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Evolution of occupational asthma: Does cessation of exposure really improve prognosis?

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Summary
Aim: To assess the evolution of occupational asthma (OA) depending on whether the patient avoids or continues with exposure to the offending agent.
Methods: Study in patients diagnosed with OA using a specific inhalation challenge. Patients underwent the following examinations on the same day: clinical interview, physical examination, forced spirometry, methacholine test and determination of total IgE. Clinical improvement, deterioration or no change were defined according to the changes seen on the GINA severity scale at the time of diagnosis.
Results: Of the 73 patients finally included, 55 had totally ended exposure and 18 continued to be exposed at work. Clinical improvement was observed in 47% of those who had terminated exposure and in 22% of those who remained exposed; clinical deterioration was observed in 14% and 17% respectively ($p = 0.805$). Logistical regression analysis, including the type of agent and the persistence or avoidance of exposure among the variables, did not show any predictive factors of clinical evolution. Similarly, the changes in FEV_1 and in bronchial hyperresponsiveness were not associated with the avoidance or continuation of exposure to the causative agent.

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Conclusions: Avoiding exposure to the causative agent in patients with OA does not seem to improve prognosis in this disease. Despite these findings, there is insufficient evidence to recommend a change in current management guidelines.

Introduction

Occupational asthma (OA) is the most frequent work-related respiratory disease in developed countries [1,2] and it is estimated that roughly 10% cases of bronchial asthma and between 15 and 25% of adult onset asthma may be of occupational origin [3,4].

For workers with OA caused by a respiratory sensitizer, complete and definitive removal from exposure to the sensitizing agent has usually been recommended as the most efficient therapeutic approach [5—9]. However, bearing in mind that cessation of exposure is often not feasible [10], in recent years a number of meta-analyses have been carried out to compare the effects of these two management options [11—14]. The results of these systematic reviews indicate that the available data on the prognosis of OA are insufficient to enable physicians to provide confident, informed advice to patients with the disease.

Probably this conclusion is reached because the majority of the more than 100 papers published so far are heterogeneous single-center studies, with small patient samples and based on a single causative agent; all apply an observational approach and, for ethical reasons, none have randomized patients to avoid or continue exposure to the causative agent [15,16].

The aim of the present study is to assess the evolution of all patients diagnosed with OA in the last ten years at two centers in our country according to the persistence or cessation of exposure to the causative agent and, on the basis of the GINA classification, of asthma severity [17]. The study design also allows an assessment of the influence on the prognosis of OA of variables that have not been widely studied to date, such as the medical treatment received and the type of causative agent.

Material and methods

Patients and design

This cross-sectional study was approved by the Ethics Committee of the two participating centers. Using the databases from each center, all patients who had been diagnosed with immunological OA by specific inhalation challenge (SIC) were selected. All patients included had at least one year of follow-up since diagnosis. Between September 2010 and June 2011, patients were scheduled for a visit at the pulmonary function laboratory after having discontinued treatment with inhaled corticosteroids and long-acting beta2 agonists 24 h previously and the use of short-acting beta2 agonists at least six hours previously. All patients provided written informed consent prior to participation.

First, a careful review of clinical histories at the time of diagnosis was carried out. The GINA classification that patients had at the time of diagnosis was made retrospectively with data from the clinical history and was based primarily on the treatment that patients were receiving at this time. Later, patients were interviewed again, placing special emphasis on whether they had avoided exposure with the causative agent, time between diagnosis and avoidance of exposure and, in the case of persistence of exposure, whether they worked with protection or not. They were also asked about any medication they used. With this information, the classification of asthma severity was established in accordance with the new GINA guidelines [17]. Patients also completed the asthma control questionnaire (ACQ) [18]. Spirometry and a methacholine challenge were then performed. Finally, blood analysis was performed, and eosinophil count and total IgE were recorded.

Patients were considered to present clinical improvement or deterioration when a change in the GINA asthma severity classification in either direction was observed. Improvement or deterioration in bronchial hyperresponsiveness and/or the degree of bronchial obstruction was recorded when changes in the PC20 > 2 folds were observed or in FEV$_1$ > 10% with respect to the value at the time of diagnosis.

Atopy and smoking status

Patients were considered atopic if they had at least one positive prick test to any common environmental allergen [19]. Non-smokers were patients who had never smoked and ex-smokers were those who had not smoked for at least six months. The number of pack-years was calculated.

Spirometry and methacholine challenge

Spirometry was performed with a Datospir 200 (Sibel, Barcelona) instrument, following the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [20]. The reference values used were those proposed for the Mediterranean population [21]. Bronchial challenge with methacholine was performed with the method described by Chai et al. [22] (Online repository). The methacholine challenge was considered negative if the PC20 FEV$_1$ was higher than 16 mg/ml, in accordance with ATS guidelines [23].

Statistical analysis

Data are tabulated providing median and range of each variable for quantitative variables and absolute frequencies
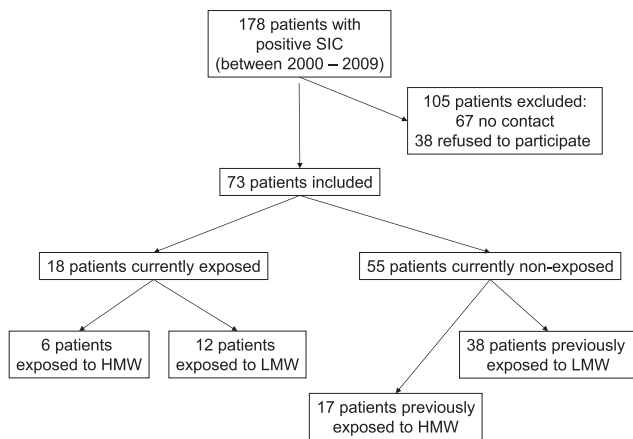
Figure 1 Number of patients who were screened and completed the study.

(counts) for each category in qualitative variables. Differences between follow-up and baseline for each group were tested using a non-parametric Wilcoxon rank test for quantitative variables and a chi-square test for qualitative variables. Logistic regression and Multiple Factor Analysis [24,25] were used to analyse the effects of potential factors on the dependent variables (online repository). SPSS 11.0 for windows (SPSS, INC, Chicago, IL) and the open-source statistical language R were used for the statistical analysis. The level of statistical significance was set at $p < 0.05$.

Results

Between 2000 and 2009, 178 patients at the two centers were diagnosed with OA with a positive SIC. One hundred and five patients were excluded from the study because contact was lost or they refused to participate (Fig. 1). Table 1 compares the baseline characteristics of the patients finally included and those excluded and Table 2 compares the baseline characteristics and the results obtained in the follow-up between exposed and non-exposed patients.

Analysing patients according to exposure to high or low molecular weight agents, changes were only observed in the variables related to atopy. Patients who avoided contact with high molecular weight agents improved their symptoms of rhinitis, conjunctivitis and the percentage of eosinophils in blood ($p = 0.002$, 0.004, 0.018, respectively), while in those who remained exposed the symptoms of rhinitis and conjunctivitis deteriorated ($p = 0.039$ and 0.012, respectively) although the percentage of eosinophils in blood also fell ($p = 0.003$). These changes, with the exception of an improvement in rhinitis in the patients who avoided contact ($p = 0.020$), were not observed in patients exposed to low molecular weight agents (Table 1 online repository).

Comparing the characteristics at the time of diagnosis of individuals who presented clinical improvement ($n = 30$) with those who remained unchanged ($n = 32$) or those who deteriorated ($n = 11$) patients who improved showed a higher degree of severity on the GINA classification,

Table 1 Baseline characteristics of individuals included and excluded from the study.

	Included $n = 73$	Excluded $n = 105$	p
Age, yrs	42 (18—65)	38 (22—60)	0.258
Sex, M/F	42/31	60/45	0.541
Smoking habit S/NS/ExS	15/48/10	28/61/16	0.563
Packs/year	15 (5—60)	15.5 (2—60)	0.967
Time from exposure to diagnosis, months	180 (6—710)	127 (4—607)	0.192
Time from symptom onset to diagnosis, months	47 (1—430)	36 (1—430)	0.216
Time from diagnosis to avoidance, months	2.5 (0—224)	—	—
Agent, LMW/HMW	50/23	75/30	0.398
Atopy, yes/no (% yes)	31/31 (50%)	51/45 (53%)	0.495
Rhinitis, yes/no (%yes)	53/20 (73%)	71/34 (68%)	0.294
Conjunctivitis, yes/no (% yes)	33/40 (45%)	52/53 (49%)	0.339
Dermatitis, yes/no, (% yes)	19/54 (26%)	31/74 (29%)	0.368
Total IgE, kU/L	115 (5—2393)	103.5 (8—2509)	0.706
% Blood eosinophils	4.7 (0—29.9)	4.4 (0—25)	0.095
FEV_1, % predicted	92 (52—131)	93 (46—126)	0.702
FVC, % predicted	94.5 (49—148)	94 (52—131)	0.999
FEV_1/FVC, %	78 (50—99.2)	80.5 (52—98)	0.039
Methacholine, % +	78%	79%	0.533
PC20, mg/ml	1.8 (0.06—16)	1.4 (0.06—16)	0.075
SIC response (E/L/D/O)	23/29/16/5	24/46/12/13	0.358
% Fall SIC	25 (12—50)	23 (14—50)	0.072
GINA NA/I/MiP/ModP/SP	0/23/11/25/14 % 0/31/15/35/19	0/25/37/36/7 % 0/24/35/34/7	0.004

LMW — low molecular weight; HMW — high molecular weight; SIC — specific inhalation challenge; NA — no asthma; I — intermittent; MiP — mild persistent; ModP — moderate persistent; , SP — severe persistent; E— early; L — late; D — dual; O — others.
*$p = 0.805$.

Table 2 Baseline and follow-up characteristics of patients finally included (divided according to exposure/non-exposure to the causative agent).

	Non-exposed $n = 55$			Exposed $n = 18$		
	Baseline	Follow-up	p	Baseline	Follow-up	p
Age, yrs	41 (18—65)	—	—	44 (25—57)	—	—
Sex, M/F	35/20	—	—	7/11	—	—
Smoking habit S/NS/ExS	11/36/8			4/12/2		
Pack/year	15 (5—60)			14.5 (7—21)		
Time from exposure to diagnosis, months	120 (6—710)	—	—	242 (12—539)	—	—
Time from symptom onset to diagnosis, months	48 (2—377)	—	—	41 (1—430)	—	—
Time from diagnosis to avoidance, months	—	1.5 (0—224)	—	—	30 (6—120)	—
Agent, LMW/HMW	38/17	—	—	12/6	—	—
Atopy, yes/no (% yes)	23/21 (52%)	—	—	8/10 (44%)	—	—
Rhinitis, yes/no (% yes)	39/16 (71%)	22/32 (41%)	0.001	14/4 (78%)	14/4 (78%)	0.182
Conjunctivitis, yes/no (% yes)	25/30 (45%)	13/41 (24%)	0.027	8/10 (44%)	9/9 (50%)	0.149
Dermatitis, yes/no (% yes)	13/42 (31%)	6/48 (11%)	0.065	6/12 (33%)	4/14 (22%)	0.125
Total IgE; kU/L	118 (5—2393)	101 (5.9—1611)	0.858	75 (10—696)	105.5 (18—1212)	0.362
% Blood eosinophils	4.5 (0—29.9)	3.0 (0.9—29.2)	0.006	5 (0—25)	2.6 (0.8—4.8)	0.028
FEV_1; % predicted	93 (60—130)	90 (52—131)	0.072	89.5 (64—113)	93 (60—131)	0.554
FVC; % predicted	95.5 (71—148)	91.5 (49—138)	0.011	93 (74—123)	90 (70—120)	0.434
FEV_1/FVC%	78 (58—99.2)	77 (50—97)	0.150	76 (52—92)	78.3 (58.4—89.7)	0.777
Methacholine, % +	89%	78%	0.0001	67%	51%	0.006
PC_{20}, mg/ml	2 (0.06—16)	1.6 (0.06—16)	0.780	1.2 (0.13—8)	1.3 (0.4—8.5)	0.925
Response to SIC (E/L/D/O)	17/24/12/2	—	—	6/5/4/3	—	—
% fall SIC	25 (12—50)	—	—	22 (8—41)	—	—
GINA NA/I/MiP/ModP/SP	0/16/6/20/13	1/30/6/8/10	0.001	0/7/5/5/1	0/8/4/4/2	0.861
Better/worse/same*	—	26/8/21 47%/14%/38%		—	4/3/11 22%/17%/61%	
ACQ: Control/Parcial Control/no control**	—	34/14/7 62%/25%/13%		—	13/2/3 72%/15%/23%	

LMW — low molecular weight; HMW — high molecular weight; SIC — specific inhalation challenge; NA — no asthma; , I — intermittent; MiP — mild persistent; ModP — moderate persistent; , SP — severe persistent; E— early; L — late; D — dual; O — others.
*p = 0.805 **p = 0.437.

although they had higher FEV_1 and better FVC than those who deteriorated (Table 3). No significant differences were observed in the univariate analysis in the rest of the variables analysed.

Performing a logistical regression analysis considering the changes in the GINA classification as independent variable and comparing subjects who improved with those who remained stable or deteriorated, no predictors of these changes in the GINA classification were found (Table 2 online supplement). Only one model which included avoidance of the agent, better FEV_1 and better FEV_1/FVC% quotient/ratio presented a sensitivity of 77% and a specificity of 65%, although the differences were not significant (Fig. 2, Table 3 online supplement). In the same analysis, considering the changes in FEV_1 or in $PC20$ as independent variables, no predictors of the effect were found (Table 2 online repository).

Performing a new logistic regression analysis, also considering the changes in the GINA classification as independent variable but comparing the individuals who improved

or remained stable with those who deteriorated, again no variables predicting the effect were found (Table 4 online repository). Only one model, which in this case included time elapsed between symptom onset and diagnosis, a poorer FEV_1, FVC and FEV_1/FVC%, presented a sensitivity of 84% and a specificity of 36%, although again the differences were not significant (Fig. 3, Table 5 online repository). Interestingly, neither avoidance of the causative agent nor the type of agent was associated with worse prognosis.

Multiple Factor Analysis showed that with three components the percentage of variability explained was 36.8%. However, when four variables were removed a rate of 50% was obtained with the three first components, the results being very similar. Representing the subjects in the three main axes in three dimensions, no groupings were formed related to the type of causative agent and continuation or cessation of the exposure. The first axis of the graph is related to improvement or deterioration, and so the chart suggests that avoiding exposure is not related to improvement or deterioration (Fig. 4).

Table 3 Baseline characteristics of patients who presented clinical improvement, deterioration, or no change on the basis of the GINA classification during follow-up.

	Improved n = 30	Worse n = 11	No change n = 32	Improved vs worse	Improved vs no change	*Worse vs no change*
Age, yrs	40.5 (21−65)	42.0 (37−55)	42.0 (18−57)	0.591	0.927	*0.651*
Sex, M/F	17/13	7/4	18/14	0.688	0.242	*0.668*
Smoking habit S/NS/ExS	10/18/2	2/6/3	3/24/5	0.176	0.059	*0.442*
Pack/year	11 (5−30)	20 (12−21)	17.5 (5−60)	0.222	0.195	*0.909*
Time from exposure to diagnosis, months	150 (6−710)	173 (18−529)	189 (12−589)	0.873	0.933	*0.924*
Time from symptom onset to diagnosis. months	48 (3−377)	77 (10−430)	42 (1−334)	0.612	0.348	*0.209*
Time from diagnosis to avoidance, months	11/19	3/8	9/23	0.574	0.525	*0.957*
Agent, LMW/HMW	14/14	2/5	16/11	0.309	0.366	*0.141*
Atopy, yes/no	23/7	7/4	23/9	0.404	0.613	*0.608*
Rhinitis, yes/no	14/16	4/7	15/17	0.556	0.893	*0.545*
Conjunctivitis, yes/no	7/23	2/9	10/22	0.724	0.437	*0.405*
Dermatitis, yes/no	105 (5−2393)	244 (23−443)	115 (7−1388)	0.643	0.901	*0.414*
Total IgE, kU/L	4.6 (2−29.9)	8 (4−15.4)	4.7 (0−25)	0.138	0.519	*0.208*
% Blood eosinophils	93 (71−119)	88 (64−100)	92.5 (60−130)	0.033	0.172	*0.328*
FEV$_1$, % predicted	100 (75−129)	91 (72−104)	93 (71−148)	0.015	0.022	*0.555*
FVC, % predicted	78 (58−90)	75 (62−87)	78.5 (52−992)	0.530	0.129	*0.110*
FEV$_1$/FVC, %	75	91	77	0.809	0.648	*0.328*
PC$_{20}$, mg/ml	1.89 (0.06−16)	1.77 (0.25−16)	2.2 (0.13−16)	0.787	0.649	*0.615*
SIC response (E/L/D/O)	10/12/6/2	4/4/3/0	8/13/7/4	0.807	0.958	*0.716*
% Fall SIC	24.5 (12−50)	26.0 (17−50)	25.0 (8−50)	0.806	0.581	*0.949*
GINA NA/I/MiP/ModP/SP	1/7/14/8	5/1/5/0	17/3/6/6	0.004	0.580	*0.218*
Avoidance of exposure: yes/no (%yes)	*26/4 (87%)*	*8/3 (73%)*	*21/11 (66%)*	*0.510*	*0.132*	*0.665*

LMW − low molecular weight; HMW − high molecular weight; SIC − specific inhalation challenge; NA − no asthma; , I − intermittent; MiP − mild persistent; ModP − moderate persistent; , SP − severe persistent; E− early; L − late; D − dual; O − others.

Discussion

The most significant result of the present study is probably the fact that avoiding exposure to the causative agent of OA did not statistically significantly improve the prognosis of these patients. The analyses performed show that avoiding exposure does not lead to clinical improvement and that the percentage of patients who deteriorate is independent both of the type of agent and of whether or not the agent is avoided. Nor was termination or persistence of exposure associated with any changes in the degree of obstruction or bronchial hyperresponsiveness.

The majority of studies included in four recent meta-analyses [11−14] focus on clinical aspects, and few studies have centered on evaluating the degree of obstruction in terms of the FEV$_1$ or the degree of bronchial hyper-responsiveness as determined by PC20 methacholine. To our knowledge, few studies to date have analysed the degree of bronchial inflammation assessed by the eosinophil count in induced sputum in patients who either continued or terminated exposure. In these studies, the cessation of exposure showed a trend of improvement in sputum eosinophilia [26,27].

In relation to the clinical aspects of OA, the systematic review conducted by Rachiotis et al. [12], found that complete symptomatic recovery varied from 0% to 100% with a pooled prevalence of 32%. Similar results were reported by Vandenplas et al. [28]. The present study is the first to establish improvement or deterioration by determining the severity of the asthma according to the GINA guidelines [17]. Although 44% of patients who avoided exposure improved compared with only 22% of those who remained exposed, the differences were not significant. In fact, the patients who improved were the ones who presented poorer classifications on the GINA at the time of diagnosis, regardless of whether or not they avoided exposure.

Delay in diagnosis, the degree of intensity of the symptoms prior to diagnosis and patients' age have been suggested as prognostic factors [7,29−33] that determine the persistence of asthma. In the present study, avoidance of exposure to the causative agent and a lower degree of bronchial obstruction may explain the improvement in symptoms, although the associations were not significant. When comparing the subjects who deteriorated with those who remained stable or improved, longer delay in diagnosis and above all the greater alteration in the spirometry parameters seemed to be associated with poor prognosis, but no association was found between poor prognosis and the type of agent or avoidance or continuation of exposure.
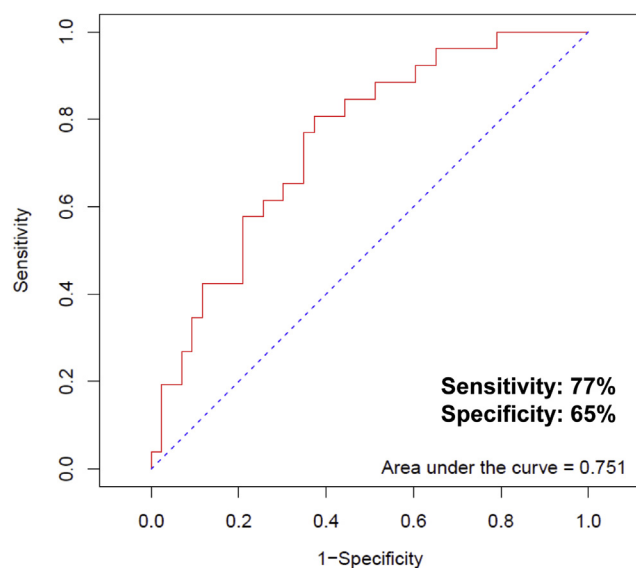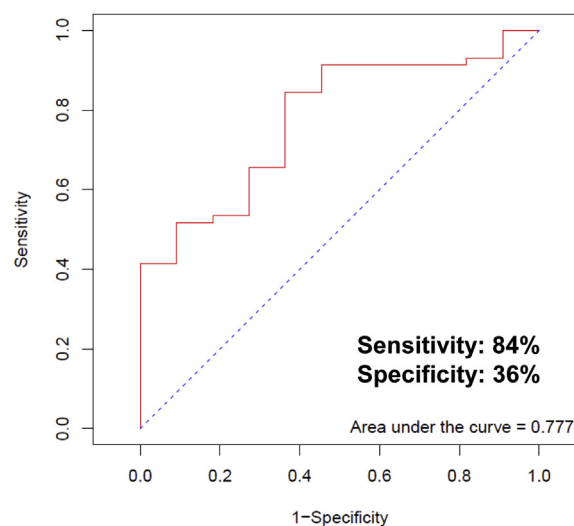
	GINA dif.		
	ESE	**z value**	**p**
Avoidance	(-1.43) − 0.75	-1.91	0.056
FEV1	0.05 − 0.02	2.23	0.026
FEV1/FVC	(-0.09) − 0.04	-2.44	0.015

gina.dif ~ avoidance + FEV1 + FEV1FVC (p = ns)

Figure 2 ROC curve considering GINA classification as independent variable, comparing patients whose symptoms improved versus those whose symptoms remained the same or deteriorated.

	GINA dif.		
	ESE	**z value**	**p**
Diagnost	0.003 − 0.002	1.56	0.119
FEV1	(-.029) − 0.16	-1.81	0.071
FVC	0.32 − 0.16	2.02	0.044
FEV1/FVC	0.37 − 0.184	2.03	0.043

Gina.dif ~ Diagnost + FEV1 + FVC + FEV1FVC

Figure 3 ROC curve considering GINA severity classification as independent variable, comparing patients whose symptoms deteriorated versus those whose symptoms improved or remained the same.

These results suggest that OA probably does not differ greatly from non-occupational allergic asthma, since the rate of patients who deteriorate is around 15% and is independent of the treatment administered and of the avoidance or continuation of exposure. The percentage of patients with difficult-to-control severe asthma in the general population is around 10% [34].

Probably the overall improvement of OA should be assessed not only in terms of the improvement of symptoms but also of the degree of obstruction and the degree of bronchial hyperresponsiveness. In the present study we did not find a relation between any of the variables (once again including the type of agent or the avoidance or continuation of exposure) and a deterioration or improvement in FEV_1. Chang Yeung et al. [32], studying 185 workers exposed to plicatic acid, found higher values for those who terminated exposure. Paradoxically, Moscato et al. [4] studying 25 patients exposed indistinctly to HMW or LMW agents found better values for subjects who remained exposed. In fact, there is little information available on how rapidly lung function declines in those who continue to be exposed, or how removal from exposure affects lung function. Piirila et al. [35] reported a mean rate of decline of 40 ml/year in 91 selected subjects with isocyanate-induced OA, although 12 of these remained exposed to the causative agent during the follow-up period. A recent report focused only on patients who terminated exposure observed that FEV_1 declined rapidly in exposed workers and continued to decline, but at a slower rate, following removal of exposure [16].

The situation is similar in the case of bronchial hyperresponsiveness. The systematic review by Rachiotiis et al. [12] found a pooled estimate of persistent hyperresponsiveness of 73%. Patients whose disease had been attributed to a LMW agent, and those from European workplaces were less likely to have persistent hyperresponsiveness. De Groene et al.'s meta-analysis [14] found differences depending on the criterion used to assess bronchial hyperresponsiveness. Indeed, only two studies out of the eight which analysed the standard mean difference in the follow-up showed an improvement in the degree of bronchial hyperresponsiveness in patients who avoided exposure [6,32]. However, the situation is more confusing in the studies that analysed the changes obtained by subtracting the PC20 values during follow-up from the baseline values. In four studies [30,33,36,37] in which the causative agent was LMW, an improvement was observed in two [32,37]. In the present study, taking as significant a two-fold change in the PC20 methacholine, no differences were found in relation to the exposure or to the type of causative agent; nor did we identify any factors that might predict these changes.

In view of these results we performed a multiple factor analysis, a descriptive multivariate statistical technique useful to analyse several groups of variables defined in the same samples [24,25]. In our study, the multiple factor
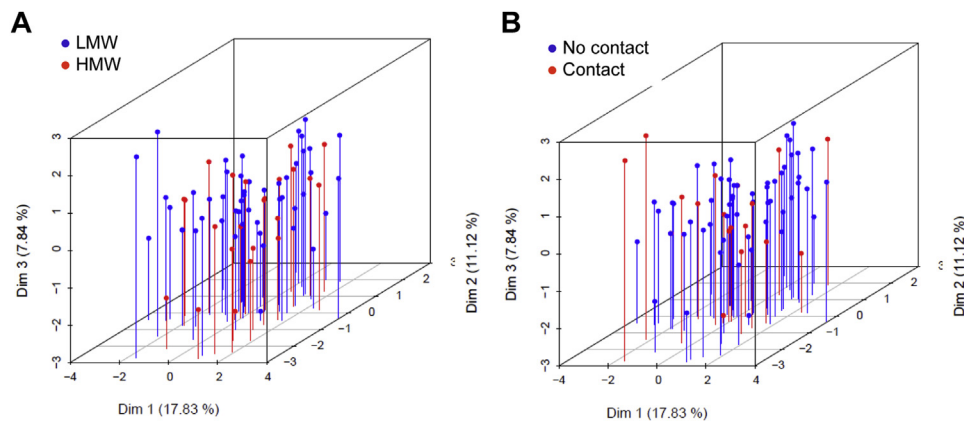
Figure 4 Multiple Factor Analysis. A: Representation of individuals according to type of agent in principal components 1, 2 and 3. B: Representation of individuals according to whether or not they avoided contact with the agent in principal components 1, 2 and 3.

analysis confirms that avoiding exposure is not related to improvement or deterioration of the disease.

This study has a number of limitations. First, the fact that the severity of asthma was significantly lower in the patients who were not included may have introduced a bias in the results. The study does not account for the healthy worker effect. The unavailability of the degree of asthma control at the moment of diagnosis may be a source of error; however, this factor would not have introduced bias, because both the exposed and the non-exposed groups received similar initial treatment. Information was available on the degree of asthma control in the follow-up assessment. Very few patients were not controlled with the ACQ [18], and there were no differences regarding avoidance or persistence of exposure to the causative agent. Other limitation of the present study is the relatively low number of study subjects. However, we consider that the results obtained are important enough to be highlighted in a descriptive manner. Finally, another possible limitation was the fact that the degree of improvement of the patients was not analysed: patients whose asthma symptoms decreased from severe to intermittent or from severe to moderate and vice versa were analysed in the same way. Breaking down these multiple changes would have created different groups and would have complicated the analysis.

In conclusion, our results do not seem to support the recommendation that patients diagnosed with OA should change their work place. Despite these findings, however, there is insufficient evidence to recommend a change in current management guidelines recommending adequate avoidance of work place sensitizers, and especially chemicals, in workers with confirmed OA. Future well-designed prospective studies to further address the efficacy of environmental interventions in treating occupational asthma are required to confirm these findings. In the meantime, the best option seems to be to individualize the treatment strategy according to the patient.

Authors contributions

Dr Munoz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Viladrich and Manso: contributed to data collection, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.

Dr Munoz: contributed to study conception and design, analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.

Dr Sastre, Pozo and Quirce: contributed to study conception and design and interpretation of data and reading and approving the final manuscript.

Dr Cruz: contributed to study conception and design, laboratory analysis and interpretation of data, drafting the manuscript for important intellectual content, and reading and approving the final manuscript.

Dr Carmona and Sanchez-Pla: contributed to statistical analysis of the results.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.08.001.

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