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The Darlington and Northallerton Prospective Asthma Study: best function predicts mortality during the first 10 years

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The Darlington/Northallerton prospective study of asthmatics referred to secondary care started in 1983, with review and new entry at 5-yr intervals. The principal outcome measures are: mortality (presented here), best function and therapeutic step. All adult asthmatics with ≥15% peak flow (PEF) reversibility to ≥200 l min^{-1} were included. Socio-demographic variables, PEF and spirometry were recorded prospectively. Best vital capacity (FVC) and PEF were assessed according to protocol. The mortality of the original cohort after 10 yr was expressed as standardized mortality ratio (SMR) against the local population, with history and pulmonary function at entry as explanatory variables. Ninety-five per cent follow-up was achieved in 628 subjects, with 173 deaths (29·1% of those traced). The excess death rate was nearly 50% (SMR 1·47, 95% CI 1·26–1·71), with 56% of deaths due to respiratory disease (expected 10%). After allowance for age and sex, there was a consistent inverse relationship between mortality and entry best FVC, increased risk of death 1·51 (95% CI 1·33–1·72) per 10% deficit of best FVC predicted.

The risk of respiratory death was eight times greater, and of non-respiratory death three times greater, in the lowest compared with the highest quartile of best FVC. There were no interactions with smoking, but possible enhancement of the effect in the socially deprived. Best FVC was a particularly powerful predictor of mortality in subjects <65 years at entry, in whom 64% of the excess deaths occurred. Most of the excess in respiratory deaths was not due to acute severe asthma but to the development of chronic obstructive pulmonary disease (COPD), as defined functionally, irrespective of smoking habit which made no further contribution to mortality.

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Introduction

The long-term prognosis of asthma in adults is ill understood both in terms of mortality and morbidity. In an attempt to elucidate this, all subjects with asthma attending hospital and private clinics in the Darlington and Northallerton Health Districts were entered into a long-term follow-up study in 1983 with further entry and review planned at 5-yr intervals. If asthma is irrespective of the development of chronic obstructive pulmonary disease (COPD), then there will be a spectrum of asthmatic subjects from those with completely reversible disease to those with severe secondary persistent obstruction. Similarly, there will be a spectrum in the contribution of acute recently reversible obstruction to mortality. It would require a special study to determine the precise nature of all respiratory deaths and therefore we have categorized respiratory deaths into those whose death was immediately related to an acute severe deterioration and to others. Socio-demographic variables and pulmonary function were recorded at entry.

The aims of this study were to follow mortality, change in best function, and treatment necessary to maintain optimal control, in the light of the socio-demographic variables and pulmonary function prospectively recorded at each of the 5-yr intervals.

From the outset, it was decided to treat the persistent and reversible components of airway obstruction as separate and potentially independent variables. The persistent component was assessed by best function, measured after bronchodilator on optimal therapy, and the reversible component expressed as the actual function recorded at the index visit, divided by best function (1,2).

It was hoped to exclude patients with established severe COPD by the entry criteria: reversibility of peak expiratory flow (PEF) by at least 15%–≥200 l min^{-1}. After excluding these subjects, the hypotheses are: first, that asthma is a risk

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factor for the further development of COPD, as assessed by best function, and second, that the development of COPD, whether caused by asthma or not, is a risk factor for mortality in asthmatics.

The relationships between history, pulmonary function and therapy at entry have been reported elsewhere (2–4). This paper presents outcome at 10 yr in terms of mortality, and examines the relevance of the entry variables.

Methods

SUBJECTS

All subjects over 18 years of age, whose working diagnosis included asthma, attending for follow-up at one of the author's (C.K.C.) clinics in the former Darlington and Northallerton Health Districts of the National Health Service and privately, were included. The diagnosis of asthma was confirmed by reversibility of PEF at least twice at any time after first referral by at least 15% to at least 200 l min^{-1}.

HISTORY

Social and demographic variables were recorded at entry as previously described (2,3). These included: atopic status, social class (Registrar General's classification), smoking habit, amount smoked, presence of pets, children, central heating and site of household. Duration of asthma was measured from first onset, or from recurrence after a symptom-free interval of at least 5 yr. Childhood asthma was defined as the presence of intermittent lower respiratory symptoms during childhood in the absence of chronic sputum production suggestive of bronchiectasis.

PULMONARY FUNCTION

The following were recorded at entry.

Actual function

PEF and FEV_1 (Rolling Seal Spirometer, Vitalograph, Maidenhead) were measured at the reference visit and corrected according to breath temperature and pressure saturated (BTPS).

Best function

Best PEF and vital capacity (maintained for 6 s) (FVC) were assessed during the period from January 1982 up to and including the first visit (review January 1992). Best function was accepted as the best recorded in the notes, subject to the following criteria (5).

If >80% predicted: after bronchodilator.
If 70–80% predicted: on regular maintenance therapy (sodium cromoglycate, inhaled corticosteroids or low-dose oral steroids) with 4-hourly charting of PEF for 7 days.
If <70% predicted: after bronchodilator, following ≥30 mg prednisolone for ≥7 days, with stable peak flow for ≥48 h.

These criteria were satisfied independently for PEF and FVC. If not, best function was immediately established using the above protocol. The reference values of Cotes (6) were used.

Actual best function

The ratio of actual function at attendance to best function established according to the above protocol was expressed as a percentage.

FOLLOW-UP

All subjects were seen, recalled or traced at 5-yr intervals. The second (10 yr) review was conducted between April 1993 and March 1994. Patients who neither attended for appointment nor whose death had been recorded in the notes were traced through their general practitioner and the local Register of Deaths. If this was not successful, an approach was made to the Family Health Services Authority. A search was also made at the Central Registry.

Classification of death

Deaths were recorded as being due directly to asthma, other respiratory or non-respiratory cause, on the basis of case records or death certificates, and accepted as of unknown cause if neither were available. Death from asthma was defined as death due to sudden or rapid deterioration of recently reversible airway obstruction. This was confirmed from the clinical records or contact with the general practitioners. All other respiratory deaths which neither satisfied this definition nor were due to carcinoma of the bronchus were classified as other respiratory deaths, the great majority of which were ascribed to bronchopneumonia or COPD. Carcinoma of the bronchus was regarded as non-respiratory death, because we were primarily concerned with deaths that might be associated with morbidity due to the asthmatic process. The mortality figures for the Darlington Health District for the 3 yr period 1990–1992 were used to calculate the expected mortality, using 10-year age bands. These expected mortality figures were then compared with the observed mortality to calculate the standardized mortality ratios (SMR). Approximately one-third of the patients were recruited in Northallerton, where the published district SMR is lower than for Darlington [SMR vs England and Wales: Darlington 1·24, Northallerton 0·92 (1991)].

STATISTICAL METHODS

Confidence intervals for SMRs were calculated using the method described by Gardner and Altman (7). Univariate and multivariate analysis of factors influencing the probability of death were based on linear logistic regression analysis, expressing pulmonary function absolutely or as

TABLE 1. Subjects

	Male	Female
n (%)	310 (49·4)	318 (50·6)
Mean age (years) (SD)	51·5 (15·8)	51·9 (16·9)
Mean duration (yr) (SD)	18·4 (16·4)	20·6 (15·9)
Atopic (%)	181 (58)	156 (49)
Current smokers (%)	62 (20)	36 (11)
Ex-smokers (%)	145 (47)	95 (30)
Non-smokers (%)	103 (33)	187 (59)
Actual PEF (l min^{-1}) (SD)	353 (141)	285 (112)
Best PEF (l min^{-1}) (SD)	432 (122)	353 (90)
Actual FEV_1 (l) (SD)	2·33 (1·09)	1·82 (0·78)
Best FVC (l) (SD)	4·04 (1·13)	2·91 (0·80)

per cent predicted before and after logarithmic transformation. The associations were further explored by expressing mortality as SMRs against the local population. Short-term outcome may be best in the third quartile of actual/best function (8) so this quartile is used as the reference value. Minor discrepancies in total numbers are due to occasional missing values. Analyses are always based on the maximum number of subjects available.

ETHICS APPROVAL

The study was approved by the Darlington and Northallerton Research Ethics Committees.

Results

GENERAL

Six hundred and twenty-eight subjects were recruited (Table 1). Median best function was approximately 80% predicted, whether assessed by vital capacity or peak flow and almost half (46·2%) had never smoked (♂ 33%, ♀ 59%). The social class distribution was similar to the population from which they were drawn, with approximately one-third each in social classes I–II, III, and IV–V. At entry, five subjects were being treated with oral steroids for a condition other than asthma. Of the remaining 623, 596 (95·7%) were maintained on treatment which was mutually agreed by patient and physician as being satisfactory. Of these, 136 (22·8%) were on bronchodilators alone, 46 (7·7%) maintained on cromoglycate, 291 (48·8%) on inhaled corticosteroids and 123 (20·6%) on oral corticosteroids. Thirty-four (5·4%) subjects were lost to follow-up and 173 of the remainder (29·1%) had died.

Table 2 summarizes the outcome for all subjects, non-smokers, those with good (>80%) best FVC at presentation, and those who would not have reached their 65th birthday by the 10-yr review. The mortality was greater than anticipated in all the sub-groups. The SMR of all subjects was 1·47 (95% CI 1·26–1·71) [♂1·52 (CI 1·24–1·85); ♀ 1·45 (1·14–1·81)]. The expected proportion of respiratory deaths was approximately 10% (Darlington Health District 1993) compared to the observed proportion of 56%, which included all respiratory deaths. The deaths from asthma represented a small fraction of the total, but of the deaths in those due to reach an age of not more than 65 years by review, nearly one-quarter were from asthma.

ASSOCIATIONS WITH ENTRY VARIABLES

Univariate analysis

The univariate associations of mortality with social, demographic and functional variables are shown in Table 3 for all subjects and for non-smokers. These associations are similar if restricted to younger subjects, those with entry best FVC >80% or respiratory deaths.

There is an apparent advantage in female gender in all subjects, and in male gender in non-smokers. This is entirely due to greater life expectancy in females, and the predominance of female gender amongst elderly non-smokers, the SMR being independent of gender. The odds ratio (OR) for actual PEF (1·32) was less than for best PEF

TABLE 2. Outcome for all subjects, showing percentage distribution of mortality and survival in those traced. The results for non-smokers, subjects with normal function at entry and those aged <65 years at review are also shown

	All	Non-smokers	Best FVC >80% at entry	Aged <65 years at review
All	628	290	492	320
Traced (%)	594 (94·6%)	275 (94·8%)	463 (94·1%)	294 (91·9%)
Alive (% traced)	421 (70·9%)	213 (77·5%)	366 (79·0%)	262 (89·1%)
Dead:				
Asthma (% traced)	12 (2·0%)	8 (2·9%)	9 (1·9%)	7 (2·4%)
Respiratory (% traced)	66 (11·1%)	19 (6·9%)	33 (7·1%)	10 (3·4%)
Non-respiratory (% traced)	62 (10·4%)	25 (9·1%)	38 (8·2%)	11 (3·7%)
Unknown (% traced)	33 (5·6%)	10 (3·6%)	17 (3·7%)	4 (1·4%)
All (% traced)	173 (29·1%)	62 (22·5%)	97 (20·9%)	32 (10·9%)

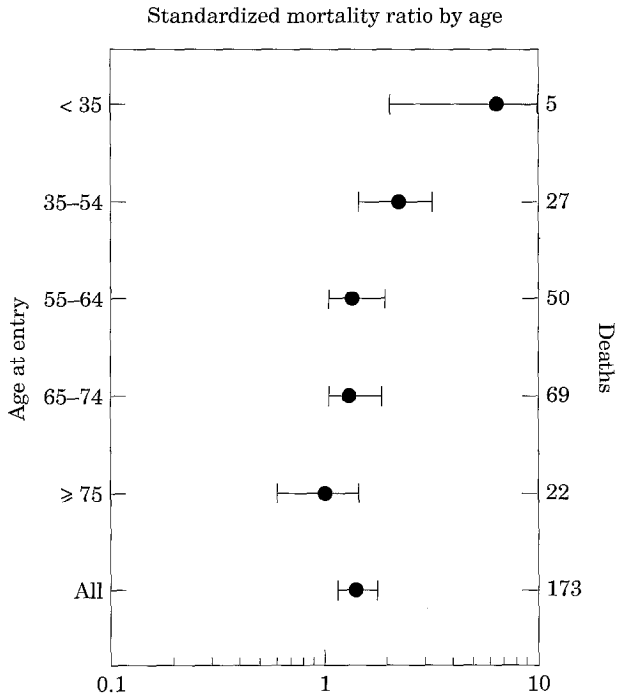

FIG. 1. Standardized mortality ratio by age. The 95% confidence intervals are shown.

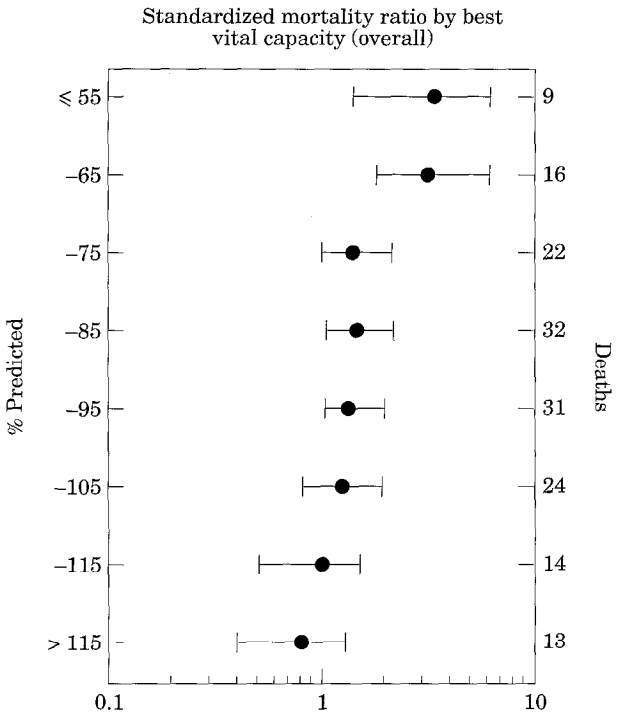

FIG. 2. Standardized mortality ratio by best vital capacity. The 95% confidence intervals are shown.

(1·37), as was that for actual FEV_1 (1·32) compared with best FVC (1·59). Nevertheless, there were associations with actual/best function which were weaker, and in particular, the odds ratio for the chosen spirometric variable (actual FEV_1/best FVC) was appreciably less than for best FEV_1 (Table 3). There were several interrelationships between the other independent variables, the principal confounding factor being age. The effects of these associations are demonstrated in the multivariate analysis.

Multivariate analysis

The effects of the demographic, social and functional variables on 10-yr mortality were explored by stepwise logistic regression analysis on several models. In each, only age, sex and best vital capacity remained significant. After allowance for age and sex, for each 10% deficit in FVC, the increased odds of dying were 51%, OR 1·51 (CI 1·33–1·72). When expressed absolutely after allowance for age, sex and height, this amounted to 14% for each 100 ml decrement in best FVC (OR 1·14, CI 110–1·19). There was no significant difference between smokers and non-smokers. The odds ratios per 10% predicted were: non-smokers 1·45 (CI 1·20–1·78), smokers 1·60 (CI 1·46–1·7); and for each 100 ml: non-smokers 1·14 (CI 1·06–1·21), smokers 1·15 (CI 1·10–1·21). Although age and best FVC emerged as significant predictors of death, the odds ratios do not reveal how the effect compares with the general population. Fig. 1 examines the SMR relation to age and shows a progressive fall from 6·2 below the age of 35 to 1·0 at over 75 years. Similarly Fig. 2 shows that mortality is more than twice that of the general population when best FVC is less than 55% and non-significantly above average when greater than 115% predicted. Those in the worst quartile of FVC were 5·5 (95% CI 2·99–10·3) more likely to die than those in the best quartile, but the pattern varied with age. In those expected to reach 65 years at review, the outlook was particularly bad in the fourth quartile (OR 8·1; CI 3·59–18·4). These patients were 14·4 (CI 4·66–44·8) times more likely to die where best FVC was 65% as opposed to 85% predicted. In older subjects the principal disadvantage was in being outside the best quartile of FVC or having a vital capacity of <105% predicted.

After allowance for age and sex, the outcome in the first and second quartiles of actual/best FVC was marginally worse than in the third. First quartile OR 1·80; (CI 0·99–3·23): second quartile OR 1·98; (CI 1·01–3·66): fourth quartile OR 1·18; (CI 0·61–2·33), suggesting a small adverse effect of poor control.

Social class was a predictor of poor outcome. The odds ratio (social classes 1 and 2) were 1·10 (CI 0·66–1·83) for social class 3 and 1·82 (CI 1·69–3·04), for social classes 4 and 5. These differences disappeared after allowance for best vital capacity. There was little apparent disadvantage in current smoking OR 1·40; (CI 0·8–2·41 P=0·22), even in heavy smokers, where there were significantly less deaths than expected.

CAUSE OF DEATH AND BEST VITAL CAPACITY

Table 4 shows the relative mortality comparing the best quartile of FVC with the others. There was no relationship

TABLE 3. Univariate analysis of the relative risk of death in all subjects and non-smokers

	All (CI)	Non-smokers (CI)
n	594	275
Gender		
Male	1·47 (1·03–2·10)	0·76 (0·42–1·40)
Female	1·00	1·00
Age (decades)	2·44 (2·03–2·93)	3·10 (2·23–4·31)
Duration (decades)	1·14 (1·03–1·27)	1·19 (1·00–1·42)
Atopic	0·68 (0·47–0·99)	0·43 (0·24–0·78)
Childhood asthma	0·54 (0·37–0·80)	0·33 (0·17–0·62)
Smoker		
Current	1·69 (1·01–2·83)	
Ex-	1·90 (1·28–2·81)	—
Non-	1·00	
Amount smoked (10 pack-years)	1·19 (1·10–1·30)	—
Social class		
I–III	1·00	1·00
IV–V	1·78 (1·23–2·59)	2·34 (1·29–4·23)
*Best PEF	1·37 (1·25–1·51)	1·24 (1·07–1·44)
†Act./best PEF	1·25 (1·13–1·39)	1·38 (1·16–1·63)
Best FVC	1·59 (1·41–1·80)	1·45 (1·21–1·74)
*Act.FEV_1/best FVC	1·16 (1·06–1·27)	1·01 (0·88–1·16)

*Per deficit of 10% predicted.
†Per 10% deficit.

between deaths attributed directly to asthma and best FVC at entry. On the other hand, there was a significant risk of other respiratory death with reduced vital capacity, which was apparent throughout the whole range. The association between non-respiratory deaths and reduced vital capacity was principally in the worst quartile.

Discussion

The primary aim of the Darlington and Northallerton Asthma Study is to follow mortality, changes in pulmonary function, and therapy required to maintain optimal function, in a group of patients sufficiently severe to be referred to secondary care. This is a clinical rather than an epidemiological study and, therefore, has the potential disadvantage of an ill-defined and selected population. Nevertheless, it is likely that a high proportion of eligible subjects from the geographical area concerned is included. The boundaries are well defined and there was only one respiratory physician in the area during the period of the study. It has the advantage that subjects so referred are likely to be more severely affected, show greater changes and hence make the assessment of risk factors easier. On the other hand, the distribution of these risk factors and their effect might be different in less severely affected subjects managed in general practice or recruited in epidemiological studies, who might fare better (9).

Previously published studies (10) have shown that a history of COPD is associated with poor outcome in asthma, but this is the first time that best function and actual/best function at entry have been considered independently as possible risk factors for mortality. On multivariate analysis, only one measure of best function (FVC) remained in the model and in the 5-yr period after 1988, when best FEV_1 was also assessed, the closest fit was with best FEV_1 (11). Although the fit is not as good with best PEF, the conclusions are the same.

The weaker univariate relationship between poor actual/best function and mortality was, nevertheless, of the same order, but did not remain in the model on multivariate analysis. Confounding factors which might explain this include the cross-sectional association of low actual/best function with greater age and lower social class (3).

Although the relationship between actual/best and best function is weak (11), both actual/best and best function were lower in patients maintained on oral corticosteroids at entry (4), who might have a worse prognosis. The relationship between actual/best function and symptoms in subjects in this study is generally U-shaped, the group of patients with no demonstrable reversible disease at attendance having more symptoms than those with minimal reversibility (8). The symptomatic patients with little reversibility, often on long-acting bronchodilator, might have a poor prognosis and so reduce the scope for showing an association between good control at attendance and poor outcome. These results are compatible with a weak relationship between actual/best peak flow at entry and mortality, which is partially confounded by a group of poor prognosis subjects with limited reversibility at entry, possibly further reduced by long-acting bronchodilator. This interpretation would support the findings of Brown *et al.*, who did find a relationship between unsatisfactory management and poor long-term outcome (13). Furthermore, a single reading of actual/best function is a crude measurement of control, and a record of diurnal variation might have proved a more powerful tool, although it is unlikely that the effect of unsatisfactorily controlled reversible airway obstruction exceeds that of entry best function.

We have shown that there is a close association between respiratory mortality and poor best function. Although the association with non-respiratory mortality was not as great, it was both significant and relevant. This is in agreement with population studies, which have shown that reduced FEV_1 is associated with increased non-respiratory mortality (14,15), particularly from coronary heart disease and stroke (16,17). This is not entirely a smoking effect, as it is also seen in lifelong non-smokers (18). Some epidemilogical studies have suggested that reversible airway obstruction is a good prognostic factor (19). However, the use of actual, rather than best function, in all previous studies would explain this paradox if, indeed, best function is the principal explanatory variable. The approach in separating the persistent and potentially reversible components has the advantage not only of looking at factors that might have different aetiology and prognostic factors, but also in ensuring that one component does not suffer from the variability inherent in single measurements of pulmonary

TABLE 4. The relative cause-specific and overall risk of death by quartiles of best vital capacity

FVC quartile	Interquartile value (% pred)	Asthma ratio (*n*)	Other respiratory ratio (*n*)	Non-respiratory ratio (*n*)	Unknown cause ratio (*n*)	All ratio (*n*)
1		1·3 (4)	8·3 (33)	2·8 (25)	2·7 (16)	3·5 (78)
	83·7					
	96·3					
	109·1					
2		0·7 (2)	3·5 (14)	1·6 (14)	0·7 (4)	1·5 (34)
3		1·0 (3)	2·5 (10)	1·1 (10)	0·7 (4)	1·2 (27)
4		1·0 (3)	1·0 (4)	1·0 (9)	1·0 (6)	1·0 (22)
All		(12)	(61)	(58)	(30)	(161)
P (exact trend test)		0·90	<0·0001	0·002	0·02	<0·0001

function. It may prove to be of particular importance in the actuarial assessment of asthmatics for insurance and medico-legal purposes. Whilst the protocol for best function used here has not been fully validated, it is the only published one and has been shown to be the denominator which produces consistent actual/best function across different regimens (5).

The classification of respiratory deaths is less than ideal. We are confident that we had sufficient information to make a diagnosis of death from acute severe asthma when this had occurred, but it proved impossible to assess the contribution of reversible wheeze to the deaths of those who had symptoms associated with chronic obstruction. There seemed no consistent difference between those recorded as dying from bronchopneumonia and various forms of obstructive pulmonary disease. It would have required a special study, with possibly a post-mortem on all occasions, to assess the contribution of the currently reversible component to these deaths. We have therefore classified them all as other respiratory deaths. However, we have shown that the increased risk of these respiratory deaths is associated with differences in best function within, as well as below the normal range. Two-thirds of the excess deaths were in patients of age less than 65 years. Although in these younger subjects the hazard was principally in the worst quartile of function, we are confident that, as subjects get older, relatively minor degrees of COPD may substantially increase the risk of mortality in asthmatics. Possible mechanisms include reduction of ability to survive a relatively modest increase in the acute reversible component of their obstruction, or during infective episodes, heightened risk of bronchopneumonia.

The overall mortality was less than that reported by Markowe *et al.* [SMR 1·6 (CI 1·3–2·0)] (8), but if allowance is made for the relative youth of the subjects studied, similar to that reported by Lange *et al.* [SMR male 1·5 (CI 1·2–1·9) female 1·7 (CI 1·3–2·2)] (20) and Ulrik [SMR 1·94 (CI 1·17–2·42)] (21). Although there were relatively few deaths directly attributable to asthma in our study, the findings are again compatible with those of Ulrik (21), if allowance is made for age. In our study, asthma deaths did make a major contribution to the mortality of the younger subjects. The incidence was compatible with the rate of 0·5–0·9 per 100 000 per year for subjects aged 5–34 years in the U.K. as a whole (22). Even in the younger subjects, concentrating on deaths directly attributable to asthma will underestimate the effect of the development of COPD as the strength of the relationship between all deaths and poor best function is inversely related to age. The analysis of changes in vital capacity in the survivors of this cohort would suggest a linear decline, little influenced by the previous determinants of entry best function. Nevertheless, reduction in parental smoking, which compromises respiratory development in susceptible subjects (23), or early intervention in children with frank asthma (24), must improve outcome in later life by ensuring a higher starting value before the adult decline in pulmonary function. There was no additional adverse interaction with cigarette smoking, with the whole of its effect being explained by reduction in best function. Similarly there was no interaction between pulmonary function and social class. Although this indicates that in the lower social classes there is no additional disadvantage in having poor pulmonary function, it is compatible with the interpretation that the difference in outcome between the socially deprived and the relevantly affluent is mediated through poor best function.

There are early indications that it might be possible to conserve pulmonary function by the early introduction of corticosteroids (25).

It is therefore particularly important that the socially deprived do have the benefit of early appropriate management of their asthma.

The results presented here suggest that maintenance of best function should be a principal aim of the management of asthma. Nevertheless, these results do not preclude the use of increased bronchodilator rather than inhaled corticosteroids to achieve better control of symptoms (26), provided that the anti-inflammatory medication is given in sufficient dosages to maintain after-bronchodilator function at its highest possible level.

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