

Mortality in adults with self-reported asthma

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Summary

Background On the question of whether asthma shortens survival the published work gives no clear answer. We have prospectively analysed overall and cause-specific mortality in persons with self-reported asthma.

Methods A sample of 13 540 individuals (6104 men) 20 years of age or older, randomly selected from the general population of the city of Copenhagen, was followed for 17 years.

Findings Survival in participants with self-reported asthma was significantly poorer than in non-asthmatics, the excess mortality being limited to pulmonary mortality. After statistical adjustment for age, length of school education, and smoking, women with asthma had a 1.7 higher risk of dying than women without asthma (95% confidence interval 1.3–2.2). Although the relative risk (RR) of dying with asthma was slightly lower in men (RR=1.5, 95% CI 1.2–1.9) the difference between sexes was not significant. The results were similar within smoking groups and the highest risk of death associated with asthma was seen among never-smokers (RR=2.1, 95% CI 1.6–2.3). Inclusion of one-second forced expiratory volume, in % predicted, in the mortality analyses showed that the increased risk of death associated with asthma was mediated mainly through reduced lung function.

Interpretation We conclude that, in the general population, self-reported asthma is associated with a slight excess of mortality, mainly from respiratory diseases.

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Introduction

Despite a general perception that great advances have been made in the treatment of asthma, asthma-associated mortality seems to be on the increase in many countries.^{1,2} A possible association between asthma deaths and use of beta-2-agonists has been vigorously debated. In addition, there have been repeated suggestions that at least some of the asthma deaths may be preventable.³

Our knowledge of the long-term prognosis of asthma, including survival, is still very weak. One large UK study of asthmatics attending general practitioners showed poorer survival than in non-asthmatics,⁴ whereas an American study of community residents revealed no excess of mortality unless asthma was associated with chronic obstructive pulmonary disease (COPD).⁵ In addition, there have been studies on patients referred to chest clinics or hospital departments, but the results may not be generalisable since the patients are likely to have more severe disease than those not referred.^{6–9}

The purpose of the present investigation was to analyse mortality in persons with self-reported asthma in the general population. In addition, we wanted to investigate the importance of lung function impairment with regard to mortality of asthmatics. The analyses are based on the 17-year follow-up of participants in the Copenhagen City Heart Study, a continuing epidemiological investigation in the inner city of Copenhagen.

Methods

Population

All persons included in these analyses participated in the Copenhagen City Heart Study, a prospective epidemiological cardiopulmonary investigation initiated in 1976. The sample, drawn from a population of about 90 000 inhabitants aged 20 years or more, was age-stratified with main emphasis placed on the age groups from 35 to 70 years and comprised 19 698 individuals. Three weeks before the planned examination the persons selected received an invitation to attend for examination at Rigshospitalet. A stamped postcard was attached to the invitation so that persons could negotiate a change, or decline the appointment. If the postcard was not returned a reminder was sent one week before the planned examination day. If the person did not show up, a further invitation was sent six months later. Thereafter, no attempt was made to contact the non-responders. The first examination round lasted 25 months from Feb 27, 1976 to March 31, 1978. The examinations were conducted by a staff of nurses and medical laboratory technicians, who were trained according to the WHO manual for cardiovascular epidemiological studies. 14 223 individuals were examined—ie, 74% of those invited.

In general, the response rates were highest among those between 40 and 70 years of age (68–80%) and lowest among those aged 80 or more (28–41%). At the end of the first examination we planned to visit a random sample of 223 non-responders to evaluate whether they differed from the responders. Only 67 (30%) could be contacted despite several attempts. The prevalence of asthma and chronic mucus

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Age (yr)	Women			Men		
	Total in age-group	Asthma n	%	Total in age-group	Asthma n	%
20-29	321	8	2.5	279	4	1.4
30-39	778	10	1.3	699	7	1.0
40-49	1643	27	1.6	1351	29	2.1
50-59	2692	66	2.5	1879	42	2.2
60-69	1590	46	2.9	1462	50	3.4
≥70	412	6	1.5	434	20	4.6
Total	7436	163	2.2	6104	152	2.5

Table 1: Distribution of participants by age and gender and prevalence of self-reported asthma at initial examination

hypersecretion among the non-responders investigated in their homes was slightly higher than among the responders. No spirometric tests were performed in this group. During the first years of the follow-up, the non-responders had a higher age-adjusted mortality than the responders.¹⁰ This trend continued throughout the observation period until 1995.

Details of the selection procedure, the characteristics of the non-responders, and the examination programme have been presented previously.¹⁰

From the total of 14 223 individuals who attended the examinations we excluded 683 who lacked the complete data required for the present analyses. The final study sample consisted of 13 540 persons—6104 men and 7436 women. These were categorised in terms of the presence or absence of asthma. Our criterion for asthma follows the convention of other epidemiological studies¹¹ by relying on people's perception of whether or not they have the disease: asthma was defined by a positive response to the question: "Do you have asthma?"

Measurements and questionnaire

The forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured with an electronic spirometer (Monaghan N403, Littleton, CO, USA), which was calibrated daily with a one litre syringe and weekly against a water-sealed Godard spirometer. Maximum effort was to be exerted throughout expiration. After at least one trial blow, three values were obtained. For a correct performance at least two measurements of FEV₁ and FVC differing less than 5% had to be produced. The best FEV₁ and FVC were used in the analyses. The procedure and the calculation of internal reference values based on a subsample of healthy nonsmokers have been described in detail previously.^{12,13} Data on FEV₁ are reported in absolute values and also as a percentage of predicted value (%p).

A self-administered questionnaire concerning symptoms, somatic diseases, social status, and smoking and drinking habits was filled out and checked by one of the investigators. All participants reported whether they were current smokers, ex-smokers, or life-long non-smokers (never-smokers), and for the first two categories the duration of smoking. Current and ex-smokers reported their daily tobacco consumption and whether they inhaled (yes/no). Participants were registered as having chronic mucus hypersecretion if they reported daily cough and phlegm production for three months or more during one year for at least two years.

Follow-up

Average follow-up was 17 years, giving a total of about 214 000 person-years. Although the vital status of the participants is known until Jan 9, 1995, the information about the causes of death is available only until Dec 31, 1993. Notification of deaths and causes of deaths was obtained from the Danish Register of Causes of Death. This register includes death rates and mortality causes for all dead in Denmark. Throughout this period Denmark used the 8th revision of the International Classification of Diseases (ICD), which in the Danish version includes no code describing chronic obstructive lung disease without mention of either asthma, bronchitis, or emphysema. In the present paper we analysed total mortality and deaths from asthma (code 493),

Characteristic	Women		Men	
	No asthma n=7273	Asthma n=163	No asthma n=5952	Asthma n=152
Age (yr)	52.4 (11.7)	53.7 (11.2)	52.5 (12.5)	56.7 (11.2)‡
FEV ₁ (L)	2.23 (0.59)	1.70 (0.67)‡	3.03 (0.87)	2.09 (1.0)‡
FEV ₁ (%p)	86.1 (17.4)	67.0 (23.0)‡	84.1 (18.0)	60.9 (25.0)‡
FEV ₁ /FVC (%)	80.4 (9.4)	72.5 (24.7)‡	78.9 (10.9)	66.4 (14.8)‡
Education	48.1%	54.0%	46.0%	60.9%‡
≤7 yr				
Never-smokers	28.1%	19.8%*	11.0%	9.2%
Non-smokers	14.4%	24.1%‡	19.6%	28.9%†
Chronic mucus hypersecretion	7.6%	46.0%‡	11.8%	43.4%‡
Deaths during follow-up				
All causes				
n	1854	67	2382	94
%	25.5	41.1	40.0	61.8

p-values calculated by chi-square and t-test: *p<0.05; †p<0.01; ‡p<0.001.

Table 2: Characteristics at initial examination and mortality during the follow-up according to gender and self-reported asthma

chronic obstructive pulmonary disease (code 491-2: bronchitis and/or emphysema), all non-malignant respiratory diseases (code 460-519), malignant diseases of trachea, bronchus, and lung (code 160-163), cardiovascular diseases (code 390-459), ischaemic heart disease (code 410-414), and all malignant diseases (code 140-208).

Statistical methods

The subject of the analysis was the intensity or instantaneous risk of death. We used the regression model of Cox.¹⁴ If t is time, $x = x_1, x_2, \dots, x_r$ is a set of explanatory variables, and $a_1, a_2, \dots, a_r$ are regression coefficients. This model assumes that the intensity of death has a simple form: $\gamma(t, x) = \lambda_0(t) \cdot \exp(a_1 x_1 + a_2 x_2 + \dots + a_r x_r)$. Time was reckoned from the initial examination until death or

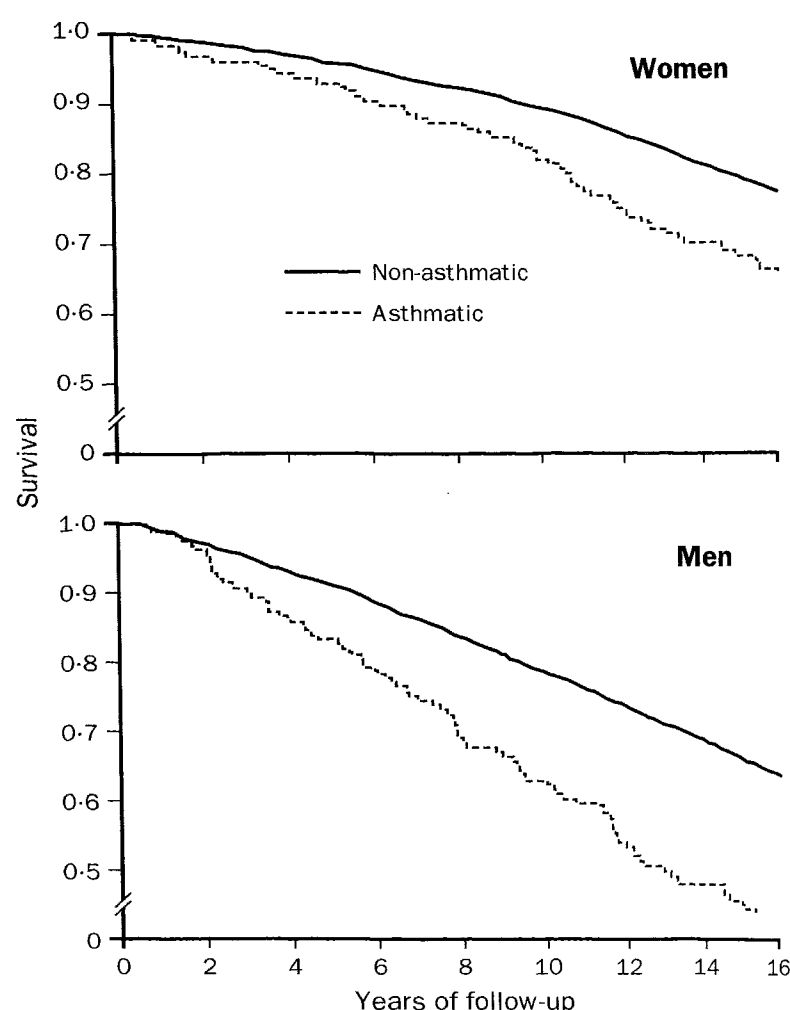


Figure: Survival in women and men according to self-reported asthma

until the end of the observation period. The assumption of proportional hazards throughout the follow-up period was tested by plotting the logarithm to the cumulated hazard in different subgroups against time of observation. The regression coefficients were estimated by the maximum likelihood method as suggested by Cox, and the hypothesis of a significant predictive effect of a variable on λ was evaluated by means of the likelihood ratio test. The need for first-order interaction terms was assessed by means of the likelihood ratio test. Initially we performed separate regressions for men and women, but since the underlying hazard was not different for men and women and since the risk of death associated with asthma was similar in the two sexes we finally analysed both sexes combined in a single model.

We performed several analyses using different end-points: all deaths, deaths from asthma, deaths from COPD, deaths from lung cancer, and so on. The explanatory variable of main interest was the presence of asthma. The other explanatory variables included in the regression model were age, smoking and inhalation habits, and the length of school education and gender. In an additional model we included FEV₁%p and chronic mucus hypersecretion (yes/no).

Results

Table 1 gives the number of participants with asthma according to age and gender; 315 had self-reported asthma. The prevalence in the 10-year age-groups ranged from 1.0% to 4.6%. In men but not in women an increase with age was observed.

Table 2 outlines the general characteristics of participants at the initial examination and the mortality during follow-up according to the diagnosis of asthma. In men but not women, mean age was higher in asthmatics than in non-asthmatics. Those with self-reported asthma were more likely to be non-smokers and had the lowest lung-function scores and the highest prevalence of chronic mucus hypersecretion. There was a trend towards a higher percentage with short school education among those with self-reported asthma.

Overall mortality

Survival of people with self-reported asthma was poorer than that of non-asthmatics ($p < 0.001$, log-rank test (see figure and table 2). Table 3 gives the results of mortality analyses with Cox regression models. Model 1, which included age, smoking, and education as covariates, yielded a significantly higher risk of death in both women and men with asthma. As expected, the risk of dying increased with age and smoking. In addition, there was a trend towards a poorer survival in groups with the shortest school education.

Because there was no significant difference between men and women with regard to the association of asthma with mortality, both sexes were combined in model 2, which in addition to covariates from model 1 included FEV₁%p, chronic mucus hypersecretion, and gender as covariates. In this model the effect of asthma was no longer significant (relative risk 1.1, 95% confidence interval 0.9–1.3). Especially FEV₁%p but also chronic mucus hypersecretion were significantly related to mortality. The exclusion of chronic mucus hypersecretion from model 2 had only a minor effect on regression coefficients for the remaining variables—an indication that FEV₁%p was more important with regard to mortality risk.

To investigate the effect of age further we performed separate Cox regressions with asthma as the variable of interest and age, smoking, and education as covariates, in

Variable	Women Model 1 RR (95% CI)	Men Model 1 RR (95% CI)	Sexes combined Model 2 RR (95% CI)
Age per 10 yr increase	2.8 (2.7–3.0)	2.5 (2.4–2.6)	2.6 (2.5–2.7)
Asthma			
No	1.0	1.0	1.0
Yes	1.7 (1.3–2.2)	1.5 (1.2–1.9)	1.1 (0.9–1.3)
Smoking			
Never	1.0	1.0	1.0
Ex	1.2 (1.0–1.4)	1.1 (0.9–1.3)	1.1 (1.0–1.3)
<15 g/day	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.2 (1.0–1.3)
15–24 g/day	1.6 (1.4–1.9)	1.4 (1.1–1.7)	1.4 (1.2–1.6)
≥25 g/day	2.2 (1.7–2.7)	1.5 (1.8–3.2)	1.5 (1.3–1.8)
Inhalation			
No	1.0	1.0	1.0
Yes	1.6 (1.4–1.9)	1.5 (1.3–1.7)	1.5 (1.4–1.7)
Education			
<7 yr	1.0	1.0	1.0
7–10 yr	0.9 (0.8–1.1)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
>10 yr	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.85 (0.8–1.0)
Gender			
F			1.0
M			1.6 (1.5–1.7)
FEV ₁ %p per 10% increase			0.87 (0.85–0.88)
Chronic mucus hypersecretion			1.3 (1.1–1.4)

Results of Cox regression models including the following independent variables: age, asthma, smoking habits, inhalation habits, and length of school education (model 1). Model 2 includes men and women together and gender, FEV₁ in percent predicted, and chronic mucus hypersecretion as additional covariates.

Table 3: Risk of death from all causes

participants 60 years of age or younger and in those older than 60. For both sexes excess mortality associated with asthma was highest in the younger group: for women the RR was 1.9 (95% CI 1.4–2.6); for men RR was 1.7 (1.2–2.3), whereas in participants older than 60 years the RR was 1.5 (1.0–2.2) for women and 1.4 (1.1–1.9) for men.

To exclude possible misclassification between self-reported asthma and COPD we performed separate analyses on 2738 participants who declared themselves never-smokers. During the follow-up, never-smokers with asthma ($n=46$) had more deaths (32.6%) than never-smokers who did not report having asthma (22.9%). In a Cox regression analysis of never-smokers, self-reported asthma was associated with double the risk of death seen in non-asthmatics (table 4).

Finally, we analysed the group of the 315 asthmatics separately using Cox regression analyses similar to those in table 3. The effects of smoking, inhalation, and the remaining variables in this group were similar to those in the whole population.

Variable	Both sexes combined RR (95% CI)
Age per 10 yr increase	2.9 (2.7–3.1)
Gender	
F	1.0
M	1.9 (1.6–2.3)
Asthma	
No	1.0
Yes	2.1 (1.6–2.3)
Education	
<7 yr	1.0
7–10 yr	0.9 (0.7–1.0)
>10 yr	0.8 (0.6–1.0)

Results of Cox regression models including the following independent variables: age, gender, asthma, and length of school education.

Table 4: Risk of death from all causes among never-smokers

	Women		Men	
	No asthma n=7273	Asthma n=163	No asthma n=5952	Asthma n=152
Asthma ICD 493 n (%)	5 (0.1)	7 (4.3)	6 (0.1)	5 (3.3)
Chronic obstructive pulmonary disease ICD 491.2 n (%)	56 (0.8)	11 (11.7)	74 (1.2)	14 (9.2%)
Non-malignant respiratory diseases ICD 460–519 n (%)	92 (1.3)	19 (11.7)	111 (1.9)	20 (13.2)
Lung cancer ICD 160.3 n (%)	108 (1.5)	5 (3.1)	260 (4.4)	7 (4.6)
Cardiovascular diseases ICD 390–459 n (%)	649 (8.9)	21 (12.9)	956 (16.1)	27 (17.8)
Ischaemic heart disease ICD 410.4 n (%)	334 (4.6)	6 (3.7)	593 (10.0)	18 (11.8)
All malignant diseases ICD 140–208 n (%)	617 (8.5)	10 (6.1)	701 (11.8)	20 (13.2)
Non-pulmonary diseases* n (%)	1605 (22.1)	42 (25.8)	2103 (35.3)	68 (44.7)

% indicates percentage of those at risk in a given asthma group. *Non-pulmonary diseases: all deaths except ICD codes 160.3 and 460.519.

Table 5: **Cause-specific mortality during follow-up according to self-reported asthma at initial examination and gender**

Cause specific mortality

Pulmonary mortality—Asthma was judged the main cause of death in only 23 participants (12 women); 11 of these had reported no asthma at the beginning of the follow-up. The mean age of those who died from asthma was 57 years (range 40–81) and their mean FEV₁%p at the beginning of the follow-up period was 60.0 (range 22.2–96.2). As shown in table 5, both women and men with self-reported asthma had a much higher mortality from COPD and from all non-malignant respiratory diseases. In Cox regression models with age, gender, smoking, and education as covariates the presence of self-reported asthma was associated with a significantly higher mortality from these diseases (table 6). Although there was a higher incidence of death from lung cancer in those with self-reported asthma, especially women (table 5), the results of the Cox regression analysis did not reveal a significant association of asthma with lung cancer death (table 6).

	Women and men combined	
	No of deaths	RR (95% CI)
Asthma	23	52 (22–119)
Chronic obstructive pulmonary disease	155	7.0 (4.5–10.8)
Nonmalignant respiratory diseases	241	7.5 (5.3–10.6)
Lung cancer	378	1.3 (0.7–2.3)
Cardiovascular diseases	1641	1.2 (0.9–1.6)
Ischaemic heart disease	948	1.0 (0.7–1.5)
All malignant diseases	1338	1.0 (0.7–1.4)
Non-pulmonary diseases	3789	1.2 (1.0–1.5)

The RR and 95% confidence intervals are derived from Cox regression models with age, gender, smoking habits, inhalation habits, and education as covariates.

Table 6: **Relative risk of death from specific causes in participants with self-reported asthma compared to non-asthmatics**

Non-pulmonary mortality—The mortality from all malignant neoplasms (including lung cancer) and from cardiovascular diseases was not significantly higher among asthmatics (tables 5 and 6). In fact, when all non-pulmonary causes of death were combined (all deaths except for ICD codes 160–163 and 460–519) and a Cox regression model was used to adjust for age, smoking, and education, mortality in asthmatics and non-asthmatics did not differ significantly (RR=1.2, 95% CI 1.0–1.5) (table 6).

Discussion

In this large study of community residents, a self-reported diagnosis of asthma was associated with poorer survival and substantially higher risk of death from pulmonary diseases. Further analyses showed that the increased risk of death was primarily determined by the level of lung function. As in the previous studies the number of deaths where asthma was judged the main cause of death was small (0.5% of all deaths).^{4,5} Survival of asthmatics in the present cohort was significantly poorer than in the group without asthma both among the younger and among the elderly, the relative risks being higher in those under the age of 60.

The most important potential bias here concerns the classification of asthma. The definition of asthma is problematic and the differential diagnosis between asthma and COPD can be difficult even in the clinical setting. Self-reported diagnosis invariably leads to a degree of misclassification, since some individuals with mild asthma remain undiagnosed whereas some with COPD will erroneously report asthma.^{15–17} To characterise the latter effect we have focused on smoking habits and their relation to mortality. Although many of our asthmatics were smokers, the prevalence of non-smokers was highest among those with self-reported asthma. Most importantly, however, the separate analyses of never-smokers in this subgroup showed excess mortality risk associated with asthma similar to that in the whole study population (table 4). This suggests that the misclassification is unlikely to have severely biased our results.

Results from previous mortality studies in asthmatics are conflicting. Some groups report survival not different from that expected,^{5,16,18} others poorer survival.^{4,6–8} In the large UK investigation, the excess mortality was of similar magnitude to that in our study and was likewise most pronounced in women.⁴ The reason for the discrepancy between the US findings of Silverstein and co-workers⁵ and our own is probably the different diagnosis of asthma. The US study workers excluded individuals older than 50 years with dyspnoea during exercise and patients with FEV₁<50% of that predicted.⁵ The relevance of this exclusion is debatable, since dyspnoea on exercise is one of the important features of asthma and since asthma in some patients is known to result in permanent airways obstruction.¹⁹ Both dyspnoea and reduced FEV₁ are strongly related to survival,^{20,21} so these exclusion criteria may be responsible for selection of individuals with mild asthma into their cohort—hence the findings of normal survival.

Like Markowe and co-workers,⁴ we found that women with asthma were at slightly higher risk of death than men. Although this trend was not statistically significant it was present in both the young and the old. There could be sex differences in asthma severity,²² but another

possibility is diagnostic misclassification whereby female COPD patients are more likely to be classified as asthmatic than males; such misclassification has been observed in the Tuscon respiratory study.^{15,17}

In the present study, the excess mortality in asthmatics was mainly caused by respiratory diseases, notably COPD. We cannot say whether this is a true picture or the result of misclassification between asthma and COPD, either at the beginning of the follow-up or at the time of death. The analysis of mortality from non-pulmonary causes showed no significant increase among asthmatics. This finding is also in keeping with the results of Markowe and co-workers.⁴

Unlike Alderson, who investigated mainly younger atopic asthmatics,²³ we found a slightly higher risk of dying from lung cancer in self-reported asthmatics, though it did not reach statistical significance. This observation is in accordance with the results of Robinette and could be due to residual confounding by smoking.²⁴ Yet it is also possible that a higher risk of lung cancer may be caused by altered airways geometry in asthmatics, with slower mucociliary clearance resulting in a higher pulmonary deposition of carcinogens and longer contact between carcinogens and mucosa. This notion is in keeping with the work of Wu and co-workers, who found a higher risk of lung cancer (RR=1.7) among lifetime non-smoking women with asthma than in non-asthmatics.²⁵ The small number of lung cancer deaths among the asthmatics in the present study does not allow for a separate analysis of females. Like Markowe⁴ but unlike other groups,^{24,26} we saw no significant increase in the mortality from ischaemic heart disease in asthmatics.

The inclusion of FEV₁%p in our analyses had a profound effect on the association between asthma and mortality. This implies that most of the increase in mortality risk is mediated through the level of lung function in accordance with the observation that, although death can occur from an acute worsening of asthma in a patient with almost normal lung function, most of the asthmatics who die have a permanent reduction of their lung function.²⁷ Chronic mucus hypersecretion was also related to overall mortality, in keeping with previous observations in the present cohort.¹² In asthmatics, mucus hypersecretion may indicate poorly controlled disease, since it has been related to increased rate of admission to hospital.²⁸

In an analysis of asthma mortality in Philadelphia from 1969 to 1991, Lang and Polansky²⁹ reported the highest mortality rates in districts with poor socioeconomic conditions. In the present study we used the length of school education as an indicator of socioeconomic status, and likewise observed a trend towards better survival in those with a long school education.

One implication of our findings is that lung function impairment must be avoided in asthmatic patients. Smoking is clearly harmful, perhaps because it can accelerate FEV₁ decline.¹³ Whether lung function in asthmatics can be preserved by use of anti-inflammatory drugs such as inhaled steroids remains to be shown. There are, however, indications that early treatment of mild asthma with these agents gives better results than bronchodilators alone.³⁰ Patients with severe asthma are at highest risk of persistent reduction of lung function. In this group the benefits of inhaled steroids are often obvious and placebo-controlled long-term trials are unlikely to be conducted.

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