

LETTER TO THE EDITOR

Is pollen-food syndrome a frequent comorbidity in adults with irritable bowel syndrome?

To the Editor

Irritable bowel syndrome (IBS) affects up to 10% of UK adults, 50% of whom may also have seasonal allergic rhinitis (SAR) and thus an increased risk of developing pollen-food syndrome (PFS) if sensitized to birch tree pollen.¹⁻³ In an exploratory prospective controlled cohort study, we compared the prevalence of PFS in IBS subjects from a secondary care clinic diagnosed using the Rome IV criteria,⁴ with that of an age and gender-matched control group with another chronic health condition (congenital heart disease). The control group were chosen as they had a chronic health condition and a younger age demographic which matched the IBS group. The study received ethical and HRA approval (REC 17/NW0577, IRAS Reference: 229644), and all subjects gave written informed consent to take part. Both groups self-completed a validated PFS diagnostic questionnaire.³ The IBS case group alone also self-completed a food and symptom questionnaire, validated IBS and SAR questionnaires (Appendix S1), underwent skin prick testing (SPT) to aeroallergens, food reagents and fresh foods (ALK Abelló) (Appendix S1) and had a 10-mL blood sample collected and analysed for ImmunoCAP 112 ISAC (Thermo Fisher Scientific).

Twenty-two of the 35 subjects in the IBS group (63%) reported hay fever; 10/22 (29%) were diagnosed with PFS. Ten control group subjects (29%) reported hay fever, none of whom were diagnosed with PFS ($P = .008$, Fisher's exact test). The IBS + PFS group had a significantly higher score for IBS severity, SAR and symptom severity compared to those with IBS alone (Appendix S2 and S3). There were no differences in IBS or SAR severity between those with IBS + SAR and IBS + SAR+PFS. When reporting symptoms and foods suspected, the most frequent foods to trigger symptoms in the whole IBS cohort were milk and wheat, predominantly provoking typical IBS symptoms of abdominal pain, bloating, vomiting and diarrhoea (Figure 1, Appendix S4). The IBS + PFS group were significantly more likely to report oropharyngeal symptoms such as tingle and numbness or itchy throat ($P = .001$), and reactions to kiwi, peach/nectarine and plum/apricot (Figure 1). None of the IBS subjects had a positive SPT to milk, and those with IBS alone were also not sensitized to wheat or the wheat allergens Tri a 14 and Tri a 19 (Appendix S5 and S6). However, 7/10 of the IBS + PFS cohort had a positive SPT to semolina ($P > .001$), six of whom also reported symptoms

to wheat. The majority (86%) of IBS + PFS patients with a positive SPT to wheat reported symptoms to pasta rather than bread, with a modest correlation between a positive SPT to wheat and reported reactions to pasta but not bread (Spearman Rank $r = 0.433$, $P = .009$). The IBS + PFS cohort was also more likely to have positive SPT to raw potato ($P = .001$), hazelnut ($P = .003$), tomato ($P = .017$), cooked potato ($P = .018$), Timothy grass ($P = .004$), mixed grass ($P = .007$) and silver birch ($P = .007$, Fisher's exact test) (Appendix S5). Those with IBS + SAR+PFS were also significantly more likely to have positive SPT to the same foods (Appendix S5). The ISAC results showed that the majority (60%) of the IBS + PFS group were sensitized to PR10 allergens compared to 4% of those with IBS alone (Table 1). Of the four IBS + PFS subjects not sensitized to PR10 allergens, two were sensitized to thaumatin-like proteins (TLP), one of whom was also sensitized to profilins. Sensitization to other allergens was rare (Appendix S6).

These data suggest individuals with IBS have a greater prevalence of PFS than the UK population level of 2%⁵ but larger studies are needed. Others have reported atopic subgroups in IBS populations, but it is unknown whether symptoms experienced by those with IBS and PFS are due to underlying immune responses.^{2,6} The onset or exacerbation of IBS during the birch pollen season has been demonstrated to occur together with an increase in inflammatory cells in the duodenal mucosa of individuals with birch pollen allergy, which might explain increased severity of IBS symptoms in individuals with IBS and SAR.⁷ It is unclear what triggered the reported hay fever in the control group as no allergy tests were performed in this group, given their inclusion was solely to determine the prevalence of PFS. There was no selection bias as control subjects were recruited purely based on age and gender. Adults in the UK usually have PFS due to cross-reactivity between Bet v 1 in birch pollen and PR10 allergens; grass sensitization is linked to allergy to profilins, which are a common cause of PFS in other countries.^{2,8} Out of the whole IBS cohort, only 3 IBS + PFS subjects had low level sensitization to profilins but not Phl p 12 (Timothy grass profilin). The 2 IBS + PFS subjects who had positive tests to the Kiwi TLP Act d 2 were not sensitized to Bet v 1 or PR10 proteins. The significance of these sensitization patterns is unclear. Cross-reactivity due to grass sensitization might explain why such a large percentage of this

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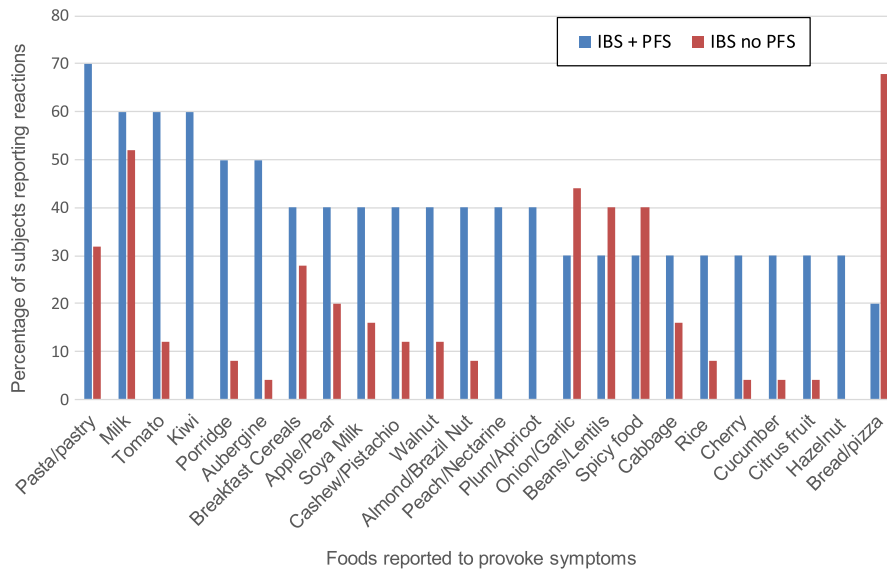


FIGURE 1 Foods reported to trigger symptoms in the IBS cohort. IBS, irritable bowel syndrome; PFS, pollen-food syndrome

TABLE 1 Selected ISAC Test results for individual aeroallergens and food allergens

Allergen	Allergen source	Allergen type	IBS + PFS positive ISAC (%)	IBS no PFS positive ISAC (%)	Sig (Fisher's exact test)
Foods					
Co a 1.0401	Hazelnut	PR10	6 (60)	1 (4)	0.001
Mal d 1	Apple	PR10	6 (60)	1 (4)	0.001
Pru p 1	Peach	PR10	5 (50)	1 (4)	0.004
Gly m 4	Soy	PR10	3 (30)	0	0.018
Ara h 8	Peanut	PR10	5 (50)	1 (4)	0.004
Act d 8	Kiwi	PR10	3 (30)	1 (4)	0.004
Api g 1	Celery	PR10	2 (20)	1 (4)	0.19
Act d 2	Kiwi	TLP	2 (20)	0	0.76
Aeroallergens					
Phl p 1	Timothy grass		7 (70)	4 (16)	0.004
Phl p 2	Timothy grass		7 (70)	2 (8)	0.001
Phl p 4	Timothy grass		6 (60)	4 (16)	0.016
Phl p 5	Timothy grass		7 (70)	3 (12)	0.002
Phl p 6	Timothy grass		6 (60)	2 (8)	0.003
Phl p 7	Timothy grass	Polcalcin	0	0	
Phl p 11	Timothy grass		8 (80)	3 (30)	0.000
Phl p 12	Timothy grass	Profilin	0	0	
Bet v 1	Birch pollen	PR10	6 (60)	1 (4)	0.001
Bet v 2	Birch Pollen	Profilin	1 (10)	0	0.286
Bet v 4	Birch Pollen	Polcalcin	0	0	
Ole e 1	Olive Pollen		3 (30)	3 (12)	0.213
MUXF3	CCD	CCD	0	1 (4)	0.714
Hev b 8	Latex	Profilin	3 (30)	0	0.018

Abbreviations: IBS, irritable bowel syndrome; PFS, pollen-food syndrome; TLP, thaumatin-like proteins.

group had a positive test to semolina. However, only 4/7 IBS + PFS group had a positive SPT to both semolina and grass, and none of the IBS alone group had a positive semolina SPT despite 6/25 being grass sensitized. Thus, although not sensitized to Tri a 19, the wheat

allergen most usually implicated in wheat allergy, the positive SPT to semolina suggests potential sensitization to other wheat allergens in some individuals with IBS + PFS, which might indicate an allergic component to symptoms. This finding might explain why wheat

exclusion is an effective intervention for some patients with IBS.⁹ The strengths of this study were the use of validated questionnaires, and a matched control group, but it was underpowered to compare differences within the IBS group.

In conclusion, our results suggest individuals with IBS have a high incidence of SAR and consequent PFS, with an increase in IBS severity in those with SAR as a comorbidity. Whether this association is causal could be tested by exploring whether dietary avoidance measures directed against PFS might have an impact on IBS symptoms, and/or test the impact of anti-allergic medication on IBS symptoms.

KEYWORDS

food allergy, irritable bowel syndrome, pollen, prevalence

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Appendix 1. Methods

This observational prospective controlled cohort study was undertaken at the Royal Brompton & Harefield NHS Foundation Trust (RBHT) and Chelsea and Westminster NHS Foundation Trust (C&WFT), London (UK). The study received ethical and HRA approval (REC 17/NW0577), IRAS Reference: 229644.

Participants:

Two cohorts of patients from secondary care clinics were recruited to the study between October 2017 and March 2018. Unselected case group participants, recruited from the gastroenterology clinic at C&WFT, were aged 17 years and over and had a medically confirmed diagnosis of IBS according to Rome IV criteria (1):

Rome IV Criteria

Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

The control group consisted of age and sex-matched participants recruited from a secondary care congenital heart disease clinic at RBHT. All participants gave written informed consent to take part. Case group participants were excluded if they were pregnant, had a concomitant severe medical condition, were on medications that might interfere with the outcome of skin prick testing or were unsuitable for skin prick testing (e.g. presence of severe eczema).

Interventions:

Questionnaires

All subjects in both the case and control groups self-completed a validated PFS diagnostic questionnaire (2). The case group also self-completed one non-validated food and symptom questionnaire and five validated questionnaires: IBS quality of life questionnaire IBS-QOL (3), IBS symptom severity questionnaire IBS-SSS (4), score for allergic rhinitis (SFAR) questionnaire (5), allergic rhinitis severity score (6) (if applicable).

Skin Prick Tests (SPT)

All subjects in the case group underwent SPT to a panel of 20 aeroallergen and food extracts (ALK Abelló), fresh foods and positive and negative control solutions (histamine hydrochloride 10mg/ml and diluent) (see Table 1). The procedure was carried out following standardised techniques and international guidelines with any resulting wheal ≥ 3 mm considered positive (7). Fresh foods were used for some of the tests as they have been shown to be more effective than reagents fruits and vegetables are being tested. (8).

Table 1.

Fresh Food	Food Reagents	Aeroallergens
Apple - Granny smith	Hazelnut	House dust mite
Cherry Tomatoes	Peanut	Mixed Grass
Carrot	Peach	Timothy Grass
Raw Potato with Peel		Silver Birch
Cooked jacket Potato		London plane tree
Walnut		Mixed Trees
Semolina (wheat)		Mugwort
Cow's Milk		
Soy Milk		

Serum analysis

Subjects in the case group had a 10-ml blood sample collected. To check allergen sensitization of each participant, ImmunoCAP 112 ISAC was performed according to the manufacturer's instructions (ThermoFisher Scientific). This is a microarray assay for simultaneous measurement of specific IgE antibodies to 112 allergen components. Specific IgE values were expressed in ISAC standard units (ISU), values equal or higher than 0.3 ISU were considered positive.

Statistical analysis

From previous studies, it could be assumed that 25% of IBS patients could have PFS. The prevalence of PFS in an unselected adult population is 2%. To achieve a power of 80% with a confidence interval of 95% and a 10% attrition rate, based on prevalence of 33%, a sample

size of 35 subjects in each group was calculated to be required using the following calculation

P_1 = 33% prevalence for the Cases group

P_2 = 5% prevalence for the Controls group

$$P = \frac{P_1 + P_2}{2}$$

$$n = \frac{2P(1-P) \left[Z_{\frac{\alpha}{2}} + Z_{\beta} \right]^2}{|P_1 - P_2|^2}$$

$Z_{\frac{\alpha}{2}} = 1.96$ and $Z_{\beta} = 0.84$

The Shapiro-Wilk test was used to determine normality of continuous variables, the Student's t-test for comparison of the normally distributed variables between groups, and the Kruskal-Wallis test for median comparison of non-normally distribution variables. Due to small sample size, Fisher's exact test was used to explore possible differences between groups. Chi-square test was used to assess for differences in gender and prevalence of PFS. A logistic regression model (binary outcomes) was used to analyse the association of PFS independently with the different outcome variables. Spearman Rank correlation was used to identify the correlations between PFS and SAR.

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Supplementary Appendix 2. Results for Case and Control Groups - demographic details, SAR and QOL

	Case Group (IBS) n = 35		Control Group (CHD) n = 35	P value
Gender	30 (86%) Female		30 (86%) Female	1.000†
Mean age in years (median, range, st. deviation)	34.31 (31, 18-70, 12.36)		33.91 (30, 18-74, 12.38)	0.893‡
	IBS no PFS (%) n=25	IBS + PFS (%) n=10		
Gender	21 ♀ (84)	9 ♀ (90)		0.553†
Mean Age (median, range, st. deviation)	34.64 (30, 17-65, 11.33)	33.5 (32, 18-70, 15.36)		0.810‡
SFAR validated Questionnaire - Overall score (i)	6.08	10.80		0.02 ¶
SAR total score (ii)	3.46	6.78		0.016*
IBS Severity Score (iii)	225.39	292.4		0.047*
IBS QOL Score (iv)	35.41	40.52		0.504*

(† Pearson Chi Square, ‡ t test, * Kruskal Wallis, ¶ Fisher's exact test)

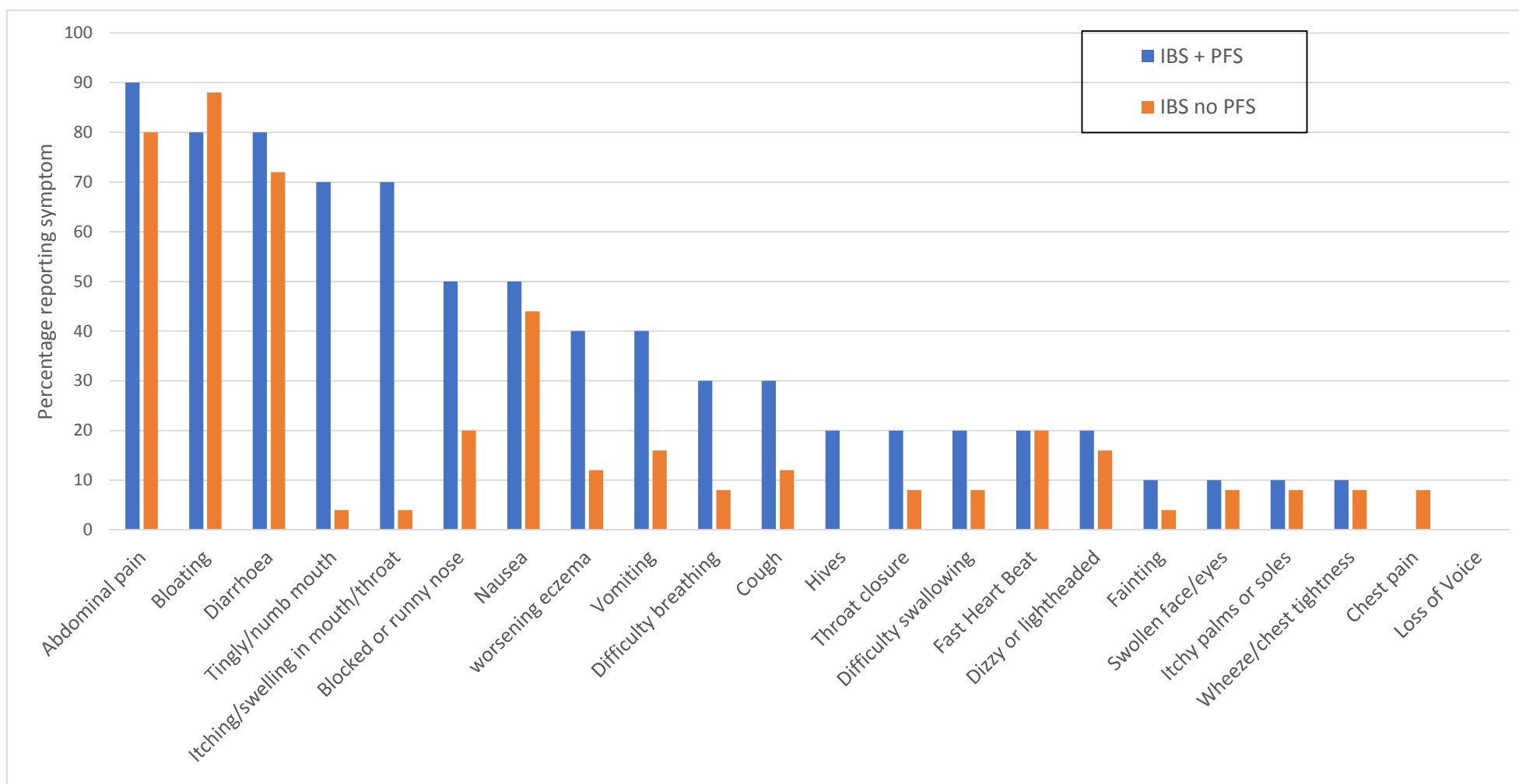
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Supplementary Appendix 4 – Reported symptoms in the IBS cohort



Supplementary Appendix 5. Skin Prick Test results

A. Comparison of IBS subjects with and without PFS

	IBS + PFS with positive SPT (%)	IBS no PFS with positive SPT (%)	P value (Fisher's exact Test)
Number of subjects	10	25	
Foods			

Semolina (durum wheat)	7 (70)	0 (0)	0.000
Raw potato + peel	6 (60)	1 (4)	0.001
Hazel nut	6 (60)	2 (8)	0.003
Tomato	4 (40)	1 (4)	0.017
Cooked potato + peel	3 (30)	0 (0)	0.018
Apple	4 (40)	2 (8)	0.043
Carrot	3 (30)	1 (4)	0.061
Peanut	3 (30)	1 (4)	0.061
Soy milk	3 (30)	2 (8)	0.120
Peach	1 (10)	0 (0)	0.286
Walnut	2 (20)	2 (8)	0.319
Celery	0 (0)	2 (8)	0.504
Cow's milk	0 (0)	0 (0)	1.000
Aeroallergens			
Timothy grass	8 (80)	6 (24)	0.004
Mixed grass	8 (80)	7 (28)	0.007
Silver Birch	6 (60)	3 (12)	0.007
Mixed trees	6 (60)	6 (24)	0.053
London Plane Tree	3 (30)	1 (4)	0.061
House dust mite	5 (50)	5 (20)	0.089

B. Comparison of IBS subjects with SAR*, with and without PFS

	IBS + SAR + PFS with positive SPT (%)	IBS + SAR with positive SPT (%)	P value (Fisher's exact Test)
Number of subjects	8	12	

Foods			
Semolina (durum wheat)	5 (62%)	0 (0)	0.004
Raw potato + peel	6 ()	0 ()	0.001
Hazel nut	5	1()	0.018
Tomato	4	0	0.014
Cooked potato + peel	3	0	0.049
Apple	3	1	0.255
Carrot	3	1	0.255
Peanut	3	0	0.049
Soy milk	3	1	0.255
Peach	0	0	1.000
Walnut	1	0	0.4
Celery	0	0	1.000
Cow's milk	0	0	1.000
Aeroallergens			
Timothy grass	7	5	0.07
Mixed grass	7	5	0.07
Silver Birch	6	2	0.019
Mixed trees	6	3	0.065
London Plane Tree	3	0	0.049
House dust mite	3	4	1.000

*SAR diagnosis made according to validated questionnaire.