Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma

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Abstract

***Background*—Patients with asthma have an increased risk of death from causes other than asthma. A study was undertaken to identify whether severity of asthma, its treatment, or associated co-morbidity were associated with increased risk of death from other causes.**

***Methods*—Eighty five deaths from all causes occurring within three years of discharge from hospital in a cohort of 2242 subjects aged 16–64 years admitted for asthma were compared with a random sample of 61 controls aged <45 years and 61 aged ⩾45 years from the same cohort.**

***Results*—Deaths from asthma were associated with a history of clinically severe asthma (OR 6.29 (95% CI 1.84 to 21.52)), chest pain (OR 3.78 (95% CI 1.06 to 13.5)), biochemical or haematological abnormalities at admission (OR 4.12 (95% CI 1.36 to 12.49)), prescription of ipratropium bromide (OR 4.04 (95% CI 1.47 to 11.13)), and failure to prescribe inhaled steroids on discharge (OR 3.45 (95% CI 1.35 to 9.10)). Deaths from chronic obstructive pulmonary disease (COPD) were associated with lower peak expiratory flow rates (OR 2.56 (95% CI 1.52 to 4.35) for each 50 l/min change), a history of smoking (OR 5.03 (95% CI 1.17 to 21.58)), prescription of ipratropium bromide (OR 7.75 (95% CI 2.21 to 27.14)), and failure to prescribe inhaled steroids on discharge (OR 3.33 (95% CI 0.95 to 11.10)). Cardiovascular deaths were more common among those prescribed ipratropium bromide on discharge (OR 3.55 (95% CI 1.05 to 11.94)) and less likely in those admitted after an upper respiratory tract infection (OR 0.21 (95% CI 0.05 to 0.95)). Treatment with ipratropium bromide at discharge was associated with an increased risk of death from asthma even after adjusting for peak flow, COPD and cardiovascular co-morbidity, ever having smoked, and age at onset of asthma.**

***Conclusions*—Prescription of inhaled steroids on discharge is important even for those patients with co-existent COPD and asthma. Treatment with ipratropium at discharge is associated with increased risk of death from asthma even after adjustment for a range of markers of COPD. These results need to be tested in larger studies.**

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There is growing evidence from recent community based studies that asthmatic subjects, particularly those who also have chronic obstructive pulmonary disease (COPD), have an increased risk of death from causes other than asthma.[1 2] Similar findings have been reported from a clinic based study.[3] In particular, these studies record an excess risk of death from other lung diseases[1 3] and from cardiovascular disease.[2 3] We have previously reported that patients who have had a hospital admission for treatment of asthma have a six fold increased risk of death from other lung diseases and from cardiovascular disease compared with the general population.[4] This raises the question of whether this excess risk is related to the severity of asthma, its treatment, or associated co-morbidity. It would be helpful for clinicians to identify patients who are at high risk of death from these causes before discharge and to know whether drugs prescribed on discharge may affect outcome from any cause.

There has only been one study of hospitalised asthmatic subjects which has examined all cause mortality[5] and this study did not report risk factors by type of death. We therefore report the results of a study of risk factors for death from asthma, COPD, and cardiovascular disease after discharge from hospital following treatment for asthma.

Methods

SUBJECTS

Cases and controls were identified from a cohort of all discharges with a primary diagnosis of asthma (ICD 9 493) from hospitals within the South East Thames Region in England. Details of the cohort have been described elsewhere.[6] Briefly, 2382 people aged 16–64 years at discharge who had at least one admission for asthma between 1 April 1989 and 30 September 1990 were included in the study. The first admission during this period was designated as the index admission. Follow up information was available on 2242 cases (94%).

IDENTIFICATION OF THE DEATHS

Vital status was ascertained by the National Health Services Central Register (NHSCR) up to 3 March 1992, the hospital patient administration systems, and the yearly regional computerised records of deaths of residents. The mean follow up period was two years and three

months (range 18 months to 3 years) during which time 92 deaths were identified. Seven deaths were excluded from further study, three because their index admission was not for treatment of asthma, one because he died before discharge, and three because age at discharge was more than 65 years. The cause of death was reviewed by an expert panel[6] whose consensus was used to categorise the deaths into four groups: (1) asthma; (2) COPD and other respiratory disorders (excluding lung cancer); (3) cardiovascular disease, and (4) other. These diagnoses were based on the clinical judgement of the experts.

IDENTIFICATION OF CONTROLS

Based on information from the NHSCR after half the cohort had been traced, we expected about 125 deaths. Due to timetabling of the study we needed to start collecting information about the control population. A sample size of 126 controls (63 aged <45 years and 63 aged ⩾45 years at discharge) were randomly selected from the cohort. Any control subjects who were later found to have died were replaced by the next control from the random selection. One hundred and twenty six controls would be able to detect an 18% difference between deaths and controls in any of the risk factors assuming a prevalence of 50% in the population (power 80% and significance 5%). Four control patients who were alive at follow up were excluded from further study (one patient aged <45 years who had not been admitted for treatment of asthma, another who was sampled twice due to different hospital numbers and a change of surname, and two patients in the older age group who were over 65 years at discharge).

Approval for the study was obtained from all the ethics committees in the Region and permission to photocopy notes was sought from consultants involved in the care of the patients and from the Family Health Service Authorities in the Region.

STUDY DESIGN

A research assistant was trained to identify relevant sections of the medical notes and, blind to the cause of death, photocopied the notes from the index admission for all deaths and controls. Data on the clinical history of asthma, symptoms on admission, physiological measures of asthma, co-morbidity, and hospital prescribed medication at discharge were abstracted by one of us (HG) from the photocopied notes. Another member of the department repeated the data abstraction on 20 sets of notes; minimal differences were found.

Clinically severe asthma

"Clinically severe asthma" was defined as any history of drowsiness as a result of asthma, loss of consciousness, respiratory arrest, mechanical ventilation, or admission to ITU for asthma treatment.

Co-morbidity

We scored co-morbid disease recorded in the past medical history at the index admission using the method described by Charlson *et al*.[7] Chronic pulmonary disease, including asthma, attracts a score of 1, but since this affected all members of the cohort we did not include it in the score. Co-morbidity from COPD was recorded as present if there was any mention in the records of the terms "chronic bronchitis", "COAD", "COPD", "emphysema", or "bronchiectasis".

Laboratory score

Sheiner *et al*[8] identified six laboratory variables (urea, aspartate transaminase, sodium, white blood cell count, haematocrit, bicarbonate) which improve the prediction of one year mortality in general medical admissions over co-morbidity alone. As a labscore of 2 was very common (91%), we used a cut off point of ⩾3 in the analyses.

All variables except urea require persistent abnormality, therefore a single abnormal result was scored as zero. Urea scored zero only if no test was carried out or there were at least two tests results of <4.4 mmol/l. A single recorded urea concentration of <4.2 mmol/l scored 1, concentrations of 4.2–6.5 scored 2, and increasing urea levels resulted in higher scores up to a concentration of >16.6 mmol/l which scored 6. Other variables scoring 1 were: AST ⩾43 U/l; sodium ⩽134 mmol/l; lowest white blood cell count $\geqslant 11.9 \times 10^9$/l; highest haematocrit ⩽37%; highest bicarbonate ⩽23 mmol/l.

Peak flow

For consistency, all peak flow values recorded as zero were recoded as 60 l/min. Peak flow difference is the difference between the highest recorded peak flow and the lowest recorded peak flow at any time during the admission. Peak flow variation is this difference divided by the highest peak flow.

Chest pain

When abstracting data from the notes there appeared to be a significant number of patients whose presenting symptom was not shortness of breath alone. Several patients were recorded as having significant chest pain at presentation. This was unexpected and was therefore added to the data collection schedule. Chest pain was recorded as present where pain of any type was noted in the presenting symptoms. Unfortunately few details were recorded about the chest pain, and therefore this variable represents chest pain which could be continuous or pleuritic.

ANALYSIS OF DATA

Logistic regression, adjusting for age and sex, was used to examine the effect of each variable individually on all cause mortality. Age was adjusted for in three categories (16–44, 45–54, and 55–64) and therefore does not assume a linear relation between age and other factors in the model. Due to missing values and the large number of variables, only those which were significant at the 10% level for individual

Table 1 Clinical history of asthma and symptoms at index admission. Number of notes in which the variable was recorded (n) and % of these where the variable was present (all associations shown if p<0.20)

	Deaths from all causes		*Controls*		
	n	*% variable present*	*n*	*% variable present*	*Adjusted[1] odds ratio (95% CI)*
Chest pain	76	25	102	9	4.15 (1.50 to 11.45)[2]
Chest tightness	76	13	102	26	0.42 (0.18 to 1.01)
Onset preceded by upper respiratory tract infection	39	38	78	63	0.43 (0.18 to 1.00)
Clinically severe asthma	77	18	102	6	3.11 (1.07 to 9.06)
Length of stay (days)	74		92		1.14 (1.04 to 1.26)[3]
Median length of stay		4.5		3.0	
Interquartile range		2–7		1–4.5	
Highest peak flow (l/min)	65		97		0.78 (0.64 to 0.94)[4]
Mean (SD)		300 (116)		364 (100)	
Difference between highest and lowest peak flow (l/min)	65		96		0.89 (0.75 to 1.06)[4]
Mean (SD)		180 (111)		220 (110)	
P_{CO_2} >6.1 kPa	54	31	54	9	3.84 (1.17 to 12.57)[5]
COPD co–morbidity	70	33	100	7	3.67 (1.39 to 9.69)
Coronary heart disease co-morbidity (ICD9 410-414)	74	11	95	2	3.47 (0.68 to 17.82)
Cardiovascular disorder co-morbidity (ICD 9 359-459)	74	28	95	9	2.36 (0.94 to 5.94)
Cardiovascular medication[6]	76	29	96	9	2.15 (0.86 to 5.36)
Labscore >3	70	36	96	10	2.93 (1.22 to 7.03)
Antibiotics on discharge	76	25	96	36	0.60 (0.29 to 1.24)
Ever smoker	73	68	102	49	2.21 (1.13 to 4.34)
Salbutamol or terbutaline	79	81	102	89	0.66 (0.27 to 1.65)
Fenoterol or Duovent[7]	79	39	102	13	2.19 (0.68 to 7.05)
Ipratropium or Duovent	79	52	102	18	3.75 (1.84 to 7.63)
Ipratropium	79	38	102	13	3.49 (1.59 to 7.62)
Any drug by nebuliser	75	33	96	16	2.49 (1.14 to 5.46)
Inhaled steroids not prescribed	76	38	97	22	2.44 (1.17 to 5.00)
Inhaled steroid dose increased on discharge	70	29	88	41	0.61 (0.30 to 1.26)
Number of asthma drugs	79		102		
≤3		44		55	1.0
4		37		35	1.21 (0.60 to 2.43)
>4		19		10	1.72 (0.65 to 4.53)

[1]Adjusted for age and sex.
[2]Adjusted for cardiovascular medication, systolic blood pressure and age and sex.
[3]Per additional day.
[4]Per 50 l/min increase in peak flow.
[5]P_{CO_2} >6.1 compared with P_{CO_2} ≤6.1 and blood gases not done.
[6]British National Formulary Chapter 2.0 drugs.
[7]Compound inhaler which contains fenoterol 90 µg, ipratropium bromide 36 µg/metered inhalation.

Table 2 Risk factors for death from any cause after hospital admission for asthma (results of a multivariable model[1], n = 156)

Variables remaining in the model	*Odds ratio[1]*	*95% CI*
Onset preceded by upper respiratory tract infection		
No URTI	1.00	
Not known	1.82	0.71 to 4.65
URTI	0.30*	0.10 to 0.89
Highest peak flow (change per 50 l/min decrease)	1.22	0.97 to 1.52
P_{CO_2}		
Not done or ≤6.1	1.00	
>6.1	7.99**	1.93 to 33.01
Ipratropium or Duovent		
Not prescribed	1.00	
Prescribed	2.90*	1.20 to 7.00
Inhaled steroids		
Prescribed	1.00	
Not prescribed	3.03*	1.15 to 8.33

*p<0.05; **p<0.001.
[1]The following variables were entered into the model: age, sex, labscore >3, chest tightness, length of stay, highest peak flow (as a continuous variable), clinically severe asthma, COPD co-morbidity, attack preceded by upper respiratory tract infection (URTI, not known, yes and no), nebuliser, ever smoked, chest pain, history of cardiovascular disorder, P_{CO_2} not done or ≤6.1 vs >6.1, ipratropium or Duovent, inhaled steroids.

variable analysis and the highest peak flow were included in the multivariable model. Backwards stepwise elimination logistic regression was used to identify the most important variables associated with death. In repeating this analysis for individual causes of death only those variables significant at the 5% level were included.

Results

ALL CAUSE MORTALITY

The mean age at discharge of those who died was 52 years and 51% were men. The mean age of the controls at discharge was 41 years and 35% were men. Table 1 shows the risk factors where the age and sex adjusted odds ratio was significant at the 20% level.

Nearly all the deaths and controls had wheeze (92% and 93%, respectively) and a greater than 20% variation in peak flow during their admission (98% and 94%, respectively). Too few patients had records of peak flow or diurnal peak flow before and after the use of a bronchodilator to assess diurnal variability.

Failure to prescribe inhaled steroids at discharge remained significantly associated with an increased risk of death from any cause in a multivariable model adjusting for age, sex, severity of attack (length of stay, highest peak flow, clinically severe asthma, COPD co-morbidity, ever smoked, Pa_{CO_2}), and co-morbidity (table 2). There was no record in the notes of intention to prescribe inhaled steroids when the course of oral steroids came to an end in all 46 patients who did not receive inhaled steroids at discharge.

An increased risk of death was associated with prescription of ipratropium (table 3). This association remained significant when those taking Duovent (ipratropium with fenoterol) were excluded. Ipratropium prescriptions in the control group were associated with older age, cough, sputum, chest pain, chest tightness, recorded co-morbidity of COPD, and prescription of theophylline or aminophylline. The increased risk of death in those prescribed ipratropium remained significant after adjusting for the number of categories of asthma drug prescribed. The association was altered very

Table 3 Individual associations (adjusted for age and sex) for risk factors for death from asthma, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVS)

	Asthma deaths vs controls			*COPD death vs controls*			*CVS deaths vs controls*		
Risk factor	*%*[1]	*OR*[2]	*95% CI*	*%*[1]	*OR*[2]	*95% CI*	*%*[1]	*OR*[2]	*95% CI*
Clinically severe asthma	29	6.29*	1.84 to 21.52	16	1.64	0.32 to 8.37	10	1.03	0.16 to 6.52
Chest pain	22	3.78*	1.06 to 13.50	21	4.92	0.85 to 28.43	15	4.99	0.91 to 27.48
Onset preceded by URTI	42	0.55	0.15 to 2.04	56	1.06	0.22 to 5.11	25	0.21*	0.05 to 0.95
Mean (SD) highest peak flow per 50 l/min decrease	326 (109)	1.25	0.96 to 1.62	213 (82)	2.56**	1.52 to 4.35	340 (136)	0.92	0.66 to 1.28
P_{CO_2} >6.1 kPa	40	2.75	0.66 to 11.39	44	5.63*	0.99 to 32.00	27	2.27	0.40 to 12.82
COPD co-morbidity	24	3.55	0.88 to 14.28	67	11.70*	2.37 to 57.70	17	0.94	0.20 to 4.51
Labscore ≥3	37	4.12*	1.36 to 12.49	33	1.79	0.47 to 6.74	47	2.94	0.78 to 11.10
Ever smoked	59	1.34	0.54 to 3.30	84	5.03*	1.17 to 21.58	56	1.23	0.41 to 3.70
Ipratropium or Duovent	54	4.56*	1.73 to 11.99	60	5.36*	1.65 to 17.43	57	5.43*	1.79 to 16.41
Ipratropium only	41	4.04*	1.47 to 11.13	55	7.75*	2.21 to 27.14	33	3.55*	1.05 to 11.94
Any drug by nebuliser	44	4.59	1.71 to 12.36	47	3.98*	1.16 to 13.61	10	0.53	0.10 to 2.81
Inhaled steroids not prescribed	46	3.45*	1.35 to 9.10	37	3.33	0.95 to 11.10	80	0.85	0.22 to 3.33

*p<0.05; **p<0.001.
[1]% represents number of death group with the risk factor divided by the number for whom the risk factor is recorded × 100.
[2]Adjusted for age and sex.

little and remained significant for asthma deaths when adjusted for markers of COPD and severity (table 4). The association with COPD deaths remained significant after adjustment for peak flow, COPD co-morbidity, a history of ever having smoked, and a history of past coronary heart disease. The association became non-significant after adjustment for age at onset of asthma. Age at onset was poorly recorded in 41 out of 123 (33%) COPD deaths and controls and could account for this finding. The association with deaths from cardiovascular disease became non-significant after adjustment for highest peak flow, having ever smoked, age of onset, and history of coronary heart disease (table 4). Ipratropium was not more readily prescribed to patients with a history of heart disease as all patients who were prescribed ipratropium were also prescribed a β agonist.

DEATH BY CAUSE

There were 29 deaths from asthma, 10 of whom (34%) were aged ≤45 years, and 21 from COPD, of whom two were aged <45 years. Most of the deaths in this category were from COPD or COAD,[17] two patients died from mixed COPD and ischaemic heart disease, one from cystic fibrosis (co-existent asthma clinically diagnosed), and one from cor pulmonale. There were 21 deaths from cardiovascular causes, two of whom were aged <45 years. Ten of the cardiovascular deaths were due to myocardial infarction (5), ischaemic heart disease (4), or congestive cardiac failure (1), and a further three were principally cardiac causes of death (one vegetation on the valve, one cardiomyopathy, and one Churg Strauss syndrome). The remaining eight deaths were vascular (one deep vein thrombosis, two pulmonary embolism, two cerebrovascular accidents, two aortic aneurysms, and one multiple arterial thrombosis). In 14 cases, four of which were aged <45 years, deaths were from other causes including lung cancer (4), other cancers (3), accident/poisoning/drugs (4), epilepsy (2), and one not known.

FACTORS ASSOCIATED WITH DEATHS FROM ASTHMA

Only deaths from asthma were associated with a history of "clinically severe asthma", chest pain, and a poor laboratory score (table 3). Nine of the 20 cases with a history of clinically severe asthma were given an outpatient appointment within two weeks of discharge, but three patients were given no appointment.

Of the six patients who had died from asthma in whom chest pain had been recorded at the index admission, three described severe pleuritic chest pain and these patients had abnormal chest radiographs (one consolidation of right lower lobe, one showed heart failure, and one with breast cancer had lymphangitis). Three patients described dull severe chest pain. Only two had undergone electrocardiography (ECG), both of which were normal, and in one case cardiac enzymes were measured and were normal. Only one of the patients with dull severe chest pain had a radiograph taken; this showed "shadowing" and no other details were available.

Ten of the 27 patients (37%) who died from asthma had labscores of ≥3. Of these, eight had a raised urea level of >6.5 mmol/l and seven had a white cell count of $>11 \times 10^6$/l.

Table 4 Relationship between death from asthma, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVS) and ipratropium prescribed on discharge. Effect of adjustment for markers of fixed lung disease

	Asthma deaths vs controls		*COPD deaths vs controls*		*CVS deaths vs controls*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Ipratropium prescribed	4.04	1.47 to 11.13	7.75	2.21 to 27.10	3.55	1.05 to 11.90
Adjusted for highest peak flow	3.53	1.21 to 10.33	21.55	2.38 to 195.37	2.97	0.71 to 12.38
Adjusted for COPD co-morbidity	3.57	1.17 to 10.92	7.80	1.90 to 31.93	3.73	1.01 to 13.82
Adjusted for both peak flow and COPD	3.64	1.12 to 11.78	21.54	1.92 to 242.28	2.72	0.50 to 10.24
Adjusted for ever smoked	3.57	1.26 to 10.08	5.71	1.50 to 21.74	2.68	0.73 to 9.91
Adjusted for age at onset (categorical ≤18, 19–40, >40)	4.25	1.19 to 15.16	3.89	0.74 to 20.43	4.04	0.91 to 17.90
Adjusted for past history of coronary heart disease	4.96	1.72 to 14.29	8.42	2.16 to 32.79	3.82	0.87–16.82

All adjusted for age (as a categorical variable) and sex.

FACTORS ASSOCIATED WITH DEATHS FROM ASTHMA, COPD AND OTHER RESPIRATORY DISORDERS

Similar drugs were related to deaths from asthma and COPD (ipratropium with and without fenoterol, any drug by nebuliser, and lack of inhaled steroids; table 3). Prescription of inhaled steroids was associated with a 70% reduced risk of death from both asthma ($p<0.009$) and COPD ($p<0.06$).

FACTORS ASSOCIATED WITH DEATHS FROM ASTHMA, COPD, AND OTHER RESPIRATORY DISORDERS AND DEATHS FROM CARDIOVASCULAR DISEASE

Deaths from cardiovascular causes only shared one risk factor with deaths from any other cause—namely, prescription of ipratropium (either alone or with fenoterol in Duovent). More patients who died from cardiovascular causes were prescribed theophylline and aminophylline (73%, 14/19) than controls (55%, 53/97), but this was not significant when adjusted for age and sex (OR 1.35 (95% CI 0.45 to 3.98)).

DEATH FROM OTHER CAUSES

The only significant risk factor for death from other causes was a history of having ever smoked (OR 10.97 (95% CI 1.24 to 97.1)).

Discussion

The findings from this study confirm known risk factors for death from asthma such as the failure to prescribe inhaled steroids on discharge.[9 10] In our study this association was also significant for death from any cause and was significant after adjusting for age, sex, severity of attack, and co-morbidity. It was not possible from the notes to ascertain why some patients were not prescribed inhaled steroids at discharge. Only two patients refused steroids and two patients discharged themselves; none of these patients died.

There is sufficient evidence to show that most of the cohort had clinically recognisable asthma at the time of the index admission, though there was evidence of concomitant COPD in 7% of the controls and in 33% of those who died. This finding is compatible with other reports in the literature,[11] including reports of young people dying of asthma. For example, Bullen[12] reported emphysema at necroscopic examination in the majority of young people who died from status asthmaticus. Our expert group decided on cause of death on the basis of a clinical judgement about how they would have certified the death rather than on whether the patient had asthma at the index admission.

Failure to receive inhaled steroids at discharge was also associated with an increased risk of subsequent death from COPD. It has been hypothesised that, since survival in COPD correlates inversely with FEV_1, treatment which improves lung function would be expected to reduce mortality.[13] Two studies have shown that inhaled steroids can improve lung function in patients with COPD. Weiner *et al*[14] have shown that 75% of those patients with COPD who respond to β agonists also show significantly greater improvement (>20% in FEV_1) in response to inhaled steroids compared with placebo. Paggiaro *et al*[15] have recently shown significant improvements in lung function in response to six months of treatment with inhaled steroids in a group of patients with bronchodilator reversibility of less than 15%. Greater improvement was found in patients with COPD of more than 10 years duration. The authors suggest that this indicates a greater likelihood of asthma in the past. Bourbeau *et al*,[16] in a study of patients with COPD who had shown no improvement with high dose steroids over a two week period, found that this subgroup also did not improve after six months of treatment with an inhaled steroid. Our finding of a decreased risk of death in those prescribed inhaled steroids at discharge who have a history of asthma but who have concomitant COPD is consistent with these findings, and also with the conclusion by Paggiaro *et al*[15] that patients with COPD with "a long history of symptoms or any features consistent with asthma are more likely to respond to treatment with inhaled steroids". These findings together suggest that important reductions in mortality could be made if steroid inhalers were more readily prescribed to people with mixed asthma/COPD.

Use of inhaled steroids can reduce the need for oral steroids[17] and therefore all patients with asthma or a mixed picture of COPD/asthma discharged on oral steroids should also be prescribed inhaled steroids. However, we found that 13 of 46 (28%) of those not receiving inhaled steroids were given prescriptions for maintenance oral steroids.

Deaths from asthma, COPD, and cardiovascular disease were all associated with prescription of ipratropium. We were surprised by this association, particularly as ipratropium has a good safety record.[18 19] Control patients prescribed ipratropium were more likely to have COPD co-morbidity, for which it is indicated. Since poor pulmonary function predicts cardiovascular deaths,[20] and COPD is a strong competing cause of death from cardiovascular disease[21] and asthma,[22] these associations could be due to confounding with COPD co-morbidity at admission. Adjustment for highest peak flow reduced the association between ipratropium and both cardiovascular and asthma mortality and rendered the latter non-significant. A similar adjustment in the model for COPD mortality increased the association. This occurs when the confounding variable operates negatively with the outcome and positively with the risk factor (or vice versa). In this case COPD and peak flow are negatively associated with death from COPD and positively associated with ipratropium prescription.

There are two possible explanations for the association between deaths from asthma and COPD and the prescription of ipratropium: (1) the drying effect that ipratropium has on lung secretions which might lead to difficulty in expectoration and mucus plugging; and (2) the development of tachycardia, though higher

doses than are usually given are needed to produce this and there is poor absorption across the lung parenchyma. There were seven post mortem reports available on patients who had died from asthma or COPD who had received ipratropium on discharge. All described the airways as plugged and five specifically reported widespread airways plugging. In comparison, only five of eight post mortem reports of asthma or COPD deaths in patients who had not received ipratropium reported mucus plugging and two of these reported extensive plugging.

There may be alternative explanations for the association between ipratropium and death from asthma, COPD, or cardiovascular disease. The measures of COPD may have been inadequate to control for confounding from this source and ipratropium may simply be a marker of the severity of COPD in all these deaths. It is of note that no association was found between ipratropium and deaths from other causes (OR 1.77 (95% CI 0.33 to 9.56)),

Regular follow up of patients with asthma has been shown to reduce hospital admissions.[23] Of the 20 patients with clinically severe asthma nine (45%) were given outpatient appointments within two weeks of discharge but a worrying 15% (3/20) had no record of follow up arrangements.

Laboratory scores of three or more identified a high risk group for death from asthma. Most of these patients were dehydrated and had high white blood cell counts. Weiss *et al*[24] have shown that peripheral blood leucocyte counts predict total mortality independently from cigarette smoking and FEV_1, though the confounding effect of leucocytosis as a result of inhaled or oral steroid treatment[25] was not explored. In our study 85% of patients who died and 86% of patients alive at follow up were treated with oral steroids. It was therefore not possible to explore whether leucocytosis occurred in the absence of inducement by steroids.

We expected co-morbidity to be an important factor for death in this group of hospitalised asthmatic patients but found no association with the Charlson co-morbidity index. Incalzi *et al*[26] in a study of patients admitted to hospital for treatment of COPD also found the index lacked predictive ability. His study found that more specific measures of co-morbidity such as electrocardiographic signs of right ventricular hypertrophy or overload and ischaemic heart disease predicted death. It could be that our study has underestimated the extent of cardiac co-morbidity. However, our study group was on average at least 15 years younger than those in Incalzi's study, few (n = 15) had electrocardiographs filed in the notes, and most of these (n = 9) were normal.

The association found between chest pain and death from asthma, COPD, and cardiovascular disease was interesting but the numbers involved were too small to explore this finding in greater depth. The reasons for the association between upper respiratory tract infections and protection from deaths from cardiovascular disease were also unclear.

One of the strengths of this relatively small study is that we have been able to gather large amounts of clinical data to explore risk factors for death from various causes. This does, however, mean that the ratio of information gathered to the number of cases is high and therefore the results should be regarded as preliminary and should be tested in a larger study.

For efficiency we needed to match on age but decided to match loosely by two broad age groups (<45 years and ⩾45 years) to avoid over-matching and masking potentially important associations which may be confounded by age.[27] All analyses were adjusted for age as a categorical variable to avoid assuming a linear relation between variables and age.

Ideally, peak flow should be adjusted for height as well as age and sex. We found very few recordings of height in the notes and therefore were unable to adjust for this. All analyses involving peak flow measurements were adjusted for age and sex, but some bias may be present as a result of not being able to adjust for height as well.

This study has shown the importance of prescription of inhaled steroids on discharge in a UK population of hospitalised asthmatic patients and has identified that even those patients with co-existent COPD in addition to asthma are likely to benefit. It has also shown that few risk factors are shared between causes of death following hospital admission for asthma and, since this group of patients is at high risk of death from COPD and cardiovascular disease, they require as much attention to co-morbidity as to their asthma. Prescription of ipratropium at discharge was associated with increased risk of death from asthma even after adjustment for several measures of COPD. This association should be tested further in larger studies.

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