

Risk Factors, Predictors, and Markers for Work-related Asthma and Rhinitis

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Abstract The burden of asthma attributable to occupational exposures is significant. A better evaluation of markers of asthma and rhinitis in occupational settings may help reduce the frequency of occupational asthma (OA) and rhinitis (OR). This publication reviews articles published in 2008 and 2009 to provide an update on aspects related to markers of asthma and rhinitis. Markers derived from occupational exposure assessment, questionnaires, clinical data, and noninvasive tests such as functional tests or measures of serum antibodies are used to develop prediction models for the likelihood of OA and OR development. Findings from prospective studies highlight the course of preclinical signs and markers of airway inflammation in the natural history of OA and OR. Airway inflammation, evaluated by quantification of cells and mediators in induced sputum or nasal lavage and by exhaled nitric oxide, is associated with OA and OR; however, the sensitivity and specificity of these means, especially exhaled nitric oxide, have not been sufficiently assessed.

Keywords Asthma · Rhinitis · Work-related asthma · Work-related rhinitis · Occupational asthma · Occupational rhinitis · Work-related chest symptoms · Work-related symptoms of rhinitis · Immunologic sensitization · Occupational exposure · Occupational allergens · Irritants ·

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Introduction

Work-related rhinitis and asthma symptoms, defined as symptoms that are present or more marked at work, are common. Occupational rhinitis (OR) and occupational asthma (OA) are conditions that affect the upper and lower airways, are characterized by reduced airway caliber and hyperresponsiveness as well as inflammation, and are caused by agents present in the workplace [1, 2]. Two types of OR and OA exist: one that occurs after a latency period that is necessary for becoming “allergic” and in which a sensitizing process can be identified or suspected, and the other that occurs without a latency period and after an inhalational accident. The latter condition is also labelled *reactive upper airways dysfunction syndrome* in the case of upper airways or *reactive airways dysfunction syndrome* in the case of lower airways. OR and OA often coexist, with OR being more frequent than OA [3], although a recent study showed that it was 10 times less often reported in sentinel-based registers [4].

When OA and OR appear after a latency period, high molecular weight (HMW) and some low molecular weight (LMW) substances are involved. HMW agents, such as flour-, latex- or animal-derived proteins, cause sensitization through an IgE-mediated mechanism, such as in common atopic asthma. Some LMW agents—mostly chemicals (isocyanates, plicatic acid)—can induce asthma through an immunologic mechanism different from the classical IgE-mediated pathways. The immunologic response may be

initiated by recognition of an LMW agent bound to a protein (a hapten–protein conjugate) by an antigen-presenting cell [2].

General reviews were published on the topics of OA and OR in 2008 and 2009 [1, 5, 6•, 7]. The purpose of this article is to review key articles that have been issued in this period to update on aspects related to markers of OA and OR.

In this publication, the expression *markers of asthma and rhinitis* includes both the markers of risk factors for these occupational conditions, such as the characteristics of the environmental exposure at work and host determinants, and the preclinical and biological markers of these occupational diseases (eg, inflammation of the airways). These different categories of markers are presented in three separate sections; however, some overlap exists between categories, reflecting associations between markers.

Frequency of Occupational Asthma and Rhinitis

The frequency of OA can be assessed in sentinel-based projects, population-based studies from data in general registers, or in workforce-based cross-sectional and longitudinal studies.

Population-Attributable Risk

In a systematic analysis of estimates of the population-attributable risk (PAR) of asthma caused by occupational exposure, Toren and Blanc [8•] reassessed the PAR in the same way that they originally proposed in 1999 [9] in a paper that is frequently quoted. They found an overall median PAR value of 17.6%, a figure comparable to their previous estimate of 15%. The PAR provides an estimate, given as a percentage, of the overall burden of disease resulting from occupational exposures.

A community-based study was carried out in Montreal among 2959 respondents to a mail survey. A subsample of 498 people answered a detailed health questionnaire and an occupational questionnaire on current and past jobs and occupational exposures as administered by an interviewer and had allergy skin tests and a methacholine challenge test. The results showed that bronchial hyperresponsiveness (BHR) was associated with exposure to occupational sensitizers with a PAR of 30.7%, while wheeze was associated with irritant exposure (PAR, 4.5%) and exposure to sensitizers (PAR, 4.8%). PAR was estimated using the proportion of individuals with occupational exposures and prevalence odds ratios (ORs) adjusted for pertinent risk factors for asthma [10].

Sentinel-based Studies

According to the sentinel-based Shield surveillance scheme, initiated in the Midlands, United Kingdom, 15 years ago,

metal fluid is emerging as a new and frequent potential cause of OA, while isocyanates remain the most common causal agent [11]. Latex as a cause of OA is less and less frequent, this being related to a reduction in use of powdered gloves (with the powder representing a vehicle for dispersion of latex particles) [12]. For some unknown reason, the causal agent remaining unidentified, asthma in the educational services (teachers, teachers' aides) is an occupational health problem, as 9% of cases reported to the SENSOR (Sentinel Event Notification System for Occupational Risks) project in four states were in this category [13].

Prevalence

Prevalence studies remain the most widely done investigations. Although symptoms related to the upper and lower airways are common in bakers, Hur and coworkers [14] found relatively low prevalence figures of 4.5% and 1.5%, respectively, for IgE-mediated sensitization and OA in South Korea. Jeebhay and coworkers [15] also found a low prevalence of probable OA of 1.5% in water fish-processing workers. Hur et al. [16] showed that the prevalence of OA in individuals exposed to diisocyanates, an LMW agent, is of the order of 10%, thus confirming a general opinion [17].

Several studies have steadily shown that the frequency of asthma in cleaners is increased, a finding that was extended to nondomestic cleaners in a cross-sectional study carried out in Ontario, Canada [18]. A survey conducted among 1000 Finnish construction workers showed that outdoor painting with exposure to chemical products (such as water-based paints, putties, plasters, solvent-based epoxy/urethane paints, glues, and traditional paints) that may contain well-known sensitizers (eg, latex, formaldehyde, and epoxy products) was associated with increased asthma symptoms [19]. Arif and coworkers [20] found that reported asthma (physician diagnosed after entry into the health profession) among nurses compared with other health professionals was significantly associated with exposure to various disinfectants (OR, 1.72; 95% CI, 1.00–2.95), as was use of latex gloves from 1992 to 2000 (OR, 1.6; 95% CI, 1.01–2.50), but not after 2000.

Incidence

Incidence studies are uncommon in the field of OA. A register-based population study carried out by record linkage from 1986 to 1998 showed an increased RR (1.5; 95% CI, 1.2–1.8) of asthma in wood-processing industries in Finland [21].

Apprentices represent an ideal population for assessing the natural history of OA and OR from beginning of exposure. Our group examined the long-term (8-year) incidence of

sensitization and nasoconjunctival and respiratory symptoms in a cohort of 408 individuals exposed to HMW agents (animals, latex, flour, and enzymes) and previously assessed at a time they started and finished an apprenticeship program. We found much lower incidence of rhinoconjunctivitis symptoms and sensitization after they began their employment (1.7; 95% CI, 0.2–3.1 and 1.3; 95% CI, 0.05–2.5, respectively) than in the apprenticeship period (12.9; 95% CI, 9.7–16.0 and 7.3; 95% CI, 4.7–9.8) in the 78% of individuals who were still exposed to the occupational allergen. We identified many personal factors that were significantly associated with a loss of sensitization and symptoms in those who were no longer exposed or with the onset of sensitization and symptoms in those who continued to be exposed [22••].

A prospective study also carried out by our group in 385 apprentice car painters during an 18-month period assessed the incidence of work-related respiratory symptoms. The incidence of work-related lower and upper airway symptoms was 4.4% and 6.4%, respectively (corresponding to 6.1 per 100 person-years [PYs] and 8.9 per 100 PYs, respectively) [23•].

Risk Factors and Predictors

Occupational Exposure

Quantitative assessment of exposure based on measures of exposure levels in representative zones of a workplace obtained from area and/or personal sampling devices is important to estimate exposure–response relationships.

In the context of the Nationwide Health Surveillance System for early detection of occupational airway diseases among Dutch bakers, a study was conducted in a subgroup of 860 bakery workers to describe the association between levels of wheat allergen exposure and specific IgE sensitization to wheat allergens, work-related upper and lower respiratory symptoms, and asthma [24]. Both average and cumulative personal exposures to wheat allergens were predicted using a job exposure matrix (JEM) developed earlier by the investigators [25]. In accordance with earlier studies, a bell-shaped exposure–response relationship was shown, especially for cumulative exposure; interestingly, the associations were found only in atopic individuals. This was the largest workforce cross-sectional study of bakery workers with exposure and health outcome data and specific IgE measurements.

In the spray-painting industry, a survey was conducted to estimate the exposure–response relationship between isocyanate levels of exposure and the prevalence of respiratory symptoms and sensitization in 581 workers mainly exposed to isocyanate oligomers. Personal exposure was estimated

by combining personal task-based inhalatory exposure measurements and detailed time activity information obtained by questionnaires regarding work history. Specific IgE and IgG to hexamethylene diisocyanate (HDI) were assessed in serum using ImmunoCAP assay (Phadia AB, Uppsala, Sweden) and enzyme immunoassays. Log-linear exposure–response associations were found for asthma symptoms, chronic obstructive pulmonary disease–like symptoms, work-related chest tightness, and work-related conjunctivitis. Specific IgE was found in only a minority of symptomatic workers, whereas specific IgG was more prevalent and strongly associated with exposure [26].

A similar approach was used in the snow crab processing industry, in which the relationship between estimates of exposure to airborne snow crab allergens and probable OA and allergy was assessed for the first time [27, 28••]. In this study of 215 workers, the estimates of cumulative exposure were based on 1) measured exposure levels from personal breathing zone air sampling ($n=115$) to characterize different job types, areas, and use of equipment in four different plants; 2) work history from which were considered the three longest-held jobs since first employment in the plant; and 3) time spent in each of them. Findings are presented below.

Exposure in large populations of workers may be estimated by extrapolating quantitative measures obtained in a subsample of workers in a similar industry. Since the first asthma-specific JEM was developed by Kennedy and coworkers [29], several specific JEMs were subsequently developed in given industrial sectors such as the JEM based on personal sampling measurements in flour-processing sectors mentioned previously [25].

Delclos and coworkers [30] compared self-reported occupational exposures with the workplace-specific JEM developed earlier in a survey of Texas health care professionals ($n=3650$) by asthma status. There, the workplace-specific JEM was developed based on estimates of exposures independently coded by a panel of experts [30]. The authors examined sensitivity, specificity, agreement, and associations of self-reported exposures versus JEM-based exposure with asthma. Differences between self-reported exposures and the JEM were small, except for exposures associated with perceptible odors (eg, cleaning products), for which sensitivity of self-reported exposures compared with the JEM was higher among asthmatics, suggesting a reporting bias for this category of exposures. The findings from this study tend to favor using methods of exposure classification developed by individuals and experts outside the workforce.

In a long-term follow-up of apprentices in three different trades who were formerly exposed to laboratory animals, flour, or latex during their training [22••], the agreement between self-reported investigator score on job training relatedness and the asthma-specific JEM was satisfactory [31•]. According to the JEM estimates, being further exposed

to HMW allergens was associated with the incidence of occupational sensitization, work-related rhinoconjunctivitis symptoms, and BHR. This study also showed that the asthma-specific JEM can be used for other outcomes related to asthma.

Chronic exposure to low levels of irritant materials for the airways may cause irritant-induced asthma [32] or aggravate asthma. Whether or not teenagers with respiratory symptoms are influenced by their health status when choosing a job has only rarely been studied [33]. This question was addressed recently in a conscription cohort in Sweden [34]. The long-term outcomes among young adults with asthma or allergic rhinitis from this cohort were investigated in relation to their work history, focusing on the probability of exposure to irritating agents. Data were collected from the linkage of four Swedish national registers. A JEM for exposures to irritating substances was developed especially for application to this cohort (40,321 men conscripted in 1969 and 1970). Three groups (healthy, asthma, and allergic rhinitis without asthma) were identified at conscription and analyzed for mortality (1969–2002), inpatient care (1971–2003), and strategies for choice of an occupation considering exposure to irritating agents (1970–1990). Compared with healthy individuals, asthmatics had an increased risk for morbidity and mortality, while those with allergic rhinitis had less risk. Individuals with asthma, especially severe asthma, tended to avoid jobs with a high probability of exposure to irritant substances; this strategy was more pronounced and significant among those with allergic rhinitis.

Host Risk Factors

In a recent editorial, Mapp [35] discussed the role of genetics in OA. The article outlines the important progresses made during the past decades in asthma genetics that led to the recognition of the multifactorial pathogenesis of the disease. One of the main focuses of research today is to determine how environmental factors interact with genes and how this influences disease susceptibility. This concept follows from previous discussions [36]. A perceived problem with studies on the genetics of OA is the inability to replicate results. A possible explanation provided by the author is that most genetic studies do not take into account the contribution of the wide spectrum of the environment—from the intrauterine environment to the general and occupational environment—and its exposures. Identifying genes of interest based on relevant exposure rather than on disease outcomes may provide a better understanding of gene–environment interactions. More thoughts on genetic susceptibility to occupational isocyanate exposures were expressed in an article by Christiani and coworkers [37].

Atopy has been consistently shown in epidemiologic studies to be a risk factor for work-related allergy and asthma

caused by HMW agents such as flour [38]. To characterize the development of baker's asthma, Marraccini et al. [39] developed a murine model. Although they could not sensitize mice to bakery flour dust or flour dust extracts (a sterile, low-endotoxin aqueous extract of commercial bakery flour), they assessed total inflammatory cells, cellular differentials, total serum IgE, and the proinflammatory response to oropharyngeally instilled bakery flour dust and flour dust extracts in nonsensitized mice and in mice sensitized to and challenged with ovalbumin. These experimental exposures caused a neutrophilic inflammation of the airways and significantly enhanced the eosinophilic inflammatory response in ovalbumin-sensitized mice. The authors concluded that these agents are strongly proinflammatory and can cause nonallergic inflammation and enhance allergen-mediated airway inflammation. If extrapolated to an occupational setting, we may speculate that these experiments may contribute to our understanding of how preexisting allergy is aggravated by occupational exposures.

By investigating the immunologic status and airway mucosal factors of individuals before employment, Krop et al. [40] sought to determine if these characteristics were associated with the development of work-related sensitization. A 2-year prospective study was carried out in 110 starting laboratory animal workers. Health questionnaire data, skin test results, lung function measures, methacholine airway challenge thresholds, and nasal lavage fluids were obtained. Serum total IgE and allergen-specific IgE antibodies to common inhalants and laboratory animals were measured, and cytokine production profiles were assessed in whole blood. In this cohort, 22 workers developed specific sensitization to rat and/or mice (10.7 per 100 PYs). Using a multivariate regression analysis, it was shown that atopy and total IgE were the two factors that best predicted the incidence of sensitization, whereas parameters of airway inflammation or cytokine production profiles did not further contribute to the prediction of specific sensitization. After validation in another population of workers, the results suggest that if the prediction model was to be used in preemployment counseling for laboratory animal worker applicants with atopy and total IgE levels greater than 100 IU/mL, it could reduce occupational sensitization substantially.

Markers of Work-related Asthma and Rhinitis

Tools developed for the assessment of clinical and biological markers of asthma in a clinical setting for an objective diagnosis of OA and OR cannot always be used in the workplace. Consequently, algorithms based on questionnaire data and a varying number of objective test results have been developed, leading to a diagnosis of probable asthma and/or rhinitis [22•, 41, 42].

Symptoms of Allergy: Work-related and Non-Work-related

In the 8-year follow-up study of apprentices conducted by our group and described above, several markers of new-onset outcomes related to work-related allergy were identified in those with continued exposure to HMW agents after completion of apprenticeship [22••]. Thus, for sensitization to a work-specific allergen, significant associations were found with immunologic sensitization to common allergens, symptoms of rhinitis, and BHR assessed at baseline; for incident work-related chest symptoms and increase in bronchial responsiveness, allergic symptoms reported at baseline or during the apprenticeship were among the significant markers. The study also identified markers that were inversely related to remission of the same features in individuals who reported working in a training-related environment; these markers included positive skin tests to common allergens and hayfever at baseline. Also, work-related cutaneous and conjunctival symptoms acquired during apprenticeship or afterward were significantly associated with persistence of the outcomes at follow-up.

Recently, models were developed to quantify the probability of developing sensitization to laboratory animal allergens and/or respiratory symptoms at work in the cohort of Canadian animal health technology apprentices described above. Information from a respiratory symptom questionnaire at inception provided an accurate prediction of the incidence of specific laboratory animal sensitization and respiratory symptoms on occupational exposure to laboratory animal allergens. The added predictive value of skin prick testing and/or bronchial challenge to methacholine was limited in this relatively healthy population of young adults [43].

Serum-Specific Antibodies

When work-related asthma is caused by an HMW agent, serum-specific IgE antibodies to the allergens derived from the causative agent are found in association with respiratory symptoms and work-related allergy and asthma. In the first survey among Korean bakery workers from an industrial bakery, Hur and coworkers [14] found a high prevalence of lower respiratory symptoms (13.5%, 53 of 392) that was correlated with specific IgE to wheat flour ($P < 0.01$), although only 13 of 52 of the symptomatic individuals had positive wheat-specific IgE, suggesting that mechanisms other than IgE mediated are involved. Wheat-specific IgG₁ and IgG₄ were associated with exposure to wheat dust, as shown earlier [44], whereas wheat-specific IgG₄ was the only IgG subtype associated with lower respiratory symptoms. The investigators performed IgE and IgG₄ immunoblotting using serum from workers with asthma

and/or rhinitis and demonstrated that these sera contained five identical components (ie, 11-, 17-, 21-, 54-, and 96-kD) bound to both IgE and IgG₄ antibodies; they suggested that wheat-specific IgG₄ antibodies may play a role in the development of respiratory symptoms in exposed workers who lack wheat-specific IgE antibodies.

Few studies have assessed the predictive value of occupational agent-specific antibodies for the further development of asthma and allergic symptoms in a prospective design. Dragos et al. [23•] sought to determine if immunologic markers of diisocyanate asthma could help identify occupationally exposed individuals at risk of work-related symptoms. In their inception cohort, 298 of 385 apprentice car painters completed the follow-up study; they were assessed upon entering and finishing their 18-month training using questionnaires, methacholine challenges, and measurement of HDI-specific IgE using a radioallergosorbent assay and of HDI-specific IgG and IgG₄ using an enzyme-linked immunosorbent assay. A small number ($n=9$) showed increases in HDI-specific IgE ($\geq 0.34\%$ binding) and IgG (≥ 0.5 optical density); the respective cut-off values at the 97th percentile of the distribution. These increases were significantly associated with duration of exposure in apprenticeship, which is in accordance with earlier findings from a cross-sectional study [26]. In this study, increases in specific IgG and IgG₄ over the duration of the apprenticeship seemed to have a protective effect on the incidence of lower and upper respiratory symptoms, respectively [23•]. The presence of measurable levels of HDI-specific antibodies in individuals without previous occupational exposure to HDI was not expected; this could be due to prior high reactivity to isocyanates present in the general environment.

A high prevalence of probable OA and allergy to snow crab (15.8% and 14.9%, respectively) has been reported consistently on Canada's East Coast for more than a decade [28••]. The diagnosis was based on objective evidence of specific sensitization to snow crab assessed by immunoassays and/or skin prick tests with snow crab extracts combined with a history of work-related chest symptoms (for probable OA) and with nose, eye, and/or skin symptoms (for probable occupational allergy). An immunologic study was conducted to identify relevant allergenic proteins in cooked snow crab meat and crab cooking water. Specific IgE antibody reactivity to crab meat and cooking water was determined by radioallergosorbent test in the sera from 207 exposed workers. The 24 sera with the highest radioallergosorbent test reactivity ($\geq 3.5\%$) were tested for reactivity to nitrocellulose membranes containing crab meat and cooking water proteins separated with sodium dodecyl sulfate polyacrylamide gel electrophoresis. Most sera from snow crab processors with probable OA reacted to four proteins at 34.0 kD, 25.0 kD, 18.5 kD, and 14.4 kD [45].

Markers of Inflammation

Rizzo et al. [46] have shown that in moderate to severe allergic asthma, there is a deficit of interleukin (IL)-10 secretion that could prevent the production of soluble HLA-G (sHLA-G) that has protective effects against inflammatory responses. A recent study from the same group compared the production of sHLA-G and secretion of IL-10 in the culture supernatants of peripheral blood mononuclear cells (PBMCs) from individuals with isocyanate asthma, asymptomatic individuals with exposure to isocyanates, individuals with nonoccupational allergic asthma, and healthy controls [47]. They found that exposure to isocyanates was associated with high levels of IL-10 secreted by PBMCs regardless of whether or not the individuals were symptomatic. Spontaneous production of sHLA-G by PBMCs was significantly higher in those with isocyanate asthma compared with asymptomatic exposed controls. In contrast, PBMCs from nonoccupational allergic asthma patients produced sHLA-G only after stimulation with lipopolysaccharide. It was concluded that IL-10 secretion and sHLA-G are influenced by exposure to isocyanates and development of asthma. The results suggest a heterogeneous biological role in asthma induced by isocyanates and nonoccupational allergic asthma for sHLA-G molecules and for IL-10.

Results are expected from a 2-year prospective study of a large cohort of 441 volunteer apprentices at risk of OA in trades involving exposure to HMW and LMW agents. In this study, noninvasive tests of airway inflammation, including forced expiratory technique measurement of fraction exhaled nitric oxide and eosinophil counts and differentials in nasal lavage fluids, were performed to detect early airway inflammation that may develop into OA [48].

Means of Assessment of Markers at Early Stages of Disease

Although assessment of specific IgE and IgG antibodies to isocyanates was proposed almost half a century ago, such testing still faces many methodologic challenges and does not have sufficient sensitivity and specificity to be used as the sole means of surveillance or diagnosis [16]. Specific IgG antibodies were present in 4 of 7 (57%) individuals with OA ($n=5$) or eosinophilic bronchitis ($n=2$) but also in 8 of 51 (16%) individuals without such a diagnosis, which shows a statistically significant association but does not demonstrate a sufficient degree of association to be used in a surveillance program or for clinical purposes. The same comment applies for specific IgE that were present in only two of seven (29%) individuals with a positive diagnosis but also in three individuals (6%) without such a diagnosis [16].

Recent trends advocate the assessment of airway inflammation with noninvasive methods such as evaluation of cells and mediators in induced sputum and monitoring of exhaled nitric oxide. A review in the form of a position paper has been proposed [49]. Recent studies in patients with OR have shown that rhinometry, and to a lesser extent nasal lavage, are promising tools, their principal advantage being that they are noninvasive. Using rhinometry as the objective test, Castano and coworkers [50••] confirmed a diagnosis of OR in 25 of 43 (58%) individuals investigated for OA, all of whom also complained of nasal symptoms related to work. The association between OA and OR was higher in those sensitized to HMW agents (11 of 22, 50%) than those sensitized to LMW agents (2 of 21, 9.5%). In individuals with a positive nasal challenge according to rhinometry results, there was a significant increase in nasal eosinophils 30 min after the oronasal challenge with the relevant occupational agent. Castano et al. [51] also have shown that nasal lavage provides satisfactory reproducibility in terms of number and percentage of inflammatory cells, as well as of eosinophilic cationic protein. Pignatti et al. [52] recently proposed examining nasal blown secretions in the assessment of nasal response to challenges with occupational agents. They found a significant increase in eosinophils in 13 individuals with OR by comparison, with no significant changes in an equal number of individuals with negative challenges to the occupational agent [52]. For the time being, exhaled nasal nitric oxide has not been sufficiently assessed in occupational settings to warrant its use [49].

Conclusions

Extensive work has been done to characterize exposure to flour allergens in the bakery industry in the Netherlands; the data were used effectively to develop prediction models that can be used for counseling on recruitment of workers and apprentices or for assessing workplace interventions aimed at reducing exposure levels. Such a global approach could be applied in other industrial sectors associated with a high risk of OA and OR and employing large numbers of workers.

More studies are needed to validate exporting existing prognostic models of disease (and disease features) in different workplaces (eg, different populations, different work practices, different countries.). Host markers related to an atopic phenotype are well-known now; however, more research is needed to reveal other potential markers. Studies are in progress to fill a gap for a better understanding of the impact of socioeconomic and psychological factors (eg, anxiety, depression, and hypochondriasis) on work-related asthma and rhinitis.

Early markers of disease and tools for sampling these in blood, induced sputum, exhaled breath, and nasal lavage

are being used not only in clinical settings but increasingly so in the workplace. This poses some challenges because the predictive value of the tests performed is low due to the low prevalence of the preclinical signs of work-related asthma and rhinitis (eg, markers of inflammation in induced sputum) in relatively healthy populations. Thus, these tests should be performed in a subset of workers (yet to be identified) to maximize their predictive value. Moreover, more evaluation of noninvasive methods for assessing inflammation of the airways is needed.

Newly employed workers or apprentices at risk of developing work-related rhinitis and asthma form the ideal population for the study of early markers of disease. It is important, however, that very large cohorts are assembled given the relatively low incidence rate of work-related allergies and of their early markers. Register-based studies are a complement to prospective workforce studies. More multidisciplinary and multicentric studies are needed to integrate state-of-the-art investigations on a large spectrum of markers of asthma and rhinitis in occupational settings, from the characteristics and level of exposure to the early biological markers.

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- Of importance
- Of major importance

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