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New evidence of risk factors for community-acquired pneumonia: a population-based study

Short title: Risk factors for community-acquired pneumonia.

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Abstract (word count 200)

Question of the study: To identify risk factors for community-acquired pneumonia (CAP) with special emphasis on modifiable risk factors and generalizable to the general population.

Materials/patients and methods: Population-based case-control study with a target population of 859,033 inhabitants >14 years of age. A total of 1336 patients with confirmed CAP over 1-year were matched to control subjects by age sex, and primary center.

Results: In the univariate analysis, outstanding risk factors were passive smoking in never smokers >65 years, heavy alcohol intake, contact with pets, household with >10 people, contact with children, interventions on the upper airways, and poor dental health. Risky treatments included amiodarone, N-acetyl-cysteine, and oral steroids. Influenza and pneumococcal vaccine, and visiting the dentist were protective factors. Multivariable analysis confirmed cigarette smoking, usual contact with children, sudden changes of temperature at work, inhalation therapy (particularly containing steroids and using plastic pear-spacers), oxygen therapy, asthma, and chronic bronchitis as independent risk factors.

Answer to the question: Interventions for reducing CAP should integrate health habits and lifestyle factors related to household, work and community, together with individual clinical conditions, comorbidities, and oral or inhaled regular treatments. Prevention would include vaccination, dental hygiene, and avoidance of upper respiratory colonization.

Keywords: Community-acquired pneumonia, population-based study, risk factors.

Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality. Preventive strategies identifying and acting on modifiable risk factors are of paramount importance in reducing CAP-related death. Population-based studies of risk factors for CAP are scarce. In a Finish study of subjects aged 60 years or older, alcoholism, heart disease, lung disease, and immunosuppressive therapy among others were independent risk factors for pneumonia [1]. Similar results were obtained in a study carried out in the UK, in which the importance of cigarette smoking was added [2]. In a study carried out in Spain, other risk factors identified included low body mass index, previous respiratory infection, and previous pneumonia [3]. Some studies in US population-based cohorts confirmed these findings and emphasized the influence of excessive weight gain, asthma, and diabetes [4]. Other risk factors for CAP suggested in these studies have been inconsistently observed or statistical confirmation was not possible. A systematic review of 10 studies analysing risk factors for CAP, concluded that there is insufficient evidence for other factors like medication, dangerous substances, alcohol consumption, or sociodemographic factors [5].

With the aim of providing further evidence on known and new risk factors for pneumonia, a large population-based study on CAP in adults was performed with special emphasis on the identification of modifiable risk factors and generalizable to the general population.

Patients and methods

Study population

A population-based, case-control study was conducted in an extensive area of the eastern coast in Spain, in which approximately 95% of the population belongs to the National Health Care System, with public primary care centers and regional hospitals in each county. This is a mixed residential-industrial urban area with Mediterranean climatic conditions. The target population included 859,033 inhabitants older than 14 years of age assigned to any of the 64 primary care centers participating in the study. They comprised a total of 345 general practitioners, the

recruitment of which was made according to willingness to take part in the study. In order to demonstrate association with an odds ratio (OR) of 1.5 for risk factors for CAP with a prevalence of exposure in the control group of 5%, with 80% statistical power and significance level of 0.05, a sample of 1,500 cases and 1,500 controls was required.

Identification of cases

All patients with clinically suspected CAP presenting from November 1, 1999 to November 30, 2000 were prospectively registered. An active surveillance system was established to ensure the identification of all cases. This register 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 of each primary care center. In order to maintain the system of reporting cases, the coordinator in each of the study areas established periodic contacts with responsible persons of all participating centers. Periodic meetings with all professionals involved in the study were also held.

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 previously unrecorded focal signs on physical examination of the chest and new radiological findings suggestive of pneumonia infiltrate [3]. Criteria for clinical suspicion of acute lower respiratory tract infection included the presence of three or more of the following manifestations: cough with or without sputum production, dyspnea and/or wheezing, pleuritic chest pain or abdominal pain, fever, headache, pneumonic consolidation on auscultation of the chest, sweating, arthromyalgias, dysphagia and coryza. For clinically atypical CAP, one or more of the following criteria were considered: sweating, arthromyalgias, dysphagia, and coryza that required antibiotic prescription or persisted $\geq$ 5 days without antibiotics. In elderly patients, the possibility of pneumonia was also considered in the presence of prostration and/or anorexia and/or confusion or disorientation. In all cases in which criteria for clinical suspicion were met, a chest radiograph was ordered. Patients with initial doubtful radiographic images of CAP were tentatively included in the study and then excluded or definitively included according to clinical

evolution and subsequent roentgenographic findings. All cases of CAP were re-evaluated by chest roentgenograms on the 5th day of illness and at monthly intervals until complete recovery.

Patients with aspiration pneumonia (witnessed aspiration with respiratory symptoms or oral content of aspiration) or active pulmonary tuberculosis, and patients coming from nursing homes or having been discharged from hospital at least within 7 days before the onset of symptoms were excluded.

Selection of controls

Cases and controls were matched by gender, age (± 5 years), and primary care center. Broadly matching (frequency matching) was performed. Cases were matched to controls in a 1:1 proportion. Controls were randomly selected from the list of subjects assigned to each primary care center, and were recruited every 3 months. Controls who could not be contacted by telephone or home visits after three attempts were replaced following the same selection and matching criteria.

Data collection

A questionnaire on CAP risk factors was composed from the current literature and the opinion of international experts, the reliability of which has been demonstrated in previous studies [3,6]. It was administered directly to participants by trained physicians or nurses at home. The questionnaire included standardized information related to the following three aspects: a) health habits and lifestyle, b) clinical conditions and comorbidity, and c) regular treatments during the last year. Items are briefly described in the Appendix. The complete questionnaire is available from the authors upon request.

The study protocol was approved by the Ethics Committee of the *Consorci Sanitari del Maresme* and all participants gave written informed consent before enrolment. The funding sources had no role in the study.

Statistical analysis

As a measure of association between risk factors and the occurrence of CAP, estimations of the relative risk through odds ratios (OR) and 95% confidence intervals (CI) were used. These were calculated using unconditional logistic regression. The chi-square (χ^2) was used to assess differences between cases and controls in the frequency of variables related to health habits and lifestyle, clinical conditions and comorbidity, and regular treatments during the last year. All variables that were statistically significant in the univariate analysis with a *P* value < 0.10 were entered in a multivariable model with a stepwise approach. Moreover, it was consider appropriate to complement the multivariable analysis strategy by adjusting the effect of some drug treatments or vaccines for the underlying illness which were the reason of prescription. This was focused on treatments for heart failure, respiratory diseases, and the influenza and the pneumococcal vaccine. In all cases, if multicollinearity among different variables was detected, the most generic variable was selected. No interaction assessment was systematically performed due to the broad number of risk factors considered.

Results

During the period of field work 1,833 cases of clinical suspicion of CAP were identified, the diagnosis of which was not confirmed in 394 (21.5%). There were 1,439 patients with CAP, with an annual incidence rate of 1.54 cases per 1,000 inhabitants >14 years of age. A total of 2,107 control subjects was selected. The final study population included 1,336 patients with CAP and 1,326 controls. Disposition of cases and controls, and reasons for exclusion are shown in Figure 1. In the group of patients with CAP, 52.9% were males with a mean age of 58.6 (19.8) years and 47.1% were women with a mean age of 54.6 (20.7) years. In the group of controls, 52.6% were males with a mean age of 58.9 (19.6) years and 47.4% were women with a mean age of 54.6 (20.6) years. Sixty-one percent of patients were treated at home and the remaining patients were admitted to hospital.

Univariate results

A comparison of health habits and lifestyle factors between cases and controls is shown in Table 1. Risk factors for CAP were as follows: underweight; different measures related to cigarette smoking; alcohol intake in males; contact with animals, excrements or visceras; sudden temperature changes in the workplace; living with more than 10 persons at home; usual contact with children; and contact with pets. As compared with never smokers both current smokers (OR = 1.34) and ex-smokers (OR = 1.37) showed a higher risk for CAP. Ex-smokers who had quit smoking for more than 4 years showed a statistically significant reduced risk compared with ex-smokers of less than one year (OR = 0.39, 95% CI 0.17–0.89). In the never smokers older than 65 years, exposure to passive smoking was associated with a statistically significant increased risk for CAP (OR = 1.59, 95% CI 1.02–2.48). In men a statistically significant effect of the intensity of alcohol intake was observed above 40 g/day (OR = 1.62, 95% CI 1.10–2.39). With regard to job, building workers showed a higher risk for CAP (OR = 1.62, 95% CI 1.15–2.28) as were painters and carpenters (OR = 1.48, 95% CI 1.10–2.0). The greater the number of pets, the greater the risk for CAP (OR = 1.19, 95% CI 1.097–1.30 for each additional animal).

Risk factors for CAP related to clinical conditions and comorbidities are shown in Table 2. Previous hospital admission, previous CAP, history of upper respiratory tract infection, interventions on the upper respiratory tract (bronchoscopy, nasogastric tube), diabetes, heart diseases, chronic bronchitis, asthma, non-active pulmonary tuberculosis, epilepsy, chronic renal failure, cancer, VIH, dental dysesthesia, and dental prosthesis were risk factors for CAP. Visit to the dentist in the last month was a protective factor.

The bivariate effect of regular treatments is summarized in Table 3. Treatment with digoxin, amiodarone, diuretics, N-acetyl-cysteine, xanthines, oral steroids, inhaled steroids, inhaled beta-agonists, and inhaled anticholinergics drugs were risk factor for CAP. Moreover, the use of inhalers was a risk factor for CAP, particularly when medication was delivered through plastic pear-spacers or when medication contained steroids. Influenza and pneumococcal vaccine were protective factors.

Multivariable results

Variables selected in the multivariable model (Table 4) included cigarette smoking, sudden temperature changes at work, contact with children, civil status, previous hospitalization, history of upper respiratory tract infection, chronic bronchitis, asthma, epilepsy, oxygen therapy, and use of inhalers with or without plastic pear-spacers. Visits to the dentist in the last month had a protective effect. In the multivariable strategy designed to adjust the effect of some drug treatments or vaccines for the underlying illness (Table 4), amiodarone and heart failure were statistically significant variables in the model of treatments for heart diseases, whereas N-acetyl-cysteine, inhalation therapy, oxygen therapy, chronic bronchitis, and asthma were statistically significant factors in the model of treatments for respiratory diseases. Influenza vaccine was an independent protective variable for CAP but a statistically significant increased risk was observed in association with heart failure, chronic bronchitis, HIV infection, and use of oral steroids. In relation to pneumococcal vaccine, pneumococcal vaccine was also an independent protective factor, although a statistically significant increased risk in association with heart failure, chronic bronchitis, asthma, HIV infection, oral steroids, and radiation therapy or chemotherapy was found.

Discussion

This population-based study has provided an optimal framework to assess risk factors for CAP, in particular those modifiable risk factors and insufficiently proven in previous studies.

Underweight was a risk factor for CAP probably in relation to a possible deficient nutritional status or associated diseases that may affect the immune system [7] In contrast to the study of Baik et al., [8] neither overweight nor obesity were associated with an increased risk for pneumonia. In our study, like others [6,8] cigarette smoking was a risk factor for CAP. We also found a statistically significant decrease in CAP risk in the second year following quitting [8], which has been attributed to normalization of immune and inflammatory function of lung tissue. Although other respiratory diseases in adults associated with exposure to environmental tobacco smoke have been reported [9], this is the first study showing a direct relationship between passive smoking and CAP in subjects older than 65 years of age.

High alcohol intake was an important risk factor for CAP [1], in men, alcohol consumption above 40 g/day had a statistically significant effect. Alcohol consumption was not a risk factor for CAP in women may be due to a lower prevalence of alcohol use or higher underreporting. Heavy alcohol use causes alterations of the immune system, increasing host susceptibility to infectious diseases especially bacterial pneumonia [10]. In other studies, however, a statistically significant effect of alcohol use has not been found probably by the lack of statistical power [3] or the inclusion of populations with low alcohol intake [8].

Exposure to certain environmental factors predisposes to occupational respiratory diseases [11]. Contact with dust in the previous month and some interrelated jobs (builders, carpenters, painters) were more frequent in cases than in controls, but in the multivariable analysis sudden changes of temperature in the workplace was the only independent environmental factor for CAP. It has been shown that inhalation of cold air causes cooling of the nasal epithelium, and that this reduction in nasal temperature is sufficient to inhibit respiratory defences against infection such as mucociliary clearance and the phagocytic activity of leukocytes [12].

Living with more than 10 persons at home was associated with an increased risk for CAP. Contact with children was an independent risk factor in the multivariable analysis. Other studies have shown a higher incidence of CAP in adults with preschool children in the family, probably in relation to a higher carriage rate of *Streptococcus pneumoniae* [13]. Contact with pets was also associated with an increased risk for CAP, which tended to be higher as the number of pets increases. This effect has been only previously observed in cases of psittacosis or zoonotic pulmonary infections [14]. In relation to civil status, being single, widowed or divorced was independently associated with a higher risk for CAP than being married or living with a partner but the reasons for this finding are unknown.

Previous admission to the hospital was associated with CAP independently of patient's comorbidity and other risk factors. This finding has been corroborated in other studies [15]. Insertion of a nasogastric tube and the performance of a bronchoscopy can be also risk factors for CAP. Nasogastric tube favors bacterial growth and does not prevent oropharyngeal

aspiration, and bronchoscopy may facilitate passage of oropharyngeal organisms to the bronchial tree [16]. A very high risk of CAP was observed associated to upper respiratory tract infections [17], either presented in the previous month or repeated in the last year. Previous infection by respiratory viruses has long been regarded as a risk factor that predisposes to pneumonia. A previous diagnosis of pneumonia, confirmed by radiologic findings, is also an independent risk factor of a subsequent CAP. The risk increases with the number of previous CAP and recentness of infection. According to previous studies, an increased risk for CAP is maintained at least following 2 years after diagnosis [18].

With regard to underlying chronic diseases, patients with treated diabetes, heart disease, and non-active pulmonary tuberculosis showed an increased risk. Heart failure and treatment with amiodarone were risk factors for CAP in the multivariable analysis. Treatment with amiodarone is associated with pulmonary toxicity, which may favor bacterial superinfection [19]. Chronic bronchitis and asthma showed a strong relation with CAP, which was independent of the remaining clinical factors and drug therapy.

In relation to regular treatments, N-acetyl-cysteine appeared as a statistically significant risk factor for CAP. In other studies, treatment with N-acetyl-cysteine was not effective for the prevention of acute exacerbations in patients with COPD [20]. Oxygen therapy in the last year was selected as an independent risk factor in the multivariable analysis. Oxygen therapy may cause nasal and oropharyngeal dryness with difficulties in swallowing and favoring aspiration [21].

The use of oral and especially inhaled steroids was associated with CAP in the bivariate analysis. Other studies have shown an increased risk of pneumonia in patients treated with oral steroids [22] but evidence of the impact of inhaled steroids has not been previously documented, except as an unexpected finding in the TORCH study [23]. The use of inhalers was also an independent risk factor for CAP. Poor hygienic measures and contamination of inhalers, particularly of plastic pear-spacers, is a recognized mechanism of infection [24]. In addition, deep inhalation from pressurized aerosols may favor penetration of organisms from the oropharyngeal cavity to the bronchial tree. One of the most striking findings of the present study

is that the risk of acquiring CAP was increased in patients using inhalers especially with a chamber-spacer. When we looked at different medications, patients using inhaled steroids showed a higher risk compared with beta-adrenergics and anticholinergics. These results fit well with the information provided by the TORCH study [23] in which patients treated with inhaled steroids (plus beta-adrenergics) presented a statistically significant higher risk of pneumonia when compared to those only treated with beta-adrenergics. Our results have to alert on a predisposition to acquire pneumonia when using long-term inhaled steroids. Definitely, further research is needed in this field.

Having visited a dentist in the last month was an independent protective factor for CAP. This finding may be related to a better oral hygiene. Several studies provide evidence that the oral cavity may influence the initiation and/or the progression of respiratory infections [25]. In contrast, symptoms of dental dysesthesia suggestive of dental caries and the use of dental prosthesis were associated with CAP in the bivariate analysis. In other studies, dental caries and periodontal disease was also associated with a higher probability of aspiration pneumonia by aspiration of contaminated saliva [12]. Other factors facilitating aspiration and organisms reaching the lower respiratory tract are gastric acid-suppressive drugs. In a recent study, the use of proton pump inhibitors, especially when recently begun, was associated with an increased risk of CAP [26]. However, we did not find a relationship between acid-suppressive therapy and CAP. Although bronchial aspiration was an exclusion criterion, we cannot rule out that some cases of silent undiagnosed aspiration as a cause of pneumonia would have been included. This may be the reason for the finding of epilepsy as risk factor for CAP in the multivariable analysis. On the other hand, dementia did not reach statistical significance probably by the lack of statistical power.

The effectiveness of influenza vaccine in preventing CAP found in observational studies [27] was also confirmed by our data. Regarding pneumococcal vaccine, it should be noted that after adjusting by risk factors, which in turn were the reason of vaccination, pneumococcal vaccine accounted for a 46% reduction of the risk for CAP. This finding is consistent with

previous studies [28] but in another study, the effect of pneumococcal vaccine in preventing CAP was not observed [29].

Finally, it has been suggested that inappropriate antibiotic treatment could be a risk factor for CAP especially pneumonia caused by *Legionella pneumophila* or *Chlamydia pneumoniae* [30]. In some patients who are smokers or with chronic bronchitis, the use of antibiotics in the previous 3 months may determine a selection of respiratory flora, predisposing to opportunistic infection with colonization of more aggressive organisms, which would be causative pathogens of CAP. Our study seems to support this hypothesis for cephalosporins and macrolides, a group of antimicrobials that is frequently used more indiscriminately.

The present results should be interpreted taking into account the influence of possible confounding factors and the presence of correlation between some of the analyzed factors.

This study provides useful clinical information to establish preventive interventions for CAP in adults especially directed to modifiable risk factors. Not only new risk factors, such as passive smoking, usual contact with young children, contact with pets, or use of inhalers have been identified, but also the statistically significant effect of other controversial factors in the literature, including pneumococcal vaccine, alcohol consumption, and oxygen therapy has been recognized. Timely medical care and preventive strategies directed to the general population or to those persons at risk are relevant clues for reducing the incidence of CAP.

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Table 1. Results of univariate analysis: association between health habits and lifestyle factors and CAP

Variable	CAP (n = 1336)	Controls (n=1326)	OR	95 % CI	*P* value
Body mass index					
Normal	769 (64.0)	780 (64.5)	1	---	
Underweight	115 (9.6)	53 (4.4)	2.20	1.57 – 3.09	<0.001
Overweight	214 (17.8)	245 (20.2)	0.89	0.72 – 1.09	
Obesity	103 (8.6)	132 (10.9)	0.79	0.60 – 1.04	
Smoking status					
Never smoker	548 (41.0)	643 (48.5)	1	---	
Ex-smoker	423 (31.7)	363 (27.4)	1.37	1.14 – 1.64	0.001
Current smoker	365 (27.3)	320 (24.1)	1.34	1.11 – 1.62	
Passive smoker*	143 (30.4)	140 (26.3)	1.22	0.93 – 1.61	0.155
Pack-years					
0	548 (43.4)	643 (51.8)	1	---	
1-150	354 (28.0)	358 (28.8)	1.16	0.96 – 1.40	<0.001
151-300	233 (18.4)	169 (13.6)	1.62	1.29 – 2.03	
>300	129 (10.2)	71 (5.7)	2.13	1.56 – 2.91	
Frequency of alcohol intake (men)					
Never	205 (31.2)	210 (31.5)	1	---	
Occasionally	178 (27.1)	156 (23.4)	1.17	0.88 – 1.56	0.269
Usually	274 (41.7)	300 (45.0)	0.94	0.73 – 1.21	
Frequency of alcohol intake (women)					
Never	353 (59.2)	365 (60.2)	1	---	
Occasionally	160 (26.8)	163 (26.9)	1.02	0.78 – 1.32	0.860
Usually	83 (13.9)	78 (12.9)	1.1	0.78 – 1.55	
Alcohol intake (g/day) (men)					
0	239 (33.8)	237 (34.1)	1	---	
0.1 – 20	292 (41.3)	304 (43.7)	0.95	0.75 – 1.21	
21 – 40	91 (12.9)	103 (14.8)	0.88	0.63 – 1.22	
41 - 80	59 (8.3)	41 (5.9)	1.42	0.92 – 2.21	0.037
>80	26 (3.7)	11 (1.6)	2.34	1.13 – 4.85	
Alcohol intake, g/day (women)					
0	396 (63.0)	394 (34.1)	1	---	
0.1 – 20	218 (34.7)	221 (43.7)	0.98	0.78 – 1.24	
21 – 40	11 (1.7)	10 (14.8)	1.09	0.46 – 2.61	0.980
>40	4 (0.6)	5 (0.75)	0.80	0.21 – 2.99	
Work-life contact with					
Smoke	185 (14.2)	163 (12.7)	1.14	0.97 – 1.43	0.243
Petrol	103 (7.9)	102 (8.0)	1.00	0.75 – 1.33	0.989
Dust	257 (19.8)	219 (17.0)	1.20	0.99 – 1.47	0.068
Organic fibers	82 (6.3)	80 (6.2)	1.02	0.74 – 1.40	0.919
Inorganic fibers	87 (6.7)	70 (5.4)	1.25	0.90 – 1.72	0.182
Ionized radiation	22 (1.7)	14 (1.1)	1.56	0.80 – 3.10	0.190
Non-ionized radiation	8 (0.6)	12 (0.9)	0.66	0.27 – 1.62	0.357
Animals, excrements, visceras	149 (11.5)	115 (9.0)	1.78	1.00 – 3.19	0.036
Sudden work temperature changes, last 3 months **	113 (8.7)	36 (2.8)	3.28	2.24 – 4.82	<0.001
> 10 persons at home	35 (2.6)	16 (1.2)	2.20	1.21 – 4.00	0.009
Usual contact with children <15 years at home or work	472 (35.4)	356 (27.0)	1.48	1.26 – 1.75	<0.001
Contact with pets					
Any	673 (50.6)	565 (42.8)	1.37	1.18 – 1.60	<0.001
Birds	320 (24.0)	254 (19.2)	1.33	1.10 – 1.60	0.003
Cats	189 (14.1)	143 (10.8)	1.36	1.08 – 1.72	0.009
Dogs	380 (28.4)	314 (23.7)	1.28	1.08 – 1.52	0.005

Educational level					
Low	501 (37.7)	441 (33.4)	1		
Middle	540 (40.6)	557 (42.2)	0.86	0.72 – 1.01	0.048
High	288 (21.7)	323 (24.5)	0.78	0.64 – 0.96	
Civil status					
Married, living with partner	886 (66.7)	924 (70)	1	---	
Single, widowed, divorced	443 (33.3)	396 (30)	1.17	0.99 – 1.37	0.065

* Never smokers are only considered, taken as reference those without passive exposure to tobacco smoke.
Percentages in parenthesis.
** Sudden work temperature change when coming in or out of a refrigerator, a furnace or a kitchen.

Table 2. Results of univariate analysis: association between clinical conditions and comorbidities and CAP

Variable	CAP (n =1336)	Controls (n =1326)	OR	95 % CI	*P* value
Hospital admissions, last 5 yrs	621 (46.5)	452 (34.1)	1.68	1.44 – 1.96	<0.001
Interventions on upper respiratory tract, last year					
Nasal or pharyngeal examination	42 (3.1)	36 (2.7)	1.16	0.74 – 1.83	0.512
Bronchoscopy	27 (2.0)	13 (1.0)	2.09	1.07 – 4.06	0.027
Gastroscopy	36 (2.7)	29 (2.2)	1.24	0.76 – 2.04	0.393
Nasogastric tube	16 (1.2)	5 (0.4)	3.21	1.17 – 8.77	0.026
General anaesthesia	40 (3.0)	30 (2.3)	1.33	0.83 – 2.16	0.237
Upper respiratory tract infections					
More than 1 during the last year	592 (44.4)	447 (33.7)	1.57	1.35 – 1.84	<0.001
Any during the last month	424 (31.8)	183 (13.8)	2.91	2.40 – 3.53	<0.001
Previous CAP confirmed by radiograph during life					
None	1104 (82.6)	1219 (91.9)	1	---	
Any	232 (17.4)	107 (8.1)	2.39	1.88 – 3.05	<0.001
1 CAP	179 (13.4)	94 (7.1)	2.10	1.62 – 2.73	<0.001
2 CAP	36 (2.7)	10 (0.8)	3.98	1.96 – 8.05	
>2 CAP	17 (1.3)	3 (0.2)	6.25	1.83 – 21.40	
Time since the last CAP					
During last year	18 (6.4)	1 (0.7)	11.12	1.46 – 84.40	
Since 1 year	40 (14.2)	11 (8.0)	2.25	1.11 – 4.56	0.001
Since 2 years	40 (14.2)	12 (8.8)	2.06	1.04 – 4.09	
Since 3 or more years	183 (65.1)	113 (82.5)	1	---	
Diabetes mellitus (treated)	135 (10.1)	95 (7.2)	1.43	1.11 – 1.92	0.007
Heart failure	114 (8.6)	65 (4.9)	1.81	1.33 – 2.49	<0.001
Heart valve disease	59 (4.4)	35 (2.6)	1.70	1.11 – 2.61	0.014
Coronary artery disease	80 (6.0)	76 (5.7)	1.05	0.76 – 1.45	0.782
Chronic bronchitis	216 (16.2)	81 (6.1)	2.96	2.26 – 3.87	<0.001
Asthma	375 (28.1)	190 (14.3)	2.33	1.92 – 2.84	<0.001
Pulmonary tuberculosis (non-active)	50 (3.8)	28 (2.1)	1.81	1.13 – 2.89	0.013
Epilepsy	17 (1.3)	6 (0.5)	2.83	1.11 – 7.21	0.029
Parkinson’s disease	10 (0.79	15 (1.1)	0.66	0.30 – 1.47	0.309
Stroke	33 (2.5)	37 (2.8)	0.88	0.55 – 1.42	0.601
Dementia	17 (1.3)	8 (0.6)	2.12	0.91 – 4.94	0.074
Psychiatric disorders (excluding dementia)	178 (13.3)	209 (15.8)	0.82	0.66 – 1.02	0.070
Gastroesophageal reflux	352 (26.4)	356 (26.8)	0.98	0.82 – 1.16	0.797
Chronic liver disease	38 (2.9)	23 (1.7)	1.67	0.99 – 2.82	0.550
Chronic renal failure	20 (1.5)	21 (1.6)	0.98	0.51 – 1.75	0.860
Cancer	106 (7.9)	76 (5.7)	1.42	1.04 – 1.92	0.025
VIH	15 (1.1)	2 (0.2)	7.49	1.71 – 32.81	0.008
Dental dysesthesia	245 (23.3)	210 (19.7)	1.24	1.01 – 1.53	0.043
Dental prosthesis	567 (45.6)	512 (40.8)	1.22	1.04 – 1.42	0.016
Visit to the dentist in the last month	116 (8.7)	156 (11.8)	0.71	0.55 – 0.92	0.008

Percentages in parenthesis.

Table 3. Results of univariate analysis: association between treatments, vaccinations and CAP

Variable	CAP (n =1336)	Controls (n =1326)	OR	95 % CI	*P* value
Regular treatments during the last year					
Acetylsalicylic acid	98 (7.3)	94 (7.1)	1.04	0.77 – 1.39	0.806
Digoxin	32 (2.4)	13 (1.0)	2.48	1.30 – 4.74	0.005
Amiodarone	24 (1.8)	6 (0.5)	4.02	1.64 – 9.88	0.001
Calcium antagonists	71 (5.3)	84 (6.3)	0.83	0.60 – 1.15	0.261
Diuretics	182 (13.6)	128 (9.7)	1.48	1.16 – 1.88	0.001
Benzodiacepines	109 (8.2)	127 (9.6)	0.94	0.64 – 1.10	0.198
Gastric acid-suppressive drugs					
Any	123 (9.2)	107 (8.1)	1.16	0.88 – 1.52	0.296
Proton pump inhibitors	44 (3.3)	32 (2.4)	1.38	0.87 – 2.18	0.173
Histamine H_2 receptor antagonists	42 (3.1)	38 (2.9)	1.10	0.70 – 1.72	0.675
Antacids	44 (3.3)	43 (3.2)	1.02	0.66 – 1.56	0.942
N-acetyl-cysteine	30 (2.2)	8 (0.6)	3.78	1.73 – 8.29	<0.001
Xanthines	22 (1.6)	5 (0.4)	4.42	1.67 – 11.72	0.001
Oral corticosteroids	43 (3.2)	12 (0.9)	3.64	1.91 – 6.94	<0.001
Inhaled steroids	15 (1.1)	1 (0.1)	15.05	1.98 – 114.06	0.001
Inhaled beta-agonists	103 (7.7)	59 (3.9)	2.05	1.45 – 2.88	<0.001
Inhaled anticholinergic drugs	93 (7.0)	27 (2.0)	3.60	2.33 – 5.56	<0.001
Oxygen therapy	45 (3.6)	18 (1.4)	2.58	1.49 – 4.49	<0.001
Inhalers					
Without spacer device	144 (11.5)	65 (5.2)	2.39	1.76 – 3.23	<0.001
With spacer device	79 (6.3)	25 (2.0)	3.30	2.09 – 5.22	<0.001
Antibiotic treatment during last 3 months*					
Penicillins	30 (2.3)	33 (2.5)	0.90	0.55 – 1.49	0.691
Cefalosporins	15 (1.1)	6 (0.5)	2.50	0.97 – 6.46	0.051
Macrolides	22 (1.6)	11 (0.8)	2.00	0.97 – 4.14	0.057
Aminoglycosides	1 (0.1)	0 (0.0)	---	---	---
Quinolones	9 (0.7)	4 (0.3)	2.24	0.69 – 7.30	0.266
Vaccinations					
Influenza, last year	469 (35.2)	477 (36.0)	0.96	0.82 – 1.13	0.650
Pneumococcal	50 (3.9)	64 (5.0)	0.78	0.53 – 1.13	0.190
Haemophilus influenzae type b, ever in life	4 (0.3)	1 (0.1)	4.03	0.45 – 36.12	0.217

*Cases and controls treated with antibiotics in the last 7 days were excluded from the analysis.

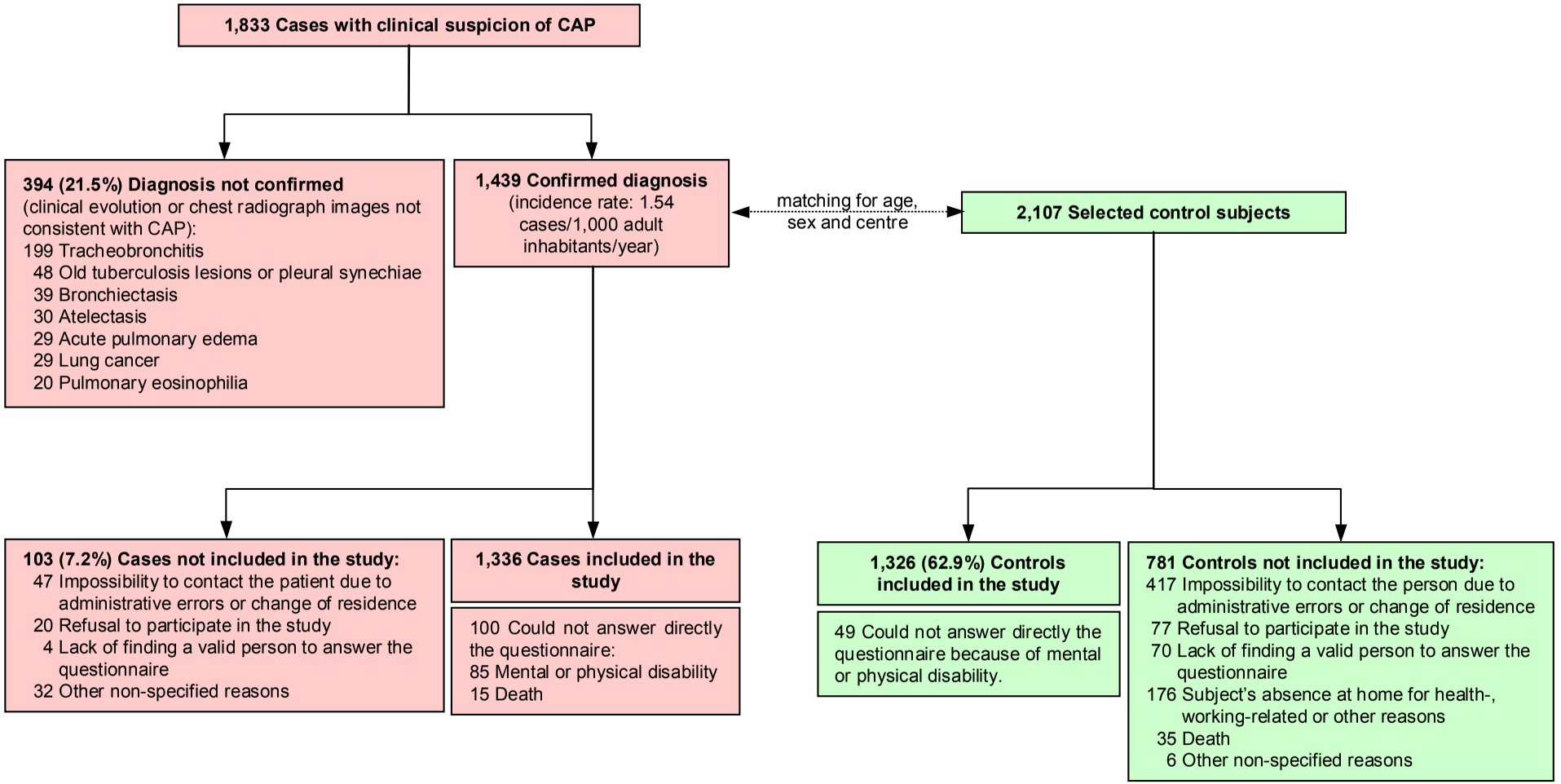
Table 4. Results of multivariable analysis: risk factors for CAP

Variables[*]	Odds ratio	95% CI	*P* value (Wald χ^2)
Smoking, packs year			0.006
0	1		
≤ 150	1.01	0.81–1.26	
> 150	1.46	1.14–1.86	
Sudden temperature changes at work, last 3 months	2.64	1.67–4.15	<0.001
Usual contact with children < 15 years at home/work	1.48	1.20–1.82	<0.001
Civil status			0.021
Married or living with partner	1		
Single, widowed, divorced	1.28	1.04–1.59	
Hospital admission in the previous 5 years	1.39	1.14–1.70	0.001
Upper respiratory tract infections, last month	2.28	1.81–2.89	<0.001
Number of previous CAP confirmed by chest radiography	1.48	1.17–1.87	0.001
Chronic bronchitis	1.81	1.19–2.75	0.006
Asthma	1.67	1.28–2.19	<0.001
Epilepsy	5.95	1.62–21.74	0.007
Visit to the dentist, last month	0.69	0.81–1.26	0.022
Oxygen therapy, last year	2.42	0.81–1.26	0.018
Use of inhalers with or without plastic pear-spacers	1.57	0.81–1.26	0.031
Treatment for heart failure[†]			
Amiodarone	3.27	1.31–8.13	0.011
Heart failure	1.68	1.22–2.32	0.001
Treatment for respiratory diseases[‡]			
N-acetyl-cysteine	2.59	1.15–5.83	0.021
Use of inhalers with or without plastic pear-spacers	1.44	1.02–2.04	0.038
Oxygen therapy	2.08	1.16–3.73	0.014
Asthma	1.85	1.49–2.29	<0.001
Chronic bronchitis	1.84	1.32–2.59	<0.001
Influenza vaccine[§]			
Heart failure	1.48	1.05–2.07	0.024
Chronic bronchitis	3.14	1.64–2.56	<0.001
Asthma	2.05	1.64–2.56	<0.001
HIV infection	7.96	1.81–35.1	0.006
Oral steroids	2.22	1.12–4.37	0.022
Influenza vaccine	0.81	0.68–0.96	0.014
Pneumococcal vaccine[¶]			
Heart failure	1.43	1.01–2.03	0.046
Chronic bronchitis	3.16	2.36–4.24	<0.001
Asthma	2.20	1.75–2.77	<0.001
HIV infection	8.99	1.98–40.8	0.004
Oral steroids	2.20	1.07–4.50	0.031
Radiation therapy or chemotherapy	2.73	0.97–7.65	0.05
Pneumococcal vaccine	0.54	0.36–0.81	0.003

[*]Variables with $P < 0.10$ detailed in Tables 1, 2, and 3 were included.
[†]Variables included in the model: digoxin, amiodarone, diuretics, and heart failure.
[‡]Variables included in the model: N-acetyl-cysteine, oral steroids, use of inhalers with or without plastic pear-spacers, xanthines, oxygen therapy, asthma, and chronic bronchitis.
[§]Variables included in the model: heart failure, chronic bronchitis, asthma, diabetes, renal failure, chronic liver disease, HIV infection, oral steroids, radiation therapy or chemotherapy, and influenza vaccine.
[¶]Variables included in the model: heart failure, chronic bronchitis, asthma, diabetes, renal failure, chronic liver disease, HIV infection, oral steroids, radiation therapy or chemotherapy, and pneumococcal vaccine.

Legends

Figure 1. Disposition of cases and controls.


1,833 Cases with clinical suspicion of CAP
394 (21.5%) Diagnosis not confirmed
(clinical evolution or chest radiograph images not consistent with CAP):
199 Tracheobronchitis
48 Old tuberculosis lesions or pleural synechiae
39 Bronchiectasis
30 Atelectasis
29 Acute pulmonary edema
29 Lung cancer
20 Pulmonary eosinophilia
1,439 Confirmed diagnosis
(incidence rate: 1.54 cases/1,000 adult inhabitants/year)
matching for age, sex and centre
2,107 Selected control subjects
103 (7.2%) Cases not included in the study:
47 Impossibility to contact the patient due to administrative errors or change of residence
20 Refusal to participate in the study
4 Lack of finding a valid person to answer the questionnaire
32 Other non-specified reasons
1,336 Cases included in the study
100 Could not answer directly the questionnaire:
85 Mental or physical disability
15 Death
1,326 (62.9%) Controls included in the study
49 Could not answer directly the questionnaire because of mental or physical disability.
781 Controls not included in the study:
417 Impossibility to contact the person due to administrative errors or change of residence
77 Refusal to participate in the study
70 Lack of finding a valid person to answer the questionnaire
176 Subject's absence at home for health-, working-related or other reasons
35 Death
6 Other non-specified reasons

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.