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Bronchodilator treatment and asthma death: A new analysis of a British case-control study

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Summary
We investigated the relationship between asthma mortality and long-acting beta$_2$-agonists (LABA), including interactions with age, inhaled corticosteroids (ICS) and social deprivation.

We used a new, expanded dataset of recorded medication extracted blind from the anonymised primary care records of an earlier British case-control study. The cases were 532 asthma deaths aged $<$ 65 occurring between 1994 and 1998 and the controls were 532 asthma admissions, matched for age, hospital, and index date (date of death/asthma admission). The exposure periods prior to the index date were current ($\leq$ 2 months) or recent ($>$ 2–6 months).

We found no evidence of an overall association with current (OR = 0.89 [95% confidence interval 0.61–1.30]) or recent (1.08 [0.76–1.53]) mention of LABA, but there was some evidence of a positive interaction with age. Among controls with mention of LABA, a concurrent mention of ICS (within 1 month) was common (85% and 93% for the two respective periods) which limited our power to investigate any interaction between LABA and ICS. There was no coherent evidence of effect modification by social deprivation.

In a population based case-control study where prescription of LABA without concomitant ICS was uncommon there was no evidence of an overall association between LABA and asthma death.

Introduction

Concerns that the prescription of inhaled long-acting beta$_2$-agonists (LABA) might be associated with a higher risk of asthma death were first raised by Castle et al. in 1993.[1] More recently the SMART trial[2–4] found evidence of an increased risk of asthma related death, and 'combined asthma related death or life threatening experiences' among those in the Salmeterol *versus* the placebo group. For both outcomes the increase was possibly tempered by concomitant use of inhaled corticosteroids (ICS) and for 'combined asthma related death or life threatening experiences', the increase was largely confined to African-Americans.[2,3]

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The original analysis of the ADCCS (Asthma Death Case-Control Study[5–7]) found no evidence of an adverse effect of LABA whether mentioned in the primary care record in the 3 months, > 3–12 months, or > 1–5 years before the index date (date of death for cases and date of hospital admission for controls). Mention of SABA in the > 1–5 years prior was associated with a higher risk of asthma death while mentions of antibiotics in the 3 months and > 1–5 years prior and oral corticosteroids in the 3 months prior were associated with a lower risk of asthma death.[5,7] However, this analysis had certain limitations 1) potential biases were noted which may have influenced case-control comparisons, particularly in the 3 months prior to index date 2) there was no analysis of the interaction between LABA and ICS and 3) there was no attempt to examine interactions with socioeconomic deprivation.

We have conducted a new, more detailed and quality controlled extraction from the original records and made adjustments for potential biases. Using this dataset, we aim to investigate the association between asthma death and mention of LABA in the 2 and > 2–6 months prior to index date and to consider as possible modifying effects, age, concomitant prescribing with ICS and a socioeconomic deprivation index.

Materials and methods

Study subjects and design

Full details are described in earlier publications.[5–7] The study areas were based on regions participating in confidential inquiries into asthma deaths and covered 27% of the British population (a population in which medical care is provided free of charge at the point of delivery). The case series comprised all asthma deaths aged < 65 years occurring in the study areas of England and Wales between 1994 and 1998 inclusive and in the study areas of Scotland between 1996 and 1998 inclusive. Fixed dose ICS/LABA combination inhalers were not prescribed during the period covered by the study.

All cases had 'asthma' in part 1 of the death certificate with no more credible non-respiratory underlying cause. After exclusions (detailed elsewhere[6,7]), 532 cases were included in the study. For each case, one control was selected from the asthma discharge list of the hospital where the case had died (or the next nearest hospital or, for a community death, the hospital to which the case would have been admitted). The control was selected firstly to have a similar index date to its case (96% within 6 months, maximum difference 13 months) and secondly to be of a similar age (98% within 5 years, maximum age difference 12 years).[6,7] For each case and control, their primary care record was first anonymised and then photocopied for the 5 years prior to the index date.[5–7]

The Asthma Death Case-Control Study was approved by the South Thames Multi-centre Research Ethics Committee (MREC) in September 1997. Permissions to photocopy anonymised primary care records were obtained in writing from general practitioners.

Methods

Using these photocopied records, nursing/medically qualified personnel conducted a new and more detailed extraction of data on drugs, COPD (i.e. mention of COPD, COAD, chronic bronchitis and emphysema) and other chronic lung diseases. Data were extracted twice in a blinded fashion by different extractors and later reconciled. The same person was allocated to extract information on a case and its matched control.

Deprivation data were obtained by linking, via the National Postcode Directory,[8] the GP post-code of each subject to either a Lower Layer Super Output Area (average population 1500) within England and Wales or a Data Zone (average population 750) within Scotland and thence to a country specific Index of Multiple Deprivation (IMD) and its rank.[9] We used the 2004 index for England,[10] the 2005 index for Wales[11] and the 2006 index for Scotland.[12] Using within country mid-ranks, subjects were categorised according to whether their primary care services were based in a more or less deprived area of England, Scotland or Wales, as appropriate. The way in which the Index of Multiple Deprivation is calculated differs between England, Scotland and Wales but all three measures combine area level information on various aspects of deprivation including income, employment, health and education.[9]

The only variables included in the new analysis, but obtained as part of the original study[5–7] were sex, age of asthma onset, mention of obesity ever and number of hospital admissions for asthma in the 1 year and > 1–5 years prior.

Of the 532 cases, 112 (21%) died in hospital after the day of admission. Given the difference in index date definition between cases and controls and the lack of information recorded in the primary care notes during a period of hospital admission, this could lead to bias; a bias that was not adjusted for in the previous analysis. Any data relating to drugs for the period of the index admission (including the day of admission) was therefore removed/censored from the GP record of the case and for an equivalent period from the GP record of its matched control. A similar censoring process was used to deal with the correction of errors in index dates made after the photocopying of the primary care record. As a result, the period of observation prior to the index date was shortened by more than 2 weeks for 52 matched pairs (10%), more than 4 weeks for 28 matched pairs (5%), more than 2 months for 15 matched pairs (3%) and by more than 6 months for 5 matched pairs (1%). Censoring was only implemented in relation to information on drugs and the number of previous hospital admissions for asthma.

Statistical analysis

Data were analysed using conditional logistic regression and the likelihood ratio test. The variables investigated included six main classes of respiratory drugs (inhaled short-acting beta$_2$-agonists (SABA), inhaled long-acting beta$_2$-agonists (LABA), inhaled corticosteroids (ICS), oral corticosteroids, antimuscarinics and methylxanthenes), two named drugs (Salmeterol and Fenoterol), injected corticosteroids and antibiotics. Fenoterol, an inhaled short-acting beta$_2$-agonist, was of interest, as case-control studies of severe asthmatics conducted in New Zealand in the 1970s and 1980s suggested that its prescription was associated with a higher risk of asthma death.[13] For each drug or class, two variables were created representing any mention (yes/no) in the

primary care record in the 2 and the > 2–6 months prior to index date. Variables for LABA were further divided by the presence/absence of a concomitant mention (1 month either side but prior to index date) of ICS. The full confounder model included sex, age of asthma onset, ever mention of obesity, mention of COPD in the past 5 years, mention of other chronic lung diseases in the past 5 years, previous admissions for asthma in the past year and the > 1–5 years prior, other main respiratory drug classes, and deprivation rank within country. Quantitative and ordinal variables (including deprivation ranks) were treated in the full confounder model as continuous. Deprivation rank group (less deprived, more deprived) and age group (1–44, 45–64) were used to model and test for interactions.

Our analysis makes the assumption that within a specified period of observation (e.g. 2 months prior to index date), odds ratios do not change with time (e.g. are the same for the 1 month prior and the > 1–2 months prior), and are therefore invariant to loss of data through censoring.

Results

Among the 1064 study subjects only 55 (5.2%) were under the age of 18 years. As reported previously[5–7] and described here in Table 1, cases and controls were similar with respect to age (median 53 years interquartile range (40–59) in both groups) and female sex (60.2% *versus* 63.5%) but cases had a significantly ($p = 0.013$) earlier median age of asthma onset (30 years (10–47) $n = 493$ *versus* 33 years (13–49) $n = 502$) and a higher proportion had mention of obesity ever (30.6% *versus* 25.0%; $p = 0.037$). Mention of other chronic lung diseases (6.0% *versus* 3.6%) was also significantly ($p = 0.046$) higher among cases than controls as was mention of COPD (45.1% *versus* 38.2%; $p = 0.010$), with the latter association differing significantly ($p = 0.020$) between the 45–64 age group (60.7% *versus* 48.9%) and the 1–44 year age group (10.8% *versus* 14.9%). By contrast similar proportions were mapped by GP post-code to the most deprived areas in England (68.4% *versus* 69.2%), Scotland (68.3% *versus* 66.3%) and Wales (70.6% *versus* 67.6%) and even with censoring, similar proportions of cases and controls had mention of one or more asthma admissions in the past year (34.0% *versus* 33.3%) and in the > 1–5 years prior (40.8% *versus* 42.5%).

Table 2 displays odds ratios and 95% confidence intervals adjusted firstly for sex alone and then using the full confounder model. For the > 2–6 months prior, only SABA were positively associated with asthma death and although this association persisted in magnitude following full adjustment it fell short of statistical significance at the 5% level. A non-significant association of similar magnitude was observed for mention of SABA in the 2 months prior, providing a relatively consistent picture across the two time intervals. Fenoterol was rarely prescribed but in the 2 months prior it was mentioned in the notes of 4 cases but no controls.

There was a modest positive association between anti-muscarinics mentioned in the 2 months prior and asthma death which persisted in magnitude after full adjustment but fell short of statistical significance at the 5% level. By contrast, after full adjustment, oral corticosteroids, injected corticosteroids and antibiotics mentioned in the 2 months prior were each associated with a significantly

Table 1 Descriptive statistics for cases and controls by age group.

Variable		Total		Age 1–44 years		Age 45–64 years	
		Cases ($N = 532$)	Controls ($N = 532$)	Cases ($N = 166$)	Controls ($N = 168$)	Cases ($N = 366$)	Controls ($N = 364$)
Deprivation Score[a]	England (most deprived): n (%)	238 (44.7)	240 (45.1)	80 (48.2)	75 (44.6)	158 (43.2)	165 (45.3)
	England (least deprived): n (%)	110 (20.7)	107 (20.1)	29 (17.5)	38 (22.6)	81 (22.1)	69 (19.0)
	Scotland (most deprived): n (%)	56 (10.5)	55 (10.3)	20 (12.0)	22 (13.1)	36 (9.8)	33 (9.1)
	Scotland (least deprived): n (%)	26 (4.9)	28 (5.3)	11 (6.6)	9 (5.4)	15 (4.1)	19 (5.2)
	Wales (most deprived): n (%)	72 (13.5)	69 (13.0)	17 (10.2)	17 (10.1)	55 (15.0)	52 (14.3)
	Wales (least deprived): n (%)	30 (5.6)	33 (6.2)	9 (5.4)	7 (4.2)	21 (5.7)	26 (7.1)
Females: n (%)		320 (60.2)	338 (63.5)	92 (55.4)	110 (65.5)	228 (62.3)	228 (62.6)
Age at onset (yrs)[b]: Median (interquartile range(IQR))		30 (10–47)	33 (13–49)	10 (4–24)	13 (5–28)	42 (23–51)	44 (29–52)
COPD mentioned in the last 5 years: n (%)		240 (45.1)	203 (38.2)	18 (10.8)	25 (14.9)	222 (60.7)	178 (48.9)
Other chronic lung disease in the last 5 years[c]: n (%)		32 (6.0)	19 (3.6)	2 (1.2)	2 (1.2)	30 (8.2)	17 (4.7)
Obesity mentioned ever: n (%)		163 (30.6)	133 (25.0)	33 (19.9)	27 (16.1)	130 (35.5)	106 (29.1)
Any hospital admission for asthma in the last year[d]: n(%)		181 (34.0)	177 (33.3)	48 (28.9)	55 (32.7)	133 (36.3)	122 (33.5)
Any hospital admission for asthma in the > 1 to 5 years[d]: n (%)		217 (40.8)	226 (42.5)	67 (40.4)	73 (43.5)	150 (41.0)	153 (42.0)

Note: Figures for age and age of onset may differ slightly from those previously published due to additional data cleaning.

[a] Less Deprived = deprivation rank (numerically) at or higher than the mid-rank for the country; More deprived = deprivation rank (numerically) lower than the mid-rank for the country.

[b] Information on age of onset missing for 39 cases and 30 controls.

[c] Other chronic lung diseases include bronchiectasis, aspergillosis, pulmonary TB and pulmonary fibrosis.

[d] Figures take account of length of index admission etc. through censoring.

Table 2 Odds ratios (95% confidence intervals) describing the association between asthma death and the prescription[a] of drugs in the 2 months and > 2–6 months before the index event.

Drug class		Mention in the past 2 months (n = 1032)					Mention in the > 2–6 months prior (n = 1052)				
		Controls n (%)[b] N = 516	Adjusted for sex		Adjusted for sex and other factors[c]		Controls n (%)[b] N = 526	Adjusted for sex		Adjusted for sex and other factors[c]	
			OR	(95% CI)	OR	(95% Ci)		OR	(95% CI)	OR	(95% CI)
Inhaled short-acting beta$_2$-agonists	All	289 (56.0)	1.20	0.93–1.56	1.37	0.97–1.93	311 (59.1)	1.35*	1.05–1.75	1.40	0.99–1.99
Inhaled long-acting beta$_2$-agonists	All	100 (19.4)	0.96	0.69–1.32	0.89	0.61–1.30	115 (21.9)	1.16	0.86–1.57	1.08	0.76–1.53
	Salmeterol	98 (19.0)	0.89	0.63–1.24	0.82	0.56–1.20	114 (21.7)	1.12	0.83–1.52	1.02	0.72–1.45
	All with ICS[d]	86 (16.7)	0.98	0.70–1.38	0.92	0.61–1.37	107 (20.3)	1.14	0.83–1.56	1.05	0.73–1.51
	All without ICS[d]	14 (2.7)	0.80	0.36–1.81	0.75	0.32–1.78	8 (1.5)	1.39	0.56–3.48	1.39	0.53–3.65
Antimuscarinics	All	130 (25.2)	1.34*	1.01–1.77	1.35	0.94–1.95	148 (28.1)	1.30	0.99–1.70	1.10	0.78–1.55
Corticosteroids	All	346 (67.1)	0.79	0.61–1.03	0.52***	0.36–0.73	347 (66.0)	1.27	0.98–1.64	1.00	0.70–1.43
	Inhaled (ICS)	241 (46.7)	0.99	0.77–1.28	0.86	0.61–1.22	298 (56.7)	1.13	0.89–1.45	0.85	0.60–1.20
	Oral	258 (50.0)	0.86	0.67–1.09	0.65**	0.48–0.88	253 (48.1)	1.16	0.91–1.48	0.98	0.72–1.33
	Injected	21 (4.1)	0.41*	0.18–0.92	0.34*	0.14–0.81	27 (5.1)	1.42	0.87–2.33	1.47	0.84–2.58
Methylxanthines	All	55 (10.7)	1.14	0.77–1.69	1.13	0.73–1.73	72 (13.7)	1.11	0.77–1.60	0.93	0.62–1.38
Antibiotics	All	251 (48.6)	0.79	0.62–1.01	0.68*	0.50–0.92	250 (47.5)	1.10	0.85–1.42	0.92	0.67–1.26

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Note: Due to censoring and the exclusion of one matched pair mapped to different countries based on GP post-code, analyses for the 2 months prior and the > 2–6 months prior were based on 516 and 526 matched pairs respectively.

[a] Prescription = mention of drug in primary care notes including computer printouts, referral letters, hospital discharge and outpatient letters.

[b] Percentage of controls prescribed drug.

[c] Additionally adjusted for age of asthma onset (including missings), mention of obesity ever, number of hospital admissions in the past year and > 1–5 years prior, mention of COPD in the past 5 years and mention of other chronic lung disease in the past 5 years, mention/prescription in the relevant time period of other asthma drug classes (inhaled corticosteroids, oral corticosteroids, inhaled short-acting beta$_2$-agonists, inhaled long-acting beta$_2$-agonists, antimuscarinics and methylxanthines) as appropriate and for any linear trend in deprivation rank within country.

[d] Mention of inhaled corticosteroids within 1 month either side of a mention of inhaled long-acting beta$_2$-agonists but prior to index date; comparison group – no mention of inhaled long-acting beta$_2$-agonists. Final adjustment includes adjustment for mention/prescription of inhaled corticosteroids in the 2 months or > 2–6 months prior as appropriate.

lower risk of asthma death. However these three associations were not independent and when adjusted for each other (an extension of the full confounder model), the association with oral steroids became more consistent with a chance effect (OR = 0.76 (95% confidence interval 0.55 to1.04)), while associations with antibiotics (OR = 0.67 (0.49–0.91)) and injected steroids (OR = 0.33 (0.14–0.80)) were little changed.

Even with full adjustment, there was no evidence of an overall association between LABA and asthma death whether mentioned in the 2 months (OR = 0.89 (95% confidence interval 0.61 to 1.30)) or > 2–6 months prior (OR = 1.08 (0.76–1.53)). Where LABA were mentioned in the primary care notes it was usual to find a mention of ICS within 1 month. Such evidence of concomitant prescribing was found in 86% of controls with a mention of LABA in the 2 months prior and 93% of controls with mention of LABA in the > 2–6 months prior. Fully adjusted odds ratios for LABA with and without concomitant mention of ICS were 0.92 (0.61–1.37) and 0.75 (0.32–1.78) respectively for the 2 month period and 1.05 (0.73–1.51) and 1.39 (0.53–3.65) for the > 2–6 month period but for both periods these differences were not statistically significant ($p = 0.671$ and $p = 0.579$ respectively).

Table 3 displays odds ratios, and 95% confidence intervals adjusted for the full confounder model, extended to include age group interactions with sex, COPD and other chronic lung diseases. For the > 2–6 month period, odds ratios for Salmeterol differed significantly between the 1–44 and 45–64 year age groups as did the odds ratios for all LABA which were 0.63 (0.34–1.15) and 1.35 (0.90–2.03) respectively. There was no evidence of any similar age interaction with Salmeterol or all LABA when mentioned in the 2 months prior.

Table 4 shows the results for the analysis of deprivation ranks, within each country. In the 2 months prior odds ratios for Salmeterol differed significantly across the 6 categories defined by country and within country deprivation rank. This finding appeared to be due to differences between deprivation groups within countries ($p = 0.023$; df = 3) rather than differences between countries ($p = 0.389$; df = 2) but given the lack of consistency in the direction of association within countries, it provides no coherent evidence of effect modification by deprivation.

Odds ratios for mention of SABA in the > 2–6 months prior provided little evidence of a positive association with mortality within Scotland or Wales but within England, odds ratios for the less and more deprived areas were 2.72 (1.48–5.00) and 1.56 (0.97–2.52) respectively. However differences across the 6 groups appeared to be due to differences between countries ($p = 0.003$; df = 2) rather than between deprivation groups within countries ($p = 0.437$; df = 3). Odds ratios for LABA mentioned in the > 2–6 months prior, exhibited a similar pattern to SABA, although for this variable the difference across all six groups was not statistically significant at the 5% level.

Discussion

In this fresh analysis of the ADCCS, we have used a dataset which has a higher level of detail and fewer potential biases than that used for the original report. Using different time references we have found, overall, a similar pattern of associations to those found by the previous analysis. In particular we found no evidence of any overall association between LABA and asthma death but some evidence that antibiotics and oral steroids when mentioned close to the index date, were associated with a lower risk of asthma death. A similar association with injected steroids is a new finding. Despite similarities with the original results, there are also material differences especially in terms of age group interactions which in the earlier report were only adjusted for sex. The results in this paper should therefore be viewed as replacing and adding to those previously published for the period 3 months prior to the index date.

Long-acting beta$_2$-agonists (including salmeterol)

In this British study of severe asthmatics, there was no evidence that LABA, whether mentioned in the 2 or > 2–6 months prior, was associated with asthma mortality. Even for the > 2–6 month period, mention of LABA though consistent with up to a 53% higher risk of asthma death was also consistent with as much as a 24% lower risk (based on the upper and lower 95% confidence limits). This makes the finding of a significant age interaction in the > 2–6 months prior difficult to interpret especially as there was no significant odds ratio in either the 1–44 year or the 45–64 year age group.

There was no evidence that any association between LABA and mortality differed in a consistent fashion between those attending a GP surgery in a more or less deprived area. However our deprivation measures were somewhat limited, being neighbourhood rather than person specific, based on GP rather than patient post-code and relying on information which post-dated our study period e.g. Index of Multiple Deprivation for England 2004.

It has been suggested that any positive association between LABA and mortality might be reduced in the presence of ICS.[2,14] In our study mention of LABA without a concomitant mention of ICS was uncommon. It has been suggested that this explains the lack of association between LABA and mortality reported in our previous analysis of this case-control study. However, it also means that if a modifying effect of ICS exists we have little statistical power to detect it. Odds ratios for LABA with and without ICS (Table 2) add little to the debate as they do not provide a consistent pattern across the two time windows.

Inhaled short-acting beta$_2$-agonists

In line with other studies[15–18] we found some evidence of a higher risk of asthma death associated with any mention of SABA in the > 2–6 months prior, an association which did not appear to be explained by our adjustment for potential confounding factors. Final adjusted odds ratios for mention in the 2 and > 2–6 months prior were similar in magnitude, though somewhat lower than the adjusted odds ratio of 2.05 (1.26–3.33) reported by our previous analysis of the > 1–5 years prior.[5]

There was no evidence of a modifying effect of age or background levels of deprivation (based on GP post-code) but

Table 3 Age-group specific adjusted[a] odds ratios (95% confidence intervals) describing the association between asthma death and the prescription[b] of drugs in the 2 months and > 2 to 6 months before index event.

Drug/Drug class	Age group	Mention in the past 2 months (n = 1032)			Mention in the > 2 to 6 months (n = 1052)		
		Cont % (n/N)[c] N = 516	OR (95% CI)	Test for age interaction	Cont % (n/N)[c] N = 526	OR (95% CI)	Test for age interaction
Short-acting beta$_2$-agonists (inhaled)	1—44	58.8 (97/165)	1.51 (0.89—2.57)	$P = 0.674$	58.3 (98/168)	1.27 (0.75—2.15)	$P = 0.683$
	45—64	54.7 (192/351)	1.33 (0.90—1.97)		59.5 (213/358)	1.43 (0.96—2.13)	
Long-acting beta$_2$-agonists (inhaled)	1—44	23.0 (38/165)	0.89 (0.48—1.62)	$P = 0.986$	27.4 (46/168)	0.63 (0.34—1.15)	$P = 0.028$
	45—64	17.7 (62/351)	0.89 (0.57—1.40)		19.3 (69/358)	1.35 (0.90—2.03)	
Salmeterol (inhaled)	1—44	23.0 (38/165)	0.77 (0.41—1.42)	$P = 0.792$	27.4 (46/168)	0.56 (0.30—1.04)	$P = 0.016$
	45—64	17.1 (60/351)	0.85 (0.53—1.35)		19.0 (68/358)	1.32 (0.87—1.99)	
Antimuscarinics	1—44	22.4 (37/165)	1.19 (0.65—2.16)	$P = 0.700$	22.0 (37/168)	0.94 (0.50—1.77)	$P = 0.636$
	45—64	26.5 (93/351)	1.35 (0.89—2.05)		31.0 (111/358)	1.11 (0.76—1.64)	
Corticosteroids (inhaled)	1—44	47.3 (78/165)	0.83 (0.48—1.42)	$P = 0.891$	49.4 (83/168)	1.03 (0.62—1.72)	$P = 0.331$
	45—64	46.4 (163/351)	0.86 (0.59—1.27)		60.1 (215/358)	0.79 (0.53—1.16)	
Corticosteroids (oral)	1—44	48.5 (80/165)	0.46 (0.28—0.77)	$P = 0.088$	43.5 (73/168)	0.81 (0.50—1.33)	$P = 0.337$
	45—64	50.7 (178/351)	0.76 (0.54—1.07)		50.3 (180/358)	1.07 (0.75—1.53)	
Antibiotics	1—44	46.7 (77/165)	0.63 (0.38—1.04)	$P = 0.798$	47.6 (80/168)	0.61 (0.35—1.05)	$P = 0.067$
	45—64	49.6 (174/351)	0.68 (0.48—0.98)		47.5 (170/358)	1.09 (0.75—1.58)	

Note: Due to censoring and the exclusion of one matched pair mapped to different countries based on GP post-code, analyses for the 2 months prior and the > 2—6 months prior were based on 516 and 526 matched pairs respectively.

[a] Adjusted for sex, an age group interaction with sex, age of asthma onset (including missings), mention of obesity ever, number of hospital admissions in the past year and > 1—5 years prior, mention of COPD in the past 5 years and mention of other chronic lung disease in the past 5 years (including age group interactions with COPD and other chronic lung diseases), mention/prescription in the 2 months prior of other asthma drug classes (inhaled corticosteroids, oral corticosteroids, inhaled short-acting beta$_2$-agonists, inhaled long-acting beta$_2$-agonists, antimuscarinics and methylxanthines) as appropriate and for any linear trend in deprivation rank within country.

[b] Prescription = mention of drug in primary care notes including computer printouts, referral letters, hospital discharge and outpatient letters.

[c] Within age group, percentage of controls prescribed drug.

Table 4 Adjusted[a] odds ratios for asthma death associated with the prescription[b] of beta$_2$-agonists in the 2 months and > 2 to 6 months prior by high (less deprived) vs. low (more deprived) deprivation rank within country.

Drug/Drug class	Country	Deprivation Score[c]	Mentioned in the past 2 months			Mentioned in the > 2 to 6 months prior		
			Cont %[d] (n/N)	OR (95% CI)	Test for differences in OR across groups (df = 5)	Cont %[d] (n/N)	OR (95% CI)	Test for differences in OR across groups (df = 5)
Short-acting beta$_2$-agonists (inhaled)	England	Less Deprived	55.3 (57/103)	1.87 (0.99–3.52)	$P = 0.069$	47.7 (51/107)	2.72 (1.48–5.00)	$P = 0.015$
		More Deprived	58.4 (136/233)	1.50 (0.94–2.39)		62.0 (147/237)	1.56 (0.97–2.52)	
	Scotland	Less Deprived	59.3 (16/27)	0.70 (0.22–2.23)		64.3 (18/28)	1.04 (0.28–3.83)	
		More Deprived	47.2 (25/53)	1.45 (0.62–3.44)		59.3 (32/54)	0.87 (0.39–1.93)	
	Wales	Less Deprived	51.5 (17/33)	2.81 (0.92–8.58)		75.8 (25/33)	0.48 (0.14–1.64)	
		More Deprived	56.7 (38/67)	0.58 (0.27–1.23)		56.7 (38/67)	0.72 (0.33–1.55)	
Long-acting beta$_2$-agonists (inhaled)	England	Less Deprived	20.4 (21/103)	1.09 (0.51–2.32)	$P = 0.077$	17.8 (19/107)	2.08 (0.99–4.37)	$P = 0.205$
		More Deprived	18.9 (44/233)	1.01 (0.61–1.69)		21.1 (50/237)	1.19 (0.71–2.00)	
	Scotland	Less Deprived	25.9 (7/27)	0.21 (0.04–1.01)		32.1 (9/28)	0.54 (0.15–1.95)	
		More Deprived	18.9 (10/53)	0.99 (0.38–2.60)		27.8 (15/54)	0.78 (0.32–1.95)	
	Wales	Less Deprived	18.2 (6/33)	1.77 (0.52–6.05)		30.3 (10/33)	0.49 (0.14–1.65)	
		More Deprived	17.9 (12/67)	0.27 (0.08–0.88)		17.9 (12/67)	0.81 (0.31–2.11)	
Salmeterol (inhaled)	England	Less Deprived	20.4 (21/103)	0.95 (0.44–2.06)	$P = 0.044$	17.8 (19/107)	1.94 (0.92–4.07)	$P = 0.224$
		More Deprived	18.9 (44/233)	0.96 (0.57–1.61)		21.1 (50/237)	1.14 (0.68–1.92)	
	Scotland	Less Deprived	25.9 (7/27)	0.21 (0.04–0.99)		32.1 (9/28)	0.54 (0.15–1.93)	
		More Deprived	18.9 (10/53)	0.90 (0.34–2.43)		27.8 (15/54)	0.78 (0.31–1.93)	
	Wales	Less Deprived	15.2 (5/33)	1.64 (0.45–6.00)		30.3 (10/33)	0.49 (0.14–1.65)	
		More Deprived	16.4 (11/67)	0.16 (0.04–0.67)		16.4 (11/67)	0.66 (0.24–1.84)	

Note: Due to censoring and the exclusion of one matched pair mapped to different countries based on GP post-code, analyses for the 2 months prior and the> 2–6 months prior were based on 516 and 526 matched pairs respectively.

[a] Adjusted for sex, age of asthma onset (including missings), mention of obesity ever, number of hospital admissions in the past year and > 1–5 years prior, mention of COPD in the past 5 years and mention of other chronic lung disease in the past 5 years, and mention/prescription in the > 2–6 months prior of other asthma drug classes (inhaled corticosteroids, oral corticosteroids, inhaled short-acting beta$_2$-agonists, inhaled long-acting beta$_2$-agonists, antimuscarinics and methylxanthines) as appropriate.

[b] Prescription = mention of drug in primary care notes including computer printouts, referral letters, hospital discharge and outpatient letters.

[c] Less Deprived = deprivation rank (numerically) at or higher than the mid-rank for the country; More deprived = deprivation rank (numerically) lower than the mid-rank for the country.

[d] Percentage of controls prescribed drug.

we unexpectedly found evidence in support of a modifying effect of 'country'. This comparison was not postulated *a priori* and should be viewed with caution. It may be due to chance or reflect real regional differences in: prescribing; record keeping (due to the use of 'mentions' rather than prescriptions); access to both primary and secondary care; and/or patient behaviour in terms of compliance and the severity threshold for seeking medical treatment.

Antimuscarinics and methylxanthines

Mention of antimuscarinics (predominantly ipratropium bromide) was associated with a higher risk of asthma death in the 2 months prior, an association that persisted in magnitude after full adjustment. Some other indications of a positive association between asthma death and ipratropium bromide, or the regular use of all antimuscarinics have been reported from the General Practice Research Database[18,19] and a small case-control study.[20] However, as suggested in these studies, such associations may result from confounding by co-morbidity with COPD or by asthma severity. The latter may explain our findings as, based on BTS guidelines,[21] antimuscarinics were only prescribed to those with very severe asthma or whose asthma was not adequately controlled by high-dose ICS (Step 4).

We found no evidence of an association between methylxanthines and asthma death, even though, like antimuscarinics, these drugs were also reserved until Step 4.[21]

Inhaled corticosteroids

Regular use of ICS is well established as beneficial in preventing asthma exacerbations[22] and is associated with a lower risk of asthma admissions.[23,24] However we found little evidence of an association between asthma death and ICS, although in the 2 months, $>2-6$ months and in the $>1-5$ years prior,[5] odds ratios, though non-significant, were of similar magnitude (0.86, 0.85, 0.86 respectively).

Oral and injected corticosteroids

Oral corticosteroids tend to be prescribed as a short 'rescue' course in response to an acute attack, or as maintenance (BTS Step 5) among severe asthmatics.[21] The inverse association observed both for oral corticosteroids and for injected corticosteroids in the 2 but not the $>2-6$ months prior may therefore indicate the benefit of appropriate treatment in the immediate lead up to the index event.

Antibiotics

Mention of antibiotics in the 2 months prior was associated with a 32% lower risk of asthma death and although there was no evidence of an association in the $>2-6$ months prior, the former was consistent with previously published results for the $>1-5$ year period (OR = 0.59).[5] This merits further investigation because there is little evidence in the literature to indicate whether or not antibiotics should be prescribed in the treatment of acute asthma without evidence of bacterial infection[25] and current guidelines clearly warn against over-use.

Study limitations

In this study we have gone to great lengths to obtain good quality data and to adjust for potential bias. Nevertheless, the quality and completeness of the information contained in the general practitioner notes was not within our control, leading us to base our drug variables on mention in the GP notes (Yes or No). Mention is not the same as prescription but in common with prescription is dependent on the level of use of primary and secondary care services. How to disentangle use leading to prescription or use increasing the likelihood of picking up a mention of a prescribed drug is problematic but to some extent will be adjusted for by the inclusion of other asthma drugs, prior hospital admissions and co-morbidity in our final model. As in all observational studies adjustment for confounding is important and in this new analysis we have introduced adjustment for deprivation in addition to markers of asthma severity and co-morbidity. However, the possibility of confounding by other factors cannot be discounted. Finally given that we present results for two time periods it is important that we do not place too much emphasis on unexpected significant results which may be the spurious outcome of multiple testing.

Conclusion

While associations of oral corticosteroids, injected corticosteroids and antibiotics with a lower risk of asthma death may simply indicate the benefits of appropriate medication for an acute asthma episode or infective exacerbation, the geographic pattern of results observed for inhaled short-acting beta$_2$-agonists though unexpected may point to differences in regional prescribing patterns and health service provision/utilisation. In a population of severe asthmatics in whom long-acting beta$_2$-agonists and inhaled corticosteroids appeared to be commonly prescribed concomitantly, there was no evidence overall that long-acting beta$_2$-agonists were associated with increased risk of asthma death.

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Conflict of interest statement

BKB owns shares in GlaxoSmithKline, she was involved in obtaining funding for this project from GlaxoSmithKline (US) and her post at St George's was funded on a fixed term basis by GlaxoSmithKline (US). HRA has received research funds from GSK for investigating the associations between drug treatment and mortality from asthma and several other projects, has received a consultancy fee for a meeting in San Francisco to discuss methods of investigating the mortality risks of asthma medications and has 680 shares in GSK. CJC has no competing interest to declare and received no funding for participation in this project.

References

1. Castle W, Fuller R, Hall J, Palmer P. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;**306**:1034—7.
2. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;**129**:15—26.
3. Nelson HS. Is there a problem with inhaled long-acting β-adrenergic agonists? *J Allergy Clin Immunol* 2006;**117**:3—16.
4. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev* 2008;(3). CD006363.
5. Anderson HR, Ayres JG, Sturdy PM, Bland JM, Butland BK, Peckitt C, et al. Bronchodilator treatment and deaths from asthma: case-control study. *BMJ* 2005;**330**:117—20 (BMJ, doi: 10.1136/bmj.38316.729907.8F (published 23 December 2004)).
6. Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BDW, et al. Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study. *Thorax* 2002;**57**:1034—9.
7. Sturdy PM, Butland BK, Anderson HR, Ayres JG, Bland JM, Harrison BDW, et al. Deaths certified as asthma and use of medical services: a national case-control study. *Thorax* 2005; **60**:909—15.
8. Office for National Statistics, Postcode Directories [computer file] ESRC Census Programme, Census Dissemination Unit, Mimas (University of Manchester) / Census Geography Data Unit (UKBORDERS), EDINA (University of Edinburgh). The data are crown copyright.
9. Office for National Statistics. Similarities and differences between the indices of deprivation across the UK, http://www.neighbourhood.statistics.gov.uk/dissemination/Info.do?page=analysisandguidance/analysisarticles/indices-of-deprivation.htm (accessed 14.09.10).
10. Office of the Deputy Prime Minister. Index of Multiple Deprivation 2004. [computer file]. The data are crown copyright.
11. Welsh Assembly Government. Welsh Index of Multiple Deprivation 2005 [computer file]. The data are crown copyright.
12. The Scottish Government. Scottish Index of Multiple Deprivation 2006 [computer file]. The data are crown copyright.
13. Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981—7: a further case-control study. *Thorax* 1991;**46**:105—11.
14. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775—89.
15. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled β-agonists. *Am J Respir Crit Care Med* 1994;**149**: 604—10.
16. Suissa S, Blais L, Ernst P. Patterns of increasing β-agonist use and the risk of fatal or near-fatal asthma. *Eur Respir J* 1994;**7**:1602—9.
17. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;**343**:332—6.
18. Lanes SF, Garcia Rodriguez LA, Huerta C. Respiratory medications and risk of asthma death. *Thorax* 2002;**57**:683—6.
19. Meier CR, Jick H. Drug use and pulmonary death rates in increasing symptomatic asthma patients in the UK. *Thorax* 1997;**52**:612—7.
20. Guite HF, Dundas R, Burney PG. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999;**54**:301—7.
21. The British Thoracic Society, The National Asthma Campaign, The Royal College of Physicians of London in association with the General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, the British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;**52** (suppl 1):S1—21.
22. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;**142**:832—6.
23. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalisation for asthma. *JAMA* 1997;**277**:887—91.
24. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;**57**:880—4.
25. Graham V, Lasserson TJ, Rowe BH. Antibiotics for acute asthma. *Cochrane Database Syst Rev* 2001;(2). CD002741.