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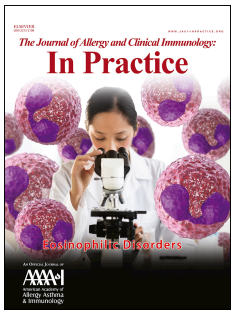

Severe occupational asthma: Insights from a multicenter European cohort

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Severe occupational asthma: Insights from a multicenter European cohort

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Word Count: 3,625 words

Keywords: Occupational asthma; Severe asthma; Asthma exacerbations; Asthma control; Airflow obstruction.

Abstract

Background: Although sensitizer-induced occupational asthma (OA) accounts for an appreciable fraction of adult asthma, the severity of OA has received little attention.

Objective: The aim of this study was to characterize the burden and determinants of severe OA in a large multicenter cohort of subjects with OA.

Methods: This retrospective study included 997 subjects with OA ascertained by a positive specific inhalation challenge completed in 20 tertiary centers in 11 European countries during the period 2006-2015. Severe asthma was defined by a high-level of treatment and any one of the following criteria: 1) daily need for a reliever medication; 2) two or more severe exacerbations in the previous year; or 3) airflow obstruction.

Results: Overall, 162 (16.2%; 95% CI: 14.0-18.7%) subjects were classified as having severe OA. Multivariable logistic regression analysis revealed that severe OA was associated with persistent (vs. reduced) exposure to the causal agent at work (odds ratio [OR], 2.78 [95% CI: 1.50-5.60]); a longer duration of the disease (OR, 1.04 [1.00-1.07]); a low level of education (OR, 2.69 [1.73-4.18]); childhood asthma (OR, 2.92 [1.13-7.36]); and sputum production (OR, 2.86 [1.87-4.38]). In subjects removed from exposure, severe OA was associated only with sputum production (OR, 3.68 [1.87-7.40]); a low education level (OR, 3.41 [1.72-6.80]); and obesity (OR, 1.98 [0.97-3.97]).

Conclusions: This study indicates that a substantial proportion of subjects with OA experience severe asthma and identifies potentially modifiable risk factors for severe OA that should be targeted in order to reduce the adverse impacts of the disease.

Word count: 249 words

Highlights Box

What is already known about this topic?

- There is only scarce information on the burden and determinants of severe sensitizer-induced occupational asthma (OA).

What does this article add to our knowledge?

- This cohort study indicates that a substantial fraction of subjects with OA (16.2%; 95% CI: 14.0-18.7%) experience severe asthma.
- The findings highlight exposure-related and individual risk factors for severe OA.

How does this study impact current management guidelines?

- The findings of this cohort study may assist clinicians and health policy makers identify potentially modifiable risk factors for severe OA that should be targeted in strategies aimed at minimizing the health and socioeconomic impacts of the disease.

List of abbreviations:

AIC - Akaike information criterion

ATS - American Thoracic Society

CI - Confidence interval

ERS - European Respiratory Society

FEV_1 -Forced expiratory volume in one second

FVC - Forced vital capacity

GINA - Global initiative for asthma

HMW - High-molecular-weight agents

IQR - Interquartile range

LMW - Low-molecular-weight agents

NSBH - nonspecific bronchial hyperresponsiveness

OA - Occupational asthma

OR - Odds ratio

SABA - Short-acting $beta_2$-agonist

SA - Severe asthma

SIC - Specific inhalation challenge

INTRODUCTION

Severe asthma (SA) imposes a substantial public health burden since the condition has a major impact on patients' quality of life and accounts for a disproportionately large portion of health care costs associated with asthma (1, 2). Clinical practice guidelines advocate the identification and remediation of exposures contributing to asthma severity as a key step in disease management (1, 3). Among potentially modifiable exposures, the workplace environment is likely to hold a notable position since workplace exposures to high-molecular-weight (HMW) and low-molecular-weight (LMW) asthmagenic agents have been associated with an increased risk of poor asthma control and severe exacerbations (4, 5).

Sensitizer-induced occupational asthma (OA), a distinguishable phenotype of work-related asthma, is characterized by the *de novo* inception of asthma or the recurrence of previously quiescent asthma induced by immunologically-mediated sensitization to a specific agent at the workplace (6, 7). Enhancing our knowledge of the burden and determinants of severe OA may be relevant from both clinical and health-economic perspectives. Complete avoidance of exposure to the causal agent is the recommended treatment option for OA but is associated with a higher socioeconomic impact as compared to reduction of exposure (6, 8-11). The severity of asthma at the time of diagnosis has been consistently identified as a risk factor for a worse outcome after removal from exposure (6, 8, 12). However, the determinants of OA severity have so far received little attention (13, 14).

The aim of this study was to estimate the burden of severe OA and to identify its determinant factors in a large multicenter cohort of subjects with OA confirmed by specific inhalation challenge (SIC).

METHODS

Study Design and Population

This retrospective, cross-sectional, observational study was conducted in an international, multicenter cohort of subjects with OA recruited from 20 tertiary centers in 11 European countries. Eligible subjects were those with a diagnosis of OA ascertained by a positive SIC completed between January 2006 and December 2015. From the 1,180 eligible subjects with a positive SIC, 183 subjects with missing data pertaining to the variables used for assessing asthma severity and control were excluded form this analysis (Figure 1 and Appendix E1 and in this article's Online Repository).

Ethics

Each participating center was requested to obtain approval from its local Institutional Review Board for this analysis of retrospective anonymized data. The central database at the Strasbourg University was approved by the "*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé*" and the "*Commission Nationale de l'Informatique et des Libertés*".

Demographic and Clinical Characteristics

Information on demographic, clinical, occupational, and physiological characteristics of the subjects at the time of the diagnostic evaluation were entered in a standardized database in each participating center (see Appendix E1 and in this article's Online Repository). The requested data were retrospectively retrieved from medical charts in 10 centers while they had been longitudinally entered in existing local databases in the remaining centers.

Briefly, the database gathered information on the following items: 1) causal agent and job; 2) demographic characteristics; 3) clinical features; 4) nature and timing of exposure to the causal agent and work-related respiratory symptoms; 5) co-existing disorders (i.e. physician-based diagnosis of work-related rhinitis, conjunctivitis, daily sputum production,

dysphonia, contact urticaria and/or dermatitis, and sinusitis). Investigators were asked to provide detailed asthma medications used: 1) during the last month of exposure at work and 2) during the last month before the SIC procedure for those subjects who were no longer exposed to the causal agent at that time. The frequency of short-acting $beta_2$-agonist (SABA) use was categorized as "never", "once a week or less ", "two or three times a week", "once or two times per day", or "three or more times a day" similar to the Asthma Control Test (15). The number of severe exacerbations during: 1) the last 12 months at work and 2), during the last 12 months before the SIC procedure for those subjects who had been removed from exposure were also collected. The level of exposure to the causal agent during the last month at work was graded by the investigators as being “unchanged/persistent” (i.e. similar to the conditions of exposure that prevailed at the time of asthma onset) or “reduced”. Data on biomarkers of airway inflammation were not included in this analysis because this information was available for a limited fraction of the subjects.

Lung Function Assessments

The database collected the baseline prebronchodilator forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1) values measured at the time of the SIC procedure before challenge exposure to the causal agent. The level of nonspecific bronchial hyperresponsiveness (NSBH) at baseline and 24 hours after challenge exposure was recorded and expressed as the concentration or dose of the pharmacological agent inducing a 15% or 20% fall in FEV_1 according to the bronchoprovocation method used in each center (see Appendix E2 and Table E1 in this article’s Online Repository).

SICs were performed according to international recommandations pertaining to the performance of a control (placebo) challenge and the duration of the functional monitoring after the end of the active challenge exposure (16, 17). For each SIC, the database requested information on the method used for delivering the suspected occupational either through a “realistic” approach mimicking the workplace exposure or the inhalation

of "allergen extract". More detailed Information on the methodology of SICs is available in Appendix E3 of this article's Online Repository.

Asthma Outcomes

Asthma treatment: The intensity of asthma treatment was graded *a posteriori* according to the treatment steps proposed by the Global Initiative for Asthma (GINA) (3). High-level treatment was defined as treatment step 4-5 (i.e. use of a high dose of inhaled corticosteroid and a second controller or systemic corticosteroid use >50% of the previous year).

Asthma control: The need for an inhaled SABA for symptom relieve was used as a proxy for the level of symptom control because most centers did not use validated instruments for the assessment of asthma control. For the purpose of this study, "poor symptom control" was therefore defined by the need for a SABA once or more a day as proposed in the American Thoracic Society (ATS) recommendations issued in 2000 (18).

Exacerbations: Severe exacerbations were defined as those requiring oral corticosteroids for at least three consecutive days or emergency room visit or hospitalization (19, 20).

Airflow obstruction: Baseline airflow obstruction was defined by a FEV_1<80% predicted value together with a FEV_1/FVC ratio <0.70.

Severe asthma: The definition of SA was adapted from the ERS/ATS criteria (1, 3) and required a high-level treatment (i.e. GINA treatment step 4-5) together with any one of the following criteria indicating uncontrolled asthma: 1) "poor symptom control"; 2) two or more severe exacerbations in the previous year; or 3) airflow obstruction.

Data Analysis

Continuous measures were summarized by medians and interquartile ranges (IQR) and categorical variables by their frequencies and proportions. Comparison between subjects

with and without severe OA was made using the Fisher's exact or chi-squared test for categorical variables and the Wilcoxon rank-sum test for numerical variables.

Multivariable logistic regression analysis was carried out using a binomial generalized linear model and the best parsimonious models were selected using a stepwise procedure based on Akaike information criterion (AIC) to identify the clinical and physiological characteristics that were associated with severe OA. The potential explanatory variables incorporated into these regressions are detailed in Appendix E4 in this article's Online Repository. Additional multivariable logistic regression analyses were conducted in order to investigate the variables associated with each of the domains used to define SA: high-intensity treatment; poor symptom control; ≥2 severe exacerbations during the last 12 months at work; and airflow obstruction measured at the time of the SIC procedure (see Appendix E4 in this article's Online Repository).

In subjects who were removed from exposure at the time of the diagnostic evaluation (n=467), the components of asthma severity at this time point were compared to those recorded when the subjects were still exposed at work. A multivariable logistic regression was also used to identify the clinical and physiological characteristics that were associated with severe asthma at the time of the SIC. Missing values were not imputed and subjects with missing data were not incorporated in multivariable analyses. Statistical analysis was performed using the R software version 3.4.1 (*https://cran.r-project.org*). A *P*-value <0.05 was considered significant.

RESULTS

Population

The population included 997 patients with OA ascertained by a positive SIC result (see Appendix E1 and Figure E1 in this article's Online Repository). The demographic, clinical, and functional characteristics of the cohort are presented in Tables I and II. The occupational agents that induced a positive SIC response are summarized in Table E2 of in this article's Online Repository.

Severe Occupational Asthma While at Work

The prevalence rates of high-level treatment, poor symptom control, ≥2 severe asthma exacerbations during the last 12 months of exposure at work, and airflow obstruction were 30.3%, 30.2%, 8.7%, and 11.9%, respectively (Tables I and II). Overall, 162 (16.2%; 95% confidence interval [CI]: 14.0-18.7) subjects were categorized as having severe OA.

Multivariable logistic regression analysis revealed that severe OA while at work was associated with "unchanged/persistent" (vs. reduced) exposure to the causal agent at work (odds ratio [OR], 2.78 [95% CI: 1.50-5.60], $P = 0.002$) and a longer duration of work-related symptoms prior to SIC (OR: 1.04 [1.00-1.07] for every 12-month period of symptomatic exposure, $P = 0.036$) (Table III). There were also significant and independent associations between severe OA and a low level of education (i.e., ≤6 years of school attendance) (OR, 2.69 [1.73-4.18], $P < 0.001$); a history of childhood asthma (i.e., ≤12 years) (OR, 2.92 [1.13-7.36], $P = 0.024$); daily sputum production (OR, 2.86 [1.87-4.38], $P <0.001$); and dysphonia at work (OR, 1.81 [1.00-3.18], $P = 0.043$). Subjects with severe OA were 2.5 times more likely (OR, 2.50 [1.16-7.08]; $P = 0.040$) to have been investigated in centers with a "high SIC activity" (i.e. >4 positive SIC per year).

The multivariable logistic regression models for each dimension of severe OA while exposed at work (i.e. high-intensity treatment; poor symptom control; ≥2 severe

exacerbations during the last 12 months at work; and airflow obstruction) are summarized in Table IV.

Asthma Severity in Subjects Removed From Exposure

At the time of the SIC procedure, 467 (46.8%) subjects had already been removed from exposure to the causal agent for a median duration of 7.0 (3.0-13.0) months. The rates of poor symptom control and exacerbations were significantly reduced at the time of the SIC while the intensity of treatment remained unchanged (Table V). Overall, the proportion of subjects with severe asthma was 18.0% when the subjects were exposed at work and decreased to 11.1% (p=0.004) when the subjects were removed from exposure at the time of SIC. In these subjects, a multivariable analysis showed that SA after removal from exposure was only associated with daily sputum production (OR, 3.68 [1.87-7.40], $P < 0.001$); a low level of education (OR, 3.41 [1.72-6.80], $P < 0.001$); and a body mass index ≥30 kg/m^2 (OR, 1.98 [0.97-3.97], $P = 0.056$).

DISCUSSION

Prevalence of Severe Occupational Asthma

This cohort study indicates that a substantial fraction of subjects with OA (16.2%; 95% CI: 14.0-18.7%) experience SA according to the multidimensional ERS/ATS consensus definition of the disease (1). This estimate is higher than those found in the general adult asthma population in two studies which applied the same definition of SA: 4.5% (95% CI, 3.9-5.1%) (21) and 6.3% (22). The prevalence of SA in the general adult asthma population remains, however, largely uncertain since available estimates have ranged from 2.3% to 36.2% in studies that used different definitions of SA in various population- and clinic-based samples of adult asthmatics (21-26). The findings in our OA cohort further support the data reported by Lemière and coworkers (27, 28) who demonstrated that OA is associated with a higher risk of severe asthma exacerbations requiring emergency room visit or hospitalization and a greater use of healthcare resources than non-work-related asthma. Nevertheless, further studies comparing OA with asthma unrelated to work are needed to confirm the challenging hypothesis that "*asthma may be more severe if it is work-related*" (29).

Determinants of Severe Occupational Asthma

Few studies have investigated the factors that determine the severity of OA at the time of diagnosis. In a multicenter Italian study of subjects with OA confirmed by SIC, ever smoking was the only factor associated with asthma severity graded according to symptom frequency, activity limitation and lung function parameters (13). A multicenter French study found that only the duration of the symptomatic period before the diagnostic evaluation was a significant predictor of "moderate-persistent" asthma defined by the level of airway obstruction and NSBH (14).

This cohort study is, to our knowledge, the first attempt to comprehensively characterize the determinants of asthma severity in a large cohort of subjects with OA using a multidimensional approach (1, 19, 20). The multivariable analyses confirmed strong

interactions between the individual dimensions of asthma severity and control (i.e., treatment level, symptom control, severe exacerbations, and airflow obstruction), similar to what has been found in general asthma populations. More specifically, poor symptom control was linked to an increased risk of severe exacerbations (5, 30, 31) and severe exacerbations were associated with greater airflow limitation (32, 33). In addition, these analyses highlighted differential effects of identified risk factors and the type of causal agent (i.e. HMW vs. LMW agents) on the individual domains of asthma severity and control, further supporting the importance of capturing separately the diverse dimensions of the disease (1, 3, 19, 20).

The results of this study indicated that severe OA while exposed at work, and predominantly its high-intensity treatment component, was associated with “unchanged/persistent” exposure to the causal agent. This relationship was significant although workplace exposure was only qualitatively evaluated by the investigators as being "unchanged/persistent" or "reduced" compared with the conditions that prevailed at the time of the onset of work-related asthma symptoms. Due to the retrospective design of the study, it was not possible to quantify the duration and magnitude of exposure to “reduced” levels of causal agents. A longer duration of work-related asthma symptoms also increased the risk of severe OA, mainly through an impact on the intensity of asthma treatment and the level of airflow obstruction. Although systematic reviews of follow-up studies indicated that subjects with OA related to HMW agents are more likely to have a worse outcome after complete avoidance of exposure to the causal agent (12, 34), the risk of severe OA was not affected by the type of causal agent (i.e., LMW vs. HMW) in this cross-sectional cohort study that assessed the severity of OA at the time of diagnosis. Nevertheless, when the diverse domains of asthma severity were considered separately, subjects with OA due to LMW agents showed slightly higher rates of severe exacerbations and high-level treatment as compared to OA caused by HMW agents which is consistent with previous cross-sectional studies (35, 36). These discordant findings warrant further investigation in longitudinal studies.

In addition, the multivariable logistic regression analyses identified socio-demographic and clinical risk factors for severe OA that have been implicated in SA unrelated to work. The most clinically relevant finding in our cohort was that chronic sputum production was strongly associated with all dimensions of severe OA independently from smoking. These results are consistent with studies in adult asthmatics that documented significant associations between sputum production and uncontrolled (37) or severe (23, 26) asthma.

Despite its low prevalence in this cohort, childhood asthma was a strong predictor for severe OA, especially for poor symptom control and – with borderline significance – airflow obstruction. Although atopy is a well identified risk factor for the development of OA in workers exposed to HMW agents, a history of childhood asthma was not more frequently found in severe OA caused by HMW agents (12.2%) as compared to LMW agents (11.5%). In adult asthma cohorts, the respective effects of the age at asthma onset and its duration on the severity of asthma were often not disentangled. Nevertheless, some investigators reported that an older age at asthma onset had a greater effect than asthma duration in adult asthmatics (26, 38). Interestingly, the analysis of this OA cohort indicated that both a history of childhood asthma and the duration of work-related asthma symptoms had independent effects on asthma severity through different domains.

A low level of education was a significant risk factor for severe OA, mainly through a strong association with poor symptom control. Non-Caucasian ethnicity was also independently associated with poor symptom control and severe asthma exacerbations, but was not significantly associated with the multicomponent definition of severe OA. These features are likely to reflect a lower socioeconomic status which can lead to increased risk of SA through various pathways (39, 40).

This OA cohort revealed several differences compared to the findings of studies conducted in general adult asthma populations. Demographic and clinical risk factors for SA that have been identified in some studies of general asthma populations, namely

female gender (41, 42), obesity (26, 42, 43); cigarette smoking (23, 26, 44, 45), rhinitis (23), and sinusitis (42, 43, 46-48) did not show an association with severe OA here although chronic sinusitis was associated with high-level treatment (Table IV). By contrast, no relationship was observed between work-related rhinitis and the severity of OA, which is discordant with the findings of Moscato and co-workers who reported that moderate-severe ocupational rhinitis was associated with more severe OA (49). However, the severity of rhinitis symptoms was not graded in our study. Of note, obesity showed a borderline significant association with severe OA but only at the time of the SIC procedure in subjects who were no longer exposed to the causal agent. This finding suggests that individual risk factors for SA may become apparent only after avoidance of the causal allergen. In this respect, OA may be regarded as a unique opportunity to investigate the factors that determine the outcome of allergic asthma after avoidance of exposure.

An intriguing observation was the association between dysphonia and severe OA. Dysphonia may result from different mechanisms, including a local adverse effect from the inhalation of high doses of corticosteroids, concomitant “work-associated irritable larynx syndrome” triggered by irritants at work (50), or paradoxical vocal cord movement, which is prevalent in asthmatics with airflow obstruction and may mimic asthma symptoms (51). It is unlikely that paradoxical vocal cord movement may have led to misclassification of SA in this study since dysphonia was not associated with poor symptom control in multivariable analyses. Although there is increasing awareness of the association between upper/middle airway dysfunction and SA (51), its clinical relevance warrants further investigation.

Strenghts and Limitations

The strengths of this study are in its large sample size, the homogeneous diagnostic criteria used for identifying OA, and the multidimensional assessment of asthma severity (1, 3, 19, 20). However, several limitations deserve thorough discussion. Inherent to the lack of a standardized clinical assessment of workers with suspected OA among participating centers, some potential determinants of SA could not be collected, including

nonsteroidal anti-inflammatory drug sensitivity, gastro-esophageal reflux disease, psychological disorders, and magnitude of postbronchodilator FEV_1 reversibility. More importantly, the level of asthma control could not be fully captured (1, 3, 19, 20) because detailed information about the frequency of daytime/nighttime symptoms and asthma-related limitation of daily activities was not systematically collected. ~~In addition,~~ The retrospective design of the study limited our ability to distinguish severe "refractory" asthma (i.e., asthma that remains uncontrolled despite GINA treatment step 4/5) from severe "difficult-to-control" asthma (i.e., uncontrolled asthma resulting from poor adherence, poor inhalation technique, or untreated comorbidities despite follow-up by a respiratory specialist for at least 6 months) (1, 3, 19, 20). In addition, it was not possible to ascertain that the subjects were uniformly treated according to GINA guidelines and that a high-level treatment was necessay to prevent asthma from becoming uncontrolled (1). The retrospective collection of data pertaining to asthma severity and control may have have introduced some bias, especially for subjects who were no longer at work at the time of the diagnostic evaluation.

We acknowledge that this multicenter cohort may not be fully representative of the whole population of workers affected with OA. The proportion of subjects with severe OA might have been overestimated because recruitment from tertiary centers could have introduced a selection bias toward subjects with more severe asthma. Conversely, the prevalence of severe OA might have been underestimated because the assessment of asthma severity was based on spirometry measurements that were available only at baseline of the SIC procedure, at a time where half the subjects had already been removed from exposure. In addition, a potential bias toward inclusion of less severe asthmatics might have occurred since most centres did not perform SIC in subjects with marked airflow obstruction (see Appendix E3 in this article's Online Repository). However, the broad recruitment from 20 centers throughout Europe is likely to minimize as far as possible the potential selection bias due to local clinical and recruitment practices and to enhance the generalizability of the findings.

Conclusions

This study shows that the determinants of severe OA include not only potentially modifiable factors (i.e. “unchanged/persistent” exposure to the causal agent and duration of symptomatic exposure before diagnosis), but also a low sociodemographic status and clinical characteristics (i.e. childhood asthma and daily sputum production). Interestingly, data collected in the subset of subjects removed from the causal agent at the time of the diagnostic evaluation suggest that the persistence of SA was predominantly driven by individual risk factors. These results further support the need for an early diagnosis and prompt implementation of environmental interventions in order to reduce the burden of severe OA. In addition, our findings may help clinicians to identify subjects with OA at high risk for a more severe outcome and contribute to a more personalized management approach aimed at minimizing the health and socioeconomic impacts of the disease.

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Table I. Demographic and clinical characteristics of the subjects

Characteristic	Missing values	All subjects (n=997)	Subjects with severe asthma‡ (n=162)	Subjects with non-severe asthma (n=835)	P-value
Age, yr*	0	42 (33-51)	44 (35-51)	42 (33-51)	0.190
Sex (male)	0	586 (58.8)	105 (64.8)	481 (57.6)	0.100
Body mass index:					
kg/m^2*	15	27 (24-30)	27 (24-31)	27 (24-30)	0.130
≥30 kg/m^2	15	246 (25.1)	50 (30.9)	196 (23.9)	0.070
Smoking habits:	21				0.570
Current smoker		195 (20.0)	36 (22.2)	159 (19.5)	
Ex-smoker		271 (27.8)	47 (29.0)	224 (27.5)	
Never-smoker		510 (52.2)	79 (48.8)	431 (53.0)	
Level of education:	144				**<0.001**
Primary (≤6 years)		217 (25.4)	58 (45.7)	159 (21.9)	
Secondary (7-12 years)		562 (65.9)	62 (48.8)	500 (68.9)	
Post-secondary (>12 years)		74 (8.7)	7 (5.5)	67 (9.2)	
Ethnicity, non-Caucasian	3	60 (6.0)	18 (11.2)	42 (5.0)	**0.006**
Atopy†	29	500 (51.6)	79 (51.6)	421 (51.7)	1.000
Age of asthma onset	19				**<0.001**
<12 years		46 (4.7)	19 (11.8)	27 (3.3)	
12-18 years		15 (1.5)	3 (1.9)	12 (1.5)	
>18 years		917 (93.8)	139 (86.3)	778 (95.2)	
Type of causal agent, high-molecular-weight	0	493 (49.4)	72 (44.4)	422 (50.5)	0.250
Duration of exposure before asthma onset, mo*	16	84 (36-180)	76 (29-210)	84 (36-180)	0.800
Duration of symptomatic exposure, mo*	12	30 (12-67)	36 (16-74)	28 (12-60)	**0.020**
Interval since last work exposure and SIC, mo [b]	1	1.0 (0.1-8.0)	1.0 (0.1-8.8)	1.0 (0.1-7.8)	0.360
Exposure last month at work, unchanged/persistent§	0	762 (76.4)	138 (85.2)	624 (74.7)	**0.003**
Coexisting conditions:					
Daily sputum production	16	287 (29.3)	80 (51.0)	207 (25.1)	**<0.001**
Work-related rhinitis	2	711 (71.5)	118 (72.8)	593 (71.2)	0.700
Work-related conjunctivitis	14	390 (39.7)	64 (39.8)	326 (39.7)	1.000
Chronic rhinosinusitis	8	117 (11.8)	25 (15.5)	92 (11.1)	0.140
Dysphonia at work	40	130 (13.6)	32 (20.5)	98 (12.2)	**0.010**
GINA treatment step while at work	0				**<0.001**
Treatment step 0		149 (14.9)	0	149 (17.8)	
Treatment step 1		143 (14.3)	0	143 (17.1)	
Treatment step 2		57 (5.7)	0	57 (6.8)	
Treatment step 3		346 (34.7)	0	346 (41.4)	
Treatment step 4		293 (29.4)	155 (95.7)	138 (16.5)	
Treatment step 5		9 (0.9)	7 (4.3)	2 (0.2)	
Inhaled short-acting β_2-agonist use while at work	0	732 (73.5)	153 (94.4)	579 (69.4)	**<0.001**
Never		265 (26.6)	9 (5.6)	256 (30.7)	
Once or less per week		195 (19.6)	5 (3.1)	190 (22.8)	
2 or more times a week		236 (23.7)	17 (10.5)	219 (26.2)	
≥1 times a day¥		301 (30.2)	131 (80.9)	170 (20.4)	
≥1 asthma exacerbation (last 12 mo at work)	0	232 (23.3)	77 (47.5)	155 (18.6)	**<0.001**
≥2 asthma exacerbation (last 12 mo at work)	0	87 (8.7)	40 (24.7)	47 (5.6)	**<0.001**
Work-related contact dermatitis	2	153 (15.4)	26 (16.1)	127 (15.2)	0.810

Legend: Data are presented as n and % of available data unless otherwise specified. ICS: inhaled corticosteroid; GINA: Global Initiative for Asthma (3), SIC: specific inhalation challenge. Values in boldface are statistically significant.

* Median value with interquartile range within parentheses;

† Atopy defined by the presence of a positive skin-prick test to at least one common allergen;

¥ The need for a short-acting b2-agonist once or more a day was used as a proxy for "poor symptom control";

‡ Definition of severe asthma adapted from the European Respiratory Society/American Thoracic Society criteria (1)

§ The level of exposure to the causal agent at work was qualitatively categorized by the investigators as "unchanged/persistent" or "reduced" compared to the conditions of exposure at the time of disease onset.

Table II. Functional characteristics of the subjects

	All subjects (n=997)	Subjects with severe asthma (n=162)	Subjects with non-severe asthma (n=835)	*P*-value
Baseline spirometry :	(n=997)	(n=162)	(n=835)	
FVC, % pred*	99 (89-109)	94 (84-105)	100 (91-110)	**<0.001**
FEV_1, % pred*	91 (81-100)	80 (71-93)	92 (83-101)	**<0.001**
FEV_1 <80%	209 (21.0)	82 (50.6)	127 (15.2)	**<0.001**
FEV_1/FVC*	77 (71-82)	70 (63-78)	77 (72-82)	**<0.001**
FEV_1/FVC <70%	219 (22.0)	77 (47.5)	142 (17.0)	**<0.001**
Airflow obstruction†	119 (11.9)	65 (40.1)	54 (6.5)	**<0.001**
Baseline level of NSBH at the time of SIC¥:	(n=915)	(n=153)	(n=762)	**0.004**
Absent	259 (28.3)	28 (18.3)	231 (30.3)	
Mild	403 (44.0)	71 (46.4)	332 (43.6)	
Moderate-to-severe	253 (27.6)	54 (35.3)	199 (26.1)	
Pattern of bronchial response to SIC:	(n=914)	(n=155)	(n=759)	
Isolated early reaction	349 (36.0)	55 (34.6)	294 (36.3)	0.720
Isolated late reaction	226 (22.9)	33 (20.5)	193 (23.4)	0.470
Dual reaction	339 (35.0)	67 (41.9)	272 (33.6)	0.050

Legend: Data are presented as n (% of available data) unless otherwise specified. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; NSBH: nonspecific bronchial hyperresponsiveness; SIC: specific inhalation challenge. Values in boldface are statistically significant.

* Median value with interquartile range (IQR) within parentheses;

† Airflow obstruction defined by a FEV_1 <80% predicted value and a FEV_1/FVC ratio <0.70;

¥ See Table E1 in this article's Onine Repository for the threshold values used for grading the level of NSBH.

Table III. Multivariable model for severe occupational asthma while at work

Independent variables	Severe asthma*	
	OR (95% CI)	***P*-value**
Exposure-related factors:		
Low-molecular-weight causal agent, vs. high-molecular-weight		
Duration of symptomatic exposure, per 12-month periods	1.037 (1.002-1.073)	**0.036**
"Unchanged/persistent" exposure at work, vs. reduced‡	2.78 (1.50-5.60)	**0.002**
Socio-demographic factors:		
Age >42 yrs		
Non-Caucasian ethnicity, vs. Caucasian		
Low level of education, ≤6 yrs	2.69 (1.73-4.18)	**<0.001**
Clinical features:		
Childhood asthma, ≤12 yrs	2.92 (1.13-7.36)	**0.024**
Daily sputum production, yes vs. no	2.86 (1.86-4.38)	**<0.001**
Chronic sinusitis, yes vs. no		
Dysphonia at work, yes vs. no	1.809 (1.002-3.179)	**0.043**
Center-related characteristics:		
"High-activity" center (i.e. >4 positive SIC/yr), yes vs. no †	2.50 (1.16-7.08)	**0.040**

Legend: 784 subjects were included in the multivariable model. An empty cell means that the independent variable was not retained in the final multivariable model and the corresponding odds ratio was not available.
SIC: specific inhalation challenge.
* Definition of severe asthma adapted from the European Respiratory Society/American Thoracic Society criteria (1);
† The level of activity of the centers was categorized as ''high'' and ''low'' based on the median number of positive specific inhalation challenges reported annually (4.1; IQR: 2.5-7.5).
‡ The level of exposure to the causal agent at work was qualitatively categorized by the investigators as "unchanged/persistent" or "reduced" compared to the conditions of exposure at the time of disease onset.

Table IV. Multivariable models for the factors that determine the domains of asthma severity and control while at work

Independent variables	High-level treatment*		Poor symptom control†		Severe asthma exacerbations¥		Airflow obstruction‡	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Exposure-related factors:								
Low-molecular-agent	1.46 (1.03-2.06)	**0.032**			1.83 (1.03-3.31)	**0.041**		
Duration of symptomatic exposure	1.03 (1.00-1.06)	**0.038**					1.05 (1.02-1.08)	**0.003**
Level of exposure, unchanged/persistent	1.79 (1.16-2.81)	**0.009**						
Sociodemographic factors:								
Age >42 yr							2.35 (1.50-3.73)	**<0.001**
Non-Caucasian ethnicity,			2.30 (1.93-4.92)	**0.029**	2.61 (0.98-6.45)	**0.044**		
Low level of education, ≤6 yr	1.40 (0.95-2.05)	0.086	2.43 (1.68-3.53)	**<0.001**				
Clinical features:								
Childhood asthma, ≤12 yr			4.07 (1.70-10.18)	**0.002**			2.26 (0.94-4.96)	0.052
Daily sputum production (yes vs. no)	1.93 (1.35-2.77)	**<0.001**	1.62 (1.13-2.32)	**0.008**	1.98 (1.11-3.50)	**0.019**	1.62 (1.05-2.49)	**0.028**
Chronic sinusitis	1.99 (1.21-3.24)	**0.006**						
Dysphonia at work	1.96 (1.20-3.16)	**0.006**						
Asthma-related factors:								
High-level treatment*	NA		1.61 (1.11-2.31)	**0.011**	2.48 (1.41-4.37)	**0.002**		
Poor symptom control†	1.76 (1.20-2.57)	**0.004**	NA		4.46 (2.56-7.88)	**<0.001**	1.58 (0.97 2-54)	0.060
Exacerbation, ≥2 last 12 mo¥	2.63 (1.50-4.61)	**<0.001**	4.02 (2.32-7.08)	**<0.001**	NA		2.31 (1.10-4.62)	**0.021**
Center-related characteristics:								
"High-activity" center (i.e. >4 positive SIC/yr)#	1.76 (1.02-3.30)	0.054	5.21 (2.40-14.92)	**<0.001**				

Legend: An empty cell means that the independent variable was not retained in the final multivariable model and the corresponding odds ratio was not available. NA: not applicable; SIC: specific inhalation challenge.

* High-level treatment defined according Global Initiative for Asthma (GINA) as treatment step 4-5 (782 subjects were included in the multivariable model);

† Poor symptom control defined by the use of an inhaled short-acting β_2-agonist at least once a day (827 subjects were included in the multivariable model);

¥ Two or more severe escerbations during the last 12 months at work; severe exacerbations were defined as those requiring oral corticosteroids for at least 3 consecutive days or emergency room visit or hospitalization (19, 20) (780 subjects were included in the multivariable model);

‡ Airflow obstruction defined by a FEV_1 <80% predicted value and a FEV_1/FVC ratio <0.70 at the time of the SIC. Multivariable regression analysis for airway obstruction used the level of treatment and the need for a SABA at the time of the SIC as well as the number of exacerbations during the last 12 months before the SIC procedure (831 subjects were included in the multivariable model);

§ The level of exposure to the causal agent at work was qualitatively categorized by the investigators as “unchanged/persistent” or “reduced” compared to the conditions of exposure at the time of disease onset;

The level of activity of the centers was categorized as ‘‘high’’ and ‘‘low’’ based on the median number of positive specific inhalation challenges reported annually (4.1; IQR: 2.5-7.5).

Table V. Asthma severity at the time of the SIC in subjects removed from exposure (n=467) compared to the severity of their asthma while previously exposed at work

Characteristic	At work	Off work (SIC procedure)	P-value
GINA treatment step:			
Treatment step 0	79 (16.9)	96 (20.6)	0.417
Treatment step 1	61 (13.1)	56 (12.0)	
Treatment step 2	24 (5.1)	29 (6.2)	
Treatment step 3	151 (32.3)	154 (33.0)	
Treatment step 4	152 (32.5)	131 (28.1)	
Treatment step 5	0	1 (0.2)	
Frequency of SABA use:	332 (71.1)	286 (61.2)	**<0.001**
Never	135 (28.9)	181 (38.8)	**<0.001**
Once or less per week	73 (15.6)	146 (31.3)	
2 or more times a week	110 (23.6)	66 (14.1)	
Once or more a day*	149 (31.9)	74 (15.8)	
≥1 severe asthma exacerbations	124 (26.6)[†]	22 (4.7)[¥]	**<0.001**
≥2 severe asthma exacerbations	40 (8.6)[†]	4 (0.9)[¥]	**<0.001**
Severe asthma[‡]	84 (18.0)	52 (11.1)	**0.004**

Legend: Data are presented as n and % of available data unless otherwise specified. GINA: Global Initiative for Asthma (3); SABA: short-acting β_2-agnosit; SIC: specific inhalation challenge. Values in boldface are statistically significant.

* Need for a SABA once or more a day used as a proxy for "poor symptom control";

[†] Number of exacerbations during the last 12 months of exposure at work;

[¥] Number of exacerbations during the last 12 months before the SIC procedure;

[‡] Definition of severe asthma adapted from the European Respiratory Society/American Thoracic Society criteria (see Methods) (1).

LEGEND TO FIGURES

FIGURE 1

Flowchart of the study population. FEV_1: forced expiratory volume in one-second; NSBH: nonspecific bronchial hyperresponsiveness; SIC: specific inhalation challenge (see Appendix E1 in this article's Online Repository).

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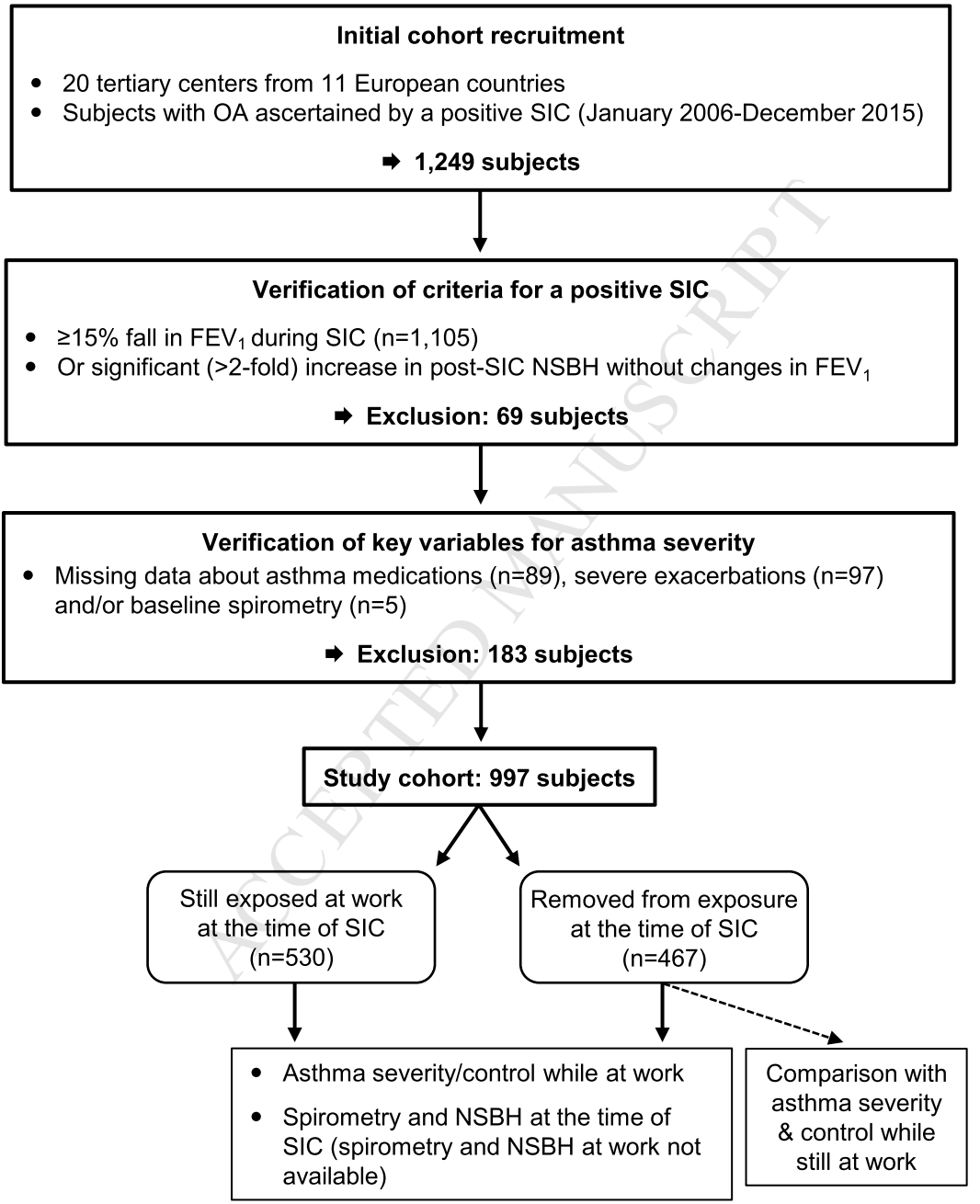

SEVERE OCCUPATIONAL ASTHMA: INSIGHTS FROM A MULTICENTER EUROPEAN COHORT

ONLINE REPOSITORY MATERIAL

APPENDIX E1

Cohort Recruitment

Twenty-four European tertiary centers performing specific inhalation challenges (SICs) for the diagnosis of occupational asthma (OA) (1) were invited to participate to this retrospective cohort, of which 20 agreed to complete the standardized database. Patient eligibility for inclusion in this cohort was based on a diagnosis of OA objectively confirmed by a positive SIC result.

Nine centers reported over the full 10-year study period while 11 centers included patients with a positive SIC over periods ranging from 3 to 9 years according to available data. The median annual number of positive SICs per center was 4.1 (interquartile range, 2.5-7.5).

For each subject entered in the database, investigators were asked to provide the maximum fall in forced expiratory volume in 1 second (FEV_1) expressed as percent from baseline value that was recorded after the end of the challenge exposure as well as the level of nonspecific bronchial hyperresponsiveness (NSBH) measured before the SIC and 24 hours after the end of challenge exposure (see below “Assessment of nonspecific bronchial hyperresponsiveness”). A positive SIC result was defined by either a ≥15% fall in FEV_1 at any time-point during the post-challenge monitoring period or a significant increase in the post-challenge level of NSBH as compared to the baseline value (2-4).

One thousand one hundred eighty of the 1,249 reported subjects had either a documented ≥15% fall in FEV_1 during SIC (n=1,105) or a significant increase in the post-challenge level of NSBH in the absence of a ≥15% fall in FEV_1 (n=75). Of these 1,180 eligible subjects, 183 were excluded from analysis because of incomplete information on asthma medications (n=89), asthma exacerbations (n=97), and/or baseline spirometry (n=5), which were considered key variables for this analysis. The final cohort included 997 analyzable subjects.

Data Collection

Detailed information on demographic, clinical, occupational, and physiological characteristics of the subjects at the time of the diagnostic evaluation were entered in a standardized Excel database in each participating center by local investigators (see Appendix E1 and in this article's Online Repository). The requested information was exclusively retrieved from medical charts in 10 centers while in the other centers, all or part of the data had been prospectively entered in existing local databases. The standardized databases were then checked by three investigators (OV, CR, and JD), pooled together and centralized at the Strasbourg University (FdB, NM, and JG).

APPENDIX E2

Assessment of Nonspecific Bronchial Hyperresponsiveness

The database collected information on the level of NSBH measured at baseline and 24 hours after the end of challenge exposure. The level of NSBH was expressed as the concentration or dose of the pharmacological agent inducing a 15% or 20 % fall in FEV_1 ($PC/PD_{15\text{-}20\%}$) according to the bronchoprovocation method used in each center. Since participating centers used six different methods, the level NSBH was only categorized as “absence of NSBH”, “mild NSBH”, and “moderate-to-severe NSBH” based on available recommendations (5-7) or using a consensus Delphi approach among investigators. The bronchoprovocation methods and threshold values used for defining the level of NSBH are detailed in Table E2. Overall, NSBH was not assessed in 82 of 997 subjects. Among these subjects, the diagnosis of asthma was documented by reversible airflow obstruction on spirometry (n=37) or daily variations in peak expiratory flow (n=30). The diagnosis of asthma was not formally documented in 15 subjects. A significant increase in post-challenge level of NSBH was defined as a ≥2-fold decrease in the $PC/PD_{15\text{-}20\%}$ value recorded 24 hours after the challenge exposure as compared to the baseline value (i.e. a pre/post $PC/PD_{15\text{-}20\%}$ ratio ≥2) (2-4).

APPENDIX E3

Methodology of Specific Inhalation Challenges

Participating investigators completed a questionnaire in order to evaluate whether: 1) a control (placebo) test was performed before challenging the subjects with the suspected occupational agent(s) and 2) a functional monitoring of at least 6 hours after the end of challenge exposures was completed in order to ensure compliance with international recommendations (4, 5). They were also requested to state which lower limit value of FEV_1 they considered a contra-indication for performing a SIC procedure. This lower limit of FEV_1 was 70% of predicted value in 11 centers, 65% in one center; 60% in six centers, and 50% in 2 centers.

Asthma medications were adapted according to the Global Initiative for Asthma guidelines in subjects who showed increased variability in FEV_1 or peak expiratory flow rates before the SIC procedure or during the control day. Long-acting and short-acting bronchodilators were stopped before the SIC according to their duration of action. Inhaled corticosteroids were withdrawn for two to seven days before the SIC procedure in 18 centers and for longer periods (i.e. at least 15 days or 28 days) in two centers. However, the daily dose of inhaled corticosteroids could be administered as a single evening dose during the SIC procedure in subjects whose asthma became unstable after inhaled corticosteroids withdrawal.

For each specific inhalation challenge (SIC), the database requested information on the method used for delivering the suspected occupational either through a “realistic” approach mimicking the workplace exposure (n=944) (8) or the inhalation an “allergen extract” (n=53). A detailed description of the methods used for delivering various occupational agents during SICs has been compiled by the European Taskforce on SIC from twelve specialist centers participating to the current cohort study (4). This “*Handbook of procedures for specific inhalation challenge testing in the diagnosis of occupational asthma*” is available from *www.erj.ersjournals.com* as an online supplementary material to the European Respiratory Society consensus statement on specific inhalation challenge in the diagnosis of occupational asthma (4).

The database collected the maximum fall in FEV_1 expressed as percent from baseline value that was recorded during two distinct time periods of the post-challenge functional monitoring: 1) the period between the end of the challenge exposure and the 60th minute post-exposure (i.e. the “early component” of the bronchial response) and 2) the period between the 60th

minute post-challenge and the end of the post-SIC follow-up (i.e. the “late component” of the bronchial response).

The results of the SICs were interpreted *a posteriori* according to standardized criteria (4). A positive SIC result was defined by either a ≥15% fall in FEV_1 at any time during the post-challenge monitoring or a twofold or greater increase in the post-challenge level of NSBH in the absence of significant changes in FEV. Among the 997 subjects included in this analysis, 935 subjects showed a ≥15% fall in FEV_1 during SIC and 62 a significant increase in the post-challenge level of NSBH.

APPENDIX E4

Statistical Analysis

Multivariable logistic regression analysis was carried out using a binomial generalized linear model to identify the clinical and physiological characteristics that were significantly and independently associated with severe OA. The potential explanatory variables incorporated into these regressions were selected based on bivariate exploratory analyses and potential risk factors for SA identified in the literature. The model consisted of the following variables: age (>42 yr vs. ≤42 yr); sex; ethnicity (Caucasian vs. non-Caucasian); body mass index (BMI, ≥30 kg/m^2 vs. <30 kg/m^2; atopy (presence vs. absence of a positive skin-prick test response to at least one common aeroallergen); smoking status (never vs ever being a smoker); level of education (≤6 yr vs. >6 yr); age at asthma onset (<12 yr vs. ≥12 yr); type of causal agent (low-molecular-weight [LMW] vs. high-molecular-weight [HMW] agent); duration of asthma symptoms at work; level of exposure during the last month at work (persistently high vs. reduced); work-related rhinitis or conjunctivitis (yes vs. no); daily sputum production (yes vs. no); chronic sinusitis (yes vs. no); dysphonia at work (yes vs. no); and recruitment from a center with a “high-activity” (i.e., >4 positive SICs per year) vs. a “low-activity” (i.e. ≤4 positive SICs per). The various components of asthma severity (i.e. high-intensity treatment; poor symptom control; ≥2 severe exacerbations during the last 12 months at work; and airflow obstruction) were not included in this analysis because they are part of the definition of severe asthma. Model selection was performed on this dataset with removed missing values using a stepwise algorithm (both forward and backward stepwise searches) based on Akaike information criterion (AIC) (stepAIC function in the MASS package). This procedure selects the most parsimonious model with informative variables. Odds ratio (and CI) are reported for each variable retained in the final model. Missing values were not imputed.

Additional multivariable logistic regressions were conducted in order to identify the variables associated with each of the domains used to define SA while at work: high-intensity treatment (i.e. GINA treatment step 4-5); poor symptom control (i.e. SABA ≥1/day); ≥2 severe exacerbations during the last 12 months at work; and airflow obstruction. The same independent variables as those used in the multivariable analysis of severe OA were included into these logistic regressions and the best models were selected based on AIC. The severity

domains were also included as independent variables in the models where appropriate, but airway obstruction was not included since spirometric values were those measured at the time of the SIC procedure when 46.8% of the study subjects where already removed from exposure. Likewise, the level of treatment and the need for a SABA at the time of the SIC procedure, and the number of exacerbations during the last 12 months before the SIC were used in the multivariable regression analysis of airway obstruction in order to take into account the potential effect of cessation of exposure in a substantial fraction of the subjects.

Table E1. Methods used for measuring the level of nonspecific bronchial hyperresponsiveness

Method (pharmacological agent)	No. of centers (subjects)	Threshold values for nonspecific bronchial hyperresponsiveness		
		Moderate-to-severe	Mild	Absent
Tidal breath method (histamine/methacholine) (5, 6)	5 (404)	PC_{20} <1 mg/ml	PC_{20}: 1-16 mg/ml	PC_{20} >16 mg/ml
Five-breath dosimeter method (methacholine) (5, 6)	9 (257)	PD_{20} <0.1 mg PC_{20} <1 mg/ml	PD_{20}: 0.1-1.5 mg PC_{20}: 1-16 mg/ml	PD_{20} >1.5 mg PC_{20} >16 mg/ml
Rapid dosimeter method (histamine) (7)	2 (185)	PD_{15} <0.4 mg	PD_{15}: 0.4-1.6 mg	PD_{15} >1.6 mg
APS dosimeter method (histamine/methacholine) (9)	2 (66)	PD_{20}<0.1 mg PC_{20} <1 mg/ml	PD_{20}: 0.1-1.4 mg PC_{20}: 1-16 mg/ml	PD_{20} <1.4 mg PC_{20} >16 mg/ml
Reservoir bag dosimeter method (methacholine) (10)	1 (2)	PD_{20} or PD_{100}sRt <0.1 mg	PD_{20} or PD_{100} sRt: 0.1-0.3 mg	PD_{20} or PD_{100}sRt >0.3 mg
Dosimeter method (mannitol) (11)	1(1)	PD_{15} ≤250 mg	PD_{15}: 251-635 mg	PD_{15} >635 mg

Legend: $PC/PD_{15/20}$: provocative concentration of pharmacological agent inducing a 15 or 20% fall in forced expiratory volume in 1 s (FEV_1); PD_{100} sRt: provocative concentration of pharmacological agent inducing a doubling of specific airway resistance.

Table E2. Causal agents

High-molecular-weight agents	n (%)*	Low-molecular-weight agents	n (%)*
Flour/grains	341 (34.6)	Isocyanates	139 (14.1)
Latex	35 (3.6)	Persulfate salts	57 (5.8)
Enzymes	23 (2.3)	Quaternary ammonium compounds	38 (3.9)
Storage mites	10 (1.0)	Metals	30 (3.0)
Cow dander	9 (0.9)	Welding	30 (3.0)
Rodents	9 (0.9)	Wood dusts	28 (2.8)
Fish/seafood	8 (0.8)	Acrylate compounds	28 (2.8)
Ornemental plants	6 (0.6)	Cleaning products/disinfectant (NOS)	26 (2.6)
Insects and derived products	5 (0.5)	Aldehydes	15 (1.5)
Vegetal gums	3 (0.3)	Metal working fluids	15 (1.5)
Soybean flour	3 (0.3)	Resins/glues/paints (NOS)	15 (1.5)
Spices	3 (0.3)	Epoxy resins	14 (1.4)
Moulds	2 (0.2)	Amines	10 (1.0)
Various plant-derived products	22 (2.2)	Acid anhydrides	10 (1.0)
Various animals and derived products	14 (1.4)	Drugs	9 (0.9)
		Colophony	4 (0.4)
		Reactive dyes	2 (0.2)
		Styrene	2 (0.2)
		Triglycidylisocyanurate	1 (0.1)
		Various low-molecular-weight agents	17 (1.7)
Total:	493 (50.1)	Total:	492 (49.9)

Legend: NOS: not otherwise specified

* % of total identified agents (n=985); the causal agent was not precisely identified in 12 subjects.

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