Cite this article as: BMJ, doi:10.1136/bmj.38316.729907.8F (published 23 December 2004)

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Bronchodilator treatment and deaths from asthma: case-control study

H Ross Anderson, Jon G Ayres, Patricia M Sturdy, J Martin Bland, Barbara K Butland, Clare Peckitt, Jennifer C Taylor, Christina R Victor for the Mortality and Severe Morbidity Group of the National Asthma Task Force

Abstract

Objective To investigate the association between bronchodilator treatment and death from asthma.
Design Case-control study.
Setting 33 health authorities or health boards in Great Britain.
Participants 532 patients under age 65 who died from asthma and 532 controls with a hospital admission for asthma matched for period, age, and area.
Main outcome measures Odds ratios for deaths from asthma associated with prescription of bronchodilators and other treatment, with sensitivity analyses adjusting for age at onset, previous hospital admissions, associated chronic obstructive lung disease, and number of other drug categories.
Results After full adjustment, there were no significant associations with drugs prescribed in the 4-12 months before the index date. For prescriptions in the 1-5 years before, mortality was positively associated with inhaled short acting β_2 agonists (odds ratio 2.05, 95% confidence interval 1.26 to 3.33) and inversely associated with antibiotics (0.59, 0.39 to 0.89). The former association seemed to be confined to those aged 45-64, and the association with antibiotics was more pronounced in those under 45. Significant age interactions across all periods suggested inverse associations with oral steroids confined to the under 45 age group. An inverse association with long acting β_2 agonists and a positive association with methylxanthines in the 1-5 year period were non-significant.
Conclusion There was no evidence of adverse effects on mortality with medium to long term use of inhaled long acting β_2 agonist drugs. The association with short acting β_2 agonists has several explanations, only one of which may be a direct adverse effect.

Introduction

The possibility that drugs for asthma might have adverse effects became an important issue in the mid-1960s, when several countries, including the United Kingdom, experienced a rise and fall in deaths from asthma that corresponded to the introduction and subsequent withdrawal of a non-selective β agonist drug (isoprenaline) in a high concentration formulation.[1 2] In New Zealand in the 1970s an increase in deaths from asthma corresponded with an increase in prescriptions of the β_2 agonist fenoterol, and several case-control studies[3] and one cohort study[4] found that fenoterol was associated with an increased risk of death from asthma. Other factors, however, such as changing patterns in the use of steroids, may have played a part.

Concern remains about the possible adverse effects of drug therapy. Short acting β_2 agonists have been associated with rebound hyperresponsiveness,[5] worsening of severity,[6 7] and increased risk of death.[4 8] A randomised controlled trial of short acting β_2 agonists, however, did not show a clinically adverse effect.[9] Adverse associations have also been reported for ipratropium[10] and theophylline.[11] Available evidence suggests that the more recently introduced long acting β_2 agonists do not increase the risk of death,[12] while the use of inhaled steroids is associated with a reduction in mortality.[8 13] We investigated the role of long to medium term drug treatment for asthma in causing or preventing death from asthma in a large population based case-control study.

Methods

Details of the methods have been published elsewhere.[14] The study areas covered 33 health authorities or health boards in Great Britain (27% of the population). For the years 1994 to 1998, we obtained from the relevant registries listings of all deaths in which asthma (code 493, international classification of diseases, ninth revision) was mentioned in part I of the death certificate. To be included in this study patients had to be aged under 65 at the time of death, part I of the death certificate had to mention asthma, and there had to be no more credible non-respiratory underlying cause of death, such as cancer. We obtained primary care records from the relevant health authority. To select controls, we identified the hospital in which each death occurred or, if the patient died in the community, the hospital to which he or she would probably have been admitted. We obtained from each hospital a list of patients with a discharge diagnosis of asthma (code 493) and selected one control per case, matched firstly for admission date and then for age.

We used removable opaque tape to anonymise the primary care records. We then photocopied the entire record for the five years before the index date, together with computerised records, hospital discharge letters, and hospital outpatient letters. Extraction of drug data was carried out in the academic department by researchers blind to the status of the subject. Data were collected for the periods 0-3 months, 4-12 months, and 1-5 years before the index date. Information on dose was not extracted. We supplemented some data, including age at onset of asthma and presence of chronic obstructive pulmonary disease, with information extracted non-blind from practice records for the period earlier than 5 years before the index date. The details of previous hospital admissions were validated against hospital records, which could not be done totally blind.

Table 1 Clinical features of people who died from asthma (cases) and matched controls†

	Total		Age 0-44 years		Age 45-64 years	
	Cases (n=532)	Controls (n=532)	Cases (n=165)	Controls (n=167)	Cases (n=367)	Controls (n=365)
No (%) by age (years):						
0-14	20 (4)	21 (4)	20 (12)	21 (13)	—	—
15-24	33 (6)	31 (6)	33 (20)	31 (19)	—	—
25-34	40 (8)	44 (8)	40 (24)	44 (26)	—	—
35-44	72 (14)	71 (13)	72 (44)	71 (43)	—	—
45-54	128 (24)	131 (25)	—	—	128 (35)	131 (36)
55-64	239 (45)	234 (44)	—	—	239 (65)	234 (64)
Median (IQR) age (years)	53 (40-59)	53 (40-59)	—	—	—	—
Males (%)	39.8	36.5	44.8	34.7	37.6	37.3
Median (IQR) age at onset (years)	30 (10-47)*	33 (13-49)	10 (4-22)	13 (5-27)	42 (24-51)	44 (30-52)
COPD (%)	42.3**	34.6	7.3	10.8	58.0**	45.5
Episodic asthma in past year (%)	81.7*	86.9	77.3	85.7	83.6	87.5
Recorded atopic disease (%)	39.5	41.4	55.8	56.9	32.2	34.2
Family history of asthma (%)	25.2	24.2	33.9	35.3	21.3	19.2
Obesity (%)	30.6*	25.0	20.0	15.6	35.4	29.3
Mean No of GP contacts in past year	9.8 (8.8)**	11.1 (8.6)	7.9 (7.8)**	10.9 (8.9)	10.7 (9.2)	11.3 (8.6)
Outpatient appointments for respiratory illness in past year (%)	35.3	38.0	29.7	30.5	37.9	41.4
Admission for asthma in past year (%)	35.2	35.0	29.7	34.1	37.6	35.3
Admission for asthma in past 1-5 years (%)	41.2	43.0	40.0	43.7	41.7	42.7

IQR=interquartile range; COPD=chronic obstructive pulmonary disease.
†Denominators for age at onset, episodic asthma in past year and mean number of GP contacts vary due to missing data.
*P<0.05, **P<0.01.

After our analysis we discovered that a proportion of controls had accidentally been coded for recorded drugs that related to the index admission or beyond. Because this might be a cause of bias, but also because treatment in the weeks before the index date may be a short term response to the deteriorating state of the patient, the results for the 0-3 months period, while presented, are not emphasised in the interpretation of the results.

We used conditional logistic modelling to investigate statistical interactions and independent effects, with significance tests based on differences in log likelihood. Where there was a significant association in the all ages analysis, we tested for age interactions (<45 *v* 45-64 age group). In controlling for severity we used age at onset of asthma, presence of chronic obstructive pulmonary disease (mention of chronic bronchitis, emphysema, or chronic obstructive airways/pulmonary disease), previous hospital admissions for asthma, and the number of other categories of drug prescribed. Following a study design used by others which further stratifies by severity,[15] we also analysed a subgroup of 122 deaths in patients admitted in the year before the index date, matched with controls who had also had an admission in the previous year.

Results

We identified 681 deaths from asthma that met our criteria, of which 149 (22%) were excluded from the final analysis for reasons that are detailed elsewhere[15] but mostly because of incomplete or missing records (82) or miscoded diagnosis (33). Of the 532 deaths included in the final sample, 236 (44%) occurred in hospital. Table 1 shows the clinical characteristics of cases and controls. Those who died from asthma (cases) were more likely to have an earlier age at onset, evidence of associated chronic obstructive disease, and mention of obesity.

Table 2 describes the associations between mortality and prescribed asthma drugs, adjusted for sex only. Table 3 compares these results with those from models controlling additionally for chronic obstructive pulmonary disease, previous hospital admissions, number of other drug categories recorded, and all of these together. The prescription of short acting β_2 agonist drugs in the 1-5 years before the index date was associated with an increased risk of asthma death. The odds ratio was 1.54 (95% confidence interval 1.06 to 2.24) rising to 2.05 (1.26 to 3.33) in the fully adjusted model. For the 1-5 year period, there was a significant age interaction with an odds ratio of 2.09 (1.31 to 3.36) in the 45-64 age group, compared with 0.80 (0.41 to 1.57) in the younger age group (table 4). There was no evidence of an association in the year before the index date (table 3). Fenoterol was infrequently prescribed and not significantly associated with risk of death (table 2).

Long acting β_2 agonist drugs (mostly salmeterol) were commonly prescribed (38% of controls in the 1-5 year period). There was no evidence of any positive association with death in any period, and the upper 95% confidence intervals exclude the possibility of any important adverse effect. In the full model adjusted for severity, the odds ratio for prescription in the 1-5 years before the index date fell from 0.90 (0.70 to 1.16) to 0.74 (0.55 to 1.01, $P=0.06$), suggesting, if anything, an inverse association with mortality (table 3).

Antimuscarinic drugs were prescribed alone or with a short acting β_2 agonist (usually fenoterol) in about 40% of controls in the 1-5 year period. The associations of all prescriptions (alone or combined) with death varied according to the prior period concerned. The only significant associations were in the 0-3 month period after adjustment for the number of other drug categories (1.45, 1.06 to 1.98) and in the 4-12 month period in the base model (1.29, 1.01 to 1.65).

There was no convincing evidence that inhaled corticosteroids were associated with mortality. Oral steroids showed a significant age interaction across all periods, suggesting an inverse association with death from asthma confined to those aged under 45. The odds ratios for methylxanthines were not

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Table 2 Odds ratios (95% confidence intervals) for death associated with prescriptions of drugs† in 3 months, 4-12 months, and 1-5 years before index date (n=532 matched pairs)

	Past 3 months		Past 4-12 months		Past 1-5 years	
Drug	Control (%)‡	OR§ (95% CI)	Control (%)‡	OR§ (95% CI)	Control (%)‡	OR§ (95% CI)
β adrenoceptor:						
Inhaled:	69.0	0.97 (0.75 to 1.25)	74.4	1.12 (0.85 to 1.48)	86.1	1.52* (1.04 to 2.22)
Short acting	66.5	1.03 (0.80 to 1.32)	72.6	1.12 (0.85 to 1.47)	85.7	1.54* (1.06 to 2.24)
(Fenoterol)	0.2	2.00 (0.18 to 22.1)	0.4	1.00 (0.14 to 7.10)	0.8	1.23 (0.33 to 4.59)
Long acting	21.8	0.94 (0.70 to 1.27)	29.9	1.01 (0.77 to 1.32)	38.3	0.90 (0.70 to 1.16)
(Salmeterol)	21.2	0.95 (0.70 to 1.29)	29.9	0.99 (0.76 to 1.30)	38.3	0.90 (0.70 to 1.16)
Oral	5.3	0.88 (0.51 to 1.53)	5.5	0.79 (0.45 to 1.37)	13.7	0.96 (0.66 to 1.38)
All routes¶	69.7	0.96 (0.74 to 1.24)	74.6	1.13 (0.85 to 1.49)	86.5	1.53* (1.05 to 2.23)
Antimuscarinic	24.4	1.23 (0.93 to 1.62)	31.0	1.23 (0.95 to 1.58)	41.2	1.03 (0.81 to 1.33)
β adrenoceptor and antimuscarinic	5.6	1.16 (0.70 to 1.90)	6.2	1.28 (0.79 to 2.06)	7.1	0.87 (0.54 to 1.42)
All fenoterol	2.8	1.05 (0.52 to 2.13)	2.8	1.17 (0.59 to 2.33)	4.9	1.10 (0.65 to 1.87)
All antimuscarinic	27.6	1.27 (0.97 to 1.67)	32.7	1.29* (1.01 to 1.65)	43.2	1.06 (0.83 to 1.36)
Corticosteroids:						
Inhaled	59.6	0.85 (0.66 to 1.08)	67.9	1.08 (0.83 to 1.40)	83.1	1.04 (0.76 to 1.44)
Oral	58.5	0.75* (0.59 to 0.96)	59.2	1.00 (0.78 to 1.28)	72.0	1.02 (0.78 to 1.32)
Injected	3.0	0.41 (0.16 to 1.06)	3.0	0.88 (0.43 to 1.81)	8.1	0.92 (0.57 to 1.47)
All routes	75.8	0.72* (0.55 to 0.95)	75.6	1.20 (0.90 to 1.59)	86.5	1.09 (0.76 to 1.54)
Cromoglycates	2.3	0.75 (0.30 to 1.86)	4.1	0.73 (0.38 to 1.39)	10.5	0.93 (0.60 to 1.42)
Methylxanthines	22.2	1.24 (0.92 to 1.67)	26.1	1.15 (0.86 to 1.54)	42.1	1.28 (0.99 to 1.65)
All antibiotics	53.9	0.75* (0.58 to 0.96)	69.9	0.85 (0.65 to 1.11)	90.4	0.67* (0.46 to 0.97)

† As recorded in GP notes, computer printouts, and hospital discharge and outpatient letters.
‡ Proportion of those in control group exposed to each group.
§Adjusted for sex.
¶Oral and inhaled (not injected).
*P<0.05.

significantly greater than 1.0. Further, the overall odds ratio decreased in size after additional adjustment for coronary obstructive pulmonary disease. We found an inverse association with antibiotics that was significant for the 0-3 month and 1-5 year periods. This seemed to be more pronounced in those aged under 45. There was no evidence of a difference between macrolides and other types of antibiotics (not shown). We found no evidence for an association with the number of different drugs prescribed. For cases and controls respectively, the median (interquartile range) was 3 (1-4.5) and 3 (1-4) for the 0-3 month period, 3 (2-5) and 3 (1-5) for the 4-12 months period, and 5 (3-7) and 5 (3-7) for the 1-5 year period. Table 5 shows the association with combinations of drugs. Excluding the 0-3 month period, we found a negative association with no prescriptions of asthma drugs and an increased risk associated with prescription of β_2 agonists only.

When we compared the subgroup of 122 cases and 122 matched controls with an admission in the past year, we found no significant associations in the fully adjusted model (table 6).

Discussion

Main findings

In this large case-control study we found no evidence associating long acting β_2 agonists with an increased risk of death in people with asthma. We did, however, find evidence of a positive association between death and the use of short acting β_2 agonists. The main strengths of our study were that it included all certified deaths from asthma in people aged under 65 in defined populations, comprehensively recorded primary care and hospital outpatient prescriptions in an unbiased manner, and had sufficient power to exclude a doubling in the risk of death from asthma associated with commonly prescribed drugs.

Comment on methods and study design

The case-control approach enabled us to study a large number of deaths from asthma. A cohort approach using the UK general practice research database would have been limited in power and less able to reliably identify controls with life threatening asthma.[8 12] An important but insoluble limitation of using hospital controls is that their asthma is unlikely to be as severe as in those who die. We made every effort to tighten control for severity by including chronic obstructive lung disease, age at onset, and previous hospital admissions in the model and by analysing a subgroup of deaths and controls with an admission in the past year. Nearly half of those who died had not been admitted for asthma in the previous five years, and 56% were not in hospital when they died. Deaths in the community probably differ in various ways from those in hospital, but to have restricted the study to those who died in hospital would have diminished the generalisability of the findings.

Misdiagnosis of asthma as a cause of death is common and increases with the age at death.[16] [17] We did not set out to establish systematically the immediate cause of death because records relating to the final event are usually absent or incomplete. In all of our cases, however, asthma was mentioned in part I of the death certificate (in 94% as the underlying cause) and there was evidence in the primary care record that was consistent with asthma in life (diagnosis or asthma treatment).

Though we could comprehensively ascertain which drugs were prescribed, limitations included a lack of information on dose, difficulty in distinguishing clearly between the prescription of oral steroids for a short course as opposed to long term use, and an inability to distinguish whether short acting bronchodilators were being used on a regular basis or as required.

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Table 3 Odds ratios (95% confidence intervals) for death associated with prescription of drugs in 3 months, 4-12 months, and 1-5 years before index date. Sensitivity to control for chronic obstructive pulmonary disease (COPD), hospital admissions, and number of other drug categories prescribed (n=532 matched pairs)

Drug type	Unadjusted†	Adjusted (COPD)‡	Adjusted (hospital admisssions)§	Adjusted (other drug categories)¶	Adjusted (all)
Past 3 months					
β adrenoceptor:					
Inhaled short acting	1.03 (0.80 to 1.32)	1.04 (0.80 to 1.34)	1.03 (0.79 to 1.33)	1.12 (0.82 to 1.54)	1.21 (0.88 to 1.67)
Inhaled long acting	0.94 (0.70 to 1.27)	0.93 (0.69 to 1.27)	0.92 (0.67 to 1.25)	0.95 (0.68 to 1.32)	0.97 (0.70 to 1.36)
Antimuscarinic	1.23 (0.93 to 1.62)	1.12 (0.84 to 1.51)	1.19 (0.87 to 1.61)	1.40* (1.01 to 1.93)	1.25 (0.88 to 1.76)
All antimuscarinic	1.27 (0.97 to 1.67)	1.15 (0.86 to 1.52)	1.22 (0.91 to 1.64)	1.45* (1.06 to 1.98)	1.29 (0.92 to 1.79)
Corticosteroids:					
Inhaled	0.85 (0.66 to 1.08)	0.82 (0.64 to 1.05)	0.84 (0.66 to 1.07)	0.78 (0.58 to 1.05)	0.80 (0.59 to 1.09)
Oral	0.75* (0.59 to 0.96)	0.67** (0.52 to 0.87)	0.69** (0.53 to 0.90)	0.63** (0.47 to 0.85)	0.58*** (0.43 to 0.78)
Methylxanthine (oral)	1.24 (0.92 to 1.67)	1.16 (0.85 to 1.58)	1.21 (0.89 to 1.66)	1.38 (1.00 to 1.93)	1.26 (0.90 to 1.77)
All antibiotics	0.75* (0.58 to 0.96)	0.67** (0.51 to 0.87)	0.71** (0.55 to 0.91)	0.70* (0.53 to 0.92)	0.65** (0.49 to 0.87)
Past 4-12 months					
β adrenoceptor:					
Inhaled short acting	1.12 (0.85 to 1.47)	1.13 (0.84 to 1.51)	1.14 (0.85 to 1.54)	1.10 (0.78 to 1.55)	1.14 (0.80 to 1.61)
Inhaled long acting	1.01 (0.77 to 1.32)	0.99 (0.75 to 1.30)	0.99 (0.75 to 1.31)	0.93 (0.68 to 1.25)	0.94 (0.69 to 1.27)
Antimuscarinic	1.23 (0.95 to 1.58)	1.09 (0.83 to 1.44)	1.19 (0.89 to 1.59)	1.24 (0.91 to 1.67)	1.07 (0.77 to 1.50)
All antimuscarinic	1.29* (1.01 to 1.65)	1.16 (0.88 to 1.52)	1.27 (0.96 to 1.68)	1.31 (0.99 to 1.75)	1.16 (0.85 to 1.60)
Corticosteroids:					
Inhaled	1.08 (0.83 to 1.40)	1.07 (0.81 to 1.41)	1.08 (0.81 to 1.43)	1.01 (0.73 to 1.41)	1.04 (0.74 to 1.45)
Oral	1.00 (0.78 to 1.28)	0.93 (0.71 to 1.21)	0.95 (0.72 to 1.25)	0.85 (0.62 to 1.16)	0.82 (0.59 to 1.13)
Methylxanthine (oral)	1.15 (0.86 to 1.54)	1.09 (0.81 to 1.47)	1.12 (0.82 to 1.52)	1.10 (0.80 to 1.53)	1.06 (0.76 to 1.48)
All antibiotics	0.85 (0.65 to 1.11)	0.79 (0.60 to 1.05)	0.83 (0.63 to 1.10)	0.77 (0.57 to 1.04)	0.75 (0.55 to 1.01)
Past 1-5 years					
β adrenoceptor:					
Inhaled short acting	1.54* (1.06 to 2.24)	1.66* (1.08 to 2.55)	1.75** (1.14 to 2.69)	1.97** (1.22 to 3.18)	2.05** (1.26 to 3.33)
Inhaled long acting	0.90 (0.70 to 1.16)	0.82 (0.63 to 1.08)	0.83 (0.63 to 1.10)	0.77 (0.57 to 1.03)	0.74 (0.55 to 1.01)
Antimuscarinic	1.03 (0.81 to 1.33)	0.90 (0.68 to 1.19)	0.97 (0.72 to 1.29)	0.96 (0.71 to 1.29)	0.83 (0.60 to 1.15)
All antimuscarinic	1.06 (0.83 to 1.36)	0.92 (0.70 to 1.21)	0.99 (0.75 to 1.32)	0.98 (0.73 to 1.32)	0.87 (0.63 to 1.19)
Corticosteroids:					
Inhaled	1.04 (0.76 to 1.44)	0.92 (0.63 to 1.34)	0.98 (0.67 to 1.43)	0.90 (0.57 to 1.41)	0.86 (0.55 to 1.36)
Oral	1.02 (0.78 to 1.32)	0.93 (0.69 to 1.25)	0.97 (0.72 to 1.31)	0.89 (0.63 to 1.27)	0.89 (0.63 to 1.26)
Methylxanthine (oral)	1.28 (0.99 to 1.65)	1.20 (0.91 to 1.57)	1.26 (0.95 to 1.66)	1.33 (0.98 to 1.81)	1.28 (0.94 to 1.75)
All antibiotics	0.67* (0.46 to 0.97)	0.63* (0.43 to 0.92)	0.65* (0.44 to 0.95)	0.59* (0.39 to 0.89)	0.59* (0.39 to 0.89)

†Adjusted for sex.
‡Adjusted for sex, age at asthma onset, and COPD (defined as mention of COPD, COAD, chronic bronchitis, or emphysema).
§Adjusted for sex, age at asthma onset, and hospital admission for asthma as two continuous variables, in past year and past 1-5 years.
¶Adjusted for sex, age at asthma onset, and other drug categories (No of other tabulated drug categories (excluding antibiotics) prescribed in relevant time period).
*P<0.05, **P<0.01, ***P<0.001.

Interpretation of results

In a case-control study like this, an increased risk of death associated with drug therapy may have various explanations[6][18][19][20]—for example, more severe disease or an increasing severity of the disease before death (confounding or effect modification by severity), or both; treatment for associ-

Table 4 Age interactions (odds ratios* (95% confidence intervals)) for the risk of death associated with prescriptions of drugs in 3 months, 4-12 months, and 1-5 years before index date (n=532 matched pairs)

	Past 3 months			Past 4-12 months			Past 1-5 years		
Age (years)	Control (%)†	OR (95% CI)	P value‡	Control (%)†	OR (95% CI)	P value‡	Control (%)†	OR (95% CI)	P value‡
Inhaled short acting β_2 agonists									
<45	72	0.66 (0.42 to 1.04)	0.02	72	0.96 (0.58 to 1.58)	0.48	89	0.80 (0.41 to 1.57)	0.02
45-64	64	1.27 (0.93 to 1.74)		73	1.19 (0.86 to 1.66)		84	2.09 (1.31 to 3.36)	
Inhaled corticosteroids									
<45	62	0.61 (0.40 to 0.94)	0.06	62	1.25 (0.80 to 1.96)	0.42	85	0.69 (0.39 to 1.23)	0.08
45-64	58	0.99 (0.74 to 1.34)		71	1.00 (0.72 to 1.38)		82	1.28 (0.86 to 1.91)	
Oral corticosteroids									
<45	59	0.30 (0.18 to 0.50)	<0.001	57	0.61 (0.37 to 1.01)	0.03	72	0.60 (0.37 to 0.98)	0.009
45-64	58	1.04 (0.78 to 1.38)		60	1.19 (0.89 to 1.59)		72	1.29 (0.93 to 1.78)	
Antibiotics									
<45	54	0.44 (0.27 to 0.71)	0.007	71	0.43 (0.26 to 0.72)	0.001	93	0.39 (0.19 to 0.82)	0.09
45-64	54	0.94 (0.70 to 1.26)		69	1.16 (0.84 to 1.61)		89	0.82 (0.53 to 1.28)	

*Adjusted for sex.
†Proportion of those in control group exposed to each group.
‡For interaction.

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Table 5 Odds ratios (95% confidence intervals) for death associated with different combinations of four main drug categories in 3 months, 4-12 months, and 1-5 years before index date (n=532 matched pairs). Adjusted for sex, COPD, age at onset, and hospital admissions in past year and in 4 years prior to that

	Past 3 months		Past 4-12 months		Past 1-5 years	
	Control (%)	OR (95% CI)	Control (%)	OR (95% CI)	Control (%)	OR (95% CI)
No asthma drugs	17.7	1.42* (1.04 to 1.93)	18.6	0.76 (0.53 to 1.08)	9.6	0.54* (0.32 to 0.91)
One category:						
β agonists† only	4.9	1.70* (1.00 to 2.90)	4.5	1.04 (0.55 to 1.94)	3.2	2.52** (1.28 to 4.98)
Steroids‡ only	9.6	0.57* (0.36 to 0.92)	4.3	1.07 (0.59 to 1.94)	2.4	0.72 (0.30 to 1.77)
Two categories:						
β agonists and steroids only	30.6	0.70* (0.53 to 0.94)	31.8	0.98 (0.75 to 1.28)	28.9	0.97 (0.71 to 1.33)
Three categories:						
β agonists, steroids, and antimuscarinics only	13.7	0.98 (0.68 to 1.40)	13.3	1.16 (0.82 to 1.65)	12.8	0.85 (0.58 to 1.24)
β agonists, steroids, and methylxanthines§ only	7.3	1.16 (0.74 to 1.83)	7.0	1.09 (0.67 to 1.78)	12.0	1.26 (0.88 to 1.82)
Four categories:						
β agonists, steroids, antimuscarinics, and methylxanthines only	12.0	1.26 (0.85 to 1.87)	17.7	0.98 (0.68 to 1.41)	29.3	0.98 (0.71 to 1.36)
Other combinations of asthma drugs	4.1	0.72 (0.37 to 1.40)	2.8	1.45 (0.71 to 2.96)	1.7	1.40 (0.58 to 3.34)

†Oral and/or inhaled.
‡Oral and/or inhaled and/or injected.
§Oral only.
*P<0.05, **P<0.01.

ated chronic obstructive lung disease (confounding by indication); a tendency for patients whose disease is not responding to receive a wider range of treatments; lack of more appropriate asthma care; and an adverse effect of the drug itself. A reduced risk of death may have the opposite connotations. As our main hypothesis related to the toxic effects of asthma drugs in the medium to long term, we attempted to reduce the likelihood of other explanations by choosing controls with severe asthma, using additional adjustments for severity and associated disease and for the number of other drug categories used.

β_2 agonists

There was no evidence to associate long acting bronchodilators (such as salmeterol) with an increased risk of death and this is in line with studies of mortality[12] and of near death.[21] If anything, there was some indication that this category of drug was associated with a reduced risk of death.

There was, however, a modestly (odds ratio 1.5 to 2.0) increased risk associated with short acting β_2 agonists (mainly salbutamol) but mainly in the previous 1-5 years. This is consistent with the results of two cohort studies,[4 8] including one of 43 deaths based on the UK general practice research database.[8] As in that database study we also observed a tendency for more deaths in those prescribed β agonists alone and fewer deaths in those taking β agonists with inhaled corticosteroids (table 5). Considering the modest increase in risk, and the potential for other explanations, we conclude that the evidence for a direct adverse effect of short acting β_2 agonists is inconclusive but remains a matter of concern. Our study had insufficient power to come to any conclusion about the effects of fenoterol, which was rarely prescribed alone. On the basis of the upper 95% confidence intervals, however, we can probably exclude the possibility of a 2.3-fold increase in the risk of death (table 2).

Other drugs

The risk of death associated with antimuscarinic preparations (mainly ipratropium bromide) was increased but not significant in the full confounder model. Our estimate was considerably lower than that reported by Guite and colleagues, who followed a cohort of patients who had been admitted to hospital.[10] Methylxanthines have been implicated in deaths from asthma,[11] but we observed only a small and non-significant increase in risk.

The inverse association between asthma death and oral steroids was confined to those aged under 45. Oral steroids are an effective treatment in severe asthma, and our finding supports the theory that insufficient treatment with oral steroids increases the risk of death. In the Saskatchewan cohort, regular use of inhaled steroids was associated with reductions in mortality and hospital admissions,[13] [22] but we found little evidence of an association. One possible explanation is the higher overall level of prescribing of inhaled corticosteroids, together with an absence of data on dose.

The inverse association between death and prescription for antibiotics, which seemed to be confined in the main to the under 45 age group, has not to our knowledge been reported before. The evidence from two randomised controlled trials was inconclusive about the value of antibiotics in acute asthma.[23] Apart from a protective effect, other explanations include a lower use of primary care services or greater adherence to UK guidelines which caution against the use of antibiotics.

We are grateful for the advice and support of our steering committee, the Mortality and Severe Morbidity Working Group of the National Asthma Task Force, which included J Ayres (chairman), B Harrison (past chairman), D Stableforth, M Burr, W Berrill, V Fox, T Williams, S Wright, C Bucknall, F Chung, C Godley, G Houghton, T MacKay, S McKenzie, G Mohan, J Poundsford, and A Ross. We thank R Beasley, J Crane, and N Pearce of the Wellington Asthma Research Group, who are involved with another part of this study, for their advice. We thank our research assistants B Khoshaba, B Davies, B Eldridge, S MacArthur, and M Wardroper for their diligent fieldwork and the medical students who assisted with data extraction. We thank the large number of general practices, health authority personnel, and hospital staff who assisted us. The office for national statistics and the general register office supplied copies of death certificates.

Contributors: All authors contributed to the drafting of the final paper. Additionally, HRA was principal investigator and contributed to all stages of the study, PMS contributed to the entire conduct of the study, JMB contributed to the design and analysis, BKB designed, supervised, and contributed to the statistical analysis, CP contributed to the statistical analysis, JCT contributed to the conduct of the study in the field, CRV and JGA contributed to the design of the study and interpretation of data. HRA is guarantor.

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Table 6 Odds ratios (95% confidence intervals) for death associated with prescriptions of drugs in 3 months, 4-12 months, and 1-5 years before index date. Sensitivity to control for chronic obstructive pulmonary disease (COPD), hospital admissions, and number of other drug categories prescribed (n=122 matched pairs). Analysis restricted to cases and controls with admission for asthma in previous year

Drug type	Unadjusted†	Adjusted (COPD)‡	Adjusted (hospital admisssions)§	Adjusted (other drug categories)¶	Adjusted (all)
Past 3 months					
β adrenoceptor:					
Inhaled short acting	1.86* (1.00 to 3.46)	1.75 (0.91 to 3.37)	1.93* (1.02 to 3.67)	1.51 (0.66 to 3.45)	1.84 (0.77 to 4.39)
Inhaled long acting	1.01 (0.58 to 1.77)	0.93 (0.51 to 1.67)	0.98 (0.55 to 1.73)	0.67 (0.35 to 1.28)	0.70 (0.35 to 1.39)
Antimuscarinic	1.59 (0.93 to 2.73)	1.22 (0.68 to 2.19)	1.63 (0.92 to 2.89)	1.29 (0.68 to 2.44)	1.01 (0.49 to 2.05)
All antimuscarinic	1.56 (0.93 to 2.62)	1.19 (0.68 to 2.09)	1.58 (0.92 to 2.74)	1.24 (0.66 to 2.34)	0.96 (0.48 to 1.93)
Corticosteroids:					
Inhaled	1.46 (0.84 to 2.52)	1.36 (0.76 to 2.44)	1.50 (0.85 to 2.63)	1.06 (0.53 to 2.11)	1.16 (0.56 to 2.39)
Oral	1.35 (0.75 to 2.43)	1.16 (0.62 to 2.17)	1.38 (0.75 to 2.51)	0.92 (0.45 to 1.89)	0.87 (0.40 to 1.87)
Methylxanthine (oral)	2.02* (1.16 to 3.53)	1.63 (0.90 to 2.93)	2.10* (1.17 to 3.78)	1.88* (1.03 to 3.42)	1.62 (0.85 to 3.07)
All antibiotics	0.90 (0.50 to 1.60)	0.82 (0.45 to 1.52)	0.86 (0.48 to 1.55)	0.71 (0.38 to 1.33)	0.66 (0.34 to 1.30)
Past 4-12 months					
β adrenoceptor:					
Inhaled short acting	1.28 (0.56 to 2.95)	1.36 (0.51 to 3.57)	1.27 (0.51 to 3.15)	0.98 (0.36 to 2.65)	1.06 (0.36 to 3.11)
Inhaled long acting	0.98 (0.56 to 1.69)	1.01 (0.56 to 1.81)	0.93 (0.53 to 1.63)	0.72 (0.39 to 1.35)	0.79 (0.41 to 1.53)
Antimuscarinic	1.60 (0.91 to 2.79)	1.39 (0.76 to 2.54)	1.56 (0.87 to 2.79)	1.53 (0.82 to 2.86)	1.32 (0.67 to 2.62)
All antimuscarinic	1.99* (1.12 to 3.53)	1.69 (0.92 to 3.12)	1.95* (1.08 to 3.52)	1.98* (1.05 to 3.74)	1.66 (0.84 to 3.29)
Corticosteroids:					
Inhaled	1.16 (0.58 to 2.32)	1.01 (0.47 to 2.18)	1.15 (0.55 to 2.39)	0.88 (0.39 to 1.99)	0.71 (0.29 to 1.71)
Oral	1.81 (0.86 to 3.80)	1.89 (0.85 to 4.19)	1.72 (0.78 to 3.79)	1.50 (0.60 to 3.76)	1.94 (0.73 to 5.15)
Methylxanthine (oral)	1.23 (0.74 to 2.04)	1.25 (0.72 to 2.15)	1.19 (0.71 to 2.01)	1.09 (0.63 to 1.89)	1.13 (0.63 to 2.04)
All antibiotics	1.44 (0.70 to 2.93)	1.30 (0.61 to 2.78)	1.46 (0.71 to 3.03)	1.40 (0.67 to 2.92)	1.23 (0.57 to 2.68)
Past 1-5 years					
β adrenoceptor:					
Inhaled short acting	1.97 (0.67 to 5.82)	1.79 (0.50 to 6.44)	1.99 (0.57 to 6.92)	2.22 (0.54 to 9.06)	2.53 (0.58 to 11.05)
Inhaled long acting	1.14 (0.67 to 1.97)	1.04 (0.59 to 1.85)	1.06 (0.60 to 1.87)	1.04 (0.56 to 1.93)	1.05 (0.55 to 2.01)
Antimuscarinic	1.11 (0.65 to 1.92)	0.92 (0.50 to 1.68)	1.01 (0.55 to 1.87)	1.03 (0.55 to 1.92)	0.84 (0.42 to 1.69)
All antimuscarinic	1.12 (0.65 to 1.93)	0.91 (0.49 to 1.66)	1.03 (0.56 to 1.90)	1.05 (0.56 to 1.94)	0.83 (0.41 to 1.65)
Corticosteroids:					
Inhaled	1.06 (0.39 to 2.85)	0.64 (0.20 to 1.99)	0.89 (0.30 to 2.65)	0.74 (0.21 to 2.64)	0.50 (0.13 to 1.97)
Oral	1.20 (0.56 to 2.54)	0.94 (0.42 to 2.11)	1.09 (0.48 to 2.45)	1.08 (0.46 to 2.52)	0.87 (0.35 to 2.14)
Methylxanthine (oral)	1.06 (0.60 to 1.85)	1.04 (0.58 to 1.89)	1.00 (0.56 to 1.81)	0.98 (0.53 to 1.83)	1.05 (0.55 to 2.02)
All antibiotics	0.79 (0.29 to 2.11)	0.75 (0.27 to 2.09)	0.77 (0.28 to 2.09)	0.70 (0.24 to 2.01)	0.74 (0.25 to 2.19)

†Adjusted for sex.
‡Adjusted for sex, age at asthma onset, and COPD (defined as mention of COPD, COAD, chronic bronchitis, or emphysema).
§Adjusted for sex, age at asthma onset, and hospital admission for asthma as two continuous variables, in past year and past 1-5 years.
¶Adjusted for sex, age at asthma onset, and other drug categories (No of other tabulated drug categories (excluding antibiotics) prescribed in relevant time period).
*P<0.05.

Funding: UK Department of Health, national research and development programme (contract AM1/05/002) and UK National Asthma Campaign, through a grant from GlaxoSmithKline. No part of the design, conduct, analysis, or interpretation of the study was influenced by the funders. Comment on an early draft of this report was received from GlaxoSmithKline. This drew attention to an arithmetical error in one of the tables and raised one point of clarification.

Competing interests: HRA has received funding for epidemiological research into asthma from GlaxoSmithKline in the past. BKB owns shares in GlaxoSmithKline. JGA has received funding from various pharmaceutical companies for attending meetings, advisory work, and research.

Ethics approval: This study was approved by the South Thames multicentre research ethics committee and all relevant local ethics committees.

What is already known on this topic

Various bronchodilator therapies have been reported to increase the risk of death in people with asthma

The number of studies is small and the interpretation of associations is often limited by low statistical power and the possibility of uncontrolled confounding

What this study adds

In a large population based study, there was no evidence that long acting β_2 agonists increase the risk of death

Short acting β_2 agonists, however, were associated with increased mortality

Oral corticosteroids and antibiotics were associated with reduced mortality

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(Accepted 23 November 2004)

doi 10.1136/bmj.38316.729907.8F

Department of Community Health Sciences, St George's Hospital Medical School, London SW17 0RE
H Ross Anderson *professor of epidemiology and public health*
Patricia M Sturdy *senior research fellow*
J Martin Bland *professor of medical statistics*
Barbara K Butland *lecturer in medical statistics*
Clare Peckitt *statistician*
Jennifer C Taylor *research manager*
Christina R Victor *professor of social gerontology*

Department of Environmental and Occupational Medicine, Liberty Safe Work Research Centre, University of Aberdeen, Aberdeen AB25 2ZP
Jon G Ayres *professor of environmental and occupational medicine*

Correspondence to: H R Anderson r.anderson@sghms.ac.uk

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