Associations between post natal weight gain, change in post natal pulmonary function, formula feeding and early asthma

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ABSTRACT
Objectives. This study examined factors that might influence lung function during infancy and tested the hypothesis that change in weight during infancy is negatively associated with change in lung function.

Patients and methods. Weight, length and maximal flow at functional residual capacity (V’maxFRC) were measured at ages one and 12 months. V’maxFRC was adjusted for length. Asthma symptoms and age at introduction of formula feeds were identified from questionnaires. Groups were dichotomised by V’maxFRC at one month and change in V’maxFRC.

Results. There were 154 infants assessed at ages one and 12 months. Change in V’maxFRC was inversely associated with change in weight (p<0.001). The group with lower V’maxFRC at one month and reduced change in V’maxFRC over infancy had greatest weight gain (p=0.003) and increased risk for asthma symptoms by three years (p=0.017) but not afterwards. Exclusive breast feeding to six months was associated with a mean reduction in weight gain at age 12 months in comparison with earlier introduction of formula milk (mean difference 0.65kg, p=0.001), and was also associated with reduced asthma symptoms at three years (odds ratio 0.44, p=0.043) but not at six or 11 years of age.

Conclusions. Weight gain in infancy was inversely associated with change in lung function during infancy. Postnatal weight gain may be indirectly associated with early transient asthma symptoms via an influence on lung growth during infancy, and this potentially modifiable by breast feeding. These associations could be relevant to the clinically recognised syndrome of the “fat happy wheezer”.
INTRODUCTION
Wheezing is a common symptom in early life, affecting up to a third of young children. There are several factors associated with early wheeze including abnormalities of pulmonary function. Wheezy infants have obstructed pulmonary function and increased airway responsiveness prior to the onset of respiratory symptoms. Factors that may be important to abnormal pulmonary function in early life include male gender, a family history of asthma, maternal smoking during pregnancy and low birth weight.

In a recent publication, Lucas et al demonstrated that lung function (maximal flow at functional residual capacity, V’maxFRC) in young infants was negatively associated with postnatal weight gain, independent of length and birth weight. A negative relationship between weight and infant lung function has also been reported in a population of infants born prematurely. One suggestion is that these associations may be due to “catch up” in somatic growth in infants of low birth weight, after a period of in utero stress, and that the postnatal somatic growth exceeded growth in pulmonary function. An alternative mechanism could be that some babies of normal birth weight experience rapid postnatal weight gain due to an excessively calorie-rich diet and growth in pulmonary function is either impaired due to less favourable airway wall or airspace growth or is unable to match somatic growth.

In the present study, we sought to determine whether the change in V’maxFRC between ages one and 12 months was negatively influenced by the change in weight over infancy. Our secondary aim was to relate change in V’maxFRC to infant feeding practices and the development of asthma symptoms. The data were taken from a longitudinal cohort study (Perth Infant Asthma Follow-Up Study) where serial measures of pulmonary function were taken during infancy, a contemporaneous record of infant feeding was made and a detailed follow up was completed at 11 years of age.

PATIENTS AND METHODS
Subjects and study protocol
Study participants were recruited from among expectant parents attending a local antenatal clinic. The details of recruitment have been described previously. There was no selection for parental asthma or atopy and exclusion criteria included delivery before 36 weeks gestation and the presence of respiratory symptoms in the first month of life. A history of maternal or paternal smoking during the pregnancy and of asthma (ever) was recorded at enrolment. At ages one, six and 12 months, weight, length and pulmonary function were measured; also skin prick reactivity to common allergens was determined and urinary cotinine was measured. During infancy, mothers returned monthly postal questionnaires that reported details of feeding and respiratory symptoms. Annual postal questionnaires were returned between ages two and six years which detailed the presence of respiratory symptoms. At 11 years of age, the children completed an assessment which included respiratory questionnaire; spirometry, inhaled histamine challenge and skin prick reactivity to common allergens. The Institutional Ethics Committee of Princess Margaret Hospital approved this study. Written consent was obtained from parents and verbal assent was obtained from the children.
Classification of respiratory symptoms
Current doctor diagnosed asthma (DDA) at all ages was defined as an affirmative response to the question “does your child have asthma which has been diagnosed by a doctor?” Doctor diagnosed asthma by three years of age was defined as the presence of DDA at either two or three years of age, DDA between 4 and 6 years was defined as the presence of DDA at either four, five or six years.

Infant pulmonary function
The techniques used have previously been described in detail. After induction of sleep with chloral hydrate, a tightly fitting, non-distensible jacket was applied to the chest. A balloon within the jacket was rapidly inflated at the end of tidal inspiration and V’maxFRC was derived from the resultant partial forced expiratory manoeuvre. The mean of at least five technically acceptable manoeuvres was reported.

Urinary cotinine analysis
Urine collection bags were placed by the parents a few hours prior to attending the hospital. Urine samples were stored for a maximum of five days at 4°C until transfer to a freezer at -20°C. The urine was analysed later in batches. Cotinine was measured by radio-immunoassay, standardised to creatinine concentration to adjust for urine dilution and expressed in units of nanograms per milligram of creatinine. The distribution of urinary cotinine was skewed with long right hand tail and was log transformed prior to analysis to achieve a near normal distribution

Skin prick testing
Skin reactivity of infants to cows’ milk, egg white, rye grass and Dermatophagoides farinae was determined using the skin prick test as described by Pepys. For the assessment at 11 years, skin reactivity to the following additional six allergens was also assessed: mixed grass (no.7); Dermatophagoides pteronyssinus; cat dander; dog dander; Alternaria alternans; and Aspergillus fumigatus. All allergens were supplied by Hollister-Stier, Elkhart, IN. Histamine sulphate (10 mg/ml) was used as the positive control and 0.9% saline as the negative control. A positive skin test was defined as a weal to any allergen ≥3mm in its longest dimension or ≥3mm greater than the negative control.

Childhood pulmonary function
A portable spirometer (Pneumocheck Spirometer 6100; Welch-Allyn, Skaneateles Falls, NY) was used in accordance with published guidelines. The rapid inhalation technique was used to determine bronchial hyperresponsiveness (BHR) to histamine; BHR was defined as a fall of at least 20% in FEV1 after inhalation of a dose of ≤7.8 micromoles histamine. Short acting bronchodilators were withheld for at least six hours and long acting beta agonists were withheld for 12 hours prior to testing, no children were treated with leukotriene antagonists.
Statistical analysis

\[ V'\text{maxFRC} \text{ was log transformed prior to linear regression analysis to achieve a near-normal distribution and divided by length (in centimetres) to adjust for length. Student’s T test (two-tailed, equivariance assumed), Chi square analysis or analysis of variance were used as appropriate to compare differences between groups. The primary outcome variable (which was normally distributed) was } \% \text{ change in length adjusted } V'\text{maxFRC} \text{ and this was calculated as follows:} \]

\[ \frac{(\log V'\text{maxFRC at 12 months})/\text{length at 12 months}}{\text{(log V'\text{maxFRC at 1 month})/length at 1 month}} \times 100 \]

The primary explanatory variable was \% change in weight (weight aged 12 months/weight aged 1 month x 100). A multiple linear regression model was constructed to adjust for potential confounding variables (including birth weight, V’maxFRC at 1 month, exclusive breast feeding ≥6 months and gender). In a forward step-wise manner, these variables were introduced into the model and were retained if they changed the \( r^2 \) value of the model by >30%; change in weight was the first variable entered. Logistic regression models were created to adjust the relationship between asthma and predictive variables for confounders which were introduced in a forward step-wise manner and only retained in the model if they were significant. A standard statistical programme was used for the analyses (SPSS version 13.0) and significance was assumed at 5%.

RESULTS

Subjects studied

The study population included 253 individuals, 142 boys (56%) of whom V’maxFRC was measured in 243 aged one month, 194 aged six months and 165 aged 12 months. Paired measurements of V’maxFRC were available in 154 infants at one and 12 months of age, of whom the presence or absence of DDA between ages two and three years was known in 145, the presence or absence of DDA between ages four and six years was known in 136 and duration of breast feeding for > six months was established in 127. Paired measurements of V’maxFRC were also available in 182 infants at one and six months of age and in 159 infants at six and 12 months of age. The 53 infants lost to follow up after one month of age did not differ from the remaining cohort (table 1).

Lung function, weight, feeding practices, urinary cotinine and atopy during infancy

The median (interquartile ranges) values for V’maxFRC at one, six and 12 months of age were 93 (64, 124), 150 (120, 196) and 188 (139, 277) ml/s respectively. The mean (SD) change in length adjusted V’maxFRC between one and 12 months of age was 87% (15); the corresponding change between one and six months was 92 % (13) and between six and 12 months was 94% (13). V’maxFRC/length was reduced in boys compared with girls at each assessment and this difference was significant at 1 month of age (p=0.017). The mean (SD) weight at each assessment was as follows: 4.9 kg (0.7) at one month, 8.3 kg (1.0) at six months and 10.4 kg (1.2) at 12 months of age. The mean (SD) % change in weight was 215% (30) between one and 12 months, 173% (24) between one and six months and 128% (12) between six and 12 months. Boys were heavier on each assessment but % change in weight between assessments did not differ between boys and girls. Seventy infants received only breast milk for the first six months and 90 received formula milk within the first six months of life.
Solids were introduced before four months of age in 87 and after this age in 101 infants. The median (interquartile values) for urinary cotinine were 101 (51, 352) ng/mg creatinine at one month (n=104), 60 (25, 303) at six months (n=82) and 48 (26, 98) at 12 months (n=72). There were 32 individuals with at least one positive skin prick test during infancy.

% change in weight and % change in V’maxFRC
There was a negative relationship between % change in V’maxFRC and % change in weight between ages one and 12 months (r=-0.18, r²=0.13, p<0.001, figure 1), this relationship was consistent over the first and second six months of infancy (r=-0.18, r²=0.11 p=0.001 and r=-0.34, r²=0.15 p<0.001 respectively). The relationship between change in V’maxFRC and weight between one and 12 months remained significant when confounders were considered; r=-0.14 when V’maxFRC at 1 month was considered; r=-0.18 when gender, birth weight urinary cotinine at one month or atopy was considered and; r=-0.20 when breast feeding was considered. When individuals were dichotomised by weight gain and V’maxFRC/length at one month, the greatest % change in V’maxFRC between one and 12 months of age was present for those with lower V’maxFRC at one month and lower weight gain between ages one and 12 months (mean change 99%), figure 2; the remaining mean % changes in V’maxFRC were as follows: 88% for low V’maxFRC and high weight gain; 81% for high V’maxFRC and low weight gain; 77% for high V’maxFRC and high weight gain (ANOVA p<0.001 for trend).

Weight gain, infant lung function and asthma
Asthma symptoms were not associated with % change in V’maxFRC per se or % change in weight between ages one and 12 months. The proportion with DDA by three years of age was highest (38%) among individuals with low V’maxFRC at one month and lower change in V’maxFRC between one and 12 months and lowest (13%) among those with high V’maxFRC at one month and higher change in V’maxFRC, p=0.017 for trend (adjusting for % change in weight), table 2.

Weight gain, infant feeding and asthma
Infants where formula milk was introduced by six months were no heavier at birth or one month compared with those breast fed to at least six month but had greater weight gain between one and 12 months (mean increase 0.65kg [95% CI 0.27, 1.04], p=0.001) and increased weight at six (mean increase 0.34kg [95% CI 0.02, 0.70] p=0.036) and 12 months of age (mean increase 0.65 kg [95% CI 0.25, 1.05], p=0.002). Diagnosed asthma by three years was reduced in association with exclusive breast feeding until at least six months of age (OR 0.44 [95% CI 0.19, 1.00]) p=0.043), independent of gender, maternal asthma and maternal smoking during pregnancy and weight gain between 1 and 12 months; this relationship did not persist for asthma during the second three years (OR 0.80 [95% CI 0.37, 1.70]) or at 11 years of age (OR 0.92 [95% CI 0.37, 1.70]). Percentage change in V’maxFRC between one and 12 months was not associated with duration of exclusive breast feeding. The introduction of solids before or after four months of age was not associated with change in weight and V’maxFRC or asthma.
Relationship between factors measured in infancy and outcomes at 11 years of age
Of the 154 individuals where V’maxFRC was determined at one and 12 months of age, 127 had a detailed assessment at 11 years of age. Mid expiratory flow (FEF25-75) at 11 years of age was independently and positively associated with % change in V’maxFRC; this was also independent of birth weight, V’maxFRC/length at one month, breast feeding and atopy and BHR at 11 years (table 3). Eighteen children assessed at 11 years of age (14%) had current DDA, 65 (51%) were atopic and 41 (32%) had BHR and none of these were related to % change in V’maxFRC or weight, nor the duration of exclusive breast feeding.

DISCUSSION
The present analysis of this cohort studied the influence of post natal weight gain on lung function during infancy. Our study has demonstrated potentially important relationships between somatic and pulmonary growth during infancy, infant feeding practices and early transient asthma symptoms, and also pulmonary function in later childhood. Our hypothesis was that weight gain would be negatively related to change in V’maxFRC between one and twelve months of age and the data supported this. A series of interrelated associations became apparent when exploring the relevance of changes in post natal weight gain and pulmonary function to respiratory symptoms, and this indicated a rather complex potentially causative mechanism (figure 3). Infants with lower birth weight and greater somatic growth during infancy had relatively reduced growth in lung function which was associated with transient asthma symptoms when in combination with reduced lung function at one month. Exclusive breast feeding to six months had a potentially modifiable effect on excessive weigh gain during infancy and was associated with reduced transient asthma symptoms. These associations could be one explanation for a transient wheezing syndrome in the infant who becomes a “fat happy wheezer”.

Relationship between changes in post natal weight gain and V’maxFRC
A mechanism for increased post natal weight gain being associated with a relative reduction in lung growth, as evidenced by change in V’maxFRC, is not clear. This study has demonstrated that the mechanism is independent of gender, atopy and antenatal and postnatal exposure to products of tobacco smoke. In a previous report based on observations taken from this cohort, we have observed that low V’maxFRC at one month of age persist at 12 months in some individuals but not others, and that those individuals where low V’maxFRC did persist were more likely to wheeze in the first and second years of life 17. A mechanism whereby low V’maxFRC occurs throughout infancy in some individuals but not others has not previously been reported, and the findings of the present study suggest that increased post natal weight gain, possibly in infants of reduced birth weight, may be one factor associated with relatively low growth in pulmonary function during infancy.

Relationship between lung function in infancy and childhood
Previous studies, including those based on the present cohort, have reported tracking of pulmonary function from early life into later childhood 4,18; however in the present study we have demonstrated that the relationship between pulmonary function in very early life (“baseline”) and that in later life may be modified. Pulmonary function in very early life is mostly influenced by antenatal factors however during infancy, the level of “baseline” pulmonary function may be modified by post natal factors and this
may include weight gain; thus lower weight gain during early life could ameliorate adverse later respiratory outcomes associated with reduced “baseline” pulmonary function. Alternatively, the increased weight gain observed among those with low baseline and % change in V’maxFRC may be inevitable “catch up” growth after in utero stress and this may not be modifiable.

**Infant feeding practices**

In the present study, the introduction of formula feeds by six months of age was associated with increased postnatal weight gain and early asthma symptoms, and a similar relationship has previously been described among children from Western Australia 19 20. In their follow up of a large birth cohort, Oddy et al 19 20 report associations between less exclusive breastfeeding and increased respiratory symptoms in infancy and at six years of age; this group also found that a higher BMI was a risk factor for asthma aged six years. In the present study, we found no relationship between duration of breastfeeding and increased asthma beyond three years of age and this may be due to the relatively small numbers studied or the effect being limited to early childhood. The relationship between asthma and duration of breast feeding is complex and there are many inconsistencies between studies21; some find a positive relationship, others no relationship and still others find a negative relationship 21. The results of the present study could indicate more than one mechanism associating exclusive breast feeding to six months with respiratory outcomes; the first could be via altered post natal weight gain and involve abnormalities in pulmonary function and the second acting independently of pulmonary function.

**Limitations**

There are issues which could be considered when interpreting our results. First, there is invariably regression to the mean for V’maxFRC and weight and this may partly explain the inverse relationship observed for change in V’maxFRC and change in weight. Infants where regression to the mean was not present, ie low baseline and % change in V’maxFRC or high baseline and % change V’maxFRC (table 2), were different in terms of early symptoms, birth weight and post natal weight gain and these differences cannot be explained by regression of V’maxFRC or weight to the mean. Second, a number of analyses were performed during this study, and this increases the chance of false positive results however our findings were of sufficient consistency to suggest that multiple testing has not influenced our results. Finally in the present study, we present a series of associations which might indicate causative mechanisms but do not prove them; proof could only be inferred from a longitudinal study of infant lung function where infant weight gain was modified in a randomised-controlled manner.

**Conclusions**

In summary, this study reports two novel findings: (1) The change in V’maxFRC between one and 12 months of age was negatively related to weight gain over that period (2) Infants with reduced change in V’maxFRC between one and 12 months of age, in association with reduced V’max FRC at one month of age, have increased early transient asthma symptoms and reduced FEF25-75 at 11 years of age. The relationships described are complex but these observations will help understand possible mechanisms and useful therapeutic interventions.
ACKNOWLEDGEMENTS
We are extremely grateful to the children and their parents who have participated with the present study over the last 16 years. We would also like to recognise the invaluable contributions to this cohort study made by many colleagues.

REFERENCES


V’maxFRC measured only at 1 month of age (n=53)  V’maxFRC measured at one month of age and on a second occasion (n=190)

<table>
<thead>
<tr>
<th></th>
<th>V’maxFRC measured only</th>
<th>V’maxFRC measured at one month of age and on a second occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>56% (29/53)</td>
<td>56% (107/190)</td>
</tr>
<tr>
<td>Mother smoker during pregnancy</td>
<td>27% (14/52)</td>
<td>23% (43/190)</td>
</tr>
<tr>
<td>At least 1 parent with a history of asthma</td>
<td>26% (12/47)</td>
<td>33% (61/185)</td>
</tr>
<tr>
<td>Birth weight, kg (SD)</td>
<td>3.4 (0.5)</td>
<td>3.4 (0.5)</td>
</tr>
<tr>
<td>Median V’maxFRC aged 1 month, ml/sec (IQR)</td>
<td>88 (60, 119)</td>
<td>94 (66, 130)</td>
</tr>
<tr>
<td>Mean length at 1 month assessment, cm (SD)</td>
<td>56 (5)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Formula feeds introduced by one month of age</td>
<td>32% (17/53)</td>
<td>27% (34/124)</td>
</tr>
</tbody>
</table>

Table 1. This table compares details of those infants where V’maxFRC was only available at 1 month of age with those where V’maxFRC was available at 1 month of age and at least a second occasion. There were no significant differences between the groups.
<table>
<thead>
<tr>
<th></th>
<th>Low V’\text{max}FRC 1 month and low V’\text{max} growth (n=21)</th>
<th>High V’\text{max}FRC 1 month and low V’\text{max} growth (n=56)</th>
<th>Low V’\text{max}FRC 1 month and high V’\text{max} growth (n=56)</th>
<th>High V’\text{max}FRC 1 month and high V’\text{max} growth (n=22)</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed asthma by 3 years of age</td>
<td>38% (8/21)</td>
<td>29% (15/52)</td>
<td>32% (14/52)</td>
<td>13% (3/24)</td>
<td>p=0.017*</td>
</tr>
<tr>
<td>Diagnosed asthma between 4 and 6 years of age</td>
<td>33% (6/18)</td>
<td>20% (10/50)</td>
<td>33% (16/49)</td>
<td>11% (2/19)</td>
<td>p=0.149*</td>
</tr>
<tr>
<td>Diagnosed asthma at 11 years</td>
<td>20% (4/20)</td>
<td>13% (6/46)</td>
<td>16% (7/45)</td>
<td>5% (1/20)</td>
<td>p=0.456*</td>
</tr>
<tr>
<td>Mean % change in weight between 1 and 12 months (SD)</td>
<td>230 (28)</td>
<td>222 (32)</td>
<td>206 (29)</td>
<td>210 (24)</td>
<td>p= 0.003</td>
</tr>
<tr>
<td>Mean birth weight, kg (SD)</td>
<td>3.2 (0.5)</td>
<td>3.6 (0.4)</td>
<td>3.5 (0.5)</td>
<td>3.4 (0.5)</td>
<td>p=0.039</td>
</tr>
<tr>
<td>Exclusive breast feeding for at least six month</td>
<td>24% (4/17)</td>
<td>37% (18/49)</td>
<td>44% (18/41)</td>
<td>31% (5/16)</td>
<td>p=0.495</td>
</tr>
<tr>
<td>Male (number)</td>
<td>67% (14)</td>
<td>54% (30)</td>
<td>63% (35)</td>
<td>41% (9)</td>
<td>p=0.253</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>19% (4/21)</td>
<td>13% (7/56)</td>
<td>23% (13/56)</td>
<td>23% (5/22)</td>
<td>p=0.493</td>
</tr>
<tr>
<td>Parental asthma</td>
<td>35% (7/20)</td>
<td>35% (19/55)</td>
<td>33% (18/55)</td>
<td>23% (5/22)</td>
<td>p=0.772</td>
</tr>
</tbody>
</table>
Table 2. This table compares the details (rows) of groups of children defined by V’maxFRC at 1 month of age (dichotomised about the median value into high or low) and % change in V’maxFRC between 1 and 12 months of age (dichotomised about the median value into high and low). *adjusted for % weight gain between 1 and 12 months.
<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[95% confidence interval]</td>
<td></td>
</tr>
<tr>
<td>Height aged 11 years</td>
<td>3.266 [2.124, 4.409]</td>
</tr>
<tr>
<td>PD_{20} &lt; 7.8 microg histamine aged 11 years</td>
<td>-0.246 [-0.439, -0.053]</td>
</tr>
<tr>
<td>Log V’maxFRC/length one month</td>
<td>1.127 [0.496, 1.758]</td>
</tr>
<tr>
<td>% change in V’maxFRC between 1 and 12 months</td>
<td>0.012 [0.001, 0.024]</td>
</tr>
<tr>
<td>% change in weight between 1 and 12 months</td>
<td>0.003 [0.000, 0.006]</td>
</tr>
</tbody>
</table>

Table 3. Regression coefficients, confidence intervals and p values from multivariate regression model where FEF_{25-75} at 11 years of age was the outcome variable. Data from 121 individuals are included. Neither birth weight, exclusive breast feeding to six months nor atopy at 11 years were related to FEF_{25-75} and did not remain in the model. There was a significant (p=0.031) and positive interaction term between % change in weight and height at 11 years.
FIGURE LEGENDS

Figure 1. Scatter plot comparing change in weight and change in length-adjusted V’maxFRC between one and 12 months of age. The lines correspond with the mean regression line and its 95% confidence intervals. r²=0.13, p<0.001, n=154.

Figure 2. A box and whisker plot which compares % change in length adjusted maximal flow at functional residual capacity (V’maxFRC) between ages one and 12 months between groups categorised by length-adjusted V’maxFRC at one month and weight gain between ages one and 12 months. “Higher” values correspond with those greater than the median value. The trend across groups (analysis of variance with Bonferroni adjustment) p<0.001.

Figure 3. A schematic diagram summarising the associations reported in the present study. Other relevant factors include birth weight and V’maxFRC at one month.
Early introduction of formula milk

↑ weight gain between 1 and 12 months

↓ change in $V_{\text{maxFRC}}$ between 1 and 12 months

↑ transient asthma symptoms
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