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Lung function decline in asthma: association with inhaled corticosteroids, smoking and gender

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ABSTRACT

Background: Inhaled corticosteroids (ICS) provide short-term benefits in asthma, yet long-term effects are still unknown.
Methods: We studied 281 patients diagnosed with moderate to severe asthma in 1963-1975 and re-examined them in 1991-1999. Information was collected on forced expiratory volume in 1 second (FEV_1), bronchial hyperresponsiveness, atopy, smoking, use and dosage of oral and ICS. Patients were included in the analyses if they had at least 3 FEV_1 measurements during 2 consecutive years after the age of 30, and used ICS during follow-up.
Results: Analyses were performed on 122 patients. During (median) follow-up of 23 years, 71 males and 51 females had on average 37 and 40 individual FEV_1 measurements respectively. Linear mixed effect models showed that males had (mean) 20.6 ml/year less annual FEV_1 decline after ICS initiation than before (p=0.011) and females 3.2 ml/year less decline (p=0.73). In individuals with <5 pack years smoking, males had 36.8 ml/year less FEV_1 decline (p=0.0097) after ICS institution and females 0.8 ml/year (p=0.94), difference between sexes being significant (p=0.045). These effects were not observed with ≥5 pack years smoking. A higher daily dose of ICS was associated with less FEV_1 decline in males (p=0.006), an effect not observed in females.
Conclusion: Treatment with ICS in our patients with moderate to severe adult asthma is associated with a reduction in FEV_1 decline over 23-year follow-up in males who had smoked less than 5 pack years at follow-up. This effect was dose-dependent and not present in females or in males with more than 5 pack years of smoking at follow-up. The absence of an ICS effect in females on FEV_1 decline needs further studies.

INTRODUCTION

Asthma is a chronic inflammatory respiratory disease with variable and fully reversible airway obstruction in most patients. It is generally held that asthma is a benign disease in which persistent airway obstruction is virtually absent. Nevertheless, cross-sectional studies show that children and adults with asthma have on average a lower lung function than non-asthmatics, especially in case of persistent asthma symptoms.[1][2][3][4][5] Moreover, a substantially greater lung function loss over time has been reported in adult asthma as well.[1][6][7][8][9] Fixed airway obstruction and accelerated lung function decline may stem from structural airway changes that accompany the underlying airway wall inflammation in asthma, generally addressed as airway remodelling.[10][11][12][13] Virtually all short-term studies (weeks to a few years) have shown that inhaled corticosteroids benefit patients with chronic persistent asthma by decreasing airway inflammation, improving lung function and reducing symptoms and airway hyperresponsiveness. However, it has not been studied whether it also slows down progressive lung function loss over time.

Some factors have been suggested to affect the steroid response in asthma. One study showed women with asthma to have less short-term benefit from inhaled corticosteroid treatment than males[14], compatible with the observed higher prevalence of severe asthma in females.[15] Furthermore, persistent active asthma has a negative impact on annual decline in forced expiratory volume in 1 second (FEV_1) in females, but not in males.[2] Smoking has been suggested to negatively influence steroid response in asthma as well.[16][17][18]

Our study was undertaken to assess whether inhaled corticosteroids may, next to their well-established beneficial short-term effects, slow down progressive lung function loss in males and females and to assess the effect of cigarette smoking on these effects of inhaled corticosteroids. We evaluated lung function data over a median follow-up of 23 years in a population of objectively diagnosed asthmatics.

METHODS

Study population

We evaluated 281 patients diagnosed with symptomatic asthma who attended Beatrixoord, a regional referral centre (Haren, the Netherlands) in 1963-1975. At initial testing all were characterised using a standardised clinical protocol as previously described[19][20], all were younger than 45 years and showed bronchial hyperresponsiveness to histamine (30 seconds method; $PC_{20} \leq 32$ mg/ml).[21] In 1991-1999 all were re-examined with the same methodology.

Excluded from the longitudinal analyses on lung function decline were 68 of the 281 subjects, due to having only FEV_1 data before age 30 or insufficient number of FEV_1 measurements after age 30. Twelve had missing lung function records, 5 had incomplete or unknown data on smoking history, 67 never used inhaled corticosteroids and 7 had intermittent use of inhaled corticosteroids. Data of the remaining 122 individuals were included in the analyses on effect of inhaled corticosteroids on lung function decline.

The Medical Ethics Committee of the University Hospital Groningen approved this study. Participants gave written informed consent.

Clinical assessment

Initial characterisation (1963-1975) included assessment of bronchial hyperresponsiveness to histamine[21], allergen skin tests, lung function, reversibility 30 minutes after intramuscular injection of 25 mg of thiazinamium (a potent anticholinergic drug with antihistaminic properties) and peripheral blood eosinophils counts.[19]

At re-examination (1991-1999) measurements were repeated with the same methodology. Reversibility was tested 20 minutes after inhalation of 800 µg salbutamol (albuterol). In addition, total serum IgE levels were measured by either solid phase immunoassay (Pharmacia, Uppsala, Sweden) or enzyme linked fluorescent assay (Mini Vidas, Biomerieux Inc., Marcy, France) and participants answered a modified British Medical Society Respiratory Questionnaire.[22] Prior to testing participants had no exacerbation nor used oral corticosteroids during 6 weeks. Maintenance medication was stopped for the appropriate time.[19]

After initial testing subjects generally had routine check-ups for their asthma at least once a year. Data on lung function and corticosteroid use during check-ups were extracted from the medical records. Lung function was tested with a water-sealed spirometer throughout the follow-up (Lode Spirograph D53, Lode Instruments, Groningen, the Netherlands). Lung function data during hospital stays, asthma exacerbations or pregnancies were not used.

The dose of inhaled corticosteroids was calculated to an equivalent daily dose of beclomethasone, i.e. 500 µg of fluticasone, 1000 µg of budesonide and 500 µg of budesonide via Turbuhaler being equipotent to 1000 µg of beclomethasone.[23]

Statistical analyses

Linear mixed effect models on FEV_1 were used to investigate the effect of the use of inhaled corticosteroids on the annual decline in FEV_1.[24] The age of thirty was the starting point of the analyses, since the maximum lung function level would be achieved before that age and lung function is considered to be in the decline phase.[25] Following the methodology described by Naumova et al.[26] time was defined as the time relative to the start of inhaled corticosteroid therapy in years. Separate annual FEV_1 decline and FEV_1 levels (i.e. intercepts) were estimated for the period before and after the start of inhaled corticosteroid therapy by including the variables time, inhaled corticosteroid use, and their interaction. Furthermore, individual variation in these declines and intercepts were accounted for by estimating the random effects for these

variables. Effect modification by gender was incorporated in the model by adding the interaction between time, inhaled corticosteroid use and gender. Other explanatory variables in the model were height (centred at 1.75 meters), the first available FEV_1 after age thirty (FEV_1 centred at 2.8 litres, called "FEV_1 at age thirty") and their interaction with time, pack years of smoking, and oral corticosteroid use. The latter two variables were time varying. Since including the level of the FEV_1 at age thirty and their interaction with time could introduce bias due to regression-to-the-mean, random effects were also estimated for these variables. The results of these analyses indicated that there was no regression-to-the-mean bias, i.e. the estimates of the variables in the model did not change and the model fit was not better and therefore the results are presented without these random effects. Several within-subject correlation structures were investigated but none of these gave a better fit than the independent within-subject correlation. To investigate possible effect modification by smoking on the effect of inhaled corticosteroid use on FEV_1 decline the analysis was stratified by pack years of smoking (<5 and ≥5 pack years) at re-examination. Additional potential risk factors were introduced in the model one at a time, i.e. severity of bronchial hyperresponsiveness to histamine at initial testing, number of blood eosinophils, atopy and reversibility (% of predicted) at initial testing and re-examination, total IgE at re-examination, age at introduction of inhaled corticosteroids, untreated period (time between the onset of symptoms and the first visit to Beatrixoord), and age at onset of symptoms. To investigate whether the effect of inhaled corticosteroid use on the annual decline in FEV_1 was dose dependent, subjects were divided into a low dose group (< 720 μg per day) and a high dose group (≥720 μg per day), based on the median value of individually calculated mean daily doses of inhaled corticosteroids, i.e. 720 μg per day. This grouping variable was then introduced in the model and separate slopes were fit before and during the use of inhaled corticosteroid for the two dose groups. To avoid a four-way interaction and the difficulties in interpreting this (i.e. dose group * time * inhaled corticosteroid use * gender), analyses were stratified by gender.

To be able to make valid interpretations of the results individual FEV_1 series had to meet basic criteria to be included in the analyses. First subjects who never used inhaled corticosteroids were excluded. Secondly subjects had to have 3 or more FEV_1 measurements over a period of at least 2 years in which they did not use inhaled corticosteroids and/or 3 or more FEV_1 measurements over a period of at least 2 years in which they used inhaled corticosteroids. In subjects who had measurements both with and without inhaled corticosteroids, the earliest measurements should be without inhaled corticosteroids and the later with inhaled corticosteroids. If subjects started using inhaled corticosteroids but had discontinued the use of inhaled corticosteroids after a few years all measurements after the discontinuation were discarded, even if they restarted again. Subjects who had sufficient measurements without inhaled corticosteroids but less than 3 measurements with inhaled corticosteroids or during less than 2 years only the measurements without inhaled corticosteroids were included in the model.

All calculations were conducted in S-plus 2000 (Insightful Corporation, Seattle, WA, USA).

RESULTS

Baseline characteristics

The characteristics of the included and excluded individuals, compared with the excluded individuals, are shown in Table 1.

Table 1. Characteristics of excluded and included subjects

Characteristics	Excluded subjects (n=159)	Included subjects (n=122)
Males (%)	99 (62)	71 (58)
Age of onset symptoms, yrs	4 (2 to 14)	6 (2 to 21)
Mean daily dose of inhaled corticosteroids, µg/day *	--	720 (426 to 1116)
Initial testing		
Age, yrs	20 (15 to 28)	28 (21 to 37)
FEV_1 %predicted post BD, %	94 (82 to 104)	85 (68 to 97)
BHR $\leq$ 16.0 mg/ml, %	87	87
$\geq$ 1 positive skin test, %	98	87
Blood eosinophils, $*10^6$/l	385 (220 to 539)	330 (220 to 528)
Reversibility, %predicted	21 (14 to 31)	25 (17 to 33)
Smoking		
pack years smoking, yrs	0.0 (0.0 to 2.9)	0.1 (0 to 5.6)
non / ex / current-smokers, %	50 / 5 / 45	49 / 6 / 45

Data are presented in median values (inter-quartile range) unless stated otherwise; BHR= bronchial hyperresponsiveness; pre BD= before administration of bronchodilator; post BD= after administration of bronchodilator. * Calculated for individuals who ever used inhaled corticosteroids only. Differences tested by chi-square-test (categorical variables) or Mann-Whitney U test (continuous variables).

Included participants were older, were less frequently atopic and had, as expected lower FEV_1 and higher reversibility at initial testing. Median (inter-quartile range (IQR)) follow-up of the included group was 23.3 years (15-29 years). Table 2 shows characteristics of male and female participants.

Table 2. Characteristics of males and females

Characteristics	Males (n=71)	Females (n=51)
Age of onset symptoms, yrs	6 (2 to 22)	6 (3 to 21)
Untreated period, yrs	14 (4 to 22)	16.0 (9 to 25)
Age at start of inhaled corticosteroids, yrs	40 (34 to 48)	45 (35 to 53)
Mean daily dose of inhaled corticosteroids, µg/day *	794 (527 to 1129)	618 (400 to 1114)
Period of inhaled corticosteroids use, yrs	13.6 (7.0 to 19.4)	14.0 (8.5 to 20.7)
Duration of inhaled corticosteroids use, yrs of 100 µg use daily *	110.1 (47.7 to 165.9)	88.6 (46.4 to 155.9)
Initial testing		
Age, yrs	27 (21 to 34)	30 (24 to 37)
FEV_1 %predicted pre BD, %	56 (45 to 71)	56 (39 to 69)
FEV_1 %predicted post BD, %	85 (66 to 97)	87 (68 to 97)
BHR $\leq$ 16.0 mg/ml, %	86	88
$\geq$ 1 positive skin test, %	86	88
Blood eosinophils, 10^6/l	341 (237 to 534)	280 (215 to 481)
Reversibility %predicted	24 (18 to 32)	28 (17 to 33)
Smoking		
pack years smoking, yrs	2.4 (0 to 7.2) †	0 (0 to 0.5)
non / ex / current-smokers, %	34 / 10 / 56 †	71 / 0 / 29
Re-examination		
Age, yrs	53 (46 to 59)	57 (50 to 62)
FEV_1 %predicted pre BD, %	57 (42 to 74)	61 (39 to 81)
FEV_1 %predicted post BD, %	70 (54 to 85) ‡	78 (62 to 95)
BHR $\leq$ 16.0 mg/ml, %	88	85
$\geq$ 1 positive skin test, %	77	73

Blood eosinophils, 10^6/l	130 (70 to 220)	132 (66 to 220)
Reversibility %predicted	12 (8 to 16) [§]	15 (9 to 21)
Total IgE, IU/l	96 (27 to 442) [ll]	47 (25 to 193)
Total IgE $\geq$ 120 IU/l, %	46	32
Smoking		
pack years smoking, yrs	8.4 (0.3 to 16.9) [†]	0 (0 to 3.6)
non / ex / current-smokers, %	24 / 47 / 30 [†]	71 / 20 / 10

Data are presented in median values (inter-quartile range) unless stated otherwise; BHR= bronchial hyperresponsiveness; pre BD= before administration of bronchodilator; post BD= after administration of bronchodilator. [*] Calculated for individuals who ever used inhaled corticosteroids only. Differences tested by chi-square-test (categorical variables) or Mann-Whitney U test (continuous variables). Significant different between males and females: [†] p<0.0001; [‡] p=0.035; [§] p=0.018; [ll] p=0.040

There were 4663 FEV_1 measurements, median number of measurements per individual being 37 (22-48) in males and 40 (24-54) in females. The median length of the period without inhaled corticosteroids was 9.8 years (6-19), the median length with inhaled corticosteroids was 13.8 years (8-20). There was a predominance of smoking in males at baseline and re-examination, otherwise females and males had similar clinical characteristics at baseline. At re-examination, females had a significantly higher FEV_1 % predicted post bronchodilator, a higher degree of reversibility and lower total IgE level compared to males. No significant difference existed between males and females with respect to the age at which inhaled corticosteroids were initiated, the daily dose, or the cumulative dose of inhaled corticosteroids used.

Longitudinal change in lung function

Median FEV_1 at the start of the study (i.e. at age 30 years) was 2.8 litres. Mean annual FEV_1 decline (mean (95%CI)) was 36.6 (23.3 to 50.0) ml/year for a male with an FEV_1 of 2.8 litres before institution of inhaled corticosteroids. Subjects who never used inhaled corticosteroids had an annual FEV_1 decline of 12.5 (3.7 to 21.2) ml/year. The difference between subjects who never used inhaled corticosteroids and subjects who later started inhaled corticosteroids was significant (p=0.0001), the latter group having a more rapid decline.

Effect of gender

The introduction of inhaled corticosteroids was associated with a significant reduction in mean annual decline in FEV_1 of 12.9 (1.0 to 24.8) ml/year (p=0.033). When comparing the sexes, mean annual decline in FEV_1 was similar in males and females before introduction of inhaled corticosteroids, i.e. 36.6 (23.3 to 50.0) and 24.7 (9.1 to 40.3) ml/year, respectively (p=0.25, Figure 1). After institution of inhaled corticosteroids males had a significantly smaller decline in FEV_1 than before, i.e. 16.1 (8.0 to 24.1) ml/year (p=0.011), whereas it did not change significantly in females: 21.5 (11.3 to 31.7) ml/year (p=0.73). The effect of institution of inhaled corticosteroids on FEV_1 decline was not significantly different between males and females, the difference in change of FEV_1 decline between both groups being 17.4 (-41.4 to 6.5) ml/year (p=0.15).
The level of FEV_1 improved after the start of inhaled corticosteroids, i.e. 132.8 (7.1 to 258.5) ml in males (Figure 2, p=0.038), and 132.3 (-18.4 to 283.1) ml in females (p=0.085).

Effect of smoking

Decline in FEV_1 before the start of inhaled corticosteroids was not significantly different between males and females with <5 pack years smoking at re-examination, i.e. 54.4 (29.5 to 79.2) and 27.3 (7.6 to 46.9) ml/year respectively (p=0.096, Figure 1). Males with <5 pack years smoking, mean FEV_1 decline changed from 54.4 (29.5 to 79.2) to 17.7 (6.5 to 28.7) ml/year after the start of inhaled corticosteroids, the difference of 36.8 ml/year being significant (p=0.0097). In females, values were 27.3 (7.6 to 46.9) and 26.5 (15.8 to 37.1)

ml/year respectively, the difference being non-significant. Inhaled corticosteroids reduced FEV_1 decline significantly more in males than in females, i.e. 36.0 (0.9 to 71.0) ml/year more in males (p=0.045). This positive effect of inhaled corticosteroids was not observed in individuals with ≥5 pack years smoking. FEV_1 decline before and after institution of inhaled corticosteroids was 27.8 (14.3 to 41.3) and 16.1 (3.3 to 28.9) ml/year in males and 24.5 (3.1 to 52.0) and 11.6 (17.7 to 41.0) ml/year in females respectively. Differences in pre- and post inhaled corticosteroid FEV_1 declines were not different between males and females (1.1 (-46.4 to 48.5) ml/year) (p=0.96).

Dose-response effect of inhaled corticosteroids

There was no significant difference in FEV_1 decline before and after institution of inhaled corticosteroids in male patients who used <720 µg/day (the median daily dose used), i.e. 14.5 (-11.4 to 40.5) ml/year before and 23.6 (11.8 to 35.3) ml/year after initiation of inhaled corticosteroids (p=0.51, Figure 3). In males who used ≥720 µg/day, decline in FEV_1 after introduction of inhaled corticosteroids was 39.8 ml/year less compared to before introduction (p=0.0004). Males who used ≥720 µg/day of inhaled corticosteroids had significantly less deterioration in FEV_1 than males using <720 µg/day, i.e. 48.8 ml/year less decline (p=0.006) (Figure 3). This effect was not present in females.

Risk factors of lung function decline

No additional association was observed with age at onset of symptoms, age at start of inhaled corticosteroids, untreated period, bronchial hyperresponsiveness at initial testing, number of blood eosinophils, total IgE levels, atopy or reversibility (% of predicted).

DISCUSSION

We present the results of our 23-year follow-up study in adult patients who had longstanding asthma at the time inhaled steroid became available in the Netherlands (in 1974), and who had moderate to severe asthma. Results show that both males and females have comparable lung function decline before the institution of inhaled corticosteroids. In males, the use of inhaled corticosteroids was significantly associated with a reduction in annual lung function decline, a finding not observed in females. The beneficial effect of inhaled corticosteroids was dose dependent and not present in males with more than 5 pack years smoking.

We are aware that our study is observational in nature and that there is a possibility that the lack of significance of inhaled corticosteroids in females is a spurious effect. Can we, based on our observations advise not to prescribe inhaled corticosteroids to female asthmatics? First, inhaled corticosteroids are beneficial to almost all asthmatics of both sexes by their well-known short-term (up to 3-5 years) improvement in lung function, an effect also observed in our study in both males and females. Moreover, inhaled corticosteroids improve symptoms, exacerbation rate, and quality of life in short-term studies. Therefore, our study in no way implies that females should not be prescribed inhaled corticosteroids. However, given these short-term beneficial effects one cannot simply evaluate in a double blind randomised study whether inhaled corticosteroids prevent lung function decline in asthma over many years. Thus our data are the best available long-term data to date.

Our 23-year follow-up study attempted to evaluate whether inhaled corticosteroids prevent lung function loss in asthma. Therefore, we had to exclude patients who never used inhaled corticosteroids. We are aware that excluding these patients could lead to some unintended bias, yet this group was not the aim of our cohort study. As expected, we found that those not using inhaled steroids at all had better lung function at initial testing and a less rapid decline in FEV_1 over time, probably because they had milder disease. Whether they would have benefited also from inhaled corticosteroids in the long run could not be addressed by our study.

Asthma is generally a benign disease. However, it is acknowledged that lung function may decline more rapidly than in healthy individuals[6] which is thought to result from an ongoing, chronic inflammatory airway disease. Therefore, it is of interest to assess whether anti-inflammatory agents may prevent accelerated lung function loss. Double-blind studies in mild to severe asthma have consistently shown their beneficial effects over short periods of time[16][27] although other studies failed to show this.[28] Our study indicates that indeed an accelerated loss in lung function may occur in asthma, which may be reduced by long-term treatment with inhaled corticosteroids. Beneficial effects of inhaled steroids have been reported in newly diagnosed asthma with respect to lung function over longer periods of time.[29][30] Interestingly, we show that this treatment may be also of benefit in individuals with longstanding asthma. Previous (relatively) short-term studies did not stratify for gender to assess whether females and males have different responses to inhaled corticosteroids.[18][28][30] Our study shows that the observed beneficial effect of this treatment with respect to long-term decline in FEV_1 is present in male, but not in female asthmatics with moderate to severe asthma. This is consistent with a recent double-blind study in 52 asthmatics (26 placebo), showing that bronchial hyperresponsiveness improved approximately threefold more in males than in females after 6 week treatment with 2000 µg of fluticasone propionate.[14]

It is not clear why the use of inhaled corticosteroids is not associated with reduced lung function decline in females in contrast to our findings in males. There are several explanations possible. Female sex hormones may play a role. Progesterone has steroid-like anti-inflammatory actions[31][32], whereas estrogens augment inflammation by influencing lymphocyte and monocyte numbers, increasing B cell differentiation and antibody production,

and decreasing T cell suppressor activity.[33] Furthermore, estrogens enhance eosinophil adhesion to human vascular endothelial cells.[34] To what extent sex hormones interfere with the response to inhaled corticosteroids in humans is yet unknown. Females are reported to have more frequently severe asthma than males.[2][6][15][35][36][37][38] However, females in our study had similar numbers of blood eosinophils and severity of bronchial hyperresponsiveness as males both at initial testing and re-examination, and they had higher FEV_1% predicted post bronchodilator and lower IgE levels at re-examination than males. Thus, differences in asthma severity can not simply explain the smaller effect of inhaled corticosteroids in females in our study. It is also unlikely that a lower prescribed dose of inhaled corticosteroids explains the gender difference since we found neither a difference in the daily dose nor in the cumulative dose of inhaled corticosteroids used by males and females. The observed lack of effect may also have been due to different airway deposition of inhaled corticosteroids in females than in males. Females have smaller airway calibre than males, which may enhance deposition of inhaled corticosteroids in the large airways.[39] This may reduce an overall beneficial effect, since the current insight is that peripheral airways contribute significantly to airway obstruction in asthma.[40] Finally, females had somewhat less decline in lung function before initiation of inhaled corticosteroids, though the difference between males and females was not significant. It may well be that females with more extremely rapid decline in lung function would have benefited. This cannot be simply set aside with our observations.

Our study shows a dose response effect of inhaled corticosteroids on annual decline in FEV_1 in males. An additional analysis showed that this effect was not driven by the effect of smoking. Only 40% of the males using ≥720 µg/day smoked <5 pack years at follow-up. When females were treated with inhaled corticosteroids no difference in effect between low dose or high dose was seen. The latter may just reflect the influence of the lower number of females under study. Alternatively, this might suggest that females require higher doses of inhaled corticosteroids, or that females have lower compliance rates with maintenance use of treatment. It is important to clarify these issues because it is well established that inhaled corticosteroids are accompanied by side effects at high doses. Whatever are the underlying differences between females and males to explain our findings, an important message from our results is that studies investigating effects of inhaled corticosteroids should investigate the effects in males and females separately.

An interesting and important observation is that smoking interferes with the long-term beneficial effect of inhaled corticosteroids on FEV_1 decline in male smokers. It has been shown previously that smoking is accompanied by a smaller clinical benefit from inhaled corticosteroids.[16][17][18] Though the underlying mechanisms are not yet resolved, it may well be that cigarette smoking reduces histone deacetylase-2 expression and activity in the airway wall and alveolar macrophages, thereby reducing the effect of inhaled corticosteroids.[41] The effect of inhaled corticosteroids in males who smoked less than 5 pack years can not be simply explained by changes in smoking habits. Only 4 out of the 28 males who had less than 5 pack years of smoking at the end of the study were smokers at the beginning of the analyses on FEV_1 decline (at age 30) and quit smoking 2 to 10 years previous to the introduction of inhaled corticosteroids. The other males were never smokers or ex-smokers and did not start or restart smoking during follow up.

In conclusion, we show that inhaled corticosteroids are not only beneficial in asthma in short-term studies, but that their long-term use in moderate to severe adult asthma is associated with less FEV_1 decline in males in a dose dependent manner. In females there was no effect on lung function decline. Since similar doses of inhaled corticosteroids were used in males and females, further studies have to investigate whether female sex hormones, airway geometry, deposition and particle size of inhaled corticosteroids, and/or differences in compliance may

explain the difference in response between males and females. Importantly, in males with more than 5 pack years of smoking the long-term beneficial effects on FEV_1 decline were absent. All efforts should be made to motivate people with asthma to refrain from smoking, even more so since it prevents beneficial effects in the long run of the best treatment currently available.

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Figure 1. Mean annual change in FEV_1 in ml/year (with 95% confidence interval) for males and females before and after the start of inhaled corticosteroids (ICS). Data were corrected for level of FEV_1 at age 30 (centred at 2.8 litres), height (centred at 1.75 m), pack years smoking and oral corticosteroid use. Significant differences are shown between before and after introduction of inhaled corticosteroids in males and females, and in the effect of inhaled corticosteroids between males and females.

Figure 2 Initial improvement in lung function in males and females before and after introduction of inhaled corticosteroid use (ICS). Corrected for level of FEV_1 at age 30 (centred at 2.8 L), height (centred at 1.75 m), pack years smoking and oral corticosteroid use.

Figure 3. Mean annual change in FEV_1 in ml/year (with 95% confidence interval) for males and females for low and high mean daily dosage of inhaled corticosteroid use (<720 and ≥ 720 µg/day). Corrected for level of FEV_1 at age 30 (centred at 2.8 L), height (centred at 1.75 m), pack years smoking and oral corticosteroid use. Significant differences are shown between before and after introduction of inhaled corticosteroids, and between low and high daily dosage of inhaled corticosteroid use, in males and females.

Figure 1

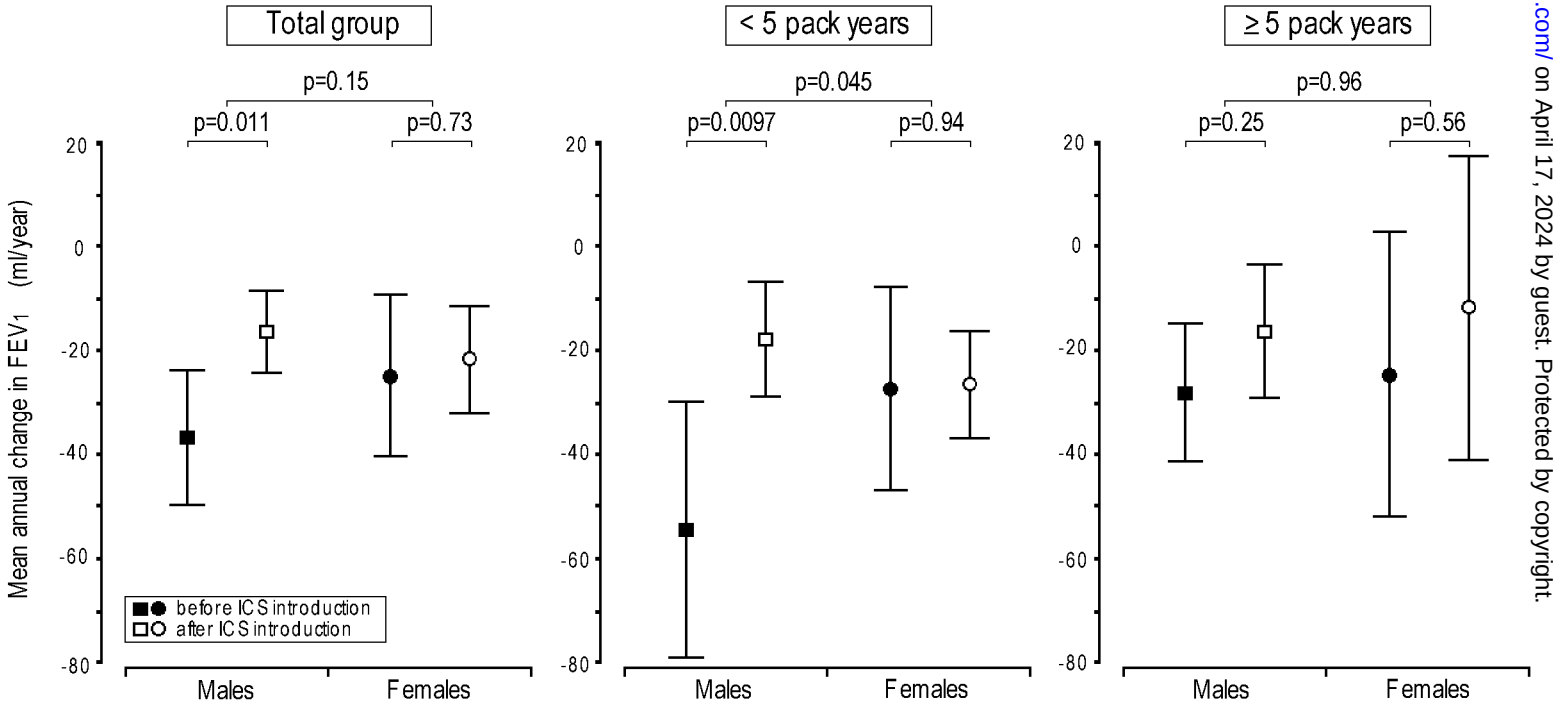


Figure 2

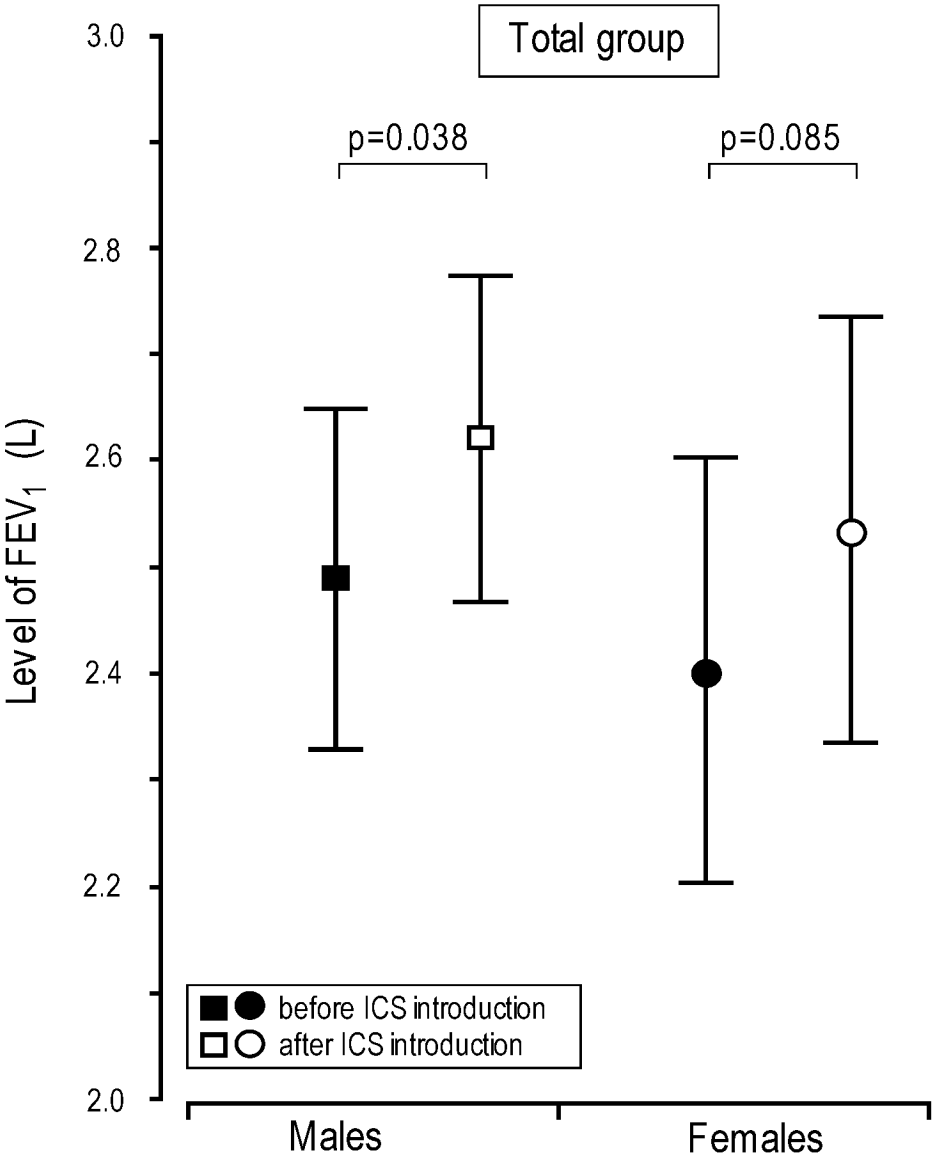
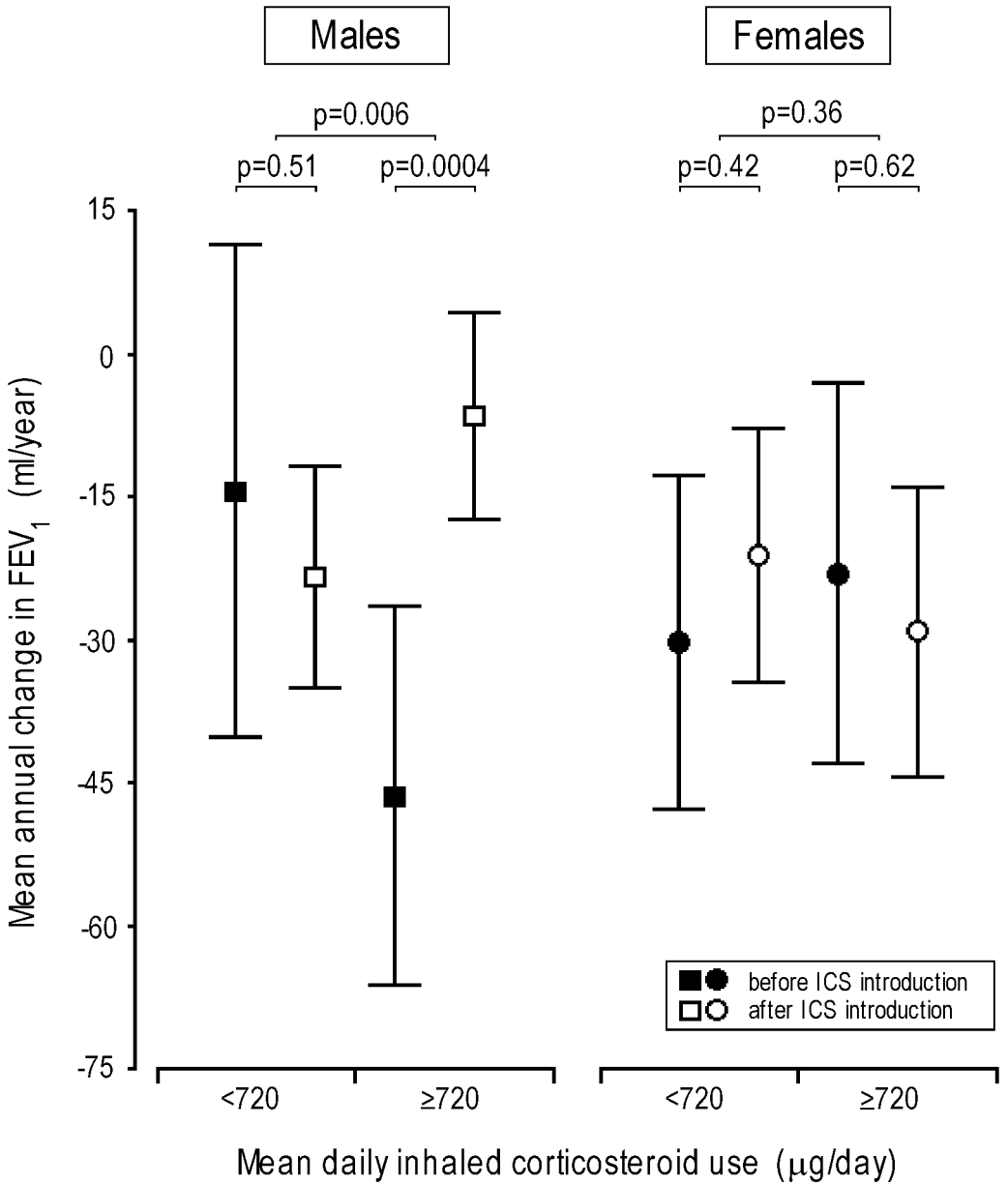

Total group
p=0.038
p=0.085
3.0
2.8
2.6
2.4
2.2
2.0
Level of FEV1 (L)
before ICS introduction
after ICS introduction
Males
Females

Figure 3


Males
Females
p=0.006
p=0.51
p=0.0004
p=0.36
p=0.42
p=0.62
15
0
-15
-30
-45
-60
-75
Mean annual change in FEV1 (ml/year)
before ICS introduction
after ICS introduction
<720
≥720
<720
≥720
Mean daily inhaled corticosteroid use (μg/day)