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Determinants of lung function and airway hyperresponsiveness in asthmatic children

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Summary
Background: Asthma patients exhibit an increased rate of loss of lung function. Determinants to such decline are largely unknown and the modifying effect of steroid therapy is disputed. This cross-sectional study aimed to elucidate factors contributing to such decline and the possible modifying effect of steroid treatment.
Methods: We analyzed determinants of lung function and airway hyperresponsiveness (AHR) in a Scandinavian study of 2390 subjects from 550 families. Families were selected for the presence of two or more asthmatic children as part of a genetic study, Scandinavian Asthma Genetic Study (SAGA).
Results: The primary analysis studied the association between the lung function and delay of inhaled corticosteroids (ICS) after asthma diagnosis among asthmatic children and young adults with a history of regular ICS treatment ($N = 919$). FEV_1 percent predicted (FEV_1% pred) was 0.25% lower per year of delay from diagnosis until treatment ($p = 0.039$). This association was significantly greater in allergy skin prick test negative children. There was no significant influence of gender, age at asthma onset, or smoking.

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In the secondary analysis of the whole population of 2390 asthmatics and non-asthmatics, FEV_1% pred was inversely related to having asthmatic siblings (−7.9%; $p<0.0001$), asthma diagnosis (−2.7%; $p=0.0007$), smoking (−3.5%; $p=0.0027$), and positive allergy skin prick test (−0.47% per test; $p=0.012$), while positively related to being of female gender (1.8%; $p=0.0029$). Risk of AHR was higher by having asthmatic siblings (OR 2.7; $p<0.0001$), being of female gender (OR 2.0; $p<0.0001$), and having asthma (OR 2.0; $p<0.0001$).

Conclusions: These data suggest that lung function is lower in asthmatics with delayed introduction of ICS therapy, smoking, and positive allergy skin prick test. Lung function is lower and AHR higher in female asthmatics and subjects with asthmatic siblings or established asthma.

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Introduction

Asthma patients with persistent symptoms may suffer loss in lung function from childhood.[1,2] Observational data from children[3,4] and adults[5,6] and one randomized controlled trial (RCT) in newly diagnosed adult asthmatics[7] suggested that early intervention with inhaled corticosteroid (ICS) therapy has a disease modifying effect on the long-term outcome of lung function maintaining better pre-bronchodilator lung function if started shortly after symptom debut. However, recent RCTs in schoolchildren[8] and preschool children[9–11] were unable to confirm such disease modifying effect from early steroid treatment.

We performed a cross-sectional observational study of lung function and airway hyperresponsiveness (AHR) in a Scandinavian population of 2390 subjects from 550 families with at least two asthmatic siblings, who were recruited for a study in asthma genetics. We hypothesized an association between delay of therapy with ICS after asthma diagnosis and lower lung function. We also report a secondary analysis of the impact of asthma, heredity, allergy, gender, smoking, and onset of asthma on lung function level and AHR in this population.

Methods

Subjects

The subjects were part of a study on asthma genetics comprising Caucasian families with at least two children aged 6–36 years with a clinical asthma diagnosis. At least one of the siblings had to be treated regularly with glucocorticosteroids or cromones for at least 1 year or two consecutive seasons prior to recruitment. All asthmatic children together with their parents (less than 66 years) and any siblings aged 6–35 years were included in the study. Subjects suffering from cancer, heart disease, mental retardation, or a chronic pulmonary disease other than asthma were excluded. The children were excluded if they were born before 34 weeks' gestation. Families in which both parents had ever been affected by asthma or COPD or were currently affected by perennial or seasonal rhinitis were also excluded from the study.

Subjects were recruited mainly from outpatient clinics at secondary and tertiary referral pediatric and adult pulmonary hospital departments, through publicity campaigns and contact with patient support groups. The phenotyping was performed in 10 centers: two in Denmark (Copenhagen, Kolding), three in Norway (Oslo, Bergen, Trondheim/Harstaad), and five in Sweden (Gothenburg, Lund, Stockholm, Uppsala, Luleå).

The study was approved by the Ethics Committee at each institution.

Lung function was measured on a pneumotachograph (Vitalograph 2120, Vitalograph Ltd., Buckingham, UK (C, K) or (Masterscope Pneumoscreen, Erich Jaeger Gmb, Essen Germany (T, O)). The measurements were performed in accordance with ATS guidelines.[12] The subjects were tested sitting, and wearing nose clips. Three acceptable flow–volume curves were obtained with less than 0.2-L difference between the largest and the second largest. The higher of the two was used as the outcome. FEV_1 was corrected for age and height with sex-specific regression equations to obtain percent predicted. Reference values according to Zapletal et al.[13] was used for children and Quanier[14] for adults.

Methacholine challenge test was performed by a tidal-volume-triggered dosimetric method[15] using the Spira Elektro 2 (Respiratory Care Centre, Hämeenlinna, Finland), administered to all subjects whose baseline FEV_1 was above 65% predicted and absolute FEV_1 was $\geqslant 1.5$ L (adults only). The subjects were required not to have had a viral respiratory infection or significant asthma exacerbation requiring oral steroids during the 2 weeks preceding the test. Baseline FEV_1 was determined after saline inhalation. Methacholine was inhaled in successively increasing doses at 2-min intervals until FEV_1 decreased by 20% compared to baseline or a cumulative dose of 5825 μg has been given. In adults, the dose was given in six, and in children nine incremental dose steps. The latter schedule was implemented after an initial pilot study on 22 children 6–16 years old at the Copenhagen center.

At the end of the challenge test, subjects received 1.0 mg of terbutaline sulfate (Bricanyl Turbuhaler), and FEV_1 was determined 30 min later to ensure its recovery to the baseline value. AHR was analyzed as a dichotomized variable ($\pm$20% fall in FEV_1 within the dose range tested). In addition, PD_{20} value (μmol) was calculated by linear interpolation between the dose points bracketing the 20% fall in FEV_1[16] and was analyzed as a continuous variable.

A more detailed methodological description is provided in Appendix A (on-line).

Skin prick tests were performed at the antebrachium of all individuals with a standard panel of allergens; dog, cat, horse, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, grass pollen mix, tree pollen mix, mugwort , *Alternaria*, and *Cladosporium* (Soluprick® SD, ALK AB). Histamine (10 mg/mL) was used as a positive control and the diluent used for the allergens as the negative control. This outcome was analyzed as a numeric variable summarizing the number of positive tests (0–10).

Allergen-specific IgE was assayed by a Phadiatop® method with a mixture of the inhalant allergens used for skin prick testing. The test outcome was dichotomized into positive or negative for analysis.

Medical history was obtained by qualified doctors or research nurses from personal interviews based on standardized questionnaires with close-end response categories. History emphasized asthma history (age when the doctor diagnosed asthma and age at the start of ICS treatment) in addition to current or passive smoking.

Statistical analysis

Siblings with asthma requiring prophylactic therapy for at least 1 year were analyzed in a multiple linear regression model describing FEV_1 percent predicted (FEV_1% pred) by variables considered related to lung function and/or ICS delay. In order not to mask the association between ICS delay and lung function, care was taken not to include variables that could be affected by ICS delay and at the same time could affect FEV_1% pred themselves, e.g., hyperreactivity. The initial model included: ICS delay, skin prick test, allergen-specific serum IgE, gender, asthma debut, smoking, and passive smoking.

All subjects were analyzed in a multiple linear regression model describing FEV_1% pred by variables considered possibly related to lung function, including sibling with asthma, skin prick test, allergen-specific serum IgE, gender, asthma, smoking, passive smoking, and AHR.

All subjects were subsequently analyzed by a logistic regression model describing AHR by variables considered possibly related to AHR including sibling with asthma, skin prick test, allergen-specific serum IgE, gender, asthma, smoking, passive smoking, and FEV_1% pred. In addition, a multiple linear regression model describing PD_{20} included the same variables.

Because individuals within a family are correlated both due to genetic and environmental similarities, we adjusted for this familial correlation using Proc Gen Med in SAS version 7.0. This appropriately reduces statistical significance based solely on the family correlation.

Results

Demographics (Table 1)

The total study comprised 550 families with 2390 individuals (53% males). Allocation to the study was unevenly distributed among centers and among the three Scandinavian countries: Denmark: 455 subjects (Copenhagen), 455 (Kolding); Sweden: 235 (Stockholm), 190 (Uppsala), 170 (Luleå), 165 (Gothenburg), 88 (Lund), Norway: 232 (Bergen), 203 (Trondheim), 197 (Oslo).

Primary study group comprised the 919 children with clinical asthma treated with prophylactic asthma therapy for at least 1 year before inclusion or for at least two consecutive seasons. AHR was found in 83% of these subjects. Mean FEV_1 was 89% predicted. Sixty-five percent had positive skin prick test and positive allergen-specific serum IgE. Mean age of asthma debut was 3 years.

Secondary study group comprised all subjects (2390 individuals) including 1321 siblings (1136 with doctor-diagnosed asthma) and 1069 parents (225 with doctor-diagnosed asthma).

Lung function

Asthmatic siblings on regular ICS treatment: FEV_1% pred was negatively related to ICS delay among asthmatic siblings (−0.25% per year; $p = 0.039$) (Fig. 1). Skin prick test, antigen-specific serum IgE, gender, smoking, and age at asthma debut did not add significantly to the asthmatic model. This association was significantly greater in skin test negative children ($p = 0.0092$).

All subjects: FEV_1% pred was negatively related to having an asthmatic sibling (−7.9%; $p<0.0001$), asthma (−2.7%; $p = 0.0007$), smoking (−3.5%; $p = 0.0027$), and positive skin prick test (−0.47% per test; $p = 0.012$) (Fig. 2), while positively related to being of female gender (1.8%; $p = 0.0029$). Passive smoking and allergen-specific serum IgE did not add significantly to the model.

The effect of age and asthma among siblings on FEV_1% pred is depicted in Fig. 3A and B. Lung function in non-asthmatic siblings was higher with increasing age ($p = 0.0001$), while no such relation was present in siblings with an asthma diagnosis ($p = 0.20$). This effect was not gender specific (data not shown).

AHR

Risk of higher AHR was enhanced by being a sibling of an asthmatic (OR 2.7; $p<0.0001$), being female (OR 2.0; $p<0.0001$), and having asthma (OR 2.0; $p<0.0001$). Active smoking, passive smoking, positive skin prick test, allergen-specific serum IgE, and FEV_1% pred did not add significantly to the model.

Analysis of AHR was repeated for PD_{20} with similar results.

Discussion

Pre-bronchodilator FEV_1 was 0.25% lower per year between asthma diagnosis and start of ICS treatment. The data did not allow an accurate estimate of the association of lung function and time after initiation of ICS because we do not know for how long the ICS treatment was maintained after initiation, but the data suggest an association between late introduction of ICS and lower lung function. This finding aligns with previous observational data from children[3,4] and adults[5,6] as well as one RCT in adult asthmatics,[7] suggesting a disease modifying effect on pre-bronchodilator lung function if started shortly after symptom debut. However,

Table 1 Demographic data for subjects in a family-based study of asthma genetics.

		All	Asthmatic siblings with a history of regular anti-inflammatory treatment
N	Number of subjects (males)	2390 (1278)	919 (533)
Age	Years (median)	24	12
Height	cm (median)	167	154
Asthma	Number with doctor diagnosis	1361 (57%)	919 (100%)
Asthma debut	Years (median)	12	3
ICS delay	Years (median)	NA	3
Smoking	Number (%)	340 (14%)	49 (5%)
Passive smoking	Number (%)	616 (25%)	225 (24%)
Positive SPT*	Number (%)	1199 (50%)	593 (65%)
Positive RAST†	Number (%)	1130 (47%)	586 (64%)
Positive AHR‡	Number (%) of positive	1631 (68%)	761 (83%)
FEV_1%pred	% (Mean (95% CI))	94 (94; 95)	89 (88; 90)

*Skin prick test.
†Antigen-specific IgE.
‡Airway hyperresponsive to metacholine.

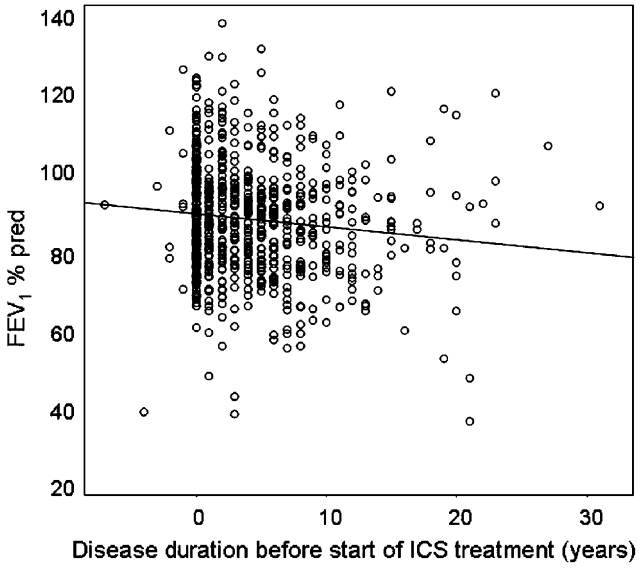

Figure 1 FEV_1% predicted in siblings with asthma related to time before regular ICS treatment was started.

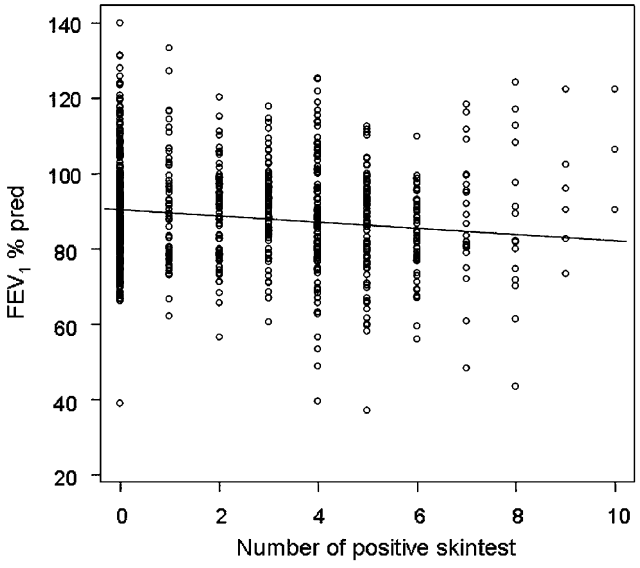

Figure 2 FEV_1% predicted in all subjects related to number of positive skin prick tests.

recent RCTs in schoolchildren[8] and preschool children[9–11] were unable to confirm such disease modifying effect from early steroid treatment. The disparate outcomes may be ascribed to fundamental differences in study designs or may be compatible with a treatment effect later in life affecting the natural decline in lung function while not apparent during childhood growth, or it may be due to differences in asthma severities.

The protective effect from ICS on lung function loss is small according to the current study (−0.25% per year). It is questionable whether a 2.5% reduction of FEV_1 for a 10-year delay in ICS treatment will have any clinical consequences for the young asthmatics in adulthood.

Age at asthma onset showed no relation to lung function. Early onset of asthma has been associated with a negative outcome[4,17,18] or no effect.[19,20] A recent large cross-sectional pediatric cohort study of asthma revealed an independent relationship between asthma duration and asthma severity.[4] The lack of evidence for such an association in the present study does not contradict this recent report.

Analyses of the secondary study group of asthmatics and their non-asthmatic siblings and parents showed that FEV_1% pred was most strongly influenced by membership in the sibling group independent of an asthma diagnosis. Siblings of asthmatics had 7.9% lower FEV_1% pred and a 2.7-fold greater AHR. The lower lung function in siblings was clearly more pronounced in the younger age group.

Smoking was associated with an additional 3.5% reduction in FEV_1% pred in the secondary study group of asthmatics

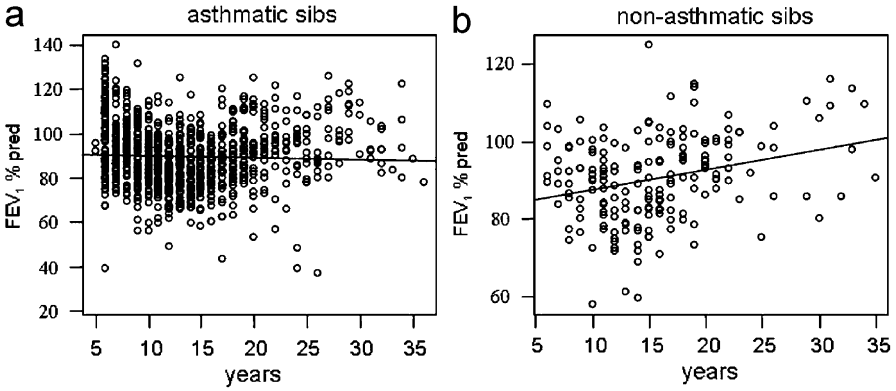

Figure 3 FEV_1% predicted related to sibling status and age.

and non-asthmatics, consistent with a recent longitudinal cohort study with a 15-year follow-up, which showed that smoking contributed significantly to the decline in lung function in both asthmatics and non-asthmatics.[1] Previous smaller reports were unable to demonstrate this additive effect of asthma and smoking.[21,22]

Allergy as reflected in positive skin prick tests was a significant predictor of lower lung function in the secondary study group. This finding is consistent with some previous longitudinal studies,[23,24] though not with others,[25–27] as positive skin prick tests have even been found to predict a milder course.[20] Allergen-specific serum IgE did not add significantly to the models describing lung function and AHR.

Being a female doubled the risk of AHR but provided a small but significantly higher lung function. Female gender was a marker of a worse prognosis in some studies,[18,28–30] though this was not apparent in other studies[22,26,31] and one study even reported a better prognosis for females.[32] That female gender is a predictor of a worse prognosis finds support in the observation that estrogen plays a role in asthma pathophysiology.[33]

Certain issues should be considered when the present data are interpreted. The study was cross-sectional and observational. The cohort had an inherent selection bias as subjects were only included if they belonged to families with at least two siblings with asthma as the study primarily aimed at genetic analyses. Recall bias could confound such retrospective collection of the time of onset of symptoms and start of ICS treatment, and we had no access to source data documenting asthma debut. Limitations include the small number of non-asthmatic siblings, which limit our ability to comment in detail on asthma development. On the other hand, the data quality was high since rigorous quality assurance was ensured and monitored in all centers, objective measurements were obtained through highly standardized methods and qualified doctors or research nurses obtained the data on asthma history from personal interviews based on standardized questionnaires with close-end response categories. Finally, the power of the study was high because of the large cohort size and the long age span. Therefore, we believe that the conclusions of the analyses are quite robust.

In conclusion, the study suggests that lower lung function is associated with delayed introduction of ICS therapy. Lung function is lower and AHR higher in subjects with asthmatic siblings, females and subjects with established asthma.

Conflict of interest. HB has been a consultant to, paid lecturer for and received research grants from Aerocrine, AstraZeneca, Altana, GSK, Merck, MedImmune and Pfizer. He does not hold stock or options in any pharmaceutical company in the respiratory field.

AG has been a paid lecturer for AstraZeneca, GSK, Merck, Boehringer and Pfizer.

LB has been paid lecturer for AstraZeneca, GSK, Merck, Boeringher and Schering-Plough.

GW has been paid lecturer for AstraZeneca, GSK and Merck. He does not hold stock or options in any pharmaceutical company.

Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2007.01.013.

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