Bronchiolitis and pneu

– asthma, lung function and quality

SUMMARY

Bronchiolitis and pneumonia in infancy have been associated with respiratory morbidity, lung function impairment and lower health-related quality of life (HRQoL) in later life. The aim of the present study was to study 30-year sequelae of bronchiolitis and pneumonia in infancy. In 1981–1982, 83 children were hospitalized for bronchiolitis and 44 for pneumonia at Kuopio University Hospital at less than 2 years of age. In 2010, 48 (58%) bronchiolitis and 22 (50%) pneumonia patients and 138 controls attended the clinical study. Asthma was defined as doctor-diagnosed or self-reported asthma as an indicator of the certainty of the diagnosis. Participants completed St. George´s Respiratory Questionnaire as a HRQoL tool and underwent pre-bronchodilatation (pre-BD) and post-BD spirometry. Doctor-diagnosed asthma was significantly more common in bronchiolitis patients (31%) compared to controls (9%). Self-reported asthma was also significantly more common in bronchiolitis group (35%) compared to controls (15%). Asthma figures were similar in the former pneumonia patients and in controls. In addition, hospitalization for bronchiolitis or pneumonia in infancy was associated with an impaired HRQoL and irreversible obstructive lung function impairment in adulthood.

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Bronchiolitis is an acute, viral, lower respiratory tract infection (LRTI) presenting in early childhood (1). It is usually defined as the first wheezing episode in the childhood (2). It is a disease with high morbidity, since about 30–40 % of children develop bronchiolitis before the 2 years of age (1). There is evidence that respiratory syncytial virus (RSV) is the predominant virus associated with bronchiolitis and pneumonia in young children (3, 4). However in older age groups the role of other viruses, especially rhinovruses, becomes more pronounced (5).

The link between early childhood respiratory infections and later respiratory morbidity has been an issue of interest during recent decades, and an association between lower respiratory tract infections (LRTI) in early childhood and later respiratory morbidity even in adulthood has been well established (6). In 60 % of wheezing infants tendency to wheeze is a self-improving condition (7). These transient wheezers form a group of children, who have wheezing symptoms at early age during viral infections, but the symptoms resolve by the age of 6 years (7). However, some children, with wheezing before the age of 3 years, continue to wheeze and develop asthma later in childhood. So, in some children early wheezing may be the first sign of respiratory morbidity such as asthma (7).

There is evidence that LRTIs like bronchiolitis and pneumonia in infancy are associated with increased risk of lung function disorders, such as asthma and chronic obstructive pulmonary disease (COPD), even in adulthood (8–10). In two post-bronchiolitis follow-up studies impaired lung function was demonstrated at the age of 17–20 years in former bronchiolitis patients (9, 10). However there are no prospective post-bronchiolitis studies including longer follow-up than this.

There are only a few studies describing health-related quality of life (HRQoL) after early childhood LRTIs. In line with impaired lung function, also impaired HRQoL has been described after LRTI´s in infancy, but so far these studies have not continued beyond childhood (11, 12).

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monia in infancy

of life at a 30-year follow-up

Bronchiolitis is an acute, viral, lower respiratory tract infection presenting in early childhood. It is a disease with high morbidity, since about 30–40 % of children develop bronchiolitis before the 2 years of age. PHOTO: COLOURBOX.COM

We have followed a group of patients hospitalized for bronchiolitis or pneumonia in early childhood in 1981–82, and found an increased risk of both asthma and lung function disorders up to the age of 18–20 years (10). In the present study, at the age of 28–31 years, our aim was to evaluate asthma prevalence and HRQoL in adulthood after bronchiolitis and pneumonia in infancy. We also studied whether permanently reduced lung function, irreversible obstruction in particular, is present in young adults after severe LRTI in infancy. If so, LRTI in early childhood could predispose infants even to chronic obstructive pulmonary disease (COPD) in adulthood.

Methods

In 1981–1982 127 children, hospitalized for LRTI in Kuopio University Hospital, Department of Pediatrics at less than 2 years of age, were enrolled in the study (13). Among the 127 recruited children with LRTI, 83 were diagnosed with bronchiolitis and

44 with pneumonia. The cohort has been followed-up since, until the age of 18–20 years (10, 14, 15).

In 2010, 48 (58 %) former bronchiolitis and 22 (50 %) former pneumonia patients and 138 population controls attended the clinical study, which consisted of an examination by a doctor , spirometry including both pre-BD and post-BD measurements, and monitoring two-week home peak expiratory flow (PEF) (16).

The study subjects completed a questionnaire including questions for example about asthma symptoms and the presence of previous doctor-diagnosed asthma and smoking status (16). Participants also completed the St. George's Respiratory Questionnaire (SGRQ), designed to measure HRQoL in adults with asthma or COPD (17). SGRQ consists of three parts: symptom scores (the frequency and severity of respiratory symptoms), the activity scores (the activities that are limited due to breathlessness), and the impact scores (social or psychological disturbances resulting from airway disease). The scores are expressed as a percentage of complete impairment; thus, the score 100 means the worst possible and the score 0 the best possible respiratory health status (17).

Bronchial asthma was defined in two different ways, reflecting the certainty of the diagnosis. For doctor-diagnosed asthma, an on-going regular maintenance medication for asthma and a previously settled asthma diagnosis were required. In addition, study subjects who reported asthma symptoms and/or repeated use of bronchodilators, and in addition had a pathological result in the home PEF monitoring, were regarded to have doctor-diagnosed asthma. For self-reported asthma, previously diagnosed asthma combined with asthma symptoms or with repeated use of bronchodilators was required. Cases with doctor-diagnosed asthma were included (16).

PEF was measured using a Mini Wright PEF meter (Clement-Clarke International LTD, Harlow, Essex UK) three times every morning and every evening for two weeks (18). Daily variability over 20 % between the PEF morning and evening values or PEF improvement of 15 % or more after bronchodilator inhalation for two or more days were considered as abnormal (16,19).

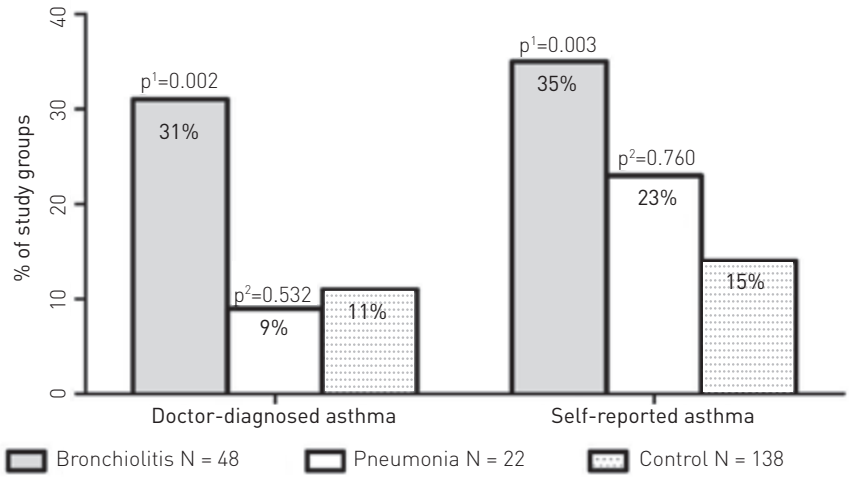
Skin prick test (SPTs) (ALK Soluprick®, Copenhagen, Denmark) included the most common inhaled allergens. Clinical atopy was defined by the presence of allergic rhinitis, allergic conjunctivitis or atopic eczema, combined with one or more positive SPT results.

Lung function was measured with a Medikro SpiroStar USB spirometer (Medikro, Kuopio, Finland) using Spiro 2000, Software version 2.2., according to international standards before (pre-BD) and after (post-BD) bronchodilatation (18, 20). The measured indices were forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) and FEV_1/FVC and the results were presented as percentages of the means of age- and sex-specific, height-related reference values (FVC %, FEV1 %, FEV1/FVC %) (21).

TABLE 1. The scores calculated from the St. George's Respiratory Questionnaire at the age of 28–31 years in the three study groups.

	BRONCHIOLITIS N=48		PNEUMONIA N=22		CONTROL N=138
SGRQ COMPONENTS	MEDIAN IQ[1] 25–75	P – VALUE[2]	MEDIAN IQ1 25–75	P – VALUE[2]	MEDIAN IQ1 25–75
Symptom score	9.1 0.0–26.3	0.044	18.4 5.1–29.9	0.005	5.0 0.0–16.3
Activity Score	5.7 0.0–12.1	0.002	0.0 0.0–13.4	0.146	0.0 0.0 – 6.0
Impact Score	2.4 0.0–9.5	< 0.001	0.0 0.0–8.4	0.475	0.0 0.0 – 2.4
Total Score	5.4 0.0–14.7	< 0.001	4.9 1.3–14.8	0.012	1.5 0.0 – 6.0

FIGURE 1. Asthma by two definitions at the age of 28–31 years in the study subjects hospitalized for bronchiolitis or pneumonia at less than 24 months of age, compared with population controls.



1paired comparison between bronchiolitis and control group, 2paired comparison between pneumonia and control group as adjusted for age, sex, clinical atopy, and current daily smoking (for definitions, see the text).

Statistics

The data was analyzed by using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Chi-square test and logistic regression were used in the analyses of the categorized asthma data. The Mann-Whitney U-test was used in the analysis of the continuous SGRQ scores. Analysis of variance (ANOVA) adjusted for asthma and current daily smoking was used in the analysis of continuous lung function data and the results are given as means and 95 % confidence intervals (95 %CI) and p-values.

Results

There were 30 (63 %) males in the bronchiolitis, 8 (36 %) males in the pneumonia and 75 (54 %) males in the control group. The mean age (SD) was

29.5 years (0.72) in the bronchiolitis, 29.4 years (0.58) in the pneumonia, and 29.6 years (0.75) in the control group, respectively. Fourteen (29 %) former bronchiolitis patients (p = 0.007 vs. controls), 10 (46 %) former pneumonia patients (p = 0.000 vs. controls), and 17 (12 %) control subjects were current daily smokers. Clinical atopy was common in all groups, since 23 (48 %) of bronchiolitis patients (p=0.724 vs. controls), 10 (46 %) of pneumonia patients (p=0.674 vs controls) and 66/136 (49 %) of controls were diagnosed to have atopy.

Doctor-diagnosed asthma was significantly more common in bronchiolitis patients (31 %) compared to controls (9 %). Self-reported asthma was also significantly more common in bronchiolitis group (35 %) compared to controls (15 %) (FIGURE 1). Asthma figures by both definitions were similar in the former pneumonia patients and in controls.

Both former bronchiolitis patients and former pneumonia patients had significantly higher total scores in the SGRQ than the controls indicating lower HRQoL (TABLE 1). The former bronchiolitis group differed from the control group in all parts of the questionnaire, whereas the former pneumonia group differed in terms of symptom scores (TABLE 1).

Pre-BD and post-BD FVC %, FEV1 % and FEV1/FVC % were lower in the former bronchiolitis patients than in controls (FIGURE 2, PAGE 44). Instead, the former pneumonia patients differed from controls only for pre-BD and post-BD FEV1 % (FIGURE 2).

Follow up studies of patients hospitalized for bronchiolitis in early childhood found an increased risk of asthma until the age of 30. There was no difference between former pneumonia patients and population controls in asthma prevalence. PHOTO: COLOURBOX.COM

Discussion

The three main results of this prospective long-term follow-up of early childhood bronchiolitis and pneumonia have been recently published (16, 20). First, after hospitalization for bronchiolitis in infancy, an increased asthma risk could be demonstrated at least until 28- to 31- years of age. Asthma was present in one-third of the former bronchiolitis patients. However there was no difference between former pneumonia patients and population controls in asthma prevalence (16).

Second, SGRQ scores were significantly higher in former bronchiolitis and pneumonia patients compared to controls, indicating impaired HRQoL after early childhood LRTI (16). Third, study subjects hospitalized for bronchiolitis or pneumonia in infancy presented with irreversible, obstructive, lung function impairment in spirometry at the age of 28–31 years (20).

The link between respiratory infections like bronchiolitis or pneumonia in early childhood and subsequent respiratory morbidity like asthma and COPD in adulthood is well documented in population-based studies (8, 22). Despite the numerous post-bronchiolitis studies going on in the world, there are only four prospective post-bronchiolitis studies, started in the 1980's and 1990´s, two in Sweden and two in Finland, that have continued beyond puberty (23–26). Thus far, the results have been published up to the early adulthood (23, 26) and two cohorts have been followed up to the age of 25–29 years (24, 25). In post-bronchiolitis studies bronchiolitis in infancy has been associated with increased risk of asthma in childhood (14, 27) and early adulthood (23–25). The 31 % asthma prevalence after bronchiolitis in the current study is in line with recently published follow-up of Swedish bronchiolitis cohort, in which *Goksör et al.* presented 37 % asthma prevalence in former bronchiolitis patients at the age of 25–28 years, compared to 7 % asthma prevalence in controls (24).

In the 1990´s Martinez et al. documented, that in about 60 % of children, wheezing tendency at early age is transient and these children become symptom free by the age of 6 years (7). However, in a proportion of children, early wheezing is a sign of asthma predicting later respiratory morbidity, as described also in the present study. Tucson study demonstrated, that in over 70 % of cases with current asthma at the age of 22 years, wheezing episodes had happened before the age of 6 years (28). So far, the results of the birth cohort studies and post-bronchiolitis studies, regarding later asthma risk have agreed in documenting that

asthma in adulthood has its roots in early childhood.

Asthma and wheezing have been associated with reduced HRQoL both in childhood (29) and adulthood (30). In the child population, pneumonia has been described to affect HRQoL in short term (31). However there are not many studies about HRQoL after early bronchiolitis or pneumonia. In a recent Norwegian study infants with a history of bronchiolitis had lower quality of life than controls in the overall health and general health domains of the Infant Toddler Quality of Life Questionnaire (ITQOL) 9 months after the index episode of wheezing (11). Similar findings were also presented in another study 3 years after hospitalization for RSV bronchiolitis (12). However there are no previous studies on HRQoL after early childhood bronchiolitis or pneumonia that would have included a longer follow-up. SGRQ scores have been described to correlate with lung function (32). So, impaired HRQoL found in the present study is in line with the obstructive airway function, presented in current study after early bronchiolitis or pneumonia.

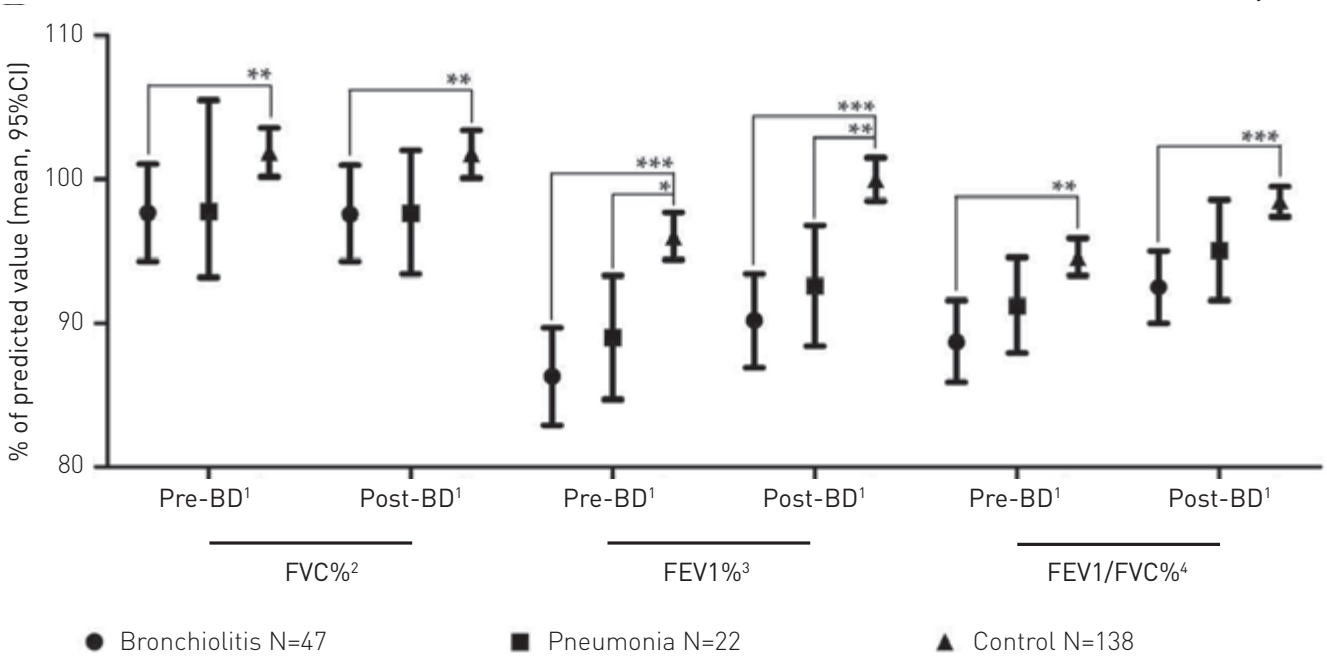
Previous prospective post-bronchiolitis studies have demonstrated that lung function may remain reduced until early adulthood after bronchiolitis in infancy (9, 10, 23). The type of the lung function impairment is in line with the 17–20 years follow-up of the Swedish post-bronchiolitis cohort, which demonstrated reduced FEV1/FVC and MEF50 before and after bronchodilatation after history of bronchiolitis in infancy, indicating irreversible airway obstruction in former bronchiolitis patients (9). However post-bronchiolitis studies have been unable to answer the question whether impairment of lung function is a consequence or a cause of respiratory infections in early childhood.

Tucson Childrens' Respiratory Study was the first birth cohort that tried to answer this question of the origin of impaired lung function. In the Tucson study, lung function was measured in young infants before any respiratory infections and it became evident, that those children who wheezed during respiratory illness in their first year of life had lower levels of lung function than the future non-wheezers. (7). Maternal smoking during pregnancy hampers lung development in utero and there is evidence that it is the most important preventable insults associated with lung function impairment of the newborn (33). In addition to Tucson results Bisgaard et al. demonstrated that 14 % of children with asthma by the age of 7 already had a significant airflow deficit as neonates. However this deficit progressed significantly during early childhood and it was concluded that approximately 40 % of the airflow deficit associated with asthma at the age of seven is present at birth, whereas 60 % develops with clinical disease (34). As a conclusion, it seems that even if part of the lung function is determined before birth or very soon after that, the lung development can be influenced by various events, such as respiratory infections in later life.

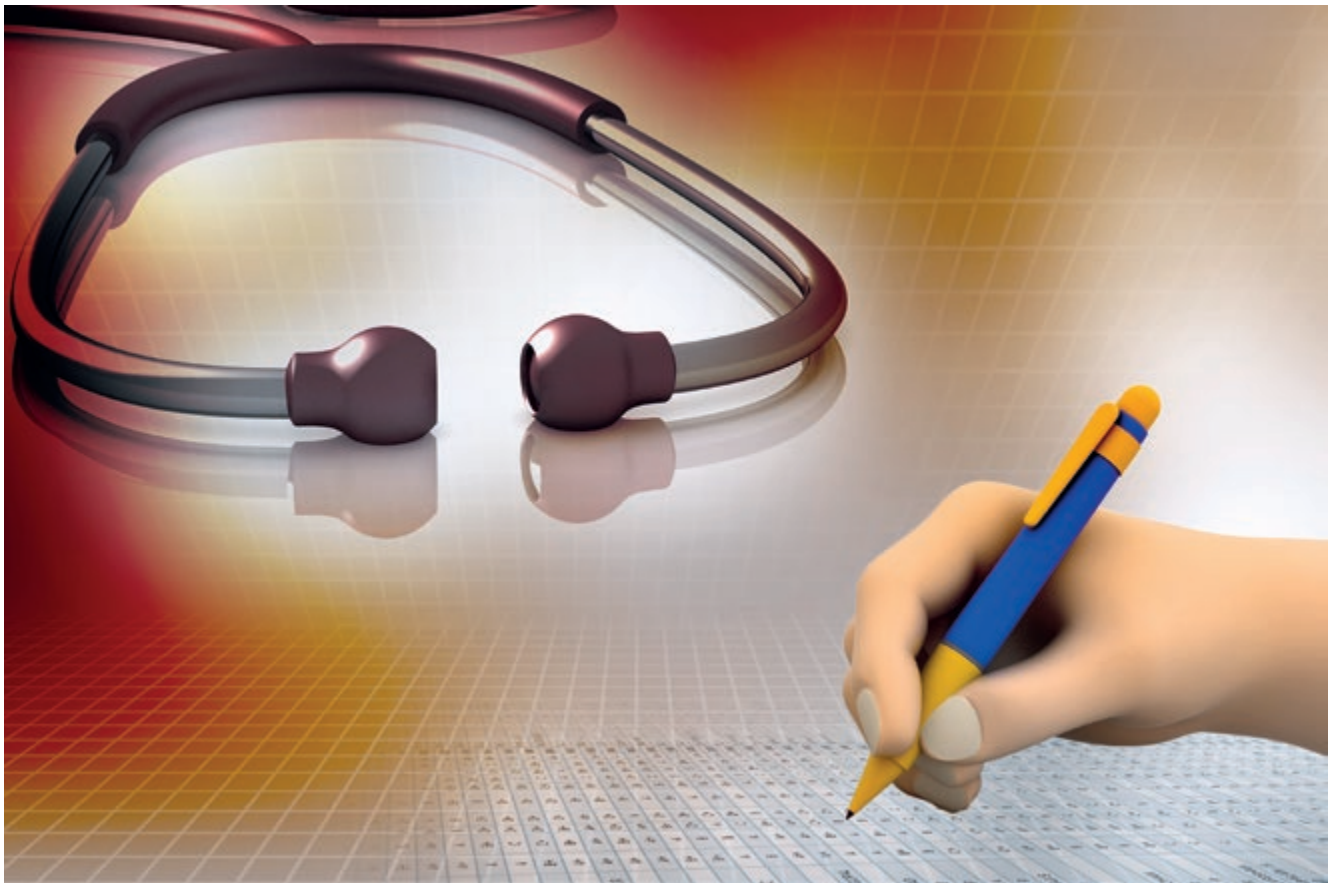
As maximal lung function is reached in early adulthood, subjects who start adult life with a lower FEV1/FVC-ratio may attain the threshold of COPD earlier during normal lung ageing than those starting with a higher FEV1/FVC-ratio (6). We found preliminary evidence that subjects with bronchiolitis in infancy more often have obstructive airways at the age of 28–31 years than controls with no history of LRTI hospitalization in infancy. There is a concern that 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

FIGURE 2. Pre- and post-bronchodilator lung function at the age of 28-31 years after bronchiolitis or pneumonia in infancy compared to controls.



Pre- and post-bronchodilator measurements are presented as means and 95 % confidence intervals (95 %CI). P-values are adjusted with asthma and current daily smoking, * p < 0.05, ** p < 0.005, *** p < 0.001. 1Pre-BD, pre-bronchodilator; post-BD, post-bronchodilator, 2FVC %, forced vital capacity (% of predicted value, 3FEV1 %, forced expiratory volume in one second (% of predicted value, 4FEV1/FVC %, FEV1/FVC ratio presented as % of predicted value.



Hospitalization for bronchiolitis or pneumonia in early childhood was associated with impaired health-related quality of life and irreversible obstructive lung function in later life. There is a concern that these alterations in airways may progress to COPD during normal lung ageing. PHOTO: COLOURBOX.COM

childhood, and a well-conducted clinical study at the age of 28–31 years. In all cases, spirometry was performed by a trained respiratory nurse of the research group, using the same spirometer and following the current international standards (18). The main shortcoming of the study was the small number of subjects. We were able to clinically examine 70 (57 %) 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 (35), which may diminish the differences in asthma prevalence between study groups, especially between pneumonia and control group. 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 LRTI, and further, to low lung function at the age of 28–31 years. However our study provides important information about the long-term outcome of patients who experience bronchiolitis or pneumonia in early childhood.

In conclusion, the study was able to confirm the high prevalence of asthma at 28–31 years of age in subjects who were hospitalized for bronchiolitis at less than 2 years of age. In addition, hospitalization for bronchiolitis or pneumonia in infancy is associated with an impaired respiratory health-related quality of life in adulthood. Irreversible, obstructive, lung function impairment is present 30 years after bronchiolitis and pneumonia in infancy.

REFERENCES

1. Zorc JJ, Hall CB. Bronchiolitis: Recent evidence on diagnosis and management. Pediatrics 2010; 125: 342–9.
2. Jartti T, Lehtinen P, Vuorinen T, Ruuskanen O. Bronchiolitis: Age and previous wheezing episodes are linked to viral etiology and atopic characteristics. Pediatr Infect Dis J 2009; 28: 311–7.
3. Jartti T, Lehtinen P, Vuorinen T, Osterback R, van den Hoogen B, Osterhaus AD, et al. Respiratory picornaviruses and respiratory syncytial virus as causative agents of acute expiratory wheezing in children. Emerg Infect Dis 2004; 10: 1095–101.
4. Pavia AT. What is the role of respiratory viruses in community-acquired pneumonia?: What is the best therapy for influenza and other viral causes of community-acquired pneumonia? Infect Dis Clin North Am 2013; 27: 157–75.
5. Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpaa R, Reijonen TM. Rhinovirus-associated wheezing in infancy: Comparison with respiratory syncytial virus bronchiolitis. Pediatr Infect Dis J 2004; 23: 995–9.
6. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. Proc Am Thorac Soc 2009; 6: 272–7.
7. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. the group health medical associates. N Engl J Med 1995; 332: 133–8.
8. de Marco R, Accordini S, Marcon A, Cerveri I, Anto JM, Gislason T, et al. Risk factors for chronic obstructive pulmonary disease in a european cohort of young adults. Am J Respir Crit Care Med 2011; 183: 891–7.
9. Goksor E, Gustafsson PM, Alm B, Amark M, Wennergren G. Reduced airway function in early adulthood among subjects with wheezing disorder before two years of age. Pediatr Pulmonol 2008; 43: 396–403.
10. Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy: Results from a prospective follow-up study.

Arch Pediatr Adolesc Med 2004; 158: 1070–6.
11. Rolfsjord LB, Skjerven HO, Bakkeheim E, Carlsen KH, Hunderi JO, Kvenshagen BK, et al. Children hospitalised with bronchiolitis in the first year of life have a lower quality of life nine months later. Acta Paediatr 2015; 104: 53–8.
12. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. Pediatr Infect Dis J 2004; 23: 414–7.
13. Korppi M, Halonen P, Kleemola M, Launiala K. Viral findings in children under the age of two years with expiratory difficulties. Acta Paediatr Scand 1986; 75: 457–64.
14. Kuikka L, Reijonen T, Remes K, Korppi M. Bronchial asthma after early childhood wheezing: A follow-up until 4.5–6 years of age. Acta Paediatr 1994; 83: 744–8.
15. Korppi M, Kuikka L, Reijonen T, Remes K, Juntunen-Backman K, Launiala K. Bronchial asthma and hyperreactivity after early childhood bronchiolitis or pneumonia. an 8-year follow-up study. Arch Pediatr Adolesc Med 1994; 148: 1079–84.
16. Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. Pediatr Pulmonol 2014; 49: 318–25.
17. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. the st. george's respiratory questionnaire. Am Rev Respir Dis 1992; 145: 1321–7.
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319–38.
19. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: Conclusions and recommendations of a working party of the european respiratory society. Eur Respir J Suppl 1997; 24: 2S–8S.
20. Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Irreversible airway obstruction in adulthood after bronchiolitis in infancy: Evidence from a 30-year follow-up study. Respir Med 2014; 108: 218–23.
21. Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. Scand J Clin Lab Invest Suppl 1982; 159: 5–20.
22. Stein RT. Long-term airway morbidity following viral LRTI in early infancy: Recurrent wheezing or asthma? Paediatr Respir Rev 2009; 10 Suppl 1: 29–31.
23. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax 2010; 65: 1045–52.
24. Goksor E, Amark M, Alm B, Ekerljung L, Lundback B, Wennergren G. High risk of adult asthma following severe wheezing in early life. Pediatr Pulmonol 2014.
25. Ruotsalainen M, Piippo-Savolainen E, Hyvarinen MK, Korppi M. Adulthood asthma after wheezing in infancy: A questionnaire study at 27 years of age. Allergy 2010; 65: 503–9.
26. Ruotsalainen M, Hyvarinen MK, Piippo-Savolainen E, Korppi M. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. Pediatr Pulmonol 2013; 48: 633–9.
27. Wennergren G, Hansson S, Engstrom I, Jodal U, Amark M, Brolin I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. Acta Paediatr 1992; 81: 40–5.
28. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: A longitudinal birth-cohort study. Lancet 2008; 372: 1058–64.
29. Covaciu C, Bergstrom A, Lind T, Svartengren M, Kull I. Childhood allergies affect health-related quality of life. J Asthma 2013; 50: 522–8.
30. Adams R, Wakefield M, Wilson D, Parsons J, Campbell D, Smith B, et al. Quality of life in asthma: A comparison of community and hospital asthma patients. J Asthma 2001; 38: 205–14.
31. Shoham Y, Dagan R, Givon-Lavi N, Liss Z, Shagan T, Zamir O, et al. Community-acquired pneumonia in children: Quantifying the burden on patients and their families including decrease in quality of life. Pediatrics 2005; 115: 1213–9.
32. Bae YJ, Kim YS, Park CS, Lee YS, Chang YS, Cho YS, et al. Reliability and validity of the st george's respiratory questionnaire for asthma. Int J Tuberc Lung Dis 2011; 15: 966–71.
33. Landau LI. Tobacco smoke exposure and tracking of lung function into adult life. Paediatr Respir Rev 2008; 9: 39,43; quiz 43–4.
34. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med 2012; 185: 1183–9.
35. Huurre TM, Aro HM, Jaakkola JJ. Incidence and prevalence of asthma and allergic rhinitis: A cohort study of Finnish adolescents. J Asthma 2004; 41: 311–7.