

## ORIGINAL ARTICLE

# Development and validation of a structured questionnaire for the diagnosis of oral allergy syndrome in subjects with seasonal allergic rhinitis during the UK birch pollen season

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## Clinical & Experimental Allergy

### Summary

**Background** Birch pollen-associated oral allergy syndrome, also known as pollen–food syndrome (PFS), is the most common food allergy in adults in the United Kingdom. Because of its characteristic rapid onset of oro-pharyngeal symptoms associated with specific plant foods, it was hypothesized that a history-based questionnaire could accurately diagnose PFS in subjects with rhino-conjunctivitis symptoms in the UK springtime.

**Objective** In this study of diagnostic accuracy, we aimed to validate a simple PFS diagnostic questionnaire and algorithm against a reference diagnostic test method (RTM) comprising diagnosis by expert evaluation of clinical history, skin prick tests and oral food challenge, in subjects reporting allergic rhinitis (AR) in the UK birch pollen season from March to May.

**Methods** Participants were UK adults reporting symptoms of spring time-AR (hayfever). They self-completed a diagnostic questionnaire in addition to undergoing an RTM comprising clinical history, skin prick testing to foods and pollens and oral food challenge. Subjects who reported anaphylaxis were excluded on the basis that they required specialist referral.

**Results** One hundred and twenty three subjects took part in the study. Data from 110 participants were analysed; of the 13 exclusions, four provided insufficient data and nine reported anaphylaxis such that they warranted specialist assessment. Fifty-two participants (47%) were diagnosed with PFS by the RTM in comparison with 51 (46%) by a diagnostic questionnaire and algorithm ( $P = 1.000$ , McNemar's test). The diagnostic questionnaire and algorithm had a sensitivity of 0.90 (0.78–0.96), a specificity of 0.93 (0.82–0.97), a positive predictive value of 0.92 (0.80–0.97) and a negative predictive value of 0.91 (0.80–0.96) when measured against the RTM.

**Conclusion and Clinical Relevance** The diagnostic questionnaire and algorithm is a practical and robust tool, which enables rapid identification, and therefore management, of individuals with PFS who experience rhino-conjunctivitis symptoms in the UK birch pollen season.

Registered with ClinicalTrials.Gov. registration number NCT00854958.

**Keywords** allergy, birch, cross-reactivity, diagnosis, food, oral, pollen, questionnaire, sensitivity, specificity, syndrome

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### Introduction

Oral allergy syndrome (OAS) is a common food allergy, especially in older children and adults. Fernández-Rivas et al. [1] have suggested that the term OAS should be confined to a description of localized oropharyngeal symptoms related to the ingestion of any food. OAS symptoms

occur most often because of IgE cross-reactivity arising from structural homologies between pollen allergens and food proteins. There is a growing consensus that symptoms associated with pollen–food IgE cross reactivity, characteristically triggered by raw fruits, vegetables and some nuts, should be specifically labelled as 'pollen–food allergy' or 'pollen–food syndromes' (PFS) [2, 3]. This is in order to

distinguish PFS from OAS symptoms related to allergy due to primary food sensitization, which may be more severe. Prevalence data indicate that allergies to fruits and vegetables are a significant problem, especially in pollen-sensitized adults [4–6]. PFS symptoms are most commonly reported by people sensitized to Silver Birch tree pollen (*Betula verrucosa*), 50% or more of whom may develop PFS [7, 8].

Cross-reacting allergens in plant foods that trigger PFS are labile, with IgE-binding epitopes altered by heat or proteolysis [9]. Diagnosis may therefore be effectively achieved on the basis of clinical history together with results from skin prick tests (SPTs) using fresh fruits, vegetables or nuts and the prick-by-prick test method [10, 11]. Specific IgE estimation using recombinant allergens may also be helpful [12], although only a relatively small number of individual fruit and vegetable allergens are currently commercially available. Oral food challenge represents an alternative strategy to confirm diagnosis, although practical problems exist due to the lack of standardized protocols, variability and perishability of food plant sources, difficulty in blinding of the procedure and variability of host factors at the time of challenge such that false-negative results occur commonly [13–17].

In the majority of cases, PFS is a self-limiting condition that could easily be managed in primary care. Unfortunately, in the setting of primary care, the lack of expertise in allergy and the necessary time to evaluate the allergy history, together with the impracticality of performing and interpreting prick-by-prick and oral food challenge tests, means that at present, such patients require referral for specialist evaluation. Furthermore, it may be difficult to identify food-allergic but non-PFS patients presenting with OAS symptoms, who may have a primary sensitization to plant foods and therefore be at risk of systemic reactions including anaphylaxis [18, 19]. A pilot study evaluated the performance of a PFS diagnostic questionnaire against skin prick testing with fresh plant foods in a cohort of 40 subjects with reported springtime hayfever, 25% of whom also underwent oral food challenge with apple. The main finding was that clinical history is a good indicator of the presence or absence of PFS, with a prototype PFS diagnostic questionnaire successfully identifying 95% of those subjects who went on to be formally diagnosed with PFS through a combination of reported symptoms and positive PPT. These data indicated that a clinical history might be sufficiently stereotypical in UK patients with PFS to be diagnostic without further specialist evaluation or investigation. We therefore hypothesized that a simple history-based questionnaire could be used to diagnose PFS with a high degree of accuracy in patients presenting with seasonal allergic rhinitis (SAR) during the UK birch pollen season. To test this hypothesis, we aimed to validate a novel patient-completed questionnaire, developed from the original questionnaire used in

the pilot study and refined using information on the characteristics of PFS in other European populations [1, 5, 7]. The revised questionnaire was interpreted by an algorithm and the results were compared with those from the current best reference diagnostic procedure comprising clinical history, taken by a specialist, together with skin prick testing to foods and pollens, combined with oral food challenge.

## Methods

### Study design

This was a prospective study with data collection planned using a PFS diagnostic questionnaire (Appendix S1) developed using data from a pilot study. The efficacy of the PFS diagnostic questionnaire was tested against a reference diagnostic test method (RTM) consisting of expert medical opinion based on clinical history, prick-by-prick testing and the results of an open and blinded oral food challenge (Fig. 1). Study subjects with allergic rhinitis (AR) during the UK birch pollen season (March, April and May) completed the PFS diagnostic questionnaire and were allocated a diagnosis of 'PFS' or 'no PFS' according to a diagnostic algorithm (Appendix S2). All participants subsequently underwent tests according to the RTM protocol and an assessment by a medical expert who also made a diagnosis of 'PFS' or 'no PFS'. The study was conducted according to the World Medical Association's Declaration of Helsinki. The study received ethical approval from the Royal Brompton, Harefield, and the National Heart and Lung Institute Ethics Committee (05/Q0404/38), and all participants were given a patient information sheet to read, following which they provided written informed consent. The study was also registered with ClinicalTrials.Gov. registration number NCT00854958.

### Subjects

In order to ensure that disease severity did not affect the generalizability of the PFS diagnostic questionnaire and algorithm once validated, the majority of subjects were recruited from the general population through advertisement in a London regional newspaper and using email networks in the Royal Brompton & Harefield NHS Foundation Trust (RBHT) and King's College London. The text of the email and advertisement asked 'Do you get hay fever in the springtime from March to May?' and invited those who did to contact the study co-ordinator if they were interested in participating in the study. A small number of additional subjects were recruited from the Allergy Clinic at RBHT. Pilot data suggested that up to 50% of subjects who report SAR during the UK birch pollen season may also have PFS. Therefore, the only

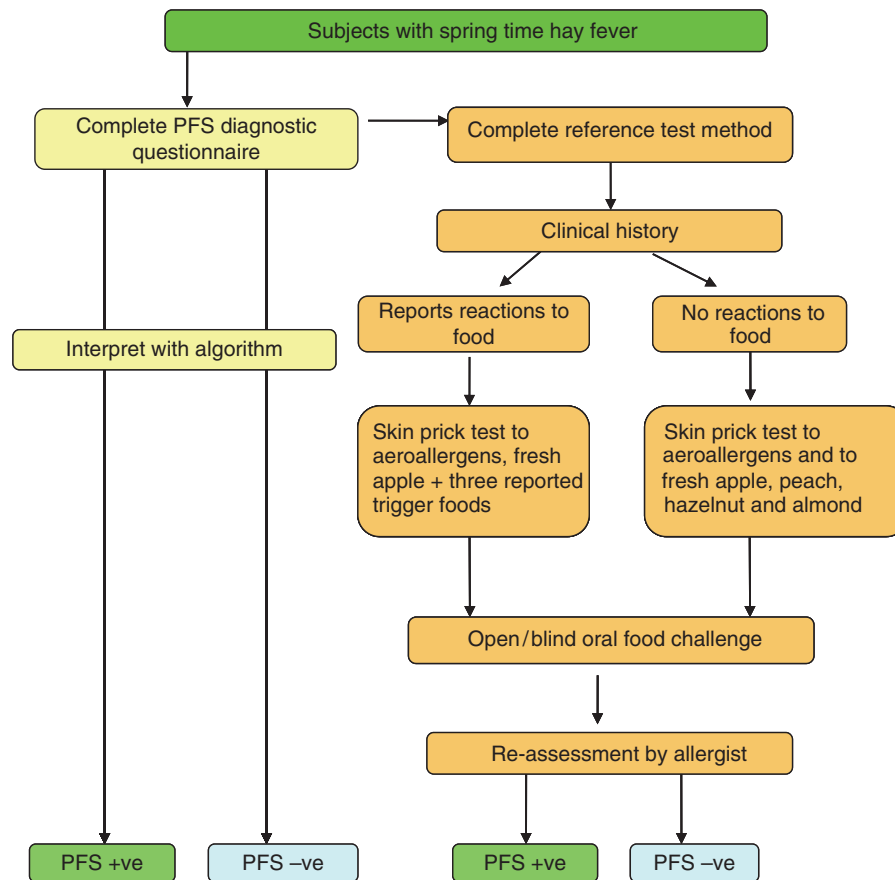


Fig. 1. Study design. PFS, pollen–food syndrome; PFS+ve, has PFS; PFS–ve, does not have PFS.

inclusion criterion was reported symptoms suggestive of SAR with or without seasonal asthma between March and May. Subjects were excluded from the study if they were below the age of 18 years, had poorly controlled concomitant asthma (forced expiratory volume in 1 L < 70% predicted), any significant pre-existing medical condition, were pregnant or required  $\beta$ -blockers, regular  $H_1$ -receptor antagonists or oral corticosteroids at the time of the study. To minimize the risk of adverse events, no challenge testing was performed during the main UK birch pollen season (March or April 2006). Using pilot data, it was estimated that a sample size of 123 subjects was required to provide a confidence interval of 0.1 for both sensitivity and specificity, assuming sensitivity and specificity of 0.8 and a prevalence of 0.5 for PFS in birch pollen SAR sufferers [20].

#### *Pollen–food syndrome diagnostic questionnaire and algorithm*

All subjects completed the PFS diagnostic questionnaire on a self-administered basis, to ensure a minimum of interviewer bias while permitting interviewer assessments and necessary explanations [21]. As a specific hypothesis was being tested, pilot data were used to construct a one-

page questionnaire, using the funnel approach and closed questions to enable rapid completion and aid analysis. The PFS diagnostic questionnaire asked subjects about their rhinitis symptoms and also whether they had experienced any reactions to foods. Those who reported reactions were asked about the foods involved, whether they were raw or cooked, the speed of onset of symptoms and symptom characteristics. Questionnaire responses were then interpreted using an algorithm (Appendix S2) that incorporated information on the chronology of reactions in relation to the birch pollen season, the involvement of raw or cooked foods, speed of symptom onset and symptom type. The algorithm assigned all participants to either 'PFS+ve' (has PFS) or 'PFS–ve' (does not have PFS).

#### *Reference test method*

**Clinical history.** A standardized clinical history was taken by a medical allergy specialist (M. C.), who was blinded as to the results of the PFS diagnostic questionnaire and algorithm allocation. The clinical history included an assessment of rhinitis and concomitant asthma, medication use, reported reactions to foods including specific foods such as apple, stone fruits and nuts, symptom type

and speed of onset. The specialist recorded a provisional diagnosis, allocating each subject as either 'provisional PFS+ve' or 'provisional PFS-ve'. Subjects then underwent prick-by-prick testing together with an oral food challenge, following which the provisional diagnosis was reviewed and revised by the specialist and a final diagnosis was made of 'PFS+ve' (has PFS) or 'PFS-ve' (does not have PFS).

**Skin prick tests.** Subjects underwent skin prick testing to a standard panel of common aeroallergens including pollens (three tree pollen mix, silver birch, oak tree, plane tree, timothy grass, mugwort), house dust mite and cat (all ALK Abelló, Høersholm, Denmark) in addition to prick-by-prick testing with four fresh foods. Prick-by-prick testing was performed by pricking the intact food through the peel or the skin with a sterile lancet (ALK Abelló), which was then immediately used to prick the skin of the forearm of the subject, using one lancet per food. One control food (apple) was prick tested in all subjects. Those reporting reactions to foods were prick tested with three additional trigger foods, whereas those reporting no reactions to foods were tested with the most common PFS trigger foods (apple, peach, hazelnut and almond) as determined by our pilot study (data not shown).

All skin prick tests (SPTs) were performed on the volar aspect of the forearm using standardized techniques according to international guidelines [22, 23]. After 15 min, a fine-point marker pen was used to draw around all weals, which were then documented by transfer to a chart with transparent adhesive tape. Each weal was compared with those obtained using positive and negative control solutions (histamine hydrochloride 10 mg/mL and diluent, respectively) and recorded as positive if the diameter was  $\geq 3$  mm greater than the negative control [22, 24–26].

**Oral food challenges.** Following skin prick and prick-by-prick testing, all subjects underwent an open oral food challenge with a fresh apple, followed by a double-blind, placebo-controlled food challenge in selected subjects (see Fig. 2). The challenge protocol was developed and adapted from published challenges involving fruits and vegetables [10, 14, 15, 17, 27]. Before each challenge, baseline peak expiratory flow rate (PEFR) was recorded. Symptoms were graded by subjects using an ordinal scale of 0–3, where 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe and categorized as either objective signs or subjective symptoms (Table 1). The open challenge commenced with a labial challenge (outer lip), followed by the 'chew and spit' phase; subjects chewed a 5 g piece of apple, both peel and flesh, for 1 min before disgorgement. The challenge was considered positive and stopped if objective signs of any grade or a subjective symptom graded  $\geq 2$  developed within 15 min of the 'chew and spit'

phase. All other subjects went on to the 'chew and swallow' phase; those who were asymptomatic in the earlier phase ate the entire apple in one sitting, while those with reported symptoms ate three bites of apple in a step-wise fashion with a 5-min interval between bites. A reported symptom graded  $\geq 2$  resulted in the challenge being stopped.

Subjects who had a positive open food challenge with objective signs were not investigated further. For the purposes of best practice, double-blind placebo-controlled food challenges were performed in participants reporting symptoms to foods but in whom the open food challenge was negative or associated only with subjective symptoms. The double-blind placebo-controlled food challenge consisted of one active and open placebo challenge given sequentially, with the order randomized immediately before the challenge was performed. The challenges were prepared by the chief investigator (I. S.) and administered by a research dietitian. The challenge material was either an apple or another trigger food reported to cause symptoms if apple was not a reported trigger food. Both active and placebo challenges contained 50 g of canned blackcurrants and juice together with 2 g of finely chopped, raw, peeled turnip to disguise the texture, colour and flavour of added foods. The active challenge additionally contained peeled, de-seeded, chopped and crushed fruit, vegetable or nut added just before consumption to maximize the amount of remaining allergen. The peel and seeds were removed in order to facilitate the blinding, although it is acknowledged that this may have also reduced the allergen content. The challenge sequence, symptom scoring and cessation guidelines were the same as for the open food challenges. Subjects were considered to have had a positive oral food challenge if they had either a positive open oral challenge with objective signs or reported symptoms on the active arm of the DBPCFC but not the placebo arm.

### Statistical analysis

Differences between diagnosis using PFS diagnostic questionnaire and algorithm and the RTM were measured using McNemar's test. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PFS diagnostic questionnaire and algorithm was measured against the results obtained by the RTM using the Bayesian analysis model as follows:

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{FP} + \text{TN})$$

$$\text{Predictive value positive} = \text{TP}/(\text{TP} + \text{FP})$$

$$\text{Predictive value negative} = \text{TN}/(\text{FN} + \text{TN})$$

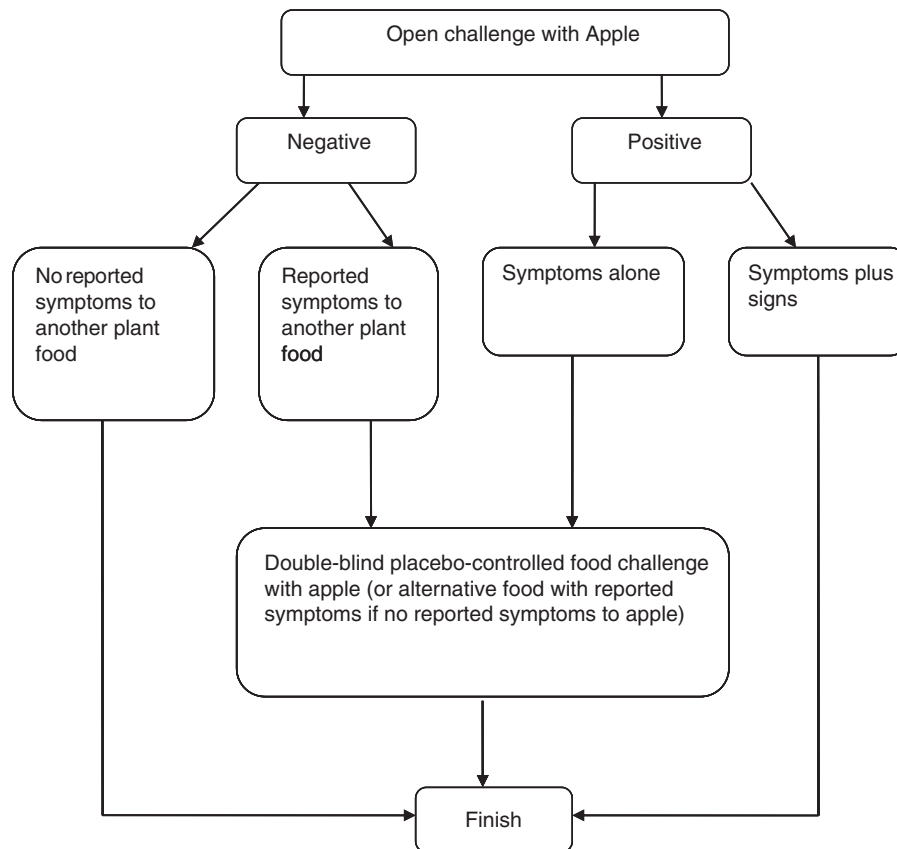


Fig. 2. Oral food challenge.

Table 1. Criteria used to determine the outcome of an oral food challenge

| Symptom type         | Objective signs                                                      | Subjective symptoms                                         |
|----------------------|----------------------------------------------------------------------|-------------------------------------------------------------|
| Asthma               | Cough, wheeze, 15% fall in PEFR                                      | Chest tightness, shortness of breath                        |
| Rhino-conjunctivitis | Sneeze, running nose, eye symptoms including redness and/or swelling | Blocked nose, itchy nose and itchy eyes                     |
| Urticaria            | Visible weals                                                        | Itchy skin                                                  |
| Oro-pharyngeal       | Oedema of the lips, tongue, gums or face, vocal changes              | Itch, tingle or soreness of the lips, mouth, throat or ears |
| Gastrointestinal     | Vomiting, diarrhoea                                                  | Nausea, abdominal discomfort                                |
| Other                | Flushing or pallor                                                   |                                                             |

PEFR, peak expiratory flow rate.

where TP is true positive, FN is false negative, TN is true negative and FP is false positive.

Bivariate rank correlation coefficients (Spearman's  $\rho$ ) were calculated to assess which variables in the PFS diagnostic questionnaire and which other variables, such

as SPT positivity to pollens, were correlated with a diagnosis of PFS using the RTM. To assess the reliability and validity of the PFS diagnostic questionnaire and algorithm, Chronbach's  $\alpha$  was used for internal consistency and item-wise correlation. All statistical analyses were carried out using SPSS version 15.0.

## Results

### Subjects

Recruitment and testing took place from June 2005 through to September 2006. One hundred and thirty four subjects who met the inclusion criteria responded to the email and newspaper advertisements. An additional 14 subjects from the allergy clinic at the RBHT were approached and invited to take part in the study. Of these 148 subjects, 123 met the inclusion criteria and participated in the study. Complete data were obtained from 119 subjects (34 males, 85 females), with a median age of 33.5 years (range 19–68 years). Of these, 105 (88%) subjects were recruited from the general population by newspaper or email advertisement, with the remainder being recruited from the allergy clinic. All subjects completed the PFS diagnostic questionnaire and underwent the RTM on the same day, although three subjects returned to

complete their double-blind, placebo-controlled food challenges on another day.

#### *Performance of the pollen–food syndrome diagnostic questionnaire and algorithm*

Of the 119 subjects, 88 (74%) reported reactions to foods; of these, 75 reported reactions to plant foods. Nine of these subjects reported anaphylaxis as one of their symptoms on the PFS diagnostic questionnaire. Subjects reporting anaphylaxis were excluded from the subsequent analysis of the performance of the PFS diagnostic questionnaire, because such patients warrant specialist assessment and diagnosis. Thus, of the 66 subjects reporting reactions to plant foods, 51 were diagnosed with PFS by a diagnostic questionnaire and algorithm in comparison with 52 diagnosed by the RTM; there was no significant difference between the two tests in terms of patient diagnosis ( $P = 1.000$ , McNemar's test).

The majority (90%) of symptoms reported in the PFS questionnaire by those diagnosed as PFS+ve by the RTM were graded as mild (48%) or moderate. Excluding the subjects who reported anaphylaxis, 55 subjects experienced symptoms during oral food challenges, including two who had previously reported no symptoms to foods. Twenty of the 55 (36%) had objective signs including visible swelling of the lip or tongue (12), sneeze (3), wheeze (4) and 15% decline in PEFR (3). A further 18 had a positive blind challenge. Thus, 38/55 (67%) had a positive oral food challenge according to the methodology. Sixteen subjects had a negative double-blind oral food challenge; six were asymptomatic to the active and placebo challenges and 10 were placebo responders with either reported symptoms to both challenges or symptoms only to the placebo challenge. Symptom severity during the oral food challenges was predominantly mild; 80% of symptoms reported by the 52 subjects diagnosed with PFS by the RTM were graded as level 1. The most prevalent symptoms reported by these subjects were itch (69%), swelling (63%) and tingle (50%).

The diagnostic questionnaire and algorithm was highly effective at diagnosing PFS when measured against the RTM. Excluding those who reported anaphylaxis, the sensitivity, specificity, PPV and NPV for the 110 subjects were all above 0.90 (Table 2). Analysis of the data

including only those 79 subjects who reported reactions to food showed an improved sensitivity, an unchanged PPV, but lower specificity and NPV with wider confidence intervals. The PFS diagnostic questionnaire and algorithm was also analysed against the RTM to produce a receiver operator curve (Table 2 and Fig. 3).

#### *Analysis of the reliability and variables in the pollen–food syndrome diagnostic questionnaire*

Of the 51 participants diagnosed with PFS by the diagnostic questionnaire and algorithm, 32 (63%) were allocated on the basis of reported reactions to raw plant foods only. Of the remainder, 14 were diagnosed on the basis of symptoms occurring within 5 min of eating and five due to reported symptoms of either mild to moderate tingling, itching, soreness or angio-oedema of the oropharynx or the throat. Four of the subjects diagnosed with PFS by the diagnostic questionnaire and algorithm, on the basis of the rapid onset of reported symptoms, were found to be misclassified by the RTM. Five participants not classified as PFS+ve by the diagnostic questionnaire and algorithm were found to have PFS by the RTM; three had reported delayed speed of onset and two had reported no symptoms to foods.

When measured against the results of the RTM, the reliability of the questions in the PFS diagnostic questionnaire was high, with a standardized Chronbach's  $\alpha$  score of 0.82; a score of  $\geq 0.75$  is generally considered to indicate a reliable test [28]. Deletion of any questions from sections 2 through to 7 decreased the reliability of the questionnaire, with all these questions having a corrected item-total correlation  $> 0.64$ . The question on the seasonal timing of AR symptoms was not included in this analysis because symptoms during the spring were the only inclusion criterion for the study.

In symptomatic subjects (excluding those with anaphylaxis), the variable from the PFS diagnostic questionnaire most significantly correlated with a diagnosis of PFS by the RTM was 'reacts to raw plant foods only' ( $\rho = 0.53$ ,  $P < 0.01$  one-tailed). Other variables that were also highly significantly positively correlated with a diagnosis of PFS included reactions to fruit and vegetables ( $\rho = 0.40$ ) and tree nuts or peanuts ( $\rho = 0.32$ ), reported symptoms of intense oral pruritis ( $\rho = 0.32$ ) and scratchy sore throat

Table 2. Performance of the PFS diagnostic questionnaire measured against the reference test method

|                                                              | No. subjects | Sensitivity<br>(95% CI) | Specificity<br>(95% CI) | Positive predictive<br>value (95% CI) | Negative predictive<br>value (95% CI) | Receiver operator<br>curve (95% CI) |
|--------------------------------------------------------------|--------------|-------------------------|-------------------------|---------------------------------------|---------------------------------------|-------------------------------------|
| All subjects (excluding those reporting anaphylaxis)         | 110          | 0.90 (0.78–0.96)        | 0.93 (0.82–0.97)        | 0.92 (0.80–0.97)                      | 0.92 (0.80–0.96)                      | 0.92 (0.86–0.97)                    |
| Symptomatic subjects (excluding those reporting anaphylaxis) | 79           | 0.92 (0.80–0.97)        | 0.86 (0.66–0.95)        | 0.92 (0.80–0.97)                      | 0.86 (0.66–0.95)                      | 0.86 (0.76–0.97)                    |

PFS, pollen–food syndrome.

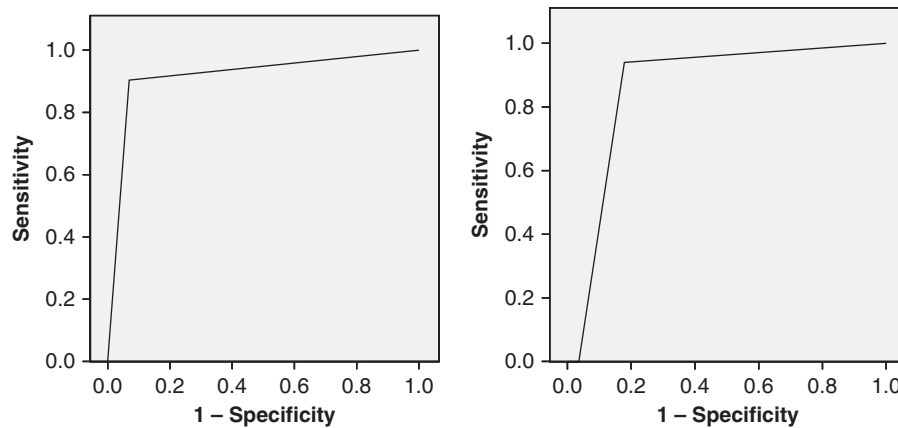


Fig. 3. Receiver operator curves. All subjects excluding those reporting anaphylaxis (left-hand figure). Symptomatic subjects excluding those reporting anaphylaxis (right-hand figure).

( $\rho = 0.29$ ) (all  $P < 0.01$ , one-tailed). The only speed of onset variable that was significantly correlated with a final diagnosis of PFS by the RTM was symptoms occurring on biting and chewing ( $\rho = 0.29$ ,  $P < 0.01$  one-tailed). Apart from the variables on the PFS diagnostic questionnaire, the number of reported trigger foods was also correlated with a diagnosis of PFS by the RTM, with four or more foods reported to cause symptoms being significant ( $\rho = 0.27$ ,  $P < 0.01$  one-tailed). Other variables not on the PFS diagnostic questionnaire but recorded elsewhere such as age, gender, family history or past allergic history were not significantly correlated with a diagnosis of PFS by the RTM.

#### *Pollen sensitization and reported trigger foods*

Ninety three percent of the 110 subjects were sensitized to one or more aeroallergen. Although all subjects reported seasonal rhinitis, only 94 (85% of the cohort) were sensitized to the tree or grass pollens tested. Sixty-nine of the 110 (63%) were sensitized to birch tree pollen, 46 (66%) of whom were ascribed a diagnosis of PFS according to the RTM. Excluding those who reported anaphylaxis, 50 of the 52 subjects with PFS according to the RTM were sensitized to pollen; 46 to birch (88%), 37 of whom were co-sensitized to grass; and four (8%) to grass only. Eight out of the nine subjects who reported anaphylaxis were also sensitized to tree pollen. A positive SPT to birch pollen ( $\rho = 0.53$ ) or co-sensitization to both birch and grass ( $\rho = 0.44$ ) were correlated with a final diagnosis of PFS by the RTM (both  $P < 0.01$  one-tailed). Eighty-six of the 119 subjects (72%) reported reactions to a total of 73 foods or food components. Excluding those who reported anaphylaxis, 32 (61%) of the 52 subjects who were diagnosed with PFS by the RTM reported symptoms to apple, making it the most common food to cause reported reactions. The other individual foods most commonly

reported to cause reactions were hazelnut, almond, peach, walnut and strawberry (Fig. 4).

#### **Discussion**

The PFS diagnostic questionnaire and algorithm had excellent sensitivity and specificity compared with the RTM, with no significant difference in the diagnosis of PFS between the two methods. All questions used in the PFS diagnostic questionnaire were appropriate and relevant and scored well on reliability analysis. Question 5 (relating reactions to raw vs. cooked foods) was particularly important: all 32 subjects diagnosed with PFS using the PFS diagnostic questionnaire and algorithm because they reported reactions to raw plant foods had their diagnosis confirmed by the RTM. A reported reaction to raw plant foods was also the variable most strongly correlated with a diagnosis of PFS by the RTM. The study results also demonstrated that, as in other northern European countries, PFS in UK subjects is common in birch-sensitized individuals; excluding those who reported anaphylaxis, 66% of those with birch pollen sensitization were diagnosed with PFS. Theoretically, 5–7% of UK subjects have birch pollen allergy [29, 30]; therefore, PFS could affect 2–3% of the UK adult population.

PFS is characterized by mild oropharyngeal symptoms. The symptoms reported by the participants and the results from the oral food challenges support this. The predominance of mild symptoms makes PFS a condition that could be managed in primary care. It is possible, therefore, that the PFS diagnostic questionnaire and algorithm could be used in a primary care setting to identify these individuals, with the possible consequence that specialist referral would be avoided. However, validation of the questionnaire within the primary care setting would be necessary to test this. The strength of this study is the

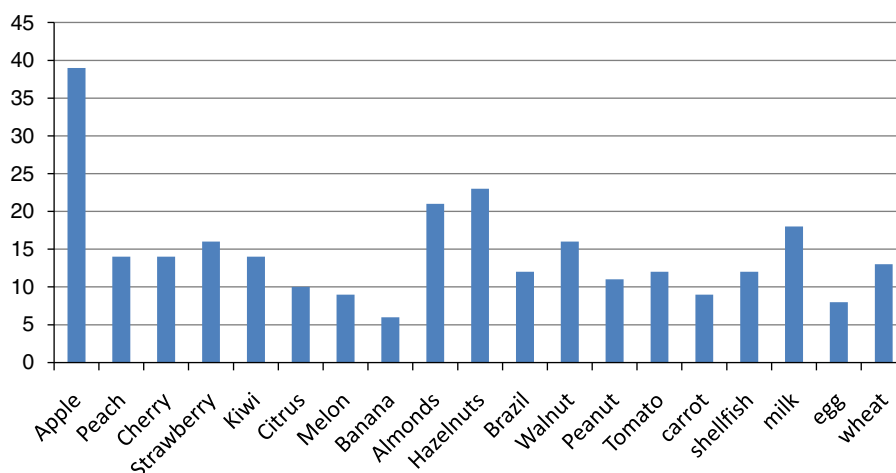


Fig. 4. Trigger foods reported by subjects diagnosed with pollen-food syndrome by the reference test method (excluding those reporting anaphylaxis).

development of a RTM to independently validate the questionnaire. Oral food challenge alone may yield misleading results due to difficulties in allergen conservation. The rigorous approach to diagnosis means that the results from the RTM have also provided the first validated UK data on PFS, including the foods most commonly reported to induce reactions and the prevalence of the condition in birch-sensitized individuals.

One limitation of the study was the inclusion only of subjects with SAR during the UK spring months (March, April and May), based on the rationale that these subjects are believed to account for the majority of cases of PFS in the United Kingdom. A study of an unselected population would have been impracticable because of the large number of participants required to achieve sufficient statistical power. However, this means that the application of the diagnostic questionnaire and algorithm outside this selected population, including populations based outside the United Kingdom, will be associated with different predictive values from those reported here, although the sensitivity and specificity of a diagnostic test are unaffected by disease prevalence [31]. We therefore do not advocate the use of the questionnaire and algorithm as a screening tool for PFS in patients *without* springtime AR or in populations outside of the United Kingdom. A second limitation of the study was that only one medical expert was used to provide the diagnosis used as the RTM.

The speed of onset was not 100% accurate in classifying those with PFS. Immediate-onset non-specific oral irritation in response to acidic fruits and vegetables in sensitive people could be misclassified as PFS by the questionnaire and algorithm. Also, symptoms in some individuals may be very mild or may require the consumption of a relatively large quantity of the food before they develop. This may explain the reporting of late-onset symptoms in those who were subsequently diagnosed with PFS by the RTM or indeed why two participants failed to report any

symptoms to foods but were subsequently diagnosed with PFS by the RTM. As the PFS questionnaire will only be used for those who report symptoms, this issue will not affect its efficacy. Variations in the allergenicity of different varieties of apple [32, 33], the effects of storage [34] or peeling or cooking [9, 35] of fruits and vegetables could also be important in precipitating symptoms.

Few, if any, validated diagnostic questionnaires have been developed for food allergy diagnosis, possibly because only 50% or fewer reported reactions to food are reported to be confirmed by a food challenge [36, 37]. However, Anhøj *et al.* [10] postulated that for PFS, history alone could be diagnostic and Alvarado and Pérez [38] showed a high diagnostic sensitivity and specificity for a questionnaire to determine the prevalence of PFS, when combined with the results of prick-by-prick testing and serum-specific IgE. Our results suggest that a structured clinical history alone, without any skin prick or immunological testing, can provide sufficient information to diagnose PFS accurately. A survey on the management of PFS by Ma *et al.* [3] concluded that the development of more tests and a specific approach to the diagnosis and management of these patients was needed. Mari *et al.* [12] suggested that component-resolved diagnosis, using individual recombinant allergens to assess sensitization to specific allergens homologous to the main birch pollen allergen Bet v 1, is more effective in diagnosing PFS than PPT or other tests for the estimation of specific IgE. However, the reality is that currently such tests are not routinely available in primary care; additionally, when testing for specific IgE levels, sensitization without clinical symptoms is still a confounding factor in common adult food allergies such as PFS. Ebo *et al.* [39] reported that birch-sensitized subjects with PFS were sensitized to the cross-reacting apple allergen Mal d 1, but those without PFS were also sensitized to Mal d 1. Thus, the use of clinical history alone in the form of a validated diagnostic

questionnaire is an attractive option; we believe the PFS diagnostic questionnaire and algorithm to be the first validated questionnaire to be developed for food allergy diagnosis.

On the basis of our findings, we propose that the PFS diagnostic questionnaire and algorithm is a practical and robust tool for the diagnosis of PFS in UK subjects reporting SAR from March to May. Once PFS has been diagnosed, the management is relatively straightforward. Therefore, to facilitate its use as a practical clinical tool, a user-friendly internet-based version of the PFS questionnaire and algorithm is being developed for routine clinical use, which will be available in conjunction with a patient information leaflet. However, this proposal is predicated on the recommendation that subjects who report symptoms to foods, but either do not meet the diagnostic criteria for birch-related PFS or have symptoms suggestive of anaphylaxis or symptoms in response to nuts, should be referred to a specialist allergy clinic for assessment. This is because, in contrast to PFS, anaphylaxis (with which it may co-exist) is more often associated with primary sensitization to foods and warrants referral for specialist assessment and management. Reported symptoms to nuts also need further investigation because both tree nuts and peanuts can trigger PFS symptoms. However, whereas most sufferers can eat trigger fruits and vegetables cooked without a problem, cooked nuts can still induce PFS symptoms as the allergens are only partially affected by roasting [40, 41]. This means that it can be difficult to assess whether reported symptoms to nuts are indicative of PFS or a primary allergy to nuts or peanuts and more tests may be required.

This study confirmed that PFS is a common manifestation in birch-sensitized individuals in the United Kingdom. However, despite an acceptance that PFS is the most

common form of food allergy in adults [42], and although fruits and vegetables are very often the foods most frequently reported to cause reactions in adults, there have been few robust studies specifically evaluating its prevalence. Schäfer et al. [43] reported that 73.1% of their food-allergic cohort had diagnosed hayfever. Vierk et al. [44] reported that 1.6% of US adults with a doctor-diagnosed food allergy report that a fruit or vegetable triggered symptoms. Fruits were the most common reported cause of adverse food reactions in Portuguese adults [45] and 16.7% of young Danish adults had a secondary food allergy mainly involving fruit and vegetable trigger foods [46]. Ma et al. [3], in their survey of US allergists, determined the probable prevalence of PFS to be 8%, which they felt was likely to be an underestimate. The prevalence within a country may vary; Asero et al. [47] reported that PFS occurred more frequently in northern and central Italy. A systematic review on the prevalence of plant food allergies concluded that population-based prevalence estimates for allergies to plant products determined by diagnostic gold standards are scarce and it is important not to rely on published prevalence estimates for allergy to plant foods [48]. Future research could therefore involve the use of the validated PFS diagnostic questionnaire and algorithm to assess the prevalence of PFS in UK adults with springtime AR.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** PFS Diagnostic Questionnaire.

**Appendix S2.** Diagnostic algorithm used to allocate a diagnosis with PFS diagnostic questionnaire.

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**STUDY NUMBER** \_\_\_\_\_ **INITIALS** \_\_\_\_\_ **DATE** \_\_\_\_\_

|                                                                                                                                                                                                          |                                                                                               |                          |                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------|--------------------------------|
| <b>Q1</b> Do you have hay fever?                                                                                                                                                                         |                                                                                               | Yes                      | No                             |
| If yes do you get symptoms mainly in the:                                                                                                                                                                |                                                                                               |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Spring time (February/March to May/June)                                                      | <input type="checkbox"/> | Autumn (October to December)   |
| <input type="checkbox"/>                                                                                                                                                                                 | Summertime (May/June to August)                                                               | <input type="checkbox"/> | Winter (November to February)  |
|                                                                                                                                                                                                          |                                                                                               | <input type="checkbox"/> | All year round                 |
| <b>Q2</b> Have you ever had any allergic reactions to food?                                                                                                                                              |                                                                                               | Yes                      | No                             |
| <b>If no – stop here and hand the questionnaire back to the researcher</b>                                                                                                                               |                                                                                               |                          |                                |
| <b>Q3</b> Do you experience reactions to foods all year round                                                                                                                                            |                                                                                               | Yes                      | No                             |
| If no – do you only get reactions to food during your main hay fever season?                                                                                                                             |                                                                                               | Yes                      | No                             |
| <b>Q4</b> Which foods do you have a reaction to:                                                                                                                                                         |                                                                                               |                          |                                |
| <b>Column A</b>                                                                                                                                                                                          |                                                                                               | <b>Column B</b>          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Fruit or vegetables                                                                           | <input type="checkbox"/> | Milk, eggs, chicken            |
| <input type="checkbox"/>                                                                                                                                                                                 | Bean sprouts, salad leaves or herbs                                                           | <input type="checkbox"/> | Fish, shellfish                |
| <input type="checkbox"/>                                                                                                                                                                                 | Nuts including all tree nuts and peanuts                                                      | <input type="checkbox"/> | Wheat or other cereal          |
| <input type="checkbox"/>                                                                                                                                                                                 | Peeling potatoes or other root vegetables                                                     | <input type="checkbox"/> | Other food                     |
| <input type="checkbox"/>                                                                                                                                                                                 | Beans, lentils, chickpeas or other legumes                                                    |                          |                                |
| <b>Q5</b> If reactions are to any food in column A, is your reaction to:                                                                                                                                 |                                                                                               |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Raw foods only                                                                                | <input type="checkbox"/> | Cooked foods only              |
| <input type="checkbox"/>                                                                                                                                                                                 | Both raw and cooked foods                                                                     | <input type="checkbox"/> | Not sure                       |
| <b>Q6</b> How quickly do the symptoms occur (tick one)                                                                                                                                                   |                                                                                               |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | On touching lips                                                                              | <input type="checkbox"/> | Within 30 minutes of eating    |
| <input type="checkbox"/>                                                                                                                                                                                 | On biting or chewing                                                                          | <input type="checkbox"/> | 1-2 hours after eating         |
| <input type="checkbox"/>                                                                                                                                                                                 | On or up to 5 minutes after swallowing                                                        | <input type="checkbox"/> | 2-4 hours after eating         |
| <input type="checkbox"/>                                                                                                                                                                                 | Within 15 minutes of eating                                                                   | <input type="checkbox"/> | More than 6 hours after eating |
| <b>Q7</b> Which of the following symptoms do you have after eating foods to which you are allergic (tick all that apply and grade each symptom from 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe)): |                                                                                               |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Tingling/numbness of lips/mouth or strange mouth sensation (____)                             |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Intense itching of the lips, mouth, palate or ears (____)                                     |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Scratchy/sore throat (____)                                                                   |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Urticarial rash (nettle rash) either on contact (e.g. peeling potatoes) or on eating (____)   |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Swelling of lips, tongue, mouth or throat (____)                                              |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Anaphylaxis (rapid onset of flushing, with severe difficulty in breathing or collapse) (____) |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Asthma (____)                                                                                 |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Rhinitis (hay fever) (____)                                                                   |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Eczema (____)                                                                                 |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Vomiting, Diarrhoea or bloating(____)                                                         |                          |                                |
| <input type="checkbox"/>                                                                                                                                                                                 | Other (____)                                                                                  |                          |                                |

