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# Chronic mucus hypersecretion in COPD and death from pulmonary infection

E. Prescott+**, P. Lange*+, J. Vestbo**

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**ABSTRACT: The association of chronic mucus hypersecretion and mortality is a matter of debate. We wished to determine whether the relationship between chronic mucus hypersecretion and chronic obstructive pulmonary disease (COPD)-related mortality could be explained by proneness to pulmonary infection.**

**We followed 14,223 subjects of both sexes for 10–12 yrs. Cases where COPD was an underlying or contributory cause of death (n=214) were included, and hospital records were obtained when possible (n=101). From the presence of increased mucus, purulent mucus, fever, leucocytosis and infiltration on chest radiography, death was classified as either due to pulmonary infection (n=38), other causes (n=51), or unclassifiable (n=12).**

**Of subjects reporting chronic mucus hypersecretion at the initial examination, pulmonary infection was implicated in 54% of deaths, whereas this only occurred in 28% of subjects without chronic mucus hypersecretion. Controlling for covariates, in particular smoking habits, a Cox analysis showed a strong inverse relationship between ventilatory function and COPD-related mortality. Chronic mucus hypersecretion was found to be a significant predictor of COPD-related death with pulmonary infection implicated (relative risk (RR) 3.5) but not of death without pulmonary infection (RR 0.9).**

**We consider that subjects with COPD and chronic mucus hypersecretion are more likely to die from pulmonary infections than subjects without chronic mucus hypersecretion. This may explain the excess mortality in subjects with COPD and chronic mucus hypersecretion found in previous studies.**

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*The Copenhagen City Heart Study, Rigshospitalet, Copenhagen, Denmark. +Medical Dept P/Chest Clinic, Bispebjerg Hospital, Copenhagen, Denmark. **The Copenhagen Center for Prospective Population Studies, Institute of Preventive Medicine, Copenhagen, Denmark.

Correspondence: E. Prescott
The Copenhagen Center for Prospective Population Studies
Institute of Preventive Medicine
Kommunehospitalet,
DK-1399 Copenhagen K
Denmark

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During recent decades, several epidemiological studies have shown that ventilatory impairment is the strongest predictor of death from chronic obstructive lung disease (COPD). The association of chronic mucus hypersecretion (CMH) and mortality is, however, a matter of debate. Several studies have found no predictive value of phlegm when controlling for level of ventilatory impairment and smoking [1–4], whereas other studies have found that the production of phlegm plays an independent role in predicting overall mortality [5–9], and COPD-related mortality [6, 7].

In a study based on a population sample from the Copenhagen City Heart Study (CCHS), CMH was found to be a significant risk factor for death from obstructive lung disease both in males and females [7]. There was a significant first-order interaction between the effects of forced expiratory volume in one second ($FEV_1$) % of predicted and CMH on obstructive lung disease mortality indicating that CMH was associated with only a slightly increased risk of obstructive lung disease death in subjects with a high $FEV_1$ % predicted, whereas the risk increased substantially in subjects with more severely impaired ventilatory function. This observation was in line with the theory of FLETCHER and PRIDE [10], who suggested that mucus hypersecretion is only likely to play a significant role in severe/terminal COPD.

The aim of this paper is to determine whether the relationship between CMH and death from obstructive pulmonary disease found in a population based study can be explained by subjects with mucus hypersecretion being more prone to pulmonary infection and, thus, to death from infectious exacerbation of COPD. To our knowledge, this has not been studied previously.

## Subjects and methods

The present study is based on data from The Copenhagen City Heart Study, which has been described in detail previously [11]. Briefly, the population comprised a randomly selected, age-stratified sample of 19,698 subjects out of 87,172, aged 20 yrs or more living in a defined area of Copenhagen. From 1976 to 1978, 14,223 subjects were examined (response rate 74%). Examination included a

self-administered questionnaire, with detailed questions regarding tobacco consumption, pulmonary symptoms, *etc*., and measurement of lung function by spirometry. Only data that are relevant for the interpretation of the present findings are presented in this paper.

Tobacco consumption was studied as follows: smoking status and inhalation habits at the time of investigation as dichotomous variables, smoking habits also as continuous variable and in multiple categories (*e.g*. lifetime nonsmoker; ex-smoker; 1–14 g tobacco/daily; 15–24 g tobacco/daily; and ≥25 g tobacco/daily). Years of smoking and cumulative tobacco consumption (pack-years) were studied as continuous variables.

Mucus hypersecretion (MH) was said to be present when subjects reported cough and sputum in the morning, during the day, or both. CMH was said to be present when cough and sputum had lasted at least 3 months a year, for more than one year.

Recording of $FEV_1$ and forced vital capacity (FVC) was made on an electronic spirometer (Monaghan N 403, Litleton, Co, USA), which was calibrated daily. As a criterion for correct performance, two measurements differing by less than 5% from each other had to be produced. The largest volume was used in the analysis.

Predicted values of $FEV_1$ were based on spirometric data recorded among the lifetime nonsmokers, with a daily consumption of alcohol of less than five drinks, who did not suffer from diabetes mellitus, bronchial asthma, or heart disease and had no pulmonary symptoms. The values were obtained by estimating the regression of $FEV_1$ on age and height. The estimates in body temperature, atmospheric pressure, and saturation with water vapour (BTPS) were: 1) Females: $FEV_1$ (mL) = 443 - 30 × age (yrs) + 23 × height (cm); and 2) Males: $FEV_1$ (mL) = -506 - 38 × age (yrs) + 35 × height (cm). For each participant $FEV_1$ was adjusted to the predicted values by calculating the observed $FEV_1$ as percentage of predicted ($FEV_1$ % pred). For statistical analysis the values were further classified into the following categories: $FEV_1$ ≥80; 60–79; 40–59; and <40% predicted.

Subjects were followed until 31 December 1988. Notification of death and causes of death was obtained from the Death Register of the National Board of Health. Deaths where COPD was considered either an immediate or contributory cause of death were sampled. In this period, Denmark used the eighth revision of the International Classification of Diseases (ICD); codes 490–93 were used.

Subjects who died in hospital and for whom hospital records could be found were studied for presence of pulmonary infection as main cause of death. Pulmonary infection was determined from at least one of the following criteria: 1) presence of increased and purulent mucus and fever/leucocytosis and no infiltration on chest radiography; 2) presence of either increased mucus or purulent mucus or fever/leucocytosis and infiltration on chest radiography or 3) two or more of the following: increased mucus, purulent mucus and fever/leucocytosis. Information on radiography was taken from the descriptions done by radiologists. Chest radiographs from subjects with lung cancer were disregarded (radiograph, but not subject, excluded from analysis). Hospital records were studied by an investigator (EP), who had no previous knowledge of the subjects.

## Statistical analysis

For differences between groups, Chi-squared and analysis of variance were used. Level of significance was set at 5%; p-values are two-tailed, when appropriate. Further analyses were concerned with COPD-related mortality, in which we used the Cox [12] proportional hazards model. Two models were developed, one in which the outcome of interest was COPD-related death where pulmonary infection was thought to play a major role in leading to death (n=38), and one concerning COPD-related death where pulmonary infection did not play a role (n=51). All subjects with available data were included in both models.

In both models, the explanatory variables of greatest interest were presence or absence of MH and CMH, which were tested separately. Other explanatory variables were: age, sex, $FEV_1$ % pred, smoking habits (including inhalation and years of smoking), and body mass index (BMI). The regression coefficients were estimated by the maximum likelihood method as suggested by Cox [12], and the hypothesis of a significant influence of a variable or a first order interaction was assessed by the likelihood ratio test. The proportionality assumption was tested by plotting cumulative hazard rates after log transformation for the categories of each variable included, and assessing parallelism of plots. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for windows. The results are given as relative risk (RR) and 95% confidence interval (95% CI).

## Results

In the CCHS questionnaire, 1,672 subjects out of 14,223 (12%) reported CMH. Distribution of key study variables

Table 1. – Comparison of key study variables in background population according to presence of chronic mucus hypersecretion (CMH)

| | CMH (n=1,672) | No CMH (n=12,533) | p-value |
|---|---|---|---|
| Female % | 43 | 56 | <0.0001 |
| Age yrs | 54 (11) | 52 (12) | <0.0001 |
| Smokers % | 80 | 61 | <0.0001 |
| Smokers who inhale % | 66 | 44 | <0.0001 |
| Heavy smokers (≥15 g·day$^{-1}$) % | 55 | 33 | <0.0001 |
| Duration of smoking* yrs | 33 (13) | 28 (13) | <0.0001 |
| $FEV_1$ L | 2.30 (0.89) | 2.60 (0.83) | <0.0001 |
| $FEV_1$ % pred | 74 (23) | 86 (18) | <0.0001 |
| FVC L | 3.03 (1.00) | 3.26 (0.96) | <0.0001 |
| BMI kg·m$^{-2}$ | 25.2 (4.2) | 25.2 (4.2) | 0.59 |

Values are presented as mean and SD in parenthesis, or as percentages when appropriate. *: only present and former smokers included. $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; BMI: body mass index.

Table 2. – Study population for the analysis

| | |
|---|---|
| Sample selected 1976 | 19,329 |
| Responders | 14,223 |
| Excluded because of missing data | 335 |
| **Population at risk** | **13,888** |
| COPD-related deaths in total | 214 |
| Died in hospital | 133 |
| Hospital records available | 101 |
| **End-points until December 31, 1988** | **10** |
| Death with pulmonary infection | 38 |
| Death without pulmonary infection | 51 |
| Death unclassified | 12 |

COPD: chronic obstructive pulmonary disease.

in this population according to CMH is shown in table 1. As expected, groups differed in age, sex, present and accumulated smoking habits, and ventilatory function; whereas, BMI did not differ.

During the 10–12 year follow-up period, a total of 2,741 subjects died. COPD was considered an underlying or contributory cause of death in 214 cases (8%) (table 2). Of these, 133 died in hospital and medical records could be obtained in 101 cases (76% of all hospital deaths). In 32 cases, hospital records could not be obtained. This was due to hospitals in other geographical areas not responding to inquiry (2), hospital ward not stated in death certificate (9), records not in corresponding ward (12), or hospitals no longer existing (9). Characteristics of the 113 "missing" subjects (termed "drop-outs" in the following) and the 100 subjects (one subject was excluded because of missing data), who could be followed, are shown in table 3.

Table 3. – Characteristics of subjects studied in whom further information about death was not obtained

| | COPD-related death | | |
|---|---|---|---|
| | Information obtained (n=100) | Information not obtained (n=113) | p-value |
| Female % | 33 | 33 | 0.96 |
| Age yrs | 61 (7) | 63 (10) | 0.05 |
| Smokers % | 78 | 77 | 0.88 |
| Smokers who inhale % | 66 | 63 | 0.66 |
| Heavy smokers (≥15 g·day$^{-1}$) % | 53 | 45 | 0.22 |
| Duration of smoking yrs | 37 (11) | 39 (14) | 0.32 |
| $FEV_1$ L | 1.53 (0.72) | 1.45 (0.67) | 0.46 |
| $FEV_1$ % pred | 54 (24) | 53 (22) | 0.80 |
| FVC L | 2.32 (0.80) | 2.29 (0.83) | 0.80 |
| BMI kg·m$^{-2}$ | 23.3 (4.0) | 24.4 (4.9) | 0.06 |
| MH % | 59 | 65 | 0.37 |
| CMH % | 39 | 55 | 0.017 |

Values are presented as mean and SD in parenthesis or as percentage when appropriate. MH: mucus hypersecretion; CMH: chronic mucus hypersecretion. For further abbreviations see legends to tables 1 and 2.

The 100 study subjects were younger, had lower BMI and reported less CMH than the "drop-outs", but did not differ regarding smoking habits or ventilatory function. Of the 100 cases obtained, 39 had previously reported CMH and 61 had not. Among the subjects previously reporting CMH, 21 (54%) died of pulmonary infection, whereas this was only the case for 17 (28%) of subjects without CMH (p=0.009). Applying the more strict second criterion, which included infiltrate on chest radiography, 12 (31%) of subjects with CMH had pulmonary infection *versus* only 10 (16%) of subjects without CMH. Subjects with CMH had poorer ventilatory function than subjects without CMH (mean $FEV_1$ % pred 46 *vs* 59; p=0.02). There were no differences in sex, age, smoking habits or BMI.

### *Deaths from infection*

In total, 38 subjects died from pulmonary infection, 51 died without major signs of pulmonary infection, and 11 (six had previously reported CMH, five had not) could not be classified because of missing information in the hospital records. Characteristics of subgroups, according to presence or absence of pulmonary infection during the final admission to hospital, are shown in table 4. Only the 89 subjects who could be classified are included. No differences in sex, age, present or cumulated smoking habits, ventilatory function or BMI were found, but the prevalence of MH and CMH differed significantly between the two groups.

Table 4. – Comparison of key study variables in subjects with COPD as main or contributory cause of death with and without pulmonary infection implicated

| | COPD-related death | | |
|---|---|---|---|
| | With pulmonary infection (n=38) | Without pulmonary infection (n=51) | p-value |
| Female % | 26 | 31 | 0.60 |
| Age yrs | 61 (7) | 61 (8) | 0.90 |
| Smokers % | 82 | 75 | 0.43 |
| Smokers who inhale % | 87 | 79 | 0.37 |
| Heavy smokers (≥15 g·day$^{-1}$) % | 53 | 53 | 0.98 |
| Duration of smoking yrs | 40 (11) | 36 (12) | 0.20 |
| $FEV_1$ L | 1.59 (0.71) | 1.54 (0.77) | 0.74 |
| $FEV_1$ % pred | 56 (28) | 54 (25) | 0.70 |
| FVC L | 2.40 (0.73) | 2.36 (0.88) | 0.82 |
| BMI kg·m$^{-2}$ | 23.5 (4.1) | 23.2 (3.8) | 0.74 |
| MH % | 76 | 49 | 0.009 |
| CMH % | 55 | 26 | 0.004 |

Values are presented as mean and SD in parenthesis, or as percentages when appropriate. For further abbreviations see legends of tables 1–3.

Table 5. – Estimated relative risks of death from COPD with pulmonary infection from Cox regression (38 relevant deaths)

| | RR | (95% CI) | p-value |
|---|---|---|---|
| Sex | | | |
| Female | 1.0 | | |
| Male | 2.4 | (1.1–5.3) | 0.03 |
| Age per 10 yrs | 2.4 | (1.7–3.5) | <0.0001 |
| $FEV_1$ % pred | | | |
| ≥80 | 1.0 | | |
| 60–79 | 2.6 | (0.9–8.1) | 0.09 |
| 40–59 | 12.2 | (4.2–35.3) | <0.0001 |
| <40 | 39.2 | (12.8–120.3) | <0.0001 |
| Daily tobacco consumption | | | |
| per 10 g | 1.4 | (1.04–1.80) | 0.02 |
| BMI $kg \cdot m^{-2}$ | | | |
| ≥20 | 1.0 | | |
| <20 | 2.2 | (0.9–5.8) | 0.10 |
| CMH | | | |
| Absent | 1.0 | | |
| Present | 3.5 | (1.8–7.1) | 0.0003 |

RR: relative risk; 95% CI: 95% confidence interval. For further abbreviations see legends of tables 1–3.

The estimated relative risks for pulmonary infection related death in COPD from the final Cox model are given in table 5. The risk increased with male sex, increasing age, decreasing $FEV_1$ % pred, and present tobacco consumption. CMH remained a significant predictor of death from pulmonary infection, with a relative risk of 3.5 (95% C.I. 1.8–7.1). BMI with cut-off point at 20 $kg \cdot m^{-2}$ was not a significant predictor of pulmonary infectious death, but has been included for comparison with the model regarding noninfectious death (table 6). Interaction between the subgroups of $FEV_1$ % pred and CMH was tested and found to be insignificant (p-values ranged 0.52–0.82). Present smoking status (smoker/nonsmoker), pack-years, and inhalation habits were not significantly related to this specific mortality when $FEV_1$ % pred was entered into the model. Interaction between age on the one hand and MH and CMH, respectively, on the other was examined and found of no significance. After entering further tobacco variables, which did not themselves improve the Cox model, the importance of sex became insignificant. All other explanatory variables remained significantly related to death from pulmonary infection in COPD.

Table 6. – Estimated relative risks of death from COPD without pulmonary infection from Cox regression model (51 relevant deaths)

| | RR | (95% CI) | p-value |
|---|---|---|---|
| Sex | | | |
| Female | 1.0 | | |
| Male | 2.1 | (1.1–4.0) | 0.02 |
| Age per 10 yrs | 2.4 | 1.7–3.2 | <0.0001 |
| $FEV_1$ % pred | | | |
| ≥80 | 1.0 | | |
| 60–79 | 1.6 | (0.6–4.2) | 0.09 |
| 40–59 | 11.9 | (5.2–27.2) | <0.0001 |
| <40 | 52.0 | (22.0–122.6) | <0.0001 |
| Daily tobacco consumption | | | |
| per 10 g | 1.4 | (1.1–1.8) | 0.006 |
| BMI $kg \cdot m^{-2}$ | | | |
| ≥20 | 1.0 | | |
| <20 | 3.7 | (1.9–7.4) | 0.0002 |
| CMH | | | |
| Absent | 1.0 | | |
| Present | 0.9 | (0.5–1.8) | 0.79 |

RR: relative risk; 95% CI: 95% confidence interval. For further abbreviations see legends to tables 1–3.

Replacing CMH with MH gave a higher degree of association (RR=4.3; 95% CI 2.0–9.5), probably caused mainly by the fact that fewer subjects report CMH than MH. However, we considered CMH a more specific indicator of pulmonary disease and, thus, included CMH as the explanatory variable in the final model. An analysis of deaths caused by pneumonia (second criterion) was made, but because of the limited number (22 events) did not yield any significant predictors apart from sex.

### *Other deaths*

The same Cox model was applied to COPD-related deaths without pulmonary infection. Results are given in table 6. Sex, age, ventilatory impairment, present tobacco consumption and BMI were significant predictors of noninfectious COPD-related death, whereas the presence of CMH or MH was of no significance.

Cox analyses excluding the deaths that occurred in the first 5 yrs after the assessment of CMH were also performed. There were 29 infectious deaths and 42 noninfectious. The results did not differ from those reported above: $FEV_1$ % pred was a strong predictor both of infectious and noninfectious death, whereas CMH was a predictor of infectious death only (RR 4.8 *vs* 1.0).

## Discussion

In the present study, we found that CMH was a significant predictor of pulmonary infectious death, but not of noninfectious death, in COPD. In addition, as in previous studies, ventilatory impairment was strongly associated with COPD-related death, regardless of pulmonary infection.

### *Possible bias*

There are a few possible sources of bias in this study. Firstly, 81 subjects died outside hospital and 32 hospital records could not be obtained for reasons described. Assuming that patients with pulmonary infection more often die in hospital than at home, and assuming that subjects with chronic bronchitis (and the history of CMH) are more likely to die in hospital than subjects with COPD but without CMH, then a spurious association between CMH and pulmonary infection would be the result. The

first assumption cannot be tested. The second is not supported by the analyses of "drop-outs"; on the contrary, subjects who were hospitalized had a lower prevalence of CMH than the "dropouts". Thus, the association between CMH and pulmonary infection does not seem to be spurious in this context. This is further supported by the fact that subjects without CMH actually reaching hospital do not have more severe COPD (their lung function is actually better). We therefore find that the study sample, although limited in size, was representative and adequate for the aim of the study.

Another possible source of bias is the fact that since increased and/or purulent mucus was part of the criteria for pulmonary infection employed, pulmonary infection would be more likely to be diagnosed in patients who were already chronically producing mucus. We did not find that mucus could be left out of our criteria for lung infection altogether, as it is an important diagnostic tool in respiratory infections, but a minimum of both increased and purulent mucus was required. However, employing the more strict second criterion, in which an infiltrate on chest radiography was a prerequisite, did not change the conclusions, since 31% of subjects with CMH fulfilled this criterion *versus* only 16% of subjects without CMH. Furthermore, the number of subjects that could not be classified concerning infection based on the information available in hospital records was actually higher among subjects with CMH than among subjects without (six (15%) *versus* five (8%)). Thus, the presence of CMH does not seem to have biased in favour of death being classified as infectious.

One further source of bias cannot be disregarded. We have considered only deaths classified as COPD-related. If the history of CMH would increase the likelihood of classification of the patient with the infection as the COPD one, this would increase a real association. This could be avoided by studying hospital records of all deaths or of large samples of subjects with and without CMH, which is beyond the reach of this study.

### *Tobacco*

Years of smoking and accumulated tobacco consumption (pack-years) were not found to improve the Cox model, but were of course significant predictors when included by themselves. This is consistent with other studies [6], and suggests that the important effect of smoking in COPD is to lower the level of $FEV_1$ and produce a more rapid decline. Increasing tobacco consumption reported in 1976–1978 significantly increased the risk both of pulmonary infectious and nonpulmonary infectious death. Because of the long observation period, this variable may not so much be an indicator of tobacco consumption at the time of death as an indicator of continuous loss of lung function. In addition, smoking also increases cardiovascular death and, thus, the number of COPD-related deaths regardless of loss of $FEV_1$.

When entering into the Cox model further tobacco variables, which in themselves did not improve the model significantly, the importance of sex became insignificant. This suggests that not sex itself but rather sex-dependent variables (such as smoking and drinking habits) render males more at risk.

### *Mucus hypersecretion*

Not surprisingly, the risk of dying with or without pulmonary infection in COPD increased with decreasing lung function, irrespective of mucus hypersecretion. Based on both epidemiological and clinical studies, it has become a well-established fact that a poor level of $FEV_1$ is the most important predictor of COPD-related mortality. As there is general agreement on this strong inverse relationship between $FEV_1$ and mortality from COPD, this point needs no further discussion.

Very few studies have included analyses both on respiratory symptoms and lung function, partly because mucus hypersecretion, initially thought of as the first step in the development of airways obstruction, was considered a symptom of minor importance after the longitudinal study by FLETCHER *et al.* [1]. Whether regarded as a cause of airway infection, following the line of "the British hypothesis", or a marker of ongoing inflammation, the role of mucus hypersecretion remains a matter of debate. In two population based studies, CMH was related to accelerated loss of $FEV_1$ [13, 14]. Regarding mortality studies, some studies have found that, after adjusting for tobacco consumption and level of lung function, CMH is not related to mortality [2–4]. Others, however, find that even after these adjustments are made, CMH is a predictor of overall [5–9] and COPD-related mortality [6, 7], particularly in subjects with a high degree of ventilatory impairment [7]. Only the two latter studies were population based.

In this study, both lung function and CMH were related to mortality from chronic obstructive pulmonary disease and other causes. Furthermore, the relative risks found may be a conservative estimate, since, as with tobacco, some effect of CMH may be in lowering the level of $FEV_1$. Proneness to pulmonary infection in subjects with CMH, which has also been found previously [10, 15, 16], could explain why CMH in the abovementioned studies has been a predictor of mortality. The present results support this hypothesis and may in the future have therapeutic implications, but must first be confirmed in other studies.

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