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Risk factors for death and hospitalization from pneumonia. A prospective study of a general population

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Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. P. Lange, J. Vestbo, J. Nyboe. ©ERS Journals Ltd 1995.

ABSTRACT: The aim of this study was to identify possible risk indicators for pneumonia leading to death and hospitalization in the general population. We followed 6,158 men and 7,265 women aged 30–70 years, who participated in the Copenhagen City Heart Study, a prospective population study, for 12 years with regard to mortality and hospital admissions for pneumonia.

A total of 260 deaths with pneumonia as main or contributory death cause had occurred, and 405 subjects had been admitted to hospital at least once because of pneumonia. Mortality and hospitalization were analysed by multivariate Cox regression models.

In addition to increasing age, forced expiratory volume in one second (FEV_1) was strongly and consistently related to both pneumonia related mortality and hospitalization. Women with FEV_1<60% predicted had a relative risk of 5.7 (95% confidence interval: 2.9–11) and 3.6 (2.1–6.4) for death and hospitalization, respectively, when compared with women with $FEV_1 \geq 100\%$ predicted. Similar, although lower, relative risks were observed in men. Other significant risk indicators for hospitalization were: self-reported asthma (women), mucus hypersecretion (women and men), history of stroke (men) and smoking (women).

We conclude that, in addition to age, reduced FEV_1 is the most important risk indicator for severe pneumonia.

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In spite of the presence of several potent antimicrobial agents, pneumonia still contributes significantly to mortality in western countries, being numerically the most important infection [1, 2]. In some countries, death rates from pneumonia have even increased during recent years, placing pneumonia among the five most common causes of death [3]. In Denmark, approximately 2.3% of all deaths in 1989 had pneumonia registered as underlying cause [4]. The burden of pneumonia-caused morbidity in terms of hospitalizations and absence from work is also high.

Although there are numerous papers dealing with causes of community acquired pneumonia [2, 5–7] and with the prognosis once the patients have been admitted to hospital, the literature concerning the identification of factors that make subjects prone to develop pneumonia is sparse. In fact, we are familiar with only one prospective study, where subjects from the general population have been followed with regard to pneumonia mortality and morbidity [8] and a few other studies that investigated cohorts of employees or ambulatory patients [9, 10].

The aim of the present study was to identify possible risk factors for severe pneumonia in the general population. We defined severe pneumonia, as pneumonia that leads to death or hospitalization. Data from an on-going longitudinal population study of approximately 14,000 subjects, The Copenhagen City Heart Study, were linked with mortality and hospitalization registers.

Material and methods

Population

The Copenhagen City Heart Study was initiated in 1976. The participants were selected among 90,000 persons living in a defined area around Rigshospitalet, the State University Hospital of Copenhagen. A sample of 19,698 subjects aged 20 years or more was selected at random after age stratification. The sample fraction was highest (50%) for persons 40 to 69 years of age. The subjects were invited by letter to an examination on a specific date during the period March 1976 to March 1978. A total of 14,223 (74% of those invited) attended this first examination. Details on the selection procedure of the study sample, the description of the nonresponders together with the complete examination programme and a flow chart depicting the subjects have been presented in previous papers [11, 12]. At the health examination, a self-administered questionnaire concerning symptoms, somatic diseases, social status, smoking,

and drinking habits was filled out and, during the further investigations, checked by one of the investigators. All subjects reported whether they were current smokers, ex-smokers or life-long nonsmokers, and for the first two categories the duration of smoking. Current and ex-smokers reported their daily tobacco consumption.

The present analysis comprised subjects who participated in the initial examination, which took place from 1976 to 1978. A total of 7,265 women and 6,158 men with sufficient data for the analyses were followed until the end of 1988 by means of the National Health Service Registers for deaths and hospital discharges. These registers cover all deaths and hospitalizations in Denmark. Cases of pneumonia were registered according to the 8th revision of the International Classification of Diseases [13] using the code numbers ICD: 480–486. The Danish hospitalization register contains information from all hospitals in Denmark, yet in the present study, which considered a relatively small geographical region (the centre of Copenhagen), more than 90% of admissions were to the 3 large city hospitals, all of them being University Hospitals. In this study, we relied on the treating physicians and on the physicians who filled in the death certificates with regard to whether the patients suffered from pneumonia or not.

Definition of end-points for the analysis

The average follow-up period was 12 years (table 1). The following end-points were analysed: a) Deaths where pneumonia was considered as main death cause b) Pneumonia-related deaths c) Hospitalizations where pneumonia was mentioned as the main diagnosis. In addition we also performed an analysis of an additional end-point: severe pneumonia, which was defined as either pneumonia related death or hospitalisation from pneumonia.

A total of 260 deaths with pneumonia listed on the death certificate as either the main or as the contributory cause of death (pneumonia-related death) were observed; of these 27 deaths had pneumonia listed as the main death cause. In total 24 of the pneumonia-related deaths took place in a hospital. In total 405 subjects were hospitalized on at least one occasion because of pneumonia: *i.e.* the main diagnosis on the discharge record was pneumonia. There were 557 subjects, who were either hospitalized because of pneumonia or who died from pneumonia related death.

Table 1. – Study population for the analysis

Sample selected January 1st 1976	19,698
Died before planned visit	369
Alive at planned visit	19,329
Responders	14,223
Excluded because of missing data	800
Population at risk	13,423
End-points until 31 December 1988	
Died from pneumonia	27
Pneumonia-related deaths	260
Hospitalized because of pneumonia	405

Potential risk variables.

The variables of interest for the present analysis were age, gender, forced expiratory volume in one second (FEV_1), body-mass index (BMI), tobacco smoking, alcohol consumption, length of school education, presence of bronchial asthma, chronic bronchitis, diabetes mellitus, and a history of stroke and myocardial infarction.

FEV_1 was measured with an electronic spirometer (Monaghan N 403, Littleton, Colorado), which was calibrated daily. As a criterion for the correct performance, at least two measurements differing less than 5% from each other had to be produced. We used internal reference values, which were generated from the spirometric data from a subgroup of never-smokers without diabetes mellitus, bronchial asthma, heart disease, pulmonary symptoms and with daily consumption of alcohol of less than 5 drinks [14]. For each participant the adjustment of the observed spirometric data to the prediction equations was done by calculating the observed FEV_1 as percent of predicted (FEV_1%p). For the final analyses the participants were classified into following categories: FEV_1%p$\geq$ 100; 80 $\leq$$FEV_1$%p$<$ 100; 60 $\leq$$FEV_1$%p$<$ 80; FEV_1%p$<$ 60. Smoking habits, alcohol consumption (drinks$\cdot$day^{-1}) and the length of school education (yrs), were obtained from the questionnaire. With regard to smoking, the subjects were grouped according to the smoking status at the time of investigation and current smokers were further subdivided according to the cumulative tobacco consumption expressed in the number of packyears.

BMI (weight/height^2 in kg/m^2) was included using three levels: <20; 20–29, >30.

The diagnosis of diabetes mellitus (DM), bronchial asthma, a history of stroke and of myocardial infarction (MI) was based on answers in the questionnaire. Chronic mucus hypersecretion was registered if the participants reported to bring up phlegm for as long as three months a year at least for 2 years.

Statistical analysis

The proportional hazards model of Cox was used for analysis of both pneumonia related deaths and pneumonia hospitalizations [15]. Analyses of hospitalizations were based on the first documented admission for pneumonia, although repeated admissions were possible. Except for the analysis of the 27 deaths where pneumonia was stated as the main diagnosis, separate models were developed for men and women. Time was reckoned from the initial examination until the occurrence of an end-point or until the end of the observation period. The regression coefficients were estimated using the maximum likelihood method as suggested by Cox, and the hypothesis of a significant effect of a risk factor was evaluated by means of the likelihood ratio test. The results are given in terms of estimated relative risks (RR).

Results

The occurence of the pneumonia related deaths and hospitalizations during the follow-up is given in table 2.

Table 2. – Occurence of end-points during follow-up

Calendar year	Pneumonia-related deaths		Pneumonia hospitalizations	
	Women	Men	Women	Men
1977	4	4	6	6
1978	2	10	6	19
1979	7	17	7	15
1980	8	9	12	17
1981	9	10	14	16
1982	19	17	25	16
1983	8	14	21	21
1984	16	16	15	22
1985	7	12	23	22
1986	11	15	14	15
1987	11	17	27	19
1988	12	13	19	28
Total	106	154	189	216
% of all at risk	1.5	2.5	2.6	3.5

The distribution of subjects according to the different levels of the investigated variables and the observed number of pneumonia-related deaths and hospitalizations showed that the unadjusted incidence of pneumonia-related deaths increased with age and with decreasing FEV1%p and BMI. Pneumonia-related deaths were also more common in subjects who reported to have asthma, chronic mucus hypersecretion, or previous myocardial infarction, and in men with a history of stroke. A similar pattern was observed with regard to hospitalization for pneumonia.

We tried to discriminate between typical bacterial pneumonias and pneumonias caused by mycoplasma and viruses (codes 480.99 and 483.00), but less than 2% of all pneumonia hospitalizations were registered as the latter types of pneumonias. More than 50% of all pneumonia hospitalizations were coded as pneumonia without specification of a microbiological agent (code 485.99). There were no deaths attributed to viral or mycoplasma pneumonia. As there were only 27 deaths, where pneumonia was listed as main diagnosis, we performed a Cox regression analysis for both sexes combined (table 3). The risk of pneumonia rose significantly with increasing age and with decreasing FEV1%p and BMI. There was no significant differences between the sexes.

In table 4 the results of the Cox regression on pneumonia-related death are given. Only the variables which were significant on the 5% level are shown: age, education and FEV1%p which was included in the previously defined groups. Although smoking did not achieve significance in the separate models for men and women, it did so in the Cox regression model where men and women were combined (not shown). In that model, current smokers had a 1.6 (95%CI: 1.1–2.6) times higher risk of pneumonia death than neversmokers.

Table 3. – Results of the Cox regression model on the 27 deaths due to pneumonia. Only the variables, which obtained significance at the 5% level are shown.

Variable	RR	95% CI
AGE yr	1.20	(1.10 – 1.25)
FEV1%pred		
≥100	1.0	
60–99	2.0	(0.3–10)
<60	10.0	(2.1–46)
BMI kg·m^{-2}		
<20	13	(1.5–113)
20–29	3.0	(0.4–22)
≥30	1.0	

RR: relative risk; 95%CI: 95% confidence interval

Table 4. – Results of the Cox regression model on pneumonia-related deaths. Only the variables, which obtained significance at the 5% level for either men or women are shown

Variable	Women		Men	
	RR	95% CI	RR	95% CI
AGE yr	1.12	(1.10 – 1.14)	1.11	(1.10–1.13)
FEV1%pred				
≥100	1.0		1.0	
80–99	1.4	(0.7–2.6)	1.2	(0.7–2.0)
60–79	1.8	(0.9–3.4)	1.5	(0.8–2.5)
<60	5.7	(2.9–11)	2.3	(1.3–4.1)
EDUCATION				
<8 yrs	1.0		1.0	
≥8 yrs	1.1	(0.8–1.7)	0.6	(0.4–0.9)

RR: relative risk; 95%CI: 95% confidence interval

Table 5 shows the variables which remained significant in the Cox regression on the hospitalization from pneumonia. Age, FEV1%p and chronic mucus hypersecretion were significant in both sexes. Although the remaining variables differed between the sexes, for most of them the trends were similar.

Finally, the results concerning the combination of death and hospitalization (severe pneumonia) were very similar to the hospitalization results. In men, however, both low education and low BMI were also significantly related to this end-point.

Table 5. – Results of the Cox regression model on pneumonia hospitalization only. Only the variables, which obtained significance at the 5% level for either men or women are shown

Variable	Women		Men	
	RR	95% CI	RR	95% CI
AGE yr	1.07	(1.06–1.1)	1.06	(1.05–1.08)
FEV1%pred				
≥100	1.0		1.0	
80–99	1.2	(0.7–1.9)	1.0	(0.6–1.5)
60–79	1.8	(1.2–3.0)	1.8	(1.1–2.9)
<60	3.6	(2.1–6.4)	3.2	(1.8–5.3)
SMOKING				
never	1.0		1.0	
ex	1.4	(0.8–2.5)	1.4	(0.8–2.7)
current	2.0	(1.3–3.0)	1.2	(0.6–2.1)
+ ASTHMA	1.9	(1.1–3.7)	2.0	(0.8–2.6)
+ MUCUS	1.6	(1.1–2.5)	1.8	(1.3–2.5)
+ STROKE	1.0	(0.2–4.0)	3.0	(1.5–6.2)

RR: relative risk; 95%CI: 95% confidence interval

Discussion

In addition to age, reduced lung function was strongly and consistently related to pneumonia morbidity and mortality in both sexes.

In the present study, pneumonia rates increased with age and were slightly higher in men than in women (table 2). Our results are similar to the findings of LaCroix *et al.* and of Lipsky and colleagues with regard to the effect of age and gender [8, 9]. In these other studies, the level of FEV1 was not investigated and, instead, a self-reported history of physician diagnosed chronic obstructive lung disease was used. Subjects with this condition had approximately 2 times higher risk of pneumonia hospitalization than those without. In the present study, including FEV1 as a risk indicator, we observed a quite similar risk in subjects who reported to have asthma, but more importantly we observed a dose-response relationship between both morbidity and mortality from pneumonia and FEV1 expressed in percent of predicted value. We cannot exclude that the importance of FEV1 reduction with regard to incidence of pneumonia is overestimated, as the general condition of subjects with low FEV1 may favour hospitalization even if the pneumonia as such is not so severe. Yet, there are several possible mechanisms which could link low FEV1 with pneumonia. Reduced FEV1 is an established risk factor for mortality from all-causes and chronic obstructive pulmonary disease (COPD) [14, 16]. In addition, it has been related to hospitalization from the latter condition [17]. In the present population, reduced FEV1 most often reflects presence of tobacco induced COPD. This condition is often accompanied by colonization of the airways with *Streptococcus pneumonia* and/or *Haemophilus influenza* [18] and impairment of antibacterial defences, in particular the impairment of mucociliary clearance [19]. Both factors could lead to a higher risk of pneumonia.

In both sexes, but in particular in men, chronic mucus hypersecretion was significantly related to pneumonia hospitalization. In the study of Jedrychowski [20], smokers did not have a higher absence rate from work compared to nonsmokers, but the subgroup of smokers with mucus hypersecretion did. Similar associations between mucus hypersecretion and infective chest episodes have been reported by others [10, 21, 22]. As recent investigations suggest that acute bronchitis and exacerbations of chronic obstructive lung disease are often due to similar microbial agents that also cause pneumonia [23], it seems relevant to compare their investigations with the present study. Smoking was significantly related to pneumonia in women but not in men, although a similar trend was observed (table 5). Previous studies of the importance of smoking on the risk of chest infections have shown conflicting results. In the study of LaCroix *et al.*[8], smoking was significantly related to pneumonia morbidity. In the study of Comstock *et al.* [10], who followed male employees of a telephone company, smoking was not related to disability from pneumonia and in the Tecumseh study of respiratory illness [21], acute lower respiratory infections were more frequent in smokers, although illness rates were not. The authors suggested different perception of disease in smokers and nonsmokers as an explanation for this finding.

Subjects with lowest BMI had a significantly higher risk of death from pneumonia and a similar, although not statistically significant, trend was seen with regard to hospitalization. In the study of LaCroix and colleagues [8], similar observations were made with regard to BMI and pneumonia mortality, an association which persisted throughout the study period. It is most likely that this association is due to low BMI indicating the presence of a chronic condition, which impairs host defences against pneumonia.

In both sexes, the history of myocardial infarction was associated with higher risk of pneumonia using simple cross-tabulation, yet in the Cox regression model this relation was not significant. In previous studies, congestive heart disease has been associated with increased risk of pneumonia [8, 9]. Previous myocardial infarction is not necessarily followed by cardial decompensation and this could explain why heart disease, which in this study was defined on the basis of previous MI, was not related to pneumonia.

Stroke can be followed by dysphagia and immobility which may lead to increased risk of developing lung infection. The discrepancy between the findings in the two sexes is most likely caused by the small number of pneumonias in women.

Finally, there was higher risk of pneumonia in subjects with shortest education. This may reflect the influence caused by poorer working and living conditions in this group of subjects, similar to that reported for tuberculosis.

Our study has various methodological weaknesses. Although we studied a very large cohort for a long period of time, we registered only 27 deaths where pneumonia was considered the primary cause of death. Therefore, we decided mainly to analyse deaths with pneumonia as a contributory cause, some of them probably representing agonal pneumonias. Also, hospitalizations from pneumonia do not represent a true attack rate, as most patients with pneumonia are treated on an outpatient basis. The decision on admittance of a patient with pneumonia depends not only on the severity of the pneumonia but also on the previous condition of the patient, and thus our analyses may favour chronic diseases, *e.g.* COPD, as candidates for risk factors for pneumonia. On the other hand, once admitted to hospital, diagnostic bias does not favour pneumonia in patients with COPD, since these patients are presumably more likely to be diagnosed as 'acute exacerbations' than others. Nevertheless, very few patients are diagnosed as having pneumonia without a chest X-ray and, thus, misclassification after admittance is of minor importance. In addition, the study was conducted in a defined geographical area involving a small number of similar hospitals, and thus reducing the likelihood of substantial regional differences in the diagnostic skills and practice. Uncertainties in coding of hospitalization are not likely to lead to differential misclassification.

The fact that subjects with the heaviest alchohol consumption are unlikely to participate in health surveys makes our negative findings regarding alcohol consumption

and pneumonia disputable because of selection bias. Despite these limitations, our prospective design using a follow-up of a sample of the general population solves the difficulties of choosing a control group; a problem always present in case-control studies. In addition, the fact that all hospitalizations and deaths were centrally registered reduces an important source of bias, making it more possible to generalize from our results.

Finally, the recording of possible risk factors years before the actual event of pneumonia is problematic. On the other hand, characteristics like FEV1, smoking and alcohol habits are quite stable in this population [24, 25] and major changes are unlikely to have occured. In addition many of the events occured shortly after the initial examination (table 2).

Although we have no information on the pneumococcal vaccination rate in our subjects, we suspect it to be very low. In Denmark, until very recently, pneumococcal vaccine was used only in asplenic patients. All studies of aetiology show that the majority of community acquired pneumonias are caused by pneumococci [2, 6, 7]. Recent studies suggest that the vaccines now available are effective in preventing this type of infection in elderly subjects with chronic diseases [26, 27]. The information on the risk factors for the pneumococcal infection may therefore be of importance for planning of vaccination campaigns. We, therefore, speculate that, in addition to age, the most important factor that should be taken into account when deciding if a pneumococcal vaccine should be given, is a reduced level of lung function.

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