



REVIEW

What is the optimal management option for occupational asthma?

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on behalf of the ERS Task Force on the Management of Work-related Asthma[§]

ABSTRACT: The optimal management of occupational asthma remains uncertain in clinical practice. The aim of this review was to analyse the published information pertaining to the management of occupational asthma in order to produce evidence-based statements and recommendations.

A systematic literature search was conducted up to March 2010 to identify original studies addressing the following different treatment options: 1) persistence of exposure; 2) pharmacological treatment; 3) complete avoidance of exposure; 4) reduction of exposure; and 5) the use of personal protective equipment.

After full text evaluation of 83 potentially relevant articles, 52 studies were retained for analysis.

The conclusions from this systematic review are limited by the methodological weaknesses of most published studies. Critical analysis of available evidence indicates that: 1) persistent exposure to the causal agent is more likely to result in asthma worsening than complete avoidance; 2) there is insufficient evidence to determine whether pharmacological treatment can alter the course of asthma in subjects who remain exposed; 3) avoidance of exposure leads to recovery of asthma in less than one-third of affected workers; 4) reduction of exposure seems to be less beneficial than complete avoidance of exposure; and 5) personal respiratory equipment does not provide complete protection.

KEYWORDS: Asthma, occupational diseases, outcome assessment, prognosis, respiratory protective devices

For many years, the recommended therapeutic approach for immunologically mediated occupational asthma (*i.e.* occupational asthma with a latency period) has been the cessation of exposure to the sensitising agent through either the movement of the worker to an unexposed job or the elimination of the sensitising agent from the workplace [1–3]. However, there has been a growing recognition that complete avoidance of exposure is often associated with not only adverse social and financial consequences for affected workers, but also with a substantial economic impact for society as a whole [4–6]. This is likely to account for the consistent finding that about one-third of workers with occupational asthma remain exposed to the causal agent [4]. In addition, the efficacy of complete exposure avoidance on asthma outcome seems quite limited [7, 8]. However, continued but reduced exposure to the causal agent may lead to an improvement in asthma and has been considered as an alternative

in order to minimise the detrimental consequences on employment, income and quality of life [1–2, 9]. The outcome of occupational asthma after treatment interventions has been examined in systematic reviews of the literature published up to 2004 [1, 7, 8], but there remains uncertainty as to whether exposure cessation is the optimal approach to manage occupational asthma. The purpose of this systematic review was to synthesise and critically analyse the scientific literature pertaining to the management options of occupational asthma in order to issue statements and recommendations aimed at the medical community, workers, employers and policy-makers.

METHODS

The statements and recommendations formulated in this article are based on a systematic evaluation of the international literature according to the methods extensively described by BAUR *et al.* [10] and in [11] (table 1).

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TABLE 1 Ancillary questions pertaining to the management of occupational asthma

What are the consequences of persistent exposure to the causal agent?
Is it possible to improve symptoms and lung function by pharmacological treatment in affected workers with persistent exposure?
What is the effectiveness of complete avoidance of exposure?
What is the effectiveness of reducing exposure through engineering control or relocation of affected workers?
What is the effectiveness of reducing exposure through personal protective equipment?

Modified from [10], with permission from the publisher.

Search results, as well as a list of considered articles, were included in evidence tables and presented in the online supplementary material of [10].

Considering the substantial heterogeneity of reported clinical and functional outcomes in follow-up studies of occupational asthma [7, 8], any quantitative analysis of the effects of interventions was deliberately restricted to simple outcomes, "symptom recovery" and "nonspecific bronchial hyperresponsiveness (NSBHR) recovery", which were evaluated according to the criteria used in each study, as proposed by RACHIOTIS *et al.* [8]. The pooled prevalence estimates of these outcomes were computed using a random-effect model through MetaAnalyst Beta 3.13 software [12].

RESULTS

462 titles were identified in the systematic literature search. After full evaluation, we selected 50 that were relevant for the questions.

The results of the bibliographic search for each of the pre-defined ancillary questions as well as the reasons for excluding some studies, and the characteristics, main findings and quality assessment of the selected publications are available in the online supplementary material of [10].

What are the consequences of persistent exposure to the causal agent?

The bibliographic search identified nine studies that compared the effects of persistence of exposure to sensitising agents with those resulting from complete avoidance in the same populations of workers affected with occupational asthma (table 2) [13–21]. Asthma symptoms persisted in almost all (93.0%, 95% CI 86.3–96.6%) patients who remained exposed, while 33.7% (95% CI 23.6–45.6%) of those who avoided exposure recovered from their asthma. The two studies that provided information on worsening of asthma reported that the condition deteriorated in 10 (59%) out of 17 subjects who remained exposed, but in none of those who avoided exposure [18, 20]. The few studies that compared the outcome in terms of functional parameters reported that persistence of exposure was associated with a decrease in forced expiratory volume in 1 s (FEV₁) [13, 16, 20] and an increase in NSBHR [13, 20] compared with cessation of exposure; although the differences were significant in only one study [20]. Two retrospective cohort studies specifically investigated changes in FEV₁ according to cessation or persistence of exposure to the sensitising agent. LIN *et al.* [22] found that patients with occupational asthma caused by red cedar dust who continued to be exposed had a more rapid decline in FEV₁ (-26 mL·yr⁻¹) than a control population of cedar sawmill workers. ANEES *et al.* [23] evaluated the changes in FEV₁ before and after removal from exposure in 44 out of 156 consecutive subjects with occupational asthma (87% due to low-molecular-weight agents) who underwent measurements within 1 yr before and after removal and could serve as their own control. The mean ± SE rate of decline in FEV₁ was significantly greater before (-119.8 ± 26.3 mL·yr⁻¹) than after cessation of exposure (+9.8 ± 31 mL·yr⁻¹), with a mean difference of -129.6 mL·yr⁻¹ (95% CI -217– -42 mL·yr⁻¹). Only one prospective study compared asthma severity, disease-related costs and work-derived income after cessation or persistence of exposure to various agents causing occupational asthma. Noticeably, the investigators did not clearly distinguish the persistence of exposure to the same conditions at work from a reduction of exposure to the causal

TABLE 2 Comparison between persistence and avoidance of causal exposure

First author [ref.]	Agent	Persistence of exposure		Cessation of exposure	
		Symptom recovery	NSBHR recovery	Symptom recovery	NSBHR recovery
CHAN-YEUNG [13]	Red cedar	0/47	NA	55/136	NA
ROSENBERG [14]	Isocyanates	0/4	0/4	10/20	0/14
MOSCATO [15]	Various	0/4	NA	9/18	NA
GANNON [16]	Various	2/34	NA	3/78	NA
TARLO [17]	Isocyanates	0/10 [#]	NA	23/104 [#]	NA
ORRIOLS [18]	Isocyanates	0/4	0/4	10/17	6/17
MERGET [19]	Platinum salts	0/9	NA	10/19	NA
VALENTINO [20]	Isocyanates	0/13	NA	9/37	NA
PADOAN [21]	Isocyanates	2/13	NA	23/74	NA
Pooled estimates[†]		4/138, 7.0% (3.4–13.7%)	0/8	152/503, 33.7% (23.6–45.6%)	6/31

Individual study data are presented as n/N. Pooled estimates are presented as n/N with or without % (95% CI). NA: not available; NSBHR: nonspecific bronchial hyperresponsiveness. [#]: "Global assessment of asthma"; [†]: pooled estimates based on a random-effect model.

TABLE 3 Avoidance of exposure: characteristics and results of studies published between 2004 and 2010

First author [ref.]	Country	Agent	Study design	Duration of FU months	Symptom recovery n/N	Recovery of NSBHR n/N
BRANT [34]	UK	Enzymes	Workforce-based survey of 35 out of 45 cases	37 (4–39)	5/35	NA
KLUSACKOVA [35]	Czech Republic	Various	Longitudinal FU of 37 cases (selection not stated) Clinic-based study	78 (12–216)	5/37	1/19
LABRECQUE [36]	Canada	Isocyanates	Retrospective cohort study of compensated subjects (89 randomly selected subjects)	~24 for all subjects	4/79 [‡]	10/79
PARK [38]	Korea	Reactive dyes	Longitudinal FU of 26 cases (selection not stated) Clinic-based study	Second visit: 104 ± 22 (n=19)	NA	11/16
PARK [37]	Korea	Reactive dyes	Longitudinal FU of 11 cases (selection not stated) Clinic-based study	164 ± 28	0/11	3/11
PISATI [39]	Italy	Isocyanates	Longitudinal FU of 53 cases (selection of 25 patients rechallenged with TDI) Clinic-based study	58 ± 7 (46–73)	10/25	12/25
YACOB [40]	Canada	Various	Retrospective cohort study of 40 compensated subjects	44 ± 34	6/40	10/40
MUNOZ [41]	Spain	Persulfate salts	Prospective longitudinal FU of 10 out of 11 cases Clinic-based study	63 ± 19 (39–101)	2/7	5/7
Pooled estimates[#]					32/234, 15.5% [‡] (8.3–27.1%)	52/197, 32.8% (16.8–54.3%)

Data for individual studies are presented as mean (range), mean ± SD or mean ± SD (range), unless otherwise stated. Pooled estimates are presented as n/N with % (95% CI). FU: follow-up; NSBHR: nonspecific bronchial hyperresponsiveness; NA: not available; TDI: toluene diisocyanate. [#]: pooled estimates based on a random-effect model; [‡]: the rate of symptom recovery was 19.2% (28 out of 155 subjects; 95% CI 11.2–30.9%) after exclusion of the study by LABRECQUE *et al.* [36], which used more stringent criteria of "clinical remission" defined by the absence of symptoms, NSBHR and medication.

agent, since 43% of the subjects with persistent exposure actually had intermittent or lower exposure [24]. When compared with persistence of exposure to causal agents, complete avoidance resulted in a significant decrease in asthma severity and health-care expenses, but also in work-derived income [24].

Is it possible to improve symptoms and lung function using pharmacological treatments in affected workers with persistent exposure?

The effectiveness of anti-asthma medications in patients with persistent exposure has been evaluated in one uncontrolled intervention study [27] and one retrospective cohort study [23]. MARABINI *et al.* [25] reported that there was no significant deterioration in any of the asthma outcomes compared with baseline values in 10 subjects with occupational asthma due to various agents who were treated with inhaled corticosteroids and long-acting β_2 -agonists over a 3-yr period. In contrast, ANEES *et al.* [23] reported that the decline in FEV₁ before removal from exposure to agents causing occupational asthma was not affected by the use of inhaled corticosteroids. Several case reports and uncontrolled case series have reported a beneficial effect of specific immunotherapy with some high-molecular-weight allergens (*i.e.* sea squirt allergens, natural rubber latex and laboratory animals) [26], but only a few well-conducted studies have been published. ARMENTIA and co-workers [27, 28] conducted a placebo-controlled, double-blind trial of subcutaneous immunotherapy with a flour extract in 30 workers with occupational asthma. The treated patients showed a significant decrease in symptoms, NSBHR to methacholine, skin sensitivity and specific immunoglobulin (Ig)E to wheat flour without any adverse

reactions. Two randomised, double-blind, placebo-controlled trials evaluated the effectiveness of specific subcutaneous immunotherapy in healthcare workers with latex allergy [29, 30]. These studies documented an improvement in rhinoconjunctivitis symptoms and a reduction in skin reactivity to latex, but there was no clear improvement in asthma outcomes. In addition, latex immunotherapy resulted in a high rate of systemic adverse reactions. There has been some suggestion that sublingual immunotherapy may be effective in latex allergy [31].

Recent case reports have provided some suggestion that treatment with omalizumab could substantially improve asthma control in subjects with flour-induced occupational asthma who remain exposed to the causal work environment [32, 33], although further investigations are required.

What is the effectiveness of complete avoidance of exposure?

Two systematic reviews examined the outcome of workers with occupational asthma after cessation of exposure to the causal agent in studies published up to 2004 [7, 8]. The bibliographic search identified eight follow-up studies of workers removed from exposure that met the inclusion criteria used by RACHIOTIS *et al.* [8] and were published after March 2004 (table 3) [34–41]. These studies yielded estimated rates of symptomatic recovery (15.5%, 95% CI 8.3–27.1%) and persistence of NSBHR (67.2%, 95% CI 45.7–83.2%) that were in line with those reported in the systematic review by RACHIOTIS *et al.* [8]. Two retrospective cohort studies explored the long-term changes in functional indices after cessation of exposure: MALO *et al.* [42] showed that the improvement in

TABLE 4 Assessment of respiratory protective equipment (RPE)

First author [ref.]	Design	Agent	Type of RPE	Effects of RPE
MULLER-WENING [54]	Laboratory challenge Non-RCT study n=26 Exposure: 1 h, not quantified	Organic farm allergens	RPE with P2 filter: "Dustmaster" (n=21), "Airstream helmet" (n=4), "Airlite" (n=1)	Suppression of symptoms in 11 out of 26, reduction in 15 out of 26, but 4 required inhaled bronchodilator Reduction of the increase in airway resistance
LAOPRASERT [55]	Laboratory challenge RCT study with placebo n=9 Exposure: 1 h, quantified	Latex	Laminar flow HEPA-filtered helmet	Reduction of symptom score Reduction of the decline in FEV ₁
SLOVAK [56]	Workplace exposure Non-controlled study n=8 Exposure: 6 weeks, not-quantified	Laboratory animals	Powered helmet respirator with AS-23-3 filter	Worsening of symptoms in 2 out of 8 (score not available) Peak flow variation at work in 2 out of 8
KONGERUD [57]	Workplace exposure RCT study n=19 workers with nonsevere disease Exposure: 2 weeks, not quantified	Aluminium pot room	AH60 Airstream helmet	Reduction of symptom score in 10 out of 17 subjects (nonsignificant) Improvement in the mean peak flow values
TAIVAINEN [58]	Workplace exposure Non-RCT study n=24 Exposure: 10 months, not quantified	Farming	Powered dust respirator helmet with P2 filter	No effect on respiratory symptoms with the exception of sputum, rhinitis symptoms, corticosteroid treatment, and number of sick leaves Increase in morning peak flow and reduced daily peak flow variability

RCT: randomised controlled trial; HEPA: high-efficiency particulate arrest; FEV₁: forced expiratory volume in 1 s.

NSBHR can continue for years after cessation of exposure, but the rate of improvement is steeper during the first 2.5 yrs. ANEES *et al.* [23] found that the decline in FEV₁ after removal from exposure is similar to that observed in healthy adults [23]. Recent studies using induced sputum analysis have documented that failure to improve NSBHR after cessation of exposure was associated with persistent airway inflammation [43, 44], but inflammation [40] and airway remodelling [45] may be present in subjects who have recovered from symptoms and NSBHR.

Two randomised controlled trials assessed the effects of systematic treatment with inhaled corticosteroids in addition to cessation of exposure [46, 47]. MAESTRELLI *et al.* [46]. found that treatment with beclomethasone dipropionate (1 mg twice daily for 5 months) was associated with reduced NSBHR. MALO *et al.* [47]. showed that beclomethasone dipropionate (1 mg daily) was associated with a significant, though minimal, improvement in symptoms, peak expiratory flow and quality of life.

What is the effectiveness of reducing exposure through engineering control or relocation of affected workers?

The bibliographic search identified 10 studies that compared the target asthma outcomes (*i.e.* improvement, recovery, and worsening of asthma symptoms and NSBHR) in subjects who reduced exposure to the causal agent with those who completely avoided exposure [13–15, 19, 41, 48–52]. The detailed methodology and results of the meta-analysis of these studies have been published elsewhere [53]. The studies evaluated 186

patients who had reduced exposure and 292 who had avoided exposure to the causal agent. The most commonly identified causal agents, in seven out of 10 publications, were low-molecular-weight agents, including isocyanates [14, 49, 50], colophony [48], red cedar dust [13], platinum salts [19] and persulfate salts [41]. Two studies involved a single high-molecular-weight agent, natural rubber latex [51, 52], and one study evaluated patients with occupational asthma caused by various agents, of which 90% were low molecular weight agents [15]. The changes in asthma symptoms and NSBHR after reduction or cessation of exposure were described in nine and five studies, respectively. The meta-analysis of pooled data showed that a reduction of exposure was associated with a lower likelihood of improvement (OR 0.16, 95% CI 0.03–0.91) and recovery (OR 0.30, 95% CI 0.11–0.84) of asthma symptoms and a higher risk of worsening of the symptoms (OR 10.23, 95% CI 2.97–35.28) and NSBHR (OR 5.65, 95% CI 1.11–28.82) compared with complete avoidance of exposure.

Two publications reported on the socioeconomic outcomes of workers with occupational asthma caused by colophony [48] and natural rubber latex gloves [51].

These studies revealed that the rate of unemployment was significantly higher among those who avoided exposure compared with those who reduced exposure. Among workers with latex-induced occupational asthma [51], a "major" loss of income was more frequently reported by subjects who ceased exposure to latex than by those who remained exposed to reduced levels of latex.

What is the effectiveness of reducing exposure through personal protective equipment?

We identified five studies that assessed the short-term effectiveness of various types of respiratory protective equipment (RPE) in patients with occupational asthma using inhalation challenges in the laboratory with organic farm allergens [54] and latex [55] or through workplace exposure to laboratory animals [56] or aluminium pot room atmosphere [57], and farming activities [58]. The characteristics and findings of these studies are summarised in table 4. Overall, these studies showed that the use of RPE led to a significant reduction in respiratory symptoms and changes in functional parameters during short-term exposures, but failed to provide complete protection. Notably, one study documented that there was no protective effect in workers with more severe asthma or in those who used RPE irregularly [58].

One retrospective study of workers with occupational asthma induced by red cedar dust who remained exposed to the causal agent provided indirect evidence supporting a beneficial long-term effect of some types of RPE [59]. In this study, the proportion of subjects who used a twin-cartridge respirator was significantly higher among the group with stable asthma than among the group with a deterioration of asthma.

DISCUSSION

Determining the most effective treatment for occupational asthma would necessitate having precise information on the effect of different management options on clinical, physiological, and socioeconomic outcomes. However, the evidence that can be derived from current data is largely limited by methodological weaknesses. Most published data are observational, nonrandomised follow-up studies. The rationale for the intervention decision (*i.e.* persistence, reduction, or cessation of exposure) is most often unknown, leading to a high potential for selection biases. In addition, asthma outcomes are measured and expressed in a highly heterogeneous manner. Finally, almost none of the studies relied on quantitative exposure assessments of environmental interventions, such as reduction of exposure. Nevertheless, the information retrieved from the systematic analysis of available data has led us to issue the following consensus statements; level of evidence was graded using the modified 1995 Royal College of General Practitioners (RCGP) three-star system [60] (see online supplementary material of [10]).

1. Persistence of exposure to the agent causing occupational asthma is more likely to be associated with the persistence of asthma and NSBHR, and an accelerated decline in FEV₁, compared with complete avoidance of exposure (** moderate evidence)

The systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) [7] concluded that workers with occupational asthma who remain exposed to the causal agent continue to experience stable or worsened asthma symptoms and tend to show a decrease in FEV₁ over time, as well as an increase in NSBHR. The consequences of persistent exposure were not specifically examined in the clinical practice guidelines issued by the British Occupational Health Research Foundation (BOHRF) [1] and the American College of Chest Physicians (ACCP) [2].

2. There is currently insufficient evidence that treatment with inhaled corticosteroids and long-acting β_2 -agonists is able to prevent the long-term deterioration of asthma in subjects who remain exposed to the agent causing occupational asthma (* limited evidence).

3. There is a lack of evidence-based information on the effectiveness and adverse effects of specific immunotherapy with high molecular weight occupational allergens (** moderate evidence)

The effectiveness of anti-asthma medications in patients who remain exposed to the causal agent was not specifically addressed in previously published guidelines [1, 2] or in the AHRQ systematic review [7]. Despite the dearth of data on the effectiveness of immunotherapy in occupational asthma, the ACCP guidelines concluded that immunotherapy may be an effective management option in individuals with sensitiser-induced occupational asthma due to selected high-molecular-weight agents when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional or other reasons [2]. As outlined by the ACCP guidelines, further investigations are required to evaluate the effectiveness of treatment with omalizumab in subjects who choose to continue exposure [2]. These therapeutic approaches were not addressed in the BOHRF guidelines [1].

4. Occupational asthma is associated with a substantial long-term morbidity, since complete avoidance of exposure to the causal agent results in symptom recovery and resolution of NSBHR in less than one-third of affected workers (** strong evidence)

5. There is insufficient evidence to support systematic treatment with high-dose inhaled corticosteroids after cessation of exposure (** moderate evidence)

The AHRQ systematic review [7] stated that most of the available studies documented an improvement in asthma symptoms and NSBHR, and an increase in mean FEV₁, although only a few reported complete resolution of symptoms in the majority of the subjects. The analysis of studies published since 2004 confirms the low rates of recovery after cessation of exposure that were found by RACHOTIS *et al.* [8] in studies published before 2004: 32% (95% CI 26–38%) for symptomatic recovery and 73% (95% CI 66–79%) for persistence of NSBHR.

6. Reduction of exposure to the causal agent can lead to improvement or resolution of symptoms and NSBHR, although the limited available evidence indicates that this approach is less beneficial than cessation of exposure (** moderate evidence)

The AHRQ systematic review [7] analysed the outcome of symptoms [14, 19, 48, 51, 61–65], asthma medications [14, 48, 51, 61, 66], FEV₁ [14, 48, 51] and NSBHR [14, 48, 51] after the reduction of exposure in studies published up to 2004. The authors concluded that these data documented some improvement in asthma symptoms; no clear pattern of changes in medication use; an improvement in FEV₁ over time in less than half of the studies; and provided insufficient data (improvement in one of three studies) to draw conclusions about the changes in NSBHR. The guidelines of the BOHRF and ACCP stated that reduction of exposure “is not always effective” [1] and that “there is little evidence for using this approach” [2].

TABLE 5 Recommendations

Recommendation	Strength of recommendation	Quality of evidence
Patients, physicians, and employers should be informed that persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction	Strong	Moderate
Patients and their attending physicians should be aware that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete recovery from asthma	Strong	Moderate
Reducing exposure to the causal agent can be considered an alternative to complete avoidance in order to minimise the adverse socioeconomic consequences, but available evidence is insufficient to recommend this option as a first-choice therapeutic strategy. This approach requires careful medical monitoring in order to ensure an early identification of asthma worsening	Weak	Low
The use of respiratory protective devices should not be regarded as a safe approach, especially in the long term and in patients with severe asthma	Strong	Low
Anti-asthma medications should not be regarded as a reasonable alternative to environmental interventions	Strong	Very low
The pharmacological treatment of work-related asthma should follow the general recommendations for asthma	Strong	Moderate

The strength of the recommendations and the quality of underlying evidence were graded using the Grading of Recommendations Assessment, Development and Evaluation approach [67].

*7. Respiratory personal equipment can result in an improvement – but not a complete suppression – of respiratory symptoms and airway obstruction in the short term (** moderate evidence)*

The conclusions of this systematic review about the effectiveness of RPE are in agreement with those of the AHRQ review [7] and the BOHRF guidelines [1]. In addition, none of these studies provided information on practical issues (e.g. compliance) that could result from the long-term use of RPE. RPE was not specifically addressed in the ACCP guidelines [2].

Based on the limited evidence provided by this systematic review, some recommendations can be made regarding the management of occupational asthma. These recommendations, along with their strength and the quality of available evidence, are presented in table 5. Large-scale prospective studies comparing the effectiveness and the socioeconomic impact of different treatment options are required in order to provide physicians, affected workers, employers and policy-makers with stronger evidence-based recommendations for the management of occupational asthma. Such studies should: investigate nonselected populations of workers with occupational asthma due to various agents; use the standard outcomes that have been validated for asthma in general; and incorporate quantitative exposure assessments.

Future research

There is a need for large-scale, standardised studies on the prognosis of occupational asthma and its determinants after environmental interventions in order to provide evidence-based recommendations to affected workers, employers, and policy-makers. Prospective studies of the prognosis of occupational asthma should use the outcomes that have been validated for asthma in general. Studies aimed at assessing the effects of reduced exposure to agents causing occupational asthma should include quantitative exposure estimates.

There is a need for prospective evaluation of the effectiveness of specific immunotherapy with validated extracts of high-molecular-weight agents and anti-IgE therapy as therapeutic alternatives when complete avoidance is not possible in IgE-mediated occupational asthma caused by agents such as flour, laboratory animals and enzymes. Investigation of the effectiveness of specific immunotherapy to alter the natural history of the disease from rhinitis to asthma is also warranted.

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STATEMENT OF INTEREST

None declared.

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