

Pragmatic randomized controlled trial of an allergy intervention for children aged 6–16 with asthma and rhinitis in general practice

H. Smith¹, D. Horney¹, C. Jones¹, S. Goubet², S. Mukhopadhyay³ and A. Frew⁴

¹Division of Primary Care and Public Health, Brighton and Sussex Medical School, ²Clinical Investigation Research Unit, Brighton and Sussex University Hospitals NHS Trust, ³Department of Paediatrics, Brighton and Sussex Medical School, and ⁴Department of Allergy & Respiratory Medicine, Royal Sussex County Hospital, Brighton, UK

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Summary

Background It is widely believed that for allergic rhinitis and asthma, avoidance of specific triggers can improve symptom control. Whilst many children with asthma or rhinitis are sensitized to airborne allergens, primary care diagnostic and management decisions are often made without a detailed history of the allergic triggers or allergy testing. Thus, treatment decisions are empirical and allergen avoidance advice is either not given or, if given, not tailored to the child's sensitivities.

Objective To ascertain whether allergy assessment and tailored advice in general practice enhances outcomes of children with asthma and rhinitis.

Method Pragmatic RCT of allergy intervention (structured allergy history, skin prick testing and appropriate allergy avoidance advice) vs. usual care in children with asthma and/or rhinoconjunctivitis. A blinded observer assessed outcomes at 12 months. Main outcome measures were symptom scores and disease-specific health-related QoL. Secondary outcomes were healthcare utilization, days unable to pursue usual activities and self-rated improvement.

Results A total of 335 participants were randomized to formal allergy assessment or normal care. There were no differences in participants' demographic or clinical characteristics at baseline (all $P > 0.05$). At 12 months, participants receiving the allergy intervention had fewer rhinitis symptoms (MD – 3.14, 95% CI – 6.01, – 0.81) and an improvement in QoL (MD – 0.50, 95% CI 0.32, 0.68). There were no significant changes in asthma symptoms, healthcare utilization or number of days unable to pursue usual activities.

Conclusion Amongst children with known asthma and/or rhinitis in primary care, taking a structured allergy history with skin prick testing and tailored advice on allergy avoidance resulted in reduced symptoms of rhinitis and improved QoL.

Keywords allergy assessment, asthma, evaluation, quality of life, rhinitis, skin prick testing, symptoms

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Correspondence:

Prof Helen Smith, Division of Primary Care and Public Health, Brighton and Sussex Medical School, Mayfield House, Village Way, Brighton BN1 9PH, UK.

E-mail: h.e.smith@bsms.ac.uk

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Background

Allergic diseases are a common reason for consulting UK general practitioners, representing up to 6% of all consultations and accounting for 10% of primary care prescribing costs [1]. Asthma and rhinitis are two of the most common chronic childhood diseases in the UK [2]. These conditions substantially impact on children's quality of life (QoL) [3] and their school performance [4]. The majority of children with asthma and/or rhinitis

have underlying allergies. In patients with allergies, avoidance of specific triggers can reduce symptoms and the need for medication. However, most primary care diagnostic and management decisions are made without obtaining a detailed history or performing allergy tests. Thus, treatment decisions are empiric and allergen avoidance advice is either not given or is not specific to the child's problem. It has been suggested that the introduction of allergen-specific testing such as skin prick tests (SPT) into general practice could improve the

cost-effectiveness of asthma and rhinitis care through appropriate targeting of medication and allergy avoidance advice.

Recent reviews of allergy services have highlighted major shortcomings of the allergy services provided throughout the UK [1]. The solution to this deficit lies in part with the development of a larger cadre of allergy specialists, but there is also a need to develop improved allergy care within primary care services. Descriptive studies in adults confirm the feasibility of allergy assessment in a non-specialist setting and its potential to avoid inappropriate allergy avoidance advice [5, 6]. However, a subsequent randomized trial of formal allergy assessment in adults with established asthma and rhinitis did not show any significant improvements in symptoms and outcomes [7]. As these previous studies have only looked at adult patients, it would be unwise to extrapolate the findings to the paediatric population without further age-specific studies.

In this trial, we investigated whether assessment of allergic status (structured allergy history and skin prick testing) in general practice together with providing appropriate advice on allergy avoidance enhances the health and well-being of children with asthma or rhinitis.

Methods

Setting

General practices in two counties in the South East of England (East Sussex and West Sussex).

Design

Pragmatic single-blinded randomized controlled trial (RCT) of allergy intervention (structured allergy history + skin prick testing (SPT) + appropriate advice on allergy avoidance). After baseline assessment, 335 children aged 6–16 years were randomized to receive the allergy intervention or usual care.

Study enrolment

Twenty general practices used their electronic patient records to identify patients aged 6–16 years with a diagnostic label of asthma, rhinitis or hayfever. Children were excluded if they had had SPT in the preceding 2 years, were suffering from a serious chronic or terminal illness, their parents did not speak English or it was known that the family were moving away from the area in the next 12 months. To ensure that the diagnoses were still active, children were only invited if they had one or more problem-related consultations in the preceding year. The general practitioner's letter of

invitation included two information sheets, one for the parents and another for the child or adolescent. A post-age-paid envelope was provided for response. Those parents who expressed interest in the study were contacted by the study-trained general practice nurse to confirm eligibility. Prior to the baseline assessment appointment, parents and children completed a questionnaire booklet about rhinitis and asthma symptoms [8] and condition-related QoL [9]. Consent and assent to participate in the trial were obtained by the practice nurse. The parent or guardian of each child signed a consent form and, if the child was aged between 13 and 16 years, their agreement to participate was confirmed by completion of a form of assent. Recruitment was conducted between November 2010 and October 2011.

Baseline information

Data were collected on demographics (age, gender, ethnicity), clinical data (height, weight and diagnoses), use of primary and secondary health services for asthma- and rhinitis-related problems in preceding 12 months and the number of days in the last month on which the child was unable to go to school or undertake usual activities because of ill health. Spirometry (Forced Expiratory Value in one second (FEV₁), peak expiratory flow and Forced Vital Capacity (FVC)) was repeated three times using a standardized method, and the best of three values were utilized in analysis [10].

Randomisation

Children were randomized to formal allergy assessment or usual care (empirical treatment for 12 months and the opportunity for a structured allergy assessment on trial completion). Randomization was blocked and stratified by general practice.

Intervention

The intervention was a structured allergy history, skin prick testing, test interpretation and relevant advice on allergy avoidance. The general practice nurses all received 3 h training in structured allergy assessment (history, skin prick testing and its interpretation) and were provided with written instructions on skin prick testing and access to senior clinicians (AJF or SM) if needed.

A structured allergy history was taken and documented using a proforma. The questions reviewed information on self-reported allergies, the duration and severity of asthma and/or rhinitis, exacerbating factors, personal history of atopy, history of atopy in first degree relatives (parents and siblings), exacerbating

circumstances (seasonality, time of day, indoors vs outdoors), exposure to pets, dust and mould.

Skin prick testing (SPT) to seven common aeroallergens was performed using standardized allergy extracts (house dust mite (*Dermatophagoides pteronyssinus*), tree pollen, mixed grass pollens, cat dander, dog dander), and two moulds (*Aspergillus* and *Alternaria alternata*). Positive (histamine) and negative (saline) controls were used. SPTs were performed on the volar surface of the forearm with 1-mm prick lancets. Wheal diameters were recorded after 15 min, as the arithmetic mean of the maximum diameter and perpendicular diameter. A mean wheal diameter greater than or equal to 3 mm was considered a positive result (99% specificity) [11].

Advice on allergen avoidance was provided following interpretation of allergy history and SPT results. A positive history and positive skin result were needed for a diagnosis of allergy. Relevant allergen avoidance advice was given verbally and reinforced with a leaflet. The leaflets were the same as those used in the local hospital allergy clinic and were specific to tree and grass pollens, to pets (including cats and dogs), to house dust mite or to mould.

Outcome measures

Primary outcomes were asthma and rhinitis symptom scores and disease-specific health-related QoL. Secondary outcomes were healthcare utilization, days unable to pursue usual activities and parental- and self-rated improvement.

Rhinoconjunctivitis and asthma symptom score. This score assesses symptoms of asthma and rhinoconjunctivitis [8]. The symptoms of these two interdependent syndromes are scored in two domains: 11 items form the *rhinitis scale*, which asks about eye (3), nose (4) and sinus symptoms (4) and nine items form the *asthma scale*, which assesses day and night experiences of cough (2), wheeze (2), sputum production (2) and shortness of breath/chest tightness (3). All symptoms are scored on a five-point scale from none (0) to severe (4). Items are weighted equally and are summed to create a score for each domain and a total symptom score, with higher scores indicating more symptoms.

Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ). This self-administered health-related QoL questionnaire encompasses effects of allergic disease on a child's or teenager's eyes, ears, nose, lungs, skin, emotions and everyday activities [9]. The questionnaire has 26 items spread over three domains: practical problems (8), symptoms (15) and emotional problems (3). Patients score their experiences of their previous week on a seven-point scale (0 = not troubled to 6 = extremely

troubled). Individual items are weighted equally, and the questionnaire is analysed directly from the scores recorded. Results were expressed as the mean score per domain. Overall QoL is estimated from the mean score of all items, with higher scores indicating greater impairment of QoL.

Frequency and duration of follow-up. Control and intervention participants were followed up at monthly intervals for 1 year from their baseline visit with a questionnaire that asked about the number of days that they had been unable to go to school or pursue normal activities. After 12 months, all participants were invited to a follow-up appointment with a research nurse who was blinded to the study arm they were allocated to. At this visit, the participants again completed symptom scores and the allergic disease QoL questionnaire and spirometry. Once the final assessment was complete, participants in the control arm were able to undergo formal allergy assessment if they wished.

Sample size calculation. The sample size calculation, based on QoL measurements, estimated a sample size of 105 participants in each arm would be sufficient to detect a clinically significant reduction of 0.5 (assuming a standard deviation of 1.1) at the 5% level of significance with 90% power. This sample size was estimated to be sufficient to detect a 15 percent point difference in rates for the binary response variable assessing patients' subjective assessment of improvement (improved/not improved). Allowing for 33% loss to follow-up required 140 recruits in each arm.

Data analysis

Data was manually entered into SPSS version 22 (IBM Corp., Armonk, NY, USA), cleaned and all variables assessed for outliers. A frequency check was performed for the response variables, and any discrepancies were checked against the case records. Twenty per cent of the data was double-entered: the predefined minimum accuracy rate was 98%, and as this was achieved no further double-data entry was undertaken. Baseline demographic characteristics were compared between the intervention and control groups using *t*-tests for continuous data and chi-square for binary data. Where the data did not satisfy the parametric assumptions, nonparametric tests were applied. The difference in pre-test and post-test measures for the Likert scale data, QoL instrument and symptom scores were analysed using Mann-Whitney *U*-test. The comparison between the intervention and control groups was analysed using analysis of covariance (ANCOVA) controlling for baseline scores on each outcome. The significance level for all tests was $P < 0.05$.

Ethical approval for the study was obtained from the Scotland A Research Ethics Committee (ref: 02/10/013). The protocol for this study was published on the UK CRN website (trial number 10034).

Results

Three hundred and thirty-five participants were recruited from 19 general practices in Sussex and randomized, 167 patients to the control arm and 168 to the intervention arm (Fig. 1). The demographic characteristics of the two groups showed no significant differences in age, gender, ethnicity, height or weight. Intervention and control participants were also comparable with respect to clinical characteristics and use of

health services for asthma and or rhinitis in the preceding 12 months (Table 1). The majority of participants had both asthma and rhinitis (54%), 22% rhinitis alone and 24% asthma alone.

Three hundred and thirteen participants (93%) completed the trial. Completers and non-completers did not differ on any demographic or clinical characteristics. Compared to controls, and controlling for baseline scores, intervention participants reported a significant reduction in rhinitis-specific symptoms (MD -2.19 , 95% CI -3.88 , -0.50) and overall symptoms (MD -3.14 , 95% CI -6.01 , -0.81), but not asthma-specific symptoms (Table 2). Intervention participants also reported significant reductions in impaired QoL both overall (MD -0.50 , 95% CI -0.68 , -0.32), and in the

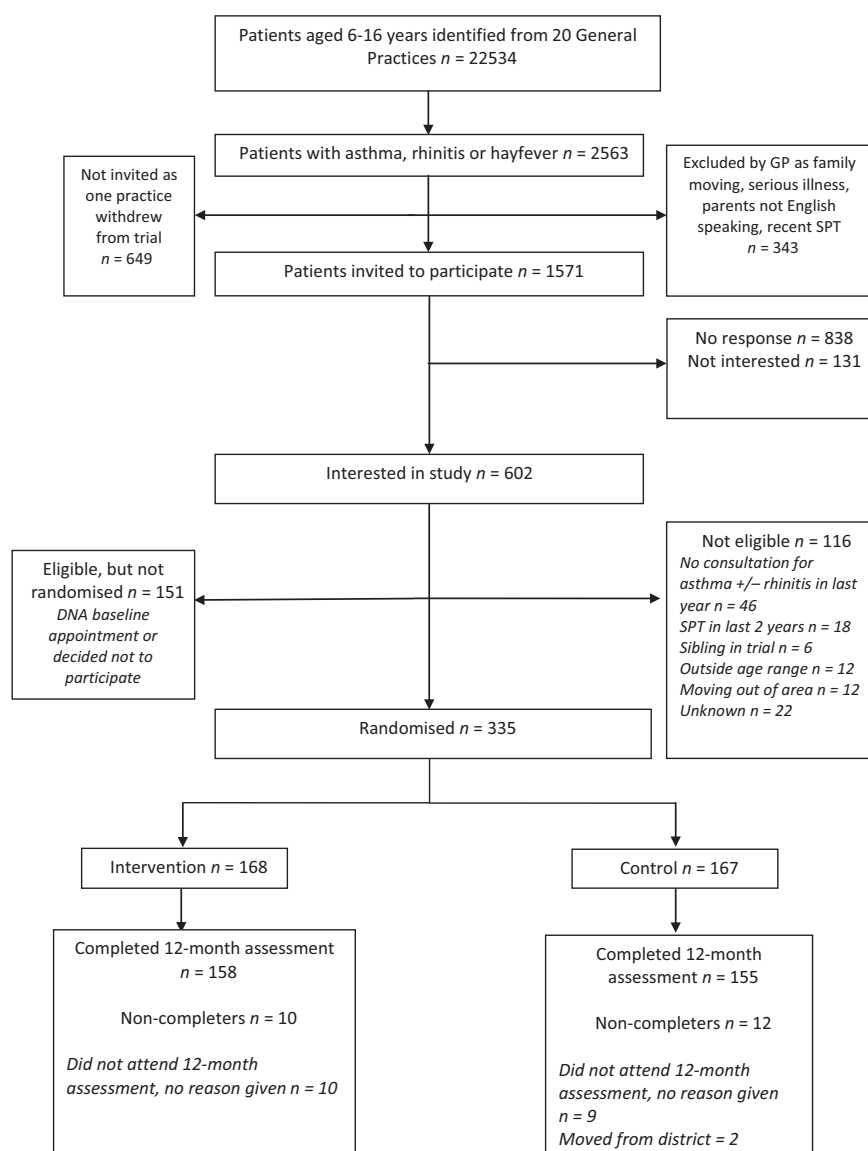


Fig. 1. Consort diagram.

Table 1. Baseline demographic and clinical characteristics for intervention and control participants

	Control N = 167	Intervention N = 168	P value (t-test/chi-square)	Total N = 335
Demographic characteristics				
Mean age in years (SD, range)	11.56 (2.78, 6–16)	11.26 (2.72, 6–16)	0.27	11.43 (2.75)
Gender	56.3	57.7	0.88	57.0
% male				
Ethnicity	91.0	88.7	0.37	89.9
% white British				
Clinical characteristics				
Mean height in cm (SD)	151.20 (16.48)	149.98 (15.97)	0.49	150.59 (16.21)
	45.12 (15.36)	44.97 (16.60)	0.93	45.05 (15.97)
Mean weight in kg (SD)				
% Rhinitis only (seasonal +/- or perennial rhinitis)	21.6	22.2		21.9
% Asthma & Rhinitis	52.1	55.7		53.9
% attending hospital (inpatient, outpatient or A&E visit) for asthma/rhinitis-related problem in previous 12 months	7.2	6.0	0.83	6.6
% attending GP or practice nurse in previous 12 months	99.4	100.0	0.49*	99.7
Mean (SD) number of days in last month when unable to pursue usual activities due to asthma/rhinitis	0.62 (1.75)	0.72 (2.51)	0.67	0.67 (2.16)
Lung function				
FEV1% predicted	88.54 (14.65)	87.15 (15.83)	0.41	
FVC % predicted	88.21 (14.64)	86.92 (16.55)	0.45	

*Fisher's exact test.

Table 2. Symptom scores assessed by Wasserfallen Symptom Score Questionnaire (SSQ) and disease-specific quality of life questionnaire (PADQLQ)

		Intervention mean (SD)	Control mean (SD)	Mean difference [95% CI]	P (ANCOVA)
Symptom scores					
Rhinitis	Baseline	11.69 (8.17)	11.77 (8.08)	– 2.19 [– 3.88, – 0.50]	0.005
	Post-intervention	8.57 (7.18)	10.76 (8.04)		
Asthma	Baseline	5.44 (6.06)	6.19 (5.80)	– 1.24 [– 2.51, 0.03]	0.115
	Post-intervention	4.25 (5.41)	5.49 (6.03)		
Overall score	Baseline	17.13 (12.18)	17.97 (11.48)	– 3.41 [– 6.01, – 0.81]	0.010
	Post-intervention	12.83 (11.25)	16.24 (12.22)		
Quality of Life scores					
Practical problems	Baseline	1.11 (1.00)	1.30 (0.96)	– 0.34 [– 0.54, – 0.14]	0.004
	Post-intervention	0.74 (0.78)	1.08 (0.99)		
Symptoms	Baseline	1.31 (1.05)	1.49 (0.94)	– 0.35 [– 0.56, – 0.14]	0.004
	Post-intervention	1.00 (0.87)	1.35 (1.03)		
Emotional problems	Baseline	0.85 (1.13)	0.97 (1.10)	– 0.26 [– 0.47, – 0.05]	0.037
	Post-intervention	0.59 (0.86)	0.85 (1.01)		
Overall score	Baseline	1.20 (0.97)	1.37 (0.89)	– 0.50 [– 0.68, – 0.32]	0.002
	Post-intervention	0.87 (0.77)	1.37 (0.89)		

Results are presented for each domain and overall, pre- and post-intervention ($n = 313$)

separate domains of practical problems, symptoms and emotional problems (Table 2). The QoL results have clinical importance, as well as statistical significance, as the minimal clinical important difference for the PADQLQ is 0.3.

On completion, there was no significant difference between intervention and control participants and their

parents reporting that either asthma or rhinitis/hayfever had improved, worsened or stayed the same (Table 3). Similarly, there were no significant differences between intervention and controls in respect to numbers of days unable to pursue usual activities in the last month (MD – 0.08, 95% CI – 0.16, 0.00), General Practitioner (GP) consultations (OR 0.73, 95% CI 0.46, 1.14) or hospital

Table 3. Self- and parental assessment retrospective, subjective assessment of asthma, rhinitis or hayfever during the 12 months of the trial

		Intervention (<i>n</i> = 158)	Control (<i>n</i> = 155)	<i>P</i> (Kendall's Tau)
Asthma	Worsened	34	32	0.492
	Same	6	13	
	Improved	118	109	
	N/A	0	1	
Rhinitis/hayfever	Worsened	38	45	0.727
	Same	19	13	
	Improved	100	97	
	N/A	1	0	
Asthma	Worsened	31	27	0.466
	Same	2	13	
	Improved	110	99	
	N/A	15	16	
Rhinitis/hayfever	Worsened	33	36	0.393
	Same	24	23	
	Improved	84	76	
	N/A	17	20	

attendances in the previous 12 months (OR 0.83, 95% CI 0.37, 1.86). The majority (86%) of intervention participants stated they would recommend skin prick testing to a friend.

At baseline, 71% participants suspected an allergic trigger for their symptoms. The most common suspected trigger was grass pollen (46%), followed by HDM (37%), cat (30%), tree pollen (23%), dog (18%) or mould (7%). After formal allergy assessment, there were 52 children (31%) in whom new triggers were identified, that is a trigger identified on structured history and confirmed by SPT that had not been suspected by the parent or child when self-reporting suspected allergies (Fig. 2). Thirty-six participants had one new trigger identified, 15 had two new triggers and one had three. Conversely, suspected triggers were not confirmed by skin prick testing in 69 patients (41%). Overall, 127 participants (76%) had one or more aeroallergen trigger.

Discussion

Statement of principal findings

In this pragmatic, single-blind, randomized controlled trial of an allergy intervention (structured allergy history & skin prick testing & tailored advice on allergy avoidance) vs. usual care in children with a working diagnosis of asthma and/or rhinoconjunctivitis at 12 months, participants receiving the allergy intervention reported a reduction in symptoms (MD − 3.14, 95% CI − 6.01, − 0.81) and an improvement in QoL (MD 0.50, 95% CI 0.32, 0.68). When symptoms were

analysed separately for rhinitis- and asthma-specific symptoms, only the observed reduction in rhinitis symptoms was statistically significant. There were no significant differences in the secondary outcome measures of health service utilization, days unable to pursue normal activities or perceived benefit.

Strengths and weaknesses

The study was rigorously designed and participants were followed up for 1 year to reduce the impact of seasonal variation of symptoms. We recognize that randomizing by patient rather than by practice may introduce contamination and reduce the differences observed between groups. However, there is very little evidence that contamination actually occurs in trials when practitioners use a structured approach to health-care delivery. Trials of the management of acute minor illness conducted in primary care [12] and the Family Heart Study [13] found no evidence of intrapractice contamination. The recruitment of only one child from each household also reduced the risk of controls being influenced by the intervention. Nonetheless, we acknowledge that those randomized to routine care may have become more attentive to allergen avoidance after recruitment.

The impact of the intervention may have been reduced as we did not review and confirm the diagnosis of asthma and/or rhinitis before intervention. It is recognized that environmental tobacco smoke can impact on symptom provocation and treatment responses [14], but as we did not ask about this exposure at the baseline assessment, we cannot comment on the equivalence of our two groups in this respect. Allergen avoidance behaviour was not assessed, so it is not known to what extent the intervention impacted on this behaviour. However, ultimately, it is the impact of an intervention on patient outcomes (symptom control and quality of life), rather than processes (such as allergen avoidance), that are of importance. We recognize that a negative skin prick test, ruling out an allergic aetiology, may be beneficial but does not require allergen avoidance.

In this study, we used an existing nurse member of the primary care team to provide the intervention rather than an external peripatetic nurse. We envisaged that this is how such an intervention could be readily incorporated in practice if the intervention was worthwhile, given the universal involvement of Practice Nurses (PNs) in the management of chronic disease, including asthma. Our intervention model also fits with the diversification of providers that has been promoted as an approach towards providing an accessible and sustainable allergy service and allowing specialists to focus their expertise on patients with complex problems [15].

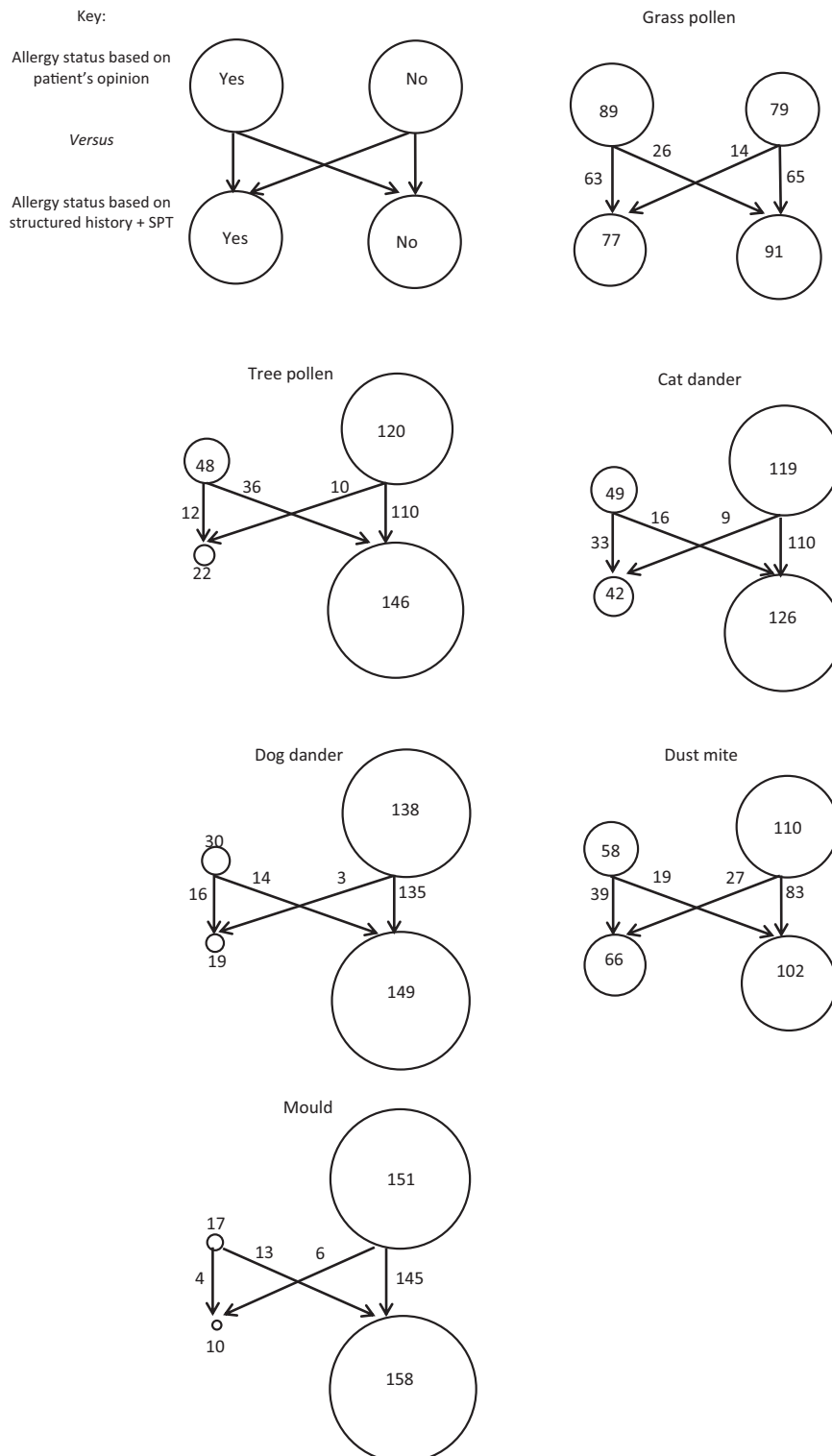


Fig. 2. Shifts in participants understanding of their allergy status ($n = 168$).

The intervention was focussed on formal allergy assessment, leading to tailored advice on removal or avoidance of allergic triggers. It did not include other characteristics of good practice such as age-appropriate

written personal management plan, information on charities, websites and patient support groups and/or patient/parent education, all of which are incorporated into the Royal College of Paediatrics and Child Health

care pathways [16]. A case could also be made for professional education in parallel, as it is well recognized that allergy training is lacking in both undergraduate and postgraduate medical curricula in the UK [17, 18].

Reasons for a negative outcome in asthma symptoms must include the possibility that 12 months is not sufficient to achieve the full impact of avoidance measures (such as removing a pet from the household). Whilst extreme forms of allergen avoidance have been effective in other studies, for example, admission to hospital for prolonged periods or relocation to altitude, where house dust mites cannot grow due to the low absolute level of humidity [19, 20], there is very little evidence of any impact on asthma symptoms from the type of allergen avoidance measures that are practical in suburban homes at sea level [20, 21]. The recruitment of this broad spectrum of patients was appropriate as it was a pragmatic trial designed to assess the impact of the intervention in routine practice in the community [22]. The invitations to participate in the trial were based on the diagnostic codes without any additional screening for symptoms severity. It is possible that the impact of the intervention might have been more pronounced if it had focused on children with more severe disease or only children with rhinitis. Further trials and economic evaluations are needed to ascertain whether the benefits of a structured allergy intervention could be of greater benefit if used in a more targeted manner in primary care. In conclusion, this well-constructed, single-blind, pragmatic study supports the introduction of a general

practice-based allergy assessments for children with asthma and/or rhinitis to reduce the symptoms of rhinitis and to improve health-related QoL.

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Authors' contribution

The project devised by HS, AJF and SM. Patient recruitment, data collection and data analysis were co-ordinated by CJ and DH and analysed by SG and CJ. All authors contributed to data interpretation and writing of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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