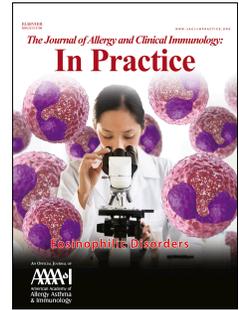


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Challenges and unmet needs in FPIES from the parents and adult patients' perspective – an international survey

M. Vazquez-Ortiz, E. Khaleva, S. Mukherjee, S. Infante, J. Meyer, A. LeFew, Q. Yuan, F. Martinon-Torres, R.C. Knibb, Marta Vazquez-Ortiz, MD PhD, Ekaterina Khaleva, MD MSc, Shubhasree Mukherjee, MD MSc, Sonsoles Infante, MD PhD, Joy Meyer, DTR, Amanda LeFew, MT-BC, Qian Yuan, MD PhD, Federico Martinon-Torres, MD PhD, Rebecca C. Knibb, PhD



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1 Title

2 Challenges and unmet needs in FPIES from the parents and adult patients' perspective – an
3 international survey

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6 Authors

7 Vazquez-Ortiz M¹, Khaleva E², Mukherjee S³, Infante S^{4,5}, Meyer J⁶, LeFew A⁶, Yuan Q⁷,
8 Martinon-Torres F⁸⁻¹⁰, Knibb R C¹¹

9

10 Marta Vazquez-Ortiz ¹, MD PhD

11 Ekaterina Khaleva ², MD MSc

12 Shubhasree Mukherjee ³, MD MSc

13 Sonsoles Infante ^{4,5}, MD PhD

14 Joy Meyer ⁶, DTR

15 Amanda LeFew ⁶, MT-BC

16 Qian Yuan ⁷, MD PhD

17 Federico Martinon-Torres ⁸⁻¹⁰, MD PhD

18 Rebecca C Knibb ¹¹, PhD

19

20 Affiliations

21

22 ¹Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial
23 College London, London, United Kingdom

24

25 ² Faculty of Medicine, University of Southampton, Southampton, United Kingdom

26

27 ³ Paediatrics Department, Royal Free London NHS Foundation Trust, London, United Kingdom

28

29 ⁴ Paediatric Allergy Unit. Hospital General Universitario Gregorio Marañón, Madrid, Spain

30

31 ⁵ Gregorio Marañón Health Research Institute (IISGM), Madrid, Spain.

32

33 ⁶ The FPIES Foundation, Stewartville, MN, United States <https://fpiesfoundation.org/>

34

35 ⁷Food Allergy Center, Pediatric Gastroenterology and Nutrition, Massachusetts General

36 Hospital, Harvard Medical School, Boston, MA, United States

37

38 ⁸Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico

39 Universitario de Santiago de Compostela, Santiago de Compostela, Spain

40

41 ⁹Genetics, Vaccines and Infections Research Group (GENVIP), Instituto de Investigación

42 Sanitaria de Santiago, University of Santiago de Compostela, Spain

43

44 ¹⁰Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES),

45 Instituto de Salud Carlos III, Madrid, Spain

46

47 ¹¹School of Psychology, College of Health and Life Sciences, Aston University, Birmingham,

48 United Kingdom

49

50

51 **Corresponding author**

52 Marta Vazquez-Ortiz, MD, PhD

53 Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial

54 College London

55 Address: B108, Medical School Building, St Mary's Campus, Norfolk Place, London W2 1PG,

56 United Kingdom

57 E-mail: m.vazquez-ortiz@imperial.ac.uk.

58 Phone number: 0044 (0)7738040591

59

60 **Conflicts of interest**

61 MJ and LFA are co-founders and co-directors of the FPIES Foundation. The authors have no
62 other conflicts of interest to declare in relation to this manuscript.

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67 **Clinical implications box**

68 Key priorities for the FPIES parent/carer/adult patient community are better awareness about
69 FPIES amongst healthcare professionals and having diagnostic/prognostic biomarkers to avoid
70 misdiagnosis and guide safe food introductions. Future research and clinical improvement
71 initiatives should focus on these areas.

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72 Food protein-induced enterocolitis syndrome (FPIES) is a potentially severe and poorly understood
73 type of food allergy. Little is known about its pathophysiology and no diagnostic or prognostic
74 biomarkers exist. Also, 'it does not look like an allergy' and awareness amongst healthcare
75 professionals is poor, which hinders prompt diagnosis and early access to appropriate care. The
76 International FPIES Association as well as experts highlighted this lack of awareness as one of the key
77 unmet needs nearly a decade ago [1,2]. Research on FPIES has increased recently, contributing to
78 better understanding of its epidemiology, natural history and clinical presentation, including increasing
79 reports in adults [3-5]. The International Consensus on FPIES published in 2017 was an important
80 milestone to help improve and harmonise clinical practice [6]. In this rapidly evolving field, an in-depth
81 up-to-date assessment of patient's perspectives is required to further develop meaningful patient-
82 centred research and improvements in clinical care. In this study, we aimed to assess the challenges
83 and unmet needs of both parents/carers of children with FPIES and adults with FPIES.

84 We conducted an observational cross-sectional study using an online survey targeted at parents/carers
85 of children with FPIES and adults with FPIES (self-reported). The survey was developed by the study
86 authors and reviewed by the FPIES Foundation Medical Advisory Board. As a 'Patient and Public
87 Involvement' initiative, review by an Ethics committee was not required. All responses were
88 anonymous and kept confidential. The survey was in English and used a parallel mixed methods
89 approach, including qualitative data (open-ended questions on challenges and needs when living with
90 FPIES) and quantitative data (demographics, clinical characteristics, as well as Likert scale ratings of
91 potential unmet needs, satisfaction with healthcare and impact on family life and wellbeing). Full
92 survey is available from authors upon request. The study was advertised through patients'
93 organisations including FPIES Foundation, FPIES UK, Food Allergy Canada and Allergy & Anaphylaxis
94 Australia, via their membership email lists and/or social media (Twitter/Facebook). The survey was
95 disseminated via link to SurveyMonkey between 5/6/2020 and 7/18/2020. Quantitative data were
96 analysed and presented as percentages/absolute numbers, mean/SD or median/interquartile range
97 (IQR) as appropriate. Comparative analysis between data relating to children and adults was
98 performed using parametric or non-parametric tests as appropriate. A p value below 0.05 was
99 considered statistically significant. PASW Statistics 27 (SPSS Inc., Chicago, Ill) was used. Qualitative
100 data were reviewed by three authors (RK/EK/SM) and analysed using Braun and Clarke's Reflexive
101 Thematic Analysis method (ref). A combined inductive and semantic approach was followed during
102 coding and theme development.

103 The survey was completed by 285 respondents, of whom 248 (87%) were parents of a child with FPIES,
104 5 (1.8%) carers of a child with FPIES, 21 (7.3%) adults with FPIES and 11 (3.9%) adults with FPIES who
105 also had a child with FPIES based on self-reporting. Mean respondents' age was 36.9 years (SD 8.2),

106 270 (94.7%) were female and 257 (90.2%) had attended College. Most respondents were based in the
107 USA (70.5%, 201/285), followed by Australia 15.8%, (45/285), Canada (7.4%, 21/285), UK (6.7%,
108 19/285) and other (3.2%, 9/285). Patients' mean current age was 4 years (SD 3.3) for children and 41.1
109 (SD 12.8) for adults with FPIES. Age at FPIES onset was 0.4 years (SD 0.5) for children and 19.1 (16.6)
110 for adults. Acute FPIES was reported in 45.6% (135 out of 296 total FPIES cases, including those 11
111 parents of children with FPIES, who also had FPIES themselves), both acute FPIES and chronic gut
112 symptoms in 49% (145/296) and chronic gut symptoms only in 6.1% (18/296). FPIES to multiple food
113 triggers was reported in 76% (225/296). A mean of 3.5 (SD: 2) professionals had been involved in
114 patients' FPIES care. Mean score for satisfaction with Allergist/Gastroenterologists' care was 4.1 (SD:
115 1.7) and for non-specialists' care was 3.5 (SD: 1.7), range 1 ('very dissatisfied') to 6 ('very satisfied').
116 Mean score for impact on family life was 2 (SD: 1) and on patient's wellbeing was 2.4 (1.1), range 1
117 ('hugely affected') to 5 ('not at all affected'). Further patients' characteristics, including differences
118 between children and adults are described in table E1.

119 The following unmet needs were rated as the 'top 5' -in decreasing order of importance (mean score,
120 SD), range 1 ('not essential') to 9 ('absolutely essential'):- increased awareness/knowledge amongst
121 healthcare professionals to avoid delay in diagnosis (8.7, 0.91); increased awareness/knowledge
122 amongst medical students to avoid delay in diagnosis (8.51, 1.14); prognostic test to predict resolution
123 of FPIES to culprit foods (8.4, 1.19); prognostic test to predict safe new foods to be introduced in
124 patient's diet (8.4, 1.2); diagnostic test to identify FPIES acutely against common differentials (8.04,
125 1.63). The top three unmet needs above received higher rating by parents/carers compared to adults,
126 as did the need for peer support, online peer forum and research into the burden of FPIES. See rating
127 for all questions in Fig 1, and further comparison between children and adults in table E1. No
128 differences were observed across countries (data not shown).

129 We conducted thematic analysis of the 132 comments from open-ended questions (106 from parents,
130 23 from adults with FPIES, 3 from parents who also had FPIES themselves). This resulted in five
131 overarching themes emerging predominantly from parents; three related to challenges and two
132 related to needs. Regarding challenges, respondents identified the 'Anxiety and stress when managing
133 FPIES', including the lack of support from health care professionals and the lack of financial help. Fear
134 of reactions and introduction of new foods was frequently cited as a source of anxiety, particularly by
135 parents. A second theme concerned 'Social restrictions and discrimination affecting quality of life'.
136 This theme related to the difficulties in social situations such as eating out and the discrimination felt
137 when trying to negotiate safe foods. Finally, respondents felt that 'Lack of knowledge and support for
138 FPIES' was a challenge. This included health care professionals, schools and the wider community.
139 Adults' comments focused predominantly on the latter two challenge themes (see table 1). These

140 themes clearly linked to the needs identified by respondents. Regarding needs, respondents wanted
141 greater 'Awareness, information, education and psychological support for FPIES'. This theme included
142 education for health care professionals, teachers and the general community as well as greater
143 information for adult patients and parents in how to manage FPIES. Secondly respondents wanted
144 more 'Research to improve knowledge regarding diagnosis and management of PFIES' including
145 improved diagnostic methods and better food labelling.

146 To our knowledge this is the first international survey exploring the challenges and unmet needs of
147 children and adults living with FPIES from the parents and adult patients' perspective. Better
148 knowledge and awareness of FPIES amongst healthcare professionals and medical students to avoid
149 misdiagnosis was identified as the key priority to address. This is in line with the reported suboptimal
150 satisfaction with care and previous reports of poor awareness amongst non-specialists [7]. Availability
151 of diagnostic tests to avoid delay or misdiagnosis, as well as prognostic tests to identify safe food
152 alternatives and tolerance development over time were perceived as key areas for future research. At
153 least 25-50% of patients with FPIES react at challenge over follow-up and, despite no fatalities being
154 reported in FPIES, anxiety due to fear of reactions seems a major concern for parents. Finally,
155 improving clinical care including listing specialised centres, an integrated care plan and access to a
156 dietitian and appropriately supervised food challenges were also highly rated as essential areas. The
157 FPIES' profound impact on health-related quality of life is beginning to be unravelled [8,9]. Our results
158 help further understand the broad-ranging difficulties experienced by adults and parents/carers living
159 with FPIES, from anxiety, social restrictions and discrimination to financial pressure and lack of
160 knowledge and support.

161 Regarding our study limitations, the diagnosis of FPIES was self-reported. Although most patients had
162 been assessed by an Allergist, whether the diagnosis of acute FPIES or chronic gut symptoms had been
163 established by a healthcare professional was not determined. Our survey was disseminated in English
164 through developed English-speaking countries only. As such, it may not reflect views from other
165 regions or communities. Similarly, the survey was completed mainly by highly educated mothers of
166 children with a relatively complex self-reported FPIES profile involving multiple foods, a persistent
167 phenotype and both acute and chronic gastrointestinal symptoms. This may suggest selection bias (e.g.
168 patients/families with more complex backgrounds liaising with patients organisations) as such a profile
169 is usually a minority in most clinician-reported FPIES series [3,4]. Whether our findings reflect the
170 challenges and unmet needs of the broader spectrum of the FPIES community requires further study.
171 Differences identified between parents and adult patients need to be interpreted with caution as
172 numbers for the latter are limited. Six percent of respondents were adults or parents of children with
173 chronic gut symptoms without evidence of profuse vomiting after eating the culprit food, which would

174 not fall in the strict definition of chronic FPIES. Finally, the survey was conducted during the first stage
175 of the covid-19 pandemic, when people were emerging from lockdown and isolation. The broad-
176 ranging impact of this, including on mental health, may have influenced our results.

177 Our study provides a valuable framework to help co-design patient-centred clinical improvement and
178 research strategies to help serve patients/families' needs and improve clinical outcomes. This should
179 include early education initiatives on the presentation, diagnosis and management of FPIES addressed
180 to all stakeholders (healthcare professionals, patients, parents, caregivers, school staff and the wider
181 community) as well as strategies to help alleviate the high psycho-social burden associated to the
182 disease.

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220 **Figure 1.** Rating of potential unmet needs by survey respondents (n=285) from 9 (absolutely
221 essential) to 1 (not essential).

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223 **Table 1.** Themes and subthemes emerging from the qualitative data thematic analysis of the
224 132 comments from the open-ended questions.

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Table 1. Themes and subthemes emerging from the qualitative data thematic analysis of the 132 comments from the open-ended questions.

Themes, subthemes and quotes
Challenges
Anxiety and stress when managing FPIES
<i>'Constant anxiety in fear of accidental exposure' (mother)</i>
<i>'Travel on a plane.....field trips with school all bring anxiety'(mother)</i>
<i>'The cost of the formula, her NG-tube supplies, hospital visits, medicines, and doctor care has been a huge stress'(mother)</i>
<i>'It's completely anxiety inducing for me as a mother every time we introduce new foods. All I do is stare at the clock waiting for that 2 hour mark after he eats to see what will happen'(mother)</i>
<i>'High anxiety during food trials and reintroduction'(mother)</i>
<i>'Keeping my toddler away from ALL foods is an exhausting challenge. Not only do I worry about acute exposure/reaction but high choking risk, as my child has never learned to chew from being on strict amino acid formula. It is a very sad, overwhelming experience and I generally, feel unsupported'(mother)</i>
<i>'Anxiety - Encountering food contamination anywhere but home. Embarrassment- vomiting in public/weddings/family events. Fear of trying new things' (adult)</i>
Social restrictions and discrimination affecting quality of life
<i>'Because of trying hard to keep our child safe, we've had to withdraw from many social gatherings and from going out or getting away for a weekend or other trips'(mother)</i>
<i>'Anywhere we go. Out to eat, holidays, school etc all have to be planned and risk assessment'(mother)</i>
<i>'Frustration due to other children not understanding FPIES and not being able to participate in celebrations due to food restrictions'(mother)</i>
<i>'Dining out is a huge challenge - people confuse rice allergy and assume gluten free is what we need. Scary. This is where our social emotional well-being is affected most - parties, camp, school events, social events, and dining out'(mother)</i>
<i>'Wanting to be polite and wanting to not appear to be picky' (adult)</i>
<i>'Can't" - I can't travel, can't take my kids out for ice cream or anything, can't go in a corn maze, can't go to a movie theater (popcorn everywhere)' (adult)</i>
<i>'I actually lost out on a very good relationship because his mother was offended when I didn't eat her food' (adult)</i>
<i>'I appreciate that you've included psychological health in this survey. It took me a good 2 years to understand what having FPIES really means after my diagnosis, and looking back, the hardest part wasn't the food trials or the appointments, it was accepting a new way of life and prioritizing my wellbeing.' (adult)</i>
Lack of knowledge and support for FPIES
<i>'Fighting with uneducated doctors, time & energy spent educating providers, having more knowledge than your providers on a diagnosis'(mother)</i>
<i>'Nobody believed there was anything wrong with my baby. Was very paranoid for a long time until allergist confirmed the allergies and FPIES'(mother)</i>
<i>'School was a nightmare. Sick so often had to homeschool. School gave him food that he can't eat several times'(mother)</i>
<i>'The lack of understanding from everyone. Doctors, family members, and friends who don't fully understand leave our family with no support' (mother)</i>
<i>'I think the lack of community knowledge and understanding and medical staff being aware of FPIES makes it a very long and lonely journey'</i>
<i>'Need more hospitals/clinics that help to properly diagnose adults' (adult)</i>

Seems like no one knows how to help me manage all the symptoms through diet. All they want to do is throw medications, which make things worse. I have had to do all the work. Very little from doctors' (adult)

'Disbelief and lack of knowledge. ' (adult who is also a parent of a child with FPIES)

Needs

Awareness, information and education for FPIES

'ER (Emergency Room) providers need more education regarding FPIES' (mother)

'ER (Emergency Room) doctors do not even know what we are talking about when we tell them about FPIES' (mother)

'Educate nurses as well as Drs. They too need to know of FPIES and all of the symptoms that comes with it'(mother)

'If we had a brochure to hand out to extended family to help them understand FPIES it would help'(mother)

Research to improve knowledge regarding diagnosis and management of FPIES

'Think having a clear understanding that we can create a diagnostic tool and guidelines but knowing that every child is different and symptoms present differently just like the foods they can/can't eat will be different from other FPIES kids' (mother)

'A test to determine if she still has FPIES without a food challenge would really be invaluable. She doesn't want to do a food challenge, and I can't really blame her'(mother)

'Really hoping more research is done soon to get diagnostic tools, more education to professionals and the general community and just gain a better understanding of the disease' (mother)

Demographic and clinical characteristics	Entire sample (n=296)	Children (n=264)	Adults (n=32)	p value
Respondent's age (years, mean, SD)	36.9 (8.2)	36.5 (7.8)	40.4 (10.7)	>0.05 [¥]
Respondent's gender (female, %)	94.3% (279)	95.8% (253)	81.3% (26)	0.012 [#]
Patient's current age (years, mean, SD)	6.8 (10.9)	4 (3.3)	41.1 (12.8)	
Patient's age at FPIES onset (years, mean, SD)	1.8 (6.7)	0.4 (0.5)	19.1 (16.6)	>0.05 [¥]
Presenting phenotype (%; No)				>0.05 ^α
Acute FPIES	45.6% (135)	45.5% (120)	46.9% (15)	
Chronic gut symptoms	6.1% (18)	4.9% (13)	15.6% (5)	
Acute FPIES + Chronic gut symptoms	49% (145)	49.6% (131)	37.5% (12)	
Foods causing FPIES				
Single food FPIES (%; No)	24% (71)	23.5% (62)	28.1% (9)	>0.05 [#]
Multiple food FPIES (%; No)	76% (225)	76.5% (202)	71.9% (23)	
Number of culprit foods (median, IQR)	2 (1-4)	2 (1-5)	1 (1-2)	0.002 [§]
Specific culprit foods causing FPIES (%; No)				
Cow's milk	54.4% (161)	55.7% (147)	43.8% (14)	>0.05 [#]
Soya	35.1% (104)	37.5% (99)	15.6% (5)	>0.05 [#]
Gluten	19.6% (58)	21.2% (56)	6.3% (2)	>0.05 [#]
Non-gluten grains	52.7% (156)	57.2% (151)	15.6% (5)	0.003 [#]
Vegetables	30.7% (91)	32.6% (86)	15.6% (5)	>0.05 [#]
Fruits	32.8% (97)	35.2% (93)	12.5% (4)	>0.05 [#]
Egg	24.7% (73)	26.5% (70)	9.4% (3)	>0.05 [#]
Shellfish	8.4% (25)	6.8% (18)	21.9% (7)	>0.05 [#]
Other	31.4% (93)	32.6% (86)	21.9% (7)	>0.05 [#]
Hospital admission due to FPIES (%; No)				>0.05 ^α
Yes	35.8% (106)	36.7% (97)	28.1% (9)	
No	63.2% (187)	63.3% (167)	62.5% (20)	

Unsure	1% (3)	0% (0)	9.4% (3)	
FPIES 'outgrown' (% , No)				>0.05 ^α
Yes	8.1 (24)	8.0% (21)	9.4% (3)	
No	67.2 (199)	65.2% (172)	84.4% (27)	
Unsure	24.7 (73)	26.9% (71)	6.3% (2)	
Allergic comorbidities (% , No)				
Other food allergies	26 (77)	26.5% (70)	21.9% (7)	>0.05 ^α
Asthma	17.2 (51)	15.9% (42)	28.1% (9)	>0.05 ^α
Rhinitis	16.9 (50)	14.4% (38)	37.5% (12)	>0.05 ^α
Atopic dermatitis	26.7 (79)	26.5% (70)	28.1% (9)	>0.05 ^α
Number of allergic comorbidities (median, IQR)	1 (0-1)	1 (0-1)	1 (0-2)	>0.05 [§]
Healthcare professional involvement (% , No)				
Primary Care	52.4% (155)	52.3% (138)	53.1% (17)	>0.05 [#]
Emergency department	49.3% (146)	51.1% (135)	34.4% (11)	0.01[#]
General Paediatrician	51% (151)	55.7% (147)	12.5% (4)	0.003[#]
Allergist/Paediatric Allergist	77.7% (230)	84.8% (224)	18.8% (6)	<0.001[#]
Gastroenterologist/Paediatric Gastroenterologist	54.4% (161)	58.3% (154)	21.9% (7)	0.011[#]
Dietitian	49.7% (147)	52.3% (138)	28.1% (9)	<0.001[#]
Other	14.5% (43)	12.1% (32)	34.4% (11)	>0.05 [#]
Number of healthcare professionals involved (mean, SD)	3.5 (2.0)	3.7 (1.9)	2.1 (1.9)	<0.001[§]
Satisfaction with care and impact on life				
Satisfaction with Allergy or Gastro specialist* (1-6, mean, SD)	4.1 (1.7)	4.2 (1.6)	2.7 (1.8)	0.001^α
Satisfaction with Non specialist* (1-6, mean, SD)	3.5 (1.7)	3.5 (1.7)	2.3 (1.5)	>0.05 ^α
Satisfaction with FPIES foundation [∞] (1-5, mean, SD)	4.1 (1)	4.1 (0.9)	3.4 (1.2)	>0.05 ^α
Impact on family life [~] (1-5, mean, SD)	2 (1)	1.9 (0.9)	2.7 (1.3)	0.002^α
Impact on patient's wellbeing [~] (1-5, mean, SD)	2.4 (1.1)	2.4 (1.1)	2.7 (1.1)	0.044^α

Ratings of potential unmet needs	Entire sample	Parents/carers	Adults (non parents)	p value
	(n=296)	(n=253)	(n=21)	
Q1 - Diagnostic test acutely [#] (1-9, mean, SD)	8.04 (1.63)	8.04 (1.63)	7.95 (1.9)	>0.05 [#]
Q2 - Predictive test (resolution) [#] (1-9, mean, SD)	8.40 (1.19)	8.45 (1.1)	7.67 (1.85)	0.034[#]
Q3 - Predictive test(safe foods) [#] (1-9, mean, SD)	8.40 (1.20)	8.41 (1.16)	8 (1.7)	>0.05 [#]
Q4- HCP knowledge [#] (1-9, mean, SD)	8.71 (0.91)	8.74 (0.83)	8.19 (1.63)	0.003[#]
Q5- Medical students knowledge [#] (1-9, mean, SD)	8.51 (1.14)	8.53 (1.1)	8.19 (1.57)	0.044[#]
Q6 - Care plan [#] (1-9, mean, SD)	7.88 (1.79)	7.87 (1.83)	7.71 (1.7)	>0.05 [#]
Q7 - Community knowledge [#] (1-9, mean, SD)	7.85 (1.39)	7.87 (1.38)	7.43 (1.69)	>0.05 [#]
Q8 - List of specialist centres [#] (1-9, mean, SD)	7.94 (1.45)	7.95 (1.4)	7.71 (1.8)	>0.05 [#]
Q9 - Access to food challenges [#] (1-9, mean, SD)	7.55 (1.94)	7.53 (1.93)	7.29 (2.39)	>0.05 [#]
Q10 - Guidelines for challenges [#] (1-9, mean, SD)	7.38 (2.18)	7.35 (2.15)	7.29 (2.9)	>0.05 [#]
Q11 - Access to dietitian [#] (1-9, mean, SD)	7.56 (1.81)	7.56 (1.83)	7.67 (1.7)	>0.05 [#]
Q12 - Access to psychologist [#] (1-9, mean, SD)	5.78 (2.48)	5.63 (2.54)	7 (1.79)	>0.05 [#]
Q13 - Peer support [#] (1-9, mean, SD)	7.02 (1.73)	7.03 (1.69)	6.67 (2.4)	0.043[#]
Q14 - Expert for questions [#] (1-9, mean, SD)	7.26 (1.56)	7.24 (1.52)	7.29 (2.3)	>0.05 [#]
Q15 - Psychological support [#] (1-9, mean, SD)	6.60 (2)	6.55 (2.04)	6.67 (1.9)	>0.05 [#]
Q16 - Online peer forum [#] (1-9, mean, SD)	6.89 (1.89)	6.94 (1.84)	6.14 (2.6)	0.04[#]
Q17 - Research on burden [#] (1-9, mean, SD)	7.26 (1.82)	7.26 (1.82)	6.86 (2)	0.038[#]
Q18 - Peer support on financial aspects [#] (1-9, mean, SD)	6.94 (1.97)	6.94 (1.97)	6.48 (2.2)	>0.05 [#]
Q19 - Resources for school age [#] (1-9, mean, SD)	6.90 (2.18)	6.89 (2.17)	6.19 (2.5)	>0.05 [#]
Q20 - Research for school age [#] (1-9, mean, SD)	7.08 (2.09)	7.1 (2.06)	6.76 (2.3)	>0.05 [#]

Table E1. Demographic and clinical characteristics, and rating of satisfaction with care received and impact of FPIES on wellbeing and family life in children (n=264) and adult individuals (n=32) with FPIES reported in the survey.

*Scale 1-6 from 'very dissatisfied' (1) to 'very satisfied' (6); ∞ Scale 1-5 from 'Not at all helpful' (1) to 'Extremely helpful' (5); ~ Scale 1-5 from 'Extremely affected' (1) to 'Not at all affected' (5) ; Scale from 1 ('not essential') to 9 ('absolutely essential') Tests used for comparative analysis: †T Test, #Fisher, °Chi Square, §U-Mann Whitney

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