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Airway hyperresponsiveness and development of lung function in adolescence and adulthood

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Epidemiology;
General population

Summary
Background: Long-term longitudinal studies of lung function from childhood to adulthood are important in linking our understanding of childhood risk factors to adult disease. Airway hyperresponsiveness has been shown to independently affect lung function growth in studies of adolescence. The objective of the study was to test the hypothesis that airway hyperresponsiveness has an independent deleterious effect on lung function in adolescence that extends into adulthood.
Methods: A random population sample ($n = 983$) aged 7–17 from Copenhagen was followed longitudinally for 20 years with four examinations.
Results: A total of 780 (79.3%) subjects contributed with lung function measurements and bronchial provocation testing. Among these, 170 (21.8%) had airway hyperresponsiveness at one examination or more during the study period. There was no difference in initial FEV_1 levels between subjects with and without airway hyperresponsiveness. In a repeated measures regression model with adjustment for asthma and smoking, airway hyperresponsiveness was independently associated with reduced rates of growth in lung function in both sexes of 23 ml/year. Reduced growth rates resulted in deficits in maximal attained level of lung function at age 18, which persisted throughout the follow-up until the last examination at age 27–37 years.

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Conclusion: Airway hyperresponsiveness has an independent deleterious effect on lung function development from 7 to 37 years resulting in a lower maximal attained lung function and persistent deficits in lung function in adulthood.

Introduction

Development of lung function during childhood and adolescence determines the maximal attained lung function in young adulthood, and this level together with the rate of decline in lung function determines the subsequent lung function levels during adult life [1,2]. As such, deficits in maximal attained lung function may potentially contribute to the risk of later development of chronic obstructive pulmonary disease (COPD). Factors that influence lung function growth in children and adolescents are therefore interesting to study, as well as factors with effects on lung function that extend beyond the growth phase.

Only one general population study has studied lung function development from birth to the age of 22 [3]. In this study, the authors found, that children with low lung function in infancy had significantly lower lung function at the age of 22. Furthermore, they investigated the influence of wheeze, smoking, atopy, and parental asthma on this association, and found no modifying effects of these parameters on the development of lung function measures.

Two general population studies have addressed the independent effect of AHR on lung function in adolescents, and found that AHR is related to short-term deficits in lung function growth independently of asthmatic symptoms [4,5]. One study found AHR to be the single most important risk factor for reduced maximal level of lung function [6]. In adult populations, AHR has been related to lung function decline in individuals both with and without asthma [7]. We therefore hypothesized that AHR may be independently associated with lung function growth during adolescence in the general population, and that this association possibly have long-term effects extending into adulthood.

Consequently, the aim of this study was to investigate the association between AHR and lung function development from childhood to adulthood. Analyses were performed on a non-selected cohort of subjects followed over 20 years from childhood to adulthood covering the ages from 7 to 37 years.

Methods

Study subjects

Subjects participated in a prospective epidemiologic study initiated in 1986 [8]. A random sample of subjects were drawn from the civil registration list according to the year of birth between 1969 and 1979, and the date of birth during the first 7 days of each month of the year. As such, 983 children and adolescents aged 7–17 years from Copenhagen were included. Follow-ups took place in 1992, 1998, and 2006 as a 20-year follow-up.

Methods

Measurements of lung function

Measurements of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were performed on a 7-L dry wedge spirometer (Vitalograph®, Buckingham, UK) at all examinations. Each measurement consisted of at least three forced expiratory manoeuvres from total lung capacity to residual volume with a variation of less than 5%. Manoeuvers were performed with the subjects in standing position without use of nose-clip. The highest FEV_1 and FVC values were the reported in absolute values. For the first and second examination, when subjects were still children and adolescents, the reference values by Zapletal were used to calculate FEV_1%pred and FVC in percent of predicted value (FVC%pred) [9]. For the examinations three and four, when subjects had become adults, the reference values for pulmonary function testing published by the European Community for Coal and Steel (ECCS) [10], was used to calculate FEV_1%pred and FVC%pred.

Before testing, subjects were instructed not to use theophylline for at least 24 h, and short-acting beta-agonist (SABA) for 6 h. When long-acting beta-agonists (LABA) and leukotriene antagonists became available in Denmark, subjects were asked not to use LABA for 12 h, and leukotriene antagonists for 24 h. They were allowed to continue use of ICS. Subjects had no respiratory infections within 6 weeks of testing. Otherwise the examination was postponed.

Bronchial challenge tests

Bronchial challenge tests were performed with histamine according to the method described by Cockcroft et al. [11] at the first three examinations, and with methacholine according to the method of Yan et al. [12] at the fourth examination. Cut-off was a fall in FEV_1 of 20% or more at a concentration of less than 8 mg/ml at the first examination, due to constraints placed by the ethical committee at the time, 16 mg/ml at the second and third examination, and a dose less than 8 μmol at the fourth examination.

Height and weight

Height (in standing position without shoes) and weight were measured, and body mass index (BMI) was calculated.

Case history

Case history was obtained in part by questionnaires and in part by semi-structured interviews performed by a trained physician at all examinations. Case history included data on asthma, allergic diseases, and lifestyle factors.

Questions about asthma were adopted from studies by the ATS, Division of Lung Disease of the National Heart, Lung and Blood Institute [13] and Global Initiative for Asthma (GINA) [14].