and secondary school) and family conflict can sometimes result from differences in attitude between parents, and between parents and children [52, 53].

Environmental factors drive adolescents and young people to develop particular strategies to deal with allergen avoidance and ensuring emergency medication is available. Risk decision-making around consuming unfamiliar foods is based on parameters such as whether they are eating in a familiar environment, whether their parents are present, the distance to the next emergency department, or the availability of an AAI [7, 53, 66]. For example, living in student accommodation or shared housing, heightened feelings of uncertainty and participants described numerous reactions and fear of reactions, from poor kitchen hygiene and management [53]. Food venues are generally held to be unsafe and hence choice in venue is greatly restricted [7, 52, 53, 66]. Perceived susceptibility and expectation of adverse outcome are therefore higher in new or unfamiliar environments due to the likely increased presence of a particular allergen [52, 53].

Where no information on food ingredients is available, adolescents often report using a strategy whereby they try small amounts and, in the absence of an adverse reaction,

continue eating until symptoms appear [52, 53]. This approach has been shown to lead to more frequent adverse reactions [10, 67]. In a British study, a third of adolescents reported that they had not checked the list of ingredients prior to their last adverse reaction [67]. Only a quarter consistently refrained from consuming products containing trace elements of the relevant allergen. A substantial proportion of individuals (38%) did not have an AAI with them during severe reactions, including those with numerous food allergies, and frequent and severe reactions [7, 10–68]. For those who do carry an AAI, many (of all ages) are unsure as to how and when they should use an autoinjector and even when this step has been taken, they are unclear on how to effectively manage a reaction [53].

As children grow up, they develop a gradual awareness of difference in the social environment. The inability to take part in social rituals, such as accepting food and being subject to special considerations, gives rise to the feeling of 'being apart' from others. The presence of a food allergy has been found to affect school performance with allergic children having a greater number of school absences and in adulthood being less likely to be in full-time employment than their peers [69]. Bullying behaviour toward food-allergic children at school and during leisure time has also been reported [70]. Thirty five percent of children and adults report being bullied and of these greater than 20% were bullied, teased, or harassed by a teacher or other school staff. The children reported, among other things, being threatened with or chased with an allergen, having their safe food removed or contaminated, threats to use or break their autoinjectors, being called names, called blamed for not being allowed to have food at parties, and excluded from activities. Many children did not report this sort of teasing at home for fear of causing their parents more concern. In only 12% of these cases, the bullying had been punished or disciplined. Furthermore, children reported feeling angry, isolated, and confused as to why they were targeted, feeling vulnerable, and being hesitant to eat at school after an incident.

An important mediator of the effectiveness of any change in policy or legislation on food labelling in improving HRQL is at the level of the environment and depends on the attitudes and perceptions of those with food allergy, food providers, and general public.

The change in EU legislation (December 2014) requiring retailers of non-pre-packed foodstuffs to provide customers with information relating to the content of 14 allergens (peanuts, tree nuts, milk, soya, mustard, lupin, eggs, fish, molluscs, crustaceans, cereals containing gluten, sesame seeds, celery, and sulphur dioxide) (at levels above 10 mg/kg, or 10 mg/l) in their products, may improve perceptions of safety and enjoyment in eating out.

A recent study on the impact of the 'Food Information for Consumers Regulation' investigated the experience of eating

out on the Island of Ireland in 2013 for consumers with FHS or a child with FHS, prior to and following (2016) the introduction of the legislation [71]. Results showed that between 2013 and 2016, the legislation had a positive impact of service provision with a significant decrease in number of venues refusing service and food venues reported as more accommodating to those (parents and patients) with a food hypersensitivity. Participants reported a better perception of safety when eating out, improved well-being, and quality of life.

Important factors contributing to perception of safety and quality of life were as follows: ‘more choice in eating venues’, ‘more choice in food venues’, and ‘more choice in destination at both home and abroad’. They also reported ‘eating out more often’. Improvement not significantly influenced by non-modifiable independent factors, such as location, participant type, type of food hypersensitivity (food allergy, coeliac disease, food intolerance, etc.), and past severe reaction, but by modifiable factors, such as better information provision and level of accommodation by staff.

The integrated approaches to food allergen and allergy management (iFAAM) aimed to develop evidence-based approaches and tools for management of allergens in food, integrate knowledge derived from their application into food allergy management plans and dietary advice, and develop strategies to reduce the burden of food allergies in Europe. The iFAAM labelling survey [72] was developed for adults and parents of children with food allergy and distributed across five countries in Europe. iFAAM is a EU-funded project that aims to improve the management of food allergens by the food industry for the benefit of consumers, especially those with food allergies. The general aim of the survey was to understand more about how those living with food allergy assess risk when making decisions based on precautionary allergen (‘may contain’) labelling. The approach focused on assessing consumers’ preference in how the risk of allergen contamination was communicated on the food label within the context of a quantitative risk assessment framework across Europe. The outcomes from this research are intended to inform issues of acceptability and provide a basis for the development of more informative communication around food risk and safety.

The iFAAM survey was targeted at adults and parents of children with food allergy and distributed across five countries ($N = 1582$) in Europe (Ireland, the UK, Germany, the Netherlands, and Spain). Results showed a large proportion of consumers currently do not understand or have any confidence in how food manufacturers communicate the risk of allergen contamination and, for this reason many do not look at precautionary labels. Participants wanted a label that stated clearly that a product had undergone a risk assessment and stated that this would improve anxiety, perception of safety, confidence, and trust. In effect, these results show that clearly communicating to consumers the process that has led to a decision to place a label on a food product may positively

impact on a wide array of attitudes and on HRQL related to making purchasing decisions [72].

The Impact of Coping Style on HRQL

The way in which children and adolescents perceive and cope with chronic health conditions is considered as an increasingly important predictor of health and psychological well-being in clinical and psychosocial research [73]. Since the foundation for food allergy management begins at a young age, taking a developmental perspective in how coping evolves is important [73]. Parental attitudes have a strong impact on how children themselves cope with food allergy [15, 52, 53]. A high proportion of parents were found to be not confident in managing food allergy with regard to recognising, treating a reaction, reading labels, or feeling in control of their environment [74].

Qualitative studies can help to bridge the gap between scientific evidence and clinical practice [75], providing a nuanced picture of complex phenomena, while also allowing for cross case comparison. They are also an important step in the development of quantitative instruments [75]. In food allergy, qualitative studies have typically been carried out with very small samples, making it difficult to discover the pathways between common factors.

A developmental model on experiences, emotions, and management related to growing up and living with food allergy has been described [52]. Data was analysed from 16 focus groups conducted in Ireland, with children aged 6–18 years, and found three main themes: experiences (living with uncertainty, living with difference, living with the rules); search for normality (integration, control, identity, health, well-being); and management and coping (maximisation, balanced adaptation, minimisation). The applicability of this developmental model was then investigated in a large data set from six countries (Ireland, England, Scotland, the USA, the UK, Italy, Australia) and to generate a first phase item pool that will form the basis for four short user-friendly FA-specific questionnaires to measure coping and emotions in children, teens, and young people [53]. In the analysis, attention was paid to any external and internal mediators between emotions and coping in food allergy.

The expanded Food Allergy Coping and Emotions (FACE) developmental model [53] shows how food allergy impacts experiences and emotions in children and young people, mediators of coping style, and demonstrates why outcomes might vary from patient to patient. The use of a large qualitative data set was innovative ($N = 380$). It has five major themes: (i) experiences and emotions; (ii) search for normality; (iii) management and coping; and (iv) ‘external mediators’ and (v) ‘internal mediators’ (between emotions and coping) Fig. 5.

The FACE model describes how the emotions attached to living with food allergy (including embarrassment, fear, anger, frustration, worry, anxiety, and confusion) drive a search for ‘normality’ which in turn gives rise to particular types of coping strategies. The link between emotions and coping is influenced by external and internal mediators (including context, developmental stage, type of allergen and experience of reactions, food allergy beliefs and perception of disease intrusiveness). The themes were present and consistent across countries, with remarkably similar wording and phrasing used by participants, although these differed according to age. Both genders had similar emotions and coping styles although males felt less able to communicate their fears to friends and peers, particularly in adolescence and young adulthood. A further paper specifically relating to parents is currently in preparation.

Early life experiences provide the foundation for later behaviours. The first developmental period occurs between 0 and 7 years, when children feel a strong sense of protection. The period between 8 and 11 years a time of ‘growing awareness’. As their social worlds expand, feelings of ‘otherness’ and difference develop, along with a perception of threat and uncertainty. Increasing autonomy, particularly between the years of 12 to 15, necessitates ‘adaptation’ to new circumstances and unfamiliar contexts. Participants face a ‘tension’ as they attempt to balance a search for

safety with integration and positive identity. In emerging adults, we see a ‘consolidation’ of coping style. Participants’ experiences and the emotions attached to these heighten their perception of threat without impacting constructively on their level of perceived control and confidence in management. Although some who use minimization or maximisation are aware that this type of coping causes them distress or harm, they find it difficult to imagine alternative ways of coping. In contrast, participants who were adaptively balanced used ‘the rules’ flexibly, minimising risk while enjoying a high degree of social integration and positive self-identity. The findings confirm and extend previous qualitative and quantitative research on the experience of living with and managing food allergy, discussed above. Adolescents and young people are at high risk of adverse outcomes relating to reactions [10–13], sense of self [9, 26], management style [13, 14], and mental health and well-being [5–8, 15]. These findings throw light on the possible precursors to these documented outcomes and underscore why HRQL or other PROMs may differ in individuals during, or following any treatment or intervention. Success, as defined by improved HRQL, may therefore necessitate ensuring that intervention protocols are tailored to the characteristics and needs

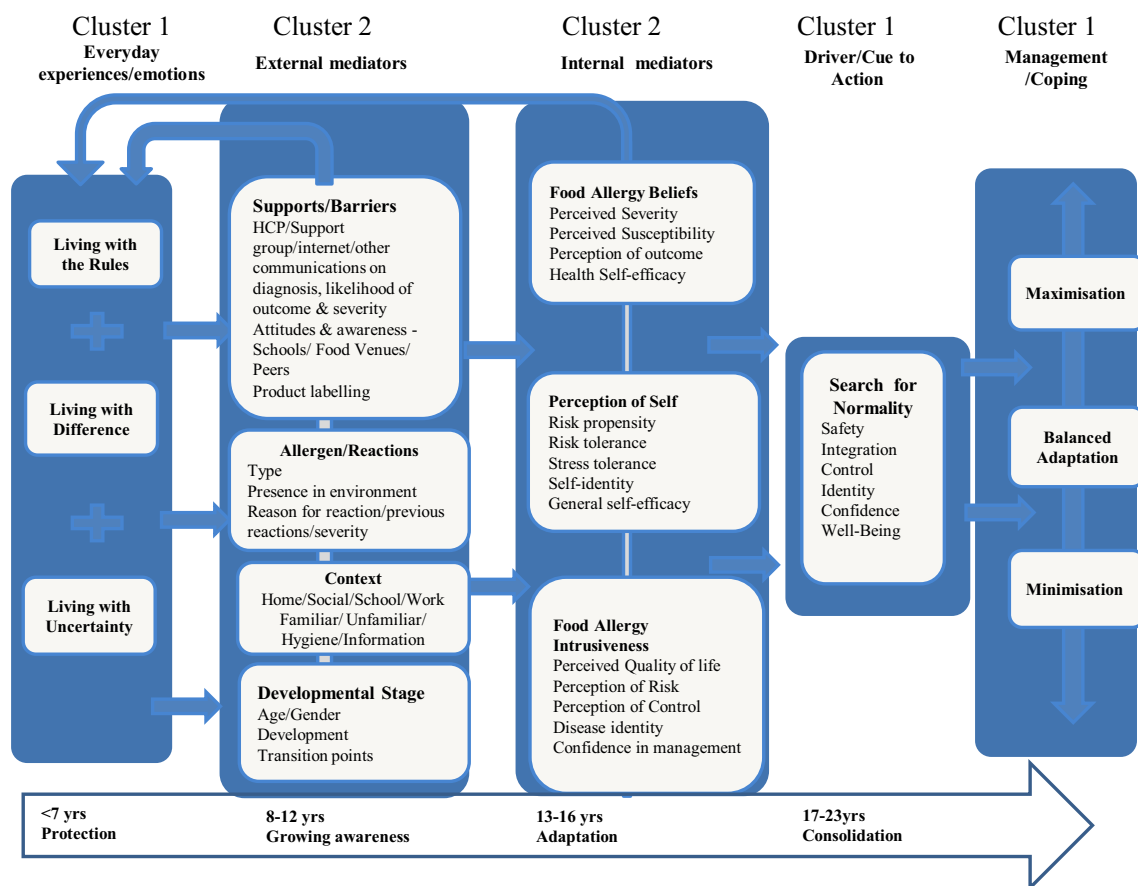


Fig. 5 The Food Allergy Coping and Emotions (FACE) developmental model. From [76]

of patients. Understanding the key emotional and coping factors relating specifically to food allergy may provide an important complement to HRQL and offer a more nuanced or sensitive way to measure outcomes.

The Impact of Self-Efficacy on HRQL

In 2002, the World Health Organization (WHO) released *Innovative Care for Chronic Conditions: Building Blocks for Action*, drawing global attention to the rise of chronic conditions [77]. The document emphasises the importance of putting people at the forefront of their own care, that is supporting, facilitating, and encouraging individuals to make informed decisions about management.

Self-efficacy (SE) is conceptualised as the belief that one can perform confidently and capably in a given situation [78]. It is an important determinant of emotional and behavioural response to stressors. SE is not a fixed trait, but varies with experience and with contextual or environmental factors [78]. Therefore, it can be modified through intervention. S.E. has been found to be a distinct but related concept to HRQL in food allergy [74]. In other healthcare fields, self-efficacy has been associated with successful chronic disease management [79], but has been minimally explored in food allergy. Since it is important that disease-specific measures are developed that are clearly linked to relevant issues for a particular condition or phenomenon, the development of a validated outcome measure for food-allergic families could help better monitor life with the disease, as well as helping to evaluate emerging food allergy therapies, both clinical and educational. Use of such a measure would also allow us to understand how self-efficacy influences HRQL (and vice-versa). A study describing a first phase development of a Caregiver Self-Efficacy Scale for Food Allergy Self-Management (FASEQ) assessed how self-efficacy is related to caregiver food allergy HRQL [74]. The data was collected from a diverse United States caregiver population, including two different groups of caregivers of children with food allergy, multiple patient support groups, and a clinical referral centre. Results supported the preliminary psychometric soundness of the FASEQ as a tool to assess caregiver self-efficacy and self-management in food allergy. The measure comprises eight self-efficacy items comprising two domains covering medical care and social functioning aspects, each of which can differentiate between reaction severity, epinephrine use, race, allergen type, and number of allergens. The FASEQ has a minimally clinically important difference of 0.3. In multivariable analysis, FAQL-PB score is independently associated with FASEQ score. Since they covary, if self-efficacy is improved, HRQL will also improve. The FASEQ is also able distinguish key features of 'known groups' (reaction severity, treatment, allergen type/number). The model also shows that S.E. is an

important but not sufficient predictor of HRQL and therefore other variables, such as age and population type, must be taken into consideration. In addition, individual differences such as illness-perception, personality and health beliefs are likely to influence HRQL and to moderate or mediate the association with self-efficacy [78].

An increased understanding of the interplay between HRQL and self-efficacy may potentially enhance patient-clinician communication and allow for the clinician to select interventions that are appropriate and targeted specifically to that patient. HRQL measures together with the FASEQ might be used as tools to focus communication on coping with food allergy or in difficulties in managing risk and exploring adaptive strategies. Coping skills training and techniques and communications skills might be particularly useful. With regard to treatments or interventions, an increase in self-efficacy is a valid and important outcome, particularly in the context of food allergy, where management is central.

The Impact of Mental Health Factors and Personality on HRQL

Research has shown that children and adolescents with food allergies perform worse in overall general health scores than their non-allergic siblings or healthy controls [25]. With regard to mental well-being, adolescents and young people (between the ages of 13 and 25) with food allergy are at increased risk of developing problems such as anxiety, depression, relational difficulties, and psychological problems in general, when compared to their peers [80–83]. This period is also associated with the highest death rate due to allergic reactions to foods [9–12].

Compliance with clinician advice on safety and management is often poor, leading to adverse outcomes [13–15].

In terms of personality characteristics, research has found that young people with food allergy reported higher levels of alexithymia compared to a matched healthy sample and is associated with anaphylaxis among patients [83]. Alexithymia is a multifaceted personality construct described as 'a lack of words to express emotions' [81, 82]. Alexithymia is described on a continuum and normally distributed in the general population, where prevalence is 10–13% [81, 82]. Interest in alexithymia has increased considerably particularly within interdisciplinary research, with numerous investigations in clinical research, cognitive psychology, neurobiology, and psycho-neuro-endocrinology [84]. There is evidence linking alexithymia to impaired immune function [85, 86], with some research reporting a diminished immune-mediated cellular response in alexithymic individuals with over-secretion of glucocorticoids [87, 88].

Alexithymia may skew the Th-1/Th-2 balance toward Th-2 dominant immunity and lower cell-mediated (Th-1) immune

response and may increase an individual's risk for stress related disorders. The up-regulation of Th-2 response with impaired Th-1 response could contribute to the pathophysiology observed in allergic disease.

The alexithymia construct describes a difficulty in identifying feelings and distinguishing between feelings and the bodily sensations of emotional arousal; constricted imagination and difficulty describing feelings to other people; and a stimulus-bound, externally oriented cognitive style [84]. Alexithymia plays a role in influencing clinical outcomes and is associated with a lack of constructive coping strategies such as the ability to modulate emotional arousal, to properly express or suppress emotions, to gain and use social support, or to cope with painful emotions [84], therefore resulting in avoidant coping and negative affect. Avoidant coping strategies are associated with psychological distress in food allergy and can mediate the link between illness perceptions and outcome [52, 53, 89]. Focusing on and venting of emotions significantly predicted greater stress, somatic symptoms, anxiety and insomnia and severe depression [84]. A recently published study [90] explored the associations between coping strategies, alexithymia, and anxiety among 92 food-allergic adolescents and young adults.

Respondents with higher alexithymia also had higher levels of trait anxiety, used avoidance as coping strategy over and above other coping strategies such as problem solving and positive thinking, were younger in age (< 19 years), will have experienced anaphylaxis, and will have lower social support. Accurate perception of symptoms is a crucial factor for correct self-management in food allergy and may also have an impact on the perception of the effectiveness of any intervention or treatment. Recognising the specific role of affect regulation in health behaviours may constitute an important step in supporting patients. HRQL and other patient outcome measures might be used as tools to focus communication on coping with food allergy or in difficulties in managing risk.

The Impact of Oral Immunotherapy on HRQL

Changing the natural course of disease in patients with food allergy is a hot topic of research. Recent research in food allergy treatment has focused on developing safe and effective therapies, and the most active area of research for food allergy involves immunotherapy [45].

Allergen immunotherapy has been used to treat allergic diseases since the early 1900s [37]. For food allergy, the major forms of immunotherapy are oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).

The first successful use of OIT to treat a food allergy was reported in 1908 in a child with severe egg-induced anaphylaxis [37]. After this first successful trial, no additional trials of

OIT for food allergy were reported until Patriarca et al. [38] published results of a successful OIT for milk, egg, fish, and orange allergies in 1984. Significant progress has been made in the field in the last decade, particularly with regard to allergen-specific immunotherapies [45].

Success is balanced by potential risk of an allergic reaction with every dose. With peanut allergy, the annual rate of severe reactions is 1.6% [45]. In their retrospective study of 5 clinical practices performing peanut OIT in the USA, Wasserman and colleagues [91] reported 95 uses of epinephrine in 352 patients over an average of 1.8 years (annual rate of 22%). However, it must be appreciated that in the context of OIT, severe reactions are anticipated and thus recognised and treated promptly. Only 3 of the 95 reactions required a second epinephrine and none required more intensive treatment [91]. More importantly, it should be noted that from a patient's point-of-view, those severe reactions are generally acceptable. Food allergy is associated with a decrease in quality of life mainly due to the anxiety of potential reactions and secondary social impact. The context of 'expected' reactions with OIT differs from the uncertain but potential accidental reactions with avoidance. DunnGalvin et al. [54] examined factors related to HRQL that may influence parents' decision to allow their children to participate in research on clinical food allergy. Parents of children with food allergies were offered investigational oral immunotherapy (OIT) in a regular outpatient clinic. Forty parents (group A) declined, and 25 parents (group B) agreed to take part. Both groups agreed to complete the Food Allergy Quality of Life–Parent Form and the Food Allergy Independent Measure. Children were aged between 1 and 12 years (mean 6.5 years). Groups A and B displayed a similar and typical distribution for gender, age, number of foods, severity and number of symptoms, and socioeconomic variables. Parents who chose to enrol their children in the OIT trial reported a similar impact of food allergy on the HRQL of their children as parents of children who did not volunteer for the study. Participating parents perceived a significantly higher likelihood (odds ratio 6.753) of their child having a severe reaction and dying if food is ingested. By using this model, the likelihood of taking part in immunotherapy could be predicted accurately in 90% of cases. This study, together with finding that a food challenge (open or double blind) may be valuable, not only as an essential diagnostic tool, but as a therapeutic one [14] has implications for the selection, recruitment and management of patients in OIT trials. The results suggest that by providing a sense of certainty and a safe context, a treatment may have a positive impact on HRQL, irrespective of outcome, and echoes the point made above on tailoring interventions to the characteristics and needs of patients.

This positive impact may have been reinforced by specialist consultation, personalised information and interaction with other children with food allergy during the food challenge.

Preliminary results from a qualitative study carried out in the USA, suggest that OIT operates as a buffer against an accidental exposure and is a major motivator for entering a child in peanut allergy therapy [92], personal communication). Nineteen semi-structured interviews of OIT/EPIT participants were conducted with caregivers. Partial review of the coded transcripts to date show that caregivers of peanut allergic children enrolled in OIT/EPIT phase III trials are motivated by the potential of decreased reaction severity upon exposure, increased time to react to allow for assessment by others, or increased threshold of peanut exposure tolerated. Interestingly, some, but not all, caregivers reported that trial participation decreased their anxiety secondary to experiencing a severe allergic reaction that was promptly treated.

However, as noted in the 'Introduction' section, despite an increase in the awareness and prevalence of food allergy, and the adverse outcomes reported in HRQL, there is limited patient-related outcomes based research into food allergy OIT [45].

In 2013, Otani and colleagues investigated multiple food allergens oral immunotherapy (mOIT) on FA-specific HRQL in the caregivers of participants with multiple, severe food allergies [93].

Caregiver HRQL was assessed using the Food Allergy Quality of Life–Parental Burden (FAQL-PB) Questionnaire. Parents of participants in two single-center Phase I clinical trials receiving mOIT ($n = 29$) or rush mOIT with anti-IgE (omalizumab) pre-treatment ($n = 11$) completed the FAQL-PB prior to study intervention and at 2 follow-up time points (6 months and 18 months).

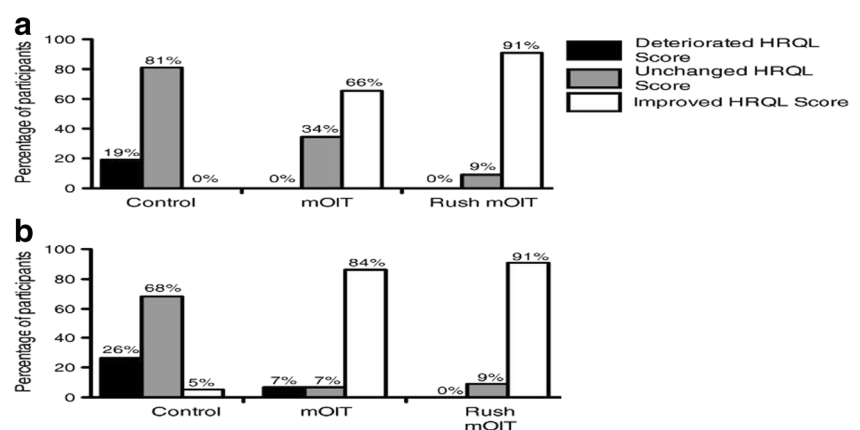
Parents of subjects not receiving OIT (control group, $n = 10$) completed the FAQL-PB for the same time points. Caregivers of participants in the mOIT group ($n = 29$) had a significant improvement in HRQL score at 6-month follow-up (mean 2.5, 95% CI 2.0–3.0) and 18-month follow-up (mean 1.8, 95% CI 1.4–2.1) compared to baseline ($p < 0.0001$). Caregivers of participants in the rush mOIT group ($n = 11$) also had a significant improvement in HRQL score at 6-month follow-up (mean 1.7, 95% CI 0.9–2.6) and 18-month follow-up (mean 1.3, 95% CI 0.3–2.4) compared to baseline

($p = 0.001$ and $p = 0.005$, respectively). HRQL worsened significantly ($p < 0.01$) in the control group ($n = 10$) from baseline (mean 3.6, 95% CI 2.9–4.3) to 6-month follow-up (mean 4.3, 95% CI 3.9–4.8) although at the 18-month follow-up, scores were comparable to baseline HRQL. The authors did not find an association between the number of foods or adverse events and the change in HRQL score in either group although they attributed this to a possible lack of power for a subgroup analysis (Fig. 6).

Although this was a phase I study and was not placebo-controlled, the findings are important in that the efficacy of OIT is typically measured by the ability to tolerate food allergen after discontinuation of therapy (clinical tolerance or sustained unresponsiveness). As in the studies described above, this finding shows that the intervention or treatment itself, in this case desensitisation even without discontinuing therapy, provides significant and persistent improvement in caregiver quality of life. This suggests OIT can be of benefit to caregiver HRQL even in the absence of sustained unresponsiveness and may be preferred by caregivers to allergen avoidance. Home dosing reactions, which are expected and for which the patient is prepared, may be less anxiety-producing than the constant fear of accidental reactions and uncertainty of day to day living with food allergy. However, it is also possible that the intense follow-up with bi-weekly visits to see food allergy specialists during OIT escalation phase positively affects the treatment group.

The same authors carried out a follow-up study in 2014 with a new population, a larger sample size ($n = 57$), and a longer follow-up of 24 months [94]. Factors associated with worse or improved HRQL scores were examined, including age, asthma, and respiratory allergic reactions during therapy. The same parent answered the FABQL-PB questionnaire at baseline and for 6-month, 12-month, 18-month, and 24-month time points. The authors report that this study lacked power to detect significant differences between some types of food allergens and between quality of allergic reactions (severe, moderate vs. mild). There was no untreated control group. Results showed that caregiver HRQL improved significantly (change < -0.5 , $p < 0.0001$) at

Fig. 6 Percentages of participants with deterioration, no change, or improvement in HRQL scores. Percentages of participants whose HRQL scores deteriorated (change > 0.5) remained unchanged (change between -0.5 and 0.5), or improved (change < -0.5) in the control group, mOIT group, and rush mOIT group at **a** 6-month follow-up and **b** 18-month follow-up



each follow-up time point compared to baseline. The percentages of caregivers with improvement in HRQL progressively increased (92% at 24-month follow-up time point compared to baseline). Results showed more improvement in caregivers of participants older than 10 years or desensitised to more than 4 food allergens ($p < 0.0001$). Caregivers' HRQL scores of 6 subjects treated with cow's milk had a significantly greater improvement ($p = 0.006$) than subjects treated with other food allergens ($n = 31$). This improvement was detected most significantly in the questions regarding the concern about child's nutrition ($p < 0.001$), the need to spend extra time preparing meals ($p < 0.001$) and to take special precautions before going out of the home with their child ($p < 0.001$).

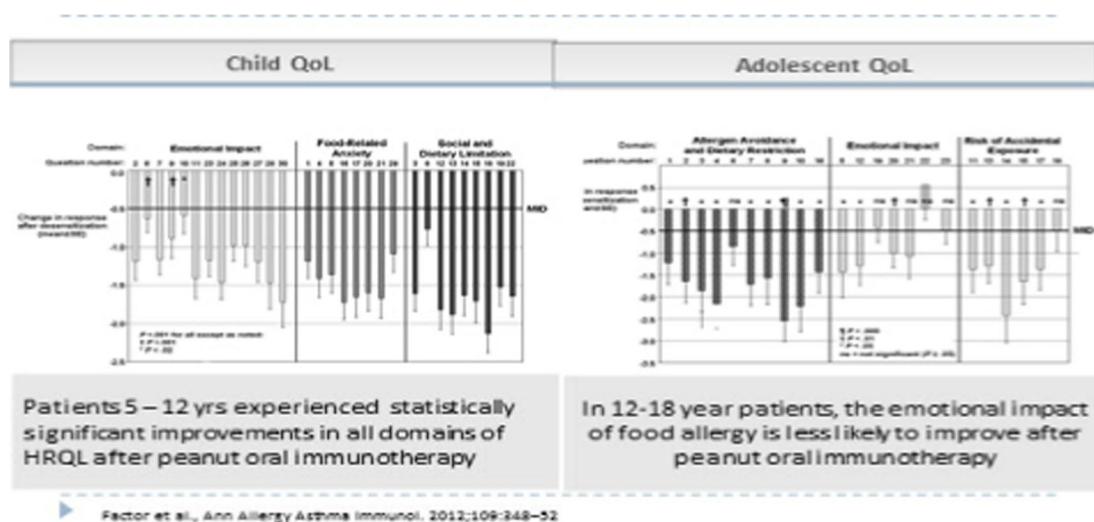
Caregivers of participants with pre-existing asthma or dose-related respiratory allergic reactions had less improvement in HRQL than those who did not ($p < 0.01$). It is possible that these participants may need more tailored support to ensure optimum outcomes in terms of HRQL.

Another study that investigated the effect of oral immunotherapy to peanut on food-specific quality of life was carried out by Factor and colleagues [95]. One hundred patients (5–18 years of age) were enrolled in an open trial of peanut oral immunotherapy. Parents of children 5 to 12 years old, children 8 to 12 years old, and teenagers completed the FAQLQ-PB, FAQLQ-PF, FAQLQ-CF, and FAQLQ-TF before and after peanut oral immunotherapy. Ninety patients (76 children 5–12 years old and 14 adolescents 13–18 years old) achieved the maintenance daily dose of 450 mg of peanut protein. A significant improvement in HRQL was found for patients and parents in all survey domains for patients and parents (allergen avoidance, dietary restriction, risk of accidental exposure, emotional impact, food-related anxiety, and social and dietary

limitations) with the exception of the 'emotional impact' domain on the adolescents' survey (Fig. 7). This suggests that the psychological impact of food allergy has generalised beyond food allergy itself, as described in quantitative and qualitative research on age differences in HRQL (refs) and that early treatment may be important.

The STOP II study examined HRQL as a secondary outcome at study end in a phase 2 randomised-controlled crossover trial designed to compare the efficacy of active OIT (using characterised peanut flour; protein doses of 2–800 mg/day) with control (peanut avoidance, the present standard of care) [41]. Randomisation [1] was by use of an audited online system; group allocation was not masked. Eligible participants were aged 7–16 years with an immediate hypersensitivity reaction after peanut ingestion, positive skin prick test to peanuts, and positive by double-blind placebo-controlled food challenge (DBPCFC). The primary outcome was desensitisation, defined as negative peanut challenge (1400 mg protein in DBPCFC) at 6 months (first phase). Control participants underwent OIT during the second phase, with subsequent DBPCFC.

Desensitisation was recorded for 62% (24 of 39 participants, 95% CI 45–78) in the active group and none of the control group after the first phase (0 of 46, 95% CI 0–9, $p < 0.001$). Eighty-four percent (95% CI 70–93) of the active group tolerated daily ingestion of 800 mg protein (equivalent to roughly five peanuts). After the second phase, 54% (95% CI 35–72) tolerated 1400 mg challenge (equivalent to roughly ten peanuts) and 91% tolerated daily ingestion of 800 mg protein. Side effects were mild in most participants. Intramuscular adrenaline was used after 0.01% of doses (one participant). Both intervention and control groups showed a similar and



Factor et al., Ann Allergy Asthma Immunol. 2012;109:348–52

Fig. 7 Differences in HRQL outcomes according to age. From [95]

clinically meaningful improvement in HRQL in children (FAQLQ-PF) after treatment. HRQL in children (FAQLQ-PF) was also shown to improve in a multicentre, randomised, double-blind, placebo-controlled study conducted in the USA in 2012 [40]. The findings also showed that a longer duration of therapy led to more successful desensitisation (55% at 10 months vs 75% at 22 months) and that sustained unresponsiveness was achievable for a small group (28%).

The highest level of sustained unresponsiveness to date as compared with placebo treatment (82% vs 3.6%) was attained by the probiotic and peanut oral immunotherapy (PPOIT) study in a double-blind, placebo-controlled randomised trial [96, 97]. A separate study evaluated the impact of PPOIT on health-related quality of life (HRQL) during the course of the trial for both the intervention and control groups [98].

Sixty-two children with peanut allergy, aged between 0 and 10 years at baseline, were randomised to receive PPOIT or placebo for 18 months. A double-blind placebo-controlled food challenge (DBPCFC) was performed at 18 months (end-of-treatment, T1) to assess for desensitisation; if this challenge was passed a second DBPCFC was performed 2–6 weeks later to assess for sustained unresponsiveness (T2). Participants who failed the first or second DBPCFC were advised that they remained allergic to peanut and should avoid all peanut in the diet.

Participants who passed both the first and second DBPCFC were informed that they had attained sustained unresponsiveness and were instructed to introduce peanut into the diet and continue intake on a regular basis without specific advice on amount or frequency. The parent study concluded at 3 months after end-of-treatment. In a follow-up study, participants were assessed at 6 months post end-of-treatment by telephone questionnaire and at 12 months post end-of-treatment by clinic visit. The FAQLQ-PF [15, 16] and the Food Allergy

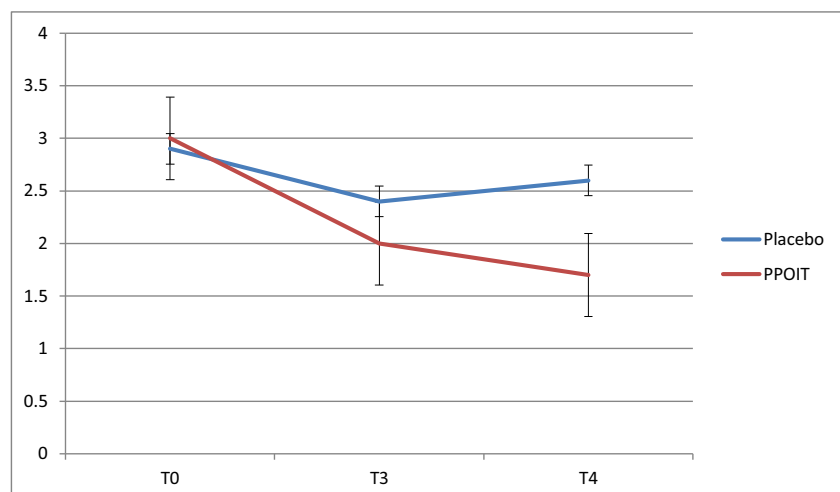
Independent Measure [25] were administered at pre-treatment (T0); end-of-treatment (when status of peanut allergy vs tolerance was not yet known, T1); 3 months after end-of-treatment (when status of peanut allergy vs tolerance was known, T3); and 12 months after end-of-treatment (T4).

PPOIT was associated with significant improvement in FAQLQ-PF ($F = 3.63$, $p = 0.02$), with mean difference 0.8 at 3 months post-treatment ($p = 0.05$) and 1.3 at 12 months post-treatment ($p = 0.005$), exceeding the 0.5 minimal clinically important difference for FAQLQ-PF. For FAIM, mean difference was 0.5 ($p = 0.03$) at 3 months and 0.4 ($p = 0.04$) at 12 months. In the placebo group, post-treatment FAQLQ and FAIM remained unchanged from pre-treatment. Improvement in FAQLQ-PF and FAIM scores related specifically to acquisition of sustained unresponsiveness rather than to receiving PPOIT treatment or participation in the trial (Fig. 8).

PPOIT treatment did not negatively affect HRQL or key aspects of emotional impact, food anxiety, and limitations on social and dietary factors during the treatment phase. Equally important, HRQL in placebo participants was not reduced following treatment and was slightly improved during the treatment phase, particularly in the anxiety subscale. These observations are reassuring as they indicate that, at the very least, involvement in a randomised controlled trial as a placebo participant does not have a negative impact on quality of life. Moreover, although improvement in the placebo group was only transient, this may have some long-term benefit in reframing an individual subject's sense of control over their disease and therefore anxiety.

Parent's expectations of adverse outcomes from food exposure (measured by FAIM) were also significantly improved with PPOIT and there was sustained benefit to 12 months after

Fig. 8 Mean Food Anxiety (FA) subscale scores for PPOIT and Placebo groups at T0 (pre-treatment); T3 (3 months post end-of-treatment); T4 (12 months post end-of-treatment)



*Higher Scores = Worse HRQL. T0: Pre-treatment, T3: 3 months post end-of-treatment, T4: 12 months post end-of-treatment.

end-of-treatment. Long-lasting improvement in these expectations is therefore an important additional measure of beneficial outcomes when evaluating a potential food allergy treatment. Although there was improvement in HRQL at 3 months post-treatment for both children ≤ 5 years and > 5 years in the PPOIT group, differences were greater in those > 5 years. As noted earlier, early intervention may have an added beneficial impact on coping skills and self-efficacy in adolescence and adulthood.

With regard to the question of whether improvement was due to the beneficial outcome of attaining SU rather than to having received PPOIT treatment or to the process of undergoing the trial itself, post hoc analysis revealed that the improvement in HRQL measures within the PPOIT-treated group related specifically to successful attainment of SU and not simply to having received the PPOIT intervention or to participation in the trial. FAQLQ-PF (both total and subscale) scores improved significantly for PPOIT-treated participants who attained SU at the end-of-study, with a mean difference exceeding the MCID, whereas no improvement was seen for either PPOIT-treated or placebo-treated participants who failed to achieve SU. A similar pattern was found for FAIM, with improvement observed only for PPOIT-treated participants who achieved SU. The beneficial effects of PPOIT on HRQL are therefore likely to relate to the outcome of achieving sustained unresponsiveness and not to simply receiving PPOIT treatment or to clinical and/or psychological support from undergoing the trial. As only 7% of PPOIT-treated participants were desensitised without achieving sustained unresponsiveness (and were advised that they should continue to avoid all peanut in their diet), the authors were unable to provide information on the potential effect of desensitisation on HRQL. Further studies are required to determine whether the outcomes of sustained unresponsiveness and desensitisation have a different impact on quality of life, ideally through comparing quality of life measures within a randomised trial. However, the authors intend to investigate this issue in a recently commenced a double blind, randomised trial comparing PPOIT vs peanut OIT vs placebo.

Discussion

Health-related quality of life (HRQL) is influenced by physiological, psychological, and environmental variables and can be best understood by considering the interactions of factors that cut across multiple levels. One of the most important issues relating to treatment in food allergy is to identify, describe, and define predictors that may contribute to modify HRQL outcomes. In a systematic review in 2017, the European Academy of Allergy and Clinical Immunology

(EAACI) assessed evidence on the effectiveness, safety, and cost-effectiveness of allergen immunotherapy (AIT) for IgE-mediated food allergy [45] and found that more data are needed in relation to adults, long-term effects, the impact on HRQL, and the cost-effectiveness of AIT.

This chapter examined studies of HRQL in food allergy to identify potential mediators of change, and treatment selection factors. Evidence shows that HRQL may be moderated by a multiplicity of factors including the following: uncertainty and fear of reactions; development, age, and gender; co-morbidity and poly-allergy; mental health and personality, coping style, and self-efficacy; and environmental factors (such as parent and general population attitudes and beliefs, social context, food and ingredient labelling, legislation and policy).

The research presented has shown that measures of HRQL are able to distinguish key features of known groups (e.g. relating to reaction severity, treatment, allergen type/number, expectation of outcome) and delineate impact on hitherto unknown groups (e.g. relating to personality types and coping styles). This heterogeneity may explain why HRQL or other patient-related outcomes may differ in individuals during, or following any treatment or intervention. To generate new and generalizable scientific knowledge, it is important to understand an intervention's mechanisms of change, as this understanding can identify critical intervention components that influence behavioural and other mediators that in turn influence the intended therapeutic outcomes.

Further evidence-based research aimed at exploring the effects of interventions on outcomes in food allergy are needed, including the influence of patient and parent factors on protocol design.

In a companion systematic review to the earlier EAACI paper on AIT for IgE-mediated food allergy [45], Dhimi and colleagues [46] examined AIT trials in allergic asthma. The authors recommended greater standardisation of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes so as to facilitate evidence syntheses, and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Treatment success in all AIT clinical trials may be defined not only by desensitisation or sustained unresponsiveness but by improved HRQL, on an interaction between the two. Both may depend on tailoring interventions to the characteristics and needs of patients. For example, HRQL heterogeneity may also impact decision-making regarding potential treatment strategies by both the patient and the clinician. Identification of predictors could optimise treatment by helping both implement appropriate, suitable, and specific approaches that will benefit patients. The decision to offer any treatment should ideally be carefully matched to a particular patient profile. However, these decisions should be based on evidence since it may seem intuitive that a very anxious parent or child would be less likely to

volunteer for OIT since the side effects may be a concern. Research [25] has shown that a modifier of the decision is a safe, protected environment such as is provided by a clinic. ‘Fear of death’ from a reaction is another important factor that can modify the decision to take part. The ability of OIT treatment to lower thresholds is very persuasive in the case where a patient or parent has a strong fear of a severe reaction or death if an allergen is accidentally ingested, and/or believes that there is a high chance that such an event may occur. They are also likely therefore to adhere closely to any regimen to ensure that they—or their child—are safe and are less likely to withdraw from the trial. In contrast, if fear is low, impact of food allergy on HRQL is low, and confidence in management is high, a potential participant may not benefit to any great extent. In either case, the severity of past reactions may not be a deciding factor since HRQL is subjective and expectation of a severe reaction may be more damaging to HRQL even if a child has experience of only mild reactions to date. Furthermore, even the most effective therapy may prove problematic for a patient that has poor management strategies that render it difficult for them to adhere to a complicated treatment regimen and are therefore also more likely to withdraw from a clinical trial.

Treatment adherence and patient drop out are a significant problem in all clinical trials, impacting the reliability, validity, and interpretation of results. No single intervention strategy can improve the adherence of all patients. For example, some patients may be unable to maintain a regimen without a strong system of support and prompts and reminders. Distance to a clinical or trial centre may be a problem for others. Experiencing side effects may overwhelm the cost/benefit ratio for patients or particularly for parents of very young children. Older children and teens may resist following rules and a strict regimen. Monitoring HRQL and other patient-related constructs (including adherence) can help in this regard. Adherence assessments that are simple (presenting as little burden to the respondent as possible) and non-threatening will also likely yield the most honest and accurate responses [99]. Measuring patient satisfaction on issues such as the process of treatment and relationships with clinical staff will also prove useful in this regard. Participation, engagement, and collaboration between providers and patients are key to greater patient satisfaction, improved patient adherence, and optimal healthcare outcomes [99].

Clinical trials provide a tremendous opportunity for more in-depth study of how patient preferences may influence decision-making and the costs, risks, and benefits of oral immunotherapy. Patient-reported outcomes are relatively poorly defined to date. Timing of measurement is also important. A standardised protocol that incorporates HRQL and other relevant PROMs and agreed definitions of outcomes would allow for the comparison of efficacy of food allergy treatments between centres, trials, or countries. To this end, it is vital that patient-related outcomes such as improved HRQL are seen as

a primary outcome and are measured at multiple intervals during the trial duration and beyond. Since HRQL has only been studied in relatively few oral immunotherapy trials to date, primarily looking at caregiver HRQL, it is unclear which factors, measures, or subscales are most predictive of short- and/or long-term treatment outcomes for which type of patient, and which time points for measurement are most informative.

The creative use of methods and designs (both qualitative and quantitative) to better understand the role of HRQL in immunotherapy treatment trials will enable improved modelling of the costs, risks, and benefits of any treatment. Systematic analysis and modelling of antecedent factors, mediators, and outcomes will be important to boost intervention effects and to maximise the overall benefits of treatment. For example, an increased understanding of the interplay between HRQL and self-efficacy would allow the clinician to select interventions that are appropriate and targeted specifically to that patient. HRQL or self-efficacy measures might then be used as tools to focus communication on patient coping with food allergy, with trial regimens, or in difficulties in managing risk. Environmental factors, including community and socioeconomic variables that can enhance or diminish the effect of the treatment on targeted therapeutic outcomes, should also be included in a pathway model.

To date, there are no cost-effectiveness studies of food allergy treatment or management interventions, and sparse data regarding food allergy health utility. Gupta et al. [100] explored ‘willingness to pay’ for a safe and effective generic food allergy ‘treatment’ among a parent sample, estimating this to be \$3504 per child, but did not assess how willingness to pay would vary with differing outcomes or potential side effects. Decision science modelling is another method that could help us understand variations in preferences for treatment, which could affect the health and economic impact of food oral immunotherapy. Assessment of patient/caregiver attribute preference and how this translates to health economic outcomes will provide a basis to understand if strategies used in food allergy can deliver value-based care, which can be applied to the development of future food allergy research. Some PROMs, such as the EQ-5D [100] and the Health Utilities Index [101], can be used to generate preference or utility assessments. Patients’ responses to these questionnaires can be converted to estimate the value of that person’s life on a scale ranging from death (scored 0) through to perfect health (rated 1). As these PROMs consist of items enquiring about impairments and functional limitations, they are measures of HRQL. Utility valuations have also been derived from responses to disease-specific HRQL instruments, providing more accurate measurement of this construct [102, 103].

Oral immunotherapy in food allergy is a promising and exciting development that has the potential to change the course of food allergy and hence patient and family everyday lives. OIT is technically not yet FDA approved in the USA;

however, the expectation that there will be an approved use in the USA within the next 2 years gives impetus and imprimatur to the development of novel and innovative ways of examining its impact on FAQLQ.

Recognising the role of HRQL in food allergy may constitute an important step in selecting and supporting those patients for whom a therapy is appropriate and who will benefit most from a particular treatment. It can also help us to tailor interventions to the characteristics and needs of patients and to provide targeted supports for patients who would benefit from treatments, but only with specific care. In summary, understanding differences and changes in the key patient-related factors using outcome measures such as HRQL can improve patient communication and adherence, allow for more nuanced outcomes and findings, and ultimately optimise patient outcomes during and following oral immunotherapy trials and treatment.

Compliance with Ethical Standards

Conflicts of Interest I am an advisory consultant for Aimmune Therapeutics Biotechnology Company

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Ethical Approval and Informed Consent All studies cited have obtained ethical approval and participants provided informed consent. The names of any participants and/or identifying information are not included in the manuscript.

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