Predictors of lung function in infants at high risk of atopy: effect of allergen avoidance

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Abstract Children of atopic parents are recognised as being at higher risk of developing bronchial asthma, drawing the attention of prevention strategies towards this population. Due to recent advances, lung function abnormalities in asthmatic children may now be measured early in life. The aim of this investigation was to examine possible predictors of lung function development in a sub sample of high-risk infants who took part in an allergy avoidance study. In 60 babies of atopic parents, measurements of upper airways inflammation were performed at 4 weeks of age, respiratory symptoms were assessed at 6 and 12 months of age, and lung function (V_max,FRC) was measured at 18 months by the rapid thoracoabdominal compression technique. Twenty-eight babies were enrolled in an allergen avoidance program, and 32 recruited as controls. No significant differences were detected for V_max,FRC between the intervention group (mean 331 ml s^-1) and the control group (359 ml s^-1), P=0.382. A multiple linear regression model could explain levels of V_max,FRC by weight gain since birth (beta = -35.35 ml s^-1 kg^-1, P=0.022) and by eosinophilic cationic protein (ECP) (beta = -0.95 ml s^-1 µl^-1, P=0.044), but not by intervention. Lung function measured at the age of 18 months in high-risk children is associated with weight gain and nasal ECP.

INTRODUCTION

Development of bronchial asthma and allergic disease in children is believed to be determined very early in life. Exposure to house dust mite (HDM) allergens in early infancy is also believed to be an important trigger in sensitisation and development of atopic disease (1). Avoidance of allergen exposure in early life has been demonstrated to increase the threshold of sensitisation, at least in “high-risk” children (2). However, besides the known effects of HDM allergen avoidance on sensitization, and besides anecdotal evidence, little is known about the effects of HDM allergen reduction on the development of lung function in infants.

Eosinophilic airway inflammation has been demonstrated to be associated with bronchial asthma (3). Moreover, elevated levels of eosinophilic cationic protein (ECP) in serum during an early episode of wheezing has been found to be associated with the development of bronchial asthma in young children (4). Recently, upper airways eosinophil inflammation in the first 4 weeks of life was demonstrated to be a risk factor for the development of recurrent wheeze in 6-month-old infants (5).

There is ongoing interest in measurement of lung function in infants, and its relationship to respiratory symptoms (6,7). Studies have found that diminished lung function may occur in currently symptom-free infants, before the onset of respiratory symptoms. This might be interpreted as a result of subclinical airway inflammation, eventually resulting in bronchial asthma.

Furthermore, a growing body of evidence shows an association between body composition and the development of asthma: studies have found a relationship between foetal growth and asthma (8), and also between obesity and asthma (9).

This study was performed to determine whether lung function at the age of 18 months was associated with neonatal upper airways inflammation or weight gain in infancy. Furthermore, we analysed whether simple methods of HDM allergen reduction influenced lung function development in “high-risk” infants.
METHODS

Study population and allergen avoidance

All children were participating in an international multi-centre study (Study on the Prevention of Allergy in Children in Europe, SPACE, Biomed II program) aimed at the prevention of allergy by means of dust mite avoidance measures (5). Mothers were enrolled either at routine visits at two obstetric wards in Vienna (Vienna general hospital, SMZ-Ost) during pregnancy or shortly after birth at the children’s departments of the centres involved. Screening questionnaires for symptoms associated with allergic disease were distributed and if a history of allergic rhinitis, hayfever, bronchial asthma or eczema was reported by any parent, skin-prick testing or serum IgE measurement were performed. Families were included if there was a positive allergy history and positive allergy test (to *Dermatophagoides pteronyssinus*, *D. farinae*, birch, ryegrass, ragweed or cat) in any parent.

After birth, participating infants were randomized into the intervention or control groups. Parents of the intervention group were encouraged to adhere to the following house dust mite avoidance procedures:

- All mattresses in the child's room should be covered with special dust mite protection casings (ACb®, Dr. Beckmann GmbH, Seefelden, Germany).
- Carpets in the child’s room should be removed and curtains that can be hot-washed should be selected.
- Soft toys and bedding should be hot-washed or frozen (weekly) as well as pillows and blankets.
- The child’s room should be ventilated whenever possible.
- The use of a damp cloth was advised when dusting and vacuum cleaning, which should be done once a week in the absence of the child.
- Smoking was discouraged in the house, as well as pets. If pets were present they were not allowed in the child's bedroom.
- Exclusive breast feeding was recommended for as long as possible and for at least 3 months.
- Introduction of solid foods was delayed until at least 4 months, milk products and cow’s milk formula until at least 6 months. If supplementation was required, a hypoallergenic formula was recommended before 6 months.
- Cow’s milk, egg and fish were recommended not to be introduced to the child’s diet before 12 months and peanut or tree nuts before the age of 3 years.

Implementation of these suggestions was checked at home visits at the age of 1, 6 and 12 months. In contrast, only brief standard recommendations from the relevant Austrian authorities were reiterated to parents for infants in the control group: breast-feeding was encouraged for at least 3 months, cow’s milk was recommended to delay until the twelfth month of life and the avoidance of pets and cigarette smoke was advised.

After 6 and 12 months children were seen again at their homes and a questionnaire regarding symptoms likely to be associated with allergy was filled out by the parents. In addition, data on smoking during pregnancy and smoking in the presence of the child were collected.

After the 12 months home visit, parents were asked for consent to participate in this study on lung function measurements. We recruited 62 subjects, and pulmonary function tests (PFT) could subsequently be performed in 60 of them, with the remaining babies failing to sleep during the measurements. Thirty-two of the babies (19 boys, 13 girls) were allocated to the control group, and 28 (14 boys, 14 girls) to the intervention group. Informed consent was obtained from the parents prior to all measurements and the study protocol was approved by Vienna University’s Ethical Committee.

Nasal lavage

Families were visited when the child was healthy as judged by the parents within the first 4 weeks of life (mean age 20.5 days, SD 7.6). Nasal lavage was thus performed at the children's homes. After inspection of the nasal lavage fluid, children were defined as being free of rhinitis, having serous rhinitis or having purulent rhinitis. Nasal lavage was obtained by instilling 2 ml of 37°C physiologic saline solution via syringe into each nasal cavity with the baby lying supine. Wash fluid and secretions were immediately aspirated into a sterile specimen trap [tracheal suction set (Fa.Dahlhausen) and a 30 cm suction catheter (Fa.Uno) attached to a portable suction device (Atmos LC-16, Fa.Draeger)]. The samples were then processed in a standardized way. They were firstly left for at least 1 h at room temperature. Samples were then weighed and diluted 1:1 with Dithiothreitol (Cleland’s reagent, Biorath/Germany). They were then centrifuged at 1454 g for 10 min at room temperature. Cells were discarded and the supernatants were stored at −30°C until analysis. Supernatant was subsequently analysed for eosinophil cationic protein (ECP) and EPX. Results are given in μg l⁻¹ after correction for dilution. Eight medical students previously trained in the procedure performed all the lavages (5).

Pulmonary function tests (PFT)

Pulmonary function tests were scheduled for 18 months of age. The children had to be free of upper airway infection 3 weeks prior to testing. Pulmonary function tests were performed by utilising the rapid thoracoabdominal compressions (RTC) technique, using the SensorMedics SM2600 System (SensorMedics Corporation, Yorba...
Linda, CA, USA), together with the 2605 Infant Hugger device (Equilibrated Bio Systems, Inc., Melville NY, USA). This system is described in detail elsewhere (10,11). Measurements were performed with the infant in the supine position, sedated with chloral hydrate (75 mg kg\(^{-1}\) body-weight). Flow was measured with a pneumotachograph (4500 series, Hans Rudolph, MO, USA), linear for the range 0–100 l\(\text{min}^{-1}\).

The infant’s upper body was wrapped into an inflatable jacket. The pneumotachograph was attached to the face via a facemask (Vital-Signs, Inc, USA). To avoid air leaks, the mask function was improved with an inflatable cuff, and whole system dead space was kept to 20 ml.

Tidal breathing of the infant was observed on the computer screen in the form of a flow–volume curve. Before performing an RTC-manoeuvre, at least six preceding tidal volume flow–volume curves had to be superimposable, suggesting reproducible tidal volume and end-expiratory level. Four RTC were performed beginning with a jacket pressure of 40 cm H\(_2\)O, and at pressures of 60, 80, and 100 cm H\(_2\)O. Maximal flow at functional residual capacity (\(V_{\text{max,FRC}}\)) was calculated as the mean of the three manoeuvres, presenting the highest flow at FRC in technically acceptable curves at the jacket pressure which gave the highest flow (12).

Weight and height was recorded prior to the measurements. Weight was measured with a calibrated digital scale with the children naked. Length was measured with the children standing upright by two investigators.

Statistics

Before investigating the data we ensured that the sample was representative of the remainder of the SPACE study. When viewing metric parameters (e.g. ECP, EPX, birthweight, etc.) we applied the two sided \(t\)-test as both samples were large enough to assume normality of the mean.

Whenever the comparison referred to categorical variables (e.g. symptoms, social status), the \(\chi^2\) test was used to draw comparisons.

We estimated the required sample size to give a power of 0·8, and \(P\) value of 0·05. Based on preliminary studies and the current literature (6,7,12), we expected the \(V_{\text{max,FRC}}\)-values for the infants in the intervention group at 370 ml s\(^{-1}\) and with an \(\text{sd}\) of 100 ml s\(^{-1}\), and the expected control group by a mean of 20% below the intervention group (297 ml s\(^{-1}\)). Both \(V_{\text{max,FRC}}\)-values were expected for children at height 80 cm. Consecutively, a sample size of 30 per group was estimated.

The comparison of metric parameters between intervention and control group in infants with PFT was drawn via a two sided \(t\)-test. In a similar manner \(\chi^2\) tests for this population were applied for detection of differences in symptom frequency, social status etc in the two groups.

General linear regression analyses were applied to analyse several potentially influential and confounding parameters on the primary outcome variable of lung function.

All statistical analyses were carried out using SAS, Version 6.11.

RESULTS

There were no significant differences between the 60 infants recruited for PFT and the remaining 340 infants of the SPACE study in terms of the following parameters: ECP, EPX, birthweight, respiratory symptoms prior to PFT, parental smoking or parental history of atopy. Of the PFT participants, 11 were affected by smoking during pregnancy and 15 by passive smoke exposure. For 46, respiratory symptoms within the first 18 months of life were reported (Table 1).

Within the infants who underwent PFT, infants in the intervention group had a significantly higher birth weight.

**Table 1.** Descriptive data of the 60 study subjects

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th></th>
<th>Control group</th>
<th></th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Weight gain since birth (kg)</td>
<td>7·86</td>
<td>0·99</td>
<td>7·77</td>
<td>0·99</td>
<td>7·89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11·29</td>
<td>1·19</td>
<td>11·34</td>
<td>1·12</td>
<td>11·12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>80·90</td>
<td>2·63</td>
<td>80·91</td>
<td>2·63</td>
<td>80·90</td>
</tr>
<tr>
<td>Age (months)</td>
<td>17·6</td>
<td>1·13</td>
<td>17·6</td>
<td>1·13</td>
<td>17·7</td>
</tr>
<tr>
<td>(V_{\text{max,FRC}}) (ml s(^{-1}))</td>
<td>346·14</td>
<td>120·53</td>
<td>359·12</td>
<td>333·35</td>
<td>333·35</td>
</tr>
<tr>
<td>Median (5^{\text{th}})–95(^{\text{th}}) percentile</td>
<td>5·02</td>
<td>0–174·56</td>
<td>4·69</td>
<td>5·10</td>
<td></td>
</tr>
<tr>
<td>ECP ((\mu\text{g l}^{-1}))</td>
<td>9·58</td>
<td>0–153·58</td>
<td>9·73</td>
<td>9·55</td>
<td></td>
</tr>
<tr>
<td>EPX ((\mu\text{g l}^{-1}))</td>
<td>22</td>
<td>24</td>
<td>15</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>46</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
compared to those in the control group (3.6 vs. 3.3 kg, \( P = 0.01 \)), while no differences were detected for ECP, EPX, respiratory symptoms prior to PFT, weight-gain, parental smoking or parental history of atopy.

No significant differences were detected for \( V'_{\text{max,FRC}} \) between the intervention group (mean 331 ml s\(^{-1}\)) and the control group (359 ml s\(^{-1}\), \( P = 0.382 \)).

In a correlation analysis, \( V'_{\text{max,FRC}} \) was correlated to weight gain (\( R = 0.297, P = 0.021 \)), but not to ECP (Fig. 1). ECP was correlated with EPX (\( R = 0.911, P = 0.001 \)).

\( V'_{\text{max,FRC}} \) was the dependent variable in our model of multiple linear regressions. We detected significant negative relationships between \( V'_{\text{max,FRC}} \) and weight gain as well as with ECP. In contrast, there was no significant relationship between \( V'_{\text{max,FRC}} \) and height, smoking, sex, respiratory symptoms or allocation to either the intervention or the control group. (For results of linear regressions see Table 2.)

**DISCUSSION**

In our cohort, the strongest predictors of lung function development were weight gain since birth and ECP in nasal lavage at 4 weeks of age. From our multiple regression model, a weight gain of 1 kg was associated with a decline of \( V'_{\text{max,FRC}} \) of 53 ml s\(^{-1}\), and an increase of ECP in nasal lavage of 1 \( \mu \text{g l}^{-1} \) was associated with a decline of \( V'_{\text{max,FRC}} \) of 1 ml s\(^{-1}\). In contrast, lung function levels at the age of 18 months were statistically not explained by the allocation to either the allergen avoidance or the control group.

There are some limitations of our study design, regarding PFT as a tool to measure effectiveness of allergen avoidance. First, one might argue that, because of the high degree of intrasubject variability for the tidal volume RTC technique, we should have performed PFT by raised volume RTC. However, this approach seemed to be too invasive for our subjects in the view of our hospital’s ethical committee. Furthermore, a larger number of subjects would have given more statistical power to our results. Unfortunately the need for sedation reduced our

**FIG. 1.** Negative linear relationship between \( V'_{\text{max,FRC}} \) and weight-gain: \( R = -0.297, P = 0.021 \).

**TABLE 2.** Multiple linear regression on \( V'_{\text{max,FRC}} \) (ml s\(^{-1}\)) at 18 months for all subjects as well as separately for subjects in the control group and the intervention group (\( P \)-values and 95% confidence intervals only for all subjects)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>( \beta ) (95% CI) for all subjects</th>
<th>( P ) value</th>
<th>( \beta ) (95% CI) for control group</th>
<th>( \beta ) (95% CI) for intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg)</td>
<td>-52.400 (-48.326 to -57.968)</td>
<td>0.022</td>
<td>-53.400 (-51.250)</td>
<td>0.012</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.400 (0.911 to 7.220)</td>
<td>0.822</td>
<td>3.422 (1.002)</td>
<td>0.03</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>8.188 (3.01 to 11.440)</td>
<td>0.326</td>
<td>8.234 (8.029)</td>
<td>0.292</td>
</tr>
<tr>
<td>Smoking (non-smoking=0)</td>
<td>19.895 (11.878 to 22.851)</td>
<td>0.600</td>
<td>17.309 (25.002)</td>
<td>0.488</td>
</tr>
<tr>
<td>Sex (male=0)</td>
<td>8.309 (7.109 to 9.522)</td>
<td>0.803</td>
<td>5.309 (11.226)</td>
<td>0.76</td>
</tr>
<tr>
<td>ECP (( \mu \text{g l}^{-1} ))</td>
<td>-0.945 (-0.987 to -0.891)</td>
<td>0.044</td>
<td>-0.991 (-0.829)</td>
<td>0.012</td>
</tr>
<tr>
<td>EPX (( \mu \text{g l}^{-1} ))</td>
<td>0.915 (0.798 to 0.981)</td>
<td>0.062</td>
<td>1.034 (0.803)</td>
<td>0.56</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>38.279 (16.001 to 52.281)</td>
<td>0.298</td>
<td>41.231 (44.561)</td>
<td>0.316</td>
</tr>
<tr>
<td>intervention group</td>
<td>1.558 (1.529 to 1.587)</td>
<td>0.096</td>
<td>1.516 (1.759)</td>
<td>0.096</td>
</tr>
<tr>
<td>Intervention or control group (control = 0)</td>
<td>1.558 (1.529 to 1.587)</td>
<td>0.096</td>
<td>1.516 (1.759)</td>
<td>0.096</td>
</tr>
</tbody>
</table>
recruitment rate down to 15% of the participants of the SPACE-study. However, based on our sample size calculation, our numbers were large enough to detect a clinically relevant difference of 20% between the groups. Quantitative analysis of mite antigen concentrations in mattresses would also have helped with measuring the results of the avoidance procedures. Surely, poor compliance can have affected lung function development also. Likewise, subjects of the control group may have performed energy avoidance strategies on their own (wild intervention). However, the effectiveness of the regime will be tested again in the future, when sensitization rates and inflammation markers will be available.

We found a negative linear relationship between ECP in nasal lavage and \( V'_\text{max,FRC} \), suggesting lung function at 18 months is already determined by airway inflammation soon after birth. This is in agreement with findings of a predictive value of ECP in nasal lavage for development of respiratory symptoms in the first 6 months of life within the entire Austrian SPACE cohort (5). However, the association of ECP and \( V'_\text{max,FRC} \) was not detectable in a univariate model, and EPX, which is strongly correlated with ECP, was not associated with \( V'_\text{max,FRC} \) in our multiple linear model. Moreover, although statistically significant the relationship may be of minimal clinical relevance. Therefore, our findings can only be interpreted as showing a very weak association between post-natal airway inflammation and lung function at 18 months of age.

The most interesting finding of our study remains the relationship between \( V'_\text{max,FRC} \) and weight gain. In previous studies, influences of foetal growth on the intrauterine programming of the respiratory and immune system (8) have been suggested. Since our study was not designed to elucidate intrauterine developments we are limited when speculating about possible foetal effects on lung function. However, birthweight was not associated with lung function in our subjects, suggesting that post-natal growth was mainly responsible for our results. As mentioned earlier, performing PFT soon after birth would have given more information for that debate.

Epidemiological studies in both children (13,14) and adults (15) have found relationships between body weight and asthma. In these studies and age groups, it remains unclear whether these relationships are real associations or biased by confounders such as lifestyle or physical activity. In a similar way, we can only speculate whether these relationships are due to a causal association (16).

Our study was initially not designed to measure body weight as an outcome and there are limitations when interpreting our results. In adults or older children, lifestyle issues like physical exercise will certainly confound findings of asthma and body weight, though it is unknown whether these issues play a major role in infants younger than 1-5 years of age. Questions about whether asthma causes obesity or whether obesity causes asthma have not been adequately answered in adult or adolescent groups (16). We can add the following finding from our study to that debate: the relationship between lung function and weight starts very early in life. To investigate these findings, further controlled studies are needed, including pre- and post-natal anthropometrical measurements and more detailed nutritional information.

In summary, we have shown that lung function at the age of 18 months may be determined by upper airway inflammation and weight gain. Our allergen avoidance regime, as described, did not significantly influence lung function.

When identifying very young children at high risk for atopy, not only parental atopy but also high infant weight-gain might be perceived as a risk factor.

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REFERENCES