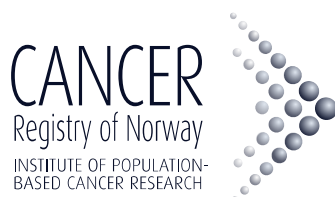


**RESPIRATORY SYMPTOMS AS RISK FACTORS FOR
MORTALITY FROM ALL CAUSES AND FROM
RESPIRATORY AND CARDIOVASCULAR DISEASE
AND FOR INCIDENCE OF LUNG CANCER**

-a 30-year follow-up of a community study in Oslo

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**Dissertation for the degree of Philosophiae Doctor (PhD)
at the University of Bergen, Norway
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At a meeting of the Norwegian Lung Association in late 2001, I asked Professor Amund Gulsvik whether the cohort of The First Asthma Oslo Study in 1972 had been followed-up. He answered that one of the aims of the study had been to determine the natural history of respiratory symptoms and obstructive lung disease in the community. He expressed an interest in following-up this cohort for morbidity and mortality and entrusted the work to me.

Large studies of the general population over many years require a large collaborative effort. Many people contributed to the work that is presented in this thesis. I would like to express my sincerest thanks to my first supervisor, Amund Gulsvik, for his scientific insight and enthusiasm. I am also very grateful to my second supervisor, Vidar Søyseth, who gave me a lot of my training. I also thank my other supervisors and co-authors, Aage Andersen and Tor Haldorsen. Aage shared his extensive knowledge about epidemiology. Tor gave me important statistical insight. My supervisors thus complemented each other. Without the guidance and unfailing support of these people through the planning and writing of this thesis, it would never have been accomplished.

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TERMS AND ABBREVIATIONS

Terms

Cohort	A designated group of persons
Cohort study	An observational study in which a defined group of persons are classified on the basis of the presence or absence of a particular exposure (symptom) and then followed for a specified period to determine the development of disease in each group
Incidence	The number of new cases of a disease in a defined population, within a specified period
Incidence rate	The rate at which new events occur in a defined period, presented as the occurrence of new disease per 100 000 of person–time in the study
Mortality rate	An estimate of the proportion of a population that will die during a specified period, presented as the occurrence of death per 100 000 person–time in the study
Prevalence	The number of cases of a given disease or symptom in a given population at a designated time

Abbreviations

CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
FEV ₁	Forced expiratory volume in 1 second
HR	Hazard ratio
ICD	International Statistical Classification of Diseases, Injuries and Death

IHD	Ischaemic Heart Disease
IR	Incidence Rate
MR	Mortality Rate
OLD	Obstructive Lung Disease

INTRODUCTION

Respiratory symptoms are one of the main reasons for contacting health-care professionals [1,2], particularly when the symptoms affect the quality of daily life [3]. Respiratory symptoms are common in all populations, and their prevalence and determinants have been studied extensively over the past 50 years [4-19]. Many more persons have respiratory symptoms than fulfil the clinical diagnosis of, for example, obstructive lung disease (OLD) [20,21]. Studies by Gulsvik and Lundbäck [9,20] showed a relation between respiratory symptoms and impairment of lung function. Respiratory symptoms are often markers of pathological conditions, primarily in the lungs and airways but also in the heart, chest wall and organs outside the chest. The symptoms are useful for helping physicians to establish diagnoses, interventions and treatment [22].

Respiratory tract symptoms

Cough

Cough is defined as a deep inspiration followed by a strong expiration against a closed glottis, which then opens with an expulsive flow of air, followed by a restorative inspiration. Cough is one of the defensive reflexes of the respiratory tract, as it ensures the removal of mucus, noxious substances and infectious organisms from the larynx, trachea and large bronchi [23,24]. Coughing can be initiated by a wide variety of inflammatory and mechanical changes in the airways and by inhalation of various chemical and mechanical irritants. Rapid, large changes in lung volume can cause cough, as can psychological reactions, such as laughter. The most sensitive sites for initiation of cough are the larynx and the tracheobronchial tree, especially the carina and the sites of bronchial branching, where cough receptors are frequently situated [25].

Cough is a symptom that affects many people. The prevalence varies between 8% and 30% [7,9,16,21,26,27] and is increasing with time [16,28]. Cough can be non-productive or productive, acute or chronic [26] and is one of the commonest respiratory tract symptoms for which persons seek medical advice [29,30]. Quality of life is often impaired by acute and chronic cough [31-33], and health status improves significantly after specific therapy for a cough [34,35].

Asthma-like symptoms

The term ‘asthma’ derives from the Greek verbal root ‘to blow’ [36]. The medical definition has changed over time; it is currently defined as a chronic inflammatory disorder of the airways resulting in increased airway hyperresponsiveness, leading to episodes of wheezing, breathlessness, chest tightness and coughing. All symptoms are associated with reversible and variable airflow obstruction [37,38]. Wheezing is due to the turbulence of air passing through unusual narrowing (obstruction) of the air passages [39]. Because asthma is defined as reversible airway obstruction, the sense of breathlessness may be short and episodic, as attacks of breathlessness. Another sign of inflammation or airway hyperresponsiveness can be long-term cough [40], such as coughing for several weeks after a cold.

As the pathogenesis of asthma is unclear, it follows that the definition of the symptoms is descriptive and inclusive. So far, there is no method for directly measuring the underlying inflammation in persons with asthma. Thus, in clinical practice, asthma is diagnosed on the basis of asthma-like symptoms alone or with the results of clinical tests for indirect measurement of airway inflammation. In epidemiological studies, asthma is usually described as ‘physician-diagnosed asthma’, ‘self-reported asthma’ or ‘asthma-like symptoms’, such as wheezing, attacks of breathlessness or other symptoms that indicate airway hyperresponsiveness [9,41-45].

The prevalence of asthma depends on how asthma is defined and varies between countries and among different areas in the same country [46]. In the Nordic countries, the prevalence varies from 3% to 15% [12,14,18,40,46]; the prevalence of self-reported asthma and asthma-like symptoms has increased over the past 20 years [12,14,18].

Dyspnoea

The word ‘dyspnoea’ comes from the Greek and means ‘painful or difficult to breath’ [47]. Dyspnoea is the physician’s term for the symptom of breathlessness or shortness of breath and is used to characterize a patient’s experience of breathing discomfort. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and it may induce secondary physiological and behavioural responses. Dyspnoea can best be perceived and described by the individual who is experiencing it [48].

The brain stem is central to our understanding of dyspnoea [47], as the cerebral respiratory centre receives input from a variety of chemical and mechanical receptors or emotions and from the lungs and chest wall, which determine the efferent breathing command [49]. A wide variety of conditions can give rise to dyspnoea, but by far the most common are disorders of the lungs and heart [23,50]. Other conditions related to dyspnoea include respiratory muscle weakness, late-stage pregnancy, anaemia, thyroid disorders, poor physical shape, panic disorder and anxiety. Dyspnoea can occur in healthy persons under stressful conditions, such as exercise and high altitude, and in patients with an underlying cardiopulmonary disorder, after little or no effort [49].

The prevalence of dyspnoea in the Nordic population varies between 3% and 25%, depending on age and level of exercise [7,16,18,28,40].

Respiratory symptom score

The commonest method for recording health status in epidemiological studies is the questionnaire, with use of dichotomous variables (yes/no answers) for further analyses of associations between symptoms and relevant variables and outcome. If diseases occur as a continuum in the population, the symptoms related to the diseases should also occur as a continuum. Use of a scoring system is an alternative to use of dichotomous variables and has been used in studies of psychiatric disorders [51], quality of life [52] and respiratory diseases [53]. An asthma score consisting of a simple sum of the positive answers to eight questions on respiratory symptoms predicted outcomes related to asthma and improved the statistical power of the analyses [54].

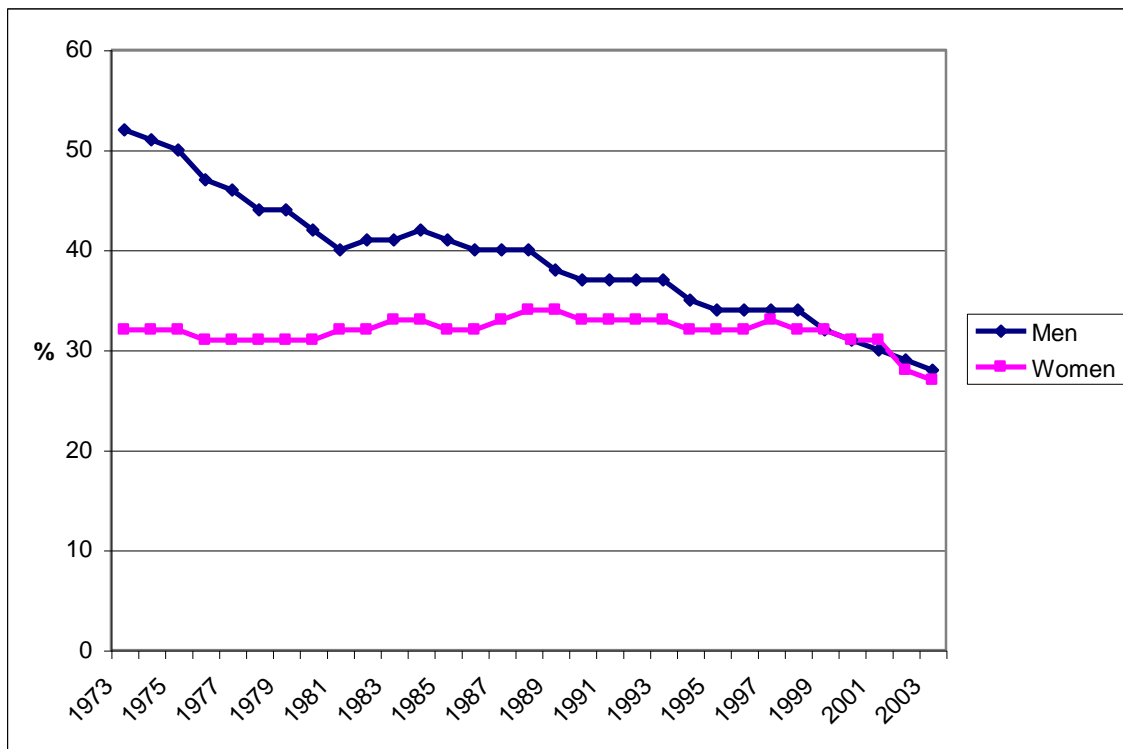
Airway irritants

Smoking

The number of daily smokers in Norway has decreased during the past few decades (Figure 1). The percentages of men and women who smoked daily were 52% and 32%, respectively, in 1973 and 28% and 27%, respectively, in 2003. The decrease occurred in all age groups. In 2003, daily smokers accounted for 26% of men and 24% of women aged 16–24 years and 22% of men and 16% of women aged 65–74 years [55].

Smokers have more respiratory symptoms than non-smokers [5,6,15], and smoking cessation has a beneficial effect on remission of respiratory symptoms [56]. The association between smoking habits and morbidity is well known [57,58]. Smokers have higher risks for OLD [59,60], invasive pneumonia [61], ischaemic heart disease (IHD) [60,62,63] and lung cancer [60,63-65]. Even smokers who smoke 1–4 cigarettes per day have a higher risk for dying from IHD than non-smokers [66].

Figure 1. Numbers of daily smokers among men and women aged 16–74 years in Norway, 1973–2003. From reference [55]



Occupational exposure

Having a job with heavy exposure to airborne particles increases the adjusted risk for OLD and lung cancer compared to those who are less exposed or unexposed [67,68]. The association between exposure to fluorides and respiratory symptoms such as dyspnoea and wheezing is well documented [69]. Blue-collar workers had a higher prevalence of respiratory symptoms than white-collar workers in a study of 1404 middle-aged Danish men [28]. Occupational exposure to airborne dust or fumes increased the occurrence of respiratory symptoms and asthma, independently of age, educational level and smoking habits in a cohort study of 2819 Norwegian men and women, with 11 years of follow-up [70].

Air pollution

Indoor air pollution, with, for instance, mould or environment tobacco smoke, can cause respiratory symptoms and dysfunction in both adults and children [71-73]. With regard to outdoor air pollution, diesel exhaust particles appear to affect the airways more than road surface particles [74]. A study of men in Oslo followed for 27 years showed that air pollution can increase the risks for cause-specific mortality [75] and lung cancer [76].

Population-based studies conducted before 2003 of mortality from all causes and from cardiovascular and pulmonary diseases and incidence of lung cancer related to respiratory symptoms

Previous studies are summarized in Table 1.

Mortality from all causes

The mortality rates (MR) of men and women who reported persistent cough and phlegm were 40% and 60% higher than those of asymptomatic persons in Norway [77]. Population-based studies elsewhere have confirmed that mortality is increased in association with symptoms of chronic mucus hypersecretion [78-85] as well as effort-related breathlessness [80]. Little data are available on the association between all-cause mortality and symptom scores [85], asthma-like symptoms such as wheezing [81,83,85], attacks of breathlessness [83] and long-lasting cough after a cold. Two of the previous studies involved only men [78,80], and three involved fewer than 3000 persons [78,81,86]. Only three studies addressed populations with age spans of 20–70 years [79,83,85]. The longest follow-up was 27 years, but that study included only 1500 persons [81]. No study was found that addressed the relation between respiratory

symptoms and mortality adjusted for occupational exposure to air pollution in addition to age and smoking habits.

Mortality from respiratory disease

Few population-based studies have focused on the association between respiratory symptoms and mortality from OLD [79,87] or pneumonia [88], although these diseases are the main causes of death from non-malignant respiratory disease [89]. Two population-based studies showed associations between cough and dyspnoea and mortality from a group of all respiratory diseases [80,85], and one showed an association between wheezing and mortality from respiratory disease [85]. Lange *et al.* [79] showed that persons who reported symptoms of chronic mucus hypersecretion had a higher risk for dying from OLD, and Vandentorren *et al.* [87] showed that persons reporting asthma or asthma symptoms had a higher risk for death from chronic obstructive lung disease (COPD).

Large cohorts are needed to obtain a sufficient number of deaths to attain power in analysing the association between respiratory symptoms and cause-specific respiratory diseases for men and women separately.

Mortality from cardiovascular disease

Impaired lung function increases the risk for death from cardiovascular disease by twofold, independently of smoking [90], and the risk for cardiac arrhythmia is inversely associated with lung function [91]. Smaller population-based studies have indicated an association between respiratory symptoms and mortality from IHD [80,82,85,92]. Todd *et al.* [82] found an association between chronic cough and mortality from IHD in both sexes. Knuiman *et al.* [85], however found that this association was significant only for men. Two studies showed

Table 1. Population-based studies of mortality from and incidence of lung cancer related to respiratory symptoms before 2003

First author and year of publication	Reference	Year symptom recorded	Participants	Length of follow-up (years)	Respiratory symptoms recorded	End-point studied
Zeiner-Henriksen (1975)	[77]	1964	18 950 men and women aged 31–71 years	6	Persistent cough and phlegm	Mortality from all causes, coronary heart disease and cerebrovascular disease
Todd (1978)	[82]	1965	10 063 men and women aged 35–69 years	12	Persistent cough and phlegm, chronic bronchitis	Mortality from all causes, coronary heart disease, stroke and lung cancer
Krzyzanowski (1986)	[83]	1968	3047 men and women aged 19–70 years	13	Chronic cough, wheeze, asthmatic syndrome, dyspnoea, attacks of breathlessness	Mortality from all causes and circulatory diseases
Carpenter (1989)	[81]	1958	1532 men and women aged 40–64 years	27	Wheeze, cough, cough and phlegm, dyspnoea	Mortality from all causes, cardiovascular disease, chronic bronchitis and lung cancer
Sorlie (1989)	[84]	1974	5209 men and women aged 53–85 years	10	Cough or wheeze, dyspnoea	Mortality from all causes
Vestbo (1989)	[78]	1974	876 men aged 46–69 years	11	Mucus hypersecretion	Mortality from all causes, lung cancer and other respiratory diseases
Lange (1990)	[79]	1976	13 756 men and women aged > 20 years	10	Chronic mucus hypersecretion	Mortality from all causes and obstructive lung disease
Lange (1990)	[93]	1976	13 946 men and women aged > 20 years	10	Chronic mucus hypersecretion	Mortality from lung cancer
Vestbo (1991)	[8]	1974	876 men aged 46–	11	Cough and phlegm, breathlessness	Incidence of lung cancer

Lange (1995)	[88]	1976	69 years 13 423 men and women aged > 20 years	12	Chronic mucus hypersecretion	Mortality from pneumonia
Lange (1996)	[92]	1976	13 540 men and women aged > 20 years	17	Self-reported asthma	Mortality from all causes, asthma, chronic obstructive lung disease, non-malignant respiratory disease, lung cancer, ischaemic heart disease, cardiovascular disease
Rosengren (1998)	[80]	1974	6442 men aged 51–59 years	16	Cough and phlegm, breathlessness	Mortality from all causes, coronary disease, stroke
Knuiman (1999)	[85]	1969–1975	4277 men and women aged 25– 79 years	26	Wheeze, bronchitis, treatment of asthma, cough with phlegm, dyspnoea	Mortality from all causes, respiratory disease, coronary heart disease, stroke, cancer
Tessier (2001)	[86]	1988	2762 men and women aged > 65 years	8	Dyspnoea	Mortality from all causes

increased risks for mortality from IHD among persons reporting moderate dyspnoea [80,85].

Two studies showed that persons with asthma or symptoms of asthma had a 20–40% higher risk for death from cardiovascular disease than those without asthma symptoms [87,92].

The results diverge with regard to mortality from stroke. Todd *et al.* and Knuiman *et al.* [82,85] showed non-significant negative associations between chronic cough and mortality from stroke in both sexes, while Rosengren *et al.* [80] observed an increased risk for mortality from stroke among men who reported dyspnoea. No information was available on the association between respiratory symptoms and cause-specific mortality from cardiovascular disease by sex, adjusted for smoking habits and occupational exposure.

Incidence of and mortality from lung cancer

Although cigarette smoking might explain 80–85% of lung cancers in the Nordic countries [94], several studies have indicated an association between lung cancer and non-malignant pulmonary diseases, even among non-smokers or after adjustment for smoking habits [95-98]. Patients with COPD have an increased risk for lung cancer, even after adjustment for smoking habits. Moreover, this risk increases inversely with level of pulmonary function expressed as forced expiratory volume in one second (FEV₁) [99].

Respiratory symptoms are often markers of inflammatory processes in the lungs and airways, and might be present before other clinical manifestations. The literature concerning the association between respiratory symptoms and incidence of lung cancer was, however, sparse [8].

AIMS

The objectives of this thesis were:

1. To investigate the association between self-reported respiratory symptoms and symptom score and mortality from all causes over 30 years and at different times during follow-up.
2. To investigate the association between self-reported respiratory symptoms and the scores of such symptoms and mortality from OLD and pneumonia over 30 years.
3. To investigate the association between self-reported respiratory symptoms and mortality from IHD and stroke over 30 years in a large population-based sample.
4. To investigate the association between respiratory symptoms in the general population and the incidences of various types of lung cancer during the following 30 years, in separate time windows.

LIST OF PAPERS

This thesis is based on the following publications:

1. 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; 259:520–529.
2. Frostad A, Soyseth V, Haldorsen T, Andersen A, Gulsvik A. Respiratory symptoms and 30-year mortality from obstructive lung disease and pneumonia. *Thorax* 2006; 61:951–956.
3. Frostad A, Soyseth V, Haldorsen T, Andersen A, Gulsvik A. Respiratory symptoms and long-term cardiovascular mortality. *Respir Med* 2007; 101:2289–2296.
4. Frostad A, Soyseth V, Haldorsen T, Andersen A, Gulsvik A. Impact of respiratory symptoms on lung cancer, 30 year follow-up of an urban survey. *Lung Cancer* 2008;60:22–30.

MATERIAL AND METHODS

Study population

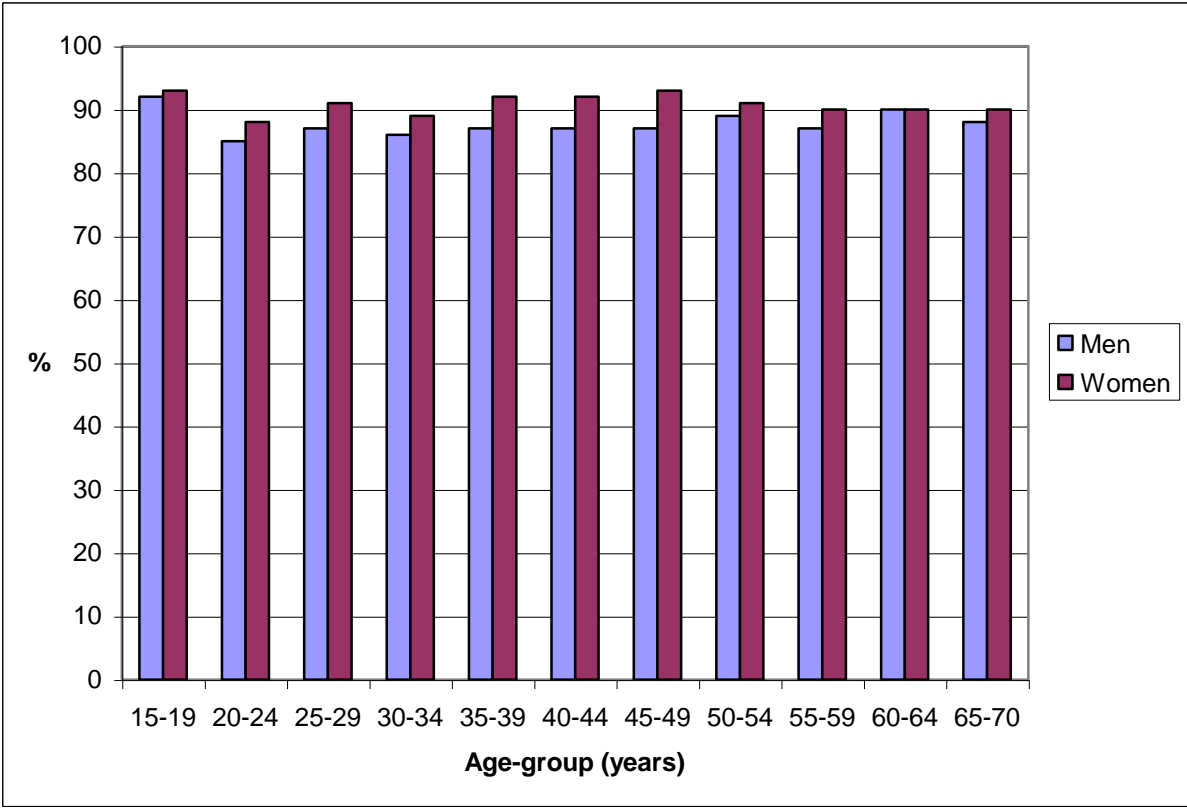
The study population was recruited from the First Asthma Oslo Study, a cross-sectional survey conducted in Oslo in 1972 to assess the age- and sex-specific prevalence of respiratory symptoms and OLD in the community and to establish a basis for studies of the natural history of OLD in the community [6]. The baseline survey has been described previously [6,100].

The population of Oslo, the capital of Norway, was 472 609 persons at the end of 1972 and comprised 12% of the total population of Norway. The sampling frame was an updated list from the Central Population Register of 340 252 persons aged 15–70 years living in Oslo on 1 June 1972. From this population, a sample of 19 998 individuals were randomly selected. During November 1972, the selected persons received a postal questionnaire. The mailing and the processing of the data have been previously described [20].

Altogether, 17 690 persons returned the questionnaire [20], giving an overall response rate of 89% (range, 85–93%). The response rate was highest for the 15–19-year age group and generally somewhat lower among men than women (Figure 2). The returned questionnaires are kept in the archives of the National Hospital in Norway.

During autumn 1972, six of the respondents died and six emigrated. These 12 persons were excluded from the study, leaving 19 678 for the analyses. Eight persons were found to have lung cancer in autumn 1972 and were excluded from the analyses of incidence of lung cancer (paper 4). (See Figure 3.)

Figure 2. Response rates (%) of persons invited to participate in the First Asthma Oslo Study by sex and age group



Age and sex

At 1 January 1973, the cohort consisted of 8147 men and 9531 women, representing 46% and 54% of the respondents, respectively. The age distribution of the respondents is shown in Table 2.

Figure 3. Flow chart of inclusion of participants in the study

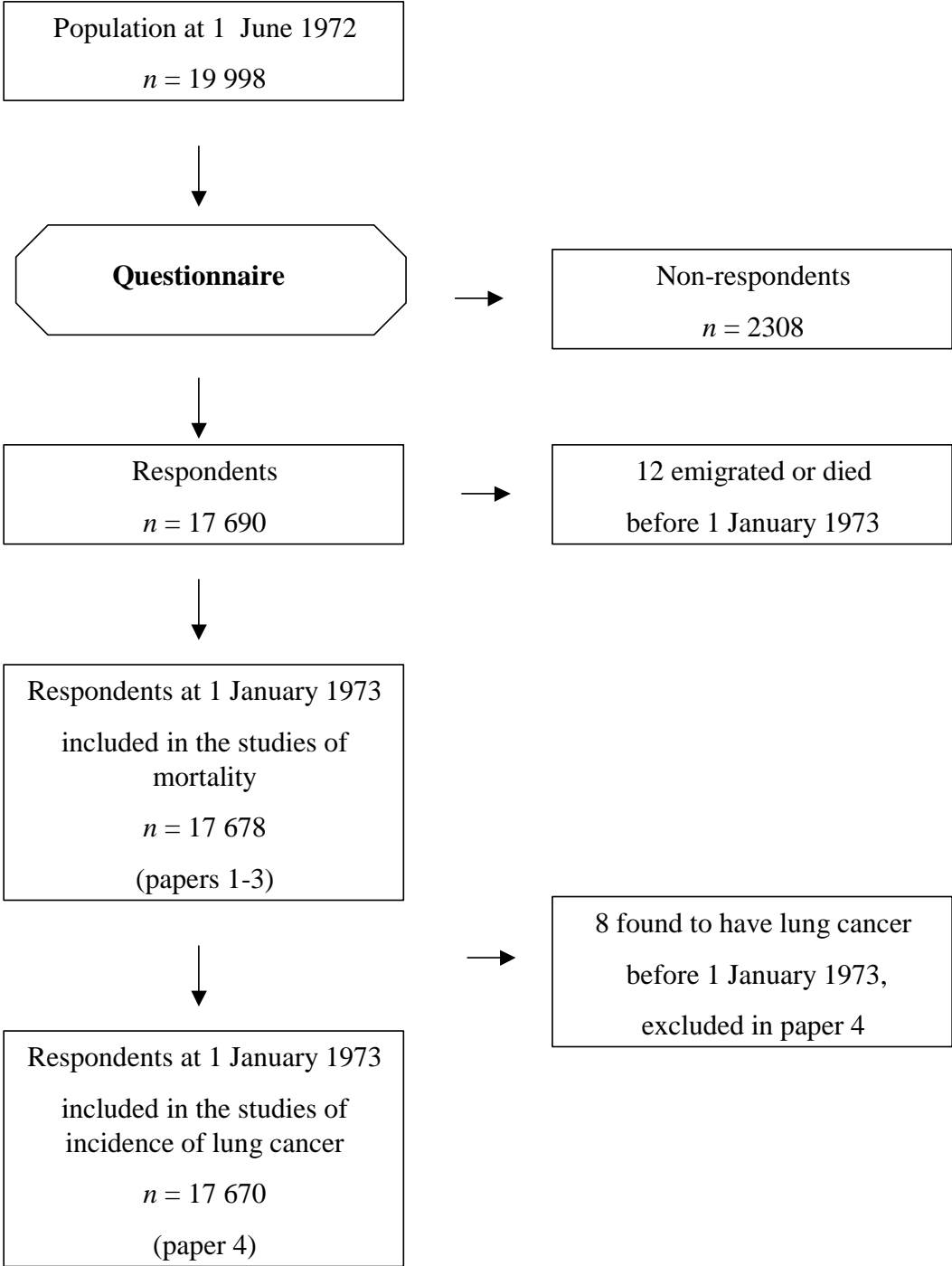


Table 2. Distribution of respondents by age and sex at 1 January 1973

Age group (years)	Men	Women	Total
15–70	8 147	9 531	17 678
15–19	640	661	1 301
20–24	842	1 079	1 921
25–29	1 142	1 184	2 326
30–34	642	639	1 281
35–39	556	609	1 165
40–44	617	673	1 290
45–49	688	778	1 466
50–54	815	948	1 763
55–59	827	1 042	1 869
60–64	717	958	1 675
65–70	661	960	1 621

The Central Population Register of Statistics Norway

Since 1964, all residents of Norway have had a unique 11-digit individual identification number containing their date of birth. Name, address and identification number are registered by the Central Population Register of Statistics Norway, which by law must be kept up to date [101]. This number simplifies the identification of individuals and is reliable; it allows linkage of the data with other, external sources. All deaths and emigrations of Norwegian

citizens are registered in the Central Population Register on the basis of the identification number.

Questionnaire and variables used in the analyses

In spring 1972, five chest physicians and one epidemiologist at the Department of Lung Diseases, National Hospital in Oslo, adapted a questionnaire from the 1966 update of the 1960 British Medical Research Council Committee on Chronic Bronchitis questionnaire [102]. The adapted questionnaire consists of 39 questions on respiratory symptoms and physician-diagnosed pulmonary and cardiac disorders, on a single sheet. The Norwegian Respiratory Questionnaire is given in Appendix 1, with an English translation in Appendix 2. The validity of the questionnaire has been evaluated by lung function levels and bronchial responsiveness and found to be in crude agreement with the British Medical Research Council questionnaire [103,104].

Definitions of respiratory symptoms used in the study

The questionnaire contained 11 questions on respiratory symptoms (Table 3), which were pooled into six symptom groups in paper 1, and four symptom groups in papers 2–4, and a symptom score described below.

Cough symptoms

Four questions concerned cough. Persons who gave an affirmative answer to at least one of the following questions were considered to have cough: “Do you usually cough or clear your throat in the morning?”, “Do you usually cough during the rest of the day?”, “When you cough or clear your throat, do you usually bring up phlegm?” and “Do you have cough for 3 months or more altogether during a year?”

Long-lasting cough after a cold (paper 1)

Long-lasting cough after a cold was defined as having cough and/or phlegm for more than 3 weeks after a cold, once or several times, during the past 2 years.

Wheezing (paper 1)

Wheezing was defined as an affirmative answer to the question: “Have you ever had wheezing in your chest?”

Attacks of breathlessness (paper 1)

Persons were considered to have had attacks of breathlessness if they answered “Yes” to the question “Do you sometimes have attacks of breathlessness?”

Asthma-like symptoms (papers 2–4)

Asthma is a chronic inflammatory disorder and may therefore give different symptoms over time. Long-lasting cough after a cold can be a sign of hyperresponsiveness of the airways. Persons giving an affirmative answer to this question and to those on wheezing or attacks of breathlessness were regarded as having asthma-like symptoms.

Moderate dyspnoea

Moderate dyspnoea was considered to be present if an affirmative answer was given to at least one of the questions “Are you more breathless than other people of your age when walking uphill?” or “Are you breathless when you climb two flights of stairs at an ordinary pace?” and no affirmative answer to the questions regarding severe dyspnoea.

Severe dyspnoea

Severe dyspnoea was defined as present if an affirmative answer was given to at least one of the questions “Are you breathless when you walk on level ground at an ordinary pace?” or “Are you breathless when at rest?”

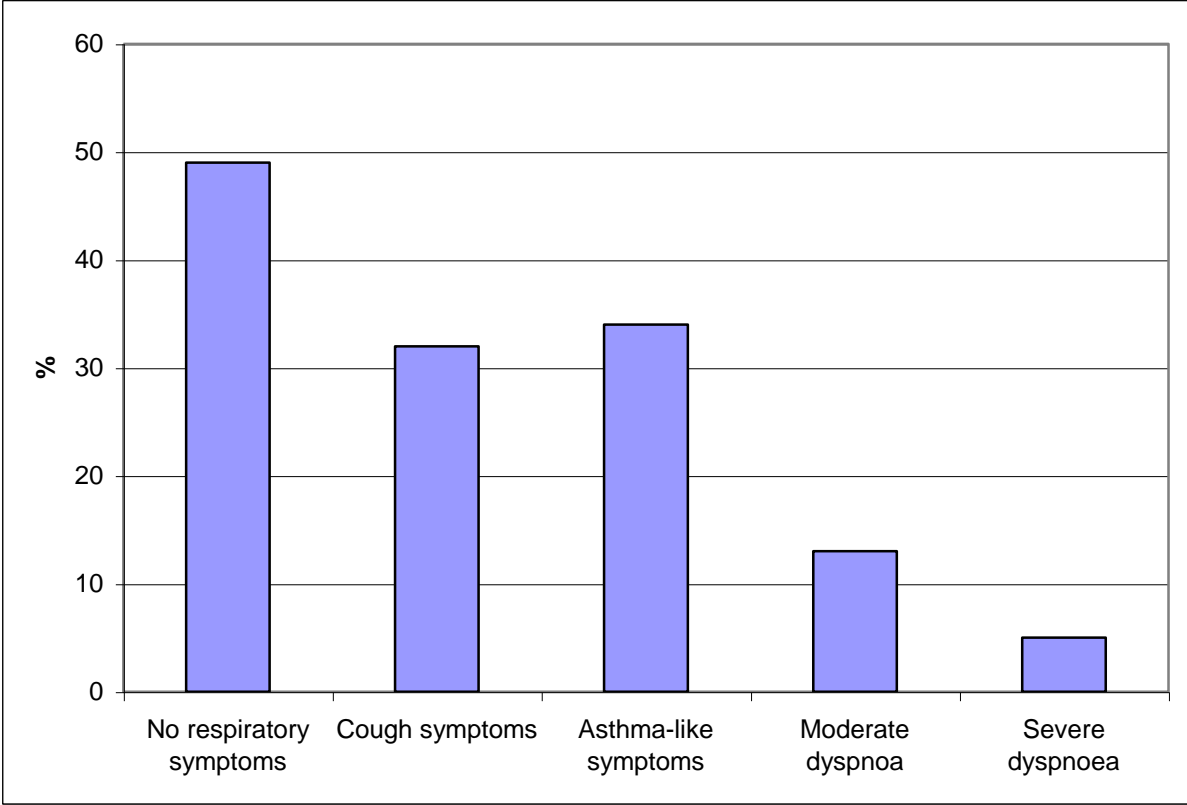
Table 3. Respiratory symptom groups and questions defining them

No. ^a	Question in 1972 questionnaire	Respiratory symptom in our study, paper 1	Respiratory symptom in our study, papers 2–4
8	Do you usually cough and clear your throat in the morning?	Cough	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 past 2 years, have you had a cough and/or phlegm in connection with a cold for more than 3 weeks?	Cold-induced long-lasting cough	Asthma-like symptoms
7	Do you have attacks of breathlessness?	Attacks of breathlessness	
18	Have you ever had wheezing in your chest?	Wheezing	
13	Are you more breathless than other people of your age when walking uphill?	Moderate dyspnoea	Moderate dyspnoea
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	Severe dyspnoea
16	Are you breathless when at rest?		

^a Number of question in Norwegian Respiratory Questionnaire

One or more affirmative answer to a single question was enough for inclusion in one symptom group. Thus, persons who reported several respiratory symptoms could be classified in a maximum of three of four symptom groups (Figure 4).

Figure 4. Distribution of respiratory symptom groups in the cohort of 17 678 persons



Symptom score

A symptom score ranging from 0 to 11 was defined as the sum of affirmative answers to 11 equally weighted respiratory symptom questions. The scores were then arbitrarily grouped as 0 (no respiratory symptoms), 1–3, 4–6 and ≥ 7 respiratory symptoms. No overlap was present. The distribution of number of symptoms reported is shown in Figure 5.

Prevalence of respiratory symptoms at baseline

No respiratory symptoms were reported by 49% of the respondents. Of the 8950 persons (51%) who reported symptoms, 4311 were men and 4639 women (Table 4). The most frequent symptom groups reported were cough and asthma-like symptoms (Figure 4). The majority of the symptomatic individuals reported three or fewer respiratory symptoms (Figure 5).

Figure 5. Distribution of number of symptoms reported in the cohort of 17 678 persons

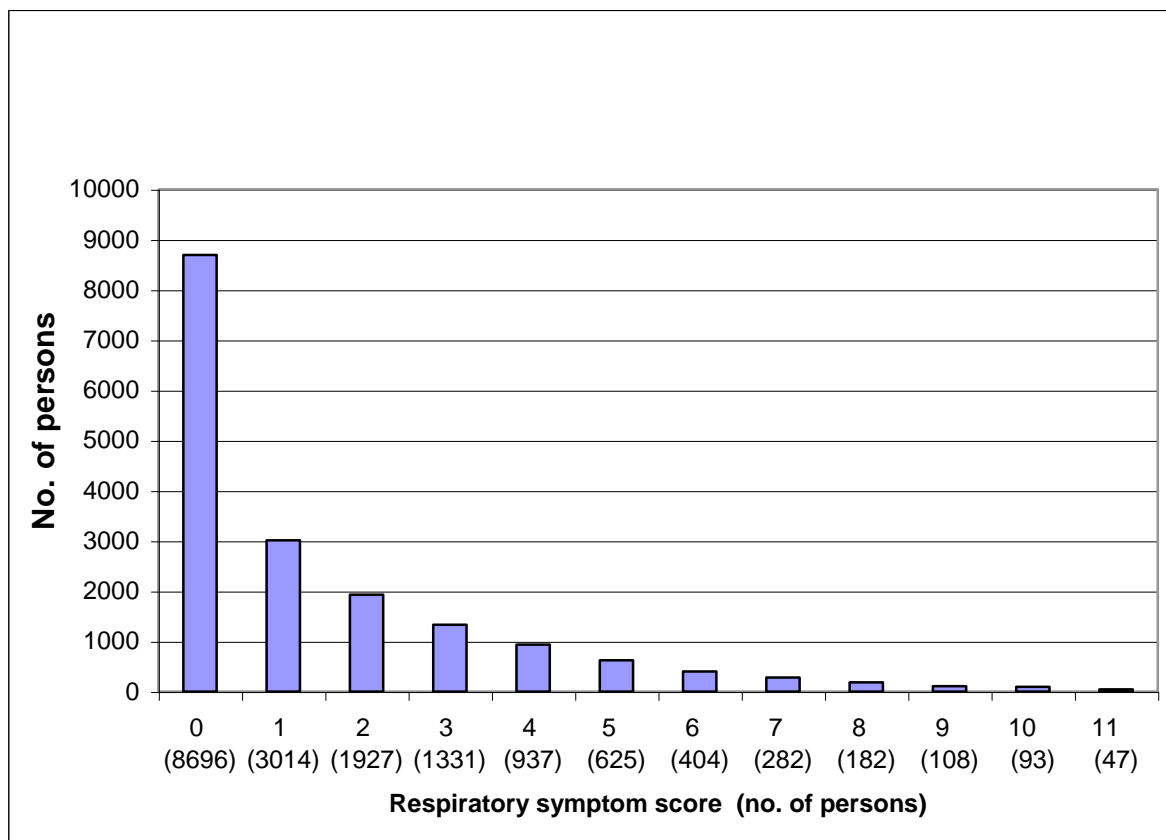


Table 4. Respiratory symptom group, symptom score and occupational exposure by smoking habit at 1 January 1973

	All respondents		Never smoked		Former smokers		Current smokers	
	Men	Women	Men	Women	Men	Women	Men	Women
	(<i>n</i> = 8147)	(<i>n</i> = 9531)	(<i>n</i> = 2197)	(<i>n</i> = 4370)	(<i>n</i> = 1251)	(<i>n</i> = 760)	(<i>n</i> = 4627)	(<i>n</i> = 4211)
Respiratory symptoms[§]								
None	3 823 (47%)	4 873 (51%)	1 517 (69%)	2 725 (62%)	700 (56%)	448 (59%)	1 567 (34%)	1 614 (38%)
Any	4 311 (53%)	4 639 (49%)	678 (31%)	1 641 (38%)	550 (44%)	312 (41%)	3 051 (66%)	2 588 (62%)
Cough symptoms	3 164 (39%)	2 568 (27%)	376 (17%)	718 (16%)	352 (28%)	143 (19%)	2 415 (52%)	1 658 (39%)
Asthma-like symptoms	2 853 (35%)	3 239 (34%)	428 (19%)	1 073 (25%)	355 (28%)	214 (28%)	2 050 (44%)	1 892 (45%)
Moderate dyspnoea	915 (11%)	1 383 (15%)	131 (6%)	510 (12%)	123 (10%)	104 (14%)	656 (14%)	740 (18%)
Severe dyspnoea	366 (4%)	485 (5%)	30 (1%)	190 (4%)	67 (5%)	39 (5%)	261 (6%)	234 (6%)
Number of symptoms								
1-3	2 933 (36%)	3 339 (35%)	570 (26%)	1 289 (30%)	393 (31%)	240 (32%)	1 950 (42%)	1 744 (41%)

4-6	1 013 (12%)	953 (10%)	90 (4%)	264 (6%)	109 (9%)	51 (6%)	808 (18%)	619 (15%)
≥ 7	365 (5%)	347 (4%)	18 (1%)	88 (2%)	48 (4%)	21 (3%)	293 (6%)	225 (6%)
Occupational exposure*								
No	5 616 (69%)	7 897 (83%)	1 729 (79%)	3 689 (84%)	855 (68%)	629 (83%)	2 986 (65%)	3 460 (82%)
Yes	2 184 (27%)	954 (10%)	400 (18%)	395 (9%)	359 (29%)	92 (12%)	1 414 (31%)	447 (11%)

§ The questions about respiratory symptoms were not answered by 13 men and 19 women.

Smoking habits were unknown for 72 men and 190 women.

* 347 men and 680 women did not answer this question.

Smoking habits

Baseline smoking status was divided into five groups. Persons who had never smoked or had smoked daily for less than 1 year were classified as never having smoked. Persons who had smoked daily for more than 1 year and had stopped smoking for more than 1 year before the survey were defined as former smokers. Current smokers were defined as persons who had smoked daily for more than 1 year, including those who had stopped smoking less than 12 months before the survey. Tobacco consumption was measured in grams per day, one cigarette being considered equivalent to 1 g of tobacco. Consumption was scored as < 10, 10–19 and ≥ 20 g of tobacco per day. This categorization of smoking habits was used in all four papers.

Persons were classified as having unknown smoking habits (total, 262 persons) when they did not answer the questions about smoking history or did not give quantitative information on their tobacco or cigarette consumption.

Occupational exposure of the airways

With regard to occupational exposure to air pollution, respondents were divided into two groups depending on whether they answered “Yes” or “No” to the question: “Are you or have you been exposed to dust, fumes or noxious vapours (gases) in your work?” Among the 3138 (18%) respondents who answered “Yes” to this question, 70% were men.

Other variables

Information about allergy in the family (question 7 of the Norwegian Respiratory Questionnaire), own allergy (questions 25–27) and physician-diagnosed lung diseases (asthma, bronchitis, emphysema and other lung diseases, questions 28–33) and heart

diseases (myocardial infarction, angina pectoris, heart failure and other heart diseases, questions 34–37) were also available from the questionnaire. The use of some of these variables is described under “Statistical analyses”.

Follow-up

Observation began on 1 January 1973, at which time 17 678 respondents (8147 men and 9531 women; response rate, 89%) were alive and living in Norway. They were followed-up until date of death (papers 1–3), lung cancer diagnosis (paper 4), emigration or 31 December 2002, whichever occurred first. The follow-up included 441 117 person–years.

End-points used in the study

When reporting diagnoses, physicians in Norway used the 8th revision of the International Statistical Classification of Diseases, Injuries and Death (ICD) during the period 1970–1985, the 9th revision up to 1995, and the 10th revision since 1996.

The analyses were based on mortality from all causes, OLD, pneumonia, IHD and stroke given as the underlying cause of death (Table 5). For mortality from OLD, we also analysed the mortality when this was given as a contributory cause of death. In analysing lung cancer incidence, we used the first occurrence only for persons who had more than one diagnosis of lung cancer.

The sources for the end-points of this study were the Death Register in Statistics Norway and The Cancer Registry of Norway. For the present study, answering and returning the questionnaire was considered to represent informed consent. The South Norwegian Regional Committee for Medical Research Ethics approved the protocol. The Data Inspectorate and the

Norwegian Directorate of Health and Social Services granted permission to perform the study.

Table 5. ICD codes for diagnoses used in the analyses, by period [105,106]

End-point diagnosis	1973–1985 (ICD8)	1986–1995 (ICD9)	1996–2002 (ICD10)
All causes	000–999	001–999	A00–Z99
Obstructive lung disease	491–493, 518	490–494, 496	J40–J47
Pneumonia	480–486	480–486	J12–J18
Ischaemic heart disease	410–414	410–414	I20–I25
Stroke	430–438	430–438	I60–I69
Lung cancer	162	162	C33–C34

Death Register in Statistics Norway

Since 1951, Norway has prepared official statistics on causes of death in accordance with the ICD as recommended by the World Health Organization [107]. The statistics cover all persons registered by the Central Population Registry as living in Norway at the time of death.

Whenever a death occurs, a certificate is issued by a physician and sent to Statistics Norway. Deaths registered on the basis of medical death certificates are matched with deaths registered in the Central Population Register. Additional information is routinely obtained from The Cancer Registry of Norway, the Medical Birth Registry of Norway and Statistics Norway,

statistics on road traffic accidents and the results of autopsies from hospitals and forensic laboratories. This process ensures the completeness of the data. The certificate always gives the underlying cause of death and, if appropriate, contributing causes. The underlying cause is defined as the disease or external cause of injury that started the chain of events leading to death. The contributory cause of death may be a disease that followed the underlying cause and that might have contributed to death [108].

The Cancer Registry of Norway

The Cancer Registry of Norway has systematically collected notifications on cancer for the Norwegian population since its inception in 1952 and is considered very close to complete from 1953. The reporting of cancer has been compulsory since a directive was issued by the Ministry of Health and Social Affairs in 1951.

The reporting system is based on pathology and cytology reports, clinical records and death certificates. Information is collected from clinicians and pathologists, as well as from the administrative patient discharge register and cause of death register. Nominal reporting of cancer cases is compulsory for physicians and includes the identification number. The incidence registry is updated continuously with information on new cases and new information on cases diagnosed previously. The Registry's in-house coding and classification system adheres to certain international standards [107,109].

Processing the data file

Data from the First Asthma Oslo Survey were initially registered on paper forms and subsequently entered into a data file. The processing of this data file, including testing for inconsistencies, has been previously described [20]. When the data file was checked against

the Central Population Register in 2002, 52 persons were found not to have valid identification number. The original questionnaires in the archives of the National Hospital in Oslo were searched manually and the personal identification numbers corrected.

For the outcome variable, the personal identification numbers in this cohort were linked to the Death Registry in Statistics Norway and The Cancer Registry of Norway. Persons for whom answers on specific items were missing were excluded from the relevant analysis.

Statistical analyses

The statistical analyses were performed in two steps. First, we calculated the crude mortality rate (MR), as the number of deaths or lung cancer cases per 100 000 person–years in the study. Then, the association between respiratory symptom category and the end-point, mortality or lung cancer was estimated from a Cox proportional hazard regression model [110]. Multiple regression analyses permit inclusion of different variables suspected of being associated with the outcome variable. All explanatory variables were adjusted for each other, ensuring that the results were not confounded by other known factors given in the questionnaire.. The estimates from the Cox proportional hazard regression model were expressed as a hazard ratio (HR) with 95% confidence intervals (CIs). If the HR was greater than 1 and the 95% CI did not include 1, the persons associated with the exposure variable (respiratory symptom) were considered to have a significantly increased risk for the outcome variable.

All-cause mortality, cause-specific mortality and incidence of lung cancer associated with each symptom group were compared with those among persons who had not reported any respiratory symptoms. As mortality and developing lung cancer were more strongly

associated with age than time in the study or calendar time, age was used as the underlying time scale [111,112].

The proportional hazard assumption of the Cox model was checked graphically and with a test based on Schoenfeld's residuals on partial likelihood [113,114].

If analyses of the univariate associations between the end-point of interest and specific covariates revealed an association between the covariate and the outcome at $p \leq 0.05$, the covariate was included in an initial multivariate model as a possible confounder. Then, a multivariate model was constructed for each symptom group, and each model was reduced by backwards elimination. Variables were removed from this model if the regression coefficient between mortality or lung cancer incidence and symptom group was altered by less than one standard error. Variables removed in this way were information about allergy in the family and own allergy.

Product terms were constructed between respiratory symptoms and smoking habits and between respiratory symptoms and occupational exposure to air pollution in order to investigate effect modification on the end-point by these variables. No such effect modification was found. Smoking habit and exposure to air pollution were included as covariates. Separate analyses were conducted for men and women.

Information about OLD, IHD and other pulmonary and heart disorders were considered steps in the causal chain between respiratory symptoms and mortality from all causes and cause specific mortality or incidence of lung cancer and were therefore not treated as possible confounders [115]. As OLD and IHD are significant predictors of early death in long-term follow-up, we also performed the analyses after excluding persons with these physician-diagnosed diseases.

As information on whether an autopsy had been performed was available only for deaths after 1986, we investigated the association between respiratory symptoms and mortality from autopsy-based cause of deaths for the period 1986–2002 separately.

Wald's test for trend was performed with symptom score and grams of tobacco smoked as continuous variables.

We also investigated the association between respiratory symptoms and mortality in separate 10-year periods of follow-up. All analyses were performed with STATA-9 for Windows [116].

Our estimate of the association between respiratory symptoms and all-cause mortality was unchanged when we adjusted for smoking habits in two different ways: by consumption in gram tobacco per day at baseline or in pack–years smoked until that day. We used tobacco consumption in gram tobacco per day at baseline in the analyses.

MAIN RESULTS

Paper 1: Respiratory symptoms as predictors of all-cause mortality in an urban community: a 30-year follow-up

During follow-up, 6710 (38%) persons, 3380 men and 3330 women, died.

The adjusted HR for mortality from all causes varied from 1.36 (95% CI, 1.25–1.48) for cough symptoms to 2.46 (2.13–2.85) for severe dyspnoea among men; the corresponding HRs among women were 1.28 (1.16–1.40) and 1.52 (1.31–1.75), in comparison with asymptomatic subjects. The HRs for all-cause mortality in persons with 1–3, 4–6 and 7 or more symptoms were 1.20, 1.60 and 2.53 for men and 1.14, 1.47 and 1.84 for women. The risk for mortality increased significantly with increasing number of symptoms reported. In the third decade of follow-up, 1993–2002, the HR for mortality from all causes was still significantly higher for persons who reported respiratory symptoms than those without symptoms.

The positive association between respiratory symptoms and mortality was observed in persons with and without cardiopulmonary diseases.

Paper 2: Respiratory symptoms and 30-year mortality from obstructive lung disease and pneumonia

Out of a total of 6710 deaths recorded in the cohort, 582 were due to respiratory disease as the underlying cause of death. Obstructive lung disease accounted for 250 (43%) deaths, pneumonia for 293 (50%) and other lung diseases for 39 (7%) of all deaths due to respiratory disease.

The HR for mortality from OLD varied from 4.0 (95% CI, 2.4–6.5) for cough to 9.6 (5.1–18.3) for severe dyspnoea in men and from 5.1 (2.3–11.3) for moderate dyspnoea to 13.0 (6.0–28.3) for severe dyspnoea in women. The symptom score was strongly predictive of

death from OLD, in a dose–response manner, from 2.3 to 13.6 in men and from 3.4 to 21.5 in women.

No significant association was found between groups of respiratory symptoms and mortality from pneumonia. The symptom score did not significantly increase the HR for this end-point, except among women who reported more than seven symptoms.

The HR for mortality from OLD decreased during follow-up for all respiratory symptoms in both sexes, but was still significantly increased in the third decade, except among men reporting severe dyspnoea. The HR in 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, for the four symptom groups.

Paper 3: Respiratory symptoms and long-term cardiovascular mortality

Of a total of 6710 deaths, 2881 were recorded as due to cardiovascular disease as the underlying cause during 1973–2002. Ischaemic heart disease accounted for 1572 (55%), stroke for 653 (23%) and other circulatory diseases for 656 (23%) of all deaths due to circulatory disease.

The adjusted HRs for mortality from IHD in men varied from 1.3 (1.1–1.5) for cough symptoms to 3.0 (2.3–3.8) for severe dyspnoea. The corresponding figures for women were 1.2 (1.0–1.5) and 1.9 (1.4–2.5). The symptom score was associated with death from IHD, in a dose–response manner. The HR for mortality from stroke varied from 1.0 to 2.3 in men and from 1.1 to 1.5 in women for the symptom groups, but was significant only for men reporting severe dyspnoea and for women reporting moderate dyspnoea. For all respiratory symptoms, the excess risk for cardiovascular mortality decreased during follow-up, but mortality from IHD was still significantly increased during the last decade.

Paper 4: Impact of respiratory symptoms on lung cancer: 30-year follow-up of an urban population

Lung cancer was diagnosed in 352 persons (228 men and 124 women) during follow-up.

Among these, 71% had reported any respiratory symptoms at baseline; cough symptoms and asthma-like symptoms being reported most often (59% and 51%, respectively).

We found a significant positive association between the incidences of lung cancer and cough symptoms, with adjusted HRs (95% CI) of 1.4 (1.0–1.9) and 1.7 (1.0–2.7) for men and women, respectively. The association between the incidence of lung cancer and asthma-like symptoms was significantly positive among women, 1.7 (1.1–2.7), and among men reporting dyspnoea when walking uphill, 1.7 (1.1–2.5). The relative risk for lung cancer increased with the number of symptoms reported; it was strongest for the first decade and decreased with duration of follow up.

The association between respiratory symptoms and lung cancer was almost unchanged after exclusion of 3653 persons with physician-diagnosed asthma, bronchitis or emphysema.

Additionally, when the start of follow-up was set with a 1-year delay (1974), the results still showed an increased risk for lung cancer among persons who had reported respiratory symptoms when compared with those who had not reported such symptoms.

Of the 352 cases of lung cancer diagnosed in the cohort, 329 (93%) were histological verified. Small-cell lung cancer was present in 78 persons, squamous-cell carcinomas in 87, adenocarcinoma in 89 and other non-small-cell carcinomas in 75 persons. The increased risk for lung cancer with increasing number of respiratory symptoms reported was more pronounced for non-small-cell lung cancer than for small-cell lung cancer.

DISCUSSION

Methods

Study design

The research questions that initiated this study were: “Are respiratory symptoms risk factors for early death, and are they risk factors for development of lung cancer during the next 30 years in comparison with persons without respiratory symptoms?” and “Is there any reason to worry when a person reports symptoms in the respiratory tract over some time?” To answer these questions, a longitudinal design was chosen in a historical cohort study [117].

Large cohorts are needed to acquire a sufficient number of cases for the analysis of cause-specific mortality and incidence of lung cancer. The strength of this population-based study is the random selection of persons, the large number of respondents and the long follow-up, which resulted in 441 000 person–years. No other published population-based study has included so many men and women and analysed so many respiratory symptoms as predictors of cause-specific mortality and lung cancer incidence. Because of the availability of the unique 11-digit personal identification number used in Norway and because Statistics Norway and The Cancer Registry of Norway are based on compulsory recording of all deaths and new cases of cancer, respectively, among residents in Norway, the estimates are not distorted by incomplete follow-up [109,118].

Statistical methods

The cohort consisted of nearly 20 000 persons, of whom 17 678 answered and returned the questionnaire. Of the respondents, about 50% reported no respiratory symptoms, and they were therefore used as the reference group in our analysis. We chose a traditional epidemiological method in which we separated the data into different groups and compared

the crude MR and crude incidence rates (IR) of the groups. We chose the Cox regression model for all analyses in order to take into account the exact time to the event and to allow censoring of data and adjustment for confounding [119].

Validity of results

We found that respiratory symptoms are risk factors for all-cause mortality, cause-specific mortality and for incidence of lung cancer. Two questions arise in the interpretation of the results: “Do our results give the correct relation between respiratory symptoms and the outcome of the study (internal validity)?” and “Can our results be generalized to the broader population (external validity)?”

Internal validity

Internal validity, or internal lack of systematic error, can be defined as the validity of the inferences drawn pertaining to the population being studied [115]. The main limitations of internal validity are selection bias, information bias and confounding.

Selection bias is distortion that can result from the sampling procedure or from factors that influence participation in the study. Our participants were selected randomly, and the response rate was high, which reduces the possibility of selection bias. Additionally, the comparison group, those individuals without respiratory symptoms, was an internal group within the cohort. The groups being compared were thus as similar as possible with respect to other factors that might be related to the diseases, except respiratory symptoms. This reduces selection bias.

Information bias involves misclassification of the exposure or outcome of persons in the study and results in differential accuracy of information between comparison groups [115].

With any diagnostic test or procedure, there is a chance of error, and this is also true for mailed questionnaires. Error can occur if persons who have respiratory symptoms answer that they do not, or vice versa. This is commonly called misclassification or reporting error. Misclassification can be differential or non-differential, depending on how it is linked to the outcome.

Differential misclassification occurs when a systematic error links the exposure (symptoms) and outcome [115]. For example, if there is error in reporting respiratory symptoms for those persons who later become ill and die. In view of the long follow-up, this seems unlikely.

Non-differential misclassification results when the inaccuracy occurs in categorization of participants by exposure or outcome status and occurs in similar proportions of each study group. In most instances, non-differential misclassification of exposures will produce a bias towards the null value, corresponding to a hazard ratio of 1.0 [115].

Using the same questions on respiratory symptoms from the Norwegian Respiratory Questionnaire, Eagan *et al.* found that the remission rate over 11 years varied from 45% for dyspnoea to 58% for chronic cough [56]. Our study design did not allow us to verify the persistence of respiratory symptoms. Despite the reported variation in individual respiratory symptoms, we found a strong association between symptoms reported in 1972 and the various end-points 30 years later.

The major source of uncertainty with regard to cause of death is physicians' reporting of diagnoses on death certificates [108,120,121]. In addition, the coding of diagnoses has changed, and three different ICD systems were used during the period of the study. In a study of deaths from active tuberculosis, considerable error was found in the reporting of diagnosis: in one third of deaths the diagnosis was under-reported and in one third it was over-reported, resulting in a fairly correct mortality rate [122].

One of the gold standards for determining cause of death is autopsy. If autopsies were conducted before 1986, they were not mentioned on the death certificates. Autopsy-verified diagnoses during the period 1986–2002 varied in this cohort from 7% for pneumonia to 32% for IHD (Table 6). Our analysis based on autopsy-recorded causes of death gave similar results to those obtained with all death certificates in this period, thus strengthening our conclusions. The diagnosis of lung cancer was obtained from The Cancer Registry of Norway and was histologically or cytologically verified in more than 90% of cases.

Table 6. Cause-specific deaths and percentages autopsied, 1986–2002

Cause of death	No. of deaths	Autopsy as source of diagnosis (%)
All causes	6 710	15
Ischaemic heart disease	1 572	32
Stroke	653	11
Obstructive lung disease	250	17
Pneumonia	293	7

Confounding: A confounder is a variable associated with both the exposure and the outcome. It should not be an intermediate step in the pathway between exposure and disease [115]. We defined the information about physician-diagnosed respiratory and/or cardiovascular disease as a possible variable in this pathway.

Smoking might be a strong confounder of the association between respiratory symptoms and outcome. Smoking habits were recorded only at inclusion into the survey in 1972 and probably changed during follow-up. Cohort studies conducted in Norway in 2001 by Eagan

and colleagues and in 2005 by Stavem and colleagues showed, however, that twice as many persons had stopped smoking than had started smoking or had started again during follow-up periods of 11 and 27 years [16,123]. Additionally, the total proportion of daily smokers among Norwegian men and women decreased during the follow-up period (Figure 1), and some of the respondents in our study might have stopped smoking in response to the Norwegian Tobacco Act and to educational programmes on smoking and health. Other studies have shown that smoking cessation reduces the relative risk for death and lung cancer when compared with continuation of smoking [124,125]. We were unable to take into account in our analyses changes in respiratory symptoms during follow-up among persons who quit smoking. If we had taken into account remission of respiratory symptoms after quitting or reducing smoking [56], our analyses would probably be underestimates rather than overestimates of the relation between symptoms and outcome. We found no modification of the relation between symptoms and outcome by smoking habit. Thus, the presence of respiratory symptoms increased cause-specific mortality and lung cancer incidence similarly among smokers and non-smokers. A similar result was found by Rosengren *et al.* [80]. Despite adjustment for smoking habits at baseline, some residual confounding by smoking could remain due to changes in smoking habits during follow-up. We found, however, that the associations between respiratory symptoms and the outcome variables were approximately the same when analysed for persons who had never smoked and when adjusted for smoking habits (Table 7).

An additional limitation of our study is the lack of information on other potential confounders, such as lung function, socioeconomic status, physical activity and other risk factors. Lung function is well known to be a predictor of mortality and lung cancer [85,90,126]; however, Knuiman *et al.* [85] and Vestbo *et al.* [127] found that dyspnoea is

Table 7. Hazard ratios (HRs) with 95% confidence intervals (CIs) for cause-specific mortality and incidence of lung cancer by respiratory symptom group, adjusted for smoking habits^a

Respiratory symptoms	Mortality from all causes		Mortality from obstructive lung disease		Mortality from pneumonia		Mortality from ischaemic heart disease		Mortality from stroke		Incidence of lung cancer	
	Adjusted <i>n</i> = 6710	Never smoked <i>n</i> = 2068	Adjusted <i>n</i> = 250	Never smoked <i>n</i> = 24	Adjusted <i>n</i> = 293	Never smoked <i>n</i> = 117	Adjusted <i>n</i> = 1572	Never smoked <i>n</i> = 440	Adjusted <i>n</i> = 653	Never smoked <i>n</i> = 265	Adjusted <i>n</i> = 352	Never smoked <i>n</i> = 19
	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI
None	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Cough symptoms	1.4	1.2	4.8	3.6	1.3	1.0	1.3	1.4	1.2	1.1	1.3	1.8
	1.3–1.5	1.0–1.4	3.2–7.0	1.4–9.3	1.0–1.8	0.6–1.7	1.2–1.5	1.1–1.8	1.0–1.5	0.8–1.5	1.1–1.7	0.5–6.6
Asthma-like symptoms	1.4	1.2	5.8	4.4	1.3	1.2	1.3	1.2	1.2	1.1	1.3	0.9
	1.3–1.5	1.0–1.4	4.0–8.5	1.8–10.3	1.0–1.7	0.8–1.9	1.2–1.5	0.9–1.5	1.0–1.4	0.8–1.5	1.0–1.7	0.3–3.0
Dyspnoea, moderate	1.5	1.4	4.9	3.2	0.9	0.9	1.8	1.9	1.5	1.3	1.5	0.9
	1.3–1.8	1.2–1.6	3.1–7.8	1.1–9.5	0.6–1.5	0.6–1.7	1.5–2.1	1.4–2.4	1.2–1.9	0.9–1.8	1.1–2.2	0.2–3.6
Dyspnoea, severe	2.1	1.4	11.1	8.8	1.6	1.3	2.5	1.9	1.9	1.8	1.4	–
	1.8–2.2	1.1–1.8	6.9–17.8	2.8–28.1	1.0–2.7	0.6–2.9	2.1–3.0	1.3–2.8	1.4–2.6	1.0–2.7	0.8–2.3	–

^a ‘Adjusted’, adjusted for age, sex, occupational exposure and smoking habits; ‘never smoked’, adjusted for age, sex and occupational exposure

related to mortality from all causes independently of lung function.

Stavem *et al.* [128] followed an occupational cohort of middle-aged men for 26 years and found that phlegm and breathlessness were associated with all-cause mortality, even after adjustment for physical fitness, lung function, known cardiovascular disease and smoking. The association was not significant for mortality from cardiovascular disease, as the cohort consisted of only 1999 men [128]. Juosilahti *et al.* [129] found in a study of nearly 20 000 Finnish men and women followed for 13 years that symptoms of chronic bronchitis (i.e. cough with phlegm 3 months or more during a year) predicted risk for death from cardiovascular disease independently of other known major cardiovascular risk factors [129]. Factors other than tobacco smoking, such as occupational exposure to asbestos, metals such as nickel, arsenic and cadmium, radon and ionizing radiation, are known to increase the risk for lung cancer [130]. In our study, however, occupational exposure to dust and gases did not appear to increase the risk for lung cancer, and, after adjustment, such exposure was significantly associated only with mortality from OLD in men. A Norwegian population-based study showed that both men and women tended to leave jobs entailing exposure to pollutants more often than jobs with no such exposure [131]. This might explain the unexpectedly weak association between occupational exposure to dust and gases and early death and lung cancer incidence. This could also be because the question about occupational exposure was not specific, and our study had too little power to establish any association between occupational exposure and mortality or lung cancer risk.

External validity

External validity (or generalizability) can be defined as the ability to generalize from observations in a community to people outside the study population [117]. The prevalences of respiratory symptoms and smoking in our study population were similar to those in other

populations studied in Norway [7,13,16,27,132,133]; however, we saw fewer deaths from pneumonia in our cohort than in the populations of Oslo and Norway (Table 8). This may be because our cohort excluded people over 70 years at baseline. The numbers of deaths from other causes among inhabitants of Oslo and Norway correlated well with those in our cohort [105]. Even though the response rate was somewhat lower among persons aged 20–34 years and lower for men than women, the overall rate was very high. The difference is small and should not prevent the generalizability of our results to the Norwegian population.

Table 8. Deaths from all causes, obstructive lung disease, pneumonia, ischaemic heart disease, stroke and lung cancer in the populations of Norway and Oslo and in our cohort in 1973–2002 [105]

Cause of death	Norway, all ages		Oslo, all ages		Our cohort, aged 15–70 years in 1972	
	No.	% of all deaths	No.	% of all deaths	No.	% of all deaths
All	1 336 192	100	185 370	100	6 710	100
Obstructive lung disease	34 708	3	5 543	3	250	4
Pneumonia	81 258	6	12 909	7	293	4
Ischaemic heart disease	317 221	24	42 381	23	1 572	23
Stroke	165 210	12	21 543	12	653	10
Lung cancer	41 926	3	6 998	4	318 *	5

* From reference [134]

Results

This study showed that respiratory symptoms reported at one time by nearly 18 000 persons in Oslo, Norway, were significant predictors of mortality from all causes, obstructive lung disease and ischaemic heart disease in the subsequent 30 years, after adjustment for age, smoking habits and occupational exposure. Weaker associations were found for mortality from pneumonia and stroke and for the incidence of lung cancer.

Associations between respiratory symptoms and the outcome variables

Cough symptoms

There are sex-related differences in the perception and reporting of respiratory symptoms: cough and sputum production are less commonly reported by women than men [27,135].

Among coughers, women report a higher prevalence of non-productive cough than men [40,136]. In a study of patients with chronic cough, women had a more sensitive cough reflex to both capsaicin and citric acid [137].

We pooled all cough symptoms, with and without phlegm, into one group. Cough symptoms were reported more often by men than women, both as individual symptoms and as a group.

Despite these differences, we found no significant difference by sex in the association between cough symptoms and all-cause or cause-specific mortality or the incidence of lung cancer.

A positive association has been reported between chronic mucus hypersecretion (chronic cough with phlegm > 3 months a year) and mortality from COPD in several studies, most of which were conducted in occupational settings [126,138]. In a population-based Danish study, a significant association was found between chronic mucus hypersecretion and mortality from OLD, adjusted for lung function [79]. Although we had no information about

lung function, we had information on reported physician-diagnosed asthma, bronchitis or emphysema. In agreement with a Swedish study, we consider that there is an accumulation of individuals with low lung function among those with already diagnosed OLD [9]. In excluding those persons, we excluded most individuals with very low lung function.

In the present study, cough symptoms were significantly associated with increased mortality from IHD. Our findings are partly in agreement with those of smaller population-based studies [80,82,85]. Todd *et al.* [82] found a positive association with chronic cough in both sexes[82], while Knuiman *et al.* [85] found a significant association only for men.

We found a positive association between cough symptoms and mortality from stroke, although the association was not significant. Two other studies showed non-significant negative associations between chronic cough and mortality from stroke in both sexes [82,85].

Vestbo and colleagues [8] found a strong positive relationship between cough and the incidence of respiratory tract cancer in a cohort of 876 middle-aged Danish men, with an age- and smoking-adjusted HR of 2.5[8]. Our findings are in closer agreement with those of cohort studies analysing the association between respiratory symptoms and mortality from lung cancer [82,93]. These studies included both men and women, and large groups were followed for about 12 years. With a reported ratio of mortality:incidence for lung cancer of 9:10 [139], we can assume that in our study with a 30-year follow up, there is a vanishing difference between the risk for developing lung cancer and the risk for dying from lung cancer.

Like us, Peto and colleagues found a moderate relation between mucus hypersecretion in men and mortality from lung cancer, and they showed that the relation between phlegm production and mortality from lung cancer remained after adjustment for FEV₁ [140]. Airway irritation that causes productive cough and neoplasm both occur predominantly in the large airways.

Asthma-like symptoms

Asthma-like symptoms can include wheezing, attacks of breathlessness and other symptoms of bronchial hyperresponsiveness such as long-lasting cough after a cold. Wheezing was found to increase mortality from all causes among men in Great Britain and Australia [81,85] and among women in Poland [83], whereas in the United States no association was found [84]. Our study showed that wheezing is a significant risk factor for mortality from all causes in both men and women. This is probably due to the greater power of our study, with a large number of person–years under observation.

The mortality risk associated with cold-induced long-lasting cough is a new observation. The association between attacks of breathlessness and mortality was reported by Krzyzanowski *et al.*, who, like us, found a greater increase in risk among men than women [83].

We found little difference in the association between mortality from all causes and wheezing, attacks of breathlessness and long-lasting cough after a cold. When we defined asthma-like symptoms as an affirmative answer to question 12, 17 or 18, (see Table 3), the significantly increased risk remained for both sexes.

A study in Busselton, Australia, showed that persons who reported wheezing had an increased risk for death from respiratory disease in general [85]. A French study showed that attacks of breathlessness and wheezing were significantly associated with death from COPD, with a relative risk of 3.5 [87]. In our study, asthma-like symptoms resulted in a higher HR for mortality from OLD than in the French study [87]. Studies in France and Denmark showed that persons with asthma or symptoms of asthma had a 20–40% increased risk for death from cardiovascular disease than those without such symptoms [87,92]. We have no explanation for the finding that asthma-like symptoms (after adjustment for other respiratory symptoms)

were associated with a lower risk for stroke in women but not in men. This observation should be confirmed in future population-based studies.

In agreement with a study of hospitalized asthma patients in Sweden [98], we found a significantly increased risk for lung cancer among persons with physician-diagnosed asthma bronchiale. Additionally, as the prevalence of diagnoses of asthma and asthma-like symptoms in adults has increased [18], we can assume a future increase in the incidence of lung cancer, given the same smoking habits. The association between asthma-like symptoms and lung cancer incidence did not change after exclusion of persons with physician-diagnosed OLD.

Dyspnea symptoms

Shortness of breath was reported more frequently by women than men in Norwegian population-based studies [6,16]. In our study, the association between severe dyspnoea and mortality from all causes was significantly higher among men than women. The association between dyspnoea and the other end-points of the study, cause-specific mortality and incidence of lung cancer, was not, however, affected by sex.

Dyspnoea on exercise is a frequent presenting symptom of both lung and heart disease. It is therefore to be expected that a considerable proportion of persons who reported dyspnoea at baseline had heart or lung disease, with a serious prognosis. It is thus not surprising that the relative mortality risk decreased during follow-up. The long-term survivors who had reported dyspnoea might have had conditions with a more favorable prognosis, such as poor physical fitness, overweight or hyperventilation. After excluding those individuals with physician-diagnosed heart or lung disease, we still found an association between dyspnoea and mortality from all causes, OLD, IHD and stroke.

Our finding of an association between dyspnoea and total mortality is in agreement with that of an occupational cohort study of Norwegian men followed for 26 years which showed an increased risk for death from all causes even after adjustment for physical fitness, smoking habits and lung function [128]. Our finding of a significant association between dyspnoea and mortality from OLD is in agreement with those of population-based surveys [80,81,85]. Our finding of increased risks for death from IHD and stroke among men and women who reported dyspnoea confirms previous results in men [80,85].

Respiratory symptom score

The number of symptoms present is an estimate of the burden of respiratory symptoms. An earlier Norwegian study showed that persons with respiratory symptoms had poorer lung function than persons without symptoms [103], independently of the presence of disease with spirometrically verified airway obstruction [141]. Our study shows that an increased number of respiratory symptoms increases both overall and cause-specific mortality from OLD and IHD, after adjustment for age, smoking habits and occupational exposure. The number of symptoms may be a simple indicator of the severity of the underlying pathological entity in the airway in both men and women.

Possible mechanisms for the associations between respiratory symptoms and earlier death and lung cancer

In recent years, there has been increasing focus on the possible role of inflammation in both malignant and non-malignant disease. Respiratory symptoms might be markers of an acute or chronic inflammatory process in the lungs and airways and might be present before other clinical manifestations.

Obstructive lung diseases are inflammatory diseases [37,142], and persons with physician-diagnosed OLD without respiratory symptoms can be satisfactorily treated with bronchodilators and anti-inflammatory drugs and be cured [37,143]. In a 3-year controlled clinical trial, patients with COPD treated with long-lasting adrenergic β_2 -agonist and inhaled steroids showed a tendency to reduced mortality [144]. In our study, persons with physician-diagnosed OLD had a significantly increased risk for mortality from all causes; however, persons with a previous history of OLD but no respiratory symptoms at baseline had no increased risk for mortality (data not shown). This finding supports the hypothesis that respiratory symptoms might be an indicator of chronic inflammatory processes in the airways and thereby of a risk for earlier death due to respiratory and cardiovascular diseases and the development of lung cancer.

Sin and Man [145] postulated that persistent pulmonary inflammation promotes release of pro-inflammatory mediators and cytokines into the circulation and that the mediators stimulate production and release of acute-phase proteins and inflammatory cells, leading to a state of low-grade systemic inflammation. High-sensitivity C-reactive protein is the best studied inflammatory marker. Airway obstruction is associated with increased blood levels of systemic inflammatory markers like C-reactive protein and fibrinogen [146-148]. The systemic inflammation, in turn, may affect blood vessels, in particular promoting atherosclerotic plaque instability and rupture. C-Reactive protein has been shown to predict myocardial infarction, stroke and vascular events [149-154]. Statins seem to attenuate inflammatory risk and have been shown to improve survival after exacerbation of OLD [155,156].

Thus, as systemic inflammation may have an important role in human cancer development in general, the plasma C-reactive protein level is a potential marker of increased cancer risk [157]. It has been proposed that chronic inflammation in the lung can stimulate cell

proliferation and growth, leading to lung cancer [158,159]. Although cigarette smoking may explain 80–85% of lung cancers in the Nordic countries [94], several studies have indicated an association between lung cancer and non-malignant pulmonary diseases such as COPD, pneumonia and lung tuberculosis, even in non-smokers and after adjustment for smoking habits [95-98,160-162]. Moreover, this risk increases inversely with level of pulmonary function expressed as FEV₁ [99].

The associations between respiratory symptoms and lung function [163-165] and between lung function and several causes of death are well known [79,85,90,166]. Our study does not elucidate why respiratory symptoms increase the risk for cause-specific mortality and lung cancer or why self-reporting of such symptoms at any time has such a long-lasting effect. We have nevertheless shown that common respiratory symptoms are important predictors of diseases over 30 years.

Recording symptoms is simple, cheap and applicable to most people. Awareness of respiratory symptoms is important in clinical practice for detecting underlying diseases. This study supports the hypothesis that modulating pulmonary inflammation might favourably affect later development of diseases that could lead to earlier death or lung cancer. This conclusion must, however, be confirmed in controlled clinical trials.

MAIN CONCLUSIONS

1. Respiratory symptoms were significantly associated with mortality from all causes over 30 years. The relation between respiratory symptoms and all-cause mortality increased with the number of symptoms and decreased during follow-up, but was still increased during the last decade of follow-up.
2. We found a strong, positive association between respiratory symptoms and 30-year mortality from OLD. The risk of mortality from OLD increased strongly with the number of symptoms and was greater than 10 for people who reported seven or more respiratory symptoms when compared with persons without symptoms. The association between respiratory symptoms and mortality from pneumonia was weak and not significant.
3. We found a significant, positive association between respiratory symptoms and 30-year mortality from IHD. A weak positive association was found between respiratory symptoms and mortality from stroke 30 years later.
4. An increased risk for the development of lung cancer was observed in both men and women reporting cough symptoms, women reporting asthma-like symptoms and men reporting dyspnoea when walking uphill. The association was strongest during the first decade and decreased with duration of follow-up, but was still increased, although not significantly, during the last decade. The risk increased with the number of symptoms reported at baseline, to a greater extent for non-small-cell lung cancer than for small-cell lung cancer.

PERSPECTIVES AND RESEARCH QUESTIONS

The present study has contributed importantly to epidemiological research as it presents estimates for the predictive value of many respiratory symptoms for cause-specific mortality and the incidence of lung cancer in a large population of adults followed over 30 years. These findings show that we must take respiratory symptoms seriously.

Our findings allow us to suggest that increasing awareness of respiratory symptoms can lead to diagnoses that will necessitate treatment to reduce the symptom load. Fewer respiratory symptoms will reduce morbidity and mortality over time and consequently increase quality of life and facilitate calculation of health costs.

This thesis has answered some research questions, but it has also raised several new questions, which should be answered in future studies.

- Was the cause-specific mortality among persons who did not return the questionnaire different from that of persons who returned a filled-in questionnaire?
- The accuracy of the information about OLD, pneumonia, stroke and IHD on death certificates completed by physicians should be established by comparison with autopsy results.
- The association between respiratory symptoms and cause-specific mortality should be examined after adjustment for lung function and for risk factors for atherosclerosis, like exercise, blood pressure, cholesterol and body weight.
- Other combinations of respiratory symptoms than those addressed in this study should be examined as risk factors for mortality and lung cancer.

- What is the association between respiratory symptoms and risk for cause-specific mortality and incidence of lung cancer among persons over 70 years at baseline?
- Will suppression of respiratory symptoms with anti-inflammatory and bronchodilatory drugs in a controlled clinical trial reduce the risks for early death and lung cancer?

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APPENDICES

Appendix 1. Questionnaire used in the First Asthma Oslo Study 1972, in Norwegian

LUNGEAVDELINGEN
RIKSHOSPITALET
OSLO 1

Undersøkelse over utbredelsen av astma og bronkitt i Oslo

Kjære Oslo-borger!

Ved Rikshospitalets lungeavdeling utfører vi nå en undersøkelse over forekomsten av astma og bronkitt i Oslo. Blant byens innbyggere er det tilfeldig trukket ut 20 000 personer som blir bedt om å svare på et spørreskjema, og De er en av disse.

Det er frivillig å svare, men det er av største betydning for undersøkelsen at flest mulig fyller ut spørreskjemaet. Jeg vil derfor be Dem være vennlig å fylle ut dette og sende det tilbake i svar-konvolutten.

Hvis De ikke kan gi et helt nøyaktig svar, så fyll ut etter beste skjønn. Hvis det er spørsmål De ikke kan svare på, så la det stå åpent. Hvor det finnes for besvarelsen av spørsmålet, settes et kryss i den som passer.

Skulle De mot formodning ikke ønske å svare i det hele tatt, vil jeg sette pris på at De anfører dette på skjemaet og sender det tilbake.

Alle opplysninger vil bli behandlet under full taushetsplikt.

På forhånd takk for hjelpen!

Vennlig hilsen

T. Wessel-Aas.

T. Wessel-Aas
professor, dr. med.

<p>1. Er navn og postadresse på skjemaet riktig og fullstendig? <input type="checkbox"/> Ja <input type="checkbox"/> Nei</p> <p>Hvis «Nei», vær vennlig å oppgi fullt navn og adresse:</p> <p>Navn:</p> <p>Adresse:</p> <p>2. Når er De født?</p> <table><tr><td>Dag</td><td>Måned</td><td>Ar</td></tr><tr><td>_____</td><td>_____</td><td>_____</td></tr></table> <p>3. Hvor mange år har De bodd i Oslo?</p> <p>.....</p>	Dag	Måned	Ar	_____	_____	_____	<p>4. Vennligst kryss av for den gruppe som best beskriver Deres nåværende arbeidsforhold:</p> <p>Jeg er i arbeid <input type="checkbox"/> (husarbeid, skolegang eller annet arbeid. Kryss av her selv om De for tiden er kortvarig sykmeldt eller arbeidsledig).</p> <p>Jeg er uføretrygdet <input type="checkbox"/> (invalidpensjonert). Vennligst opplys om årsak:</p> <p>.....</p> <p>Jeg er ikke i arbeid <input type="checkbox"/> av annen grunn. Vennligst opplys om årsak:</p> <p>.....</p>
Dag	Måned	Ar					
_____	_____	_____					

VEND

5. Er De eller har De vært utsatt for støv, røyk eller irriterende damper (gasser) i Deres arbeid? 1 Ja 2 Nei

6. Hvis «Ja», hva slags støv, røyk eller irriterende damp?

7. Har noen av Deres foreldre, søsken eller barn hatt eksem, høysnue, elveblest, astma eller bronkitt? 1 Ja 2 Nei 3 Vet ikke

8. Hoster eller harker (kremter) De vanligvis om morgenen? 1 Ja 2 Nei

9. Hoster De vanligvis ellers om dagen? 1 Ja 2 Nei

10. Har De vanligvis oppspytt når De hoster eller harker? 1 Ja 2 Nei

11. Hoster De daglig i tilsammen 3 måneder eller lenger i løpet av ett år? 1 Ja 2 Nei

12. Har De i løpet av de siste par årene i forbindelse med forkjølelse hatt hoste og/eller oppspytt som har vart i mer enn 3 uker? 1 Ja, én gang 2 Ja, flere ganger 3 Nei

13. Blir de mer tungpusten (andpusten) enn jevnaldrende når De går i motbakker? 1 Ja 2 Nei

14. Blir De tungpusten når De går opp 2 etasjer i vanlig fart? 1 Ja 2 Nei

15. Blir De tungpusten når De går med vanlig fart på flat mark? 1 Ja 2 Nei

16. Er De tungpusten når De sitter i ro? 1 Ja 2 Nei

17. Hender det at de har anfall av tung pust? 1 Ja 2 Nei

18. Har De noen gang piping i brystet? 1 Ja 2 Nei

19. Har De røkt daglig i mer enn 1 år? (Bes også besvart av tidligere røkere). Hvis «Ja» besvares spørsmålene 19—22:

20. Hvor mange år har De røkt tilsammen?

21. Hvor mange sigaretter har De i alminnelighet røkt pr. dag? (Fabrikkfremstilte og håndrullede tilsammen. En pakke (50 gram) tobakk regnes som 50 sigaretter.)

22. Hvor mange pakker à 50 gram har De i alminnelighet røkt i pipe pr. uke?

23. Sluttet De å røke for mer enn 1 år siden? 1 Ja 2 Nei

24. Hvis «Ja», for hvor mange år siden?

Har De noen gang hatt en av de sykdommer som er nevnt nedenfor?

25. Eksem 1 Ja 2 Nei 3 Vet ikke

26. Elveblest 1 Ja 2 Nei 3 Vet ikke

27. Høysnue 1 Ja 2 Nei 3 Vet ikke

Er De noen gang blitt behandlet av lege eller har De vært innlagt i sykehus for en av de sykdommer som er nevnt nedenfor?

28. Astma 1 Ja 2 Nei 3 Vet ikke

29. Bronkitt 1 Ja 2 Nei 3 Vet ikke

30. Emfysem («utvidete lunger») 1 Ja 2 Nei 3 Vet ikke

31. Plevritt 1 Ja 2 Nei 3 Vet ikke

32. Lungetuberkulose 1 Ja 2 Nei 3 Vet ikke

33. Annen lungesykdom 1 Ja 2 Nei 3 Vet ikke

34. Hjertefarkt 1 Ja 2 Nei 3 Vet ikke

35. Hjertekrampe (angina pectoris) 1 Ja 2 Nei 3 Vet ikke

36. Hjertesvikt 1 Ja 2 Nei 3 Vet ikke

37. Annen hjertesykdom 1 Ja 2 Nei 3 Vet ikke

38. Er De noen gang blitt behandlet av lege eller har De vært innlagt i sykehus for annen sykdom som kan ha virket på pustevevnen? 1 Ja 2 Nei 3 Vet ikke

39. Hvis «Ja», angi hvilken sykdom:

Appendix 2. Questionnaire used in the First Asthma Oslo Study 1972, in English

Lung Department, National Hospital, Oslo

Study of the occurrence of asthma and bronchitis in Oslo

Dear inhabitant of Oslo!

The Lung Department at the National Hospital is performing a study of the occurrence of asthma and bronchitis in Oslo. From the population, 20 000 people have been asked to answer a questionnaire, and you are one of them. Participation is voluntary, but a high participation rate is vital to the study. Because of this, I would kindly ask you to fill out the questionnaire and return it in the envelope. If you cannot provide an accurate answer, please answer to the best of your ability. If you cannot answer a question, leave it blank. Questions in a thick box should be marked in the thick box that is most appropriate. If you should decide not to participate, I would appreciate you marking this on the questionnaire and returning it. All information will be treated fully confidentially. Thank you in advance!

Yours sincerely, T. Wessel-Aas, Professor, MD PhD

1. Is the name and address on the questionnaire correct and complete? Yes/No. If no, please provide your full name and address. Name: Address:
2. When were you born? Day/Month/Year
3. For how many years have you lived in Oslo?
4. Please tick that group that best describes your current job status:
 - I am working (housework, education or other work. Please tick this even if you presently are on sick leave or are unemployed).
 - I am on disability benefits. Please tell us why:
 - I am not working, for other reasons. Please tell us why:

(New page)

5. Are you or have you been exposed to dust, fumes or noxious vapours (gases) in your work? Yes/No
6. If yes, what kind of dust, fumes or noxious vapours?
7. Have any of your parents, siblings or children had eczema, hay fever, hives, asthma or bronchitis? Yes/No/Don't know
8. Do you usually cough or clear your throat in the morning? Yes/No
9. Do you usually cough during the rest of the day? Yes/No
10. When you cough or clear your throat, do you usually bring up phlegm? Yes/No
11. Do you have a cough for 3 months or more altogether during a year? Yes/No
12. During the past 2 years, have you had a cough and/or phlegm in connection with a cold for more than 3 weeks? Yes, once/Yes, several times/No
13. Are you more breathless than other people of your own age when walking uphill?
Yes/No
14. Are you breathless when you climb two flights of stairs at an ordinary pace? Yes/No
15. Are you breathless when you walk on level ground at an ordinary pace? Yes/No
16. Are you breathless when at rest? Yes/No
17. Do you sometimes have attacks of breathlessness? Yes/No
18. Have you ever had wheezing in your chest? Yes/No
19. Have you ever smoked daily for more than 1 year (former smokers please also respond)? Yes/No
20. For how many years altogether have you smoked? ___ years.
21. How many cigarettes did you usually smoke daily? (Factory-rolled and hand-rolled together. One pack of tobacco (50 grams) counts as 50 cigarettes) ____ cigarettes.
22. How many packs of 50 grams did you usually smoke in a pipe weekly? ___ packs.
23. Did you stop smoking more than 1 year ago? Yes/No

24. If yes, how many years ago? ____ years

Have you ever had any of the diseases listed below?

25. Eczema. Yes/No/Don't know

26. Hives. Yes/No/Don't know

27. Hay fever. Yes/No/Don't know

Have you ever been treated by a doctor or have you been admitted to hospital for one of the diseases listed below?

28. Asthma. Yes/No/Don't know

29. Bronchitis. Yes/No/Don't know

30. Emphysema ("inflated lungs"). Yes/No/Don't know

31. Pleuritis. Yes/No/Don't know

32. Pulmonary tuberculosis. Yes/No/Don't know

33. Other pulmonary diseases. Yes/No/Don't know

34. Myocardial infarction. Yes/No/Don't know

35. Heart cramp. Yes/No/Don't know

36. Heart failure. Yes/No/Don't know

37. Other heart disease. Yes/No/Don't know

38. Have you ever been treated by a doctor or have you been admitted to hospital for any other diseases that can affect respiration? Yes/No/Don't know

39. If yes, please describe which disease: