

A case-control study of deaths from asthma

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ABSTRACT A population based case control-study was initiated in 1981 to identify risk factors for death from asthma. Over a two year period all deaths in the Auckland population possibly due to asthma, in people less than 60 years of age, were investigated. From the 47 people who died from asthma 44 who had useful reversibility of airways obstruction (records showing >20% variability of peak flow or a history indicating equivalent variability of shortness of breath) before death were selected as cases for the study. Both hospital and community based controls were used. The cases were more likely than were the community controls to have had severe disease, a hospital admission or visits to a hospital emergency department in the previous year (odds ratios 4.4, 16.0, 8.5 respectively). The asthmatic patients who died were more likely than either group of controls to have had a previous life threatening asthma attack. Poor management of the disease and poor compliance on the part of the patient increased the risk of death. In addition, use of three or more types of asthma drug within the past year was associated with an increased risk of dying that was independent of disease severity. Of interest was a similarity between asthmatic patients admitted to hospital and those who died. Nevertheless, a history of a previous life threatening attack and a recent admission to hospital identified a group at high risk.

We report the results of a population based case control study of fatal asthma, which was initiated as part of our investigation into the recent epidemic of deaths from asthma in New Zealand.¹ The objectives of this study were to describe more fully the patients who die of asthma and to examine the significance of characteristics previously suggested as being associated with death in descriptive studies.²⁻⁹

Methods

The cases were all people less than 60 years of age, who had died from 1 January 1981 to 31 December 1982 of asthma that was deemed to have been usefully reversible in the year before death, and who were normally resident in the Auckland region (March 1981 Census population 825 958, about a quarter of the total New Zealand population). Usefully reversible asthma was said to have been present if, in the year before death, there were recordings of swings in peak

flow or FEV₁ of more than 20%. If this information was not available then a subjective assessment of reversibility from hospital notes, the general practitioner, or a relative was accepted. Forty seven people died from asthma in Auckland over the two years in the age group being studied and 44 (94%) of these were categorised as having had usefully reversible asthma.

Two sets of asthmatic patients were selected as matched controls for those who died. A hospital control patient was randomly selected from all patients discharged from Auckland hospitals after admission for acute asthma. Controls were matched for age (± 5 years), sex, race, and date of hospital admission. Community controls were identified by asking a random sample of Auckland general practitioners to submit lists of all patients known to have asthma who consulted them over a four week period. This was repeated each quarter so that a control could be found for each patient who died close to the date of death. Like the hospital controls, they were matched for age, sex, and race. All the controls satisfied the definition of "usefully reversible asthma" in the year before their index event.

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For the cases and hospital controls, a detailed questionnaire was administered by one nurse to a close relative or friend, usually a cohabitant of the deceased. The same nurse interviewed the hospital controls themselves and one other nurse interviewer gave the same questionnaire to the community controls. The two nurse interviewers worked closely together, following a detailed instruction manual, and discussed equivocal responses in an attempt to achieve uniformity. Separate questionnaires were administered to any specialist concerned and to the patient's general practitioner. Questionnaires were usually done six to eight weeks after the death, admission, or visit to the general practitioner. The questionnaire covered the nature of the disease, medical management in the last 12 months, and features of the last episode.

Asthma was defined as severe, moderate, or mild. If in the year before entry to the study there had been one or more admissions to hospital or three or more urgent visits to a general practitioner or accident and emergency department, the asthma was classified as severe. The asthma was defined as moderate if the patient had been frequently prevented from working, often woke at night, or needed to visit the doctor urgently because of asthma once or twice in the last year (or any combination of these). A life threatening attack was defined as an attack where consciousness had been disturbed or appreciable hypercapnia had been recorded. Discontinuity of general practice care was defined as failure to attend a general practitioner between acute attacks and visiting several doctors, so that previous records would not be available. Details of the data collection and review methods have been published elsewhere.¹⁰

To facilitate comparisons of medical care, a scoring system was devised to judge medical management in the previous 12 months. This scoring system was based on accepted criteria for sound medical management,^{11 12} and was assessed by calculating a score for each patient from the 12 items shown in table 1. Some of the items were not applicable or were unanswerable for individual patients, and in that case the question was excluded from the achievable total rather than scored as a "no." Each item was given equal weighting and the optimal score for a particular patient was 100%.

Relative risks were estimated in univariate analyses by use of the matched pairs odds ratio with 95% confidence limits computed from the binomial distribution.¹³ The proportional hazards model of Cox was used to perform conditional multivariate logistic regression, so that the net relative risk of dying from asthma associated with a particular variable could be estimated after control for confounding variables—for example, severity.¹⁴ Differences in proportions

Rea, Scragg, Jackson, Beaglehole, Fenwick, Sutherland

were tested by means of the test for independent samples.¹⁵

Results

Forty four cases were identified; postmortem results were available for 32. Matched hospital controls were found for 39 cases and community controls for all cases. Previous hospital records were available for 27 of the cases, 22 of the hospital controls, and 11 of the community controls (table 2a). Hospital notes relating to admissions in other parts of New Zealand and in other countries were not reviewed. For all 39 hospital controls notes pertaining to the index admission were perused. Few patients in any of the groups were currently attending a hospital clinic (table 3b). Information for all cases and controls was available from the general practitioner records. This information will have been less reliable for those with discontinuity of general practice care (table 3b). From the various sources we used documented objective evidence for useful reversibility of airways obstruction was available for 27 cases, 38 hospital controls, and 14 community controls.

The mean age of the cases was 33 (range 10–58) years; 25 were male and 19 female. Twenty six of the cases were caucasian, nine Maori and nine Pacific Islanders.

NATURE OF THE DISEASE

Characteristics of the patients dying from asthma are compared with those of the control patients in table 2a and the relative risk of death associated with these is shown in table 2b. More of the cases and hospital controls than of the community controls had had previous admissions to hospital. The differences were more striking when we considered only admissions in the previous year. Cases and hospital controls presented to accident and emergency departments in the previous year for the management of severe acute

Table 1 *Scoring of medical management during past 12 months*

1	Shown how to use inhaler
2	Used a peak flow meter at home
3	Substantial agreement between GP and patient about drugs in regular use
4	Continuity of GP care
5	Referred to hospital clinic (only applicable to those with severe asthma)
6	Adequate communication between GP and clinic where applicable
7	Lung function measured by GP in past 12 months
8	Lung function measured by GP at each consultation
	Evidence that in an unusually bad attack the patient:
9	had been given some advice on what action to take
10	knew he had to increase β agonist
11	knew when to start steroids (only applicable to those with severe asthma)
12	knew where to get appropriate help

Table 2 Indices of severity and psychosocial problems
(a) Indices of severity in cases and controls

	Cases (n = 44)	Hospital controls (n = 39)	Community controls (n = 44)
Hospital admission ever (includes past year)	28	22	14
Hospital admissions in past year	17	17	2
Previous life threatening attack (ever)	20	8	0
Previous life threatening attack and admission in past year	13	4	0
Accident and emergency department visit in past year	17	13	2
Emergency visit to GP in past year	23	21	16
Psychosocial problems noted in hospital or GP records*			
Alcoholic	4	1	—
Personality disorder	4	2	—
Depression	3	2	—
Recent bereavement	3	0	—
Recent unemployment	3	1	—

*Only for cases and hospital controls.

(b) Indices of severity and relative risk* of dying from asthma

Variable	Cases v hospital controls (matched pairs = 39)		Cases v community controls (matched pairs = 44)	
	Ratio of discordant pairs	Relative risk (95% CL)	Ratio of discordant pairs	Relative risk (95% CL)
1 One or more hospital admissions for asthma in past year	10/12	0.8 (0.3, 2.1)	16/1	‡16.0 (2.5, 665.7)
2 One or more accident and emergency department visits for asthma in past year	11/10	1.1 (0.4, 2.9)	17/2	‡8.5 (2.0, 75.9)
3 Two or more emergency visits to GP for asthma in past year	11/10	1.1 (0.4, 2.9)	12/6	2.0 (0.7, 6.5)
4 Severe asthma§	12/10	1.2 (0.5, 3.1)	22/5	‡4.4 (1.6, 14.9)
5 One or more previous respiratory arrests	5/1	5.0 (0.6, 237.1)	7/0	‡α (1.4, α)
6 One or more previous life threatening asthma attacks	15/4	†3.8 (1.2, 15.5)	20/0	‡α (4.9, α)
7 Psychosocial problems	14/4	†3.5 (1.04, 13.7)	—	—

*Relative risk = ratio of discordant pairs.

†p < 0.05; ‡p < 0.01, compared with a relative risk of 1.0.

§4 is derived from 1, 2, and 3.

CL—confidence limits.

attacks more commonly than did community controls. Seventeen cases had attended accident and emergency departments in the year before death—on an average of five occasions (median 2, range 1–45). Thirteen hospital controls had used accident and emergency departments, with an average of three visits each (median 3, range 1–6), whereas only two of the community controls had presented to accident and emergency departments. There was less difference between cases and controls with regard to the number of urgent visits to a general practitioner in the past year. The 23 cases had on average visited three times (median 3, range 1–8), the 21 hospital controls 2.8 times (median 3, range 1–4), and the 16 community controls 2.4 times (median 3, range 1–4).

Table 2b shows that the asthmatic patients who died were more than four times as likely as the community controls to have had severe asthma, 16 times as likely to have had a prior admission to hospital for asthma, and over eight times as likely to have visited

a hospital accident and emergency department in the previous 12 months. In contrast, asthmatic patients who died could not be distinguished from the hospital controls by these indicators of the severity of asthma.

Previously reported respiratory arrests or life threatening asthma attacks were significantly more common among asthmatic patients who died than among the community controls. Life threatening attacks were also significantly more common among the cases than among hospital controls.

No significant differences between the cases and either group of controls were found with respect to the age of onset of asthma, family history of asthma, or smoking habits.

Psychosocial problems were more common in cases than in hospital controls (only information from hospital or general practice records was accepted as evidence of psychosocial problems). The relative risk of dying from asthma associated with a psychosocial problem was 3.5 (95% confidence limits = 1.004,

Table 3 Aspects of medical management

(a) Medical care and prescription of drugs in mild, moderate and severe asthma

	Cases (n = 42†)	Hospital controls (n = 39)	Community controls (n = 44)
<i>Severe asthma</i>			
Number	27	21	10
Medical care score* (mean %)	49	58	62
Categories of asthma drugs prescribed (mean)	3.5	3.8	3.4
<i>Moderate asthma</i>			
Number	12	11	20
Medical care score* (mean %)	48	58	65
Categories of asthma drugs prescribed (mean)	3.1	2.5	2.8
<i>Mild asthma</i>			
Number	3	7	14
Medical care score* (mean %)	29	65	73
Categories of asthma drugs prescribed (mean)	1.3	2.4	2.1

*See under "Methods."

†Two never attended a general practitioner.

(b) Drug prescription, general practitioner and specialist care, and patients' compliance

	Cases (n = 44)	Hospital controls (n = 39)	Community controls (n = 44)
Categories of drug prescribed (mean for group as a whole*)	3.2	3.2	2.7
Discontinuity of GP care	14	4	1
Pulmonary function not measured by GP in last year	29	19	15
Compliance poor as judged by GP	23	16	8
Ever attended a specialist or chest clinic	16	17	13
Currently attending a hospital or chest clinic (> 2 visits in past year)	7	6	0

*No of cases 42.

(c) Medical management and the relative risk* of dying from asthma

Variable	Cases v hospital controls (matched pairs = 39)		Cases v community controls (matched pairs = 44)	
	Ratio of discordant pairs	Relative risk (95% CL)	Ratio of discordant pairs	Relative risk (95% CL)
Below average medical care score	15/8	1.9 (0.7, 5.1)	20/7	†2.9 (1.2, 8.0)
Pulmonary function not measured by GP in past year	10/9	1.1 (0.4, 3.1)	19/7	†2.7 (1.1, 7.6)
Three or more categories of asthma drugs prescribed by doctor in past year	12/7	1.7 (0.6, 5.1)	15/5	†3.0 (1.04, 10.5)
Three or more categories of asthma drugs taken by patient in last year	13/13	1.0 (0.4, 2.3)	17/7	2.4 (0.96, 6.9)
Patients' non-compliant with medical treatment	13/9	1.4 (0.6, 3.8)	21/0	‡α (5.2, α)

*Relative risk = ratio of discordant pairs

†p < 0.05; ‡p < 0.01, compared with a relative risk of 1.0.

CL—confidence limits.

13.7) when cases were compared with hospital controls. Psychosocial variables were not examined in community controls. Among cases and hospital controls psychosocial problems did not appear to be more common in any particular racial group, affecting 16 Europeans, four Pacific Islanders and three Maoris.

MEDICAL MANAGEMENT IN THE PAST 12 MONTHS
Tables 3a and 3b show aspects of medical management and table 3c the relative risks of dying from asthma associated with these. In table 3a medical care scores are shown with the patients stratified according to the severity of their disease. There is no clear relationship between medical care scores and severity

but for all grades of severity those who died appear to have received poorer medical care than either group of controls—that is, they had lower medical care scores. Two of the cases had never sought routine general practice care; instead they used accident and emergency departments or emergency general practice services during attacks. Below average scores (that is, below the average for all cases and controls combined) were estimated to be three times as frequent in those who died than in community controls and twice as common as in hospital controls (table 3c). This increase was significant when cases were compared with community controls, and was independent of the degree of asthma severity. One component of the medical care score—failure by the general practitioner to measure pulmonary function within the last year—was associated with about a threefold increase risk of dying from asthma when cases were compared with community controls (table 3c). Multivariate analyses showed that this was independent of asthma severity.

The role of multiple medication was investigated. Asthma drugs were classified into five categories: β agonists, theophyllines, sodium cromoglycate, inhaled corticosteroids, and oral corticosteroids. The information was obtained from two sources: from the general practitioner for drugs prescribed and from a patient or relative for the drugs taken. The mean number of categories of asthma drugs prescribed is shown for the cases and controls stratified for severity of disease and for the groups as a whole in tables 3a and 3b. Patients with mild asthma were prescribed fewer drugs but the mean number of drugs prescribed for the groups as a whole did not differ greatly. The use of three or more categories of asthma drugs within the past years was, however, associated with an increased risk of dying from asthma when cases were compared with community controls (table 3c), regardless of the source of information. This relationship was also independent of severity of asthma. Non-compliance by patients with medical treatment was determined from the opinion of the patient, relative, or doctor (only the general practitioner's judgment is shown in table 3b) or from hospital notes, or both. Admittedly, non-compliance was difficult to assess but it appeared to be associated with an increased risk of dying from asthma. This was particularly so for comparisons between cases and community controls, and multivariate analyses showed that this result was independent of asthma severity (table 3c). Discontinuity of general practice care was also more common in cases than in controls.

Discussion

This study, apparently the first study of asthma mor-

tality to include control groups, has identified several factors that delineate patients with asthma who are at high risk of death and allows confidence limits to be applied to these risk factors. The study confirms earlier findings that a recent hospital admission, recent visits to an accident and emergency department, a previous respiratory arrest or life threatening attack, poor medical management, and poor compliance are significant risk factors for death from asthma.²⁻⁹ In addition, the similarity between cases and hospital controls is in accord with the common experience that patients admitted to hospital have more troublesome asthma than those with no previous admissions. Indeed, the best way to identify asthmatic patients at risk of death is to identify those who have had a recent hospital admission and in particular those who have ever had a life threatening attack.

Asthmatic patients who are admitted to hospital and those who die appear to come from a similar portion of the asthmatic population—that is, they have troublesome disease (admissions to hospital), are non-compliant, and use accident and emergency departments for treatment of acute attacks. There is, however, a suggestion of some dissimilarities between those who die and the hospital controls. Those who die may have had more severe disease (previous life threatening attacks), received poorer medical care, had more discontinuous general practice care, and had more psychosocial problems. The importance of some of these factors was, however, hard to judge. The assessment of psychosocial problems was made only from general practice records and hospital notes. The latter were infrequently available for community controls so psychosocial data are not shown for this group. Furthermore, community controls were selected by their attendance at a general practice, so judgment about continuity of care may be biased. Medical care appeared to have been better for hospital controls than for cases but the relative risk estimate did not reach significance. Medical care scores were better for community controls than for either cases or hospital controls. Clearly attitudes of patient and family to compliance and the need for continuous general practice care would influence medical care scores. Non-compliance was difficult to assess since it could not always be judged from already documented sources.

The major strength of this study is that it is population based, and thus avoids the selection biases that may occur in hospital based studies. By comparison with controls it also allows confidence limits to be applied to previously described risk factors. The cases included all asthma deaths in people with reversible asthma aged less than 60 years occurring in Auckland during 1981-2 and represented 94% of all those who died from asthma. Within the constraints of the

matching variables (age, sex, race, date of death), the controls were representative of their respective hospital or general practitioner treated asthma populations since they were randomly selected from all asthmatic patients admitted to hospital with acute asthma and those treated by all general practitioners within Auckland during 1981–2.

It is possible that misclassification biases—specifically recall, interviewer, and reviewer biases—are present in this study. Recall bias could have been introduced since some of the basic information about cases came from relatives whereas for controls the corresponding information came from the patients themselves. For example, the reviewers found that more of the items listed in table 1 lacked an answer for the cases than for the controls because of vague or indeterminate answers from the relatives. But by excluding such items in the scoring of medical management the bias would tend to favour the cases—that is, where a relative answered “Don’t know” the question was excluded even though the correct answer may have been “No.” For the first 10 controls recruited, answers from relatives and the patients themselves were compared. For hospital admissions, previous life threatening attacks, urgent medical care, and estimates of compliance concordance was excellent.

Interviewer and reviewer bias was harder to deal with. It was not possible to “blind” the reviewers on whether they were assessing a patient who died or a control. An attempt was made to look for such bias by having an independent reviewer assess many of the cases. Concordance was extremely high between this independent reviewer and the Auckland reviewers.

Misclassification bias is less likely where recorded information was available and for many of the assessments hospital notes or general practitioners’ records were the source. Most of the comparisons presented in this paper are based on recorded information. More subjective features such as the circumstances surrounding the death were not investigated as they do not lend themselves easily to a comparison of patients who died with the controls because of the major potential for recall bias.

It was unfortunately not possible to judge accurately whether oral theophylline or the use of nebulisers, which have been implicated as possible reasons for the increased asthma mortality rates in New Zealand,^{16 17} were associated with an increased risk of death. Although there was no anecdotal evidence for an excessive use of drugs immediately before death, nebulisers, for example, were used by so few patients that the power of this study to identify increased risks was very low. It was also difficult to determine whether cases or controls were currently taking oral theophylline. For both the cases and the controls recall about drugs might well have been biased. The

information came from relatives of the cases but directly from the controls, often many weeks after the event under study. Medical records of the drugs given were often incomplete and differed considerably from the information obtained from patients and relatives—particularly so for the various drug groups other than β agonists. These doubts about the validity of the information on drugs in this study indicate the need for further and more specific studies of their possible role in asthma deaths.

There is some evidence from the study that factors in the asthmatic patient’s life style may be associated with an increased risk of death from asthma. For example, the cases were found to be less compliant than the community controls. Because of the partly subjective nature of this measurement, however, we cannot be certain about the importance of this. Cases were more likely to have prior psychosocial problems than hospital controls.

The findings from this study are compatible with the hypothesis that some of those who die may be confused about how and when to use their various asthma medications. The prescription of three or more categories of asthma drugs was associated with an increased relative risk of death that was independent of asthma severity. Disagreement between the patient and the usual doctor about drug usage was more common in those who died than in community controls. This is unlikely to be related to the number of drugs taken by subjects as there was little difference in the number of drugs prescribed for cases and controls (table 3*b*). These risk factors may be further confounded by non-compliance and by psychosocial problems. Such confusion may partly explain why in a large proportion of the recent deaths from asthma in New Zealand medical advice had not been sought during the final asthma attack.¹⁰

We have identified several risk factors for death from asthma in this study that are important for the clinician. The results show that asthmatic patients who have had a recent admission to hospital, a recent visit to an emergency department, or a previous life threatening asthma attack are at increased risk of dying from asthma.

That patients with these risk factors require special medical attention is emphasised by the finding of an increased risk of dying from asthma associated with a below average medical care score. Over 60% of those who died in this study had had previous hospital admissions because of asthma and could have been selected for special care and follow up at least by their general practitioners. Hospital follow up, in addition, could be offered to asthmatic patients who have had a recent hospital admission plus a previous life threatening attack, especially if there is evidence of poor management in general practice or poor use of gen-

eral practice care. This might have helped the 30% of patients in this study who could have been identified in this way before their death.

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References

- 1 Jackson RT, Beaglehole R, Rea HH, Sutherland DF. Mortality from asthma: a new epidemic in New Zealand. *Br Med J* 1982;**285**:771-4.
- 2 Anonymous. Fatal asthma [editorial]. *Lancet* 1979;ii:337-8.
- 3 Johnson AJ, Nunn AJ, Somner AR, Stableforth DE, Stewert CJ. Circumstances of deaths from asthma. *Br Med J* 1984;**288**:1870-2.
- 4 Cochrane GM, Clark TJH. A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax* 1975;**30**:300-5.
- 5 Macdonald JB, Seaton A, Williams DA. Asthma deaths in Cardiff in 1963-74: 90 deaths outside hospital. *Br Med J* 1976;i:1493-5.
- 6 Macdonald JB, Macdonald ET, Seaton A, Williams DA. Asthma deaths in Cardiff 1963-74: 53 deaths in hospital. *Br Med J* 1976;ii:721-3.
- 7 Omerod LP, Stableforth DE. Asthma mortality in Birmingham 1975-7: 53 deaths. *Br Med J* 1980;**280**:687-90.
- 8 Hetzel MR, Clark TJH, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J* 1977;i:808-11.
- 9 Fraser PM, Speizer FE, Waters SDM, Doll R, Mann NM. The circumstances preceding death from asthma in young people in 1968 to 1969. *Br J Dis Chest* 1971;**65**:71-84.
- 10 Sutherland DC, Beaglehole R, Fenwick J, Jackson RT, Mullins P, Rea HH. Death from asthma in Auckland: circumstances and validation of causes. *NZ Med J* 1984;**97**:845-8.
- 11 Hetzel MR, Clark TJH. Management of adult asthma. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1983:457-84.
- 12 Paterson JW, Tarala RA. Asthma: common pitfalls in management. *New Ethicals* 1981;**18**:39-48.
- 13 Breslow NE, Day NE. *Statistical methods in cancer research*. Vol 1: *The analysis of case-control studies*. Lyon: International Agency for Research in Cancer, 1980. IARC Scientific Publications, No 32.
- 14 Harrell FE. The PHGLM procedure. In: *Sugi Supplemental Library Users Guide*. North Carolina. SAS Institute Inc, 1983:267-94.
- 15 Colton T. *Statistics in medicine*. Boston, Mass: Little, Brown, 1974.
- 16 Wilson JD, Sutherland DC, Thomas AC. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? *Lancet* 1981;i:1235-7.
- 17 Grant IWB. Asthma in New Zealand. *Br Med J* 1983;**286**:374-7.