Respiratory symptoms and 30-year mortality from obstructive lung disease and pneumonia

A. Frostad [1,3], V. Soyseth[1,2], T. Haldorsen[1] , A. Andersen[1], A. Gulsvik[3]

[1] Cancer Registry of Norway, Montebello, N-0310 Oslo
[2] Department of Thoracic Medicine, Akershus University Hospital, N-1478 Lorenskog
[3] Department of Thoracic Medicine, Institute of Medicine, University of Bergen, N-5021 Bergen

Keywords: Cohort study, mortality, obstructive lung disease, pneumonia, respiratory symptoms

Correspondence to:
A. Frostad, Cancer Registry of Norway, Montebello, N-0310 Oslo, Norway
af@kreftregisteret.no
Tel: +47 22 45 13 00
Fax: +47 22 45 13 70

Abstract

Background: As the long-term relationship between respiratory symptoms and mortality from non-malignant respiratory diseases is limited studied, we wanted to investigate the predictive value of respiratory symptoms and symptom load for mortality from obstructive lung disease (OLD) and pneumonia in a long term in a Norwegian population.

Methods: In 1972, 19 998 persons aged 15–70 years, living in Oslo, were randomly selected for a respiratory survey. The response rate was 89%. All were followed for 30 years. The association between cough, asthma-like symptoms, two levels of dyspnoea on exercise, a symptom score and mortality from OLD and pneumonia were investigated separately for men and women by multivariable analyses, with adjustment for age, occupational exposure to air pollution and smoking habits.

Results: OLD accounted for 43% and pneumonia for 50% from all respiratory deaths. The hazard ratio for mortality from OLD in men varied from 4.0 (95% confidence interval, 2.4–6.5) for cough to 9.6 (5.1–18.3) for severe dyspnoea and in women from 5.1 (2.3–11.3) for moderate dyspnoea to 13.0 (6.0–28.3) for severe dyspnoea. The symptom score was strongly predictive of death from OLD, in a dose–response manner.

Conclusions: We found a significant, positive, strong association between respiratory symptoms and 30-year mortality from OLD. The association between respiratory symptoms and mortality of pneumonia was weaker and not significant.

Introduction

Few population studies have focused on the predictive value of respiratory symptoms for mortality from obstructive lung disease (OLD) [1][2] or pneumonia [3], although these diseases are the main causes of death from non-malignant respiratory disease.[4] There are known associations between respiratory symptoms and lung function [5][6][7] and between lung function and several causes of death.[1] [8][9][10] The results of lung function tests depend, however, on the instruments used, the time at which the tests are conducted and the level of training of personnel. Recording of respiratory symptoms is a cheaper and easier screening method than conducting lung function tests.

Two population-based studies showed associations between cough, dyspnoea and mortality from all respiratory diseases combined;[9] [11] one showed an association between wheezing and mortality from respiratory disease.[9] Lange *et al*. showed that persons who reported symptoms of chronic mucus hypersecretion had a higher risk for death from OLD, [1] and Vandentorren *et al*. showed that persons reporting asthma or asthma symptoms had a higher risk for death from chronic obstructive lung disease (COPD).[2]

Large cohorts are needed to observe a sufficient number of deaths due to cause-specific respiratory diseases. In a previous paper we found a consistent positive association between respiratory symptoms reported and all cause mortality.[12] In this large cohort we found it well justified expanding the analyses, to investigate the long-term relationship between respiratory symptoms and mortality due to non-malignant respiratory diseases, which was not covered by the previous paper. We therefore investigated the predictive value of self-reported respiratory symptoms and the load of such symptoms for mortality from OLD and pneumonia over a 30-year period in a large population-based sample, covering nearly 500 000 person–years.

Methods

Study population

The study population was derived from a cross-sectional survey conducted in Oslo in 1972.[13] The sample frame was an updated list from the Central Population Register of 345 630 persons, aged 15–70 years, living in Oslo on 1 June 1972 From this population, a random sample of 19 998 persons was selected who received a postal questionnaire. During autumn 1972, 163 persons in the random sample died or emigrated and were therefore excluded from the analysis.

All inhabitants of Norway have a unique personal identification number that allows complete follow-up until death or emigration. The observation time started on 1 January 1973. The 17 678 respondents (response rate 89%) were followed-up until the date of death or emigration or until 31 December 2002, whichever occurred first. By 31 December 2002, the population had been followed-up for 30 years, contributing a total of 489 218 person–years. The baseline characteristics of the respondents are given in Table 1.

Table 1. Baseline characteristics at 1 January 1973 and crude mortality rate per 100 000 person–years (MR) from obstructive lung disease (OLD) and pneumonia of respondents in the Norwegian study during follow up 1973–2002, by sex, respiratory symptoms, occupational exposure and smoking habits.

Characteristic	Total at baseline (n = 17 678)		Deaths from OLD (n = 250)		Deaths from pneumonia (n = 293)	
	n	%	n	MR	n	MR
Sex						
Men	8 147	46	146	74	107	55
Women	9 531	54	104	35	186	66
Respiratory symptoms *						
None	8 696	49	36	16	143	64
Symptom score						
1–3 symptoms	6 272	36	86	55	95	60
4–6 symptoms	1 966	11	62	137	30	66
≥ 7 symptoms	712	4	66	511	23	178
Groups						
Cough symptoms	5 732	32	175	129	106	78
Asthma-like symptoms	6 092	34	182	107	90	61
Moderate dyspnoea on exercise	2 298	13	53	101	28	37
Severe dyspnoea on exercise	851	5	59	383	24	156
Occupational exposure #						
Yes	3 138	18	82	88	47	47
No	13 513	76	143	35	210	53
Smoking habit						
Never	6 567	37	24	14	117	69
Former	2 011	11	25	51	44	90
Current (g tobacco/day)						
< 10	2 521	14	31	48	35	55
10–19	4 399	25	107	99	59	55
≥ 20	1 800	10	56	135	25	60
Unknown	262	2	3	48	8	129

* 32 persons did not answer any questions about respiratory symptoms.
# 1027 persons did not answer this question.

Questionnaire and variables used in the analysis

The questionnaire used was a modification of that published by the British Medical Research Council's Committee on Research into Chronic Bronchitis in 1966. The validity of the Norwegian questions on respiratory symptoms has been examined by various methods.[14] The agreement between the British and the Norwegian questionnaires varied by 85–99%.[15]

The questionnaire contained 11 questions on respiratory symptoms, which were pooled into four symptom groups (Appendix). Persons, who answered "yes" to one of the questions 8, 9, 10 or 11, were considered to have cough symptoms. Similarly, persons who answered "yes" to one of the questions 12, 17 or 18 were considered to have asthma like symptoms. Subjects, who answered "yes" to 13 or 14, but not 15 or 16, were considered to have moderate dyspnoea, whereas subjects who answered "yes" to question 15 or 16 were considered to have severe dyspnoea. The respondents were separated into three groups on the basis of their answers to questions about smoking habits: persons who had not smoked daily for more than 1 year were classified as 'never' smokers; current smokers were defined as persons who had smoked daily for more than 1 year and were still smoking at the time of the survey; the remaining persons were defined as former smokers.[13] Smoking was measured as daily tobacco consumption, calculated on the basis that one cigarette = 1 g of tobacco. The amounts smoked by current smokers were grouped as < 10 g, 10–19 g and ≥ 20 g of tobacco per day. Regarding occupational exposure to air pollution, the respondents were divided in two groups according to a "yes"- or "no"-answer to the question: " Have you been exposed to particles, gases or damp at your working place?"

Follow-up

Notifications of death and causes of death were obtained from Statistics Norway, with permission granted by the Data Inspectorate, the Norwegian Directorate of Health and Social Services and the Regional Committee for Medical Research Ethics. The Norwegian death certificate is based on the international medical certificate recommended by the World Health Organization,[16] and physicians complete a certificate for every death. The certificate always gives the underlying cause of death and, if appropriate, contributing causes. The underlying cause is defined as the disease or injury that initiated the train of events leading to death. The contributory cause of death is often a disease that followed the underlying cause and that might have contributed to death. Norway used the eighth revision of the International Statistical Classification of Diseases, Injuries and Death (ICD) during the period 1970–85 and the ninth revision up to 1995 and has used the tenth revision since 1996.

The coding and diagnosis of asthma and COPD have changed in Norway over the past 30 years.[17] Many cases of COPD were previously coded as asthma when they had a similar pattern of symptoms and signs. To avoid misclassification, we pooled diagnoses related to asthma and COPD into OLD.

The analyses were based on mortality from OLD (ICD10 J40–J47) and pneumonia (ICD10 J12–J18) [4], given as the underlying cause of death. Associations between respiratory symptoms and mortality from OLD and pneumonia were also estimated when the two diagnoses were given as either the underlying or the contributing cause of death.

Statistical methods

The association between each respiratory symptom group and mortality was expressed as an adjusted hazard ratio (HR), estimated from a Cox proportional hazard

regression model.[18] Mortality associated with each symptom group was compared with mortality among persons who had not reported any respiratory symptoms. A symptom score ranging from 0 to 11 was defined on the basis of the sum of affirmative answers to 11 equal weighted respiratory symptom questions. The scores were then grouped as 0 (no respiratory symptoms), 1–3, 4–6 and ≥ 7 respiratory symptoms. Tests for trend were performed with symptom score and grams of tobacco smoked as continuous variables.
As mortality was more strongly associated with age than time in the study or calendar time, age was used as the underlying time scale.[19][20] The proportional hazard ratio assumption of the Cox model was derived with the test of Schoenfeld's residuals on partial likelihood.[21] Information about physician diagnosed obstructive lung disease and coronary heart disease were considered as steps in the causal chain between respiratory symptoms and mortality, and were therefore not treated as possible confounder We did the analyses also after excluding those individuals with these self reported physician diagnosed diseases.

The covariates added to the multivariable models as confounders were smoking habit and exposure to air pollution. Separate analyses were conducted for men and women. All analyses were performed with STATA-9.[22]

Results

Out of total 6710 deaths, 582 deaths due to respiratory diseases, 2881 deaths due to cardiovascular diseases and 1882 deaths due to cancer diseases were recorded in the cohort as underlying cause during 1973–2002. OLD accounted for 250 (43%), pneumonia for 293 (50%) and other lung diseases for 39 (7%) of all deaths due to respiratory disease. Among 250 subjects with OLD as underlying cause of death, 16% had no contributory cause of death. Cardiovascular diseases (CVD) occurred as contributory cause in 36%, pneumonia and subgroups of OLD such as bronchitis, asthma and emphysema in 20% and 16%, respectively, whereas other diagnoses occurred in 12%. Among 293 subjects with pneumonia as underlying cause of death, 40% had no contributory cause of death. Senility and dementia occurred in 21% as contributory cause, whereas CVD and stroke sequelae counted for 10% and 5%, respectively. Other diagnoses such as diabetes, cancer and abdominal diseases occurred in 24% as contributory causes. Among 39 deaths due to other respiratory diseases, interstitial lung diseases counted for 16 deaths. The remaining, in decreasing order, died from viral infection in respiratory tract (13), pulmonal hypertension (5), respiratory failure (2) and other respiratory deaths without exactly death diagnosis (5).

The crude mortality rate from OLD was higher for men than for women, while an opposite result was found for pneumonia (Table 1). When contributory causes of death was included in the end-points, mortality from OLD increased by 105 deaths, to 355, while mortality from pneumonia increased by 861 deaths, to 1154.

For persons reporting any respiratory symptoms, the crude mortality rate per 100 000 person–years was 99 from OLD and 69 from pneumonia. The rate of death from OLD increased strongly with increasing respiratory symptoms reported, while that from pneumonia showed a weaker dose–response association (Table 1). Among those 23 individuals dead in pneumonia with reported 7 and more respiratory symptoms, 17 individuals reported physician diagnosed obstructive lung disease or other respiratory disease.

The crude mortality rate from OLD was 2.5 higher among persons exposed to dust or gases at work than among those not so exposed, while there was little difference in mortality from pneumonia. The crude mortality rate due to OLD was lowest for 'never' smokers, but a dose–response relation was found between mortality rate and amount smoked for current

smokers. The mortality rate due to pneumonia was highest for former smokers and did not differ by amount smoked for current smokers (Table 1).

The association between each respiratory symptom group and mortality from OLD showed a considerable increase in risk for mortality in both sexes. The HR was ≥ 4.0 for all symptom groups and ≥ 10 for severe dyspnoea (Table 2). No significant association was found between respiratory symptom groups and mortality from pneumonia. Mortality from OLD increased in a dose–response manner with the symptom score. Symptom score did not significantly increase the HR for mortality from pneumonia, except in women who reported more than seven symptoms.

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for mortality from obstructive lung disease and pneumonia as underlying cause of death by respiratory symptom groups, symptom score and sex, adjusted for occupational exposure, smoking habits and age, Norway, 1973–2002. Separate models for each symptom group

Symptom	Obstructive lung disease *n* = 250				Pneumonia *n* = 293			
	Men		Women		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No respiratory symptoms	1.0		1.0		1.0		1.0	
Symptom group								
Cough symptoms	4.0	2.4–6.5	6.2	3.1–12.3	1.5	0.9–2.4	1.2	0.8–1.8
Asthma-like symptoms	4.7	2.9–7.7	7.8	4.0–15.0	1.2	0.7–2.1	1.3	0.8–1.8
Moderate dyspnoea	4.5	2.5–8.3	5.1	2.3–11.3	1.2	0.5–2.7	0.8	0.4–1.3
Severe dyspnoea	9.6	5.1–18.3	13.0	6.0–28.3	1.5	0.5–4.6	1.5	0.9–2.7
Symptom score								
1–3 symptoms	2.3	1.4–4.0	3.4	1.7–6.8	1.5	1.0–2.4	0.9	0.6–1.3
4–6 symptoms	4.1	2.3–7.5	9.6	4.5–20.8	1.5	0.7–3.2	1.1	0.6–1.9
≥ 7 symptoms	13.6	7.1–25.9	21.5	9.4–49.5	2.0	0.6–6.2	3.0	1.5–6.0
p trend for symptom score	< 0.001		< 0.001		0.09		0.02	

The adjusted HR for mortality from OLD associated with the question "Do you have cough for 3 months or more altogether during a year?" was 7.4 (4.2–13.1) for men and 13.3 (6.0–29.4) for women, and that for mortality from pneumonia was 1.6 (0.7–3.5) for men and 2.3 (1.2–4.0) for women. After exclusion of individuals who reported physician-diagnosed asthma, bronchitis or emphysema at baseline, the association between "cough for 3 months or more… " and mortality from OLD was 4.0 (2.4-6.5) in men and 6.2 (3.1-12.3) in women.

Up to 1986 all death certificates were based on clinical diagnosis. Causes of death based on autopsies were available for the period 1986–2002. During this period the proportion clinical death-diagnosis regarding OLD were 78% and 88% in the periods 1986-1995 and 1996-2003, respectively. The corresponding proportions regarding pneumonia-deaths were 89% and 98%. Regarding autopsies, mortality from OLD represented 17% (32/184) of the underlying causes of death, and pneumonia represented 7% (16/247). After adjustment for age, sex, occupational exposure and smoking habits, the HR for mortality from autopsy-confirmed OLD varied from 3.7 (2.4–5.7) for cough to 6.3 (3.4–11.6) for severe dyspnoea. The HR for mortality from autopsy-confirmed pneumonia based on symptoms, however, was not significant.

Table 3. Age-adjusted hazard ratio (HR) with 95% confidence interval (CI) for mortality from obstructive lung disease and pneumonia as underlying causes of death by respiratory symptom, sex, occupational exposure and smoking habits, Norway, 1973–2002. One model

Symptoms	Obstructive lung disease *n* = 250				Pneumonia *n* = 293			
	Men		Women		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No respiratory symptoms	1.0		1.0		1.0		1.0	
Cough symptoms	2.3	1.5–3.7	1.5	0.9–2.5	1.5	0.9–2.5	1.2	0.8–1.8
Asthma-like symptoms	2.0	1.3–3.0	4.0	2.3–7.1	0.8	0.5–1.4	1.4	0.9–2.1
Moderate dyspnoea	1.5	1.0–2.4	1.1	0.6–2.0	0.8	0.3–1.7	0.6	0.4–1.1
Severe dyspnoea	3.3	2.1–5.3	2.8	1.6–4.8	1.2	0.4–3.5	1.2	0.7–2.1
Occupational exposure								
No	1.0		1.0		1.0		1.0	
Yes	1.4	1.1–2.1	0.7	0.4–1.3	0.8	0.5–1.3	0.9	0.5–1.5
Smoking								
Never	1.0		1.0		1.0		1.0	
Former	7.4	1.7–31.8	0.6	0.1–2.7	1.5	0.7–2.6	1.6	1.0–2.6
Current (g tobacco/day)								
< 10	7.9	1.8–35.2	2.6	1.3–5.2	1.5	0.7–3.3	1.1	0.7–1.8
10–19	13.0	3.1–53.6	5.2	2.9–9.4	1.8	0.9–3.4	1.2	0.7–1.9
≥ 20 g	19.9	4.8–83.2	5.9	2.7–13.0	2.1	1.0–4.7	2.7	1.2–5.7
p trend for daily smoking	< 0.001		< 0.001		0.04		0.08	

The results of the final multivariable model, with all four symptom groups, are shown in Table 3. The association between respiratory symptoms and mortality from OLD was, as expected, weaker when all symptoms were included in the same model and adjusted for each other than when each symptom group was investigated separately. Nevertheless, for all respiratory symptom groups in men and for asthma-like symptoms and severe dyspnoea in women, the HR was still significantly increased. None of the respiratory symptoms was a significant predictor of deaths due to pneumonia.

There was a significant association between smoking habits and mortality from OLD, even after adjustment for respiratory symptoms, except for former smoking in women. The association between smoking and mortality from pneumonia was significant for men and women current smokers who smoked more than 20 g of tobacco per day. Occupational exposure to air pollution was also a significant predictor of deaths from OLD among men when smoking and symptom groups were taken in account.

After exclusion of 3656 persons who reported physician-diagnosed asthma, bronchitis or emphysema at baseline, the association between all respiratory symptoms and mortality from OLD was still significantly increased for both men and women (Table 4). The HR for mortality from OLD and pneumonia did not change after further exclusion of 4146 persons who reported physician-diagnosed heart failure or cardiovascular disease.

Table 4. Hazard ratio (HR) with 95% confidence interval (CI) for mortality from obstructive lung disease and pneumonia as underlying causes of death by respiratory symptoms and sex, adjusted for smoking habit, occupational exposure and age, Norway, 1973–2002. Persons who reported physician-diagnosed asthma, bronchitis or emphysema are excluded. Separate models for each symptom group

Symptoms	Obstructive lung disease $n = 112$				Pneumonia $n = 243$			
	Men		Women		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No respiratory symptoms	1.0		1.0		1.0		1.0	
Cough symptoms	2.5	1.4–4.6	3.1	1.2–7.8	1.6	1.0–2.7	1.1	0.7–1.8
Asthma-like symptoms	2.9	1.6–5.5	4.5	1.9–10.9	1.4	0.8–2.5	1.3	0.8–2.0
Moderate dyspnoea	2.3	1.0–5.3	3.3	1.1–9.6	1.1	0.5–2.8	0.8	0.4–1.6
Severe dyspnoea	4.2	1.5–11.7	4.6	1.4–14.7	1.4	0.3–5.9	1.2	0.5–2.5

The HR for mortality from OLD decreased during follow-up for all respiratory symptoms in both sexes and was still significantly increased in the third decade, except among men reporting severe dyspnoea. The HR for the third decade varied from 2.5 (1.3–4.8) to 3.0 (1.2–7.3) for men and from 5.0 (1.7–14) to 6.7 (2.7–16) for women.

The magnitude of the associations between OLD and symptom groups did not change after OLD were added as a contributory cause (Table 5). When pneumonia was added as a contributory cause of death, however, the HR for mortality from pneumonia was slightly higher for most symptom groups.

Table 5. Hazard ratio (HR) with 95% confidence interval (CI) for mortality from obstructive lung disease and pneumonia as underlying or contributory causes of death, by respiratory symptoms and sex, adjusted for occupational exposure, smoking and age, Norway, 1973–2002. Separate models for each symptom group

Symptoms	Obstructive lung disease *n* = 355				Pneumonia *n* = 1154			
	Men		Women		Men		Women	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No respiratory symptoms	1.00		1.00		1.00		1.00	
Cough	4.1	2.9–5.9	4.2	2.7–6.5	1.5	1.2–1.8	1.2	1.0–1.5
Asthma-like symptoms	4.6	3.2–6.7	5.0	3.3–7.6	1.5	1.3–1.9	1.2	0.9–1.5
Moderate dyspnoea	5.1	3.3–7.1	4.0	2.4–6.6	1.6	1.2–2.2	1.2	0.9–1.5
Severe dyspnoea	12.7	8.0–20.2	8.5	5.1–14.2	2.7	1.9–3.9	1.8	1.4–2.4

Discussion

We found a significant, positive, strong predictive value of respiratory symptoms for mortality from OLD over 30 years in nearly 18 000 men and women in Oslo. The relative risk for mortality decreased slightly during follow-up but was still significantly increased in the third decade after recording of symptoms. The predictive value of respiratory symptoms for mortality from pneumonia was weaker and not significant. When causes contributory to the underlying cause of death were added, the association between mortality from pneumonia and respiratory symptoms changed slightly.

The large number of persons and the long follow-up in our study resulted in a large number of deaths, making it possible to estimate the relative risk for mortality from OLD and pneumonia. The individuals were selected randomly, and they answered the

questionnaire at home, thus reducing sampling and observer bias, respectively. As there was no connection between how they answered the questionnaire and the outcome, there was no outcome-dependent bias. As the 11-digit unique personal identification number used in Norway and because Statistics Norway, by law, records all deaths in the country, the estimates are not distorted by incomplete follow up.

The main source of uncertainty with regard to cause of death is the diagnosis and physicians' reporting on death certificates is potentially the largest source of error. In addition, the coding of diagnoses has changed, and three different ICD systems were used during the period. Uncertain associations can lead to non-differential misclassification of diagnosis and will alter the association between respiratory symptoms and mortality.[23] One of the gold standards of diagnosis of cause of death is, however, the autopsy. In our study, the risk for mortality from OLD and pneumonia based on autopsies was similar to that for the whole cohort, thus strengthening our conclusions.

Smoking might be a strong confounder of the association between respiratory symptoms and outcome. Although we controlled for smoking habits before inclusion, the prevalence of smoking in our cohort might have changed during follow-up. Stavem *et al*. found that 32% of a Norwegian cohort of middle-aged men had quit smoking and only 16% had started smoking or started smoking again.[24] In addition, the total proportion of daily smokers among Norwegian men and women decreased during the follow-up period.[4] Some of the respondents might have stopped smoking in response to the Norwegian Tobacco Act and to educational programmes on smoking and health.[25] As a considerable proportion of the persons who smoked and reported symptoms might have had fewer symptoms after quitting during follow-up,[26] our analysis probably underestimates the relation between symptoms and mortality, rather than overestimates it.

We found an increased risk for mortality from OLD among smokers, which was two to three times higher among male than female current smokers. A similar trend was reported by Lange *et al*.[1]

A positive association has been reported between chronic mucus hypersecretion, i.e. chronic cough with phlegm > 3 months a year, and mortality from COPD in several studies, most conducted in an occupational setting,[27][28][29] although Peto *et al*. [28] found that mortality from COPD was not significantly related to mucus hypersecretion. In a population-based Lange *et al*. [1] found a significant association between chronic mucus hypersecretion and mortality from OLD. In the Danish study the HR was adjusted for lung function. We did not have any information about lung function. We have, however, information about reported physician-diagnosed asthma, bronchitis or emphysema. We believe that there is an accumulation of individuals with low lung function among those with already diagnosed OLD. When excluding those individuals, we exclude the majority of subjects with low lung function. In our study, all the questions about cough were pooled into one cough symptom group., When, however, we analysed reports of cough and phlegm for at least 3 months per year during at least 1 year separately with exclusion of those individuals with reported physician-diagnosed asthma, bronchitis or emphysema, the HR for mortality from OLD was 1.5 times higher than in the Danish study. This could be explained by the reference-populations; in the Danish study the reference-population reported not having that symptom, while in our study the reference population had no respiratory symptoms at all. In line with the findings in Denmark [1],, we found that the association between respiratory symptoms and mortality from OLD were similar when OLD was included as the underlying and contributory or only as the underlying cause of death.

With regard to asthma-like symptoms, Knuiman *et al*.[9] found that persons who reported wheezing had increased mortality from respiratory disease in general, and Carpenter *et al*.[30] confirmed this finding for mortality from chronic bronchitis. Vandentorren *et al*.[2] found that having asthma or asthma symptoms such as attacks of breathlessness associated with wheezing was significantly associated with mortality from COPD, with a relative risk of 3.5. In our study, asthma-like symptoms, i.e. having at least one of the symptoms wheezing, attacks of breathlessness or long-lasting cough after a cold, resulted in a higher HR for mortality from OLD than in the study of Vandentorren *et al*.[2] [9]

Our finding of a significant association between degree of dyspnoea symptoms and mortality from OLD is in agreement with those of previous epidemiological surveys.[9] [11] [29][30] Dyspnoea on exercise is frequently a presenting symptom of both lung and heart disease. An affirmative answer to having severe dyspnoea, could be an indicator of organ failure with a poor prognosis and therefore an important predictor for mortality from OLD.

When all symptoms were adjusted for each other in the same model, the risk associated with each respiratory symptom decreased, probably because some of the symptoms are expressions of the same pathological entity in the airways. Except for cough and moderate dyspnoea in women, the risk for mortality was still significantly increased.

According to death from pneumonia, the crude mortality rate was higher in subjects who reported 7 and more respiratory symptoms than those who reported less than 7 respiratory symptoms. Among these individuals 74% reported physician diagnosed obstructive lung disease or other respiratory disease. This could indicate that OLD as underlying cause of death is underestimated. We found a slightly increased risk for mortality from pneumonia associated with reports of respiratory symptoms, and the relative risk increased with increasing number of respiratory symptoms reported. Except when seven or more respiratory symptoms were reported in women, the association between symptoms and mortality from pneumonia was not significant, in agreement with the study of Lange *et al*.[3] The persons who died from pneumonia had fewer respiratory symptoms at baseline and were on average 8 years older at death than those who died of OLD. These observations might explain the lack of association between respiratory symptoms and mortality due to pneumonia.

Our study does not elucidate the mechanisms by which respiratory symptoms cause earlier death or why a single self-report of symptoms has such a long-lasting effect on mortality rates. We have nevertheless shown that common respiratory symptoms are important predictors of mortality from OLD over a period of 30 years. We believe that this information is easily obtained, and very useful to keep in mind for many physicians in clinical practice

Acknowledgements

This study was financed by EXTRA funds from the Norwegian Foundation for Health and Rehabilitation. We thank Bjarte Aagnes for technical help with the data.

Conflict of interest:

No conflict of interest to declare.

Reference List

1 Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45(8):579-585.

2 Vandentorren S, Baldi I, Annesi M, I, Charpin D, Neukirch F, Filleul L et al. Long-term mortality among adults with or without asthma in the PAARC study. *Eur Respir J* 2003; 21(3):462-467.

3 Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *Eur Respir J* 1995; 8(10):1694-1698.

4 Statistics Norway. http://statbank.ssb.no/statistikkbanken/. *Statistics Norway*, editor. 2005.

5 Krzyzanowski M, Camilli AE, Lebowitz MD. Relationships between pulmonary function and changes in chronic respiratory symptoms. Comparison of Tucson and Cracow longitudinal studies. *Chest* 1990; 98(1):62-70.

6 Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV1 reduction and respiratory symptoms in the general population. *Eur Respir J* 2003; 21(4):658-663.

7 Sunyer J, Basagana X, Roca J, Urrutia I, Jaen A, Anto JM et al. Relations between respiratory symptoms and spirometric values in young adults: the European community respiratory health study. *Respir Med* 2004; 98(10):1025-1033.

8 Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313(7059):711-715.

9 Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. *Ann Epidemiol* 1999; 9(5):297-306.

10 Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003; 58(5):388-393.

11 Rosengren A, Wilhelmsen L. Respiratory symptoms and long-term risk of death from cardiovascular disease, cancer and other causes in Swedish men. *Int J Epidemiol* 1998; 27(6):962-969.

12 Frostad A, Soyseth V, Andersen A, Gulsvik A. Respiratory symptoms as predictors of all-cause mortality in an urban community: a 30-year follow-up. *J Intern Med* 2006; 259(5):520-529.

13 Gulsvik A. Prevalence of respiratory symptoms in the city of Oslo. *Scand J Respir Dis* 1979; 60(5):275-285.

14 Gulsvik A, Bakke P, Humerfelt S, Omenaas E, Baste V. Measurements of respiratory symptoms and sample size to detect a given difference between treatment groups in obstructive lung disease. *Eur Respir Rev* 1991;436-443.

15 Brogger JC, Bakke PS, Gulsvik A. Comparison of respiratory symptoms questionnaires. *Int J Tuberc Lung Dis* 2000; 4(1):83-90.

16 World Health Organization. International statistical classification of diseases and related health problems: *ICD-10. World Health Organization*, 10-th edition. 1992. Genova.

17 Holten K, Tofte T. [Obstructive lung disease in a department of pulmonary medicine during the period 1979-80]. *Tidsskr Nor Laegeforen* 1997; 117(11):1585-1589.

18 Cox DR. Regression Models and Life-Tables. *J Roy Statist Soc (B)* 1972; 34:187-220.

19 Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997; 145(1):72-80.

20 Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004; 23(24):3803-3820.

21 Marubini E, Valsechi MG. Validation of the proportional hazard models. In: John Wiley & Sons, editor. *Analysing Survival Data from Clinical Trials and Observational Studies*. West Sussex: 2004: 223-265.

22 StataCorp. Stata statistical software, release 9.0. College Station,TX, 2005.

23 Rothman KJ, Greenland s. Precision and Validity in Epidemiologic Studies. In: Lippincott Williams & Wilkins, editor. *Modern Epidemiology*. Philadelphia: 1998.

24 Stavem K, Aaser E, Sandvik L, Bjornholt JV, Erikssen G, Thaulow E et al. Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. *Eur Respir J* 2005; 25(4):618-625.

25 Ronneberg A, Lund KE, Hafstad A. Lifetime smoking habits among Norwegian men and women born between 1890 and 1974. *Int J Epidemiol* 1994; 23(2):267-276.

26 Eagan TM, Gulsvik A, Eide GE, Bakke PS. Remission of respiratory symptoms by smoking and occupational exposure in a cohort study. *Eur Respir J* 2004; 23(4):589-594.

27 Kauffmann F, Drouet D, Lellouch J, Brille D. Twelve years spirometric changes among Paris area workers. *Int J Epidemiol* 1979; 8(3):201-212.

28 Peto R, Speizer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM et al. The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to

mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983; 128(3):491-500.

29 Ebi-Kryston KL. Respiratory symptoms and pulmonary function as predictors of 10-year mortality from respiratory disease, cardiovascular disease, and all causes in the Whitehall Study. *J Clin Epidemiol* 1988; 41(3):251-260.

30 Carpenter L, Beral V, Strachan D, Ebi-Kryston KL, Inskip H. Respiratory symptoms as predictors of 27 year mortality in a representative sample of British adults. *BMJ* 1989; 299(6695):357-361.

Appendix: Respiratory symptoms and questions defining them

	Question in 1972 questionnaire	Respiratory symptom in our study
8	Do you usually cough and clear your throat in the morning?	Cough-symptoms
9	Do you usually cough during the day?	
10	When you cough or clear your throat, do you usually bring up phlegm?	
11	Do you have cough for 3 months or more altogether during a year?	
12	During the last 2 years, have you had a cough and/or phlegm in connection with a cold for more than 3 weeks?	Asthma-like symptoms
17	Do you have attacks of breathlessness?	
18	Have you ever had wheezing in your chest?	
13	Are you more breathless than people of your own age when walking uphill?	Moderate dyspnoea on exercise
14	Are you breathless when you climb two flights of stairs at an ordinary pace?	
15	Are you breathless when you walk on level ground at an ordinary pace?	Severe dyspnoea on exercise
16	Are you breathless when at rest?	