Original Article

Disposition of Work-Related Asthma in a Spanish Asthma Cohort: Comparison of Asthma Severity Between Employed and Retired Workers

Christian Romero-Mesones, MD[b,c], Maria-Jesus Cruz, PhD[a,b,c], Isam Alobid, MD, PhD[c,d,e], Blanca Barroso, MD[c,f], Ebymar Arismendi, MD, PhD[c,g], Pilar Barranco, MD, PhD[c,h], Diana Betancor, MD[c,f], Irina Bobolea, MD, PhD[c,g], Blanca Cárdaba, PhD[c,i], Elena Curto, MD, PhD[c], Gemma Domenech, PhD[j], Javier Domínguez-Ortega, MD, PhD[c,h], David Espejo, MD[a], Francisco-Javier González-Barcala, MD, PhD[k], Juan-Alberto Luna-Porta, MD[c,h], Carlos Martínez-Rivera, MD, PhD[c,l], Paula Méndez-Brea, MD[m], Joaquim Mullol, MD, PhD[c,n], José-María Olaguibel, MD, PhD[o], Cesar Picado, MD, PhD[d,e], Vicente Plaza, MD, PhD[p], Victoria del Pozo, PhD[c,i], Santiago Quirce, MD, PhD[c,h], Manuel-Jorge Rial, MD, PhD[q], José-María Rodrigo-Muñoz, MD, PhD[c,i], Joaquin Sastre, MD, PhD[c,f], Sandra Serrano, BSC[j], Lorena Soto-Retes, MD[p], Antonio Valero, MD, PhD[c,g], Marcela Valverde-Monge, MD[c,f], and Xavier Munoz, MD, PhD[a,b,c] *Barcelona, Madrid, A Coruña, and Navarra, Spain*

What is already known about this topic? Exposure to certain agents in the workplace can trigger occupational asthma or work-exacerbated asthma, both of which come under the heading of work-related asthma. Up to 16% of patients who attend specialized asthma units have work-related asthma.

What does this article add to our knowledge? Eighty percent of patients who continued to work and 96% of those who did not had moderate or severe asthma. The highest-risk professions are cleaners, both domestic and industrial, and workers in the metal industry.

How does this study impact current management guidelines? Because we found little difference in the severity of asthma, treatment administered, changes in lung function, or number of exacerbations between employed and unemployed workers with work-related asthma, advice regarding a change of job or changes in workplace exposures should be customized to the individual situation.

BACKGROUND: Exposure to certain agents in the workplace can trigger occupational asthma or work-exacerbated asthma, both of which come under the heading of work-related asthma (WRA). Understanding the burden that WRA represents can help in the management of these patients.

OBJECTIVE: To assess the influence of occupation on asthma in real life and analyze the characteristics of patients with WRA included in an asthma cohort.

METHODS: This was a prospective multicenter study of a cohort of consecutive patients with asthma. A standardized clinical history was completed. Patients were classified as having WRA or non-WRA. All patients underwent respiratory function tests, FeNO test, and methacholine challenge (methacholine concentration that causes a 20% drop in FEV_1) at the beginning of the study. They were classified into two groups, depending on their employment status: employed (group 1) or unemployed (group 2).

RESULTS: Of the 480 patients included in the cohort, 82 (17%) received the diagnosis of WRA. Fifty-seven patients (70%) were still working. Mean age (SD) was 46 (10.69) years in group 1

[a]Servicio de Neumología. Hospital Universitario Vall d'Hebron, Barcelona, Spain
[b]Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain
[c]CIBER de Enfermedades Respiratorias, Madrid, Spain
[d]Rhinology Unit and Smell Clinic, ENT Department, Hospital Clinic Barcelona, Universitat de Barcelona, Barcelona, Spain
[e]Clinical and Experimental Respiratory Immunoallergy, Instituto de Investigaciones Biomédicas August Pi i Sunyer, Barcelona, Spain
[f]Allergy Department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
[g]Allergy Unit and Severe Asthma Unit, Pneumonology and Allergy Department, Hospital Clínic, Instituto de Investigaciones Biomédicas August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain
[h]Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain
[i]Immunology Department, Instituto de Investigación Sanitaria Fundación Jiménez Díaz-Universidad Autónoma de Madrid, Madrid, Spain
[j]Medical Statistics Core Facility, Instituto de Investigaciones Biomédicas August Pi i Sunyer, Hospital Clinic Barcelona, Barcelona, Spain
[k]Pulmonology Department, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain
[l]Pulmonology Department, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona Badalona, Barcelona, Spain
[m]Allergy Department, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain
[n]Rhinology Unit and Smell Clinic, ENT Department, Clinical and Experimental Respiratory Immunoallergy (Instituto de Investigaciones Biomédicas August Pi i Sunyer), Universitat de Barcelona, Barcelona, Spain
[o]Allergy Department, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain
[p]Servicio de Neumología y Alergia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[q]Allergy Department, Complexo Hospitalario Universitario, A Coruña, Spain

Abbreviations used
OA- Occupational asthma
SIC- Specific inhalation challenge
WEA- Work-exacerbated asthma
WRA- Work-related asthma

and 57 (9.91) years in group 2 ($P < .0001$). Significant differences were observed in adherence to treatment (64.9% in group 1 vs 88% in group 2; $P = .0354$) and in severe asthma exacerbations (35.7% in group 1 vs 0% in group 2; $P = .0172$). No significant differences were observed in the rest of the variables analyzed.

CONCLUSIONS: The burden of WRA in specialized asthma units is not negligible. The absence of differences in the severity of asthma, the treatment administered, alterations in lung function, and the number of exacerbations in those working versus not working may support the idea that advice regarding changing jobs should be customized for individual patients. **(J Allergy Clin Immunol Pract 2023;11:3407-13)**

Key words: *Occupational asthma; Work-exacerbated asthma; Exacerbation*

INTRODUCTION

Work-related asthma (WRA), defined as asthma caused or triggered by exposure to agents in the workplace, is the most common respiratory occupational disease.[1] It is associated with difficult to control symptoms, severe exacerbations, and loss of lung function.[2] Work-related asthma encompasses two entities: occupational asthma (OA), defined as asthma resulting from causes and conditions attributable to a particular occupational environment and not to stimuli encountered elsewhere; and work-exacerbated asthma (WEA), defined as preexisting or concomitant asthma worsened by exposure to certain conditions or agents in the workplace.[3] Occupational asthma is further divided into immunologic and irritant-induced forms.[4] In general, the diagnosis of irritant-induced OA is based on the clinical history. In the case of immunologic OA, however, a specific inhalation challenge (SIC) is often necessary to differentiate it from WEA.[5]

The best therapeutic option in patients with WRA is not well-defined. It is generally accepted that complete avoidance of exposure to the causal agent is the best strategy in patients with OA, despite its significant socioeconomic impact both for the patient and for society.[6,7] Recent research has challenged this option, finding that the percentage of patients with OA who develop severe asthma is similar regardless of whether exposure to the causal agent is avoided.[8] Risk factors for developing severe OA are a history of asthma in childhood, the presence of expectoration and/or aphonia, a low level of schooling, a diagnostic delay, and persistent high exposure.[9] The recommendation in the case of patients with WEA is generally to maintain the patient in the place of work, improve environmental conditions, reduce exposure as much as possible and adapt the pharmacologic treatment.[10]

The mechanism underlying to genesis and evolution of asthma project is a prospective study of a cohort of over 500 patients with asthma of different degrees of severity, who attended eight specialized asthma units in Spain.[11] Most studies in the field of WRA are carried out at specific occupational respiratory pathology units and few are carried out in real-life contexts in asthma units not specifically dedicated to this form of the disease. The aims of this study were to assess the influence of occupation on asthma in real life and to analyze the characteristics of patients with WRA in this cohort. The study also assessed differences in asthma severity, depending on whether patients remained exposed to the causal agent.

METHODS

Study population and design

We conducted a prospective multicenter study of a cohort of 480 consecutive patients with asthma recruited from eight university hospitals in Spain (the mechanism underlying to genesis and evolution of asthma cohort). Standard data collection methods were

This study was funded by Grant FIS PI15/0190 (Instituto de Salud Carlos III), and Fondo Europeo de Desarrollo Regional y SANOFI.

Conflicts of interest: D. Betancor is supported by a Rio Hortega research contract from Instituto Carlos III, Ministry of Science. M. Valverde-Monge has received fees for a lecture from GSK and is part of the advisory board for Organon. M.-J. Rial reports personal fees from GSK, Allergy Therapeutics, and AstraZeneca outside the submitted work. F.-J. González-Barcala reports personal fees from ALK, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Gebro Pharma, GSK, Laboratorios Esteve, Menarini, Mundipharma, Novartis, Rovi, Roxall, Stallergenes-Greer, and Teva; and grants from Mundipharma outside the submitted work. S. Quirce reports personal fees from AstraZeneca, Novartis, Sanofi, Boehringer Ingelheim, Teva, ALK, Mundipharma, GSK, Chiesi, and Leti, outside the submitted work.. L. Soto-Retes reports nonfinancial support from CIBER de Enfermedades Respiratorias during the conduct of the study; personal fees from Stallergenes-Greer, Menarini, and Novartis; personal fees from GSK, Hal Allergy, Allergy Therapeutics, and AstraZeneca; and grants from Sociedad Española de Alergología e Inmunología Clínica SEAIC and Sociedad Española de Neumología y Cirugía Torácica SEPAR, outside the submitted work. C. Martínez-Rivera reports grants and personal fees from AstraZeneca, Teva, GSK, Novartis, and Mundipharma, outside the submitted work. X. Munoz reports personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Mundipharma, Chiesi, and Faes Farma, outside the submitted work. J. Sastre reports grants and personal fees from Sanofi, GSK, Novartis, AstraZeneca, Mundipharma, and Faes Farma, outside the submitted work. J.-M. Olaguibel reports grants from Sanofi and/or personal fees from AstraZeneca and Mundipharma, outside the submitted work. V. Plaza reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Merck, Chiesi, Novartis, Menarini, and Sanofi, outside the submitted work. J. Mullol reports personal fees and others from Sanofi-Genzyme, Regeneron, Novartis, Viatris (Mylan pharma), Uriach group, Mitsubishi-Tanabe, Menarini, UCB, AstraZeneca, GSK, and MSD, outside the submitted work. V. del Pozo reports personal fees and others from Sanofi, AstraZeneca, and GSK, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 18, 2022; revised June 14, 2023; accepted for publication June 15, 2023.

Available online June 28, 2023.

Corresponding author: Maria-Jesus Cruz, PhD, Servicio de Neumología, Hospital Universitario Vall d'Hebron, Passeig Vall d'Hebron 119, 08035 Barcelona, Spain. E-mail: mj.cruz@vhir.org.

2213-2198

https://doi.org/10.1016/j.jaip.2023.06.040

TABLE I. Demographic characteristics of study population

Study variables	Non-WRA (n = 398)	Total WRA (n = 82)	P*	Employed (n = 57)	Unemployed (n = 25)	P†
Age, y (mean [SD])	46.98 (13.24)	49.55 (11.49)	.1034	46.23 (10.6)	57.12 (9.9)	<.0001
Sex, male, n (%)	143 (36.02)	21 (25.61)	.0743	15 (26.3)	6 (24)	1.000
Body mass index, kg/m^2	27.02 (5.12)	27.29 (6.20)	.7144	26.98 (6.5)	27.99 (5.6)	.503
Smoking habit, n (%)§						
Smokers	36 (9.16)	4 (4.88)	.3946	3 (5.3)	1 (4.0)	.297
Ex-smokers	123 (31.30)	25 (30.49)		14 (24.56)	11 (44.0)	
Nonsmokers	234 (59.54)	53 (64.63)		40 (70.18)	13 (52.0)	
Blood test (mean [SD])						
Blood eosinophil count, cells/μL	327.93 (342.61)	303.97 (260.78)	.4825	314.57 (286.38)	279.25 (191.21)	.520
Total IgE, kU/L	441.73 (893.74)	334.99 (455.37)	.1332	308.08 (414.11)	402.91 (551.59)	.423
Eosinophilic asthma (yes), n (%)‡	153 (40.16)	21 (26.58)	.0298	15 (27.27)	6 (25.00)	1.000
Comorbidities (yes), n (%)		50 (61.0)		31 (54.4)	19 (76.0)	.086
Comorbidities, n (%)						
Psychiatric illness	50 (23.0)	14 (28.0)	1.000	8 (25.8)	6 (31.6)	.750
Heart disease	12 (5.5)	3 (6.0)		2 (6.5)	1 (5.3)	1.000
Diabetes	18 (8.3)	6 (12.0)		2 (6.5)	4 (21.1)	.184
Hypertension	54 (24.9)	13 (26.0)		7 (22.6)	6 (31.6)	.521
Hyperlipidemia	58 (26.7)	14 (28.0)		7 (22.6)	7 (36.8)	.338
Thyroid disease	44 (20.3)	7 (14.0)		3 (9.7)	4 (21.1)	.404
Obesity	74 (34.1)	21 (42.0)		13 (41.9)	8 (42.1)	1.000
Obstructive sleep apnea	18 (8.3)	4 (8.0)		0	4 (21.1)	.017
Bronchiectasis	30 (13.8)	5 (10.0)		3 (9.7)	2 (10.5)	1.000
Others	66 (30.4)	13 (26.0)		9 (29.0)	4 (21.1)	.741

WRA, work-related asthma.
*Non-WRA vs WRA.
†Employed vs unemployed.
‡Eosinophils >300 cells/mm^3 in blood.
§There were five missing values in the non-WRA group.

used at all participating centers. An electronic database and case report form were designed to collect study data.[11] The study was approved by the ethics committees of the participating centers. All patients provided informed consent at the beginning of the study.

A standardized clinical history was completed for each patient. Special emphasis was placed on the age of asthma onset, symptoms, the number and severity of exacerbations during the year before inclusion in the cohort, smoking habit, and comorbidities. Employment status at the time of inclusion in the cohort was recorded (employed or unemployed). We used the European Community classification of socioeconomic status to code reported occupations.[12] The time that patients had worked in each of their jobs was also recorded, as was the diagnosis they had received (OA or WEA). Validated versions of the following questionnaires were administered: Asthma Control Test[13] Morisky Green adherence questionnaire,[14] Asthma Quality of Life Questionnaire,[15] Sino-Nasal Outcome Test,[16] and Hospital Anxiety and Depression.[17]

We assessed asthma severity according to the classification of the Global Initiative for Asthma.[18] The diagnosis of asthma (based on Global Initiative for Asthma guidelines) preceded the inclusion of patients by at least 1 year. All subjects underwent a detailed clinical examination, including body mass index and respiratory function tests (baseline spirometry, bronchodilator test, lung volume measurement by plethysmography, FeNO, and diffusing capacity of the lung for carbon monoxide test using the single-breath method), according to the recommendations of the European Respiratory Society.[19] Methacholine challenge (the methacholine concentration that causes a 20% drop in FEV_1), induced sputum, chest computed tomography scan, and skin prick tests with common aeroallergens were performed at the beginning of the study. Skin prick tests were considered positive for wheal diameters of at least 3 mm compared with the negative control (saline); we used histamine (10 mg/mL) as a positive control. Atopy was defined as the presence of at least one positive skin prick test or aeroallergen-specific IgE in serum. Adherence to treatment was classified as adequate, regular, or bad, according to medical criteria.

Patients were classified into two groups, depending on their employment status at the time of the study (employed or unemployed).

Work-related asthma diagnosis

The diagnosis of WRA was made based on clinical suspicion and the demonstration of a relationship between the patient's symptoms and work, through any or all of these tests: spirometry (at work decrease greater than 12%), changes in peak flow (visual interpretation) and/or methacholine (at work decrease greater than twofold in the methacholine concentration that causes a 20% drop in FEV_1), FeNO (at work increase greater than 30%), and eosinophilic/neutrophilic inflammation studies in sputum (at work increase greater than 3% and greater than 20% in eosinophils and/or neutrophils, respectively) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

The differentiation between OA and WEA was made through clinical history, evaluating specifically whether there were sensitizing agents with irritating characteristics in the workplace, by demonstrating the patient's sensitization to the agent suspected of causing

TABLE II. High-risk occupations of patients included in study

Occupation	Total with work-related asthma (n = 82)	Employed (n = 57)	Unemployed (n = 25)
Cleaning homes	12 (9)	10 (11)	2 (4)
Industrial cleaning	8 (6)	4 (4)	4 (9)
Nurses and nurse aides	11 (8)	7 (8)	4 (9)
Farmers with birds	4 (3)	4 (4)	0
Farmers with greenhouses	1 (0.7)	1 (1)	0
Hairdressers	7 (5)	4 (4)	3 (7)
Laboratory technicians without animal experimentation	3 (2)	2 (2)	1 (2)
Woodworkers	1 (0.7)	0	1 (2)
Food processors working with refrigerators	5 (4)	5 (6)	0
Food processors not working with refrigerators	6 (4.4)	4 (4)	2 (4)
Bakers	7 (5)	4 (4)	3 (7)
Workers in plastic industry	5 (4)	2 (2)	3 (7)
Workers in chemical industry	1 (0.7)	0	1 (2)
Workers in textile industry	4 (3)	2 (2)	2 (4)
Workers in metal industry	10 (7)	6 (7)	4 (9)
Other processes of metal and electrical products	2 (1)	1 (1)	1 (2)
Other painters	2 (1)	2 (2)	0
Construction workers	4 (3)	2 (2)	2 (4)
Miners	1 (0.7)	1 (1)	0
Transport and storage workers	3 (2)	2 (2)	1 (2)
Others	38 (28)	27 (30)	11 (24)

Data are shown as n (%). Some patients reported more than one high-risk occupation.

the pathology (a positive specific IgE, positive prick test, or both) and/or by a positive SIC (Table E1).

Statistical analysis

We carried out a descriptive study of variables collected in the cohort and performed a comparative study between the groups. Data are expressed as absolute numbers and their corresponding percentages for qualitative variables, and means and SDs for quantitative variables. Comparison of demographic and clinical variables was performed using Fisher exact test for categorical variables, Student *t* test for continuous variables, and Mann-Whitney test for ordinal-scale variables, as appropriate. All statistical tests were applied with a .05 two-sided significance level. Analyses were conducted using SAS software (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

A total of 82 patients (17%) received the diagnosis of WRA; 32 had OA and 50 had WEA. Table I lists the demographic characteristics of the study population. In the WRA group, 74% were women. A higher percentage of blood eosinophilia was observed in patients in the non-WRA group compared with the WRA group ($P = .0298$).

In the WRA group, 57 patients were employed at the time of the study and 25 were unemployed. Mean age (SD) was 46 (10.69) years in the group of employed people, and 57 (9.91) years in the group of unemployed people ($P < .0001$). Unemployed people had a higher rate of comorbidities (76% vs 54% in group 1), although this did not reach statistical significance when it was analyzed globally ($P = .086$). However, when comorbidities were analyzed individually, obstructive sleep apnea was found in 21% of unemployed patients but was not recorded in employed people ($P = .017$).

Table II lists occupations of the patients with WRA included in the study. The occupations most frequently related to asthma were domestic cleaners (8%), nurses and nurse aides (7.3%), workers in the metal industry (6.7%), industrial cleaners (5.3%), hairdressers (4.7%), and bakers (4.7%). In the non-WRA group, 68% of patients were administrative workers, students, and retirees, or had other professions without risk exposures.

Table III lists the characteristics of asthma as well as the treatment that patients followed. Greater asthma severity was observed in the WRA group compared with patients with non-WRA ($P = .0126$). They also had lower results for the Asthma Control Test and Asthma Quality of Life Questionnaire ($P = .0012$ and .0001, respectively). In the WRA group, a higher level of anxiety was observed compared with the non-WRA group ($P = .0041$).

In the WRA group, a trend toward greater asthma severity was observed in unemployed people, although this did not reach statistical significance ($P = .0765$). No significant differences were observed in asthma treatment or lung function studies. Although no differences were observed in the number of exacerbations, they were more severe in patients who continued to work: 35.7% of severe asthma exacerbations occurred in employed people versus 0% in unemployed people ($P = .0172$). In addition, employed patients had lower adherence to treatment, as measured by the Morisky-Green questionnaire: 64.9% in employed people versus 88% in unemployed people ($P = .0354$). No differences were found in relation to asthma control, quality of life, or the anxiety/depression index.

DISCUSSION

This study shows that asthma may be related to work in up to 17% of patients who are treated in specialized asthma units. The

TABLE III. Characteristics of asthma and treatment of study population

Study variables	Non-WRA (n = 398)	Total WRA (n = 82)	P*	Employed (n = 57)	Unemployed (n = 25)	P†
Severity of asthma, n (%)						
Intermittent	23 (5.81)	3 (3.66)	.0126	2 (3.5)	1 (4.0)	.0765
Mild	82 (27.71)	9 (10.98)		9 (15.8)	0	
Moderate	138 (34.85)	28 (34.15)		20 (35.1)	8 (32.0)	
Severe	153 (38.64)	42 (51.22)		26 (45.6)	16 (64.0)	
Symptoms, n (%)§						
At least one symptom	346 (87.8)	74 (90.2)	.5349	51 (89.5)	23 (92.0)	.7226
Cough	248 (62.9)	60 (73.2)	.0779	41 (71.9)	19 (76.0)	.7018
Dyspnea	266 (67.5)	61 (74.4)	.2218	44 (77.2)	17 (68.0)	.3799
Wheezing	213 (54.1)	44 (53.7)	.9470	32 (56.1)	12 (48.0)	.4962
Expectoration	163 (41.4)	40 (48.8)	.2171	28 (49.1)	12 (48.0)	.9254
Chest pain	173 (43.9)	49 (59.8)	.0089	34 (59.6)	15 (60.0)	.9762
Asthma control						
Asthma Control Test (mean [SD])	20.71 (4.62)	18.81 (5.16)	.0012	18.48 (5.13)	19.61 (5.26)	.3818
Asthma Quality of Life Questionnaire (mean [SD])	5.61 (1.35)	4.86 (1.39)	<.0001	4.85 (1.39)	4.86 (1.42)	.9404
Severe exacerbations/y, n (%)						
0	233 (59.29)	51 (62)	.4449	38 (67)	13 (52)	.2889
1	61 (15.52)	14 (17)		9 (16)	5 (29)	
2	35 (8.91)	8 (10)		3 (5)	5 (20)	
3	32 (8.14)	5 (6)		3 (5)	2 (8)	
4	12 (3.05)	1 (1.2)		1 (1.75)	0	
5	2 (0.51)	1 (1.2)		1 (1.75)	0	
6	1 (0.25)	0		0	0	
8	3 (0.076)	1 (1.2)		1 (1.75)	0	
9	2 (0.51)	0		0	0	
10	3 (0.76)	1 (1.2)		1 (1.75)	0	
>10	9 (2.29)	0		0	0	
Intensity of exacerbations, n (%)						
Moderate	131 (71.58)	31 (75.61)	.7013	18 (64.29)	13 (100.0)	.0172
Severe	52 (28.42)	10 (24.39)		10 (35.71)	0	
Pulmonary function test (mean [SD])						
FVC before bronchodilator (%)	101.11 (50.48)	94.75 (19.44)	.0603	96.19 (20.60)	91.63 (16.65)	.3350
FEV_1 before bronchodilator (%)	86.04 (21.00)	81.90 (21.01)	.1113	83.5 (22.7)	78.5 (16.9)	.3366
FEV_1/FVC before bronchodilator (%)	78.52 (15.86)	81.99 (18.51)	.1165	83 (18.4)	80.1 (19)	.5296
FEV_1 after bronchodilator (%)	86.48 (32.81)	81.16 (34.99)	.2822	83.9 (35.3)	72.8 (34)	.3242
Diffusing capacity of lung for carbon monoxide (%)	96.54 (20.12)	93.81 (28.60)	.5993	93.7 (28)	94.52 (34)	.9482
Asthma treatment, n (%)						
At least one	392 (99.2)	82 (100.0)	.6422	57 (100.0)	25 (100.0)	NA
Inhaled corticosteroids	363 (91.9)	79 (96.3)	.1747	54 (94.7)	25 (100.0)	.5498
Systemic corticosteroids	42 (10.6)	5 (6.1)	.2312	5 (8.8)	0	.1818
Long-acting bronchodilators	317 (80.3)	73 (89.0)	.0824	50 (87.7)	23 (92.0)	.7153
Short-acting bronchodilators	219 (55.4)	47 (57.3)	.8070	35 (61.4)	12 (48.0)	.3341
Long-term anticholinergic	79 (20.0)	20 (24.4)	.4550	13 (22.8)	7 (28.0)	.7803
Short duration anticholinergics	11 (2.8)	4 (4.9)	.4855	2 (3.5)	2 (8.0)	.5708
Montelukast	124 (31.4)	38 (46.3)	.0109	23 (40.4)	15 (60.0)	.1489
Theophyllines	2 (0.5)	3 (3.7)	.0373	2 (3.5)	1 (4.0)	1.000
4-Phosphodiesterase inhibitors	0	0	NA	0	0	NA
Omalizumab	57 (14.4)	10 (12.2)	.6121	8 (14.0)	2 (8.0)	.5010
Specific immunotherapy	33 (8.4)	5 (6.1)	.5213	4 (7.0)	1 (4.0)	.6771
Macrolides	7 (1.8)	2 (2.4)	1.000	2 (3.5)	0	.5737
Other	13 (3.3)	7 (8.5)	.0397	4 (7.0)	3 (12.0)	.6678

(continued)

TABLE III. *(Continued)*

Study variables	Non-WRA (n = 398)	Total WRA (n = 82)	P*	Employed (n = 57)	Unemployed (n = 25)	P†
Adherence to treatment (yes), n (%)	242 (62.7)	59 (72)	.1281	37 (65)	22 (88)	.0354
Hospital Anxiety and Depression questionnaire, n (%)‡						
Anxiety						1.000
Normal	225 (62.85)	42 (55)	.0041	30 (56)	12 (54)	
Questionable	78 (21.79)	10 (13)		7 (13)	3 (14)	
Clinical problem	55 (15.36)	24 (32)		17 (31)	7 (32)	
Depression						.8094
Normal	313 (87.43)	61 (80)	.1881	43 (80)	18 (82)	
Questionable	30 (8.38)	9 (12)		6 (11)	3 (14)	
Clinical problem	15 (4.19)	6 (8)		5 (9)	1 (4)	
Sino-Nasal Outcome Test (mean [SD])		35.33 (0-90)		34.92 (0-90)	36.32 (0-79)	.8115

NA, not applicable; WRA, work-related asthma.
*Non-WRA vs WRA.
†Employed vs unemployed, Fisher exact test, Student *t* test, or Mann-Whitney test.
‡Administered in 76 patients.
§There were four missing values in the non-WRA group.

highest-risk professions are cleaners, both domestic and industrial, and workers in the metal industry. Up to 70% of patients continue to work despite the diagnosis of WRA. This study assessed the burden of patients with WRA on the health system in real life by assuming that patients seen at these specialized units were those with the greatest severity. We found that 80% of patients who continued to work, and 96% of those who did not, had moderate or severe asthma.

A prevalence of 17% of WRA in the general referral population with asthma is a common finding in studies of patients with OA. A collaborative study involving three specific occupational health units found that approximately 15% of patients who had received the diagnosis of OA by means of an SIC had severe asthma, and that this was not influenced by their employment status. Variables that seemed to explain this finding were, above all, diagnostic delay and the presence of greater bronchial obstruction.[8] The European Network for the Phenotyping of Occupational Asthma international cohort of patients with OA, in which more than 1,000 patients are being evaluated cross-sectionally at the time of the diagnostic evaluation throughout Europe, established that 16% of patients may have severe asthma and that variables that seem to account for severity in a patient with OA are having experienced asthma during childhood, diagnostic delay, expectoration, dysphonia during work, and persistent high exposure.[9] Detecting these patients at risk is essential because they will have the highest rates of morbidity and even mortality. In a study conducted in Michigan in which a surveillance program identified 3,634 workers with WRA between 1988 and 2018, nine deaths resulted from WRA and there were 2,242 emergency room visits and 1,128 hospitalizations.[20] The costs associated with WRA, regardless of whether the patient has WEA or OA, are around 10 times higher than those for patients with non-WRA.[21]

When a patient receives the diagnosis of WRA, most authors continue to recommend switching jobs if the patient is unable to avoid the causal agent.[22] However, some meta-analyses concluded that the evidence for this recommendation may not be entirely solid.[23-25] The results of the current study support the idea that the unfavorable evolution in patients with WRA does not seem to be related to patients' employment status, because no significant differences were found in the number of exacerbations, maintenance treatment, or lung function. We observed a trend toward a greater number of patients classified as having severe asthma in the nonworking group. This group also had an overall higher rate of comorbidities, which suggests a possible healthy worker effect, although the differences found were not statistically significant. Nevertheless, we observed that patients with WRA generally have a greater severity of asthma, worse asthma control, and a higher level of anxiety compared with patients with non-WRA. On many occasions, the decision to change jobs or stop working is not easy to make, even when financial compensation is forthcoming; it may imply significant losses at the socioeconomic level.[26] Many patients are reluctant to give up their jobs, and doctor–patient agreements must be reached in which the benefits and risks of these decisions are assessed.[27] In our series, the mean age of patients with WRA who continued to work was 46 years, significantly younger than those who had stopped work (57 years). This difference is probably explained by these socioeconomic conditions and by the difficulty of finding a new job at an older age.

It is also interesting to comment on two possibly related findings: namely, lower adherence to treatment in patients who continued to work, and that the exacerbations these patients had were more likely to be serious, although they were not more numerous than those in patients who had left work. A systematic review analyzing 2,319 articles, 23 of which were considered suitable for study, showed that lack of adherence to treatment in patients with asthma entails a greater risk of severe exacerbations.[28] The reasons why patients with asthma may have poor adherence to treatment are multiple and include insufficient knowledge of the disease, difficulty in using inhalers, the feeling that inhaled corticosteroids are ineffective or dangerous, costs, and limited access to health care.[29] These two last points (cost and access to health insurance) may be especially important in the context of patients with WRA and may also be closely related to the age difference between the groups. It has been shown that adherence to treatment is clearly influenced by the sociopolitical context in individual countries.[30]

This study had some limitations. First, we were unable to establish whether all patients with a diagnosis of WRA were advised to change jobs. If they were, the results may have been biased, which could explain, for example, the age difference between groups. Second, the final number of patients with a diagnosis of WRA in this cohort meant that we were unable to perform differential studies between patients with OA and WEA. Nevertheless, in most recent studies on the burden of the disease, the trend was not to differentiate between the entities but to assess patients with WRA as a whole, especially considering that some subtypes of OA (such as irritant-induced asthma) may be difficult to differentiate from WEA.[20,22,31] Another possible limitation is the probable lack of uniformity in performing the WRA diagnosis, because only three participating centers have the infrastructure needed to conduct an SIC. Although an SIC is the reference standard test for the diagnosis of OA, the clinical history, the peak flow study, the methacholine test, and the cellular study in induced sputum in periods in work and out of work have been shown to be useful for the diagnosis of OA and WEA, and therefore of WRA.[32] Finally, the study did not consider differences in the type or intensity of workplace exposures or whether those remaining at work had modified their exposures.

To our knowledge, this study is the first to assess the burden that WRA represents in the real-life setting of specialized asthma units. Up to 17% of the patients who attend these units have WRA. The differences observed in age, adherence to treatment, and the severity of exacerbations, depending on whether patients with WRA continue to work, may be related more to the sociopolitical idiosyncrasy of the country in question than to the effect of employment status on the disease. The absence of differences in the severity of asthma, the treatment administered, alterations in lung function, and the number of exacerbations may support the idea that advice regarding changing jobs should be customized to individual patients. Nevertheless, future studies with a larger number of patients are necessary to corroborate these results.

REFERENCES

1. Cullinan P, Muñoz X, Suojalehto H, Agius R, Jindal S, Sigsgaard T, et al. Occupational lung diseases: from old and novel exposures to effective preventive strategies. Lancet Respir Med 2017;5:445-55.
2. Tarlo SM, Lemiere C. Occupational asthma. N Engl J Med 2014;370:640-9.
3. Cruz MJ, Muñoz X. Work-related asthma: the dawn of knowledge? Arch Bronconeumol 2017;53:180-1.
4. Malo JL, Vandenplas O. Definitions and classification of work-related asthma. Immunol Allergy Clin North Am 2011;31:645-62.
5. Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. Eur Respir J 2014;43:573-87.
6. Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. Chest 2008;134:1S-41S.
7. Vandenplas O, Dressel H, Nowak D, Jamart J. ERS Task Force on the Management of Work-Related Asthma. What is the optimal management option for occupational asthma? Eur Respir Rev 2012;21:97-104.
8. Munoz X, Viladrich M, Manso L, del Pozo V, Quirce S, Cruz MJ, et al. Evolution of occupational asthma: does cessation of exposure really improve prognosis? Respir Med 2014;108:1363-70.
9. Vandenplas O, Godet J, Hurdubaea L, Rifflart C, Suojalehto H, Walusiak-Skorupa J, et al. Severe occupational asthma: insights from a multicenter European cohort. J Allergy Clin Immunol Pract 2019;7:2309-18.
10. Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemière C, Martin J, et al. An official American Thoracic Society statement: work-exacerbated asthma. Am J Respir Crit Care Med 2011;184:368-78.
11. Muñoz X, Álvarez-Puebla MJ, Arismendi E, Arochena L, Ausín MDP, Barranco P, et al. The MEGA Project: a study of the mechanisms involved in the genesis and disease course of asthma cohort creation and long-term follow-up. Arch Bronconeumol (Engl Ed). Published online March 19, 2018. https://doi.org/10.1016/j.arbres.2017.12.012
12. Kogevinas M, Antó JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. Lancet 1999;353:1750-4.
13. Vega JM, Badia X, Badiola C, López-Viña A, Olaguíbel JM, Picado C, et al. Validation of the Spanish version of the asthma control test (ACT). J Asthma 2007;44:867-72.
14. Val Jiménez A, Amorós Ballestero G, Martínez Visa P, Fernández Ferré ML, León Sanromà M. Descriptive study of patient compliance in pharmacologic anti-hypertensive treatment and validation of the Morisky and Green test. Aten Primaria 1992;10:767-70.
15. Perpiñá M, Belloch A, Pascual LM, de Diego A, Compte L. The quality of life in asthma: an evaluation of the AQLQ questionnaire for its use on a Spanish population. Asthma Quality of Life Questionnaire [in Spanish]. Arch Bronconeumol 1995;31:211-8.
16. De los Santos G, Reyes P, del Castillo R, Fragola C, Royuela A. Crosscultural adaptation and validation of the Sino-Nasal Outcome Test (SNOT-22) for Spanish speaking patients. Eur Arch Otorhinolaryngol 2015;272:3335-40.
17. Terol MC, López-Roig S, Rodríguez-Marín J, Martín-Aragón M, Pastor MA, Reig MT. Hospital Anxiety and Depression Scale (HAD): psychometric properties in Spanish population [in Spanish]. Ansiedad y Estrés 2007;13:163-76.
18. Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed September 3, 2020. https://ginasthma.org/
19. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200:e70-88.
20. Reilly MJ, Wang L, Rosenman KD. The burden of work-related asthma in Michigan, 1988-2018. Ann Am Thorac Soc 2020;17:284-92.
21. Lemiere C, Boulet L-P, Chaboillez S, Forget A, Chiry S, Villeneuve H, et al. Work-exacerbated asthma and occupational asthma: do they really differ? J Allergy Clin Immunol 2013;131:704-10.
22. Lau A, Tarlo SM. Update on the management of occupational asthma and work-exacerbated asthma. Allergy Asthma Immunol Res 2019;11:188-200.
23. Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, Cullinan P. Outcome of occupational asthma after cessation of exposure: a systematic review. Thorax 2007;62:147-52.
24. Vandenplas O, Dressel H, Wilken D, Jamart J, Heederik D, Maestrelli P, et al. Management of occupational asthma: cessation or reduction of exposure? A systematic review of available evidence. Eur Respir J 2011;38:804-11.
25. de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MH, et al. Workplace interventions for treatment of occupational asthma. Cochrane Database Syst Rev 2011;5:CD006308.
26. Lypszic IC, Silverman F, Holness DL, Liss GM, Lavoie KL, Tarlo SM. Comparison of psychological, quality of life, work limitation and socioeconomic status between patients with occupational asthma and work-exacerbated asthma. J Occup Environ Med 2017;59:697-702.
27. Henneberger PK, Patel JR, de Groene GJ, Beach J, Tarlo SM, Pal TM, et al. The effectiveness of removal from exposure and reduction of exposure for managing occupational asthma: summary of an updated Cochrane systematic review. Am J Ind Med 2021;64:165-9.
28. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J 2015;45:396-407.
29. McQuaid EL. Barriers to medication adherence in asthma: the importance of culture and context. Ann Allergy Asthma Immunol 2018;121:37-42.
30. Riley IS, Jackson B, Crabtree D, Riebl S, Que LG, Pleasants R, et al. A scoping of International barriers to asthma medication adherence mapped to the theoretical domains framework. J Allergy Clin Immunol Pract 2021;9:410-8.
31. Cormier M, Lemire C. Occupational asthma. Int J Tuberc Lung Dis 2020;24:8-21.
32. Muñoz X, Cruz MJ, Bustamante V, Lopez-Campos JL, Barreiro E. Work-related asthma: diagnosis and prognosis of immunological occupational asthma and work-exacerbated asthma. J Investig Allergol Clin Immunol 2014;24:396-405.

ONLINE REPOSITORY

TABLE E1. Diagnostic test results in study population

Data expressed as n (%)	Work-related asthma (n = 82)	Occupational asthma (n = 32)	Work-exacerbated asthma (n = 50)
Diagnosis of work-related asthma (at work and out of work)			
Spirometry (at-work decrease >12%)	19 (23)	4 (12)	15 (30)
Peak flow compatible (visual interpretation), yes	32 (39)	15 (47)	17 (34)
FeNO (at-work increase >30%)	18 (22)	5 (16)	13 (26)
PC_{20} (at-work decrease greater than twofold in PC_{20})	6 (7)	6 (19)	0
Eosinophilic inflammation (at-work increase >3%)	8 (10)	8 (25)	0
Neutrophilic inflammation (at-work increase >20%)	3 (4)	0	3 (6)
Occupational asthma vs work-exacerbated asthma			
Sensitizing agents, yes	27 (33)	18 (56)	9 (18)
Irritating agent, yes	48 (58)	8 (25)	40 (80)
Positive specific IgE and/or positive prick test	28 (34)	15 (47)	13 (26)
Positive Specific Inhalation Challenge	11 (13)	11 (34)	0

PC_{20}, methacholine concentration that causes a 20% drop in FEV_1.
In some patients, more than one diagnostic test was performed.