

Bronchodilator treatment and deaths from asthma: case-control study

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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 has been an important issue since the mid-1960s, when the high concentration formulation of a non-selective β agonist drug (isoprenaline) was withdrawn. Adverse associations have also been

reported for the short acting β_2 agonist fenoterol, and also ipratropium, and theophylline. Possible adverse effects of short acting β_2 agonists remain, although no clinically adverse effect was found in a recent randomised controlled trial.¹ Available evidence suggests that the more recently introduced long acting β_2 agonists do not increase the risk of death, while the use of inhaled steroids is associated with a reduction in mortality. 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.² 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 listings of all deaths in which asthma was mentioned in part I of the death certificate for patients aged under 65 at the time of death, and for whom there was no more credible non-respiratory underlying cause of death, such as cancer. 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 and selected one control per case, matched firstly for admission date and then for age.

We obtained primary care records for both cases and controls. We anonymised and then photocopied the primary care records, including computerised records, hospital discharge letters, and hospital outpatient letters for the five years before the index date. Extraction of drug data, but not dose, was carried out 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. We supplemented some non-drug related data with information extracted non-blind from practice records for

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Odds ratios (95% confidence intervals) for death associated with prescription of drugs in the 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 admissions)§	Adjusted (other drug categories)¶	Adjusted (all)
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					
All 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)
Corticosteroids:					
Inhaled:					
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:					
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)					
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					
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 of asthma onset, and COPD (defined as mention of COPD, COAD, chronic bronchitis, or emphysema).

§Adjusted for sex, age of asthma onset, and hospital admission for asthma as two continuous variables, in past year and past 1-5 years.

¶Adjusted for sex, age of 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.

the period earlier than five years before the index date. The details of previous hospital admissions were validated against hospital records, which could not be done totally blind.

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 so the results for the 0-3 month 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, previous hospital admissions for asthma, and the number of other categories of drug prescribed.

Results

We identified 681 deaths from asthma that met our criteria, of which 149 (22%) were excluded from the final analysis. Of the 532 deaths in the final sample, 236 (44%) occurred in hospital. 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 (see *bmj.com*).

The table describes the associations between mortality and prescribed asthma drugs, adjusted for various potential confounding factors, including markers of severity, in the 1-5 years before the index date. The prescription of short acting β₂ agonist drugs in the 1-5 years before the index date was associated with an increased risk of asthma death. In the unadjusted analysis (adjusted only for sex and matching) 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. There was no evidence of an association in the year before the index date.

Long acting β₂ 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. After

full adjustment, the odds ratio for prescription in the 1-5 years before the index date fell, suggesting, if anything, an inverse association with mortality (table).

Antimuscarinic drugs were prescribed alone or with a short acting β₂ 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 (see *bmj.com*). There was no convincing evidence that inhaled corticosteroids were associated with mortality. In the unadjusted analysis, 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 significantly greater than 1.0. Further, the overall odds ratio decreased in size after additional adjustment for chronic obstructive pulmonary disease.

We found an inverse association with antibiotics which was significant for the 0-3 month and 1-5 year periods. This seemed to be more pronounced in those aged under 45. We found no evidence for an association with the number of different drugs prescribed. When we looked at 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 β₂ agonists only.

Discussion

We found no evidence associating long acting β₂ agonists with an increased risk of death in people with asthma. We did, however, find evidence for an increased risk with short acting β₂ 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.

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. We also analysed a subgroup of deaths and controls with an admission in the past year and found no significant associations after full adjustment (see bmj.com). 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; inclusion of deaths in the community increased the generalisability of the findings. In all cases, 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.

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.

In a case-control study such as this, an increased risk of death associated with drug therapy may have various explanations³⁻⁶—for example, more severe disease or an increasing severity of the disease before death (confounding or effect modification by severity), or both; treatment for associated 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.

There was no evidence to associate long acting bronchodilators with an increased risk of death and this is in line with other studies.^{7, 8} 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.^{9, 10} 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.

The risk of death associated with antimuscarinic preparations was increased but not significant in the full confounder model. Our estimate was considerably lower than that reported in a hospital cohort.¹¹ Methylxanthines have been implicated in deaths from asthma,¹² 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. Our finding supports the theory that insufficient treatment with oral steroids increases the risk of death. Regular use of inhaled steroids has been associated with reductions in mortality and hospital admissions,¹³ but we found little evidence of an association. One possible

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 this large population based study, there was no evidence to suggest 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

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.¹⁴ Apart from a protective effect, other explanations include a lower use of primary care services or greater adherence to the guidelines which caution against the use of antibiotics.

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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.

1 Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, et al. Regular inhaled salbutamol and asthma control: the TRUST randomised trial. Therapy Working Group of the National Asthma Task Force and the MRC General Practice Research Framework. *Lancet* 2000;355:1675-9.

- 2 Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BD, et al. Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study. *Thorax* 2002;57:1034-9.
- 3 Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
- 4 Chung KF. The current debate concerning beta-agonists in asthma: a review. *J R Soc Med* 1993;86:96-100.
- 5 Beasley R, Pearce N, Crane J, Windom H, Burgess C. Asthma mortality and inhaled beta agonist therapy. *Aust N Z J Med* 1991;21:753-63.
- 6 Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. *Am J Epidemiol* 1996;144:1161-9.
- 7 Meier CR, Jick H. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the UK. *Thorax* 1997;52:612-7.
- 8 Williams C, Crossland L, Finnerty J, Crane J, Holgate S, Pearce N, et al. Case-control study of salmeterol and near-fatal attacks of asthma. *Thorax* 1998;53:7-13.
- 9 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
- 10 Lanes SF, Garcia Rodriguez LA, Huerta C. Respiratory medications and risk of asthma death. *Thorax* 2002;57:683-6.
- 11 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.
- 12 Suissa S, Hemmelgarn B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996;154:1598-602.
- 13 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.
- 14 Graham V, Lasserson T, Rowe BH. Antibiotics for acute asthma. *Cochrane Database Syst Rev* 2001;(2):CD 002741.
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Timing of birth and risk of multiple sclerosis: population based study

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Abstract

Objectives To determine if risk of multiple sclerosis (MS) is associated with month of birth in countries in the northern hemisphere and if factors related to month of birth interact with genetic risk.

Design Population based study with population and family based controls and a retrospective cohort identified from death certificates. A post hoc pooled analysis was carried out for large northern datasets including Sweden and Denmark.

Setting 19 MS clinics in major cities across Canada (Canadian collaborative project on the genetic susceptibility to multiple sclerosis); incident cases of MS from a population based study in the Lothian and Border regions of Scotland; and death records from the UK Registrar General.

Populations 17 874 Canadian patients and 11 502 British patients with multiple sclerosis.

Main outcome measure Diagnosis of multiple sclerosis.

Results In Canada (n = 17 874) significantly fewer patients with MS were born in November compared with controls from the population census and unaffected siblings. These observations were confirmed in a dataset of British patients (n = 11 502), in which there was also an increase in the number of births in May. A pooled analysis of datasets from Canada, Great Britain, Denmark, and Sweden (n = 42 045) showed that significantly fewer (80.5%) people with MS were born in November and significantly more (9.1%) were born in May. For recent incident data, the effect of month of birth was most evident in Scotland, where MS prevalence is the highest.

Conclusions Month of birth and risk of MS are associated, more so in familial cases, implying interactions between genes and environment that are related to climate. Such interactions may act during gestation or shortly after birth in individuals born in the northern countries studied.

Introduction

Studies of twins, adoptees, half siblings, and families¹⁻⁴ have led to a widely accepted notion that multiple sclerosis (MS) is a complex trait in which susceptibility is determined by the interplay of genes and environmental factors. Environment seems to influence risk at a population level, but specific details remain unclear. The most striking clue to the role of environment has always been the gradient with latitude (see bmj.com).

Studies of month of birth and risk of MS have been carried out in several cohorts of people with MS, but sample sizes, ethnic groups, and statistical methods differed for each study and findings have been inconsistent.⁵⁻⁹ Although significant differences in month of birth compared with population based controls have been reported, they have not been for the same months.

Methods

Data on month of birth, along with detailed information on demographics and clinical and family history, were collected as part of the population based longitudinal Canadian collaborative project on genetic susceptibility to multiple sclerosis¹⁰ in 17 874 patients with MS. The first control group comprised all the recorded births in Canada from 1926 to 1970 (Statistics Canada). A second control group comprised unaffected siblings of people with MS.

As Scandinavian studies have shown an increase of MS in people born in spring, we hypothesised a similar increase, but we analysed each month separately. We compared the births in a single month with the 11 other months for cases and controls (population or siblings). For months for which we found no previous evidence of association, we corrected the P value for the 12 comparisons using Bonferroni correction.



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