

REVIEW ARTICLE

Anxiety and food allergy: A review of the last two decades

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Abstract

Food allergy (FA) is recognized as a growing public health burden affecting 5%-10% of children worldwide. Several unique features specific to FA elicit high levels of emotional distress and anxiety in patients and caregivers, the first among all the possibility of a life-threatening reaction. Anxiety disorders are highly prevalent in patients with chronic disease, but remain undertreated despite significant negative consequences on patient health. This review aimed to offer a comprehensive overview of literature data on FA and anxiety of the last two decades. A review of the medical and psychological literature from the year 2000 (MEDLINE, PubMed and PsycINFO) was done using the keywords “anxiety” and “food allergy.” Clinical implications for disease management, various manifestations in different target groups, proper interventions and possible explanations on the nature of the association between FA and anxiety have been discussed, as well as limitations and further research directions. The relationship between FA and anxiety is attributed to FA-specific fears and anxiety, rather than a general propensity towards anxiety. Some anxiety—short-lived and related to key events—is to be expected and may even be helpful if it sustains allergen avoidance and preparedness to emergency. However, some data reported that increased anxiety did not improve adherence. Rather, high levels of anxiety have been demonstrated counterproductive and related to maladaptive coping. Further research is needed to elucidate the association between FA and anxiety, especially to understand biopsychosocial directions of the underlying mechanisms and to build proper, effective, standardized protocols of intervention. Clinicians must be aware of the association between FA and anxiety, understand their role in recognizing maladaptive anxiety and encouraging to seek psychological support when needed.

KEYWORDS

affective disorder, anxiety, coping, emotional stress, food allergy, mental health

1 | INTRODUCTION

Food allergy (FA) is recognized as a growing public health burden. Current evidence suggests that FA is common, affecting 5%-10% of children worldwide, and has been increasing in prevalence in the last few decades.¹⁻³ The increase in FA has led to greater awareness of the burden of living with FA in its emotional, social and financial issues.⁴⁻⁶ Despite growing data supporting specific immunotherapy, allergen

avoidance and emergency plans remain the primary care for FA management.⁷ However, accidental ingestion is common, and fatal reaction, even if very rare, can occur. The real fear factor of life-threatening reactions, the need of constant vigilance and carrying medication at all times, and the potential limitations on social activities represent a source of anxiety for patients and families.^{6,8} While quality of life (QoL) studies agrees in affirming that FA affects emotional and social life,^{6,9-13} data available on patients and families' mental health are fragmented

and vague. Studies varied widely in their focus, approach, methodologies and measures and lack of a theoretical framework. Anxiety disorders are highly prevalent in patients with chronic disease, but remain undertreated despite significant negative consequences on patient health.¹⁴ Among children with physical conditions, anxiety disorders (eg, separation anxiety, phobias or generalized anxiety) have been found the most common condition at diagnosis and 6 months later.¹⁵

In FA, an appropriate level of anxiety may contribute to maintain vigilance and take appropriate precautions for allergens avoidance without inhibiting normal daily life. However, a sustained intense anxiety is considered maladaptive since it enhances the risk for increased burden and psychopathology.^{6,12,16–18}

Health professionals must be aware of the association between FA and anxiety in order to help patients and families to achieve positive adjustment and effective coping skills, and know when to suggest psychoeducational guidance and/or mental health support.

1.1 | Fear, anxiety and anxiety disorders

The terms fear and anxiety are often improperly used as synonymous, and symptoms of anxiety are sometimes confused with anxiety disorders. In this review, we adopted the American Psychological Association (APA) definitions according to which fear is the emotional response to real or perceived imminent threat, whereas anxiety is an emotion characterized by apprehension and somatic symptoms of tension elicited in anticipation of future or potential threat.¹⁹ The characteristic set of behavioural and physiological responses of anxiety, such as caution, avoidance, vigilance and arousal, evolved to protect the individual from danger. Anxiety can be divided into two categories: state anxiety, a measure of the immediate, or acute, level of anxiety; and trait anxiety, which reflects the long-term tendency of an individual to show an increased anxiety response. Sensations of anxiety are a normal part of human experience, but excessive or inappropriate anxiety can become an illness.^{20,21} Symptoms of anxiety lie on a continuum of severity ranging from a short-lived, appropriate response to a chronic pathologic state that causes great distress and interferes with daily life and social functioning. A certain amount of anxiety will improve our level of functioning and thereby enhance performance. However, some individuals experience high levels of anxiety that go beyond normal limits, either because of an abnormal reaction to “normal” circumstances or through reaction to abnormal circumstances.^{21,22} Pathological anxiety is conceptualized as an exaggerated state in which hyperexcitability of fear circuits is expressed as hypervigilance and increased behavioural responsivity to fearful stimuli.²² The term anxiety disorder is used to describe conditions in which pathological anxiety is the predominant factor. The American Psychiatric Association classified pathological anxiety into the disorders described in the Diagnostic and Statistical Manual of Mental Disorders—5th Edition (Table 1).^{20,21,23} It is important to make this distinction between normal, adaptive anxiety, versus anxiety as a disorder. First, it would be improper to assert someone has an anxiety disorder simply because they are experiencing some degree

of anxiety. Second, it is crucial to individuate patients suffering from pathological anxiety to address them to proper interventions.

This review aimed to offer a comprehensive overview of literature data on FA and anxiety during the last two decades, exploring implication for some relevant clinical areas such as FA management and coping and oral immunotherapy (OIT), various manifestations in different target groups (paediatrics, caregivers, adults) and proper interventions. Finally, possible explanations on the nature of the association between FA and anxiety have been discussed, as well as limitations and further research directions.

2 | METHODS

A review of the medical and psychological literature from 2019 to 2000 (MEDLINE, PubMed and PsycINFO) was done using the keywords “anxiety” and “food allergy.” The following inclusion criteria were used for selection: (a) articles focused on anxiety in relation to FA and (b) articles available in the English language. Articles on food intolerance or perceived food hypersensitivity have been excluded. The search produced 211 papers: 4 were not in English; 102 did not investigate anxiety and/or FA; 12 only mentioned a possible link between anxiety and FA, but they did not offer any empirical or theoretical evidences as it was not the aim of the study; and 6 were reviews that did not contain new data or critical interpretation. The remaining 87 papers were considered relevant to this paper. A summary of the characteristics of studies in the review and principal findings related to anxiety is available in Table 2. Studies varied widely in sample characteristics, methodology and instruments used, but we chose to not exclude anyone for methodological reasons to give a comprehensive framework of the issue. Results have been summarized (based on the objects of the studies) in the following topics considered of relevance for clinical practice and research in FA: *anxiety and FA management; anxiety and coping; anxiety and oral immunotherapy; anxiety in children and adolescents with FA; anxiety in parents and caregivers; anxiety in adults with FA; interventions for anxiety in FA; and mechanisms underlying the link between anxiety and FA.*

TABLE 1 Anxiety disorders in the DSM—5th edition²³

- Separation anxiety disorder
- Selective mutism
- Specific phobia
- Social anxiety disorder (social phobia)
- Panic disorder
- Panic attack specifier
- Agoraphobia
- Generalized anxiety disorder
- Substance/medication-induced anxiety disorder
- Anxiety disorder due to another medical condition
- Other specified anxiety disorder
- Unspecified anxiety disorder

Note: Obsessive-compulsive disorder and Post-traumatic stress disorder have been removed into new separate categories in the 5th edition.

TABLE 2 Summary of the characteristics of the studies in the review and principal findings related to anxiety

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Abdurrahman ⁷²	2013	184 caregivers of children (age ≤18 y) with a newly diagnosed food-related allergic reaction	Qualitative study	Online survey Telephone interview	Identified gaps included education about FA, anaphylaxis management, for example, how to use epinephrine autoinjectors, and coping strategies for fear and anxiety	Results will inform the development of educational strategies for patients newly diagnosed with food allergy
Akeson et al ⁶⁹	2007	7 adolescents 13–16 y with previous anaphylaxis and 8 of their parents	Qualitative study	Interview	Having a child with anaphylaxis can have a significant long-term psychological impact on parents and this anxiety may in some cases be transferred from parents onto their children	Parents and adolescents may benefit from tailored information to support the transition from parental to self-management by adolescents
Anunziato et al ⁶⁴	2015	190 children and 59 adolescents with FA and their parents	Questionnaire-based study	Ad hoc questionnaire	History of a life-threatening allergic reaction was associated with greater self-management for children only, while among adolescents, it was associated with greater anxiety	Given that shifting to self-management may be challenging, discussion and preparation about this process are warranted
Arasi et al ⁴⁸		Caregivers of 57 children with FA enrolled in OIT clinical trials	Prospective randomized study	FAQL-PB	HRQL, included food-related anxiety, improved more in caregivers of participants older than 10 y than those who were not	IT leads to improvement in caregiver HRQL. Certain characteristics were associated with greater improvements in caregiver HRQL
Atim et al ⁷⁰	2018	10 adults with FA and 10 parents of children with FA from Ghana	Qualitative study	Semi-structured interview	Anxiety, social exclusion and increased household expenditure linked to FA are due to structural forces such as the lack of familiarity and awareness, lack of health system resources, policy guidelines and cultural norms	FA has a global reach, and policymakers must heed the message to integrate FA into the broader chronic disease prevention agenda
Avery et al ⁹	2003	20 children with PA and 20 children with insulin-dependent diabetes mellitus (IDDM)	Cross-sectional controlled study	Adapted version of Vespiderg Allergy QoL questionnaire	PA children reported more fear of an adverse event and more anxiety about eating, especially when eating away from home. However, they felt safe when carrying EAI	QoL is more impaired in children with PA than those with IDDM. Their anxiety may be considered useful in some situations, promoting better adherence
Baricic et al ⁷⁴	2015	702 Croatian children with FA aged 6–48 mo and their parents	Questionnaire-based study	Ad hoc questionnaire (not validated)	Parents of children with proven FA allergy do not experience high degree of anxiety	The perception of FA among general paediatricians is limited, and information to parents was insufficient. Need of additional education in FA
Basso et al ¹⁰⁶	2003	Sensitized mice	Animal model, controlled study	Behaviour analysis Serum and tissue sample analysis	After oral ovalbumin (OVA) challenge, allergic mice present higher levels of anxiety, increased Fos expression in emotionality-related brain areas and aversion to allergens. Induction of oral tolerance abrogates both	Findings establish a direct relationship between brain function and FA, creating a ground for understanding the aetiology of psychological disorders in allergic patients

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Begin et al ³²	2016	154 peanut-naïve younger siblings of peanut-allergic children and their parents	Prospective study	Ad hoc questionnaire (not validated)	The option of introducing peanut to siblings at home without prior skin testing was associated with high levels of anxiety when compared to supervised introduction or home introduction after negative skin test	There is an increased risk of anaphylaxis upon peanut introduction in siblings of children with PA, and parents are reluctant to introduce at home without testing
Birdi et al ⁷⁶	2016	150 parents of children (0-11 y) from a general population	Cross-sectional study	HADS WHOQoL-BREF	Parents of children with FA have significantly poorer mental health compared with healthy controls, irrespective of whether FA is medically diagnosed or not	Encourage parents recognize and refer for psychological support where needed
Boyle et al ⁹⁹	2017	Mothers of children aged 0-18, diagnosed with FA and prescribed with AAI	Randomized controlled trial	STAI	Significantly reduced state anxiety at 6 wk in the intervention group, in the subgroup of participants with moderate/high anxiety at enrolment	A brief psychological intervention which incorporates accurate risk information may impact on maternal anxiety, risk perception and physiological stress
Brew et al ¹⁰⁰	2018	Twins from the child and adolescent twin study in Sweden	Cross-sectional study	SCARED SMFQ-short	If 1 twin had at least 1 current atopic disease the partner twin was at risk of having an internalizing disorder regardless of their own atopic status	Familial aggregation of depression/anxiety seems to be linked to environmental/epigenetic rather than genetic factors
Butler et al ¹⁵	2018	50 children (6-16 y) with physical condition, included FA, and their parents	Prospective pilot study	Mini international neuropsychiatric interview for Ch. & Ad; KIDSCREEN-27; STAI	The prevalence of mental disorder in physical conditions was 58% at baseline and 42% at 6 mo. Multimorbidity was associated with declines over 6 mo in the QoL domain of psychological well-being	Preliminary evidence suggests that mental disorder in children with a physical condition is very common and has a negative impact on quality of life over time
Carraro et al ⁴⁶	2012	30 parents of children (3-12 y) undergoing OIT for milk allergy	Prospective study	FAQLQ-PF	The emotional impact and the food-related anxiety improved in children older than 4, while the social domains improved in each age group	OIT significantly improves QoL in children with cow milk allergy. The improvement seems particularly evident in older children
Chooniedass ⁷¹	2019	10 parents of 5 children (under 12), with FA and an EAI who recently experienced anaphylaxis	Qualitative study	Semi-structured interviews	Parents uniformly described multiple life challenges and feelings of isolation, anxiety and hesitation during a reaction that lead to subsequent guilt	Witnessing the effects of an EAI and receiving positive feedback from clinicians strengthened parents' confidence to competently intervene in future reactions
Chow et al ⁷⁹	2015	533 mothers of children with FA	Cross-sectional study	FAQL-PF PedsQL	Maternal depression, anxiety and stress are significantly linked with child psychological functioning and health-related QoL. Children of higher stress mothers showed a stronger link between autoinjector use and anxiety	It is important to assess history of FA-related challenges, parental psychological distress and overprotection

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Cortes et al ⁸⁰	2018	101 mothers/children with IgE-mediated FA	Cross-sectional study	HADS	Significant associations between children's allergic symptoms and maternal anxiety and depression; family budget; social interactions, understanding of child health; and sleep disorders	Results support a comprehensive and multidisciplinary therapeutic approach to offer more ecological health care for "families living with FA"
Cortes et al ⁸⁷	2013	63 parents of children with FA (median age 11 mo)	Cross-sectional study	HADS SPS-FA	In the sample, depression (15.9%) and anxiety (44%) levels described are higher than in general population (9% approximately)	The SPS-FA correlated significantly with anxiety and depression measures, and it can provide a tool to assess the interaction of biopsychosocial factors on FA
Costa-Pinto and Basso ¹⁰⁵	2012	Sensitized mice	Animal model, controlled study	Behaviour analysis Serum and tissue sample analysis	Mice allergic to ovalbumin avoid a palatable sweet solution in order to escape contact with antigen. This choice is associated with increased levels of anxiety, compatible with a conflicting situation	FA responses are associated with increased activity in brain areas linked to emotional and affective behaviour, which are also important for anxiety and stress responses
Costa-Pinto et al ¹⁰⁴	2006	Sensitized mice	Animal model, controlled study	Behaviour analysis Serum and tissue sample analysis	Mice with FA display higher levels of anxiety and increased serum corticosterone levels, and allergy-activated neurons express corticotropin-releasing factor	Understanding neuroimmune interactions during allergic responses that may contribute to the comprehension of psychological disorders associated with FA
Cummings et al ⁶	2010	Children, adolescents and families with FA	Narrative review	—	FA appears to have a considerable detrimental effect on certain aspects of QoL such as emotional QoL, physical functioning and quality of school life. Certain subgroups of patients and caregivers seem to be most affected	It is evident that FA has a profound psychosocial impact on children, adolescents and their families
Cummings et al ³⁹	2010	41 nut-allergic children (aged 6–16 y) and their mothers	Cross-sectional study	FAQL-PB, WHOQOL-BREF, STAI, SCAS, PedsQL	Maternal and child QoL and anxiety were not influenced by the severity of previous reactions. Mother and child reported lower anxiety when the child was prescribed an EAI	EAI is associated with reduced anxiety but is not associated with improved adherence with medical management or reduced risk-taking behaviour
Deschliere et al ³⁰	2016	785 patients with PA (median age 3 y)	Observational multi-centre survey	11 questions about anxiety adapted from the FAQLQ	Anxiety was significantly associated with strict avoidance but not to a history of severe reaction	Precautionary allergen labelling and criteria guiding dietary advice need to be improved
DunnGalvin et al ⁵²	2009	40 parents of children (1–12 y) who refused investigational OIT and 25 parents who took part	Cross-sectional controlled study	FAQLQ-PF FAIM	Parents who chose or not to enrol their children in the OIT trial reported similar HRQL. OIT participating parents perceived a significantly higher likelihood of severe and fatal reactions	Parents who had higher anxiety about negative outcomes were more likely to consent to experimental therapy for their child. Ethical implications for investigators

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Elbert et al ¹⁰¹	2017	Mothers and fathers of 5205 children	Population-based prospective cohort study	Brief symptom inventory	Maternal overall psychiatric and anxiety symptoms during pregnancy were associated with an increased risk of inhalant allergy and eczema, but not FA	Maternal psychiatric symptoms during pregnancy were associated with increased risks of childhood inhalant allergy and eczema
Epstein-Rigbi et al ⁵⁰	2019	Parents of 191 consecutive children aged 4–12 y undergoing OIT for FA	Prospective cohort-controlled study	FAQLQ-PF	Emotional impact, food anxiety and social and dietary limitation significantly improved from OIT initiation to reaching maintenance Additional significant improvement after 6 mo	The detrimental effect of OIT on some patients' QOL during up-dosing is reversed upon reaching maintenance
Epstein-Rigbi et al ⁴⁷	2016	Parents of 119 consecutive children (4–12 y) undergoing OIT for FA	Cohort-controlled study	FAQLQ-PF	A moderate correlation between the number of tolerated doses and total FAQLQ-PF scores, food anxiety and social and dietary limitations emotional impact, was found following OIT induction week	The induction week has the potential to create fear and anxiety in OIT participants
Factor et al ⁴⁴	2012	100 patients (5–18 yofage) enrolled in an open trial of peanut OIT	Prospective study	FAQLQ-PF FAQLQ-Child Form FAQLQ-Teen Form	A significant improvement in quality of life was found in all domains with the exception of the Emotional Impact domain among adolescents	Peanut OIT significantly improves food-specific quality of life
Fedele et al ¹⁷	2016	57 children (6–12 y) with FA, and their mothers	Cross-sectional study	FAMAS Interview FAQL-PB MASC STAI and STAI-C	Families with FA were categorized into four groups that differed on their adequacy of family FA management, levels of anxiety, and balanced psychosocial functioning	Identified adaptation patterns provide a framework for identifying families in need of intervention
Ferro et al ⁶⁰	2016	1303 participants at 14 and 21 y of age from a birth cohort and their mothers	Prospective controlled study	YSR YASR CBCL	FA was associated with increased maternal-reported symptoms of depression, anxiety and ADHD in adolescence	Clinician should be aware of elevated rates of emotional and behavioural problems in adolescents with FA
Ferro et al ⁵⁹	2016	4972 participants at 14 and 21 y of age from a birth cohort	Prospective controlled study	YSR YASR	In adolescents, asthma is associated with increased risk of clinically relevant depression and FA with increased risk of clinically relevant and persistent symptoms of anxiety	Health professionals should be aware of the increased risk of mental health problems in adolescents with asthma or FA
Friedman and Morris ⁵³	2006	Children and adolescents with FA	Narrative review	–	A review of studies examining comorbid anxiety and allergies in children and adolescents demonstrated a consistent association between these disorders despite differences in methodology	
Germundson et al ¹⁰⁷	2018	Mice sensitized and orally challenged	Animal model, controlled study	Behaviour analysis Serum and tissue sample analysis	FA induced behavioural abnormality, increases in the number of mast cells, epigenetic DNA modification in the brain, microglia and astrocyte hypertrophy in a sex- and age-dependent manner	Findings provide a potential mechanism by which peripheral allergic responses evoke behavioural dysfunction

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Goodwin et al ⁵⁵	2017	80 children (4-12 y) with FA, and their caregivers	Cross-sectional controlled study	MASC	FA is associated with increased symptoms of social anxiety and higher levels of anxiety overall, but not depression, in ethnic minority children of lower socioeconomic status	Future studies should investigate potential pathways between FA and anxiety that may be unique to children in underserved populations
Greenhawt et al ⁴⁹	2018	22 caregivers of children with PA enrolled in OIT phase 3 clinical trials	Qualitative study	Semi-structured interviews	Caregivers strongly desire that OIT result in a buffer against an unintentional reaction, although most admitted that this would not lessen their overall level of anxiety, vigilance or avoidance practices	No caregiver viewed these therapies as a cure, and most viewed treatment as a supplement to their current avoidance practices
Herbert and Dahlquist ⁶⁶	2008	86 young adults (18-22 y) with FA and 344 healthy	Cross-sectional controlled study	BAI	Young adults with FA who had anaphylaxis reported more worry and rated their parents as more overprotective than those with FA who had not anaphylaxis	The experience of anaphylaxis may be a reliable indicator of food-allergic individuals who are at risk for psychological distress
Herbert et al ³⁵	2013	Mothers of children with FA	Cross-sectional study	STAI	Mothers whose children passed a food challenge reported significant decreases in anxiety, but intolerance of uncertainty did not predict adherence	Trust in the physician was a primary reason mothers attended the food challenge
Hu et al ⁹³	2008	44 families of children with FA from Clinic and 25 from a Consumer Organization (CO)	Qualitative study	Survey Focus group interview	Parents valued CO as sources of information and support, but viewed advice which did not acknowledge their individual circumstances and heightened anxiety from contact with other anxious parents as being unhelpful	To supplement the information and support provided by Clinics, all parents should be given the opportunity to join a CO, with guidance from their clinician
King et al ⁵⁷	2009	46 families of children with PA	Cross-sectional study	WHOQOL-BREF, PedsQL, SCAS, STAI, PSS	Mothers report that they have poorer QoL and suffer more anxiety and stress than fathers do. Children with PA had greater separation anxiety than their siblings	Mothers felt that there was a greater impact on QoL for their PA child, compared with that reported by siblings, fathers or the PA children themselves
Klennert and Robinson ¹⁶	2008	Families of children with FA	Narrative review	—	Different negative effects can result from FA daily management. Most of these are normal and expected responses. However, a small but substantial proportion of families experience significant psychological distress	Healthcare providers must be aware of the psychological burden of FA, help families to achieve positive adaptation and know when referring to psychoeducational guidance
Klennert et al ⁸⁹	2015	57 families of children with FA	Cross-sectional study	STAI, STAI-C MASC FAQL-PB	FA anxiety was correlated with general anxiety measures for children, but not parents. Parents' FA anxiety was correlated with expectations of FA negative outcomes	Identify families at high risk of poor management and negative outcomes to enhance care for families with FA.
Knibb et al ⁸⁸	2015	434 parents of children with FA from a general population	Cross-sectional study	FASE-P FAQL-PB GHQ-12	Significant relationship between greater self-efficacy and better mental health	It is therefore important for self-efficacy to be measured in order to direct appropriate healthcare advice

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Knibb ⁹⁸	2015	Five mothers of children with FA who had CBT and six controls	Prospective controlled study	HADS, GHQ-12 PSS-14 FAQL-PB WHOQOL-BREF	Anxiety, depression and worry in the CBT group significantly reduced and overall mental health and QoL significantly improved from baseline to 12 wk in mothers in the CBT group	CBT appears to be appropriate and effective in mothers of children with food allergy
Knibb and Hourihane ⁹⁴	2013	24 children with FA (mean age = 11.46, SD = 0.51)	Prospective study	PFA-QL PedsQL SCAS	Greater anxiety significantly correlated with poorer QoL Overall anxiety scores for children were higher at the start of the activity holiday and dropped over time	Attending an activity holiday could help improve a number of psychological and social dimensions of the with FA
Knibb and Semper ⁷⁵	2013	124 parents of children assessed for FA	Prospective study	HADS	Anxiety and depression are present in a small proportion of parents prior to diagnosis of FA in their child and this does not reduce in the short term after the clinic visit	Identification of parents at risk of suffering from distress is needed and ways in which we communicate allergy information before and at clinic should be investigated
Knibb et al ³⁶	2012	103 children and mothers with FA (40 undergoing food challenge—63 control group)	Prospective controlled study	FAQL-PB, WHOQOL-BREF, STAI, SCAS, PedsQL	Mothers reported raised anxiety on the day of challenge. Children-reported lower anxiety levels following the challenge, but anxiety remained unchanged in mothers	Food challenges are associated with improved food-related QoL even in those with a positive challenge
Lagercrantz et al ⁶⁸	2017	18 Swedish parents of children (6–16 y) with severe allergy (included FA)	Qualitative study	Focus group interviews	Based on parental experiences, the following themes were presented in the analysis: limitations, control, injustices and fear and anxiety	Having a child with severe allergy implies a need to constantly be on guard. A more person- and family-centred approach is needed
Lau et al ⁷⁷	2014	40 mothers of children with FA, 18 with asthma and 38 with no chronic illness	Cross-sectional controlled study	STAI PSS SDQ SCARED	Mothers of food-allergic children have increased anxiety and stress compared with mothers of children with no chronic illness. Anaphylaxis and poorly controlled asthma are associated with maternal anxiety	Future work should further explore the link between childhood anaphylaxis and maternal anxiety, in order to promote maternal mental health in this setting
Le et al ²⁷	2013	164 children with self-reported adverse food reaction and 170 ch without and their mothers	Cross-sectional controlled study	STAI	Child's state anxiety about an adverse food reaction was higher in avoiders than in non-avoiders, whereas child's trait anxiety and maternal state anxiety and trait anxiety were comparable in both groups	Food avoidance seems to be independent of a doctor's diagnosis of FA and advice on food avoidance
Lebovidge et al ⁵⁶	2009	141 mothers of children 2–17 y with FA	Cross-sectional study	BASC-2 PRS BASC-2 SRP STAI MASC	Child anxiety scores are comparable or lower than norms, with the exception of child-reported anxious coping and separation anxiety symptoms, which were significantly higher	Results suggest targets for prevention of distress and support for parental anxiety management

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Lebovidge et al ⁸⁵	2006	221 parents of children 18 y or younger with FA	Cross-sectional study	FAPQ	Medical variables (greater number of food allergies, positive history of anaphylaxis) were associated with higher scores on the anxiety/distress and psychosocial impact subscales	Preliminary findings suggest that the FAPQ may be useful in screening for parental anxiety, perceived impact of food allergies, level of family support and coping skills
Leftwich et al ⁹⁵	2011	32 adults with PA or tree nut allergy	Qualitative study	Interview	Seeking familiarity was a key strategy that enabled patients to reduce uncertainty and anxiety	Communication patterns of nut-allergic adults are often grounded in legitimate everyday social considerations around embarrassment, choice and spontaneity
Lyons and Forde ⁸²	2004	162 adults (24 reported FA)	Questionnaire-based study	Ad hoc questionnaire	Allergy status interacted with perceived health competence to affect anxiety. People with an allergy and with high health competence reported the greatest anxiety levels	Implications in terms of health education and support
Mandell ¹⁸	2005	Parents of 17 families with diagnosis of anaphylaxis	Qualitative study	Interview	The authors identify patterns in the adaptive processes related to predictable developmental and episodic events that increase anxiety and support needs	Social work clinicians and other family-serving professionals can help families maintain an optimal balance between protective and debilitating anxiety
McHenry ³¹	2014	644 Canadian parents of children with FA (mean age 9 y) and their younger siblings	Qualitative study	Online survey	Parents of children with FA receive varied clinical advice regarding the introduction of new allergenic foods, and feel moderate-to-high levels of anxiety. A similar pattern may be seen among younger siblings	A more consistent approach to the advice regarding the introduction of other highly allergenic foods may decrease parental anxiety
Mirotti et al ¹⁰³	2010	Sensitized mice	Narrative review	—	In summary, data on FA and nervous system demonstrate that, when forced to ingest the allergen (gavage), allergic animals present activation of emotion-related brain areas and increased levels of anxiety	The molecular and cellular pathways in the bidirectional interactions of nervous and immune systems are now starting to be elucidated
Ng et al ²⁸	2011	94 parents of children with sea-FA	Cross-sectional study	Ad hoc questionnaire (not validated)	Sea-FA has a significant adverse effect on anxiety and stress in the families of affected children. Parental recall of dietary advice is variable and many tend to impose more stringent dietary avoidance than that recommended	Parents of children with FA tend to impose additional dietary restrictions beyond those recommended, which may result in a greater impact on QoL
Ogg et al ²⁵	2017	202 parents of children with FA	Prospective, questionnaire-based study	FAIM HADS	Parents' risk perception of fatal anaphylaxis correlated with anxiety and mood scores	Clinicians should consider not only the child's needs but should also provide counselling for parents

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TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Otani et al ⁵¹	2014	40 Parents of children aged 4-16 enrolled in OIT Phase I clinical trials	Prospective controlled study	FAQL-PB	OIT was associated with clinically significant increases in caregiver HRQL. OIT can help relieve the psychosocial and economic burden of child FA. This change persisted with 18 mo of ongoing therapy	Home-dosing reactions, for which patients are prepared, may be less anxiogenous than the constant fear of accidental reactions and uncertainty of living with FA
Papadopoulos et al ²⁹	2018	443 patients with peanut allergy (PA) from MIRABEL survey	Multi-centre survey Questionnaire-based study	Ad hoc questionnaires (not validated)	Anxiety score significantly influenced the consumption of products which may contain unintended traces of peanut	Consumption of food products is modulated by factors related to anxiety such as label reading and knowledge of threshold and concomitant tree nut allergy
Patel et al ⁴	2017	Children and families with FA	Narrative review	—	There is a growing body of literature that demonstrates that living with FA adversely affects patients and families in the social, emotional and financial domains	Clinicians should be aware of these issues when working with these families. Implementing a multidisciplinary approach can help families
Patten and Williams ⁸³	2007	General population sample from the 2002 Canadian Community Health Study	Cross-sectional epidemiological study	Composite international diagnostic interview	Self-reported allergies to food and non-food allergies were associated with mood and anxiety disorders, but not to substance dependence	This study is the first to confirm an association between allergies and mood and anxiety disorders, as opposed to symptom ratings, in a general population sample
Peniamina et al ⁸¹	2016	108 adults with FA	Qualitative study	Internet survey	Commonly experienced allergy issues included negative physical symptoms, higher food prices, anxiety about safety of food, trouble maintaining a healthy diet and anxiety/stress at social occasions	Targeting the identified issues could reduce stress in patients with food allergies and improve their overall quality of life
Petrovic-Dovat ⁸	2016	114 patients (8-16 y) (37 with anxiety disorder; 40 with FA; and 43 from GP) and their mothers	Cross-sectional controlled study	SCARED	Children with FA did not have increased anxiety; however, there was a trend for mothers of children with allergies to report more symptoms of panic disorder in their children	It remains important to screen families for anxiety-related symptoms and refer them to mental health services when indicated
Polloni et al ⁴³	2016	92 patients with FA (mean age 18.6)	Cross-sectional study	STAI	Avoidant coping strategies had the highest contribution in explaining alexithymia, followed by trait anxiety, age, anaphylaxis and social support	Recognizing the role of affect regulation in health behaviours may help in supporting patients to explore more adaptive strategies
Polloni et al ³³	2016	81 mothers of children with FA	Prospective study	STAI	State anxiety significantly decreased after the OFC. A correlation was found between trait and state anxiety and the degree of change in nutritional habits after OFC	Reassess food consumption in patients after a negative OFC and supporting patients in the reintroduction of food
Polloni et al ⁶³	2015	116 patients with FA (11-17 y) and their parents	Cross-sectional controlled study	SDQ	Patients with FA reported significantly higher internalizing problems and impact of mental health problems on everyday life. Previous anaphylaxis and EAI were associated with internalizing and externalizing score	Clinicians must be aware of the psychological challenges these patients face, helping patients and families to achieve positive adaptation

(Continues)

TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Polloni et al ⁶⁶	2014	100 psychological treatments addressed to patients with FA and/or their families	Descriptive study	Descriptive measures	40% of treatments were required mainly because of emotional/social problems including anxiety, stress and mood disorders, internalizing problems such as excessive worry and/or fear, loneliness, social isolation	When excessive distress or anxiety, social problems and/or maladaptive coping are a concern, clinicians should consider referral to a psychologist
Polloni et al ²⁶	2013	124 mothers of children (0-16 y) with FA	Cross-sectional study	STAI	The attendance of social events was inversely associated with the number of excluded foods and the mother's trait anxiety	FA can reduce interest about food and influencing patients' approach to social life. It is important to support families in managing allergens avoidance
Ravid et al ⁶⁵	2012	Patients and families with FA	Narrative review	—	Psychological distress, which includes anxiety, depression, social isolation and stress, has been demonstrated in children and adolescents with FA, although there are variable findings	Need to improve QoL, reduce distress on the way to better coping with FA and promote evidence-based interventions
Rigbi et al ⁴⁵	2017	155 children with FA enrolled in OIT	Prospective controlled study	FAQLQ-PF	The Food Anxiety, Social and Dietary Limitation, and total FAQLQ-PF scores improved significantly in treated but not in control patients, while the Emotional Impact did not	Patients with impaired QoL at baseline improve significantly despite the treatment burden. Some patients with better QoL at baseline might deteriorate during OIT
Rouf et al ⁷³	2011	8 mothers of children with severe FA	Qualitative study	Semi-structured interviews	Mothers shared similar concerns to mothers of children with other chronic illnesses. Experience of FA should be viewed in the wider family context with specific consideration given to parental coping and anxiety	Services could better meet the psychological and social needs of those affected by FA
Roy & Roberts ⁷⁸	2011	51 parents and children (6-12 y) with PA	Cross-sectional study	RCMAS PedsQoL	Child anxiety, parenting stress, length of diagnosis and experiencing an epinephrine shot predicted self-report of HRQL	A certain subset of families with PA experiences high levels of parenting stress and child anxiety that can affect HRQL and require mental health treatment
Rubes et al ⁸⁴	2014	39 patients with FA (8-17 y) and their clinicians	Interventional study	SCARED	After an ad hoc workshop, clinicians did not more accurately detect anxiety among their patients with FA and found the process intrusive	Alternative methods for uncovering anxiety among high-risk patients are needed
Saleh-Langenberg et al ⁴⁰	2016	55 Dutch adolescents with FA and EAI, and their parents (13-17 y)	Cross-sectional study	FAQLQ-TF FAQLQ-PFT STAI	The burden of EAI of both adolescents and parents are not associated with HRQL, perceived disease severity, illness perception or trait anxiety	A higher burden of treatment is associated with self-reported non-compliance with carrying an EAI at all times
Shanahan et al ⁶⁷	2014	1420 adolescents recruited from the community and their parents	Prospective study	CAPA	FA is associated with higher separation and generalized anxiety disorder, ADHD and anorexia nervosa. FA, however, is not associated with a higher likelihood of meeting diagnostic criteria for a psychiatric disorder	Support from clinicians is needed to help adolescents with FA and their parents to achieve optimal balance between necessary vigilance and unnecessary restriction

(Continues)

TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Sharma et al ⁹²	2012	98 parents attending FA support group	Qualitative study	Online survey	The FA support group decreased anxiety about FA for 77.7% of respondents. Most (71.4%) felt the support group improved their child's QoL	FA support group meetings appear to be a good way for families of children with FA to learn more about FA and improve QoL
Shemesh et al ⁹¹	2017	60 adolescent/parent pairs randomized to self-injection versus control (education only)	Randomized controlled study	PedsQL SCARED	Self-injection was associated with a significant increase in comfort levels. On follow-up, QoL improved in 52% of intervention patients vs 25% of controls; similar differences were observed for anxiety	A self-injection (with an empty syringe) procedure in a clinic setting improves adolescents' and parents' comfort level with self-injecting
Shemesh et al ⁹⁰	2016	3143 patients with FA (1-21 y) and their parents	Post hoc review of clinical screening	Selected questions from FAQL-PB SCARED	Clinicians' suspicions that children with a medical illness might suffer from a mental health disorder are largely justified and do not mandate a dedicated screening effort	Resources may be better used on ensuring the availability of mental health care rather than on screening in paediatric specialty clinics
Somers ³⁴	2011	11-y-old boy with PA	Case report	Nutritional consultation Psychological consultation	A thorough diet history and nutrition assessment are important for identifying any growth disturbances or unusual patterns of self-restriction resulting from anxiety or deliberate intention of losing weight	It is important for nutrition practitioners to understand the psychosocial impact of living with a FA and refer to proper psychological interventions
Strinnholm et al ³⁷	2010	8 mothers of children who had a negative DBPCFC	Qualitative study	Interview	Recurrent themes of fear and anxiety emerged. For example, "living with fear of the unknown," "fear of losing control," "having faith even though fear prevails," "reintroducing despite fear" and 'fear of causing harm"	Maternal perspective—not only the professional perspective—needs to be considered if mothers are to succeed in the challenging process of reintroducing foods
Teufel ²⁴	2007	Patients with FA	Narrative review	—	Adults and children with FA show impaired QoL and a higher level of stress and anxiety. Pavlovian conditioning of adverse reactions plays an important role in maintaining symptoms	Improve diagnostic algorithms, to describe psychological aspects in patient subgroups, and to optimize management of the various types of adverse reactions to food
Vargas et al ⁴²	2011	36 parents of children with FA	Qualitative study	Focus group	Improving access to clear and concise educational materials would likely reduce stress/anxiety and improve QoL	Based on reports from experienced parents of food-allergic children, newly diagnosed parents could benefit from a comprehensive FA-management curriculum
Walkner ⁴¹	2015	Patients and families with FA	Narrative review	—	Constant vigilance associated with food allergens avoidance can put stress and anxiety in children and their families	Efforts to improve HRQL among patients and caregivers are needed

(Continues)

TABLE 2 (Continued)

Authors	Year	Sample	Design	Instruments used to assess anxiety	Findings relevant to anxiety	Conclusions
Warren et al ¹²	2016	Patients with FA	Narrative review	—	Stress and anxiety associated with continuous allergen avoidance and the looming threat of anaphylaxis were associated with significantly impaired HRQL for children with FA and their caregivers	OIT may improve HRQL among both patients and their caregivers. Other intervention modalities, such as counselling and educational workshops, also hold promise, but additional work is needed
Weinberger et al ⁹⁷	2019	60 patients with peanut allergy (aged 9-17.5) and their parents	Randomized controlled trial	FAQL-PB SCARED	Both education about the low risk of casual exposure and education in addition to having the patient touch peanut/ nut reduced patient and parent worry about being near or touching their allergen	A behavioural intervention may reduce patient and parent worry about being near or touching their allergen
Zijlstra et al ³⁸	2010	57 parents of children (mean age 7.2) with suspected PA/hazelnut who had a DBPCFC	Prospective controlled study	STAI	Prior to DBPCFC, parents had high levels of state anxiety and lower trait anxiety compared with norms. After, state anxiety was lower, regardless of the outcome. Trait anxiety was higher in those who refused DBPCFC	Parents showed high levels of anxiety about a food-allergic reaction. After DBPCFC, the anxiety was significantly lower, even in the group with a positive outcome

Abbreviations: ADHD, attention deficit hyperactivity disorder; BAI, Beck anxiety inventory; BASC-2 SRP, behavior assessment system for children, second edition self-report of personality; BASC-2, PRS behavior assessment system for children, second edition parent rating scales; CAPA, child and adolescent psychiatric assessment; CBCL, child behavior checklist; CBT, cognitive behaviour therapy; DASS-21, depression anxiety and stress scales, short version; DBPCFC, double-blind, placebo-controlled food challenge; FAIM, food allergy independent measure; FAMAS, food allergy management and adaptation scale; FAPQ, food allergy parent questionnaire; FAQL-PB, food allergy quality of life-parent burden questionnaire; FAQLQ-PFT, food allergy quality of life questionnaire-parent form teenager; FAQLQ-TF, food allergy quality of life questionnaire-teenager form; FASE-P, food allergy self-efficacy scale for parents; GHQ-12, general health questionnaire-12; HADS, hospital anxiety and depression scale; HRQL, health-related quality of life; MASC, multidimensional anxiety scale for children; PedsQL, pediatric quality of life inventory; PFA-QL, pediatric food allergy quality of life scale; PSS-14, perceived stress scale; RCMAS, revised children's manifest anxiety scale; SCARED, shortened mood and feelings; SCAS, spence child anxiety scale; SDQ, strengths and difficulties questionnaire; SMFQ-short, the short mood and feelings questionnaire; SPS-FA, scale of psychosocial factors in food allergy; STAI, state-trait anxiety inventory; STAI-C, state-trait anxiety inventory for children; WHOQOL-BREF, The world health organization QoL scale (brief version); YASR, young adult self-report; YSR, youth self-report.

3 | RESULTS FROM THE SELECTED LITERATURE

3.1 | Anxiety and FA management

A number of authors suggested that moderate or even elevated anxiety among patients and caregivers with FA may be interpreted as helpful, if it encourages developing necessary behaviours for an adequate management of FA.^{9,16,24} Mandell et al, in a qualitative study, found that parents of children with previous food-induced anaphylaxis reported initial high levels of anxiety that motivated them to obtain information to reach optimal FA management.¹⁸ Then, anxiety subsided somewhat and a high level of vigilance prevailed. If anxiety fell to a low point, the level of vigilance tended to drop, with a possible consequent decrease in caution for avoidance or preparedness for emergency. Three key events typically triggered a renewed rise in anxiety: new accidental exposures; new information regarding potential risk; or developmental transitions that threatened increased exposure to risk. This motivated families to improve their management system reactivating the coping cycle. Thus, for parents of children with FA, some anxiety—short-lived and related to key events—is to be expected and may even be constructive. However, some families are unable to return to a less anxious state, reporting a dysfunctional level of worry and a “paralysing” fear of reactions.¹⁸ Such anxiety may be manifested as distorted perceptions of the real dangers, and may lead to extreme behaviours, which are intended to protect the patient but are in fact unnecessary or even detrimental. For example, families may choose to avoid social situations involving foods, to lead an excessively restricted diet, or not allow age-appropriate outings, choices that have implications for the patient's normal growth and development.¹⁶

A study aimed to evaluate factors associated with parents' perceived risk of food-induced anaphylaxis found that 99% of parents believed that their child had a moderate-to-high chance of dying from food-induced anaphylaxis. Heightened risk perception was associated with higher anxiety.²⁵

In an Italian study, although most of patients' mothers reported a moderate or low trait anxiety mean score when compared with norms, the attendance of social events was inversely associated with mother's anxiety.²⁶ In a general paediatric Dutch population, food avoidance was found to be related to child's state anxiety about an adverse food reaction. Remarkably, doctor's advice did not influence food avoidance behaviour. Furthermore, maternal and child's trait anxiety was not influent and comparable or lower than norms.²⁷ In parents of children affected by sea-FA, over half followed a more stringent elimination than that recommended. Over-adherence was associated with high reported anxiety and decreased QoL, but not with a decreased incidence of subsequent accidental reactions.²⁸

Observational studies found that, among peanut-allergic patients, consumption of food is modulated by factors related to anxiety, with parents' anxiety significantly associated with strict avoidance.^{29,30} Most parents reported to feel anxious when

introducing new foods not only to their child with FA but also to the younger siblings.^{31,32}

Even after a negative oral food challenge (OFC), maternal anxiety before the OFC has been found to be correlated to a following limited level of change in the child's nutritional habits.³³ The emotional/behavioural influence of FA may affect nutritional status over time if fear of having a reaction impacts willingness to eat. A case of an 11-year-old boy with peanut allergy reporting a selective diet related to an anxiety disorder has been described. An accidental exposure to peanut precipitated an underlying anxiety disorder that, in turn, impacted on nutrition.³⁴

Anxiety has been investigated in relation to other important aspects of FA management, with different results from the literature. Maternal anxiety seems not to predict adherence to child's OFC referrals.³⁵ Mothers were found to experience increased state anxiety on the day of OFC, unlike the children, perhaps reflecting the differences in perceived risks. Mothers had a reduction in FA parental burden, but general anxiety and stress scores did not change significantly following the OFC.^{36,37} Zijlstra et al found that prior to double-blind, placebo-controlled food challenge (DBPCFC), parents had high levels of state anxiety but lower trait anxiety compared with norms. After DBPCFC, state anxiety was lower, regardless of the challenge outcome. Furthermore, trait anxiety was higher in parents who refused DBPCFC.³⁸

Prescribing epinephrine autoinjectors (EAI) is associated with reduced anxiety for nut-allergic children and their mothers. However, anxiety is not associated with improved adherence to strictly avoid allergen-containing foods and did not impact on carrying EAI at all times.³⁹

A study on the burden of EAI among adolescents with FA and their parents showed that the burden was not associated with QoL, perceived disease severity, illness perception or trait anxiety, but it was associated with self-reported compliance with carrying the EAI.⁴⁰

Although there have been suggestions that anxiety may be beneficial to improve compliance, some data reported that anxiety did not improve adherence to FA-management plans. As anxiety increases, probably any protective effect disappears. On the other side, an absence of anxiety may lead to a risky lack of vigilance.³⁶ Mandell et al mentioned the *Goldilocks principle* to refer to a level of anxiety that is “just right” for family's adjustment to living with FA and QoL.¹⁸ This optimal emotional response, also called “relaxed readiness,” would facilitate adaptive coping and effective disease management while minimizing maladaptive hypervigilance and potentially dangerous risk-taking behaviour.⁴¹

3.2 | Anxiety and coping

Coping with FA is more than a simple strategy and require emotional and behavioural adaptation.

Fedele et al¹⁷ suggested that children with FA and their parents can be characterized by four patterns of adaptation that differed

on their adequacy of family FA management, levels of anxiety and balanced psychosocial functioning (Figure 1). *Balanced Responders* were able to adequately manage FA without increased levels of anxiety, minimizing effects on parent/child psychosocial functioning. Conversely, *Anxious High Responders* were characterized by extremely high maternal FA anxiety and low balanced integration of FA management and psychosocial functioning. These mothers reported being immobilized by fear of life-threatening reactions; they reported worse QoL impact and parental burden, higher impairment in social activities and higher perceived risk of fatal reactions. Children in the *Anxious High* group experienced anaphylaxis, suggesting that mothers could be experiencing a post-traumatic stress reaction. Mothers' general anxiety did not differ across groups, confirming that, for mothers of food-allergic children, anxiety is not elevated compared with norms. Findings suggest that maternal FA anxiety may impact daily life for a subset of families, may be unique to FA and may require assessment and intervention approaches that are sensitive to FA-specific anxiety.¹⁷ To cope with FA-related stress and anxiety, Vargas et al described two main parental approaches. A hyper-vigilant outlook associated with a sense of loss and high stress and anxiety levels and a more optimistic, pro-active, assertive style associated with a sense of normality and reduced stress. Different styles might be the result of cultural aspects, personality or families' previous trauma regarding FA events.⁴²

In adolescents with FA, avoidant strategies of coping have been associated with higher levels of trait anxiety as well as problems in identifying, describing and regulating emotions.⁴³ This association likely reflects a lifelong worry and fear of potential allergen exposures and reactions.

3.3 | Anxiety and oral immunotherapy

Oral immunotherapy is a promising therapy for FA. Studies in patients and parents have demonstrated a general positive effect of

OIT on some aspects of QoL,⁴⁴⁻⁴⁶ especially food anxiety and social and dietary limitation but not emotional impact.^{44,46,47} Certain characteristics seem to be associated with greater improvements in caregiver QoL: in a prospective randomized study, QoL improved more in caregivers of participants older than 10 years or desensitized to more than 4 food allergens than those who were not.⁴⁸

In a qualitative study, caregivers of children with peanut allergy reported to strongly desire that OIT results in a buffer against an unintentional reaction, although most admitted that this would not significantly change their anxiety and family's current lifestyle.⁴⁹ OIT can be a source of anxiety as it carries risk for allergic reactions. In particular, the induction phase of OIT—during which patients are exposed to increasing amounts of food allergen until an allergic reaction develops, to establish the maximal tolerated dose—has the potential to create anxiety in OIT participants.⁴⁷ Some patients with better QoL at baseline might deteriorate during OIT up-dosing.⁴⁵ However, a recent study showed that QoL improves significantly, included emotional impact and food anxiety, upon reaching OIT maintenance, with additional improvement 6 months later.⁵⁰ Otani et al⁵¹ suggested that possible home-dosing reactions, which are expected and for which the patient is prepared, may be less anxiety-producing than the constant worry about accidental reactions and uncertainty of living with FA. Finally, parents who had higher anxiety about negative outcomes from accidental ingestion have been found more likely to consent to investigational OIT for their child. This finding has ethical implications for investigators and clinicians.⁵²

3.4 | Anxiety in children and adolescents with FA

Children and adolescents with comorbid anxiety disorders and medical conditions are at a higher risk of developing mental health problems in adulthood, have poorer health outcomes and experience more limitations in social activities.⁵³ A prospective, longitudinal investigation on childhood atopy and mental health on a population-based birth cohort study in Australia found an association between

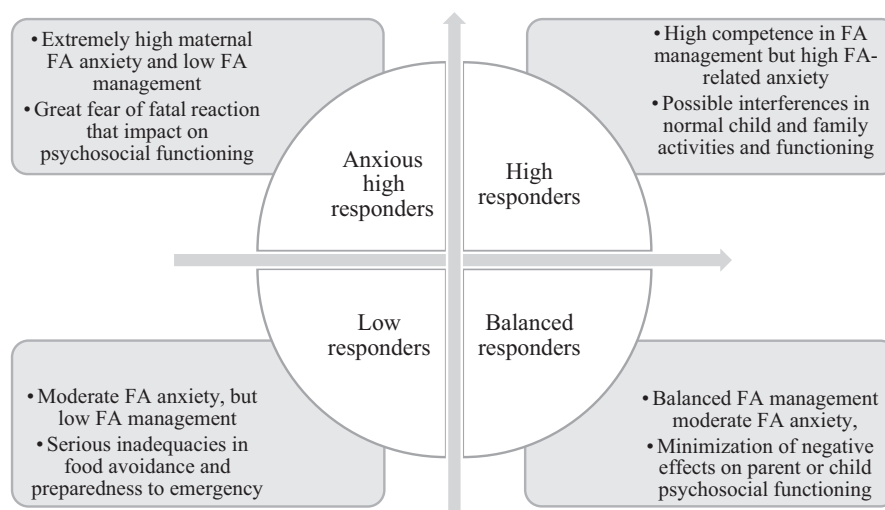


FIGURE 1 Pattern of families adjustment to children's FA. Adaptation from Fedele et al¹⁷ On the abscissa axis, FA management; on the ordinate axis, FA anxiety

allergies and increased vulnerability to affective and anxiety problems but no evident relationships between atopy and attention deficit hyperactivity disorder (ADHD) or externalizing problems.⁵⁴ Knowledge of the comorbidity between anxiety and FA in children and adolescents is especially important since these disorders generally begin during infancy or childhood and may persist until adolescence or over, having profound effects on daily functioning and developmental pathways.⁵³

Children with peanut allergy reported more fear of an adverse event and more anxiety about eating, especially when away from home, than peers with insulin-dependent diabetes mellitus.⁹

Food allergy appeared to be associated with increased symptoms of social anxiety, fear of social rejection and humiliation and higher levels of anxiety overall, in ethnic minority children of lower socio-economic status.⁵⁵ Petrovic-Dovat et al⁸ found that children and mothers with FA did not report increased level of child's anxiety compared with a control group without FA. Nevertheless, there was a trend for those with FA to report more symptoms of child panic disorder. Similarly, Lebovidge et al⁵⁶ found that in youth with FA mean scores on self-report and parent-report measures of child anxiety symptoms fell in the average range on standardized measures. However, children reported significantly higher scores compared with norms for anxious coping and separation anxiety, with nearly 40% in the elevated range for anxious coping, and nearly 30% for separation/panic. Children with peanut allergy have been found also to report greater separation anxiety than their siblings, possibly arising from a fear of having to manage their FA by themselves with no family help.⁵⁷ Findings suggest that although children with FA may not experience higher than normal rates of generalized anxiety, they may exhibit increased vigilance or fears about going places without parents. This may reflect adaptive strategies for youth with FA that can become excessive for a subset of children. DunnGalvin et al⁵⁸ asserted that a transition point occurs near 8 years, after which children change their way of perceiving FA, and thereafter, social events become source of anxiety and uncertainty. This is also the developmental stage when children begin to gain autonomy and self-efficacy. In children with FA, this takes place against a backdrop of anxiety on the part of both children and parents. The transition from childhood to adolescence marks another time of increased risk of anxiety, as result of stress associated with FA management, and/or increased risk of social exclusion^{15,16,59,60} and bullying.⁶¹ Adolescents with FA have reported also lower self-esteem⁶² which, in turn, may negatively influence their mood during this developmental period. In a cross-sectional study among Italian FA adolescents,⁶³ patients reported significantly higher internalizing problems and impact of mental health problems on everyday life but lower externalizing problems compared with healthy peers. Previous anaphylaxis and EAI prescription were associated with internalizing and externalizing score, confirming that life-threatening reactions are associated with greater psychological complaints.⁶⁴⁻⁶⁶

Epidemiological studies aimed to estimate the prevalence of emotional, and behavioural problems in youth with FA seem to

confirm the presence of relevant anxiety. Ferro et al⁶⁰ found that symptoms of depression, anxiety and ADHD are common among adolescents with FA in the general population. It must be said, however, that a discrepancy between maternal and adolescents' self-reports was found. Moreover, FA in adolescence was linked to an elevated risk for clinically relevant anxiety compared to adolescents without asthma or FA that tends to persist in adulthood.⁵⁹ Shanahan et al⁶⁷ confirmed that FA was associated with more symptoms of separation and generalized anxiety, ADHD, and, in addition, anorexia nervosa in a community-based epidemiological sample of adolescents. Longitudinally, adolescents with FA experienced increased symptoms of generalized anxiety and depression. FA was not, however, associated with a higher likelihood of meeting diagnostic criteria for a psychiatric disorder. One possible interpretation is that the elevated symptoms do not, in fact, reflect cohesive syndromes of psychopathology, but rather reasonable adaptations to living with FA. Such necessary adaptations involve increased vigilance to external and internal stimuli which could manifest as concerns about being away from primary caregivers, caution around eating and frequent monitoring of body functions.⁶⁷ However, subsyndromal anxiety has also been found to negatively impact health and functioning in youth with medical illnesses.⁵³

3.5 | Anxiety in parents and caregivers

Anxiety and fear are parental instincts that intensify when their child has been diagnosed with a FA. Qualitative studies on severe FA suggested that parents felt a need to have control of their child's everyday life and described a feeling of constantly being on guard. Insufficient knowledge of FA and anaphylaxis in preschool/school has been identified as a potential cause of anxiety.⁶⁸⁻⁷⁰ Some parents were worried their anxiety would affect the child. Parents were aware that as the child got older, they would have to learn how to let go, but extending safety zones was associated with much concern and anxiety.^{68,69} Other parents described a constant feeling of anxiety, both when they are away from their child and even when they are by their side. Some expressed that anxiety may improve with time, but may also stay for years.⁷¹ Anxiety resulting from the experience of a first severe reaction emerged as a predominant theme.^{72,73} Having a child with anaphylaxis can have a significant long-term psychological impact on parents, and this anxiety may in some cases be transferred onto the child.⁶⁹ A number of caregivers reported that once the diagnosis of FA is confirmed, anxiety and fear surprisingly decreased, also due to taking preventive measures.⁷⁴ Knibb et al⁷⁵ found that anxiety and depression was present in a small proportion of parents prior to diagnosis of FA in their child and this did not reduce in the short term after the clinic visit. Differences in reports of parental anxiety may reflect fluctuation of anxiety in different phases of the disease and/or the child development, as well as differentiations in families' adaptation and resilience.

Quantitative studies showed that parents of children with FA reported higher stress, anxiety and depression compared with healthy

controls, irrespective of whether FA was medically diagnosed or not.⁷⁶ Mothers of food-allergic children showed increased anxiety and stress compared with mothers of children with no chronic illness. Anaphylaxis and poorly controlled asthma were associated with maternal anxiety.⁷⁷

Mothers reported greater anxiety and stress than fathers did, likely because they usually take more responsibility in FA management.⁵⁷

As is the case for many paediatric populations, parental distress can be associated with poorer psychological outcomes in youth. Maternal anxiety has been shown to predict child distress among families with FA.⁵⁶ Child anxiety and parenting stress were found to significantly predict parent proxy report of the child's health-related QoL.⁷⁸ Maternal depression, anxiety and stress were each significantly and positively associated with children's food-related anxiety, social and dietary limitations, and emotional impact of FA. Maternal distress variables were significantly and negatively associated with maternal perceptions of child QoL and psychosocial health. Maternal overprotection was significantly and negatively associated with maternal perceptions of child QoL and psychosocial health and positively associated with social and dietary limitations.⁷⁹ Furthermore, significant associations between children's allergic symptoms (gastric and cutaneous) and mothers' anxiety have also been found.⁸⁰

Although many caregivers function well, a certain subset appears to experience high levels of stress and anxiety that can affect family QoL and children's mental health and may require referrals for psychological support and treatment.

3.6 | Anxiety in adults with FA

Adults with FA commonly experience allergy issues included negative physical symptoms, higher food prices, anxiety about safety of food, trouble maintaining a healthy diet and anxiety/stress at social occasions. Stress and negative mood were significantly higher on days with more allergy issues, confirming the psychological burden of FA.⁸¹

An online survey measuring self-reported autonomy, anxiety, depression and perceptions of parental behaviour found that, as a group, young adults with FA did not differ from healthy peers. However, patients who reported having experienced anaphylaxis described their disease as more severe, reported more worry and rated their parents as more overprotective. Findings highlight the need to study subclinical adjustment outcomes in FA and suggested that anaphylaxis may be a reliable indicator of higher risk for developing psychological distress.⁶⁶

Lyons and Forde⁸² examined the differences in perceptions and knowledge of allergies, perceived health competence and anxiety between young people with and without a FA. People with FA and high health competence reported the greatest anxiety levels. This increased anxiety was explained as related to the patient's need to constantly examine the environment for potential hazards.

Cross-sectional epidemiological data reported the presence of an association between FA and mood and anxiety disorders in a

general population sample, while substance use disorders are not associated with allergies.⁸³

3.7 | Interventions for anxiety in FA

A crucial goal in treating patients and families with FA is to recognize, normalize and support a level of anxiety that facilitates adaptive coping. Rubes et al⁸⁴ found that paediatric allergists were poorly prepared to identify above-threshold anxiety among patients and found the screening intrusive and poor acceptable. It is important for physicians working with FA to be alert for signs of significant distress (eg, unmanageable worry about a reaction, exaggerated avoidance or checking behaviours, and restriction of daily activities) and make appropriate referrals to mental health professionals who can help in developing adaptive anxiety management and coping skills.⁸⁵ Well-validated FA-specific measures of QoL⁸⁶ or psychosocial adjustment⁸⁷⁻⁸⁹ may be helpful in this regard, to make a first screening. Shemesh et al, in a post hoc review of a screening programme in a paediatric FA clinic, concluded that clinicians' suspicions that children with a medical illness might suffer from a mental health disorder are largely justified and do not mandate a dedicated screening effort. Resources may be better used on ensuring the availability of mental health care rather than on screening in paediatric specialty clinics.⁹⁰

With regard to intervention aimed to normalize anxiety, a range of proposals has been suggested in the literature. Many of it based on social support and education. Newly diagnosed parents could benefit from a comprehensive FA-management curriculum. Improving access to clear and concise educational materials would likely reduce stress/anxiety and improve QoL since it may increase parents' sense of control.^{42,91} A parental calm, matter-of-fact approach to FA management focusing on safety routines and model use of adaptive coping, may convey the message that FA is manageable.⁴² For some parents, participation in support groups with other families with FA may reduce burden by normalizing experiences.^{56,85,92} Parents valued consumer organizations as sources of practical information and emotional support, but viewed advice which did not acknowledge their individual circumstances and heightened anxiety from contact with other anxious parents as being unhelpful.⁹³

For children with FA, an activity holiday was found to help improve a number of psychosocial dimensions including the adoption of more health-related behaviours, a more adaptive health locus of control, a reduction in overall anxiety and in particular a decrease in obsessive-compulsive attributes. Overall anxiety and QoL were better than norm levels by 6 months after the activity holiday.⁹⁴

Goodwin et al⁵⁵ suggested that education in schools represents a potential area for intervention to reduce social anxiety in children with FA, since they would feel more comfortable about sharing their diagnosis if their classmates received education on FA.

Adults with nut allergy reported seeking familiarity as a key strategy to reduce the anxiety, uncertainty and the consequent risk

assessments that routinely accompanied the experience of eating out.⁹⁵

Few studies have been conducted about clinical interventions to treat maladaptive anxiety in patients and families with FA. Polloni et al⁹⁶ described a wide of psychological interventions addressed to children, adolescents and/or families held in a Tertiary FA Referral Centre and aimed to improve mental health and psychosocial well-being. Treatments included psycho-education, counselling, relaxation techniques and psychotherapy including cognitive-behavioural therapy (CBT) in individual or group sessions. All patients reported interventions have been helpful in resolving psychological problems—including clinically significant anxiety—or in making it more bearable. Weinberger et al⁹⁷ reported that a behavioural intervention in which patients were instructed to touch their allergen, along with verbal education about the low risk of casual exposure, reduced patient and parent worry about being near or touching their allergen. Only few studies assessed the efficacy of a clinical intervention (CBT) for mental health in caregivers. Knibb et al⁹⁸ found that, in a sample of five mothers, anxiety, depression and worry significantly reduced and overall mental health and QoL significantly improved from baseline to 12 weeks after CBT, while control group scores remained stable. Boyle et al⁹⁹ evaluated a single-session CBT intervention including a risk communication module in a randomized controlled trial of two hundred mothers of children with FA. They found no significant difference in state anxiety at 6 weeks between CBT group and control. However, there was significantly reduced state anxiety at 6 weeks in the intervention group, in the subgroup of mothers with moderate/high anxiety at baseline. The brief psychological intervention also reduced risk perception and salivary cortisol response to a simulated anaphylaxis scenario at 1 year.

Further studies are absolutely needed to determine the appropriateness of the interventions and to create validated and shared treatment protocols for anxiety in FA. The use of validated measures of anxiety and mental health before and after treatments, as well as the presence of a control group, is recommended.

3.8 | Mechanisms underlying the link between anxiety and FA

A growing body of data indicates that human susceptibility to mood disorders such as depression and anxiety can be determined early in life.²⁰ These data support the view that early developmental mechanisms can set the lifelong tendency of an organism to express anxiety in response to threatening stimuli. Such developmental mechanisms are under both genetic control and environmental control.^{20–22} It is possible that FA experience impacts on children's neurodevelopment, shaping emotional and behavioural outcomes. Cognitive-behavioural and biological explanations have been put forward to explain the link between anxiety and FA.^{6,16,24,53} Anxiety may arise from negatively biased cognitive patterns (eg high perceived risk, fear of death and loss of control) that exaggerate adverse effects of the physical

condition and can undermine confidence in adapting to threatening situations.⁵⁹ Anxiety may be an inherited trait or learnt behaviour. For example, overprotective, non-autonomy granting parenting practices have been shown to be a risk factor for child anxiety. Such parenting practices can convey messages to children about potential dangers of through vicarious means—such as modelling of anxious behaviour or restricting children's ability to explore situations autonomously—or through more direct means such as direct verbal information. These messages can, in turn, promote anxiety and avoidance in children.⁷⁹

With regard to genetic factors, the Childhood and Adolescent Twin Study in Sweden showed that atopic diseases and depression or anxiety tend to occur together in families.¹⁰⁰ However, authors did not find evidence to support a genetic explanation for comorbidity, and further exploration is needed to disentangle the environmental and epigenetic factors. Very few studies investigated the role of perinatal psychosocial factors in the development of FA. A study among 5205 children in a population-based prospective cohort from foetal life onwards found that maternal psychiatric symptoms—including anxiety—during pregnancy were associated with increased risks of childhood inhalant allergy and eczema, but not FA,¹⁰¹ while a retrospective study on maternal reports found a significantly higher number of stressful events during perinatal period of children with FA, compared with siblings.¹⁰²

There is also emerging evidence of shared biological pathways that underlie multimorbidity. The molecular and cellular pathways in the bidirectional interactions of nervous and immune systems are now starting to be investigating in order to elucidate the association of FA and brain activity and consequences on the neural modulation of allergic responses.¹⁰³ Recent studies on rat model showed that allergic reactions lead to changes in neuronal activity, particularly in brain areas involved in processing emotionality and affective behaviours, and in the activation of the HPA axis and triggering of stress responses. These areas directly or indirectly participate in adaptive behavioural changes and control of endocrine pathways, such as secretion of glucocorticoids. These changes might be important in avoiding further contact with the allergen, and minimizing future allergic reactions is mediated by specific antibodies and prevented by depletion or immunological tolerance. They are also partially mediated by C-sensitive afferents and mast cells.^{104–106} In a mouse model of milk allergy, peripheral allergic responses have been found to induce behavioural and emotional abnormality, increases in the number of mast cells, epigenetic DNA modification in the brain, microgliosis and astrocyte hypertrophy in a sex- and age-dependent manner.¹⁰⁷ These results need to be further replicated and explored, and transferred in the more complex human psycho-socio-biological scenario. However, they could have relevant clinical implications in providing safe therapeutic approaches for patients with FA, reducing the risk of behavioural and emotional dysfunctions, or effectively treating psychological complaints when present.

Actually, the theories have limited empirical support, warranting further research, and do not offer a causal explanation, instead suggesting bidirectional effects on FA and anxiety. A biopsychosocial approach seems to be the most appropriate framework for comorbid

FA and anxiety, in which biological and environmental factors influence one another.^{36,53} Longitudinal studies are needed to clarify the direction of effects between FA and anxiety in an effort to promote the best possible physical and mental health outcomes.

3.9 | Limitations and bias

Considered studies vary in their sampling methods, sample size and characteristics, in the age of participants investigated and in the instruments used, which have included a mixture of non-validated and validated generic health and FA-specific scales. Qualitative research methods or FA-specific measures may be more sensitive to patients' experience of anxiety and stress specifically associated with FA. However, only "generic" validated measures allow for comparison with general population norms. Some studies utilized validated scales designed to measure anxiety, while others relied on validated QoL instruments and self-reported anxiety symptoms through interviews and surveys. Furthermore, only few studies adopted a DSM-oriented assessment of anxiety. Most studies had an observational design and/or did not consider certain salient variables (eg previous anaphylactic reactions, severity and type of food allergies) so that inference on causality and/or conclusive comments on the social or biological mechanisms linking FA and anxiety are not allowed. The diagnosis of FA is medically confirmed by recommended tests and evaluations only in a portion of researches. Most studies used self-report and/or parental report instruments and sometimes discrepancies between maternal and children/adolescent emerged, giving rise to some uncertainty to the findings. In addition, many studies involved self-selected samples, patients attending specialist clinics and, in some cases, people belonging to patients' organizations. These kinds of sample show evident limitations related to the presence of possible bias, and generalizability of results. The authors chose "narrative review" as more appropriate to create a theoretical framework across very different studies on anxiety and FA. They tried to objectively report main results summarizing them in topics that could be relevant for clinical practice and research, as well as considering different target groups. However, narrative review may be more sensitive authors' point of view in data presentation.

4 | CONCLUSIONS AND FUTURE DIRECTIONS

Literature data of the last two decades, although difficult to compare due to significant methodological differences among studies, have shown that anxiety is a pervasive state in the FA experience. The relationship between FA and anxiety is attributed to FA-specific fears and anxiety, rather than a general propensity towards anxiety. Some anxiety—short-lived and related to key events—is to be expected and may even be helpful if it sustains allergens avoidance and preparedness to emergency. However, some data reported that increased anxiety did not improve adherence (eg, carrying EAI,

following medical dietary advices). Rather, high levels of anxiety have been demonstrated counterproductive and related to maladaptive coping. On the other side, an absence of anxiety may lead to a risky lack of vigilance. Further studies should clarify which could be the "just right" degree of anxiety for patients with FA and their caregivers. Although most individuals with FA reported moderate anxiety, a small but substantial proportion experiences relevant anxiety that interfere with optimal functioning. In many studies, this dysfunctional anxiety has been related to previous anaphylaxis.^{17,63,66,69,77} As a life-threatening event, anaphylaxis may lead to post-traumatic stress reactions in patients and caregivers who assisted, so that it seems crucial to assess and support individuals in the weeks and months following a severe reaction, and to implement effective preventive measures. Another important finding confirmed by several researches is that children and adolescents with FA reported higher separation anxiety.^{56,57,67} The unique constellation of the youth's increased anxiety in the context of FA likely reflects an adaptive increase in vigilance rather than cohesive syndromes of psychopathology. However, given the vulnerability of the developmental period and possible impacts for further psychosocial well-being and mental health, children and adolescents with FA and their parents should be supported in achieving a balance between safety and autonomy, minimizing unnecessary restrictions.

Clinicians must be aware of the association between FA and anxiety, understand their role in recognizing maladaptive anxiety and encouraging to seek psychological support when needed. Health professionals should feel comfortable referring families with FA for therapy or at least screening. Facilitated access to psychosocial interventions as well as coordination among health-care professionals should be ideally put in place for the effective care of FA adopting a multidisciplinary patient-centred approach. Although a number of studies are actually available, further studies are needed to elucidate the association between FA and anxiety, especially to understand biopsychosocial directions of the underlying mechanisms and to build proper, effective, standardized protocols of intervention. In this regard, prospective and longitudinal investigations, as well as clinical trials, and the use of validated measures are recommended to be implemented. The early identification of patients with FA at risk for mental health and the development of suitable intervention and prevention programmes should be a priority in the FA agenda.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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