Lung function at school age in infants with lower respiratory tract infections with and without wheezing: A birth cohort study

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Abstract

Objective

To evaluate the relationship between lower respiratory tract infections (LRTI), in the first 2 years of life and lung function at school age in the Piccolipiù birth cohort (Italy).

Methods

Data on LRTI (doctor diagnosis of bronchitis, bronchiolitis, pneumonia) and wheezing (≥3 episodes or a diagnosis of asthmatic bronchitis) in the first 2 years of life were obtained from parental questionnaires.

Lung function was assessed at 7 years by spirometry and forced volume vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC, forced expiratory flow between 25% and 75%,

and at 75% of FVC (FEF25–75 and FEF75) were reported as Z-scores. The associations between LRTI and spirometric variables were estimated with linear regression models.

Results

Among 877 children studied, 22.1% had LRTI only, 5.4% wheezing only, 13.2% had both, and 59.3% had neither LRTI nor wheezing. Children with LRTI had lower FVC and FEV1 than children without (Z-score differences: −0.18 [95% confidence intervals: −0.31; −0.06] and −0.15 [−0.27; −0.03]). When children were stratified by history of both LRTI and wheezing, there was no association between LRTI only and spirometric values. Conversely, having had both LRTI and wheezing was inversely associated with all lung function measures: Z-score differences of −0.24 (−0.42; −0.07); −0.42 (−0.59; −0.24); −0.25 (−0.41; −0.08); −0.37 (−0.54; −0.21); −0.30 (−0.46; −0.14) for FVC, FEV1, FEV1/FVC, FEF25–75 and FEF75, respectively.

Conclusion

Infants with wheezing and LRTI, but not those with LRTI only, had reduced lung function at school-age.

1 INTRODUCTION

Lung growth and development are the result of a progressive process, which begins in the fetal period and continues into adulthood, the main changes occurring in early life.1 The contribution of childhood lower respiratory tract infections (LRTI) in worsening lung function is still not completely clear. Infants admitted to hospital in the late seventies with a diagnosis of LRTI were found 7–10 years later to have an impairment of ventilatory function with evidence of airway obstruction when compared to controls.2, 3 Findings from more recent prospective population-based cohort studies, however, are few and the results are less consistent.4, 5

The present study was carried out in the Italian prospective birth cohort Piccolipiù.6 We aimed at evaluating the relationship between LRTI in children in their first 2 years of life and lung function at school age. Since these children often also have wheezing episodes, we further aimed at disentangling the relationship between LRTI and wheezing with subsequent lung function.

2 SUBJECTS AND METHODS

The Piccolipiù cohort was recruited in 2011–2015 in five Italian cities.6 Women completed a questionnaire in pregnancy or at delivery and when the child turned 6 months, 1, 2, 4, and 7 years.

The follow-up at 7 years was conducted in four cities (Turin, Trieste, Florence, Rome), and included lung function evaluation using spirometry.

Data on LRTI (doctor diagnosis of bronchitis, bronchiolitis, pneumonia) and wheezing (defined as ≥3 episodes of wheezing or whistling in the chest according to the standardized ISAAC questionnaire,7 or a doctor diagnosis of asthmatic bronchitis) in the first 2 years of life were obtained from questionnaires. Lung function was assessed at the paediatric pulmonary clinics of each center after tutoring by the Meyer Children's University Hospital staff. Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines.8 Each child was asked to repeat the maneuvers until at least two acceptable spirometric tests were obtained. Acceptability was inferred from the morphological characteristics of the flow-volume and volume-time curves: duration of exhalation to reach a reasonable expiratory plateau in the volume-time curve, adequacy of the peak expiratory flow in the flow-volume curve, absence of artefacts (e.g., cough, delayed onset of expiratory act, premature stopping of exhalation) in both flow-volume and volume-time curves. All curves were scored blindly by trained pulmonologists (EL and FR). Discrepancies were discussed, and a joint decision was made.

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, forced expiratory flow between 25% and 75% of FVC (FEF25–75), and forced expiratory flow when 75% of FVC has been exhaled (FEF75) were converted into sex-, age-, height- and ethnicity-adjusted Z-scores, using the Global Lung Function Initiative 2012 equations.9

The associations between LRTI in the first 2 years of life and spirometric variables were estimated with linear regression models. Analyses were adjusted for the recruiting center and the following potential confounders selected based on the literature: parental history of asthma or allergy, maternal education (≤13 vs. >13 years), maternal smoking during pregnancy (defined as mothers who continued smoking after the first trimester), a composite variable considering preterm (gestational age at birth <37 weeks) and/or low birth weight (birth weight <2500 g), breastfeeding for at least 6 months.

The Piccolipiù study was approved by the Ethics Committee of Lazio Regional Health Service–ASL ROMA E, national coordinator of the project, and by the Ethics Committee of each participating center. Parental informed consent was obtained at recruitment and at the 4- and 7-year follow-up.

3 RESULTS

A total of 948 children underwent lung function testing. Complete data on LRTI or covariates were missing for 71 children. The final study population comprised 877 children (Table 1) with a median (interquartile range) age of 6.9 (6.7–7.6) years and with complete data on exposures and potential

confounders. Children not included in the analysis ($N = 71$) had a higher proportion of mothers with a lower education (63.6% vs. 49.1%, $p = .023$), a higher prevalence of smoking during pregnancy (20.9% vs. 8.0%, $p < .001$), and a lower frequency of breastfeeding (55.6% vs. 71.8%, $p = .006$).

Children with LRTI in the first 2 years of life had lower FVC and FEV1 than children without, with Z-score differences of −0.18 (95% confidence intervals: −0.31; −0.06) and −0.15 (−0.27; −0.03), respectively; weaker and nonstatistically significant associations were found for FEV1/FVC, FEF25–75, and FEF75. When children were stratified by history of both LRTI and wheezing, there was no overall evidence of an association between LRTI only and lower spirometric values, while having had wheezing in addition to LRTI was associated with a reduction of all the spirometric indices (Figure 1). As expected, having had wheezing only was inversely associated with indices of bronchial obstruction.

4 DISCUSSION

We found that children with LRTI in the first 2 years of life had lower FVC and FEV1 Z-scores at school age. Most of these children also had wheezing episodes or asthmatic bronchitis. When we considered a composite variable (LRTI: yes/no and wheezing: yes/no), an association between LRTI and FVC and all the indices of expiratory flows was present only in children who also had wheezing. For forced expiratory flows the results were similar in the group who only had wheezing, without LRTI.

The possible relationship between infants' respiratory disorders of the lower airways and lung function was first suggested several years ago. A seminal retrospective study10 showed that adults born in England in the 1920s and 30s, who had had bronchitis or pneumonia in infancy, had a lower FEV1 and FVC when aged 59–70 years. The authors concluded that "prevention of chronic obstructive airways disease may partly depend on promotion of infant lung growth and reduction in the incidence of lower respiratory tract infection in infancy". The findings of an impaired lung function in adults with a history of LRTI in childhood have been subsequently confirmed in prospective follow up studies11 and in population-based prospective cohort studies.12, 13

Birth cohort studies on general populations of children have not fully clarified whether an impairment of lung function is already present when children with early LRTI reach school age, nor the possible role of wheezing. In the Generation R study an impairment of both FVC and forced expiratory flows at 10 years of age was found in children who had LRTI in the first 3 years of life only and not between 3 and 6 years.4 In another smaller cohort an association was found only between LRTI in the first 2 years and FEF at 50% of FVC (FEF50).5

On the other hand, it is well known from prospective cohort studies that children with early wheezing have an impairment of lung function with forced expiratory flow deficit later in life.14, 15 It

is not entirely clear whether this deficit in lung function occurs as a consequence of wheezing, or if individuals who experienced wheezing already had lower lung function from birth.16-18

Clarifying the underlying mechanisms for the association between LRTI and wheezing in early life and later respiratory morbidity is outside the scope of our study. Nonetheless, it is plausible that children with a propension to wheeze might be more likely to develop symptoms of the lower respiratory tract when infected, and that LRTI are predictors of, rather than risk factors for, later reduced lung function.

The strength of this study lies with the prospective documentation of LRTI and wheezing in the first 2 years of life and the subsequent respiratory function in a prospective birth cohort.

Information on wheezing and on LRTI was collected by self-administered questionnaires, which is a widely accepted method of data collection in epidemiologic studies. As for wheezing definition, we relied not on a single episode of wheezing but on recurrent wheezing that is more likely to identify a pathological condition, or on a doctor's diagnosis of asthmatic bronchitis. Likewise, parents were asked to report a doctor diagnosis of bronchitis, bronchiolitis, and pneumonia in the last 12 months.

We cannot exclude an overlap between early wheezing and bronchiolitis, though in Europe bronchiolitis is generally defined as a first episode of an acute LRTI in young infants presenting with respiratory distress and diffuse crackles rather than wheezing.19

In conclusion, in this study we aimed at examining the relationship between LRTI and wheezing with subsequent lung function. Our data do not allow us to discuss if an impairment of lung function was already present in these children at birth. Nevertheless, the finding of a diminished lung function at 7 years of life in children with a history of LRTI and wheezing is a matter of concern, as it is now widely accepted that low lung function tracks into adulthood and might predispose to chronic obstructive pulmonary disease.1, 20

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Franca Rusconi: coordinated and supervised data collection, conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. **Luigi Gagliardi**: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. **Enrico Lombardi**: supervised data collection, scored the spirometry tests, and reviewed and revised the manuscript. **Elena Spada**: carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript. **Lorenzo Richiardi, Ileana Stella, Luca Ronfani, Francesca Di Toro, Martina Culasso, Antonella Frassanito:** coordinated and supervised data collection, and reviewed and revised the manuscript. **Sonia Brescianini**: reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Table 1. Characteristics of the study population (877 children)

Basal characteristics, *N* (%)	
Girls	446 (50.9)
Mother born in Italy	805 (92.0)
Maternal education ≥13 years	446 (50.9)
Parental asthma or atopy, *N* (%)	354 (40.4)
Preterm (<37 weeks gestation) or low birth weight (<2500 g)	33 (3.8)
Exposed to maternal smoking in pregnancy[a]	70 (8.0)
Breastfed for at least 6 months	630 (71.8)
In the first 2 years of life, *N* (%)	
At least one LRTI	310 (35.4)
bronchitis	232 (26.8)
bronchiolitis	109 (12.5)

pneumonia	32 (3.7)
Wheezingb	163 (18.6)
Both LRTI and wheezing	116 (13.2)
LRTI and no wheezing	194 (22.1)
Wheezing and no LRTI	47 (5.4)
Neither LRTI or wheezing	520 (59.3)
Lung function indices, mean (*SD*)	
FEV1 (L)	1.51 (0.22)
FEV1 Z-score	+0.51 (0.88)
FVC (L)	1.69 (0.26)
FVC Z-score	+0.49 (0.87)
FEV1/FVC (%)	89.36 (4.81)
FEV1/FVC Z-score	−0.03(0.81)
FEF25–75 (L/s)	1.88 (0.41)
FEF25–75 Z-score	+0.12 (0.86)
FEF75 (L/s)	1.03 (0.28)
FEF75 Z-score	+0.34 (0.81)
Center, *N* (%)	
Florence	330 (37.6)
Turin	223 (25.4)
Rome	179 (20.4)
Trieste	145 (16.5)

- Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced volume vital capacity; LRTI, lower respiratory tract infections.
- a Mothers who continued smoking after the first trimester.
- b Wheezing: at least three wheezing episodes or a doctor diagnosis of asthmatic bronchitis in the first 2 years of life.

Figure 1

Lung function in children with lower respiratory tract infections (LRTI) and wheezing, LRTI only and wheezing only. Values are expressed as differences in Z-scores9 (95% confidence intervals) having as reference children with neither LRTI nor wheezing and are adjusted for center, parental history of asthma or allergy, maternal education, maternal smoking in pregnancy, preterm and/or low birth weight, and breastfeeding for at least 6 months