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The role of IgE sensitisation in acute FPIES: A systematic review and meta-analysis

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Title: The role of IgE sensitisation in acute FPIES: A systematic review and meta-analysis

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Abstract

Background: Evidence on the role of IgE sensitisation in acute Food Protein-Induced Enterocolitis Syndrome ('atypical FPIES') is limited. Initial reports claimed association with persistent disease, however recent studies have not replicated this.

Objective: To systematically review the relationship between sensitisation to the culprit food(s) in acute FPIES and the outcome of follow-up oral food challenges. To assess rates of sensitisation, seroconversion (i.e. switch from negative tests to sensitisation) and phenotype switch to IgE-mediated food allergy over time in individuals with acute FPIES.

Methods: Systematic review searching 10 databases. Studies of children and adults with acute FPIES diagnosis assessing IgE sensitisation to culprit food at onset or follow-up measured by skin prick or serological test were included.

Results: Of 1830 studies identified, 53 were eligible including 3514 participants. Ten studies had an analytical design assessing whether sensitisation was associated with disease persistence, with 4 showing an association and 6 showing no association. In individuals with acute FPIES, the sensitisation rate was 9.8% (95% CI: 7.4-12.1%; 34 studies, 2587 participants, I^2 = 82%); the frequency of seroconversion was 1.1% (95% CI: 0.1-2.1%; 9 studies, 673 participants, I^2=32%); and phenotype switch occurred in 1.1% (95% CI: 0.4-1.7%; 14 studies, 935 participants, I^2 =0%) and 13% (95% CI: 5.5-20.5%, 12 studies, 93 participants; I^2=18%) of sensitised participants.

Conclusion: We did not find consistent evidence for the relationship between IgE sensitisation and FPIES persistence. We found phenotype switch to IgE-mediated food allergy is uncommon in acute FPIES. IgE-sensitisation in FPIES does not have a clear relationship with clinical outcomes.

Highlights Box

1. What is already known about this topic? The role IgE sensitisation in acute food protein-induced enterocolitis syndrome ('atypical FPIES') is not clearly understood. Some studies claimed association with persistent disease, however recent studies have not replicated this.
2. What does this article add to our knowledge? The prevalence of sensitisation to culprit food in acute FPIES is approximately 9.8%. However, phenotype switch to IgE-mediated food allergy is uncommon (1.1%), also in those sensitised (13%). There is no clear association between sensitisation and FPIES persistence.
3. How does this study impact current management guidelines: IgE or skin prick testing in acute FPIES should not be routinely recommended as its clinical significance seems limited.

Key words.

Food protein-induced enterocolitis syndrome, food allergy, gastrointestinal disorders, immunoglobulin E, oral food challenge, children, paediatrics, natural history, sensitisation, skin prick test

List of Abbreviations:

FPIES - Food protein-Induced Enterocolitis Syndrome

IQR - Interquartile Range;

IgE - Immunoglobulin E;

IgE FA – IgE-mediated Food Allergy;

64 OFC - Oral Rood Challenge

65 SPT - Skin Prick Test

66

Introduction

Acute Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-immunoglobulin E (IgE) mediated food allergy resulting in gastrointestinal symptoms, typically projectile vomiting 1-4 hours after ingestion often with lethargy, pallor, diarrhoea and in up to 16% hypotension[1,2]. Diagnosis relies on clinical history as there are no accurate diagnostic or prognostic/predictive biomarkers for FPIES resolution[3].

IgE does not seem to be involved in the pathophysiology of FPIES[4-7] in recent data-driven studies assessing this. Specific antibody recognition or elevated titers (IgG, IgM, IgA) have not been found in patients with a history of cow's milk-FPIES[5,8]. Despite no evidence of IgE recognition of trigger food in FPIES[4,5], some patients have positive food specific IgE antibodies to their trigger food. This is termed atypical FPIES and was first described by Sicherer et al. in 1998[9]. Rates of atypical FPIES appear to differ across different geographic locations and foods[10-15]. Children with FPIES have higher rates of atopic comorbidities than the general population[1] thus IgE sensitisation to the culprit food might be an epiphenomenon purely reflecting this atopic predisposition.

Children with FPIES generally develop tolerance over time and the only way to establish this is through re-exposure, usually as a supervised oral food challenge (OFC) every 12-18 months[1,3]. Studies assessing atypical FPIES and whether this is linked to a more persistent disease course have accumulated in recent years but seem to provide mixed results. Based on a study by Caubet et al.[14] who assessed tolerance development in cow's milk-FPIES children with and without cow's milk sensitisation noted that no children with positive cow's milk IgE outgrew their cow's milk-FPIES over follow-up (median 23 months). Thus, the most recent international consensus guidelines[1] published in 2017 recommended to "*consider specific IgE testing of children with FPIES to their trigger food".* However, it also stated that one should not "*routinely*

93 *perform testing for food sIgE to identify food triggers"* unless in "*certain comorbid conditions*"[1],
94 leaving clinicians with ambiguity as to how to proceed.
95 Also, it has been reported that some patients 'seroconvert' over time (i.e. switch from negative
96 to positive IgE testing) and some patients 'switch phenotype' from an acute FPIES reaction to
97 an immediate (IgE-mediated) reaction. This has direct implications for management as IgE
98 testing prior to OFC could aid provision of a safer OFC. In sensitised children with FPIES, OFC
99 protocols for IgE-mediated food allergy have been recommended[1]. This implies that sensitised
100 children are likely to react in an immediate fashion, although it is unclear how common this
101 phenomenon is.
102
103 A recent invited review[16] on current perspectives on the 2017 consensus document reiterated
104 the findings of the study by Caubet et al[14] and recommended "*allergy testing for FPIES"* to be
105 "*considered in future guidelines to capture atypical FPIES*" and the occurrence of phenotype
106 switch. However, no systematic review of the literature has been conducted in this area despite
107 the direct implications for clinical practice such as the need for IgE testing at diagnosis and/or
108 follow-up, and the prognostic implications such as what type of reaction to expect, and when to
109 expect tolerance development and offer an OFC.
110
111 There is a need to systematically review the most up-to-date evidence in this area to understand
112 whether measuring for IgE sensitisation in FPIES is helpful in clinical practice. This study tried to
113 address this need.
114

Methods

We systematically reviewed the evidence on IgE sensitisation with the aim of evaluating whether IgE sensitisation to the culprit food(s) can help predict the outcome of follow-up OFC in acute FPIES, i.e. predict disease persistence or a phenotype switch to IgE-mediated reactions.

The primary objective was to assess the association between IgE sensitisation to the culprit food(s) in acute FPIES and tolerance development at follow-up OFC.
Secondary objectives included assessing the prevalence of sensitisation to the culprit food(s) at onset, the prevalence of 'seroconversion' (switch from negative to positive specific IgE or skin prick test (SPT)) to the culprit food(s) over follow-up, the prevalence of 'phenotype switch' from acute FPIES at onset to immediate food allergy to the culprit food(s) over follow-up and the potential correlation between sensitisation rates and rates of atopic comorbidities.

This SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[17].

Study eligibility criteria

The PICOS framework was used to design the study eligibility criteria[18] (see Table 1).

Information sources

Relevant articles were selected through searching electronic databases from 1st January 1980 to 10th October 2023 and included AMED, CAB International, CINAHL, EMBASE, Cochrane Library, Global Health, MEDLINE, Psych INFO, ISI Web of Science and TRIP. References of selected articles were also reviewed to identify additional studies.

Search Strategy and Selection Process

Three reviewers independently reviewed titles and abstracts of all studies. Next, the reviewers screened full text studies for inclusion. In case of disagreement, consensus on which articles for final inclusion/exclusion was reached by discussion.

Data Collection Process

Each study had data extracted by 2 independent reviewers. Extracted data were compared, with any discrepancies being resolved through discussion. Another author arbitrated any disagreements.

Risk of bias

Two reviewers independently assessed the methodological quality of eligible studies and the potential for risk of bias using the Effective Public Health Practice Project (EPHPP) [19].

Analysis

Descriptive statistics (median and IQR) are provided. Meta-analysis was conducted and presented in forest plots for prevalence of sensitisation, seroconversion and phenotype switch. Where there was substantial or considerable heterogeneity ($I^2 \geq 50\%$), possible sources for heterogeneity were explored. Spearman's rank correlation was used to assess the potential correlation between sensitisation and atopy, students t-test was used to assess the association of sIgE between those who did and didn't have phenotype switch.

Results

Study selection

We found 1830 studies in database searching, after duplicate removal, we screened 1413 studies and finally included 53 studies[2,9-12,14,15,20-65] (see Figure 1).

Study characteristics

The characteristics of the 53 included papers (total 3514 participants) are shown in Table 2 and include 34 cohort, 18 case-series and 1 case-control study. Over 90% of studies were in children (n=48). The studies were from Spain (n=13), USA (n=10), Japan (n=7), Australia (n=5), Italy (n=4), Turkey (n=4), France (n=3), Greece (n=3), and Sweden, Germany, Israel and Korea (n=1).

Regarding culprit foods assessed, this was any trigger food (documented in this SR as 'any') for 64% (n=34/53) of studies, fish only (n=5), egg/egg yolk only (n=4), nuts only (n=3), cow's milk only (n=2), solid foods only (n=2), fish and shellfish only (n=1), cow's milk and soy (n=1), avocado only (n=1).

Most studies (77%, n=41/53) completed both SPT and specific IgE (sIgE) testing, SPT only in 13% and IgE only in 9%. Total IgE was reported in 7 (13%) studies[12,29,51,58,62,64,66] and the median (IQR) result was 34 kU/L (18.5-74.9). From the studies which measured both total IgE and IgE sensitisation to the culprit food in FPIES, the potential relationship between the two was not explored. The timepoint at which sensitisation status was assessed was at initial assessment only in 19 studies, at initial and follow-up in 11 studies and for 16 studies the assessment timepoint was unclear. Only 13% of studies documented sensitisation separately for both initial and follow-up assessments.

Quality assessment of included studies

We used the EPHPP tool[19] to assess quality of included studies. A global rating of strong was given in 17 studies, moderate in 22 and weak in 14 studies.

Results of individual studies and syntheses

Sensitisation was assessed in all studies included in this SR (n=53), as per inclusion criteria and results are summarised in Table 3. The sensitisation rate across the 34 studies assessing FPIES to 'any' food was 9.8% (95% CI: 7.4-12.1%; 34 studies, 2587 participants, I^2 = 82%, p<0.001) (see Figure 2A). There was considerable heterogeneity in the dataset but despite exploration of the data (e.g. differences in sensitisation method (SPT vs. IgE), age, sample size) there remained substantial variation (I^2≥ 60%). Studies reporting only on specific foods were excluded from this meta-analysis and their results are reported individually in Table 3.

The sensitisation rate per food is shown Figure 3A and forest plots shown in Figure E1 in supplemental files. The highest rate was in egg (22.4% (95% CI: 15.5-29.4%; 32 studies, 391 participants, I^2=71%, p<0.001) followed by nuts (20.9% (95% CI: 10.2-31.6%; 12 studies, 60 participants, I^2=23%, p=0.215) and cow's milk (13.6% (95% CI: 9.7-17.5%; 34 studies, 857 participants, I^2=72%, p<0.001).

For the studies that assessed 'any' foods the highest percentage of sensitisation were seen in Turkey (21.3%), USA (16.1%) and Japan (15%). Lower percentages are seen in Australia, Sweden and Spain (4%). Figure 3B illustrates percentage of sensitisation per food per country. The highest percentage of sensitisation was found in studies that analysed specific food triggers only, as follows: 3 of the highest percentages are from Japanese studies in egg and mostly egg-yolk (57.7% (16/26)[59], 50% (4/8)[58], 35.7% (5/14)[62]).

We did not find an association between atopic comorbidities and sensitisation to culprit food in FPIES. Assessment of whether a more complex allergy phenotype (e.g. allergy multimorbidity[67]) might be associated with sensitisation to culprit food in FPIES requires further study, including individual patient data. This assessment was not possible as individual data were not available.

Seroconversion

Twelve studies reported on rates of seroconversion[9-11,14,15,28,32,34,40,52,56,63]. The seroconversion rate across the 9 studies reporting FPIES to 'any' food was 1.1% (95% CI: 0.1-2.1%; 9 studies, 673 participants, I^2=32%, p=0.163) (see Figure 2B). Three studies[14,32,40] was excluded as they reported on specific foods only. When 4 studies[9,28,52,56] with ≤20 patients were excluded, the heterogeneity reduced with a seroconversion rate of 0.8% (95% CI 0.1-1.5%; 5 studies, 609 participants, I^2=0%, p=0.487).

Meta-analysis was undertaken for individual foods in studies that reported on rates of seroconversion, as follows; milk 4.8% (95% CI: 1.5-8.2%; 10 studies, 327 participants, I^2=45%, p=0.058); fish 1.9% (95% CI: 0.3-4.2%; 7 studies,133 participants, I^2=0%, p=0.936); soy 4.9% (95% CI: 2.2-12.1%; 4 studies, 31 participants, I^2=0%, p=0.790) and rice 8.1% (95% CI: 0.09-17.1%; 6 studies, 29 participants, I^2=0%, p=0.961) (see Figure E2 in supplemental files). No meaningful data in seroconversion from positive to negative was found.

Phenotype Switch

Twenty-one studies reported on whether any of their acute FPIES individuals switched to an IgE-mediated (immediate) reaction over time (see Table 4) with 10 studies noting this phenotype switch, assessed via follow-up OFC. The phenotype switch rate in studies reporting FPIES to 'any' food in their whole population was 1.1% (95% CI: 0.4-1.7%; 14 studies, 935 participants, I^2 =0%, p=0.635) (see Figure 2C). The phenotype switch for sensitised individuals was 13% (95% CI: 5.5-20.5%, 12 studies, 93 participants; I^2=18%, p=0.266) (see Figure 2D). One study[47] was excluded as it resulted in a high heterogeneity (52%). This study characteristics are described in Table 4.

Regarding data on individual foods, the phenotype switch rate for milk in the total milk-FPIES population was 3% (95% CI: 1.2-4.9%; 15 studies, 431 participants, I^2 = 16%, p=0.274) and in milk-sensitised individuals was 28.9% (95% CI: 1.4-56.4%; 11 studies, 69 participants, I^2 = 92%, p<0.001). The phenotype switch rate for egg in the total egg population was 2.6% (95% CI: 0.3-5.0%; 11 studies, 166 participants, I^2 = 0%, p=0.923) and in egg-sensitised individuals was 14.7% (95% CI: 4.3-25.5%; 8 studies, 37 participants, I^2 = 0%, p=0.996). See Figure E3 in supplemental files for forest plots. Only one case of phenotype switch to fish was reported[28] out of 13 studies and this patient was sensitised.

Caubet et al.[14] is the only study that reported on the sIgE level (kU/L) associated with a phenotype switch. Amongst those sensitised (n=17), for those that had a phenotype switch (n=7) the median cow's milk sIgE was 11 kU/L (IQR 3.1-27.9; range 0.73->100), and for those that did not the median cow's milk sIgE was 0.91 kU/L (IQR 0.56-27.0; range: 0.39-48.9). There was no significant difference in IgE levels between the two groups (p=0.70, analysis conducted by our study group).

From the 10 studies that reported on phenotype switch, 6 reported the symptoms experienced, with only 2 reported anaphylaxis[14,49]. Three patients had anaphylaxis out of 36 patients that had phenotype switch.

Tolerance development and OFC outcome in relation to sensitisation status

Ten studies (see Table 5) completed analysis (survival analysis or subgroup comparison) on whether IgE sensitisation influenced tolerance development. Four studies[14,30,42,53] found a significant association between IgE sensitisation and disease persistence ($p<0.05$) and 6 studies[10,11,41,49,54,57,62,64] reported no association.

Regarding the 4 studies showing an association, Lee et al.[42] used Kaplan-Meier analysis for time to tolerance, and predictors of tolerance development were tested using proportional hazards regression model in 69 Australian children with acute FPIES to any food in a tertiary centre. They found a statistical difference with children who were sensitised having a more persistent course compared with non-sensitised children. Ocak et al. [53] reported an association via comparative analysis of sensitisation rates to (unspecified) culprit food in resolved vs persistent FPIES children who were referred into a tertiary Turkish centre and followed up for median 19.4 months. Caubet et al.[14] undertook subgroup analysis in CM-sensitised FPIES USA children that were tolerant vs persistent by 3 years old via Mann–Whitney U test and found a significant association. Finally, Douros et al.[30] reported an association in Greek children using survival analysis with IgE sensitisation used as a dichotomic variable.

The studies that found no association between sensitisation and disease persistence were published between 2017-2022, with 5 studies analysing over 60 patients each. The studies were from Japan, France, Germany, Greece, Italy and USA. Su et al.[57] analysed 123 cases in a USA tertiary centre (103 non-sensitised, 20 sensitised) followed up for 1 year and found no difference in resolution rate. Lange et al.[10] used the same analytical approach in 100 children from 14

German tertiary centres who were followed up for a median of 12 months (range, 0-108 months) and found that sensitisation did not influence tolerance development (p=0.92). Lemoine et al.[11] analysed 173 OFC from 2 French tertiary referral centres (44 sensitised and 129 non-sensitised) and found no association in resolved vs persistent FPIES via comparative analysis (Mann Whitney U-test).

Regarding the length of follow-up to assess for tolerance acquisition, of the 4 studies that found an association, 2 studies did not provide a median follow-up period[30,42], the other 2 were for a median 19.4[53] and 45[14] months. For the 6 studies that found no association, in 2 studies[11, 41] it was not stated, 3 studies[10,47,57] had a median follow-up of 12 months, and Papadopoulou et al. [54] had the longest median follow-up period of 92 months.

Discussion

To the best of our knowledge, this is the first SR on the role of IgE sensitisation in acute FPIES aiming to synthesize current evidence on the usefulness of testing in clinical practice. The main findings of our SR are as follows:

- The sensitisation rate across the 34 studies assessing FPIES to 'any' food was 9.8% (95% CI: 7.4-12.1%; 34 studies, 2587 participants, I^2 = 82%).
- The seroconversion rate (i.e. switching from negative to positive sensitisation over follow-up) was 1.1% (95% CI: 0.1-2.1%; 9 studies, 673 participants, I^2=32%).
- The phenotype switch rate (i.e. switch from acute FPIES to immediate/IgE-mediated reactions) in the whole population was 1.1% (95% CI: 0.4-1.7%; 14 studies, 935 participants, I^2 =0%) and amongst sensitised individuals was 13% (95% CI: 5.5-20.5%, 12 studies, 93 participants; I^2=18%), 28.9% in milk-sensitised.
- This SR did not show a consistent relationship between IgE sensitisation and FPIES persistence or outcome at OFC. Studies using similar methodologies showed conflicting results.
- No correlation was found between rates of sensitisation and rates of atopic dermatitis, IgE mediated food allergy, asthma, and family history of atopy reported in the included studies.

Our primary objective was to understand whether measuring IgE sensitisation to the culprit food(s) in acute FPIES can help predict tolerance development. The international guidelines published by Nowak-Wegryzn et al.[1], based mainly off the study by Caubet et al[14], provided a 'moderate' strength recommendation that IgE testing should be considered as comorbid IgE sensitisation can infer persistence[14]. This approach has been taken further in a recent invited review[16] although no thorough literature assessment is provided. Since the publication of the 2017 consensus there have been 10 more studies reporting on the relationship between disease persistence and IgE sensitisation with only 4/10 showing an association. Studies using similar methodologies provide conflicting results. Lee et al.[42] undertook a

methodologically robust analysis and found a delay in tolerance acquisition noted in their Australian population (n=69), but this is in contrast with negative results in similar analysis undertaken in German (n=100)[10], Greek (n=89)[54] and American populations (n=123)[57]. The follow-up periods to assess for tolerance acquisition varied (range 12-94 months) and in 4 studies it was not stated. There is significant data heterogeneity on age of tolerance for culprit FPIES foods[1, 16]. Three studies[10,47,57] that found no association only had a median follow-up period of 12 months which may have been insufficient time to see differences in tolerance acquisition. Further prospective studies with longer follow-up periods are required to assess the potential association between sensitisation and FPIES persistence.

The most reported food in these studies was milk however further studies focusing on culprit food with longer follow-up periods are required to confidently comment if there are differences amongst culprit food sensitisation and tolerance development. Overall, based on current evidence, this SR found no consistent relationship between IgE sensitisation and FPIES persistence.

Prevalence of sensitisation

The overall prevalence of sensitisation is 9.8% from the studies assessing FPIES to 'any' food. Egg, nuts and cow's milk had highest sensitisation rates of 22.4%, 20.9% and 13.6% respectively. Japan had the highest percentages of sensitisation to egg (58%[59], 50%[58], 36%[62]). As IgE-mediated egg allergy is much more common than FPIES to egg, and it can also present predominantly with gastrointestinal symptoms[68], we wondered if some sensitised individuals could have IgE-mediated egg allergy rather than FPIES. However, the studies mainly report on egg yolk-FPIES, which typically does not induce IgE-mediated reactions. Interestingly, Akashi et al[20] suggested that the perceived increase in egg-FPIES observed in Japan might be related to the new 2017 national recommendation of early egg introduction to high-risk infants. The high rate of nut sensitisation comes from studies in the USA[23,39,43] and the authors from these studies

hypothesised a potential association between early introduction of peanut and an increase in peanut-FPIES. Whether sensitisation in FPIES in the context of early introduction in infants is more common requires further study.

Sensitisation rates seem to vary across the globe. However, comparisons are difficult due to the methodological heterogeneity, and limited number of included studies and patients. For instance, sensitisation rates in Australia were 4%, which included a population-based study[2]. However, rates from the USA were 16.1%, which only included cohorts from referral centres. More population-based studies are needed to establish a more accurate estimate of sensitisation in different regions.

Correlation between rates of sensitisation and atopic comorbidities and role of total IgE

Sensitisation to the culprit food in FPIES might be just an unspecific manifestation of patients' atopic predisposition, i.e. an epiphenomenon unrelated to FPIES pathophysiology. We observed no relationship between rates of atopic comorbidities and rates of food sensitisation in FPIES.

Total IgE levels might influence specific IgE levels, partly due to unspecific allergen binding. Our SR did not find any data assessing this in FPIES. It is unclear whether measuring total IgE adds for decision making in practice.

Prevalence of seroconversion and prevalence of phenotype switch

A seroconversion rate from negative to positive IgE of 1.1% was seen for the whole cohort with acute FPIES. This suggests that testing over follow-up in non-sensitised individuals is of limited clinical value, as the overwhelming majority will continue as non-sensitised.

Likewise, the prevalence of a 'phenotype switch' was also 1.1%. In children with IgE sensitisation to the culprit food, this rate is 13%. This implies that around 85-90% of individuals with FPIES and sensitisation to the culprit food will not react with immediate/IgE-mediated symptoms on food exposure over follow-up.

The phenotype switch rate in sensitised patients for milk-FPIES was relatively high (28.9%), although this associated very high heterogeneity. This finding coupled with the 13.6% sensitisation rate and 4.8% seroconversion rates for milk-FPIES, might justify IgE testing in milk-FPIES. Given the methodological limitations and heterogeneity of available studies, further research is needed to assess this issue.

Whether higher levels of sIgE might help predict the minority who will experience a phenotype switch is unclear. Only Caubet et al.[14] in their cow's milk-sensitised patients provided sIgE levels in relation to phenotype switch. The median sIgE tended to be higher in those that had a phenotype switch, but the difference was not significant. Further studies are required to assess whether higher IgE levels can distinguish phenotype switch from the much more common seemingly clinically irrelevant sensitisation in FPIES. Overall, a switch to anaphylaxis seems rare in patients with acute-FPIES with only 2 cases reported in this SR. Future studies exploring any potential predictors of anaphylaxis in this context would be helpful.

Limitations and strengths of the study

Limitations of the evidence analysed included the retrospective design of the included studies, time point of when IgE sensitisation was assessed and the fact that not all patients were assessed for sensitisation. We attempted to minimise limitations of the review process by having 2 independent reviewers undertake screening, quality assessment and data extraction.

Conclusions

Our SR highlights that sensitisation to the culprit food occurs in around 1 in 10 individuals with FPIES. However, around 9 in 10 of sensitised individuals will not display symptoms of an immediate or IgE-mediated reaction on food ingestion over follow-up. Additionally, this SR did not find a conclusive association between sensitisation and a more persistent FPIES course. Hence, there is no definitive evidence at present to encourage routine IgE testing in FPIES in clinical practice, as most sensitisation does not seem to translate into clinical implications. A higher rate of phenotype switch (IgE-mediated reactions over time) was observed in milk-sensitised FPIES patients, which high heterogeneity across studies. Further research is needed to explore the usefulness of testing in milk-FPIES in practice. Relationship between sensitisation to the culprit food and specific atopic comorbidities should be explored longitudinally at an individual level. Our SR highlights that further prospective studies need to be undertaken in this area with more robust methodologies including longer follow-up to adequately assess the potential association between sensitisation and FPIES persistence. This should include desirably population-based designs that consistently measure SPT, sIgE, and total IgE at onset and follow-up and check for tolerance development at regular intervals to clearly understand whether IgE sensitisation influences tolerance development and/or other clinical outcomes. This will allow us to better understand if there is any value in testing for IgE to the culprit food in FPIES in clinical practice.

Authors contributions

Aisling Phelan (AP) and Dr. Marta Vazquez-Ortiz (MVO) conceived the idea, designed the systematic review and drafted the manuscript. AP reviewed all papers for data screening and data extraction. Dr. Ulugbek Nurmatov (UN) provided methodological and analytic support. Dr. Simona Barni (SB) and Dr. Sonsoles Infante (SI) were second reviews for data screening and extraction. Dr. Bob Boyle provided oversight of analysis. All authors approved the final version of the manuscript.

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Table Legends

Table 1 PICOS framework

Table 2 Characteristics of studies included in this systematic review.

Table 3 Rates of sensitisation, study characteristics and atopic comorbidities in studies (n=53) assessing sensitisation to culprit food(s) in acute FPIES - ranked from highest to lowest percentage of sensitisation.

Table 4 Studies (n=21 studies) assessing phenotype switch from acute FPIES to immediate/IgE-mediated food allergy, presented from highest to lowest percentage of sensitised patients experiencing phenotype switch.

Table 5 Studies (n=10) with analytical design assessing the potential relationship between tolerance development and sensitisation to culprit food in acute FPIES.

Figure Legends

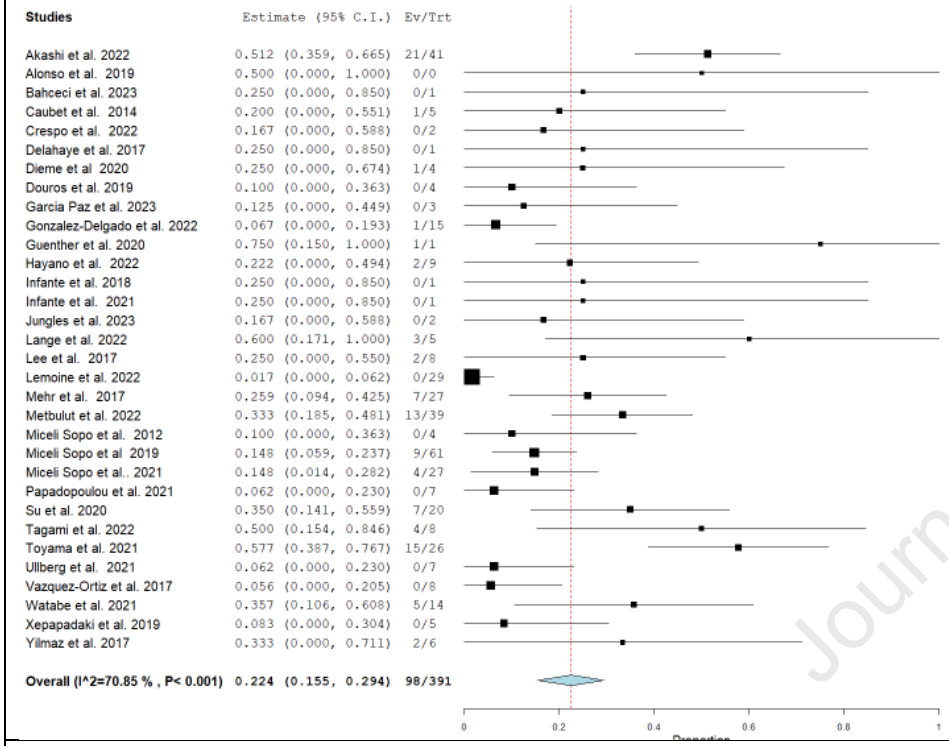
Figure 1 PRISMA 2020 flow diagram for systematic reviews (searches of databases and registers). FPIES, Food protein-induced enterocolitis syndrome; SPT, skin prick test

Figure 2 Forest plots for A. rates of sensitisation (n=34 studies), B. rates of seroconversion (n=9 studies), C. rates of phenotype switch for sensitised patients (n=14 studies), and D. rates of phenotype switch in the whole population with acute FPIES (n=14 studies) from studies that assessed ‘any’ FPIES culprit foods

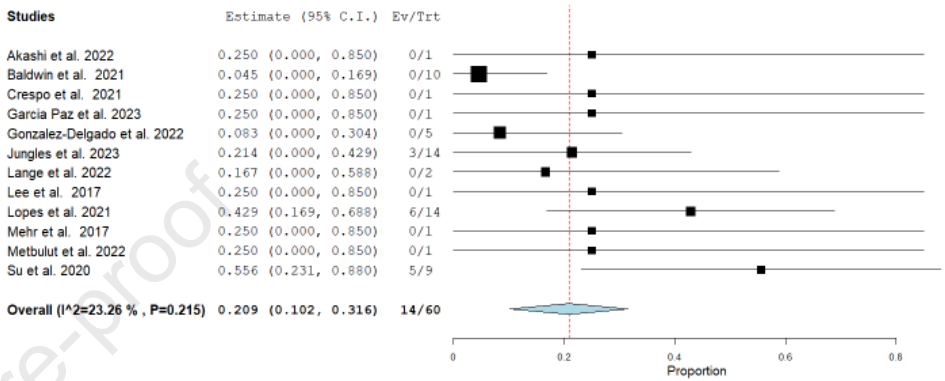
Figure 3. A. Sensitisation rate per food in studies assessing sensitisation to 'any' food and specific food culprits in acute FPIES. B. Percentage of sensitisation per food per country in studies assessing sensitisation to 'any' food and specific food culprits in acute FPIES. Data presented: Y-axis: percentage of sensitisation per food). X-axis: country (number of studies included in analysis ((number of studies excluded as culprit foods not stated)).

Figure E1

A. Egg

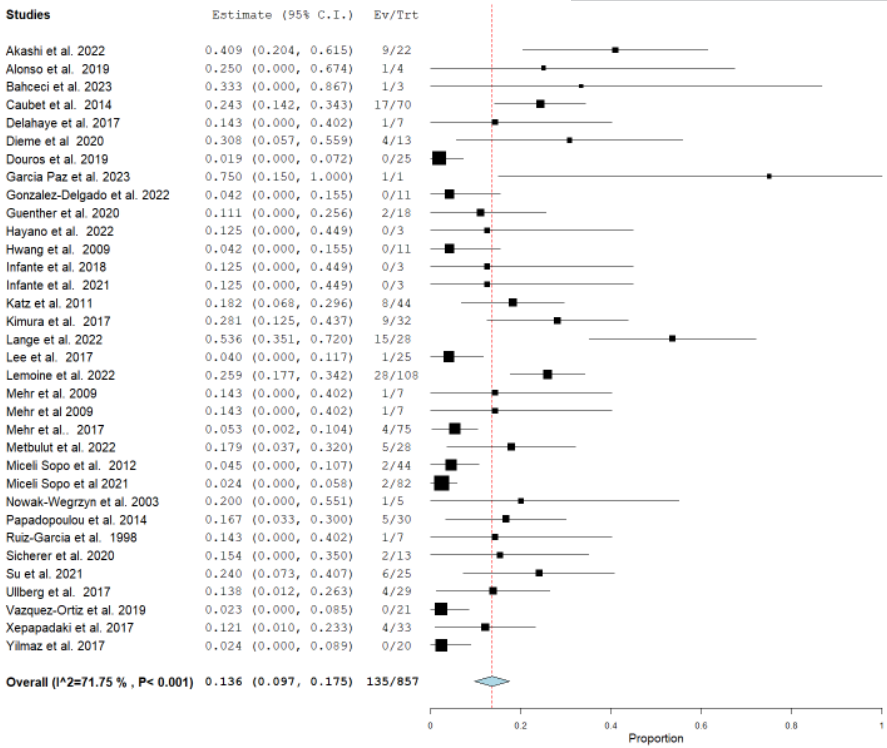


B. Nuts

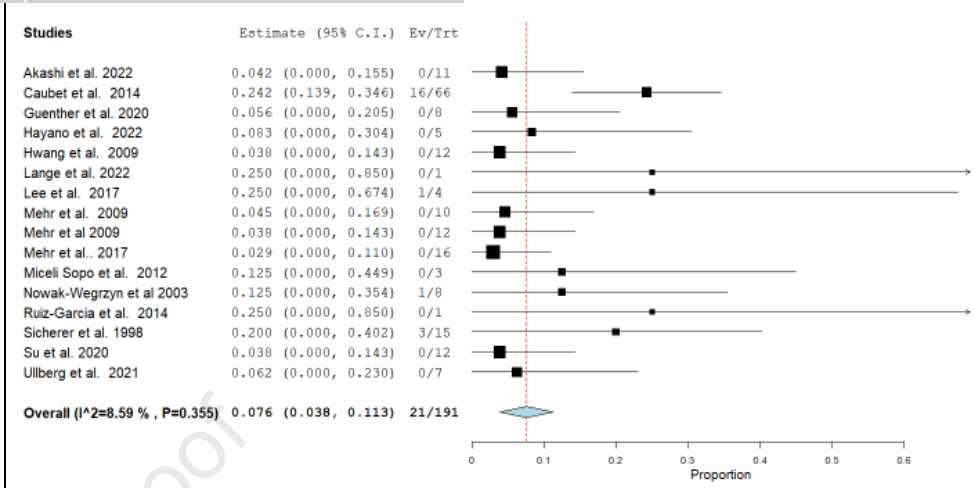


C. Milk

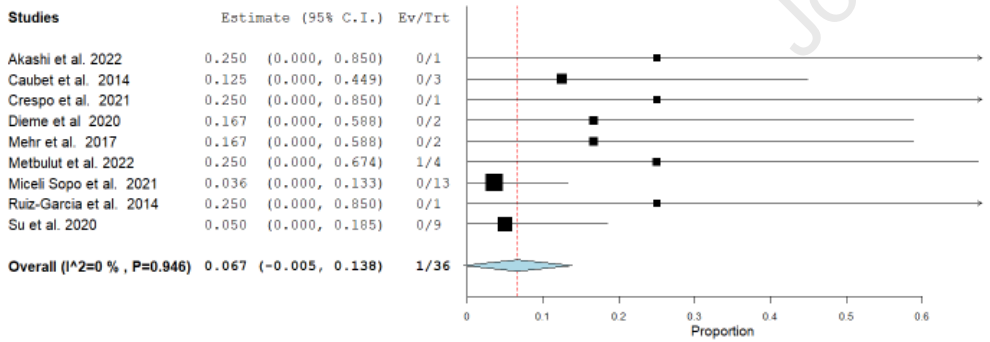
D. Soy



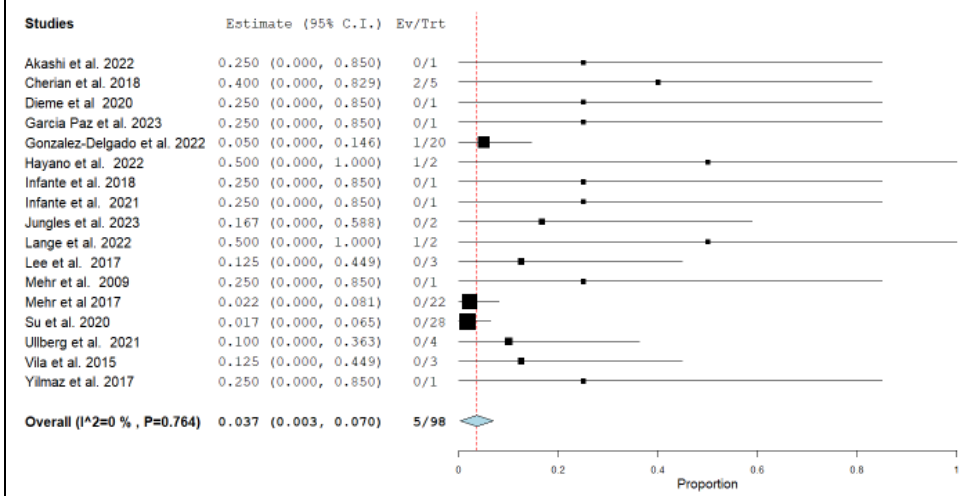
E. Legume



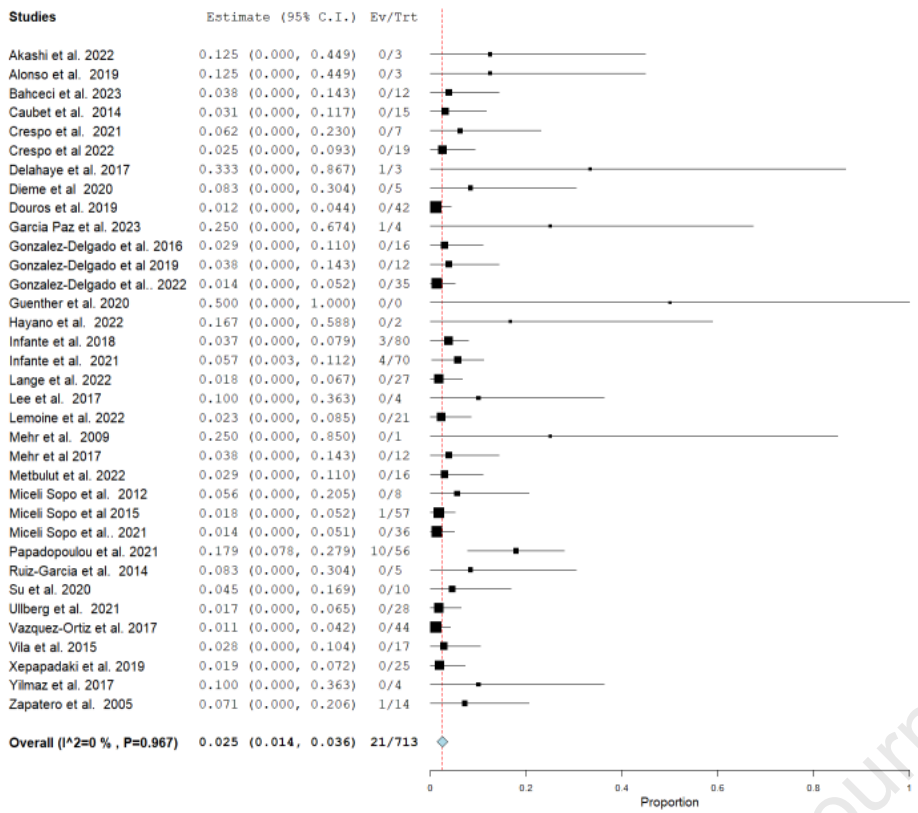
F. Fruit



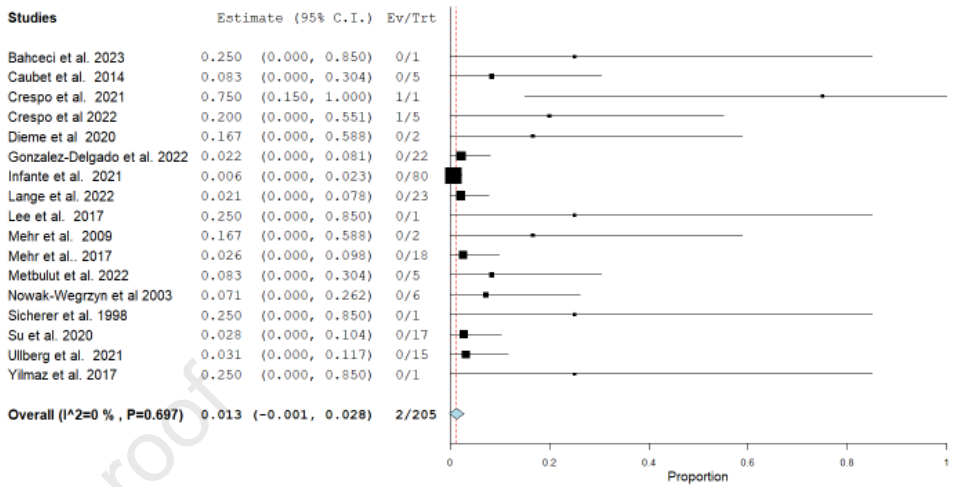
G. Fish



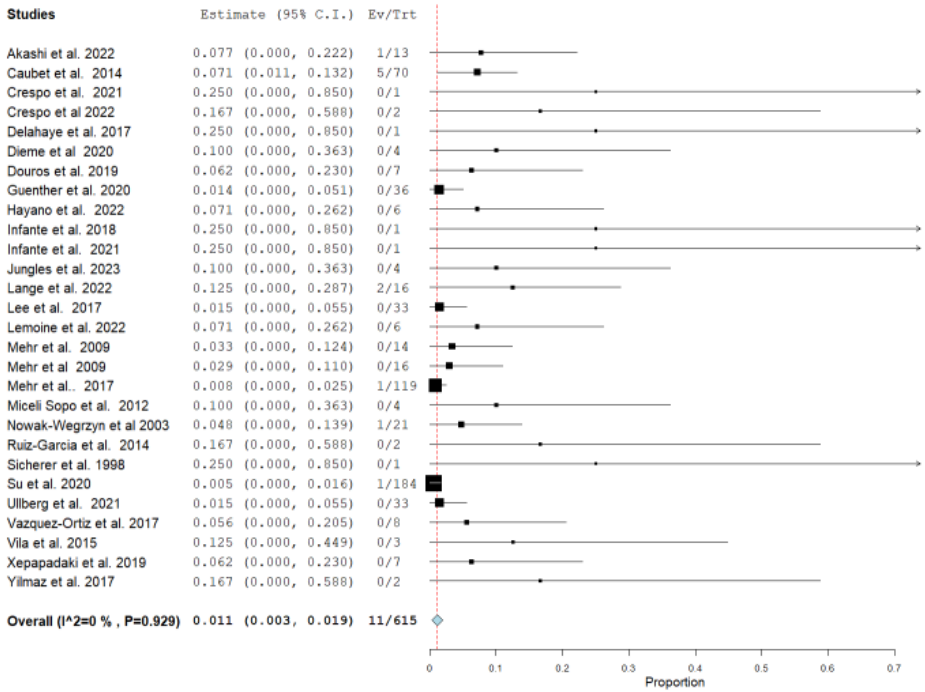
H. Vegetable

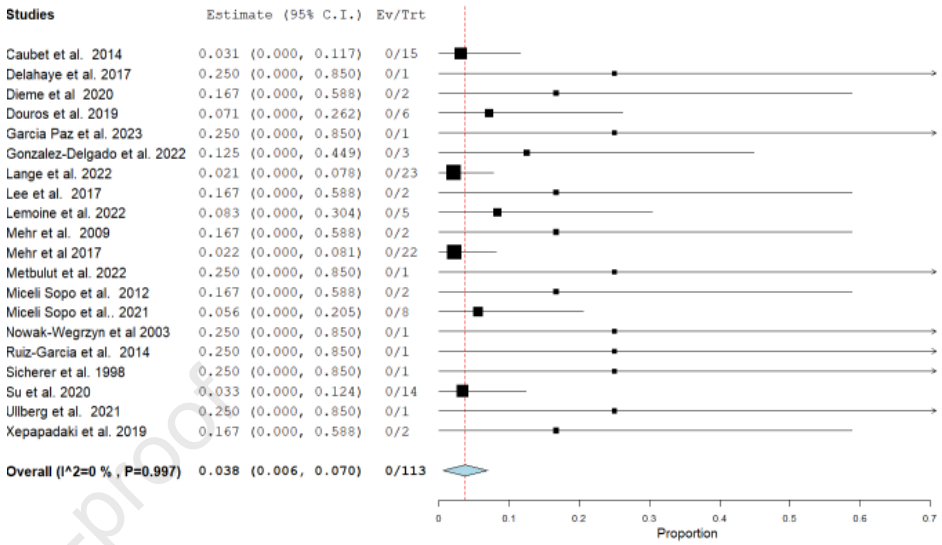


I. Grain

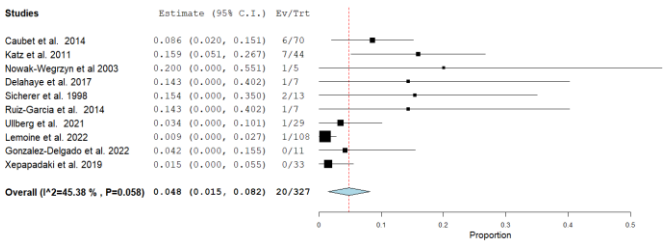


J. Meat

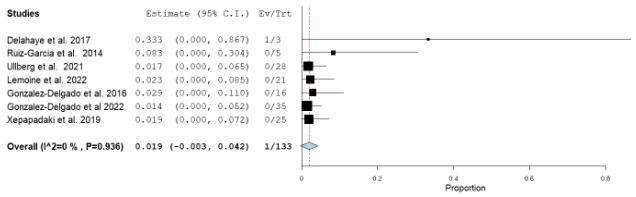




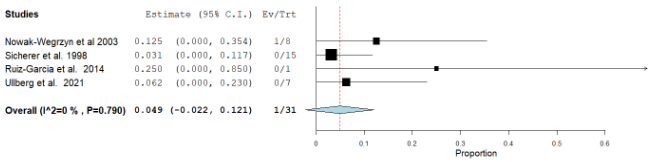
A. Milk



B. Fish



C. Soy



D. Rice

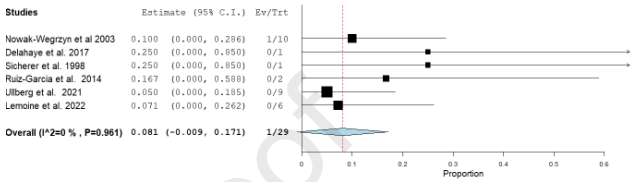
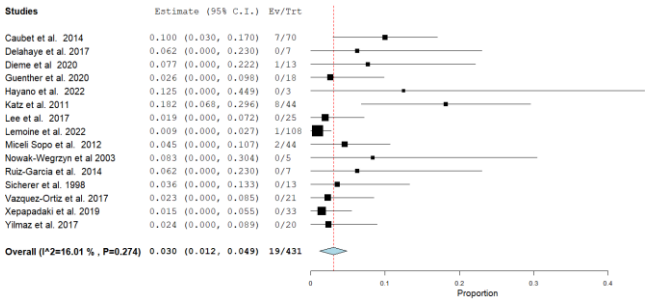
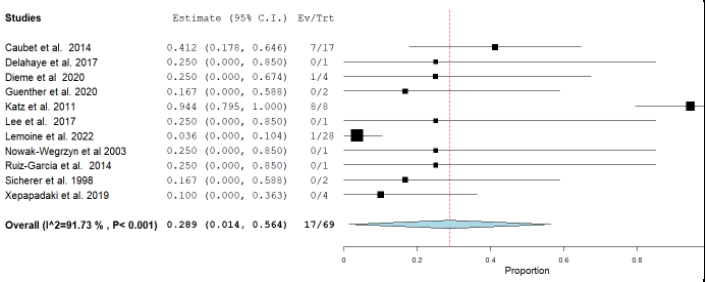


Figure E3.

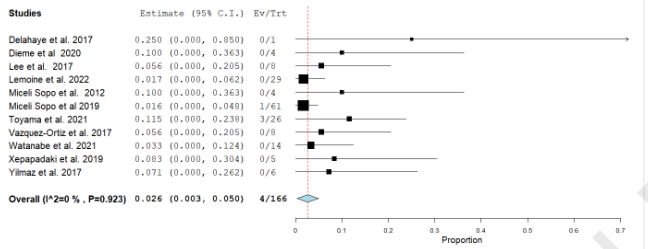
A. Total milk population



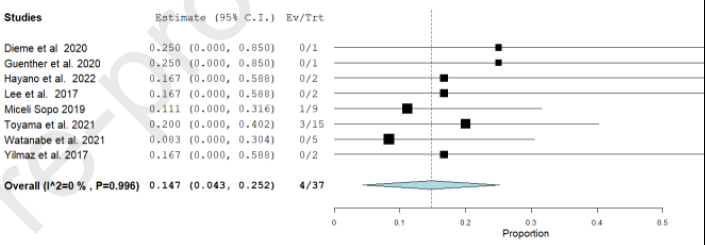
B. Milk sensitised population



C. Total egg population



D. Egg sensitised population



Supplemental Figure Legends

Figure E1. Forest plots for rates of sensitisation per food to 'any' food and specific food culprits in acute FPIES A. egg, B. nuts, C. milk, D. soy, E. legume, F. fruit, G. fish, H. vegetable, I. grain, J. meat.

Figure E2. Forest plots for rates of seroconversion per food to 'any' food and specific food culprits in acute FPIES A. milk, B. fish, C. soy, D. rice.

Figure E3. Forest plots for rates of phenotype switch for A. milk in total milk population, B. milk in milk-sensitised population, C. egg in total egg population, D. egg in egg-sensitised population

Table 1 PICOS framework

Population	Studies of children and adults with a clinical diagnosis of acute FPIES were included and studies of patients with other food allergies other than acute FIPES were excluded.
Intervention and Control	IgE sensitisation to culprit food(s) at onset or follow-up measured by serological test or SPT were included. Studies were excluded if no IgE sensitisation was measured.
Outcome	The primary outcome was to assess whether IgE sensitisation to the culprit food(s) in acute FPIES help predict an OFC outcome (negative or positive acute FPIES reaction or positive immediate reaction) at follow-up.
Study Design	All types of studies: randomised-controlled, non-randomised, cross-sectional, case-controlled, cohort and case series (defined as five or more case reports) were included. Review papers, case reports (< five), qualitative studies, studies in abstract format only were excluded. No restrictions on the language or year of publication were set.

Table 2 Characteristics of studies included in this systematic review.

Study Information						Participant information				Outcomes assessed			
Author	**Year**	**Country**	**Study Design**	**Foods Assessed in Study**	**Age of study Population** (inclusion criteria if stated)	**Sample Size**	**No. (%) males**	**Age at onset, median (IQR) months***	**Age at diagnosis, median (IQR) months***	**Sensitisation**	**Seroconversion**	**Phenotype switch**	**Tolerance development**
*Age of onset and diagnosis stated in median and IQR (month) unless otherwise state													
Akashi et al.	2022	Japan	Retrospective cohort	Any	Children 0-15	88	47 (53%)	7 (6-9)	-	✓			
Alonso et al.	2019	Spain	Prospective cohort	Any	Children 0-18	8	5 (62%)	mean 7.62		✓			
Bahceci et al.	2023	Turkey	Retrospective cohort	Any	Children	18	12 (67%)	mean 12 (SD 12.8, range 1-60)	-	✓			✓
Baldwin et al.	2021	Australia	Retrospective case series	Peanut &treenut	Infants	10	7 (70%)	mean 7.3 (SD 1.8)	mean 9.8 (SD 2.6)	✓			
Blackman et al.	2019	USA	Retrospective cohort	Any	Children 0-17	74	36 (49%)	5 (4-6)	11 (7-16)	✓			
Caubet et al.	2014	USA	Ambispective cohort	Any	Children & Adult 0-45	160	86 (54%)	-	15 (9-24)	✓	✓	✓	✓
Cherian et al.	2018	USA	Retrospective case-series	Avocado	Children	5	3 (60%)	6.6 (5-9)	-	✓			
Crespo et al.	2021	Spain	Ambispective case-series	Any	Adult >18	24	7 (29%)	37 (5.5) years	-	✓			
Crespo et al.	2022	Spain	Ambispective cohort	Any	Adult >18	42	7 (16.7%)	mean 40 (range 19-76) years	-	✓			
Delahaye et al.	2017	France	Retrospective case series	Any	Children	14	8 (57%)	-	9 (11days-5.5 years)	✓	✓	✓	
Dieme et al.	2020	France	Retrospective cohort	Any	Children	33		6.3 (0–12)	10.5 (0.2–48)	✓		✓	✓
Douros et al.	2019	Greece	Retrospective cohort	Any	Children	78	42 (54%)	-	10.1 (3-12)	✓			✓
Garcia Paz et al.	2023	Spain	Retrospective cohort	Any	Adults	28	7 (25%)	mean 32.07 (range 15-60) years	mean 39.82 (range 17-65) years	✓			
Gonzalez-Delgado et al.	2016	Spain	Prospective cohort	Fish	Children	16	7 (44%)	10 (9–17) years	-	✓	✓		
Gonzalez-Delgado et al.	2019	Spain	Prospective cohort	Fish	Adolescents & Adults (>14 years)	25	3 (12%)	28 (18.5-38) years	-	✓			
Gonzalez-Delgado et al.	2022	Spain	Prospective case series	Any		107	7 (6.5%)	30 (23-42) years	39 (29-48) years	✓	✓		
Guenther et al.	2020	USA	Retrospective cohort	Any	Children	46	21 (46%)	-	10 (range 0.5-32)	✓		✓	✓
Hayano et al.	2022	Japan	Retrospective case-control study	Any	Children 0-15years	50	-	9 (7-10)	-	✓		✓	
Hwang et al.	2009	Korea	Retrospective cohort	CM and Soy	Infants	23	16 (69%)	-	mean 36 (SD 14) days	✓			
Infante et al.	2018	Spain	Retrospective cohort	Fish	Children	80	44 (55%)	10 (9-11.75)	-	✓			

Infante et al.	2021	Spain	Retrospective cohort	Fish	Children	70	36 (51%)	10 (9-12)	-	✓	✓		✓
Jungles et al.	2023	USA	Retrospective case-series	Peanut	Children (<5years)	16	7 (50%)	-	-	✓		✓	
Katz et al.	2011	Israel	Prospective birth cohort	CM	Children (<9months)	44	23 (52%)	mean 2 days, SD 1.77 (median 30 days)	-	✓	✓	✓	
Kimura et al.	2017	Japan	Prospective cohort	CM	Infants (<2 years)	32	20 (62%)	7 days (range 0-3 month)	-	✓			✓
Lange et al.	2022	Germany	Retrospective cohort	Any	Children	142 pts (130 cases acute, 60 chronic)	79 (56%)	8 (range 1-50)	-	✓	✓	✓	✓
Lee et al.	2017	Australia	Retrospective cohort	Any	Children	69	29 (42%)	5 (4-6)	8 (6-16.8)	✓		✓	✓
Lemoine et al.	2022	France	Retrospective cohort	Any	Children	179 (132 acute, 47 chronic)	95 (53%)	5.8 (3.0–8.0)	-	✓	✓	✓	
Lopes et al.	2021	USA	Retrospective cohort	Peanut	Infants (<1 year)	14	7 (50%)	7 (range 5-10)	-	✓			
Mehr et al.	2009	Australia	Retrospective case series	Rice, CM, soy	Children	31	18 (58%)	Mean 5.4 (range 2-14)	-	✓			
Mehr et al.	2009	Australia	Retrospective case series	Any	Children	35	20 (57%)	mean 5.5 (SD 2.4)	-	✓			
Mehr et al.	2017	Australia	Retrospective population cohort	Any	Infants (<24 months)	230	110 (48%)	5.0 (4-6)	7.0 (5.5-11)	✓			
Metbulut et al.	2022	Turkey	Retrospective case series	Any	Children (0-18)	73	9 (53%)	6 (4–9.5)	9 (6–22.5)	✓			✓
Miceli Sopo et al.	2012	Italy	Retrospective case series	Any	Children	66	40 (61%)	mean 5.7 (SD 5.1)	mean 14.1 (SD 14)	✓		✓	
Miceli Sopo et al.	2015	Italy	Ambispective case series	Fish and shellfish	Infants (<9months)	70	34 (49%)	mean 14 (range 6-46)	28 (range 6-128)	✓			
Miceli Sopo et al.	2019	Italy	Retrospective case series	Egg	Children	61	34 (56%)	mean 9.8 (SD 3.8)	mean 15 (SD 8.5)	✓		✓	✓
Miceli Sopo et al.	2021	Italy	Retrospective case series	Any	Children	91	43 (47%)	mean 6.1 (SD 4.9, range 1-36)	mean 6.1 (SD 4.9, range 1-36)	✓			✓
Nishimura et al.	2022	Japan	Retrospective cohort	Any	Children	23	11 (48%)	7.0 (6.25–8.0)	8.0 (6.25–11.5)	✓			✓
Nowak-Wegrzyn et al	2003	USA	Retrospective cohort	Solid Food FPIES	Children	44 (14 acute)	8 (57%)	5.5 (range 3-7)	-	✓	✓	✓	✓
Ocak et al.	2020	Turkey	Retrospective cohort	Any	Children	81(72 acute, 9 chronic)	38 (53%))	7 (6-10)	8 (11-24)	✓			✓
Papadopoulou et al.	2021	Greece	Prospective cohort		Children	100 (89 acute, 11 chronic)	55 (55%)	mean 9.8 (SD 7.4)	-	✓			✓
Ruffner et al.	2013	USA	Retrospective cohort	Any	Children	462	279 (60%)	mean 9.5	-	✓			
Ruiz-Garcia et al.	2014	Spain	Retrospective case series	Any	Children	16	10 (62%)	-	mean 8 (range 6-30)	✓	✓	✓	
Sicherer et al.	1998	USA	Retrospective case series	Any	Children	20	8 (50%)	-	7 weeks (range 1 wk-7 month)	✓	✓	✓	✓
Su et al.	2020	USA	Retrospective cohort	Any	Children & Adult	203 (Acute	107 (53%)	6 (4.5-9.0)	10 (7.0-21.5)	✓		✓	✓

						180; Chronic 8)							
Tagami et al.	2022	Japan	Retrospective case series	Egg yolk	Infants	8	4 (50%)	8 (7-9)	-	✓			
Toyama et al.	2021	Japan	Retrospective cohort	Egg	Children	26	13 (50%)	8 (7.75-10)	-	✓		✓	
Ullberg et al.	2021	Sweden	Retrospective cohort	Any	Children	113	60 (53%)	6 (4.8-7.9)	9.6 (1.8-108)	✓	✓		✓
Vazquez-Ortiz et al.	2017	Spain	Retrospective cohort	Any	Children (0-18 years)	81	43 (51%)	-	9 (5-12)	✓		✓	
Vila et al.	2015	Spain	Retrospective case series	Solid Food FPIES	Children	21	9 (43%)	-	10 (range 4 mo-10 years).	✓			
Watanabe et al.	2021	Japan	Prospective cohort	Egg yolk	Children	14	5 (36%)	8 (8-9)	10.5 (9-12)	✓		✓	✓
Xepapadaki et al.	2019	Greece	Retrospective cohort	Any	Children (<16 years)	72	38 (53%)	mean 10.1 (95 CI 7.7–12.5)	mean 12.4 (95 CI 9.7–15.1)	✓	✓	✓	✓
Yilmaz et al.	2017	Turkey	Prospective cohort	Any	Children	64 (37 FPIAP, 27 FPIES)	15 (56%)	4 (1.5-6)		✓		✓	✓
Zapatero et al	2005	Spain	Retrospective case series	Fish	Children	14	6 (43%)	-	10.5 (range 9-12 months)	✓			

CM, cow's milk; *IgE,* immunoglobulin E; *IQR,* Interquartile range; *FPIES,* Food protein-induced enterocolitis syndrome; *no.,* number*; mo,* months

Table 3 Rates of sensitisation, study characteristics and atopic comorbidities in studies (n=53) assessing sensitisation to culprit food(s) in acute FPIES - ranked from highest to lowest percentage of sensitisation.

Author	Year	Country	Population size	Study Design	IgE FA %	Atopic Dermatitis %	Asthma %	Family History of Atopy %	Foods Assessed in Study	Age at FPIES onset (months)*	Sensitisation assessment modality and timepoint	Sensitisation (no. of patients)	Sensitisation (%)	Foods involved in sensitisation (no. of patients)
Toyama et al.	2021	Japan	26	Retrospective cohort	NA	23.1	NA	NA	Egg	8 (7.75-10)	Onset and FU. IgE only (Onset: n=23/26, 88%), FU n=11/26, 42%)	15/26 (at onset)	**57.7**	Egg (15/26)
Tagami et al.	2022	Japan	8	Retrospective case series	NA	NA	NA	62.5	Egg yolk	8 (7-9)	Onset. SPT only (n=8/8, 100%)	4/8	**50.0**	Egg yolk (4/8)
Lopes et al.	2021	USA	14	Retrospective cohort	42.9	42.9	NA	NA	Peanut	7 (5-10)	Onset. 100% of patients. SPT (n=13/14, 93%); IgE (n=11/14, 78.6%)	6/14 *4/14 had either +ve SPT or IgE>0.35 .	**43 *28% if IgE >0.35**	Peanut (6/14)
Cherian et al.	2018	USA	5	Retrospective case-series	NA	NA	NA	NA	Avocado	6.6 (5-9)	Onset. SPT (n=5/5, 100%), IgE (n=3/5,60%)	2/5	**40.0**	Avocado (2/5)
Watanabe et al.	2021	Japan	14	Prospective cohort	0	NA	NA	21.4	Egg yolk	8 (8-9)	Onset. IgE only (n=14, NA)	5/14	**35.7**	Egg Yolk (5/14)
Akashi et al.	2022	Japan	88	Retrospective cohort	NA	25	2	NA	Any	7 (6-9)	Unclear. SPT (n=4/88, 4%); IgE (n=88/88, 100%)	31/88	**35.2**	CM (9/22), Egg (21/41), Wheat (1/13)
Kimura et al.	2017	Japan	32	Prospective cohort	NA	21	3	NA	CM	7 days (range 0-3 month)	Joint. IgE only (n=32/32, 100%)	9/32	**28.1**	CM (9/32)
Sicherer et al.	1998	USA		Retrospective case series	NA	31	NA	12.5	Any	7 weeks (range 1 week to 7 months) **	Unclear. SPT (n=20, NA), IgE (n=20, NA)	5/20	**25.0**	CM (2/13), Soy (3/15)
Caubet et al.	2014	USA	20 160	Ambispective cohort	NA	57	25	77	Any *Analysis in CM only	15 (9-24)**	Unclear. SPT (n=160, NA), IgE (n=160, NA)	39/160	**24.3**	CM (17/70); Soy (16/66), Grain (5/70)), Egg (1/5)
Ocak et al.	2020	Turkey	81	Retrospective cohort	20.8	32	14	NA	Any	7 (6-10)	Joint. (n= 71/81, 88% had either SPT/IgE)	16/71	**22.5**	NA
Jungles et al.	2023	USA	16	Retrospective, case-series	14.3	50	NA	NA	Peanut	-	Onset and FU. SPT (Onset n=11/14, 78%, FU n=7/7, 100%); IgE (Onset: n=1/14, 71%, FU n= 1/7, 14%)	3/14 (SPT +ve in all 3 at FU, IgE +ve only in 1)	**21.4**	Peanut (3/16)
Nowak-Wegrzyn et al	2003	USA	44	Retrospective cohort	NA	57	7	71	Solid Food FPIES	5.5 (range 3-7)	Onset and FU. SPT (n=14/14, 100%), IgE (n=14/14, 100%)	3/14 at FU (0/14 at initial)	**21.4**	CM (1/5), Grain (1/21), soy (1/8)
Metbulut et al.	2022	Turkey	73	Retrospective case series	1.4	27	16.4	30	Any	6 (4–9.5)	Onset. SPT and IgE (both n= 60/73, 82%), breakdown NA)	12/60	**20.0**	CM (5/28), Egg Yolk (5/24), Egg White (7/15), legume (1/4) -

Su et al.	2020	USA		Retrospective cohort	11	40	13.3	NA	Any	6. (4.5-9.0)	Unclear. SPT (n=149/203 cases, 74%), IgE (NA)	24/149	**16.1**	includes data for Any food FPIES CM (6/25), Egg (7/20), wheat (1/184), peanut/treenut (5/9), other food triggers NA
Katz et al.	2011	Israel	20344	Prospective birth cohort	NA	NA	NA	NA	CM	mean 2 days, SD 1.77 (median 30 days)	Onset and FU. SPT only (n=13/44, 54% at onset, NA for FU)	8/44 (2/244 at onset)	**18**	CM (8/32)
Dieme et al	2020	France	33	Retrospective cohort	12	36	21	48	Any	6.3 (0–12)	Unclear. IgE only (n=33/33, 100%)	5/33	**15.2**	CM (4/13), Egg (1/4)
Hayano et al.	2022	Japan	50	Retrospective case-control	17	41	32	17	Any	9 (7-10)	Joint. SPT (n=15/30, 50%), IgE (n=22/30, 73%)	3/20 (IgE only, -ve SPT)	**15.0**	Egg yolk (2/9), banana (1/2)
Papadopoulou et al.	2021	Greece	100	Prospective cohort	15	16	25	NA	Any	mean 9.8 (SD 7.4)	Unclear. SPT (n=100, NA), IgE (=100, NA)	15/100	**15.0**	CM (4/30), Fish (10/56)
Lemoine et al.	2022	France	179	Retrospective cohort	5.6	28	13.4	67	Any	5.8 (3.0–8.0)	Unclear. SPT (n=121/192 reactions, 63%), IgE (n=121/192 reactions, 63%)	28/180	**14.7**	NA
Miceli Sopo et al.	2019	Italy	66	Retrospective case series	5	25	8	NA	Egg	mean 9.8 (SD 3.8)	Joint. SPT only (n=61/61, 100%)	9/61	**14.7**	Egg (9/61)
Delahaye et al.	2017	France	14	Retrospective case series	1	2	4	42.8	Any	9 (11days-5.5 yrs)**	Onset and FU. (SPT n=14/14 100%), IgE (n=8/14, 57%)	2/14	**14.3**	Fish (1/3); CM (1/7)
Lange et al.	2022	Germany	142 (152 cases)	Retrospective cohort	NA	NA	NA	NA	Any	8 (range: 1-50)	Unclear. SPT (n=152/190, 80%), IgE (n=152/190, 80%)	21/152 mixed chronic & acute 11 acute/10 chronic	**13.8**	CM (15/28), egg (3/5), wheat (2/16), banana (1/2)
Nishimura et al.	2022	Japan	23	Retrospective cohort	8.7	39	4.4	65.2	Any	7.0 (6.25–8.0)	Onset. SPT (n=23, NA), IgE (n=23, NA)	3/23 (IgE only, SPT -ve)	**13.0**	NA
Alonso et al.	2019	Spain	8	Prospective cohort	NA	NA	NA	NA	Any	mean 7.62 (NA)	Unclear. SPT (n=8/8, 100%), IgE (n=8/8, 100%)	1/8 (SPT only)	**12.5**	CM (1/4)
Douros et al.	2019	Greece	78	Retrospective cohort	NA	16.6	NA	26.9	Any	10.1 (3-12)**	Unclear. SPT and IgE (n=64/78, 82%. Breakdown NA)	8/64	**12.5**	NA
Mehr et al.	2017	Australia	230	Retrospective population cohort	16	42	3	57	Any	5.0 (4-6)	Onset. SPT (n=152/230, 66%) IgE (2 patients)	12/152	**7.8**	CM (4/75), Egg (7/27), Grain (1/119)
Yilmaz et al.	2017	Turkey	64	Prospective cohort	2	NA	NA	NA	Any	4 (1.5-6)	Onset. SPT (n=27 mixed chronic & acute, NA), IgE (n=27 mixed chronic & acute, NA)	2/27	**7.4**	Egg (2/27)
Garcia Paz et al.	2023	Spain	28	Retrospective cohort	3	NA	NA	NA	Any	mean 32.07 (range 15-60) years	Unclear. SPT (n=28, NA); IgE (n=28, NA)	2/28	**7.1**	CM (1/1), fish (1/14)

Zapatero et al.	2005	Spain	14	Retrospective case series	14	14	28.5	3	Fish	10.5 (range 9-12 months)**	Onset. SPT (n=14/14, 100%), IgE (n=14/14, 100%)	1/14	**7.1**	Fish (1/14)
Miceli Sopo et al.	2021	Italy	70	Retrospective, case series	NA	NA	NA	NA	Any	mean 6.1 (SD 4.9, range 1-36)	Onset. SPT only (NA)	6/91	**6.6**	CM (2/82), Egg (4/27)
Guenther et al.	2020	USA	46	Retrospective, cohort	NA	NA	NA	74	Any	10 (range 0.5-32)***	Unclear. SPT (n=46, NA); IgE (n=46, NA)	3/46	**6.5**	CM (2/NA), Egg (1/NA)
Ruiz-Garcia et al.	2014	Spain	16	Retrospective case series	NA	NA	NA	NA	Any	mean 8 (range 6-30)**	Unclear. SPT (n=16, NA), IgE (n=16, NA)	1/16	**6.2**	CM (1/7)
Bahceci et al.	2023	Turkey	18	Retrospective cohort	5.5	16.6	NA	33.3	Any	mean 12 (SD 12.8, range 1-60)	Onset. SPT (n=17/17, 100%), IgE (n=17/17, 100%)	1/17	**5.8**	CM (1/3)
Infante et al.	2021	Spain	70	Retrospective cohort (fish FPIES)	33	27	20	NA	Fish	10 (9-12)	Joint. SPT (n=70. NA), IgE (only if SPT positive)	4/70	**5.7**	Fish (4/7)
Xepapadaki et al.	2019	Greece	72	Retrospective cohort	NA	NA	NA	NA	Any	mean 10.1 (95% CI: 7.7–12.5) - mean	1 and 2. SPT (n=65/72, 90%), IgE (n=22/72, 30%)	4/72	**5.6**	CM (4/33)
Blackman et al.	2019	USA	74	Retrospective cohort	5	46	7	65	Any	5 (4-6)	Unclear. SPT (n=74, NA), IgE (n=74, NA)	4/74	**5.4**	NA
Lee et al.	2017	Australia	69 (81 cases)	Retrospective cohort	17	39	11.6	NA	Any	5 (4-6)	Joint. SPT only (n=81 cases, NA)	4/81	**4.9**	CM (1/25), Egg (2/8), Soy (1/4)
Crespo et al.	2021	Spain	24	Ambispective, case-series	30	8.3	29.9	NA	Any	37 (5.5) years	Onset. SPT (n=15/24, 62%), IgE (n=20/24, 83%)	1/24	**4.2**	Pepper and sunflower seed (1/1)
Ullberg et al.	2021	Sweden	113	Retrospective cohort	12	41	19	74	Any	6 (4.8-7.9)	Onset and FU. SPT (n=53/113, 47%), IgE (n=89/113, n=79%)	IgE: 4/89; SPT 1/53. Sensitisation in 4 (4%) of patients across onset and FU	**4 via IgE, 2 via SPT**	CM (4/29)
Ruffner et al.	2013	USA	462	Retrospective cohort	NA	34.3	17	NA	Any	mean 9.5	Joint. SPT only (NA)	15/379	**3.9**	CM (-ve in 93.1% of 245 cases), Soy (-ve in 99.4% of 158 cases), Egg (-ve in 88.9% of 40 cases), Wheat (-ve in 97.2% of 35 cases). Total was +ve in 28/721 cases
Gonzalez-Delgado et al.	2022	Spain	16	Prospective, case series	19	NA	29.9	NA	Any	30 (23-42) years	Onset and FU. SPT and IgE (n=107/107, 100%, breakdown NA)	4/107 (IgE only, -ve SPT)	**3.7**	Egg (1/15), Avocado (1/20), Crustaceans (2/38)
Infante et al.	2018	Spain	80	Retrospective cohort	29	24	17.5	NA	Fish	10 (9-11.75)	Joint. SPT (n=80, NA), IgE (only if SPT positive)	3/80	**3.7**	Fish (3/80)

Miceli Sopo et al.	2012	Italy	61	Retrospective case series	NA	9	NA	20	Any	mean 5.7 (SD 5.1)	Joint. SPT (NA), IgE (n= 25/66, 38%)	2/55	**3.6**	CM (2/44)
Mehr et al.	2009	Austra lia	35 (no. of epis odes 66)	Retrospective case series	13	57.5	3	NA	Any	5.4 (range: 2-14)	Onset. SPT only (n=31/31, 100%)	1/31	**3.2**	CM (1/7)
Crespo et al.	2022	Spain	42	Ambispective cohort	48	7	28.6	4.8	Any	mean 40 (range 19-76) years	Onset. SPT (n=30/42, 71%), IgE (n=30/42, 71%)	1/37 (SPT only)	**2.7**	Vegetable (1/5 profilin sensitisation)
Mehr et al.	2009	Austra lia	230	Retrospective case series	11	51	NA	NA	Any	mean 5.5 (SD 2.4)	Onset. SPT only (n=39/41, 85%)	1/39	**2.6**	CM (1/7)
Miceli Sopo et al.	2015	Italy	91	Ambispective case series	10	21	NA	21.4	Fish and shellfish	mean 14 (range 6-46)	Joint. SPT (n=63/70, 90%), IgE (n=44/70, 62.8%. IgE -ve in all)	1/62 (SPT only)	**1.6**	Fish (1/57)
Baldwin et al.	2021	Austra lia	10	Retrospective case series	10	60	NA	90	Peanut and treenut	mean 7.3 (SD 1.8)	1. SPT (n=7/10, 70%); IgE (n=2/10, 20%)	0/10	**0.0**	N/A
Gonzalez-Delgado et al.	2016	Spain	25	Prospective, cohort	NA	NA	NA	NA	Fish	10 (9–17) years	Onset and FU. SPT and IgE (n=16/16, 100%, breakdown NA)	0/16	**0.0**	N/A
Gonzalez-Delgado et al.	2019	Spain	107	Prospective, cohort	NA	12	12	72	Fish	28 (18.5-38) years	Onset and FU. SPT and IgE (n=25/25, 100%, breakdown NA)	0/25	**0.0**	N/A
Hwang et al.	2009	Korea	23	Retrospective cohort	NA	0	NA	NA	CM and Soy	mean 36 (SD 14) days**	Onset. IgE only (n=23/23, 100%)	0/23	**0.0**	N/A
Vazquez-Ortiz et al.	2017	Spain	81	Retrospective cohort	1.2	18.3	2.4	42.7	Any	9 (5-12)**	Onset. SPT (n=81, NA), IgE (n=81, NA)	0/81	**0.0**	N/A
Vila et al.	2015	Spain	21	Retrospective case series	14	0	0	0	Solid Food FPIES	10 (range: 4 mo-10 years)**	Unclear. SPT (n=21/21, 100%), IgE (n=21/21, 100%)	0/21	**0.0**	N/A

CM, cow's milk; *FU,* follow up; *IQR,* Interquartile range*; IgE,* immunoglobulin E; *IgE FA***,** IgE mediated food allergy; *mo,* months, *NA,* not available/applicable, *SPT,* skin prick test.
*Age of onset stated in median and IQR (months) unless otherwise state; **Age at diagnosis if onset not reported

Table 4 Studies (n=21 studies) assessing phenotype switch from acute FPIES to immediate/IgE-mediated food allergy, presented from highest to lowest percentage of sensitised patients experiencing phenotype switch.

Author	Year	Country	Total sample size	Study Design	Phenotype Switch Method (median age at OFC (IQR)	Foods Assessed in Study	Foods involved in phenotype switch.	No. of sensitised patients	% of positive immediate reaction with sensitisation (no. of positive immediate reactions/no. of sensitised patients)
Katz et al.	2011	Israel	44	Prospective birth cohort	OFC for 7 patients (NA), 1 observed	CM	CM	8/24	**100% (8/8)**
Miceli Sopo et al.	2012	Italy	66	Retrospective case series	OFC (37)	Any	CM	2/55	**100% (2/2)**
Delahaye et al.	2017	France	14	Retrospective case series	OFC (16)	Any	Fish	2/14	**50% (1/2)**
Caubet et al.	2014	USA	160	Ambispective, cohort	OFC (45 (IQR 23-82)	CM	CM	39/160	**41% (7/17 CM)**
Su et al.	2020	USA	203	Retrospective cohort	Unclear	Any	Egg (5), CM (4), nuts (5), wheat (1)	24/149	**37.5% (9/24)**
Toyama et al.	2021	Japan	26	Retrospective cohort	OFC (NA)	Egg	Egg white (2), Egg yolk (1)	15/26	**26.6% (4/15)**
Dieme et al	2020	France	33	Retrospective cohort	OFC (32 (8–107))	Any	CM	5/33	**20% (1/5)**
Lange et al.	2022	Germany	142	Retrospective cohort	OFC (NA)	Any	NA	21/152	**16.6% (2/12)**
Miceli Sopo et al.	2019	Italy	61	Retrospective case series	OFC (12 (range, 0-108))	Egg	Egg	9/61	**11% (1/9)**
Lemoine et al.	2022	France	180	Retrospective cohort	OFC (2.1 [1.6–3.0] yrs)	Any	CM	28/180	**3.5% (1/28)**
Guenther et al.	2020	USA	46	Retrospective, cohort	OFC, (18.5 (6-118))	Any	NA	3/46	**0% (0/3)**
Hayano et al.	2022	Japan	50	Retrospective case-control study	OFC, (NA)	Any	NA	3/20	**0% (0/3)**
Jungles et al.	2023	USA	16	Retrospective, case-series	OFC (24.5 (21-25.5))	Peanut	NA	3/14	**0% (0/3)**
Lee et al.	2017	Australia	69	Retrospective cohort	OFC (38)	Any	NA	4/81	**0% (0/4)**
Nowak-Wegrzyn et al	2003	USA	44	Retrospective, cohort	OFC (19 (14-32))	Solid food	NA	3/14	**0% (0/3)**
Ruiz-Garcia et al.	2014	Spain	16	Retrospective case series	OFC (NA)	Any	NA	1/16	**0% (0/1)**
Sicherer et al.	1998	USA	20	Retrospective case series	OFC (mean 8.2 months)	Any	NA	5/20	**0% (0/5)**
Vazquez-Ortiz et al.	2017	Spain	81	Retrospective cohort	OFC (NA)	Any	NA	0/81	**0% (0/81)**
Watanabe et al.	2021	Japan	14	Prospective cohort	OFC (37 (25-49.5))	Egg yolk	NA	5/14	**0% (0/5)**
Xepapadaki et al.	2019	Greece	72	Retrospective cohort	OFC (7.5)	Any	NA	4/72	**0% (0/4)**
Yilmaz et al.	2017	Turkey	27	Prospective cohort	OFC (NA)	Any	NA	7/27	**0% (0/7)**

CM, cow's milk; *IQR,* Interquartile range; *NA,* not applicable/available; *OFC,* oral food challenge.

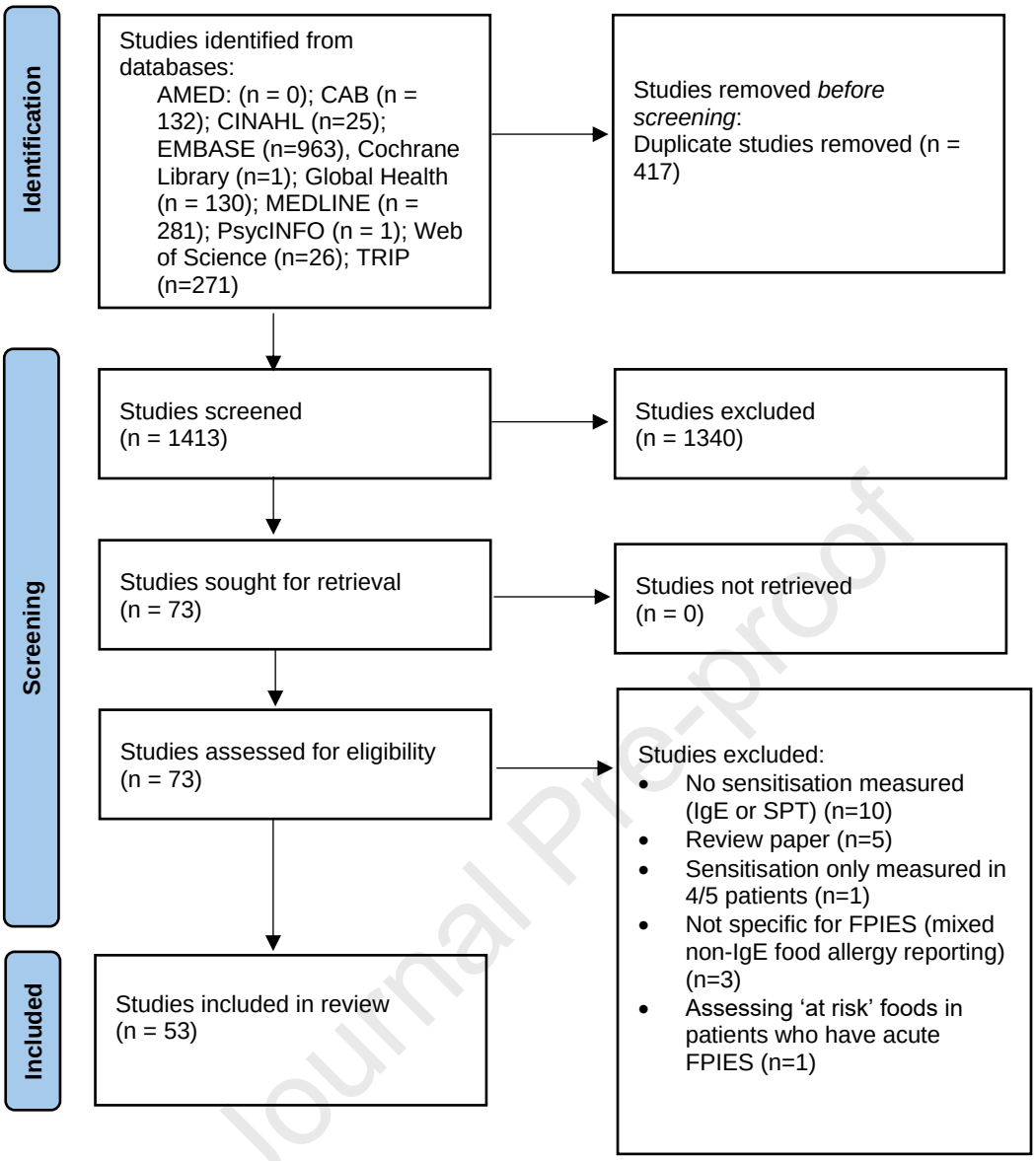
Table 5 Studies (n=10) with analytical design assessing the potential relationship between tolerance development and sensitisation to culprit food in acute FPIES.

Author	Country	Study Design	Foods with sensitisation reported on	Total no. of patients	No. of patients used in statistical analysis	Methodology	OFC outcome/FPIES resolution over time in relation to sensitisation	Relationship between sensitisation and OFC outcome or FPIES resolution (Y/N)
Caubet et al. 2014	USA	Ambispective, cohort	CM	160	70 (CM FPIES with (n=17) and without (n=53) sensitisation	A) Comparative analysis of CM sensitisation rate in tolerant vs persistent FPIES children by 3 years of age (Mann–Whitney U test). B) Survival analysis (time to resolution) using Kaplan-Meier curve and log-rank test in CM-FPIES children with and without CM sensitisation. Age of resolution assessed either via OFC (performed at least 12 months after last FPIES reaction) or parental report of food introduction at home. Follow up for a median 45 months (IQR 23-82)).	A) 36.7% (11/30) children with persistent CM-FPIES beyond age 3 were sensitised, whereas no children with resolved FPIES by age 3 were sensitised (p=0.04). B) The median age of CM-FPIES resolution for non-sensitised children was 5.1 years, whereas none of the sensitised children became tolerant in the study (**p=.003**)	**Yes**
Douros et al. 2019	Greece	Retrospective cohort	Any (NA)	78	54	Survival analysis (time to resolution) using Kaplan-Meier curve. Multivariate analysis using Cox proportional hazard model to assess factors influencing the 'time to resolution' survival function (including gender, sensitisation to culprit food, breastfeeding duration, atopic dermatitis and atopic family history). Tolerance development assessed via OFC (after at least 12 months from diagnosis, and then for positive OFC at 6-18 months' intervals). Sensitisation assessed (either via SPT or sIgE) prior to OFC.	Only IgE sensitisation to the culprit food significantly correlated with tolerance age (**p = 0.004**, hazard ratio 0.15, 95% CI 0.08–0.69).	**Yes**
Lee et al. 2017	Australia	Retrospective cohort	CM, egg, soy	69	69	Survival analysis (time to resolution) using Kaplan-Meier curve, and predictors of time to tolerance assessed using proportional hazards regression model. Tolerance development assessed via OFC, offered 6-12 months after last reaction. A total of 81 OFCs were conducted on 69 children. SPT undertaken at time of OFC.	Patients with a positive SPT to culprit food achieved tolerance more slowly (median age tolerance 54 months, 95% CI >32 months) than those with a negative SPT (median age tolerance 16 months, 95% CI 14-22; HR 0.29, 95% CI 0.09-0.94, **p= .04**). Older age at initial FPIES episode and diagnosis also associated with FPIES persistence.	**Yes**

Ocak et al. 2020	Turkey	Retrospective cohort	Any (NA)	81 (72 Acute FPIES)	81 (resolved n=26, persistent n=55)	A) Comparative analysis of sensitisation to culprit food in resolved vs persistent FPIES (U-Mann Whitney test). B) Multivariate logistic regression analysis to assess factors independently associated with FPIES persistence. Resolution of FPIES defined by either passing an OFC or introducing the trigger food at home without FPIES symptoms. Followed up for median (IQR) 19.4 (12-41) months. SPT undertaken at diagnosis and OFC.	A) Higher rate of sensitisation in persistent vs resolved FPIES group (34% vs 7%, **p 0.004**). B) IgE sensitisation to the culprit food was the only predictor for FPIES persistence (odds ratio 4.855 (95% CI, 1.131-20.844), **p=0.034)**.	**Yes**
Kimura et al. 2017	Japan	Prospective cohort	CM	32	32	Correlation analysis to assess relationship between CM-sIgE levels and age of FPIES tolerance development. Age of tolerance to CM estimated using OFC, done every 6 months up to age 2 years, then every 12months. IgE assessed during the first (4–8 months of age) and second (1–2 years of age) follow-up stages.	The CM-sIgE levels at onset did not show a significant correlation with age of FPIES tolerance development (r = 0.22, **p > 0.05).** However, 56.3% of children developed tolerance by age 12 months, but none of the 9 children, with positive CM-sIgE at onset (formal comparison not conducted).	**No**
Lange et al. 2022	Germany	Retrospective cohort	Any (CM, egg, wheat, banana)	130	100	Survival analysis (time to resolution) using Kaplan-Meier curve comparing IgE-positive versus IgE-negative patients OFC performed to determine whether FPIES had been outgrown, different time intervals “depending on the assessment of the pediatrician”, followed up for median of 12 months (0-108 months).	Sensitisation status did not influence tolerance development survival curve (**p=0.92)**	**No**
Lemoine et al. 2022	France	Retrospective cohort	Any (NA)	145 (Acute FPIES: 112 confirmed, 33 presumptive)	173 OFC (positive OFC n=44; negative OFC n=129)	Comparative analysis of sensitisation to culprit food in resolved vs persistent FPIES at first FU OFC (median age 2 years (IQR: 1.5–2.9), (U-Mann Whitney test).	IgE sensitisation to culprit food was not associated with FPIES persistence at first FU OFC (15% vs 21% of sensitisation in resolved vs persistent FPIES groups, **p = 0.3**)	**No**

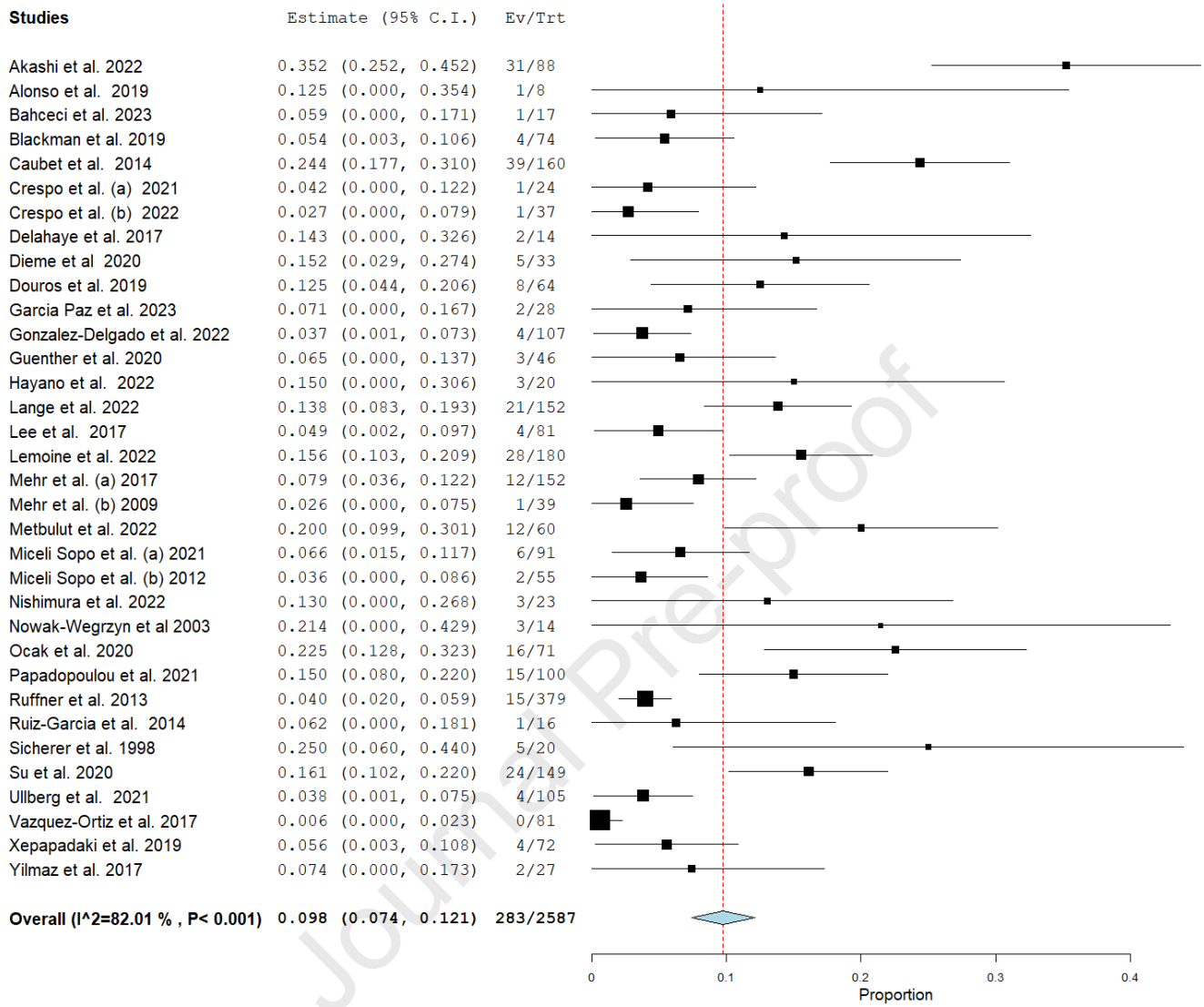
Miceli Sopo et al. 2019	Italy	Retrospective case series	Egg	61	61	Comparative analysis of tolerance development age (Students t-test) and rate (Chi square) to cooked and raw egg in sensitised vs non sensitised children with egg FPIES Tolerance development assessed via OFC offered 1 year post diagnosis. SPT performed at diagnosis and before OFC.	No differences seen in tolerance development age or rate in sensitised vs non sensitised children for entire cohort, e.g. sensitised children achieved tolerance to raw egg at 47.5 months (SD = 10.5, 95% CI 37-57), while non-sensitised achieved tolerance to raw egg at 43.4 months (SD = 24.6, 95% CI = 34-52 months) (**p = 0.57**)	**No**
Papadopoulou et al. 2021	Greece	Prospective cohort	CM, fish	89 acute FPIES, 11 chronic FPIES	82	Survival analysis (time to resolution) using Kaplan-Meier curve and log-rank test in sensitised vs non sensitised patients. B) Multivariate analysis using Cox proportional hazard model to assess factors influencing the 'time to resolution' survival function (including sensitisation to food, sensitisation to aeroallergens, offending food (fish), eczema ever and family history of atopy). Age of tolerance recorded by either home introduction or OFC. Mean follow-up period: 92 (SD: 54.4) months. IgE food sensitisation evaluated at diagnosis.	IgE sensitisation of the offending food did not influence survival curve or proportionality of tolerance (PT 1.26, **p=0.59)**	**No**
Su et al. 2020	USA	Retrospective cohort	Fish, CM, egg	180 acute	123	Survival analysis (time to resolution) using Kaplan-Meier curve and log-rank test in sensitised vs non sensitised patients Resolution of FPIES defined by either successful OFC or home introduction. FPIES resolution was analysed in 123 cases, who were followed up at least for 1 year (median (IQR), not stated).	Resolution curves were not different between sensitised vs non-sensitised groups (**p = 0.35**)	**No**

CM, cow's milk; *CI,* confidence interval; *IgE,* immunoglobulin E; *FPIES,* Food protein-induced enterocolitis syndrome*; IQR,* Interquartile range; *OFC,* oral food challenge; *PT*, proportionality of tolerance; *SD,* standard deviation.



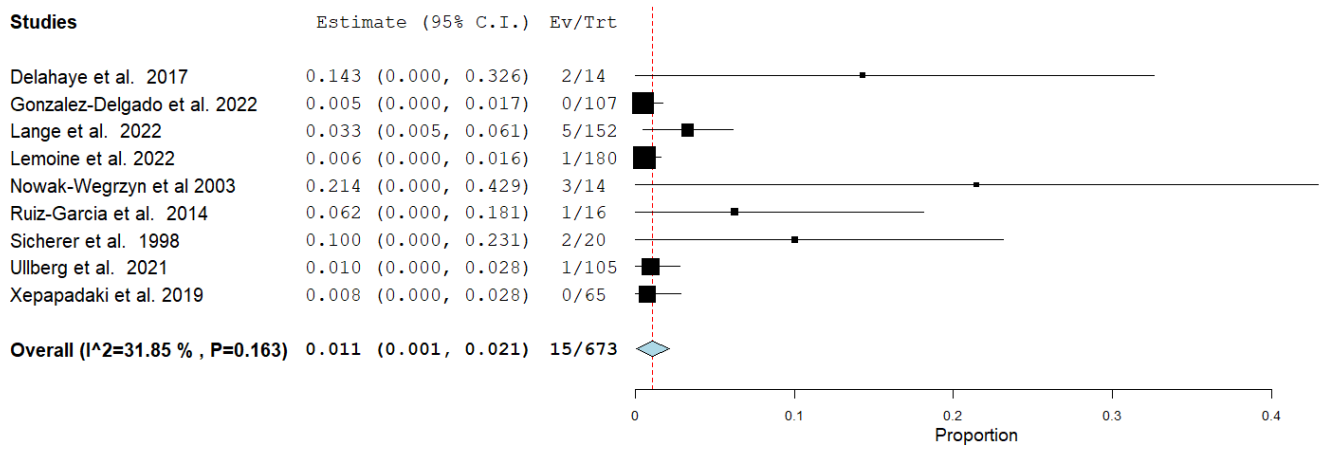
2A.

Sensitisation



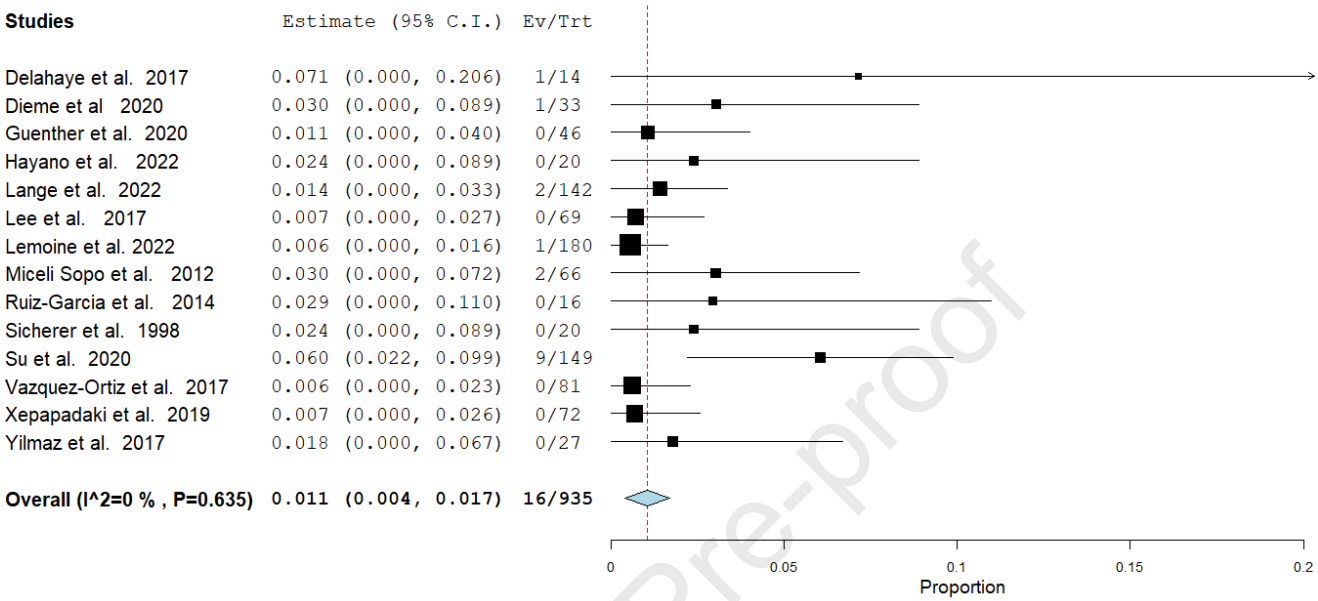
2B.

Seroconversion



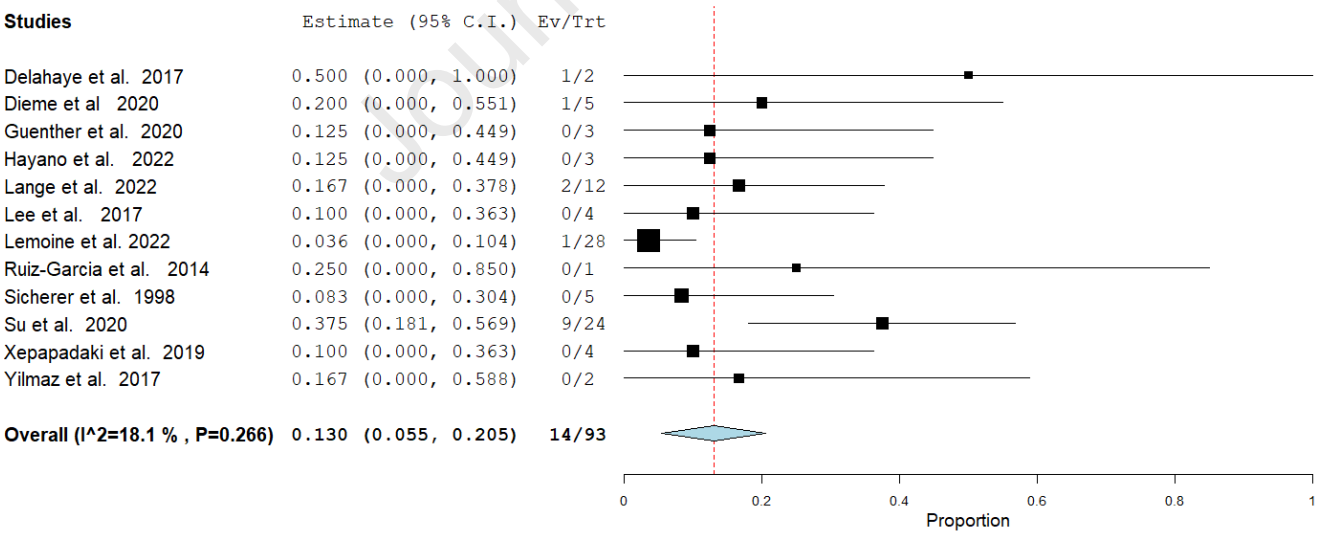
2C.

Phenotype switch whole population

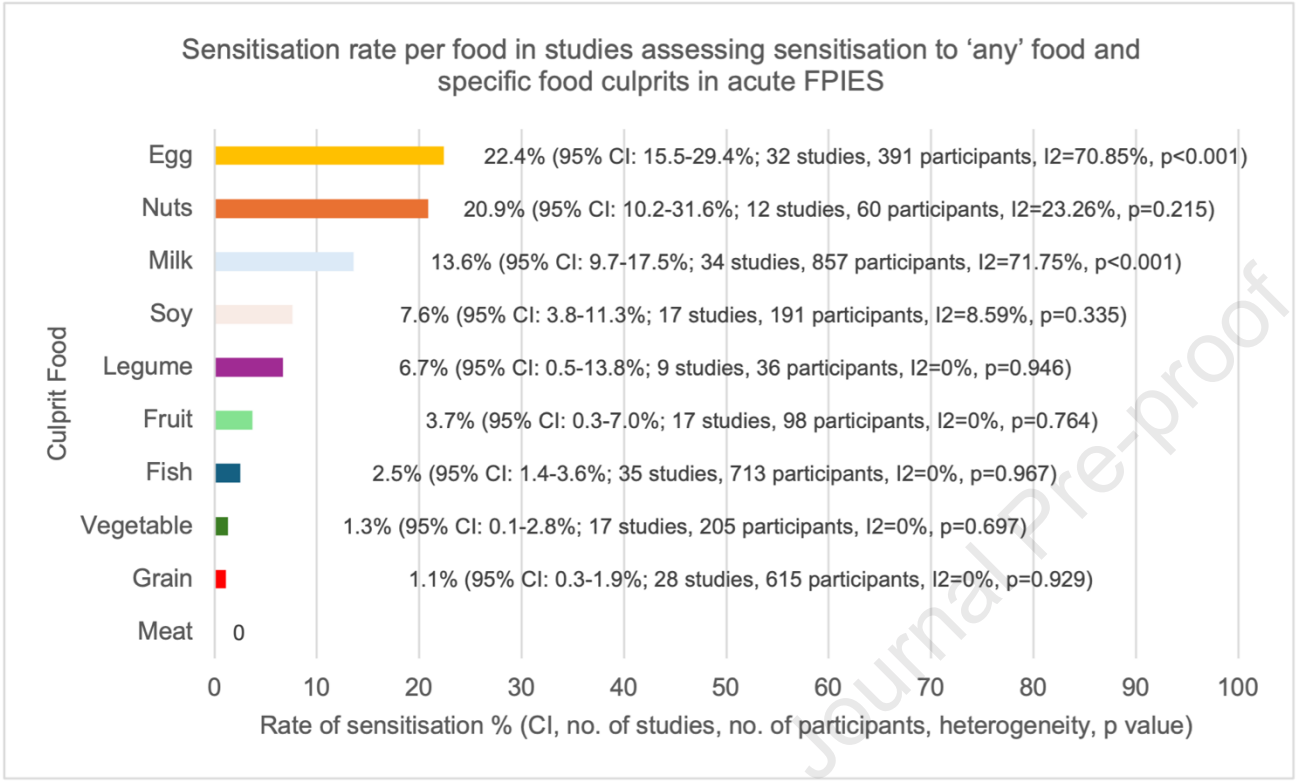


2D.

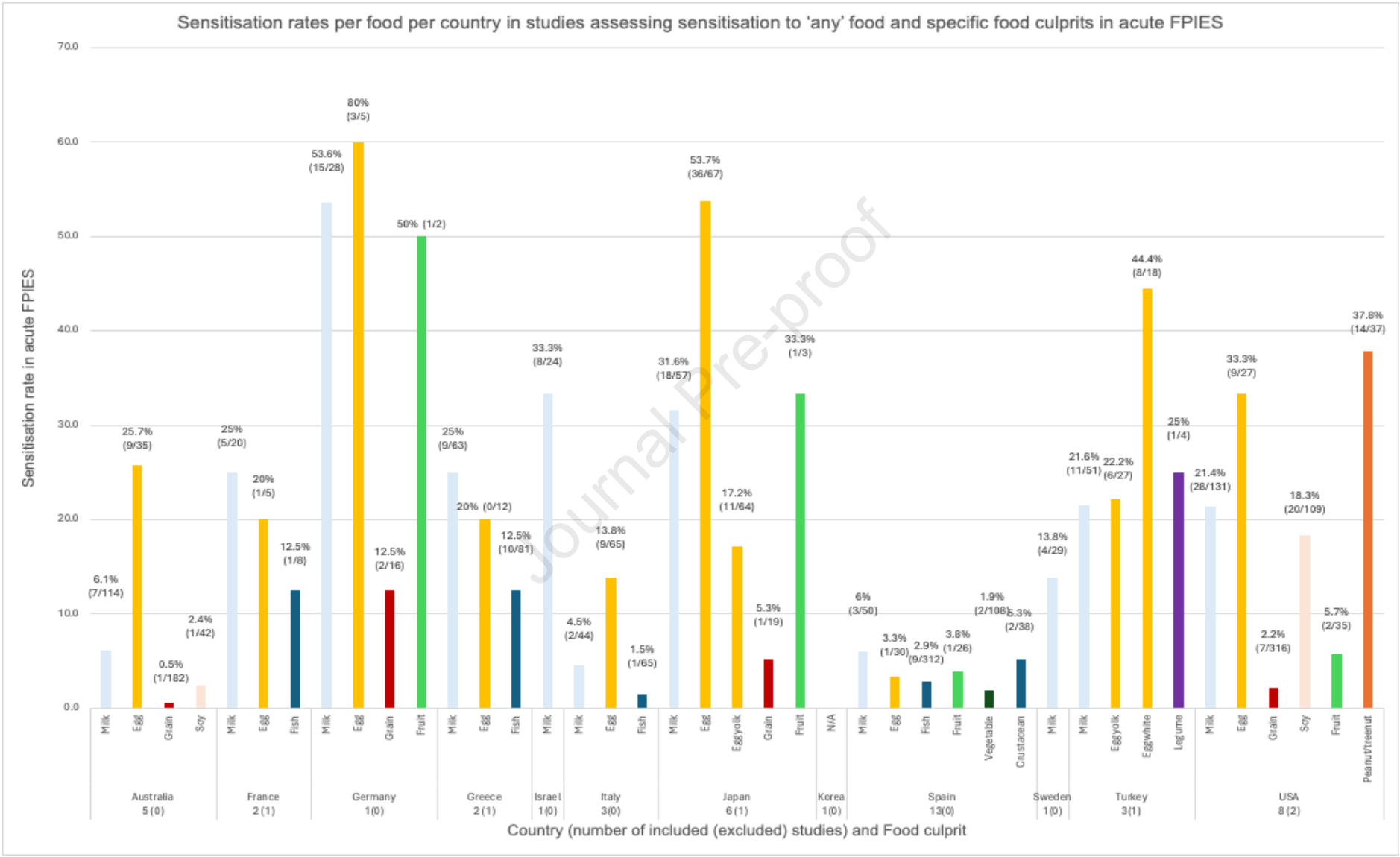
Phenotype switch sensitised population



3A.



3B.


Sensitisation rates per food per country in studies assessing sensitisation to 'any' food and specific food culprits in acute FPIES
Sensitisation rate in acute FPIES
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
6.1% (7/114)
25.7% (9/35)
0.5% (1/182)
2.4% (1/42)
25% (5/20)
20% (1/5)
12.5% (1/8)
53.6% (15/28)
80% (3/5)
12.5% (2/16)
50% (1/2)
25% (9/63)
20% (0/12)
12.5% (10/81)
33.3% (8/24)
4.5% (2/44)
13.8% (9/65)
1.5% (1/65)
31.6% (18/57)
53.7% (36/67)
17.2% (11/64)
5.3% (1/19)
33.3% (1/3)
6% (3/50)
3.3% (1/30)
2.9% (9/312)
3.8% (1/26)
1.9% (2/108)
5.3% (2/38)
13.8% (4/29)
21.6% (11/51)
22.2% (6/27)
44.4% (8/18)
25% (1/4)
21.4% (28/131)
33.3% (9/27)
2.2% (7/316)
18.3% (20/109)
5.7% (2/35)
37.8% (14/37)
Milk
Egg
Grain
Soy
Milk
Egg
Fish
Milk
Egg
Grain
Fruit
Milk
Egg
Fish
Milk
Milk
Egg
Fish
Milk
Egg
Eggyolk
Grain
Fruit
N/A
Milk
Egg
Fish
Fruit
Vegetable
Crustacean
Milk
Milk
Eggyolk
Eggwhite
Legume
Milk
Egg
Grain
Soy
Fruit
Peanut/treenut
Australia 5 (0)
France 2 (1)
Germany 1(0)
Greece 2 (1)
Israel 1(0)
Italy 3(0)
Japan 6 (1)
Korea 1(0)
Spain 13(0)
Sweden 1(0)
Turkey 3(1)
USA 8 (2)
Country (number of included (excluded) studies) and Food culprit
Journal Pre-proof