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Asthma and Rhinitis in the Workplace

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Abstract Accumulating evidence indicates that the workplace environment substantially contributes to the global burden of asthma and rhinitis. Work-related asthma and rhinitis represent a public health concern due to their health and socioeconomic impacts. This article summarizes the scientific evidence on sensitizer-induced occupational asthma and rhinitis that has been published during the past 5 years. The review addresses the strategies for diagnosing and managing these highly prevalent occupational diseases.

Keywords Asthma · Occupational disease · Rhinitis

Introduction

The workplace environment can lead to the development of different types of work-related asthma and rhinitis (Fig. 1). It is now generally acknowledged that the term *work-related asthma* encompasses asthma caused by work and preexisting or coincident asthma exacerbated by nonspecific stimuli at work, with the latter condition now commonly referred to as *work-exacerbated asthma* [1••]. Asthma caused by the work environment may result from immunologically mediated sensitization to occupational agents (ie, "allergic" occupational asthma [OA]) or from exposure(s) to high concentrations of irritant compounds (ie, irritant-induced asthma, best typified by the reactive airways dysfunction syndrome) [1••]. Considering the tight interactions between the upper and lower airways [2], a Task Force of the European Academy of Allergy and Clinical Immunology recently proposed a similar nosologic approach to defining rhinitis syndromes related to the work environment [3••].

In recent years, there has been a growing recognition of work-related asthma and rhinitis as a public health concern because of their high prevalence and societal burden. An analysis of general population-based studies published up to 2007 indicated that 17.6% of all adult-onset asthma is attributable to workplace exposures [4]. The European Community Respiratory Health Survey II provided estimates of 250 to 300 incident cases of work-attributable asthma per 1 million people per year [5]. Work-related asthma is likely to be more prevalent and severe in some developing countries than in industrialized countries, as obsolete technologies are still extensively used in developing countries, and control of exposure is lacking [6]. Work-related asthma is associated with a substantial economic impact for affected workers, employers, and society as a whole [7]. Available studies have consistently documented that work-related asthma is associated with a high rate of unemployment (ranging from 18%–69%) and loss of income (ranging from 44%–74%) [7], increased utilization of health care resources, and an adverse impact on quality of life [8]. The cost to society of an individual case of OA diagnosed in 2003 was estimated to range from £113,187 to £158,637 per year in the United Kingdom [9].

The incidence of occupational rhinitis (OR) in the general population remains largely unknown, although surveys of workforces exposed to sensitizing agents indicate that OR is two to four times more common than OA [3••]. The socioeconomic impact of OR is likely to be substantial, as it can be extrapolated from data available for allergic rhinitis in general [2].

The purpose of this review is to synthesize the recent scientific evidence pertaining to the diagnostic approaches,

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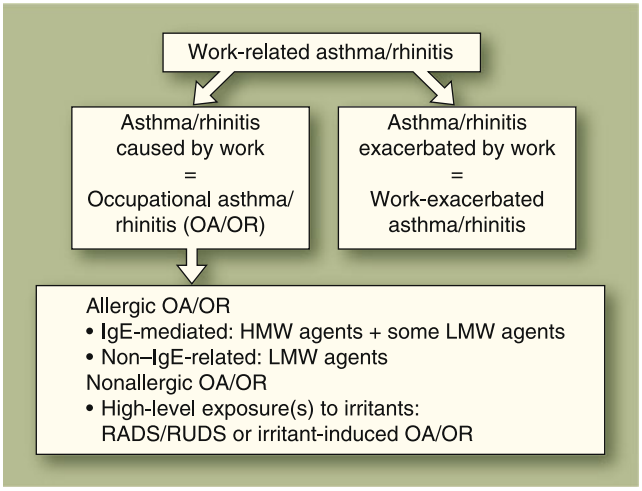

Fig. 1 Classification of asthma and rhinitis related to the work environment. HMW—high molecular weight; LMW—low molecular weight; RADS—reactive airways dysfunction syndrome; RUDS—reactive upper airways dysfunction syndrome

management options, and preventive strategies of sensitizer-induced OA (Table 1) and OR (Table 2). The information that appeared within the past 5 years is integrated with recently issued clinical practice guidelines [1••, 3••, 10, 11].

Occupational Asthma

Diagnosis

Establishing or excluding a diagnosis of OA requires a high level of accuracy because the condition has significant health and socioeconomic impacts. Missing a diagnosis of OA may lead to continued exposure and progressive worsening of asthma. Conversely, diagnosing OA when it is not present may lead to inappropriate removal from exposure and unnecessary financial and social consequences. Nevertheless, OA remains a diagnostic challenge for clinicians because there is no simple test that would allow for diagnosis of the condition with a sufficiently high level of confidence. Instead, the diagnostic approach most often has been to combine different procedures and to adapt to the suspected agent, the purpose (ie, clinical practice, surveillance program, or medicolegal evaluation), and available resources.

Many substances used in the workplace can stimulate the development of allergic OA and OR. Updated lists of causal agents and occupations are available on the Internet (http://www.asthme.csst.qc.ca; http://www.asmanet.com). The agents causing allergic OA and OR include high molecular weight (HMW) (glyco)-proteins from vegetal and animal origin, as well as low molecular weight (LMW) chemicals. HMW proteins and a few LMW compounds (ie, platinum salts, reactive dyes, acid anhydrides, and obeche wood) act through a documented IgE-mediated mechanism [12]. For most LMW agents (eg, isocyanates, persulfate salts, aldehydes, wood dusts), the immunologic mechanism has not been fully characterized.

Validity of Diagnostic Procedures

Clinicians should be aware that the clinical history has a high sensitivity but low specificity for diagnosing OA [13]. About 20% of asthmatic adults experience worsening of their symptoms at work [14], but about half of these adults fail to show objective evidence of asthma worsening when they are exposed to their workplace or to the suspected agents in the laboratory [13]. Even more, a substantial proportion of those evaluated for work-related respiratory symptoms fail to demonstrate any objective evidence of asthma. In a survey of workers referred to specialized clinics for possible work-related asthma, 57% did not show evidence of asthma, although they reported work-related respiratory symptoms that were similar to those diagnosed as having OA, or work-exacerbated asthma, except for a lower prevalence of wheezing [15]. Therefore, the first diagnostic step is to confirm the presence of asthma by a combination of symptoms and assessment of nonspecific bronchial hyperresponsiveness, although this feature may be absent in individuals with OA, particularly when they are evaluated after removal from exposure [1••, 10, 11].

The causal relationship between exposure to occupational agents and the development of asthma can be assessed through immunologic tests (ie, skin prick tests and/or determination of specific IgE antibodies against occupational agents); serial measurements of forced expiratory volume in 1 s (FEV_1), peak expiratory flow rates, nonspecific bronchial responsiveness, and/or sputum eosinophils at work and away from work; and specific bronchial provocation test (SBPT) in the laboratory or at the workplace (ie, supervised measurements of spirometry at work) [1••, 10, 11]. Addressing the advantages and limitations of each of these methods is far beyond the scope of this review. A recent systematic review by Beach and co-workers [16] provides estimates of the sensitivity and specificity of available procedures as compared with SBPT. The results indicate that none of the tests used alone yields a sufficiently high combination of sensitivity and specificity that would allow it to replace SBPT. The combination of nonspecific bronchial hyperresponsiveness assessment and immunologic tests may be a pragmatic and readily available alternative when SBPT is not available. Thus, the presence of nonspecific bronchial hyperresponsiveness and positive results of immunologic tests increases the likelihood of OA, whereas negative results do not allow for excluding OA. Other combinations of tests have not been evaluated in sufficient detail to provide recommendations.

Table 1 Summary of recent publications on occupational asthma

Study	Topic and findings
General	
Nicholson et al. [10]	Evidence-based clinical guidelines on OA commissioned by the BOHRF
Tarlo et al. [1••]	Expert-based statement on work-related asthma issued by the American College of Chest Physicians
Fishwick et al. [11]	Update of the BOHRF guidelines endorsed by the British Thoracic Society Standards of Care Committee
Diagnosis	
Vandenplas et al. [13]	Assessment of various questionnaire items for identifying OA
Chiry et al. [15]	Clinic-based survey showing that a substantial proportion of individuals experiencing work-related asthma-like symptoms fail to provide functional evidence of asthma
Beach et al. [16]	First systematic review of available procedures for diagnosing OA
Quirce et al. [17•]	Comprehensive review of noninvasive methods for assessing airway inflammation in OA
Vandenplas et al. [18]	Assessment of changes in sputum eosinophils as an early marker of bronchial response during inhalation challenges to occupational agents
Lemiere et al. [19], Ferrazzoni et al. [20]	Comparisons of the changes in sputum eosinophils and FENO after challenge exposure to occupational agents
Kennedy et al. [21]	First cost-effectiveness analysis of procedures used to diagnose OA
Fishwick et al. [22•], Shofer et al. [24], Barber et al. [25]	Surveys documenting current failures in the diagnostic process: lack of inquiry about the work relatedness of symptoms, long delay before referral to specialists for further assessment, and inappropriate assessment of possible OA
Santos et al. [23]	Identification of individual and work-related factors associated with a long delay before diagnosing OA
Management	
Beach et al. [26••]	Meta-analysis of available data on the effectiveness of different management options
Rachiotis et al. [28]	Systematic review of the effects of cessation of exposure to agents causing OA
Anees et al. [27]	Retrospective cohort study assessing the decline in FEV_1 before and after cessation of exposure in individuals with OA
Yacoub et al. [8], Brant et al. [29], Klusackova et al. [30], Labrecque et al. [31], Park et al. [32], Park et al. [33], Pisati et al. [34]	Follow-up studies of workers with OA caused by various agents
Yacoub et al. [8], Piirila et al. [36], Sumi et al. [37]	Effects of cessation of exposure on airway inflammation
Prevention	
LaMontagne et al. [38], Bousquet et al. [39]	Meta-analysis of studies assessing dose–response relationships between exposure to latex allergens and allergic disorders, and the effects of reducing exposure to latex
Vandenplas et al. [40]	Ecological survey documenting a temporal association between reduction of exposure to powdered latex gloves in Belgian hospitals and a downward trend in incident cases of latex-induced OA
Jacobs et al. [41], Suarthana et al. [42]	Development and evaluation of a prediction model for identifying workers who need further investigation for OA caused by bakery allergens

BOHRF British Occupational Health Research Foundation, *FENO* fractional exhaled nitric oxide, *FEV_1* forced expiratory volume in 1 s, *OA* occupational asthma

In recent years, noninvasive methods for the evaluation of airway inflammation have been increasingly proposed for the investigation of work-related asthma and rhinitis [17•]. Most individuals with OA show an increase in sputum eosinophils after exposure to the causal HMW or LMW agent at work or during SBPT in the laboratory. A neutrophilic inflammation also may occur after exposure to isocyanates and irritant agents such as ozone, diesel exhaust, and endotoxin. The addition of sputum eosinophil counts to serial peak expiratory flow measurements at work and away from work enhances the specificity of the test [16]. Vandenplas et al. [18] showed that sputum eosinophilia is an early marker of bronchial response to occupational agents. An increase in sputum eosinophils greater than 3%

Table 2 Summary of recent publications on occupational rhinitis

Study	Topic and findings
General	
Moscato et al. [3••]	Expert-based statement on OR issued by the European Academy of Allergy and Clinical Immunology
Moscato et al. [44]	Comparison of upper and lower airways eosinophilic inflammation in OA due to persulfates with or without OR
Diagnosis	
Vandenplas et al. [43]	Evaluation of the nature and timing of rhinitis symptoms among individuals with work-related asthma
Quirce et al. [17•]	Comprehensive review of noninvasive methods for assessing airway inflammation in OR
Castano et al. [48], Pignatti et al. [49], Castano et al. [50]	Attempts to determine the validity of acoustic rhinometry and nasal lavage cytology in identifying nasal response during challenges with occupational agents

OA occupational asthma, *OR* occupational rhinitis

after SBPTs that did not induce changes in FEV_1 predicted the development of an asthmatic response on subsequent challenges with a sensitivity of 67% and specificity of 97%. Analysis of sputum collected during SBPTs therefore may improve the diagnostic sensitivity of the procedure. In addition, sputum cytology allows for the identification of nonasthmatic eosinophilic bronchitis caused by workplace agents [17•].

Measurements of the fractional exhaled nitric oxide (FENO) concentration as a surrogate marker of eosinophilic airway inflammation have been suggested [17•]. Compared with induced sputum, assessment of FENO is an easier and less time-consuming technique, but available studies have provided inconsistent results in the investigation of OA. Recent studies found that changes in FENO are affected by treatment with inhaled corticosteroids [19], occur later (24 hours vs 6 hours) than an increase in sputum eosinophils [19, 20], and achieve a much lower sensitivity and positive predictive value for the development of an asthmatic response during SBPT [19]. However, an increase in FENO of 10 ppb after challenge exposure to occupational agents achieved good specificity and negative predictive value, which may help in the interpretation of SBPT in some instances, especially when the patients fail to provide suitable sputum samples.

Issues in Diagnosing Occupational Asthma

A major issue in the diagnosis of OA results from the lack of a widely accepted gold standard test for determining the validity of other procedures. Recent guidelines acknowledge that SBPT "comes closest to a gold standard test" and should be considered a "reference standard" [1••, 10, 11, 16]. Paradoxically, these clinical guidelines do not recommend using SBPT routinely because of the high cost, limited availability, potential risk of inducing severe asthmatic reactions, and possible false-positive and false-negative results. However, the safety of SBPT can be enhanced substantially by performing the procedure under carefully controlled conditions in specialized centers (Vandenplas, unpublished data). The accuracy of SBPT can be further improved by assessing the bronchial response to occupational agents using the most sensitive tools, namely the postchallenge changes in nonspecific bronchial hyperresponsiveness and sputum eosinophil counts [18]. Very few data are available on the relative cost-effectiveness of various diagnostic procedures. Using Canadian and American cost estimates, Kennedy and coworkers [21] found that the SBPT, used as the gold standard with an assumed 100% accuracy, was the most expensive technique but correctly diagnosed 28% more OA patients than the analysis of sputum cells collected at work and away from work, and 48% more patients than peak expiratory flow monitoring. In addition, the costs resulting from incorrect diagnosis of OA, leading to unwarranted job changes and compensation, are likely to outweigh the additional cost of SBPT.

Recent data indicate that work-related asthma remains largely unrecognized and inappropriately investigated. The diagnosis of OA is usually made 2 to 4 years after the onset of symptoms [22•, 23]. Patients may not be aware of the work relatedness of their symptoms or may be reluctant to seek medical advice for work-related symptoms because of concerns about financial consequences [23]. However, recent surveys have identified failures in general and specialized medical practices. Health care practitioners do not systematically inquire about the temporal relationship between work and asthma symptoms. They take incomplete occupational histories and fail to identify potentially relevant occupational exposures [24]. Primary care physicians delay in referring patients with work-related symptoms to occupational or respiratory specialists for further assessment [22•]. On the other hand, secondary care chest physicians fail to perform objective diagnostic procedures to investigate the possible work relatedness of asthma, probably because the

most appropriate techniques are not widely available [22•, 25]. Accordingly, a crucial step for enhancing the diagnosis of OA is to promote the prompt referral of workers suspected of having work-related asthma to specialists who have the expertise and facilities to conduct appropriate investigations.

Management

Once a diagnosis of OA is firmly established, the general recommendation has been to remove affected workers from the causal exposure [1••, 10], as continued exposure may lead to worsening of airway obstruction and nonspecific bronchial hyperresponsiveness [26••]. Anees and coworkers [27] evaluated the changes in FEV_1 before and after cessation of exposure in 44 individuals with OA (87% due to LMW agents) who had measurements within 1 year before and after removal. The rate of decline in FEV_1 was significantly greater before removal than after cessation of exposure, with a mean difference of -129.6 mL/y (95% CI, -217 to -42 mL/y). Noticeably, the decline in FEV_1 before removal was not affected by treatment with inhaled corticosteroids.

On the other hand, avoidance of exposure does not lead to complete recovery from asthma. A systematic review by Rachiotis and coworkers [28] examined the outcome of workers with OA after cessation of exposure in studies published up to 2004. The review analyzed original studies documenting complete symptomatic recovery from asthma (39 studies, 1681 patients) and nonspecific bronchial hyperresponsiveness (28 studies, 695 patients). The pooled estimates were 32% (95% CI, 26%–38%) for symptomatic recovery and 27% (95% CI, 21%–34%) for recovery of nonspecific bronchial hyperresponsiveness. Follow-up studies published between 2004 and 2009 provided quite similar findings [8, 29–34].

Improvement in nonspecific bronchial hyperresponsiveness may continue for years after cessation of exposure, but the rate of improvement is steeper during the first 2.5 years [35]. Several studies reported that a worse outcome is associated with a longer symptomatic period before removal from causal exposure and with more severe disease at the time of diagnosis, emphasizing the need for early diagnosis and intervention [10]. The systematic review by Rachiotis et al. [28] confirmed a beneficial effect of a shorter duration of symptomatic exposure on symptom recovery and a worse outcome of nonspecific bronchial hyperresponsiveness in those with OA caused by HMW agents. Recent studies found that failure to improve nonspecific bronchial hyperresponsiveness after cessation of exposure to an agent causing OA is associated with persistent airway inflammation [36], although airway inflammation and remodeling may persist in clinically and functionally asymptomatic patients [8, 37].

The management of OA remains complex because cessation of exposure by relocation of the worker to unexposed jobs or substitution of the hazard is often not feasible. There is some suggestion that reducing—rather than eliminating—exposure to the causal agent may lead to improvement or resolution of asthma symptoms and nonspecific bronchial hyperresponsiveness with lower socioeconomic consequences, but available evidence is insufficient to recommend this approach as a safe alternative to complete avoidance in the management of OA [26••].

Prevention

Primary Prevention

Accumulating evidence indicates that reduction of exposure to sensitizing agents in the workplace can substantially reduce the development of immunologic sensitization and subsequent allergic respiratory diseases. The most convincing example of the effectiveness of this approach is provided by the substitution of powdered latex gloves by nonpowdered gloves with low allergen content [38–40]. However, most of this evidence comes from ecological, observational studies, and a need exists for further prospective intervention studies evaluating the effectiveness of primary preventive measures on allergen exposure and the development of OR and OA for most other causal agents.

Secondary Prevention

There is reasonable evidence to support a better outcome for workers with OA who are removed earlier from the causal exposure [26••, 28]. Reduction in the delay between the onset of respiratory and/or nasal symptoms at work and appropriate assessment and advice should be achieved by increasing awareness of the disease among workers and health professionals, with a special focus on primary care physicians, who are first consulted for asthma symptoms [22•]. All workers with new-onset asthma or worsening of existing asthma should be asked about the temporal relationship between work exposure and their symptoms. Early detection of OA also can be achieved by implementing medical surveillance programs among workforces exposed to potential sensitizers [1••]. The rationale of medical surveillance is, however, based mostly on retrospective evaluations, and an urgent need exists for prospective assessments of the cost-effectiveness of such surveillance programs. Prediction models are being developed to estimate the risk of sensitization and work-related respiratory symptoms in workers exposed to HMW agents [41, 42]. Such models may assist decision making in medical surveillance and enable cost-effective identification of workers who need further diagnostic investigation.

Occupational Rhinitis

A close association exists between OR and OA, as most patients with OA also suffer from OR [3••, 43]. In addition, eosinophilic inflammation of the nasal mucosa may be present in individuals with OA due to persulfate salts who do not experience clinical manifestations of rhinitis, further supporting the concept of a united airway disease in occupational settings [44]. Rhinitis symptoms are more frequent and more severe when OA is caused by HMW agents compared with LMW agents [43]. The symptoms of rhinitis precede the onset of OA in about one third of cases, especially when HMW agents are involved (48%) as compared with LMW agents (28%). These clinical findings support the concept that OR is associated with an increased risk of the development of OA. However, the proportion of individuals with OR who will subsequently develop OA remains uncertain. Data from the Finnish register of occupational diseases [45] and a surveillance program of laboratory workers [46] found that OR was associated with relative risks of 5.4 (95% CI, 4.8–6.2) and 7.4 (95% CI, 3.3–16.6) for the development of OA during follow-up periods of 7.7 and 11 years, respectively. On the other hand, a prospective study of apprentices exposed to laboratory animals showed that OR had a low positive predictive value of 11% for the development of OA during the 3- to 4-year program [47].

Diagnosis

An accurate diagnosis of OR is not only important per se, but it also may be useful in the prevention and early diagnosis of OA. Similar to what has been described for OA, the clinical history and immunologic tests (when available) have a high sensitivity but a low specificity for diagnosing OR [3••]. Nasal provocation test in the laboratory or at the workplace is still considered the gold standard for confirming the diagnosis of OR. The major limitation of these tests results from the lack of standardized procedures. Various indices have been used to assess the nasal response, including symptom scores, quantification of nasal patency through rhinomanometry or acoustic rhinometry, and evaluation of nasal inflammation, but comparisons between these parameters are scarce. Sampling nasal secretions has gained increasing interest because the technique offers a noninvasive and reproducible means to monitor upper airways inflammation induced by occupational agents [17•]. Recent studies have shown that a 4% increase in eosinophils recovered in nasal lavage or nasal blown secretions should be an adequate cutoff value for defining a positive response during nasal provocation tests [48, 49]. However, Castano et al. [50] documented that a significant decrease in nasal patency (assessed by acoustic rhinometry) may occur in individuals who failed to show an increase in eosinophils in nasal lavage during specific inhalation challenges in the laboratory. These findings suggest that different pathophysiologic mechanisms may be involved in the development of nasal responses to occupational agents and indicate that both indices are complementary for assessing nasal responses during nasal provocation tests.

The previously quoted Task Force of the European Academy of Allergy and Clinical Immunology recently proposed a consensus diagnostic algorithm. The first step includes a thorough clinical and occupational history, as well as nasal examination. The second step involves the evaluation of sensitization to suspected occupational agents when standardized and validated tests are available. A suggestive clinical history associated with a positive immunologic test for an occupational agent could be considered as probable OR. The next step involves the objective evaluation of the causal relationship between rhinitis and the work environment through nasal provocation tests with the suspected agent(s) in the laboratory. If nasal provocation tests are positive, a definite diagnosis of OR can be established. If nasal provocation tests are negative, further evaluation of work-related changes in nasal parameters at the workplace is recommended. In addition, the possibility of lower airways involvement should be carefully evaluated by the questionnaire and assessment of nonspecific airway responsiveness.

Management

The management of OR aims not only to minimize nasal symptoms and their impact on patients' quality of life but may also offer the opportunity to prevent the development of OA. Complete cessation of exposure therefore should be recommended in addition to pharmacologic treatment [2]. However, having few quantitative estimates of the risk of OA in workers with OR, reducing exposure should be considered a reasonable option when complete elimination of the causal exposure is expected to induce important adverse socioeconomic consequences, especially in workers who are not at increased risk of developing asthma (eg, workers without nonspecific bronchial hyperresponsiveness or with mild/recent disease) [3••]. In such cases, affected workers should benefit from a close medical surveillance to detect OA at an early stage.

Conclusions

The key lesson clinicians should take from recently published data is that patients with work-related respiratory symptoms experience significant delays in obtaining ap-

propriate diagnostic assessment. An early and accurate diagnosis of OA and OR is, however, crucial for minimizing their adverse health and socioeconomic consequences. A need exists for improved education of workers, employers, and physicians to increase their awareness of allergic disorders related to the workplace. All patients with asthma or rhinitis should be asked about the possible work relatedness of their condition. Health surveillance of at-risk workforces may also contribute to early identification of OA and OR, although prospective evaluation of the cost-effectiveness of surveillance programs should become a priority for assisting policymakers. National and international consensus algorithms for diagnosing OA and OR should be developed and validated through tight interactions among general practitioners, chest physicians, allergists, occupational physicians, and compensations agencies. An essential component to enhance the diagnostic process of work-related asthma and rhinitis is to promote the use and availability of the most appropriate diagnostic tests through the implementation of specialized referral centers.

Early and complete avoidance of further exposure to the sensitizing occupational agent should be recommended as the most effective therapeutic approach for OA and OR, although removal of exposure leads to substantial socioeconomic consequences. When advising their patients, clinicians also should be aware that OA is not always reversible after cessation of exposure to the sensitizing agent, but the outcome is improved by early diagnosis and avoidance measures. Determining the cost-effectiveness of different management options requires prospective, large-scale investigations using the outcomes that have been validated for the evaluation of asthma and rhinitis, such as the level of disease control, disease-specific quality of life, and measurements of airway inflammation. A need exists for further assessment of the impact of environmental interventions on the clinical and physiologic indices of OR and the development of OA in individuals with OR.

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