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Mortality in asthmatics over 15 yrs: a dynamic cohort study from 1983–1998

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Mortality in asthmatics over 15 yrs: a dynamic cohort study from 1983–1998. C.K. Connolly, S.M. Alcock, R.J. Prescott. ©ERS Journals Ltd 2002.

ABSTRACT: The Darlington and Northallerton long-term asthma study observes outcome in asthmatics in the light of potential explanatory variables recorded prospectively. This paper reports changes in mortality during the study, and assesses the relevant risk factors.

All asthmatics attending secondary care were recruited at 5-yr intervals from 1983 and reviewed 5 yrs later. Demographic and functional variables, including a formal estimate of best function were recorded prospectively.

The dynamic cohort comprised 1,148 asthmatics with 95% follow-up, enabling 612 observations in the period 1983/1988, 774 in 1988/93 and 823 in 1993/98, with 101, 111 and 100 deaths respectively. Principal risk factors for mortality were lower social class and best forced vital capacity. Mortality relative to 1983 halved by 1993/98 and was reduced against the Darlington population, despite an entry forced expiratory volume in one second of 84.7%. There was no change in predictive value of risk factors during the study period, or with date of entry.

This study demonstrates a consistent reduction in mortality, which was not entirely a survivor effect, but may be associated with changes in management. By 1993/98 mortality approximated to that of the local reference population despite a lower than predicted forced expiratory volume in one second.

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The Darlington and Northallerton long-term asthma study was started in 1983 with the aim of studying the outcome of asthma in the light of prospectively recorded explanatory variables. The first subjects, recruited in 1983 [1, 2] were seen at 5-yr intervals with full review of the potential explanatory variables, and with recruitment of further patients in 1988 and 1993. This paper examines the relationship between mortality and the potential explanatory variables over three 5-yr periods from 1983 to 1998. During this time the prophylactic use of inhaled corticosteroids expanded, guidelines [3] were produced, with emphasis on patient self-management plans, and on nurse-run clinics introduced into general practice [4]. The principal predictors of mortality in the first 10 yrs were best (postbronchodilator) function and social class [5]. Over the 15 study yrs inhaled corticosteroid doses increased with better actual/best function at each step [6], suggesting more appropriate management of asthma.

Epidemiological studies suggest that although the incidence of asthma continued to increase, particularly in children [7], at least until the mid-nineties [8], the secular increase in mortality [9–11] may have been reversed earlier [12–14]. This paper presents the changes in mortality from all causes that were observed in the asthmatic subjects over three consecutive 5-yr periods.

Methods

Recruitment

Subjects were recruited at 5-yr intervals in 1983, 1988 (April–March 1989) and 1993 (April–March 1994). The survivors were re-assessed fully each time and the data was used in the analysis pertaining to succeeding quinquennium. The analysis allows for the slightly greater length of the first period.

Subjects

All subjects recruited were aged >18, with no upper age limit, and were followed in secondary care in the former Darlington and Northallerton Health Districts (including privately). The Darlington, Northallerton and South Durham Research Ethics committees approved the study at various stages.

At the time there was only one physician responsible for respiratory medicine in the two districts. In this part of the country, referral patterns followed district boundaries fairly strictly, except for one town nominally outside the district from which most respiratory problems were referred to Darlington. The physician reviewed all the notes at every clinic attended and ensured that all subjects satisfying the criteria were entered.

The diagnosis of asthma was clinical but it was confirmed by reversibility of peak flow by 15% on at least two occasions after first referral. Severe established functional chronic obstructive pulmonary disease (COPD) was excluded by requiring a peak flow of $\geqslant 200$ L·min^{-1}, and when the nature of the inflammation was in doubt, diagnosis was confirmed by sputum or blood eosinophilia.

History

Social and demographic variables were recorded at entry as previously described [1, 2]. These included: atopic status, childhood asthma, social class (Registrar General's classification), smoking habit, amount smoked, presence of pets, children, and central heating in, and site of, household. Duration was measured from first onset or recurrence after an interval of 5 yrs. Childhood asthma was defined as the presence of intermittent lower respiratory symptoms during childhood in the absence of chronic sputum production.

Therapy

Subjects were considered stable when on a mutually-agreed satisfactory regimen, without the need for a booster course of oral corticosteroids over the previous 3 months. All relevant medication was recorded, but the dose of inhaled corticosteroids was not entered in 1983, when virtually all the subjects were on <800 μg·day^{-1}. Subjects unstable at attendance were reviewed after a further 3 months, and, if then stable, the actual pulmonary function recorded was used in the analysis.

Pulmonary function

The following were recorded at entry:

Actual function. Peak expiratory flow (PEF) and forced expiratory flow in one second (FEV_1) (Rolling Seal Spirometer; Vitalograph, Maidenhead, UK) were measured at the reference visit. Subjects were not specifically requested to withhold bronchodilators before attendance, but actual function was recorded before any further bronchodilators were given.

Best function. Best PEF and forced vital capacity (FVC) were assessed at each entry and best FEV_1 in 1988 and 1993. The highest value recorded in the notes from January 1st the previous year up to and including the first visit was accepted as best, subject to the following criteria: 1) if >80% predicted: postbronchodilator; 2) if 70–80% pred: postbronchodilator stable on regular prophylactic therapy, with 4-hourly charting of PEF for 7 days; 3) if <70% pred: postbronchodilator, following $\geqslant 30$ mg prednisolone for $\geqslant 7$ days, with stable peak flow for $\geqslant 48$ h.

These criteria were considered independently for each measurement, and if they were not met, best function was immediately established using this protocol. The reference values of COTES [15] were used.

Actual over best function. The ratio of actual function at attendance to best function, as described earlier, was expressed as a percentage. Best FVC and FEV_1 were both used as denominators for actual FEV_1, and FEV/FVC was expressed as % pred.

Follow-up

All subjects were seen, recalled or traced at 5-yr intervals. Patients lost to follow-up were traced through their general practitioner and the local Registrar of Deaths. If this was not successful the Family Health Services Authority was approached.

Classification of death. Deaths were recorded as being due to asthma, other respiratory and nonrespiratory causes on the basis of case records or death certificates, and accepted as a unknown cause if neither were available. Death from asthma was defined as death due to sudden or rapid deterioration of recently reversible airway obstruction, as confirmed from the clinical records or contact with the general practitioner. All other respiratory deaths were classified as other respiratory deaths; the great majority of which were ascribed to bronchopneumonia or COPD. Carcinoma of the bronchus was regarded as nonrespiratory death, as the primary concern was deaths that might be associated with morbidity due to the asthmatic process. Mortality figures for the Darlington Health District for the 3-yr period 1990–1992 were used to calculate the expected mortality, using 10-yr age bands. These expected mortality figures were then compared with the observed mortality to calculate the standardized mortality ratio (SMR). Approximately one-third of the patients were recruited in Northallerton, where the published district SMR is lower than for Darlington (SMR *versus* England and Wales: Darlington 1.24, Northallerton 0.92 (1991)).

Statistical methods

Confidence intervals (CI) for standardized mortality ratios were calculated using the method described by GARDNER and ALTMAN [16]. Univariate and multivariate analyses of factors influencing the probability of death within each of the 5-yr periods were based on linear logistic regression analysis. This method was chosen instead of the use of survival methods such as Cox's proportional hazards with time-dependent covariates, because exact dates for loss to follow-up or death were not always available. For each 5-yr

Table 1. – Demographic details at entry

	Year of entry			Calendar period (subjects with known outcome)		
	1983	1988	1993	1983/1988	1988/1993	1993/1998
Subjects n	628	309	628	612	730	737
Male %	49.4	54.7	49.8	49.3	50.7	49.2
Age yrs	52 (16)	50 (17)	53 (16)	52 (16)	50 (17)	53 (16)
Duration yrs	19.5 (16.2)	15.3 (14.7)	18.1 (16.9)	19.5 (16.2)	20.7 (16.1)	23.3 (16.2)
Atopic %	53.7	52.4	47.9	53.6	50.6	45.4
Current smoker %	15.6	14.9	14.9	15.8	12.0	9.2
Amount smoked pack-yrs[#]	13.0 (20.1)	15.5 (22.0)	15.2 (21.1)	13.0 (20.1)	13.9 (20.7)	12.5 (20.1)
Actual FEV1	75.0 (27.1)	78.6 (28.1)	77.0 (26.7)	75.2 (27.1)	76.4 (27.3)	75.3 (26.8)
Best FEV1		77.0 (26.7)	87.6 (33.1)		84.6 (27.2)	84.6 (27.2)
Best FVC[¶,+]	96.2 (19.4)	94.8 (23.5)	94.8 (25.5)	96.3 (19.7)	94.0 (22.9)[§]	93.4 (22.3)[ƒ]
Actual/best PEF	79.6 (16.7)	86.4 (13.5)	88.2 (11.2)	79.6 (16.7)	85.1 (14.0)	86.9 (12.2)

SD is given in parentheses where appropriate. [#]: Mean of all entry values (current smokers: 29.6 (24.5) males, 21.4 (14.2) females; ever-smokers: 27.8 (23.8) males, 14.2 (14.5) females). [¶]: It was impracticable to obtain full pulmonary function tests from any subjects not actually attending. Overall, best forced vital capacity (FVC) was not obtained in 90 subjects (11.1%) in 1988 and 132 (15.2%) subjects in 1993. [+]: FVC of survivors from previous period: [§]1988, 93.6% *versus* 96.2%; [ƒ]1993, 92.7% *versus* 94.8%. FEV1: forced expiratory volume in one second; PEF: peak expiratory flow.

period, the independent variables were the respiratory and social variables as recorded at the start of that 5-yr period. Pulmonary function is expressed as % pred and actual/best FEV1 and actual/best PEF as simple percentages, as the fit of models was no better with the use of absolute values or logarithmic transformation of the pulmonary variables. The changes in mortality over successive periods in each cohort were further explored by expressing mortality by SMRs against the local population. The association between treatment step and mortality was explored by comparing the observed numbers of deaths in the succeeding 5-yr periods with the expected numbers, calculated from the logistic regression model using the respiratory and social variables.

Occasional missing values resulted in minor discrepancies in total numbers, but analyses are always based on the maximum number of subjects available.

Results

General

The total study population (from 1983, 1988 and 1993) comprised 1,148 asthmatics. The outcome was known in 612 over the period 1983–88, 811 from 1988–93 and 870 from 1993–98, giving 2,293 observations, with >95% follow-up. There were satisfactory measurements of best function at the start of the period in 2,162 cases. The principal demographic details are shown in table 1, together with pulmonary function. Overall 28% were in social class 1/2, 38% in class 3, and 34% in class 4/5; the proportion in class 4/5 increased from 30% in 1983 to 40% in 1993. Best FEV1 was not recorded in 1983. Actual/best function of new entrants improved between 1983 and 1988.

Oral corticosteroids were prescribed to 19.3% of stable subjects in 1983, 13.6% in 1988 and 4.5% in 1993 and bronchodilators alone to 20.7% in 1983, 7.9% in 1988 and 3.6% in 1993. As therapeutic options and patient expectations increased, so did the proportion "unstable", from 4.2% in 1983 to 5.6% in 1988 and 8.9% in 1993.

Mortality

Between 1983–1988 101 subjects died, in 1988/93 111 died, and 100 died in 1993/1998. Unequivocal deaths from asthma declined from nine (1983/1988), through five (1988/1993), to one 1993/1998, but deaths due to other respiratory causes remained between two and three times the expected rate (34% 1983/1988, 40% 1988/1993, and 32% 1993/1998). Mortality for each entry date in each period is shown in tables 2 and 3. Although number of deaths remained constant, age/sex adjusted survival improved substantially. The relative mortality against the Darlington population fell from 1.98 (95% CI 1.62–2.41) through 1.36 (95% CI 1.12–1.63) to 1.01 (95% CI 0.81–1.22).

Multivariate associations

In the multivariate analysis covering all of the 2,162 available observation periods (table 4), functional variables were restricted to a pair, one to assess best function and the other to measure actual/best independently. Best FVC and actual/best PEF were

Table 2. – Absolute mortality

Period	Entry date			
	1983	1988	1993	All
1983/88	101/612			101/612
1988/93	74/502	37/272		111/774
1993/98	51/413	30/220	17/190	98/823[#]

The denominator is the number of subjects in whom outcome was known. [#]: Excludes two subjects who were lost to follow up in 1993 but were subsequently known to have died between 1993–1998.

Table 3. – Relative mortality

Period	Entry date			
	1983	1988	1993	All
1983/88	1			1
1988/93	0.71 (0.60–1.01)	0.66 (0.43–1.02)		0.69 (0.50–0.95)
1993/98	0.43 (0.29–0.64)	0.52 (0.27–0.96)	0.35 (0.20–0.63)	0.44 (0.32–0.61)

The reference cell entry date 1983/period 1983/88 is assigned a value of 1. Data are expressed as relative mortality with 95% confidence intervals in parentheses after allowing for age and sex.

chosen, because the association between actual/best PEF and FVC (r=0.32) was less than that between best PEF and actual FEV1/best FVC (r=0.45). In this analysis, the predictive value of best function (best FVC per 10% deficit; odds ratio (OR) 1.29 (95% CI 1.19–1.39)) and actual/best PEF (OR 1.16 (95% CI 1.06–1.27)) were confirmed. After allowance for these two variables actual FEV1 still made a contribution (Chi-squared=5.58, p=0.02). Best FEV1 was not recorded until 1988, so it could not be used in the main analysis, but it was subsequently the strongest functional predictor of mortality (OR per 10% deficit 1.34 (95% CI 1.23–1.44)). After 1988 the most discriminating pair out of all possible combinations of best and actual best function became best FEV1 and actual/best PEF (Chi-squared=41.6), as compared with, for example, best FVC and actual/best PEF (Chi-squared=34.1).

The relevant social variables were social class (OR 1.20 (95% CI 1.04–1.39)) and current smoking (OR 1.51 (95% CI 1.00–2.28)). The period effect is highly significant before (p=0.0001) and after the multivariate analysis including all relevant risk factors (Chi-squared=9.76, p=0.008). There was no difference between the subjects who entered the dynamic cohort at the different times (p=0.70).

After allowance for all of the factors stated earlier, more intensive therapy was an independent predictor of mortality in stable subjects. The trend in mortality was consistent (low-dose inhaled steroids 0.76 (95% CI 0.59–0.96), intermediate dose 0.79 (95% CI 0.56–1.09), high dose 1.05 (95% CI 0.68–1.55), oral steroids <10 mg 1.40 (95% CI 1.06–1.82), and oral steroids >10 mg 1.79 (95% CI 1.19–2.59)). The CI did not overlap at the extremes. The trend was seen in each period with no interaction between steroid step and the other predictive variables.

Table 4. – The principal multivariate associations with mortality in the subsequent 5-yr period

Parameter	OR	95% CI	p
Age per decade	2.25	1.93–2.61	<0.0001
Male sex	1.64	1.21–2.01	0.0012
Female sex	1		
Social class[#]	1.20	1.04–1.39	0.014
Current smoker	1.51	1.00–2.28	0.049
Best FVC[¶]	1.29	1.19–1.39	<0.0001
Actual/best PEF[+]	1.16	1.06–1.27	0.0019
1983/1988	1.82	1.25–2.52	0.0018
1988/1993	1.45	0.94–1.95	0.094
1993/1998	1		

Potential maximum observations=2293. [#]: out of 5; [¶]: per 10% predicted; [+]: per 10%; FVC: forced vital capacity; PEF: peak expiratory flow; CI: confidence interval; OR: odds ratio.

Survivor effect

There was little evidence for any survivor effect. On cross-sectional analysis the effects of attrition did not raise the best FVC in survivors. At reassessments best FVC was not greater than that of the entire group at entry 5-yrs previously (best FVC of survivors in 1988 93.6% (96.2% at entry), in 1993 92.7% (94.8%)), nor that of the new entrants (table 1). The actual/best PEF (1988 84.0%, 1993 87.2%) mirrored almost exactly that of the relevant entrants (table 1). There were no consistent trends in the predictive value of any variable (interaction tests p>0.3 in all cases), although the effect of social class might have weakened by the third period in the 1983 entrants (OR 1.08 (95% CI 0.73–1.59)).

Discussion

This study was started at an opportune moment in 1983, when the idea of step-wise management was developing, leading ultimately to the development of the first British Thoracic Society Guidelines. In 1983 the prescription of high-dose inhaled corticosteroids was unusual, and nurse-run general practitioner asthma clinics were yet to be developed. The COPD Guidelines [17] were anticipated by using after-bronchodilator function to assess persistent obstruction. The present authors are confident that the vast majority of asthmatics referred to secondary care from a well-defined geographical area were included. There was only one respiratory physician, who personally reviewed all the case notes. The definition of asthma was acceptable at the time the study started and had proved satisfactory in the preliminary exercise in 1980 [18]. The authors did not attempt to exclude mild-to-moderate COPD, as defined functionally, but a best PEF of $\geqslant 200$ L·min^{-1} was required, to exclude severe established persistent obstruction.

One hypothesis of the study is that asthma is a risk factor for COPD, and another that COPD is a risk factor for mortality in asthma. This implies that asthma and COPD are not mutually exclusive and may coexist. The entry criteria excluded severe

pre-existing persistent obstruction, but thereafter the irreversible and reversible components of obstruction were treated independently of each other. The present authors confirmed that the principle functional variable determining mortality is best function, with instantaneous control of asthma, as measured by actual over best function making a lesser contribution. This is in agreement with HANSEN *et al.* [19], but not with ULRIK *et al.* [20], whose subjects were younger than those in the present study. Most of the persistent obstruction reflected airway remodelling and was believed to be directly associated with the asthmatic process, although in some subjects, particularly the smokers, the type of inflammation associated with COPD [21] may also have contributed. In practice the type of inflammation is probably unimportant. In a general population study in Paisley, Scotland [22], where COPD is very prevalent, the predictive value of FEV1 for subsequent mortality was similar to that shown here. Although there is an inverse association between social deprivation and both best and actual/best function [2], the present study confirms that there was an independent disadvantage of social class for survival.

The present authors believe that the substantial improvement in survival cannot be artefactual. Mortality, relative to the reference population early in the study is in line with previous observations [20, 23]. The association between mortality and pulmonary function was similar to that in the general population [22]. The age of new entrants was similar at each time, but in 1988 and 1993 the rest were survivors from the previous period, so the possibility of a major survivor effect must be considered. As survivors may be more tolerant of the adverse factors than those who die, the prevalence of unfavourable factors in survivor populations should fall. The contrary was observed with a small reduction in best function of survivors as compared with all subjects at the start of the period and with that of the new entrants. The predictive value of the principle risk factors might also be reduced. Whilst there was a hint of weakening in the social class effect after 10 yrs, there was no consistent trend. Tests for interaction confirmed that there were no statistically significant differences with time of entry. Although a small survivor effect cannot be excluded, it is thought that there are other reasons for the improvement in survival.

The management of asthma developed during the study period. The use of inhaled corticosteroids became almost universal with increasing doses, improved delivery devices, and guidelines published [3]. These developments in the management of asthma coincided with the improvement in survival that was observed. This was an uncontrolled study, where the clinician had the right and duty to adjust treatment according to the response of the patient, so it is virtually impossible to be certain of causation rather than chance association. Cross-sectional analysis at the start of successive periods between 1988 and 1993 demonstrated an improvement in actual/best function at each step [6], suggesting better management. As this applied equally to survivors and new entrants, the improvement must also have been in general practice. The relationship between best function and mortality was similar at each treatment step, which itself was an independent predictor of mortality. The contrary effects of better selection and better management might lead to no overall change in outcome in the more intensively treated. However, these two factors should work together in improving outcome in the less intensively treated and this is what was observed in this study. Therefore, there are strong, but nonproven, indications that treatment particularly early [24] and in general practice is at least partly responsible for improved outcome.

The best FEV1 of the subjects entering the last period was 84.7% pred. At this level of pulmonary function the estimated increased odds of dying are 48%, assuming a median of 100% pred in the comparator subjects, approximately as would be expected in the reference (Darlington) population. As there was no excess mortality in this period, the possibility that there might be survival advantages as well as disadvantages in being asthmatic might be considered. This is a more attractive explanation for the high prevalence of the apparently adverse condition, than a previous advantage from eosinophilic response in defence against parasitic infection, particularly as this hazard has been decreasing in recent centuries, whilst the prevalence of asthma has risen. Enhanced immune responsiveness might lead to a reduction in mortality from malignant disease as reported by ALDERSON [23] from the Manchester asthma clinic in the middle of the last century. A net gain in life expectancy after allowance for function might explain the paradoxical benefit of reversibility demonstrated by BURROWS *et al.* [25] in the Tucson study.

In conclusion, the authors are satisfied that a real reduction of mortality in asthmatics over the last 15 yrs has been observed. This may be related to improvement in treatment, but the nature of the study makes it impossible to be confident.

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