Irreversible airway obstruction in adulthood after bronchiolitis in infancy: Evidence from a 30-year follow-up study

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KEYWORDS
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Summary
Aim: Lower respiratory infections in infancy may be associated with lung function deficits in adulthood. Our aim was to evaluate lung function, with a special focus on irreversible airway obstruction, thirty years after bronchiolitis or pneumonia in infancy.

Methods: In 1981–1982, 83 children under two years of age were hospitalized for bronchiolitis and 44 for pneumonia at Kuopio University Hospital, Finland. In 2010, 47 bronchiolitis patients, 22 pneumonia patients and 138 controls attended the study, including spirometry before (pre-BD) and after bronchodilatation (post-BD). The measured indices were forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), that were presented as % of predicted (FVC% and FEV1%). FEV1/FVC was presented as both absolute FVC/FEV1-ratio and % of predicted (FEV1/FVC%). Irreversible airway obstruction was defined as post-BD FEV1/FVC% below 88% of predicted (FEV1/FVC% < 88%) according to Finnish reference values or FEV1/FVC-ratio below fifth percentile (FEV1/FVC < 5th percentile), according to Global Lung Function Initiative reference values.

Results: All lung function indices were lower in former bronchiolitis patients and pre- and post-BD FEV1% in pneumonia patients, compared to controls. 21% of bronchiolitis (OR, 95%CI; 5.59, 1.72–18.21) and 9% of pneumonia patients (2.24, 0.34–13.56) had FEV1/FVC% < 88% compared to controls (4%). Likewise 7 (15%) of bronchiolitis (7.07, 1.33–37.22) and 1 (5%) of pneumonia patients (1.73, 0.12–24.77) had FEV1/FVC < 5th percentile compared to controls 2 (1%).
Introduction

The association between lower respiratory infections (LRI) like bronchiolitis and pneumonia in infancy and increased risk of lung function disorders in childhood has been demonstrated in several studies [1,2], including a recent systematic review and meta-analysis on long-term sequelae of early childhood pneumonia [3]. In addition, LRI’s in infancy have been associated with subsequent lung function disorders even in adulthood [4–8]. In the Swedish post-bronchiolitis follow-up study, airflow obstruction was found in both pre- and post-bronchodilator measurements at the age of 17–18 years indicating that the obstruction was irreversible [7].

In birth cohort studies, reduced lung function has been present in infancy before any respiratory infection, and evidently reduced lung function predisposes an infant to both early childhood LRI’s and subsequent wheezing [9–12]. Moreover, subjects with reduced lung function in early life were at an increased risk for permanent bronchial obstruction at the age of 22 years, even in the absence of any persistent symptoms [13].

We have followed a group of patients hospitalized for bronchiolitis or pneumonia in early childhood in 1981–1982, and found an increased risk of both asthma and lung function disorders up to the age of 18–20 years [8]. In 2010, when the study subjects were 28–31 years old, hospitalization for bronchiolitis in infancy was associated with an increased risk for asthma and hospitalization for both bronchiolitis and pneumonia with an impaired quality of life in adulthood [14].

In the present study, we evaluated lung function by using flow volume spirometry (FVS), including both pre-bronchodilator (pre-BD) and post-bronchodilator (post-BD) measurements in these former infantile bronchiolitis and pneumonia patients, and in matched population controls, at the age of 28–31 years. We hypothesized that permanently reduced lung function, and irreversible obstruction in particular, may be present in young adults after severe LRI in infancy. If the hypothesis is true, LRI in early childhood may predispose infants even to chronic obstructive pulmonary disease (COPD) in later adulthood. The aim of the study was to evaluate if reduced lung function and irreversible bronchial obstruction are present at the age of 28–31 years after bronchiolitis or pneumonia in infancy.

Material and methods

Study subjects

In 1981–1982, altogether 127 patients were hospitalized for bronchiolitis (N = 83) or pneumonia (N = 44) at less than two years of age in the Department of Pediatrics, Kuopio University Hospital, Finland. Data on wheezing history, presence of asthma, and risk factors for asthma were collected at repeated control visits until the age of 18–20 years [8,15]. As published recently [14], an invitation to the study and a written questionnaire were sent to 122 study subjects with current addresses available. The questionnaire included inquiries about previous asthma diagnoses and current respiratory symptoms, like wheezing episodes, and medication used for asthma during the preceding 12 months [14].

In 2010, 48 (57.8%) former bronchiolitis and 22 (50.0%) former pneumonia patients attended the clinical study, which consisted of a doctoral interview and examination, FVS including both pre-BD and post-BD measurements, and monitoring two-week home peak expiratory flow (PEF). An invitation to the study was also sent to 488 population-based controls born in the area of Kuopio University Hospital and they were matched for sex and age (birth month). Four control subjects, who answered the questionnaire and had been hospitalized for lower respiratory tract infection at less than 24 months of age, were excluded. Altogether 138 (28.3%) of the invited controls attended the clinical study [14].

Acceptable FVS was obtained from all but one of the study subjects and from all controls. Thus, 47 former bronchiolitis patients, 22 former pneumonia patients, and 138 controls formed the material of the present lung function study.

Presence of asthma and smoking

There were significant differences in current asthma and current smoking between the two study groups (bronchiolitis in infancy, pneumonia in infancy) and population controls [14]. Seventeen (36.2%) former bronchiolitis patients, 5 (22.7%) former pneumonia patients and 20 (14.5%) controls had asthma [14]. Asthma diagnosis was settled based on previous doctor-diagnosed asthma, usage of asthma medication, asthma-presumptive symptoms, and a pathological result in the home PEF monitoring [14]. Fourteen (29.8%) former bronchiolitis patients, 10 (45.5%) former pneumonia patients and 17 (12.3%) controls were current daily smokers (one cigarette or more smoked daily during the preceding 12 months) [14]. The median of the smoked pack-years was 0.1 (Range 0.0–25.0, p = 0.027) in the bronchiolitis group and 0.5 (0.0–22.5, 0.064) in the pneumonia group, compared to 0.0 (0.0–25.0) in controls.

Lung function data

Baseline lung function was measured with a Medikro SpiroStar USB spirometer (Medikro, Kuopio, Finland) using
Spiro 2000, Software version 2.2. FVS was performed and the results were reported according to ATS (American Thoracic Society) and ERS (European Respiratory Society) standards [16]. At a minimum, 3 technically acceptable measurements were required, and if needed, the measurements were repeated up to 8 times. The measured indices were forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). FVC and FEV1 were presented as percentages of the means of age- and sex-specific, height-related reference values (FVC% and FEV1%) [17]. FEV1/FVC is presented as both absolute (FEV1/FVC-ratio) and age- and sex-specific, height-related (% of predicted) values (FEV1%/FVC%) [17]. FVS was performed before (pre-BD values) and 15 min after (post-BD values) inhalation of 400 µg salbutamol (Ventoline Evohaler 0.1 mg/dos, GlaxoSmithKline).

Irreversible airway obstruction was defined as post-BD FEV1/FVC% below 88% of predicted value (FEV1%/FVC% < 88%) according to the Finnish age- and sex-specific, height-related cut-off limit that was settled at the level of −2 standard deviations (SD) (z-score −1.96) in Finnish non-selected adults [17].

Since Finnish references are old, and newer up-to-dated national references are not available, we defined the irreversible airway obstruction also by using the recently published, multi-ethnic, age-, sex- and height-adjusted, Global Lung Function Initiative 2012 (GLI 2012) limits for abnormal FEV1/FVC-ratio [18]. On the basis of this criterion, irreversible obstruction was considered to be present, if post-BD FEV1/FVC-ratio was below 5th percentile (lower limit of normality), corresponding z-score −1.64 (FEV1%/FVC% < 5th percentile) [18].

Statistics

Data were analyzed by using SPSS 19.0 software (SPSSInc. Chicago, IL, USA). The results are given as means, odds ratios (OR) and 95% confidence intervals (95%CI) or p-values. Analysis of variance (ANOVA) adjusted for asthma and current smoking was used in the analysis of continuous data, and logistic regression including group (bronchiolitis, pneumonia, control), asthma (yes, no) and current smoking (yes, no) for categorized data.

Ethics

The study was approved by the Ethics Committee of the Pohjois-Savo Health-Care District. A written consent was obtained from all study subjects.

Results

Pre-BD and post-BD FVC%, FEV1%, FEV1/FVC% and FEV1/FVC-ratio were lower in the former bronchiolitis patients than in controls (Table 1). Instead, the former pneumonia patients differed from controls only for pre-BD and post-BD FEV1% (Table 1). There were no significant differences between bronchiolitis and pneumonia groups in any lung function indices (Data not shown). When comparing the improvements of FEV1 after BD, no significant differences were found between the three study groups (Table 1).

To investigate whether the presence of asthma could explain the differences in lung function, we performed the analysis also after excluding the asthma patients. In this subgroup analysis, non-asthmatic former bronchiolitis patients had lower post-BD FEV1%, FEV1/FVC% and FEV1/FVC-ratio than controls, and non-asthmatic former pneumonia patients had lower post-BD FEV1% and FEV1/FVC% than controls (Table 2).

Post-BD FEV1/FVC% was below 88% of predicted value in 10 (21%) former bronchiolitis patients, 2 (9%) former pneumonia patients and 5 (4%) controls. The respective figures for FEV1/FVC < 5th percentile, according to the GLI 2012 reference values, were 7(15%), 1(5%) and 2(1%). The group (bronchiolitis, pneumonia, control), asthma and current smoking were included as covariates in the logistic regression. Belonging to the bronchiolitis group was an independently significant risk factor for irreversible airway obstruction by the Finnish, and belonging to the bronchiolitis group and the presence of current asthma by the GLI 2012 criteria (Table 3).

Discussion

There are three main results in the present study. First, the study subjects hospitalized for bronchiolitis or pneumonia in infancy presented with lower lung function than population-based controls at 28–31 years of age. Second, 21% of the former bronchiolitis patients had irreversible airway obstruction according to the Finnish reference values and 15% by the international GLI 2012 reference values. Third, hospitalization for bronchiolitis in infancy was a significant risk factor for irreversible airway obstruction in this prospective 30-year post-bronchiolitis study.

In the bronchiolitis group, both pre- and post-BD lung function indices were, on average, lower than in controls. The significant differences in post-BD FEV1/FVC% indicated the irreversibility of airway obstruction in the bronchiolitis group. Previous prospective post-bronchiolitis studies have demonstrated that lung function may remain reduced until early adulthood after bronchiolitis in infancy [6–8], with some evidence for irreversible airway obstruction [6,7]. In the present study, evidence for reduced lung function and irreversible airway obstruction after bronchiolitis in infancy was found at 28–31 years of age.

In the pneumonia group, pre- and post-BD FEV1%, but not FEV1/FVC% or FEV1/FVC-ratio, were lower than in controls. In the birth cohort from Tucson, Arizona, radiologically confirmed pneumonia at less than 3 years of age was associated with persistent wheezing at the age of six years, and with an increased risk of asthma and reduced lung function at the age of 11 years [19]. In a recent systematic review and meta-analysis, restrictive pulmonary disease was the most common sequela after pneumonia in early childhood [3]. In the present study, post-BD FVC%, which measures lung volume and reflects the restrictive properties of the lungs, was significantly lower in the former bronchiolitis patients than in the controls. However, the difference between controls and former pneumonia patients was not significant, mainly due to the small number of cases.
In previous retrospective studies, early childhood respiratory infections have had a close association with future respiratory morbidity and diminished lung function [4,5]. However, the independent role of early respiratory infection has remained unresolved. Low lung function at birth predisposes infants to LRI’s and wheezing in early childhood [9–12], and those who had low lung function at birth presented with lower than normal lung function through childhood into adulthood [13]. This does not exclude the fact that unfavorable postnatal factors, such as exposure to tobacco smoke or LRIs during the first years of life may further worsen the reduced lung function [13,20,21]. In the present study, we were able to document the link between tobacco smoke or LRIs during the first years of life may further worsen the reduced lung function [13,20,21].

Smoking is a well-known major risk factor for both asthma, COPD, and corresponding lung function disorders [22–24]. In the present study smoking was common, reported by 29.8% of the former bronchiolitis and 45.5% of the former pneumonia patients. The figure in the controls, 12.3%, was rather similar to the Finnish age-specific population [25]. Maternal smoking during pregnancy is one of the most important risk factors for reduced lung function at birth and subsequent wheezing [10,22,26–28]. In addition, children exposed to passive smoking have an increased risk for active smoking in later life [29]. Thus, children of smoking mothers have an increased risk for respiratory infections in infancy and an increased risk for smoking in adulthood, which may explain the surprisingly high rates of smoking in our cohort. Despite the commonness, the effects of smoking seemed to be minor. This finding is in line with the previous observation that the effect of childhood respiratory infections on lung function in young adulthood was not substantially further increased by smoking [4]. At the age of 28–31 years, the cumulative exposure to tobacco

| Table 1 | Pre- and post-bronchodilator lung function at the age of 28–31 years after bronchiolitis or pneumonia in infancy compared to controls, presented as means and 95% confidence intervals (95%CI). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Lung function parameter | Bronchiolitis N = 47 | p-valuef | Pneumonia N = 22 | p-valuef | Controls N = 138 |
| FEV1%a | 98 (94–101) | 0.025 | 98 (93–106) | 0.099 | 102 (100–104) |
| Post-BDa | 98 (94–101) | 0.026 | 98 (93–102) | 0.095 | 102 (100–103) |
| FEV1/FVC%c | 86 (83–90) | <0.001 | 89 (85–93) | 0.006 | 96 (94–98) |
| FEV1/FVC%d | 90 (87–93) | <0.001 | 93 (88–97) | 0.003 | 100 (99–101) |
| FEV1/FVC-ratio | 89 (86–92) | <0.001 | 91 (88–95) | 0.143 | 95 (93–96) |
| FEV1 BD responsee | 93 (90–95) | <0.001 | 95 (92–99) | 0.093 | 99 (97–100) |
| FEV1 BD responsee | 0.75 (0.73–0.78) | 0.001 | 0.78 (0.75–0.81) | 0.324 | 0.80 (0.79–0.81) |
| FEV1 BD responsee | 0.78 (0.76–0.81) | <0.001 | 0.81 (0.78–0.84) | 0.255 | 0.83 (0.82–0.84) |
| FEV1 BD responsee | 4.3 (3.5–5.2) | 0.603 | 4.3 (2.2–6.3) | 0.881 | 4.3 (3.5–5.2) |

a Pre-BD, pre-bronchodilator; post-BD, post-bronchodilator.
b FVC%, forced vital capacity (% of predicted value).
c FEV1%, forced expiratory volume in one second (% of predicted value).
d FEV1/FVC% means FEV1/FVC ratio presented as % of predicted value.
e Change in % between pre- and post-BD FEV1 values.
f Analysis of variance, adjusted for asthma and current daily smoking, bronchiolitis group vs. controls, and pneumonia group vs. controls.

In the present study smoking was common, reported by 29.8% of the former bronchiolitis and 45.5% of the former pneumonia patients. The figure in the controls, 12.3%, was rather similar to the Finnish age-specific population [25]. Maternal smoking during pregnancy is one of the most important risk factors for reduced lung function at birth and subsequent wheezing [10,22,26–28]. In addition, children exposed to passive smoking have an increased risk for active smoking in later life [29]. Thus, children of smoking mothers have an increased risk for respiratory infections in infancy and an increased risk for smoking in adulthood, which may explain the surprisingly high rates of smoking in our cohort. Despite the commonness, the effects of smoking seemed to be minor. This finding is in line with the previous observation that the effect of childhood respiratory infections on lung function in young adulthood was not substantially further increased by smoking [4]. At the age of 28–31 years, the cumulative exposure to tobacco

| Table 2 | Post-bronchodilator FEV1%, FEV1/FVC% and FEV1/FVC-ratio in the study subjects without asthma in three study groups. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Lung function parameter | Bronchiolitis N = 30 | p-valuef | Pneumonia N = 17 | p-valuef | Controls N = 118 |
| FEV1%a | 91 (88–95) | <0.001 | 95 (91–98) | 0.022 | 100 (99–102) |
| FEV1/FVC%c | 93 (90–96) | <0.001 | 95 (93–97) | 0.027 | 99 (98–100) |
| FEV1/FVC-ratio | 0.79 (0.76–0.82) | <0.001 | 0.81 (0.8–0.83) | 0.110 | 0.84 (0.83–0.85) |

a Post-BD, post-bronchodilator.
b FEV1%, forced expiratory volume in one second (% of predicted value).
c FEV1/FVC% means FEV1/FVC-ratio presented as % of predicted value.
d Analysis of variance, adjusted with current daily smoking, bronchiolitis group vs. controls and pneumonia group vs. controls.
smoke is still low. In smokers, a greater than age-related decline in lung function will occur from the fourth decade of life onwards [22]. We repeated all analyses as adjusted for ever smoked pack-years, and the results did not change.

At least one fourth of the COPD cases are not related to tobacco smoking [30]. Asthma is a well-documented risk factor for permanent lung function impairment, including irreversible bronchial obstruction [31], and COPD [5]. In the present study, the analyses were adjusted for current asthma. In addition, we made a subgroup analysis in the study subjects with no current asthma, and the results were similar to the main analyses. The results are in agreement with those of the Swedish study after RSV bronchiolitis at under 12 months of age, in which symptom-free former bronchiolitis patients also had lower lung function than controls [6].

An important finding of the present study is that 21% of former bronchiolitis patients had irreversible airway obstruction, when the Finnish age- and gender adjusted, height-related, population-based criterion for airway obstruction (FEV1/FVC <88%) was used. On the basis of this criterion, 2.5% of the healthy population has FEV1/FVC below the settled limit. Since the Finnish references are old, we analyzed the FEV1/FVC-ratio also by using the recently published, multi-ethnic, age-, sex- and height-adjusted GLI 2012 criteria for airway obstruction (FEV1/FVC <5th percentile) [18] and irreversible airway obstruction was present in 14.5%. According to this criterion, 5.0% of the non-selected population has FEV1/FVC below the settled limit. Belonging to the bronchiolitis group remained as a significant risk factor for irreversible airway obstruction, regardless of the used definition. Thus, hospitalization for bronchiolitis in infancy is a significant risk factor for irreversible airway obstruction at 30 years of age.

As maximal lung function is reached in early adulthood, subjects who start adult life with a lower FEV1/FVC-ratio may attain the threshold of COPD earlier during normal lung ageing than those starting with a higher FEV1/FVC-ratio [32]. We found preliminary evidence that subjects with bronchiolitis in infancy have more often obstructive airways in the early middle age, compared to controls with no history of LRI hospitalization in infancy. These alterations in airways may progress to COPD during normal lung ageing.

The strengths of the present study are the long follow-up time, a careful collection of clinical data in early childhood, and a well-conducted clinical study at the age of 28–31 years. Since the former bronchiolitis and pneumonia patients lived in different parts of the country, the clinical study was performed by the same researchers at 12 outpatient clinics. In all cases, FVS was performed by a trained respiratory nurse of the research group, using the same spirometer and following the current international standards [16]. The main shortcoming of the study was the small number of subjects. We were able to clinically examine 70 (57.3%) of the 122 study subjects with a current address available. The participation rate in the control group was even lower. The asthma prevalence of the controls was 15%, which is higher than the 5% asthma prevalence in non-selected Finnish young adults of the same age [33]. The prevalence of irreversible airway obstruction in controls (4%), defined as post-BD FEV1/FVC% <88% was close to 2.5% in the non-selected Finnish adult population. Lung function was not measured before any early childhood infections, and therefore our present study was unable to answer the question of whether or not the low lung function in infancy has predisposed infants to early-life LRI, and further, to low lung function at the age of 28–31 years.

In conclusion, evidence of reduced lung function was present 30 years after hospitalization for bronchiolitis or pneumonia in infancy. Irreversible airway obstruction after severe bronchiolitis in infancy suggests permanent, structural alterations in airways. In adjusted analyses, hospitalization for bronchiolitis in infancy was a more significant risk factor for irreversible airway obstruction at the age of 28–31 years than current asthma or current smoking.

### Conflict of interest statement

All authors declare they have no conflict of interest.

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### Table 3 Logistic regression: hospitalization for bronchiolitis or pneumonia in infancy, current asthma and current daily smoking at 28–31 years of age as risk factors for irreversible airway obstruction.

<table>
<thead>
<tr>
<th>Risk factor for irreversible airway obstruction</th>
<th>FEV1/FVC% &lt;88%</th>
<th>Adjusted ORb (95%CI)</th>
<th>FEV1/FVC &lt;5th percentilec</th>
<th>Adjusted ORb (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis group</td>
<td>10/47 (21%)</td>
<td>5.59 (1.72–18.21)</td>
<td>7/47 (15%)</td>
<td>7.07 (1.33–37.22)</td>
</tr>
<tr>
<td>Pneumonia group</td>
<td>2/22 (9%)</td>
<td>2.24 (0.34–13.56)</td>
<td>1/22 (5%)</td>
<td>1.73 (0.12–24.77)</td>
</tr>
<tr>
<td>Current daily smoking</td>
<td>15/41 (12%)</td>
<td>1.21 (0.36–4.04)</td>
<td>4/41 (10%)</td>
<td>2.22 (0.49–10.05)</td>
</tr>
<tr>
<td>Asthma</td>
<td>8/42 (19%)</td>
<td>2.83 (0.97–8.30)</td>
<td>7/42 (17%)</td>
<td>7.56 (1.75–32.6)</td>
</tr>
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</table>

a Post-bronchodilator FEV1/FVC-ratio below 88% of predicted value.

b All variables (group, current daily smoking and asthma) are included in the same logistic regression model.


c FEV1/FVC - ratio below 5th percentile lower limit of normality (GLI 2013 criteria).
providing inhaled bronchodilators to be used during the home PEF monitoring. The authors are grateful to Satu Korpi and Anneli Paloranta, RN, Kuopio University Hospital, for their skillful and professional work during the study.

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