

ASTHMA

Inhaled corticosteroids and decline of lung function in community residents with asthma

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Background: Inhaled corticosteroids (ICS) constitute the cornerstone of treatment for asthma. Many studies have reported beneficial short term effects of these drugs, but there are few data on the long term effects of ICS on the decline in forced expiratory volume in 1 second (FEV₁). This study was undertaken to determine whether adults with asthma treated with ICS have a less pronounced decline in FEV₁ than those not treated with ICS.

Methods: Two hundred and thirty four asthmatic individuals from a longitudinal epidemiological study of the general population of Copenhagen, Denmark were divided into two groups; 44 were treated with ICS and 190 were not treated with ICS. The annual decline in FEV₁ was measured over a 10 year follow up period.

Results: The decline in FEV₁ in the 44 patients receiving ICS was 25 ml/year compared with 51 ml/year in the 190 patients not receiving this treatment ($p < 0.001$). The linear regression model with ICS as the variable of interest and sex, smoking, and wheezing as covariates showed that treatment with ICS was associated with a less steep decline in FEV₁ of 18 ml/year ($p = 0.01$). Adjustment for additional variables including age, socioeconomic status, body mass index, mucus hypersecretion, and use of other asthma medications did not change these results.

Conclusions: Treatment with ICS is associated with a significantly reduced decline in ventilatory function.

Although major advances in our understanding of asthma have occurred in recent years, many questions remain largely unanswered, particularly concerning those factors that determine the long term outcome of the disease. In general, lung function in asthmatics is lower than predicted, which in adults is likely to reflect an accelerated decline in lung function.^{1,2} The identification of factors having an impact—both negative and positive—on the decline in lung function is therefore of crucial importance for the understanding of disease progression and prognosis in asthma.³

Inflammation is an early feature of asthma and untreated ongoing asthmatic airway inflammation may cause remodeling of the airways leading to irreversible airflow obstruction.⁴ In addition to improving the clinical expression of asthma, inhaled corticosteroids (ICS) have also been shown to reduce the chronic inflammation seen in asthmatic airways.^{5–7} Treatment with ICS may therefore reduce the increased rate of decline in ventilatory function seen in some asthmatic patients. However, although previously published studies have shown beneficial effects on lung function during the first few years of treatment,^{8,9} only limited data are available on the long term effects of ICS on the course of lung function in asthma.

Using data from a large population survey, The Copenhagen City Heart Study, we have previously reported an accelerated decline in forced expiratory volume in 1 second (FEV₁) in asthmatic individuals.¹ At that time information on the asthma medication was not available and we were therefore unable to relate the decline in FEV₁ to treatment regimens in a prospective manner. In this paper we extend previous findings with a further 10 years of observation and focus on the association between the use of ICS and decline in FEV₁. Our hypothesis was that asthmatic individuals who are continuously treated with ICS should have a less pronounced decline in FEV₁ than those not receiving this treatment.

METHODS

Study population and procedures

All individuals participated in the third and fourth examinations of The Copenhagen City Heart Study, an ongoing epidemiological study of the inhabitants of the inner city of Copenhagen, Denmark. Details on study design, selection procedure, description of the non-responders together with the complete examination programme have been presented elsewhere.¹⁰ In the present study we have analysed FEV₁ data from the third and fourth examinations covering the period from 1991 to 2003. The third examination of The Copenhagen City Heart Study was performed from 1991 to 1994. A total of 10 127 participants were examined. All living participants were invited again approximately 10 years later for a fourth examination. 7757 subjects were alive at the beginning of the fourth examination in 2001 and 4873 participated (response rate 62.8%). The study protocol was approved by the local ethics committee and informed consent was obtained from all participants.

In both examinations FEV₁ and forced vital capacity (FVC) were measured with the same dry wedge spirometer (Vitalograph, Maidenhead, UK) which was calibrated weekly with a 1 litre syringe. At least two measurements of FEV₁ and FVC differing by less than 5% had to be produced and the best FEV₁ was used in the analyses. The intake of bronchodilators prior to lung function testing was not standardised. Data on FEV₁ are reported in absolute values and as a percentage of the predicted value where predicted values are based on analyses of never smokers in the third examination of The Copenhagen City Heart Study. With only two measurements of lung function available, linear regression analysis was used to study the decline in FEV₁ from 1991–3 to 2003. For this reason, subjects under the age of 30 years were excluded as FEV₁ may increase until

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

approximately 30 years of age and this would have been impossible to account for using a linear model.

A self-administered questionnaire concerning symptoms, somatic diseases, social status, smoking, drinking habit, and medications was completed and checked by one of the investigators at both the beginning and end of the follow up period. Participants were characterised as smokers if they were continuous smokers of cigarettes, cigars, or pipe throughout the observation period.

Subjects were categorised in terms of the presence or absence of asthma. Our criterion for asthma follows the convention of other epidemiological studies by relying on the subjects' perception of whether or not they have the disease.^{11,12} Thus, asthma was defined by an affirmative response to the question: "Do you have asthma?".

Treatment with ICS is not a constant feature. In order to be able to interpret the findings correctly, we only included those participants with asthma who did not change their treatment with ICS between the third and fourth examinations. Two subgroups of subjects with asthma were included: 190 participants who did not receive ICS throughout the observation period and 44 who did, giving a total of 234 asthmatic individuals with all the necessary variables available and unchanged treatment with regard to ICS during the 10 year follow up period. 114 asthmatic participants who either started or stopped ICS treatment during the observation period were excluded because it was assumed that changes in treatment are likely to reflect major fluctuations in asthma severity making a comparison between the groups difficult.

Statistical analysis

The characteristics of individuals treated with ICS were compared with those not treated with ICS using either the χ^2 test or Fisher's exact test when appropriate. All reported *p* values are based on two sided tests of significance.

For each individual the exact time between the two FEV₁ measurements was calculated in days and normalised so that the change in lung function could be expressed as ml/year (Δ FEV₁).

As the focus of our analyses was the possible association between the treatment of ICS and decline in FEV₁, we developed linear regression models where Δ FEV₁ (ml/year) was the dependent variable and the use of ICS (yes/no) was

the independent variable of main interest. We initially performed separate analyses for women and men but, as the results were similar, the final models comprise both women and men and include sex as covariate. As additional covariates we included variables which, based on previous studies, may have a significant effect on the Δ FEV₁ and thus affect the association between ICS and Δ FEV₁. In the initial model the covariates were sex, age (years), smoking (non-smokers, starters, quitters, light smokers (<15 g tobacco/day), heavy smokers (\geq 15 g tobacco/day)), height (cm), body mass index (BMI in kg/m²), socioeconomic status (expressed as length of school education in three groups: <8 years; 8–11 years; >11 years), presence of asthmatic symptoms such as wheezing (yes/no) and mucus hypersecretion (yes/no), and use of other anti-asthmatic medication (yes/no). However, as many of these covariates were not significantly related to Δ FEV₁ (*p*>0.1) and did not significantly improve the fit of the regression model, they were excluded from the final model which, in addition to ICS, only includes sex, smoking, and wheezing as covariates. Interaction terms between different variables and use of ICS were investigated but were not found to be significant.

The analyses were performed using SPSS for Windows statistical package Version 12.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Table 1 summarises the characteristics of the 234 individuals with asthma according to sex and treatment with ICS. The mean FEV₁ percentage predicted for the whole asthmatic population was 83.2%. Individuals treated with ICS had lower lung function, a lower prevalence of smoking, and a higher prevalence of asthmatic characteristics such as wheeze and chronic mucus hypersecretion than those not treated with ICS. There was no difference with regard to height and BMI between the two subgroups. Use of ICS was significantly related to length of school education: 13% of the participants with shortest school education were on ICS compared with 28% of those with a medium duration of education and 10% of those with the most education (*p*<0.05).

The observed mean decline in FEV₁ (ml/year), percentage predicted FEV₁, and the FEV₁/FVC ratio at the end of the 10 year follow up period are also shown in table 1. In both sexes, individuals on ICS had a significantly lower decline in FEV₁. This resulted in a smaller difference in the percentage

Table 1 Characteristics of 234 participants with asthma according to treatment with inhaled corticosteroids (ICS) during the follow up period

Variable	Women		p value	Men		p value
	No ICS (n=114)	On ICS (n=33)		No ICS (n=76)	On ICS (n=11)	
Age (years)	57.2 (11.3)	57.9 (9.8)	NS	51.7 (12.7)	58.4 (8.7)	NS
FEV ₁ (l)	2.23 (0.65)	1.74 (0.64)	<0.001	3.22 (0.99)	2.07 (0.78)	<0.001
FEV ₁ % predicted in 1991–4	88.3 (19.6)	67.8 (20.5)	0.001	85.7 (20.6)	60.2 (17.9)	0.004
FEV ₁ /FVC % in 1991–4	77.8 (8.6)	66.4 (10.3)	<0.001	72.8 (10.7)	61.1 (12.7)	<0.001
Height (cm)	163 (6.2)	163 (6.8)	NS	176 (6.0)	174 (7.2)	NS
BMI (kg/m ²)	26.3 (5.4)	26.0 (5.3)	NS	25.6 (4.9)	25.6 (2.9)	NS
Smoking 1991–2003 (%)	32.5	24.2	NS	37.3	18.2	NS
Asthma duration (years)*	17.8 (18.4)	14.6 (16.6)	NS	25.1 (20.1)	12.7 (15.9)	0.07
Chronic mucus hypersecretion (%)	19.3	39.4	0.02	20.0	36.4	NS
Wheezing (%)	64.0	93.9	<0.001	64.0	90.9	0.09
Hay fever (%)	32.5	12.5	0.03	32.0	27.3	NS
Δ FEV ₁ (ml/year) 1991–2003	46.5 (31.5)	25.8 (33.8)	<0.001	56.6 (54.5)	21.1 (44.9)	0.04
FEV ₁ % predicted in 2001–3	80.1 (21.7)	66.2 (21.0)	<0.001	78.7 (22.7)	61.3 (18.5)	0.02
FEV ₁ /FVC in 2001–3	73.6 (10.7)	64.6 (10.4)	<0.001	69.8 (10.5)	60.7 (13.1)	<0.001

ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; Δ FEV₁, decline in FEV₁. Data presented as mean (SD) values. Unless specified, all values are given at the beginning of the follow up period. The information on asthma duration was only available in 125 of the participants. Smokers are defined as participants who smoked tobacco at both the beginning and the end of the observation period.

Table 2 Multiple linear regression of ΔFEV_1 in ml/year in 234 subjects with asthma based on a mean observation period of 10 years

Variable	Estimate (ml/year)	SE	p value
Intercept ¹	49.5	5.7	<0.001
Sex			
Women	0		
Men	5.6	5.6	0.319
Smoking			
Non-smokers	0		
Starters	16.6	17.1	0.333
Quitters	8.6	7.6	0.259
Light smokers	2.1	8.7	0.805
Heavy smokers	22.5	7.3	0.002
Wheezing			
No	0		
Yes	-13.1	6.0	0.030
ICS			
No	0		
Yes	-17.8	7.1	0.013

SE, standard error of the estimate; ICS, inhaled corticosteroids.

The intercept represents the mean annual decline in a non-smoking asthmatic woman without wheezing who is not treated with ICS. The estimate for different variables represents the difference in the annual decline in FEV_1 between those with and those without these characteristics (this means that heavy smokers have an additional decline in FEV_1 of 22.5 ml/year whereas those treated with ICS have a 17.8 ml/year lower decline in FEV_1).

predicted FEV_1 and FEV_1/FVC ratio between subjects on ICS and those not receiving ICS at the end of the follow up period than at the beginning of the study: the difference in FEV_1 in women was reduced from 20.5% predicted to 13.9% predicted, whereas in men the difference was reduced from 25.5% predicted to 17.4% predicted (table 1).

Smoking is an important factor affecting the decline in FEV_1 . The observed decline in FEV_1 in non-smokers not receiving ICS ($n = 125$) was 46.1 (43.5) ml/year compared with 22.8 (39.5) ml/year in those receiving ICS treatment ($n = 34$; $p = 0.005$). In smokers the decline in FEV_1 was 57.9 (38.7) ml/year in subjects not receiving ICS treatment ($n = 65$) and 30.8 (23.1) ml/year in those receiving treatment with ICS ($n = 10$; $p = 0.035$). Similar trends were seen in both sexes and, since subdivision according to sex resulted in rather small subgroups, these results are for women and men combined. As expected, smoking accelerated the decline in FEV_1 , but treatment with ICS was associated with a significantly smaller decline in FEV_1 irrespective of smoking status.

Table 2 shows the results of the final linear regression analysis of the 234 study participants. The effects of smoking and ICS on ΔFEV_1 were opposite, and both reached statistical significance. As expected, heavy smoking accelerated the decline in FEV_1 while treatment with ICS was associated with a less pronounced decline. Wheezing was also associated with a slower decline in FEV_1 . None of the remaining variables included in the initial model (treatment with other anti-asthmatic medications, age, height, BMI, chronic mucus hypersecretion, and length of school education) had any significant effect on the decline in FEV_1 . There were no significant interactions between the investigated variables.

DISCUSSION

In this long term follow up study of lung function in community residents with asthma, treatment with ICS was associated with a more favourable course of FEV_1 . This observation was consistent in both women and men, as well as in non-smokers and smokers. The observed difference between the treated and non-treated groups of approximately 15–20 ml/year is quite substantial and is certainly of clinical significance.

The present findings are in keeping with results from studies over shorter observation periods and are also in line

with the perception that ICS are effective in preventing hospital admissions and deaths due to asthma.^{13 14} Randomised studies of early and continuous treatment of mild asthma with ICS for up to 3 years have shown beneficial effects, not only on asthma symptoms but also on lung function.^{8 15 16} Previous observational studies of patients attending asthma clinics have also suggested that ICS may be beneficial with regard to the long term outcome of lung function in children, adolescents, and in young adults.^{9 17 18}

As we did not have information on the level of lung function before starting treatment with ICS, we were not able to determine whether treatment with ICS can prevent the development of persistent airways obstruction in asthma.^{19 20} Previous studies suggest that ICS should be introduced early after the onset of asthma in order to achieve the best possible effect on airway function.^{9 15 20 21} In a Dutch study of patients with severe asthma there was a high incidence of permanent airways obstruction despite treatment with high doses of ICS,²² whereas in a study of mild asthma in children there was a favourable outcome regarding the FEV_1/FVC ratio although the effect of ICS on the FEV_1 was not different from placebo.²³ Although previous histological studies of the effects of treatment with ICS on asthmatic airways have not shown consistent results with regard to prevention or slowing of airway remodelling,^{24 25} there are studies showing that treatment with ICS can reverse at least one aspect of the airway wall remodelling—namely, subepithelial fibrosis.^{5–7} Thus, although it is unlikely that ICS can prevent the development of airway obstruction in some cases of asthma, the present findings of a slower decline in lung function with treatment with ICS are in line with the notion that long term treatment can prevent or reverse airway remodelling, at least to some degree. In keeping with our previous report which was based on the same population but in a different time period,¹ the present findings again confirm that abstaining from smoking is very important in asthmatic subjects. As in the study by Burrows *et al*, we also observed that a wheezing phenotype is associated with a slower decline in FEV_1 .²⁶

Being an observational study of community residents and not a randomised trial performed in a clinical setting, our study is subject to significant bias. Most important is the fact that the subjects were not randomised to receive ICS. The treated group differed substantially from the non-treated group with regard to several asthma characteristics—they

had much lower lung function, reported more asthmatic symptoms such as wheezing and chronic mucus hypersecretion, and had a lower prevalence of smoking. It is therefore clear that the steroid treated group is not representative of the whole asthmatic population. It is difficult to deduce how this bias of "confounding by indication" or "confounding by severity" affects our results, but we cannot rule out the possibility that the lack of adjustment for these factors may have produced a spurious association between ICS and Δ FEV₁. Although we have tried to include factors describing asthma severity such as presence of wheezing and mucus hypersecretion, our adjustment is not precise since our population is not well characterised as this is part of an epidemiological study and not a clinical investigation. In particular, the asthmatic patients on ICS had a lower initial FEV₁ than those who were not treated with ICS. On the one hand we could expect an even greater decline in FEV₁ in subjects with an already low FEV₁ and many asthmatic symptoms. On the other hand, it is possible that the decline in lung function in asthma is non-linear with an initial steep decline in FEV₁ being followed by a normal decline. If this was true, the observed low decline in the ICS treated group could reflect the fact that asthma has "burned out" in this subgroup rather than an effect of ICS per se. However, the shorter duration of asthma in the ICS treated group argues against this explanation (table 1). It is also likely that the use of ICS is associated with other factors that we have not been able to control for (such as a better compliance with environmental measures), which may have a beneficial effect on asthma itself. Only a long term, placebo controlled trial with repeated frequent FEV₁ measurements and detailed information on the ICS treatment can provide a definite answer, but such a study is unlikely to be feasible or ethical, not least because of the immediate excellent response to ICS treatment seen in most patients with asthma which precludes treatment with placebo for longer periods of time.

Another limitation of this study is the fact that the use of a self-reported diagnosis of asthma invariably leads to some degree of misclassification as some subjects with mild asthma remain undiagnosed whereas some subjects with chronic obstructive pulmonary disease (COPD) are likely to have reported asthma. However, the high average level of FEV₁ (>80% predicted) in our population speaks against significant misclassification between asthma and COPD. In addition, the fact that we observed quite a substantial association between the decline in FEV₁ and use of ICS, which is in contrast to the findings from randomised trials of patients with mild COPD, suggests that not many subjects with self-reported asthma actually had COPD.^{27 28}

A further weakness of the present study is the small number of asthmatics on ICS and the fact that we do not have any information on the dose of ICS or of compliance with this treatment. It is possible that some of the participants who reported being on ICS at the beginning and end of the study period were not on the treatment during the whole observation period. However, we feel that this bias would have been more problematic if we had been unable to show any association between ICS and decline in FEV₁. The fact that we observed such a pronounced difference in this relatively small sample of asthmatic patients gives even more support to our findings.

During our study the mean dose of ICS in the whole of Denmark was around 500 µg/day. Only 18% of the population with self-reported asthma were treated with ICS throughout the observation period. This low level of use reflects the situation in Copenhagen approximately 10 years ago. Fortunately, the point prevalence of treatment with ICS among the asthmatic participants in our survey increased from 31.4% in 1991–4 to 48.5% in 2001–3. This low number is

similar to the finding in a recent large survey showing a similar underuse of these drugs in most European countries.²⁹

In conclusion, adults with self-reported asthma treated with ICS experienced a less pronounced decline in FEV₁ than asthmatic subjects not receiving this treatment. Although this was an observational study and not a randomised trial, we think that the results suggest that ICS may have beneficial long term effects on the progression of ventilatory function in asthma.

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LUNG ALERT

Stoves with chimneys reduce risk of COPD

▲ Chapman RS, He X, Blair AE, *et al*. Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. *BMJ* 2005;**331**:1050–2

The effect of the installation of stoves with chimneys on the incidence of chronic obstructive pulmonary disease (COPD) was investigated in 20 453 farmers living in Xuanwei County, China who were lifelong users of smoky coal. 16 606 changed from unventilated stoves to stoves with chimneys during the period of data collection. Data were collected retrospectively for a period of 17 years (1976–92).

1487 subjects (7.3%) self-reported a diagnosis of COPD. The age adjusted incidence rate of COPD was lower in people with chimneys (367/100 000 person years) than in those without (767/100 000 person years). The mean age of diagnosis of COPD was 49.7 years (95% CI 48.9 to 50.4) in people with no stove improvements and 53.6 years (95% CI 52.9 to 54.3) in those with improvements. The installation of chimneys was associated with an improvement in the relative risk (RR) of COPD in both men (RR 0.58, 95% CI 0.49 to 0.70, $p < 0.001$) and women (RR 0.75, 95% CI 0.62 to 0.92, $p = 0.005$). The risk of COPD in those with chimneys installed decreased consistently with the length of time since installation. After 10 years there was a significant reduction in risk in both men (RR 0.20, 95% CI 0.16 to 0.26) and women (RR 0.26, 95% CI 0.20 to 0.34).

The installation of chimneys on formerly unventilated coal stoves reduces the risk of COPD. This intervention in developing countries would reduce the global burden of COPD.

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