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Early life determinants of lung function change from childhood to adolescence

Erica S. Schultz[a,*], Jenny. Hallberg[a,b], Niklas Andersson[a], Jesse D. Thacher[a], Göran Pershagen[a,c], Tom Bellander[a,c], Anna Bergström[a,c], Inger Kull[b,d], Stefano Guerra[e,f], Per. Thunqvist[a,b], Per M. Gustafsson[g,h], Matteo Bottai[a,1], Erik Melén[a,b,c,1]

[a] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Sachs Children's Hospital, Södersjukhuset, Stockholm, Sweden
[c] Centre for Occupational and Environmental Medicine, Stockholm County Council, Sweden
[d] Department of Clinical Science and Education, Södersjukhuset, Sweden
[e] Asthma and Airway Disease Research Center, University of Arizona, Tucson, AZ, USA
[f] ISGlobal CREAL, CIBERESP, Pompeu Fabra University, Barcelona, Spain
[g] The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[h] Central Hospital, Department of Paediatrics, Skövde, Sweden

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ABSTRACT

Rationale: Little is known about how perinatal and childhood factors influence lung function change between childhood and adolescence.
Objectives: To investigate possible early life predictors of change in FEV_1 between age 8 and 16 years. In addition, to investigate possible predictors of having persistently low lung function (FEV_1 < 25th percentiles both at age 8 and 16) up to adolescence.
Methods: The BAMSE birth cohort study collected data throughout childhood on environmental factors, individual characteristics, and spirometric measures at 8 and 16 years (n = 1425). Associations between early life predictors (n = 31) and FEV_1 increase between 8 and 16 years were assessed with linear regression. Predictors of having persistently low lung function were examined.
Results: Few factors were consistently associated with altered lung function growth, although low birth weight, asthma heredity (paternal), secondhand smoke in infancy, and season of birth had a significant impact (p-value ≤0.01). The majority of subjects stayed however within the same category of lung function between ages 8 and 16 years (in total 821/1425 = 58%). Predictors associated with having *persistently* low lung function were gestational age, secondhand smoke (at 2 and 8 years of age), and factors related to lower respiratory tract infections in infancy.
Conclusions: In summary, rather few exposures in childhood were identified to have a significant impact on lung function growth between childhood and adolescence. Our data support previous study findings indicating that lung function development is influenced by factors before birth and in infancy, including second hand tobacco smoke.

1. Introduction

Intrauterine and early life insults increase the risk of adult respiratory diseases [1,2]. This concept was first introduced by Burrows and colleagues in 1977, who showed that early respiratory illness was associated with chronic obstructive pulmonary disease (COPD) [3]. More recent studies have built upon this knowledge by showing that a reduced plateau in early adulthood lung function is associated with COPD-risk in later life [4,5]. These observations support the notion that individual lung function tracks with age, i.e. remains in a similar percentile over time in relation to the population [2,6].

The majority of longitudinal lung function studies have focused on specific respiratory phenotypes or disease severity in relation to lung function trajectories [7–11]. Some have investigated other risk factors for poor lung function development, primarily focusing on intrauterine events and post-natal life, as it becomes more evident that these are

* Corresponding author. Karolinska Institutet, Institute of Environmental Medicine, Nobels väg 13 Box 210, SE- 171 77, Stockholm, Sweden.
E-mail address: Erica.Schultz@ki.se (E.S. Schultz).
[1] Equal author contribution.

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critical time-windows of lung development [12–15]. At the same time, investigations using multiple breath washout [16] and helium-3 magnetic resonance [17] suggest that alveolarization continues during childhood, and even in adulthood. This implies that even though a large proportion of the expected peak lung function achieved in young adulthood is fixed from pre- and early postnatal life, the predicted path of lung function growth can still be changed by factors later in life. This would suggest both the possibility of catch-up growth, but also risk of further deterioration. Nevertheless, environmental exposures following the pre- and postnatal period that influence lung function growth have scarcely been investigated [18–21].

Forced expiratory volume in one second (FEV_1) as a measure of lung function is an important determinant of respiratory health [3,4,22] and mortality in the general population [23], including early mortality [24]. FEV_1 is also the most commonly used lung function outcome in studies of lung function trajectories [5]. Our primary aim was to investigate possible predictors up to 8 years of age, focusing on individual characteristics and environmental exposures, in association with change of FEV_1 between age 8 and 16 years. Following the concept of lung function tracking, we also investigated early determinants in relation to having persistently low FEV_1 throughout childhood, since subjects having normal lung function growth from school-age to adolescence, but start low, will still end up in the low lung function category (trajectory).

2. Methods

2.1. Subjects

In this study, we used data from the Swedish population based birth cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiological study).

The parents of all children born in predefined areas of Stockholm, Sweden during 1994–96 were invited to enroll their children. Of the 5488 eligible children, 4089 were included (median age 2 months). Participants were followed repeatedly with questionnaires administrated at ages 1, 2, 4, 8, and 16 years, with response rates varying between 96% and 78% [25,26]. Clinical examinations were performed at 4, 8, and 16 years of age. Data on 2052 and 2311 spirometry measurements were available at ages 8 and 16 years respectively. Inclusion criteria for the present study population was available FEV_1 data from both 8 and 16 year investigations (n = 1425; 35% of the original cohort).

2.2. Exposures

Candidate predictors of lung function growth were selected based on previous literature and on availability in the BAMSE cohort. We included 31 exposure variables comprising individual characteristics and environmental exposures from infancy and up to 8 years of age (Table 1). For details regarding variable definitions and assessments, please see Table E1.

2.3. Measurements

Details regarding height and weight measurements, as well as lung function testing have been described elsewhere (11). Briefly, spirometry was performed at 8 years of age using the 2200 Pulmonary Function Laboratory (Sensormedics, Anaheim, CA) and at age 16 years of age using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA). At both occasions, recordings of several maximum expiratory flow volume curves (MEFV) were performed and accepted for further analysis if the subject's effort was coded as being maximal by the test leader, the MEFV curve passed visual quality inspection, and the two highest readings of FEV_1 and/or forced vital capacity (FVC) were reproducible according to ATS/ERS criteria (27).

Table 1
List of included exposure variables.

Variable name	Categories/unit if continuous
Individual characteristics	
Birth weight:	Z-score
Gestational age:	Weeks
Birth season:	Winter[#], Spring, Summer, Autumn
Asthma heredity, paternal:	Yes, No[#]
Asthma heredity, maternal:	Yes, No[#]
Environmental factors from infancy up to 8 years of age	
Exclusively breastfed [+]:	Months
Maternal smoking during: pregnancy[¶]:	Yes, No[#]
Older sibling[¶]:	Yes, No[#]
Parental education[¶]:	Low[#], Mid, High
Secondhand smoke[¶, +, §, ƒ, *]:	Yes, No[#]
Traffic-air pollution: NOx and PM_{10}[##]:	Per10 $\mu g/m^3$ respectively
RSV-infection[+]:	Yes, No[#]
Mold and/or dampness[¶,*]:	Yes, No[#]
Furred pets[¶, +, §, ƒ, *]:	Yes, No[#]
Socioeconomic status[¶,*]:	Low[#], High
Antioxidant intake[*]:	Low[#], Mid, and High.

Abbreviations: RSV = Respiratory syncytial virus.
[#] Reference category, Exposure assessed in: [¶] Infancy, 1[+], 2[§], 4 [ƒ], [*]8 years of age.
[##] Mean of annual averages for first year of life, year 1–4 and 4–8 years of life.

2.4. Statistical analyses

The association between the potential predictors and the 8 to 16 years of age lung function growth, here represented by FEV_1 increase (in mL), was assessed with linear regression on the mean.

Besides investigating the change in FEV_1 growth from 8 to 16 years, we also investigated possible predictors for having persistently low FEV_1 throughout childhood. For this purpose we derived the, age-, height-, weight-, gender-specific percentiles for normal percentiles of FEV_1 in the healthy children in our sample (see Data supplement). These percentile values were used in post hoc logistic regression analyses, where we categorized the study participants according to FEV_1 percentile levels at both 8 and 16 years into low lung function trajectory vs. normal/high lung function trajectory. A low lung function trajectory was defined as FEV_1 always below the 25th percentile and a normal/high lung function trajectory as always at or above the FEV_1 25th percentile (Box 1). This cutoff was recently used in a study investigating patterns of lung growth in subjects with asthma [22].

Each model were optimized regarding included confounder (s), using backwards selection and change of coefficient by more than 10%, please see data supplement for details. In addition a sensitivity analysis was performed including FEV_1 at 8 years of age and change in weight between 10 and 16 years of age as confounders. Summary statistics for FEV_1 and FVC were presented untransformed (in mL), as z-scores using GLI-2012 reference [28], and as percentiles using own reference equation.

All analyses were performed using Stata 13 (StataCorp LP, College Station, TX). The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden and parents of participating children provided written informed consent.

3. Results

The present study population (with FEV_1 data at both 8 and 16 years) was comparable to excluded participants, even though the distribution of some covariates (such as socioeconomic variables) differed to some extent (Table E2). Overall, the study population appeared representative of the whole cohort.

The average growth of FEV_1 between 8 and 16 years in females and males was 1757 mL and 2680 mL, respectively. The average 8 to 16 years change in FVC in mL, as well as FEV_1 and FVC presented as z-