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Inhaled drugs as risk factors for community-acquired pneumonia

Short title: Inhaled drugs and community-acquired pneumonia.

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Abstract (word count 248)

Question of the study: The effect of inhaled drugs favouring community-acquired pneumonia (CAP) is unclear. This case-control study was designed to determine whether inhaled drugs were risk factors for CAP.

Materials/patients and methods: All incident cases of confirmed CAP that occurred over 1 year in patients with chronic bronchitis (CB), chronic obstructive respiratory disease (COPD) or asthma were included, as well as CB, COPD and asthma controls. Risk factors for CAP and inhaled treatment were recorded during a personal interview.

Results: An effect of inhaled drugs on the risk of CAP was observed in COPD and asthma patients after adjusting for the effect of other respiratory diseases and their concomitant treatments. In COPD patients inhaled steroids had a risk of 3.26 (1.07−9.98) and in asthma patients inhaled anticholinergics had a risk of 8.80 (1.02−75.7). In CB patients no association with CAP was observed for any inhaler. These effects were independent of adjusting variables related to severity and other respiratory and non-respiratory risk factors for CAP, including vaccines. Inhaled β2-adrenergic agonists did not show a significant effect on the risk of CAP in none of the respiratory diseases.

Answer to the question: Inhaled steroids may favour CAP in COPD patients, whereas anticholinergics may favour CAP in asthma patients. It is difficult to differentiate the effect of inhaled therapy from the effect of COPD or asthma severity on the risk of CAP, and these relationships could not be casual but call attention to inhaled therapy in COPD and asthma patients.

Keywords: Community-acquired pneumonia, inhaled drug treatment, risk factors.

Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in industrialized countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1000 inhabitants [1,2], 22–51% of which requiring in-patient care, with a lethality of 3–24% [3,4]. The mortality rate varies between 0.1 and 0.7 per 1000 persons-year [1,5].

Strategies acting on modifiable risk factors for CAP are crucial to reduce the impact of the disease. Among them, chronic obstructive pulmonary disease (COPD) and asthma are important risk factors for CAP both in ambulatory and hospitalized patients [6–8]. Recently, it has been shown that medications delivered by metered-dose inhalers (MDIs) usually administered in the treatment of COPD and asthma may also cause pneumonia [9–12]. Inhaled drugs can be delivered through pressured MDI inhalers, with or without spacer devices, dry-powder inhalers or nebulizers [13]. Bronchodilators, including β_2-adrenergic agonists and/or anticholinergic drugs, and steroids are the most common type of active drugs administered through MDIs.

Adverse pulmonary effects recently observed with the use of some MDIs makes necessary to further study the risk for CAP related with inhaled drugs [14]. The aim of the present study was to assess the effect of drugs administered through inhalation devices on the development of CAP in patients with different chronic respiratory diseases that require inhaled therapy. The study is based on cases of clinically and radiologically confirmed CAP occurring in a large general adult population.

PATIENTS AND METHODS

Study population

A population-based, case-control study was conducted in an extensive rural and urban area of the eastern coast in Spain, with predominantly Mediterranean climatic conditions. Details of the study have been published elsewhere [9]. Briefly, the target population included 859,033 inhabitants older than 14 years of age assigned to any of the 64 primary care centers, which were selected according to availability of family physicians willing to take part in the study.

Identification of cases

All patients with clinically suspected CAP presenting from November 1, 1999 to November 30, 2000 were prospectively registered. Predefined criteria for case registration were based on acute lower respiratory tract infection for which antibiotics have been prescribed in association with the appearance of new or previously unknown focal signs on physical examination or X-ray of the chest [1]. All cases of CAP were periodically re-evaluated by chest roentgenograms intervals until complete recovery. Patients with suspicion of CAP in which another non-infectious respiratory disease was later confirmed were excluded from the study as were patients with active tuberculosis, aspiration pneumonia, pneumonia acquired at nursing homes or having been discharged from hospital at least within 7 days before the onset of symptoms.

An active surveillance system was established to ensure the identification of all cases, based on the fact that 95% of the population belongs to the National Health Care System. This system involved all physicians working in public and private health care facilities in the study area and reference hospitals both inside and outside the county area. In order to maintain the system of reporting cases, a coordinator in each of the study areas established periodic contacts with the professionals of all participating centers.

Selection of controls

Each case of confirmed CAP was frequency matched to a control subject by age (± 5 years), sex and primary care centre. The selection of controls was performed every 3 months by a simple random sampling procedure from the same population-based register than cases, using the list of subjects assigned to each primary care centre. Once a control subject was identified, a maximum of three telephone calls or home visits were made at different schedules, and if after these attempts, the control subject could not be contacted, he/she was replaced following the same selection and matching criteria.

For the purposes of the present study only cases and controls with three chronic respiratory disease that require inhaled therapy were included: chronic bronchitis (CB) without spirometric study or without COPD (defined by its arbitrary epidemiological characterization of cough and expectoration over 90 days per year in two consecutive years and not secondary to any specific respiratory disease [15]), COPD (presence of persistent airflow limitation diagnosed by respiratory function tests documented in the medical records or stated by the patient) or asthma (presence of episodes of validated clinical symptoms, like attacks of cough at night or making an effort, or of occasional wheeze during a cold or an effort during the last year [16]).

Data collection

A questionnaire on CAP risk factors was administered to participants at home (see Annex). It was composed by questions from the current literature and from the opinion of international experts, and its reliability has been demonstrated in previous studies [9]. When the participant could not directly answer the questions (cognitive impairment, disease, or for CAP cases, death), the questionnaire was administered to the closest family member or caregiver. The interviewers were physicians or nurses trained in interview techniques and in the administration of the study questionnaire. The questionnaire included standardized information related to the following three aspects: health habits and lifestyle; chronic respiratory diseases (COPD, CB, asthma) and other clinical conditions; and regular treatments during the last year. Treatments were confirmed by medical records, prescriptions or, when necessary, by direct observation. Information on inhaled drugs included the classes of drugs (steroids, β_2-adrenergic agonists, anticholinergic drugs), regular dose (mean puffs per day) and use of spacer devices.

All participants gave written informed consent. The study protocol was approved by the Ethics Committee of the Consorci Sanitari del Maresme (Barcelona, Spain).

Statistical analysis

Because COPD, CB and asthma may be present concurrently in a given patient and are associated with a higher risk for CAP, particularly COPD and CB, cases and controls were stratified into the following three groups: COPD (with or without asthma), CB (with or without asthma) and asthma alone. Estimations of the relative risk through odds ratios (OR) and 95% confidence intervals (CI) were used as a measure of association between risk factors and the occurrence of CAP. These were calculated using unconditional logistic regression for each type of respiratory disease. Firstly, bivariate analysis was applied within each group of respiratory disease (CB, COPD, asthma) to compare the characteristics of the three classes of inhaled drugs (steroids, β2-adrenergic agonists, anticholinergics) between cases and controls and their relationship with the risk for CAP. Secondly, multivariate analysis of the risk for CAP within each strata of respiratory disease was performed. The effect of inhaled drug treatments was adjusted for: a) indicators of baseline disease severity, such as oxygen therapy, treatment with oral corticosteroids or use of the other classes of inhaled drugs; b) respiratory and non-respiratory variables statistically associated with CAP in the bivariate analysis with a P value < 0.10 (comorbidities, or concomitant treatments and vaccines); and c) asthma in the CB and COPD models. Statistical significance was set at $P = 0.05$.

RESULTS

From the study population of 1,336 cases of CAP and 1,326 controls [9], 473 and 235 presented CB, COPD or asthma, respectively. Overall, in the group of patients with CAP, 284 (60.0%) were males and the mean ± SD age was 59.6 ± 20.0. In the control group 132 (56.2%) were males and the mean age was 60.9 ± 20.7 years. Patient characteristics by type of respiratory disease are presented in Table 1. The prevalence of male patients, older ages and smoking were high, but more frequent in COPD patients than in CB patients and less frequent in asthmatic patients. History of hospitalizations, respiratory infections, comorbidity and influenza vaccination were common in all patients.

Upper respiratory tract infections were associated with CAP in all three groups of patients (CB, COPD and asthma); smoking and influenza vaccination were also associated with CAP in COPD patients; and depression, N-acetylcysteine, oxygen therapy and both influenza and pneumococcal vaccination were also associated with CAP in asthma patients.

Table 2 shows that in patients with CB there were no more cases of CAP using inhaled therapy regularly during the last year than controls. In patients with COPD a 48.9% of cases and a 24.2% of controls used inhaled steroids regularly during the last year, which was associated to a risk of CAP of 2.99 (95% CI 1.23−7.31). In patients with asthma the risk for CAP was associated to inhaled anticholinergics (OR = 8.13, 95% CI 1.05 – 62.79).

The effect on the risk for CAP of inhaled drugs, as well as of different respiratory diseases and their concomitant drug treatments, and other non-respiratory variables from table 1 potentially associated to CAP, is shown in table 3. In this multivariable analysis the adjusted effect of the inhaled treatments on the risk of CAP depended on the type of respiratory disease. In CB patients no effect was observed for any inhaled treatment, but upper respirtory tract infections in the last month had a significative effect on the risk of CAP. In COPD patients, inhaled steroids had a risk of 3.26 (95% CI 1.07−9.98), and packs year of smoking had also a significative effect on the risk of CAP. In asthma patients, inhaled anticholinergics had a risk of 8.80 (95% CI 1.02−75.7), whereas the pneumococcal vaccine had a 65% risk reduction on the risk of CAP.

DISCUSSION

In recent years, it has been suggested that the use of inhalers containing steroids may cause pneumonia as a severe adverse effect in patients with COPD [10–12]. This effect, together with other active medications administered with MDIs, has been further explored in the present study with chronic respiratory patients from a large population-based sample of 1,336 cases of clinically and radiologically confirmed CAP and 1,326 healthy controls. Results indicate that inhaled steroids may increase the risk of CAP in patients with COPD, inhaled anticholinergics may increase the risk of CAP in patients with asthma, and inhaled β_2-adrenergic agonists do not appear to affect the risk of CAP.

In general, the use of inhaled drugs delivered through a MDI had an effect on the development of CAP and a dose-response relationship in terms of the mean number of daily puffs [9]. This was in agreement with the hypothesis that poor hygienic measures and contamination of inhalers, particularly of plastic pear-spacers, may represent a causal component of the mechanism of infection [11]. Indeed, the effect of inhalers on the development of CAP can be attributed to the active medication contained in the MDI.

The relation between bronchodilator therapy and some severe complications has been recognized for decades [17–19]. Nevertheless, no study has focused on the analysis of infectious complications until it has been recently shown that inhaled steroids increased the risk of CAP in patients with COPD [10,11]. Evidence of the impact of inhaled steroids was unexpectedly documented in the TORCH study, which was designed to assess the benefit of inhaled drugs on long-term survival of COPD patients [12]. Other recent studies have also confirmed an association between inhaled steroids and the incidence, hospitalization and death-related CAP in patients with COPD [20–22]. Nevertheless, a recent meta-analysis showed that budesonide did not increase the risk of pneumonia in patients with COPD [23]. Findings of these studies should be interpreted with caution due to the possibility of methodologic limitations and systematic errors [20,24]. However, this association is corroborated in the current study, in which the risk of CAP for inhaled steroids was restricted to patients with COPD but not to patients with chronic bronchitis. A possible explanation of this finding may be that the risk of inhaled steroids would act only in patients with more severe bronchopathy, which in turn implies a diagnostic confirmation of chronic airflow obstruction, whereas inhaled steroids would not act in patients with only clinical symptoms of persistent cough and expectoration. In these patients as well, the contribution of inhaled steroids to the risk of CAP may be lower because they were administered at lower doses. The median (range) puffs/day in these patients was 2 (1–9) compared with 4 (1–9) in patients with more severe bronchopathy. This association between inhaled steroids and the risk of CAP could not be explained by the possible effect of confounding by severity because we attempted to control it with the inclusion of independent variables related to disease severity in the multivariable analysis.

On the other hand, inhaled steroids were not found to be a risk factor for CAP in patients with asthma. In the only two studies in which this relationship was analysed, an association between inhaled steroids and CAP was not observed [25,26]. These results suggest that, although bronchial asthma is per se a risk factor for CAP [8,9,27,28], the effect on inhaled steroids would only occur in the presence of local and systemic pathophysiological conditions of COPD. For this reason, in asthmatic patients the crude effect of inhaled steroids of 1.70 (95% CI 0.74−3.93) was diluted to 1.10 (95% CI 0.40–3.00) after adjusting by underlying respiratory diseases and other counfounding factors.

Anticholinergics was an inhaled drug treatment associated with CAP in asthma patients. Only the effect of the short-acting antimuscarinic ipratropium bromide was assessed in our study because the new generation, long-acting tiotropium bromide was not commercialised at the time of the study. The effect of inhaled anticholinergics was of considerable magnitude and independent of underlying respiratory illnesses, related treatments and the remaining risk factors of CAP. However, the uncertainty associated with this effect estimate was considerable because asthma patients who were anticholinergic users are uncommon. The CAP risk of inhaled anticholinergics did not reach the statistical significance in CB and COPD patients.

Anticholinergic drugs cause bronchodilation by inhibition or parasympathetic activity of the airways by blocking muscarinic receptors [29,30]. In patients with stable COPD, the use of tiotropium with or without β_2-adrenergic agonists is indicated according to the drug availability and the individual response, but the role of this agent as first-line or second-line option in the treatment of stable COPD is a matter of discussion pending data of further long-term studies [15,31–35]. In patients with asthma, a metaanalysis of randomized clinical trials conducted to determine whether the addition of inhaled ipratropium to inhaled beta-agonist therapy was effective in the emergency treatment of adults with acute asthma exacerbation, concluded that the use of combination ipratropium and beta-agonist therapy was reasonable since the addition of ipratropium seemed to provide physiologic evidence of benefit without risk of adverse effects [36]. In our study 5.1% of cases and 0.7% of controls with asthma used inhaled anticholinergics. We believe that they were on treatment with ipratropium because they might be patients of difficult control, either because they had moderate or serious exacerbations in the context of a severe asthma, or they were also treated with other kind of inhalers with poor response to them, or because they had other respiratory comorbidities.

In relation to its security the anticholinergics appear to have a wide therapeutic margin and to be well tolerated by patients, the only significant side effect being dryness of the mouth. Occasional prostatic symptoms, an unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide have also been reported [37,38]. The risk of CAP for inhaled anticholinergics has not been previously reported, but in all studies this effect has not been analysed as a primary outcome [33,35,39,40]. In the UPLIFT study, based on COPD patients of at least 40 years of age, anticholinergics were associated with a reduction in the risk of exacerbations, but not specifically with a reduction in the risk of CAP [40]. In fact, no association between the use of inhaled anticholinergics and CAP was found in comparison with placebo or other inhaled drugs. There are some biological explanations that can make this effect plausible: an inhibition of the ciliary activity and a reduction in the clearance mechanism of the mouth and mucous secretion related to the anticholinergic effect of dry mouth [41] may favour the growth of pathogens and increase the probability of colonization. The muscarinic antagonism may also contribute to reduce neutrophil infiltration of the airways [42]. This potentially beneficial effect could nevertheless impair the defenses of the respiratory tract, particularly cell-mediated immunological host response, and favour the propagation of pathogens and subsequent pulmonary infection.

In the present study, the use of inhaled β_2-adrenergic agonists did not show an effect on the risk of CAP after adjusting by underlying respiratory diseases and their corresponding oral drug treatments. In consequence, the use of inhaled β_2-adrenergic agonists would have no effect on the occurrence of CAP.

Our findings should be interpreted taking into account some limitations of the study especially the small number of patients in some of the subsets analysed. This circumstance also restricted to perform a rigorous adjustment for the variables of disease and severity that may be correlated with inhaled drug treatments. In addition, more hard variables related to disease severity could be used especially for asthma patients. For these reasons there is still the possibility of a residual confounding in our results. On the other hand, the adjustment by different variables that are inter-correlated may increase the inaccuracies in the estimations of the risk of CAP, introducing bias and reducing their statistical significance. Finally, missing values in the puffs/day of some treatments, particularly of inhaled steroids, limit assessment of a dose-response relationship. Therefore, and given that this is the first study that describes the effects of inhaled anticholinergics on the risk of CAP, it is necessary to perform further studies specifically designed to confirm the present findings.

This study intended to separate the effect of inhaled drugs from the effect of the underlying respiratory disease and its severity on the risk of CAP using different strategies of analysis. The present results suggest that inhaled steroids and anticholinergics (but not beta-agonists) may be risk factors for CAP according to the type of underlying respiratory disease. Inhaled steroids may increase the risk for CAP in patients with COPD, while inhaled anticholinergics may favour CAP in patients with asthma. These findings could not be casual but further confirmation of these relationships might be of clinical importance in the therapeutic management of inhalers in COPD and asthma patients.

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Table 1. Patient characteristics according to the type of respiratory disease.

	Chronic bronchitis		COPD		Asthma alone	
Variable	CAP (n=122)	Controls (n=48)	CAP (n=94)	Controls (n=33)	CAP (n=256)	Controls (n=153)
Sex (% female)	43 (29.2)	14 (37.5)	18 (19.1)	7 (21.2)	127 (49.6)	81 (52.9)
Age, mean (sd)	70.0 (15.5)	65.9 (15.7)	71.1 (11.2)	73.4 (12.2)	52.4 (21.4)	55.2 (21.4)
Smoking, packs year 0	36 (31.0)	16 (35.6)	20 (22.5)	14 (45.2)	100 (40.2)	69 (46.3)
1-150	32 (27.6)	13 (28.9)	25 (28.1)	4 (12.9)	65 (26.1)	44 (29.5)
>150	48 (41.4)	16 (35.6)	44 (49.4)	13 (41.9)*	84 (33.7)	36 (24.2)
Any hospital admission, previous 5 years	68 (55.7)	28 (58.3)	68 (72.3)	21 (63.6)	137 (53.5)	90 (58.8)
Upper respiratory tract infection, last month	56 (46.3)	13 (27.1)*	44 (46.8)	9 (27.3)**	157 (61.3)	108 (70.6)**
Chronic bronchitis	122 (100)	48 (100)	94 (100)	33 (100)	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)	94 (100)	33 (100)	0 (0.0)	0 (0.0)
Asthma	71 (8.2)	22 (45.8)	47 (50.0)	14 (42.4)	256 (100)	153 (100)
Any previous CAP confirmed by chest radiography	29 (23.8)	9 (18.8)	28 (29.8)	7 (21.2)	55 (21.5)	23 (15.0)
Non active TBC	7 (5.7)	1 (2.1)	6 (6.5)	3 (9.1)	5 (2.0)	2 (1.3)
Other respiratory disease	5 (4.2)	2 (4.2)	16 (17.6)	3 (9.7)	6 (2.4)	1 (0.7)
Diabetes	27 (22.1)	12 (25.0)	28 (29.8)	11 (33.3)	33 (12.9)	22 (14.4)
Heart failure	22 (18.3)	8 (16.7)	16 (17.0)	8 (24.2)	25 (9.8)	8 (5.2)
GER	41 (33.6)	18 (37.5)	27 (28.7)	13 (39.4)	87 (34.0)	53 (34.6)
Depression	26 (21.3)	9 (19.1)	13 (13.8)	2 (6.1)	37 (14.5)	32 (20.9)**
Cancer	12 (9.8)	3 (6.4)	13 (13.8)	3 (9.1)	16 (6.3)	11 (7.2)
N-acetylcysteine	4 (3.3)	0 (0)	3 (3.2)	2 (6.1)	13 (5.1)	1 (0.7)*
Oral corticosteroids	12 (9.8)	2 (4.2)	19 (20.2)	4 (12.1)	4 (1.6)	0 (0.0)
Theophylline	6 (4.9)	2 (4.2)	12 (12.8)	2 (6.1)	3 (1.2)	0 (0.0)
Oxygen therapy	9 (8.0)	1 (2.2)	12 (13.8)	2 (6.3)	4 (3.0)	0 (0.0)*
Influenza vaccine	53 (43.4)	21 (43.8)	64 (68.1)	28 (84.8)**	74 (29.0)	62 (40.5)*
Pneumococcal vaccine at any time of life	6 (5.1)	5 (11.4)	11 (12.4)	4 (12.5)	10 (4.0)	17 (11.9)*

Numbers are frequency of subjects with percentages in parenthesis, except otherwise stated.
COPD=chronic obstructive pulmonary disease, sd=standard deviation, CAP=community acquired pneumonia, TBC=tuberculosis, GER=gastroesophagical regurgitation.
* $p<0.05$ for differences between cases and controls within each group of patients.
** $p<0.10$ for differences between cases and controls within each group of patients.

Table 2. Regular use of inhaled treatments during the last year and risk of CAP.

Variable	CAP	Controls	OR	95 % CI	p-value
Chronic bronchitis	(n=122)	(n=48)			
Inhaled steroids	41 (33.6)	18 (37.5)	0.84	0.42 – 1.69	0.631
Puffs/day: 0	57 (77.0)	23 (82.1)	1	-	0.746
1−4	16 (21.6)	5 (17.9)	1.29	0.42 – 3.94	
>=5	1 (1.4)	0 (0)	-	-	
Inhaled beta-agonists	52 (42.6)	23 (47.9)	0.81	0.41 – 1.58	0.531
Puffs/day: 0	57 (52.8)	23 (50.0)	1	-	0.315
1−4	31 (28.7)	18 (39.1)	0.70	0.33 – 1.48	
>=5	20 (18.5)	5 (10.9)	1.61	0.54 – 4.82	
Inhaled anticholinergics	30 (24.6)	10 (20.8)	1.24	0.55 – 2.78	0.603
Puffs/day: 0	57 (65.5)	23 (69.7)	1	-	0.515
1−4	15 (17.2)	7 (21.2)	0.87	0.31 – 2.40	
>=5	15 (17.2)	3 (9.1)	2.02	0.53 – 7.63	
COPD	(n=94)	(n=33)			
Inhaled steroids	46 (48.9)	8 (24.2)	2.99	1.23 – 7.31	0.014
Puffs/day: 0	22 (44.9)	9 (64.3)	1	-	0.565
1−4	24 (49.0)	5 (35.7)	1.96	0.57 – 6.76	
>=5	3 (6.1)	0 (0)	-	-	
Inhaled beta-agonists	63 (67.0)	21 (63.6)	1.16	0.51 – 2.66	0.724
Puffs/day: 0	22 (25.9)	9 (32.1)	1	-	0.018
1−4	30 (35.3)	16 (57.1)	0.77	0.29 – 2.05	
≥ 5	33 (38.8)	3 (10.7)	4.50	1.09 – 18.5	
Inhaled anticholinergics	41 (43.6)	10 (30.3)	1.78	0.76 – 4.15	0.180
Puffs/day: 0	22 (34.4)	9 (47.4)	1	-	0.620
1−4	20 (31.7)	5 (26.3)	1.64	0.47 – 5.71	
≥ 5	21 (33.3)	5 (26.3)	1.72	0.49 – 5.97	
Asthma alone	(n=256)	(n=153)			
Inhaled steroids	22 (8.6)	8 (5.2)	1.70	0.74 – 3.93	0.207
Puffs/day: 0	210 (96.8)	134 (99.3)	1	-	0.160
1−4	7 (3.2)	1 (0.7)	4.47	0.54 – 36.7	
≥ 5	0 (0.0)	0 (0)	-	-	
Inhaled beta-agonists	39 (15.2)	15 (9.8)	1.65	0.88 – 3.11	0.116
Puffs/day: 0	210 (85.4)	134 (90.5)	1	-	0.244
1−4	24 (9.8)	11 (7.4)	1.39	0.66 – 2.94	
≥ 5	12 (4.9)	3 (2.0)	2.55	0.71 – 9.21	
Inhaled anticholinergics	13 (5.1)	1 (0.7)	8.13	1.05 – 62.79	0.017
Puffs/day: 0	210 (94.6)	134 (99.3)	1	-	0.067
1−4	7 (3.2)	1 (0.7)	4.47	0.54 – 36.7	
≥ 5	5 (2.3)	0 (0.0)	-	-	

Differences between the number of patients taking the inhaled treatment or by pufs/day does not coincide with the total number of patients due to missing values.

Table 3. Association between inhaled drug treatments and the risk of CAP adjusted for respiratory comorbidity and its severity, respiratory treatments and other non-respiratory risk factors, by strata of patients with specific respiratory diseases.

Variable		OR	95% CI	P value
Chronic bronchitis				
Upper respiratory tract infection, last month		2.56	1.16−5.65	0.020
Oxygen therapy		3.52	0.38−33.0	0.270
Inhaled steroids		0.96	0.35−2.61	0.930
Inhaled beta-agonists		0.59	0.22−1.57	0.294
Inhaled anticholinergics		1.46	0.56−3.79	0.435
Asthma		1.73	0.82−3.68	0.154
Oral corticosteroids		4.05	0.47−34.9	0.203
COPD				
Upper respiratory tract infection, last month		2.25	0.84−6.01	0.107
Oxygen therapy		1.18	0.19−7.39	0.863
Inhaled steroids		3.26	1.07−9.98	0.038
Inhaled beta-agonists		0.68	0.23−2.02	0.483
Inhaled anticholinergics		1.19	0.39−3.63	0.757
Asthma		1.00	0.38−2.62	0.998
Oral corticosteroids		1.30	0.31−5.47	0.718
Smoking, packs year	0	1	-	0.081
	1-150	4.23	1.07−16.7	0.039
	>150	2.44	0.83−7.21	0.105
Influenza vaccine		0.39	0.12−1.27	0.118
Asthma alone				
Upper respiratory tract infection, last month		1.46	0.92−2.30	0.105
Inhaled steroids		1.10	0.40−3.00	0.857
Inhaled beta-agonists		1.24	0.58−2.67	0.582
Inhaled anticholinergics		8.80	1.02−75.7	0.048
Influenza vaccine		0.67	0.42−1.08	0.096
Pneumococcal vaccine at any time of life		0.35	0.14−0.84	0.020
N-acetylcysteine		0.23	0.03−1.87	0.168
Depression		0.70	0.40−1.21	0.200

Annex. Items included in the questionnaire

Identification and sociodemographic data

- Identification number.
- Birth date.
- Sex.
- City.
- Date of the interview.
- Not responding reason.
- Person who answers the questionnaire.

Medical history

- Hospital admission in the previous 5 years, number of admissions, date of the last admission.
- Diagnostic studies in the previous year: nose, pharynx, bronchoscopy, gastroscopy, nasogastric tube, general anesthesia.
- Upper respiratory tract infection in the previous year, number of episodes, purulent tonsillitis.
- Upper respiratory tract infection in the previous month, number of episodes, purulent tonsillitis.
- Any previously radiographically confirmed pneumonia.

Pathologic conditions

- Diabetes, any diagnosis and treatment.
- Heart failure, any diagnosis.
- Valve heart disease, any diagnosis.
- Coronary heart disease, any diagnosis.
- Chronic bronchitis, any diagnosis. Type of COPD according to spirometry.
- Asthma. Any diagnosis.
- Other chronic respiratory diseases (enphysema, bronchiectasis, etc.).
- Non-active pulmonary tuberculosis, any diagnosis.
- Epilepsy, any diagnosis.
- Parkinson, any diagnosis.
- Debilitating neuromuscular disorder (amyotrophic lateral sclerosis, multiple sclerosis, etc.), any diagnosis.
- Conditions involving the cranial nerves, any diagnosis.
- Dementia or Arzheimer disease, any diagnosis.
- Stroke, any diagnosis.
- Gastroesophageal reflux, any diagnosis, hiatal hernia, peptic ulcer.
- Chronic liver disease, any diagnosis.
- Hepatitis B virus infection or hepatitis C virus infection, any diagnosis.
- Chronic renal failure, any diagnosis.
- Mental disorder or depression, any diagnosis.
- Tonsillectomy or adenoidectomy, any surgical removal.
- Cancer, type, any diagnosis, treatments in the previous year.
- HIV infection.

Drug treatment

- Regular treatments in the previous year: N-acetyl-cysteine, digoxin, amiodarone, diuretics, aminophylline, benzodiazepines, oxygen, inhalers with holding chamber (type and active drug), inhalers without holding chamber (type and active drug), antimicrobials (active compound).

Anthropometric and present conditions

- Height and weight.
- Visit to the dentist in the previous month.
- Abscess.
- Edentulous.
- Caries.
- Dental prosthesis.

Vaccinations

- Influenzae in the previous year.
- Antipneumoccocal, year of administration.

Toxic habits

- History of tobacco use to calculate packs/year.
- Passive smoking at work or home.
- Frequency of consumption of alcoholic beverages.

- Registration of consumption of alcoholic beverages to calculate daily ingestion of pure alcohol (in grams).

Lifestyle and working conditions

- Civil status.
- Living with more than 10 persons at home.
- To live or to work with children < 15 years of age.
- Pets, number and classes.
- Education level.
- Occupation (job).
- Work-life contact with smoke, vapors, petrol or hydrocarburs, dust, organic fibers, inorganic fibers, ionized radiation, non-ionized radiation, animals, excrements, or visceras.
- Sudden changes of temperature in the work place in the previous 3 months.