Children hospitalised with bronchiolitis in the first year of life have a lower quality of life nine months later

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ABSTRACT

Aim: Acute bronchiolitis increases the risk of asthma, and reduced quality of life (QoL) is reported in children with asthma and allergy. However, the impact of asthma risk factors on QoL is unclear. This study investigated whether bronchiolitis and common asthma risk factors in infancy had an influence on later QoL.

Methods: The parents of 209 infants recruited during hospitalisation for bronchiolitis at a mean age of 4 months, and 206 controls responded to the generic Infant Toddler Quality of Life Questionnaire 9 months later. We used robust regression analyses to assess the association between four asthma risk factors, atopic eczema, parental asthma, parental allergic rhinoconjunctivitis and second-hand smoke and QoL in the two groups.

Results: QoL was lower among children with previous bronchiolitis in the overall health and general health domains and lower in six of 13 domains in children with atopic eczema. Compared with no risk factors, children with previous bronchiolitis and three risk factors had lower scores in four domains, and control children with three risk factors had lower scores in three domains.

Conclusion: Having acute bronchiolitis, atopic eczema and three asthma risk factors were negatively associated with later QoL in early childhood.

INTRODUCTION

Asthma is the most common chronic disease in childhood and is often preceded by acute bronchiolitis in infancy (1). Other common risk factors for asthma are atopic eczema (2), parental asthma (2), male gender (3) tobacco smoke exposure (4) and parental allergic rhinoconjunctivitis (5).

Health-related quality of life (QoL) reflects the severity of chronic diseases such as asthma (6,7) and is reduced in subjects with allergic rhinoconjunctivitis (8). Reduced QoL has also been reported in adolescents with asthma who are exposed to second-hand smoke (9) and adults exposed to maternal smoking during pregnancy (10). The general health Infant Toddler Quality of Life Questionnaire (ITQOL) was recently validated and applied to infants with obstructive airways disease (11–13) and other diseases (13). When the ITQOL was applied to 5000 infants in the Generation R study, QoL was reduced for the majority of domains and particularly for the general health, bodily pain and family activities domains in infants with asthma-like symptoms (11). Similar reductions of QoL were reported 2–6 months after acute bronchiolitis (13). However, it is not known whether the presence of asthma risk factors per se induces a health burden, as reflected by reduced QoL in children younger than 24 months, or whether hospitalisation for acute bronchiolitis influences the susceptibility to reduced QoL.

The main aim of this study was to investigate whether bronchiolitis and common asthma risk factors were associated with later reductions in children’s QoL and the

Key notes

- This study investigated whether bronchiolitis and common asthma risk factors in infancy had an influence on later quality of life (QoL).
- The parents of 209 infants hospitalised for bronchiolitis at a mean age of 4 months, and 206 controls responded to the Infant Toddler Quality of Life Questionnaire 9 months later.
- Having acute bronchiolitis, atopic eczema and three asthma risk factors were negatively associated with later QoL in early childhood.

Abbreviations

ITQOL, Infant Toddler Quality of Life Questionnaire; ns, Not significant; QoL, Quality of life; SD, Standard deviation.
METHODS AND SUBJECTS

Study design

This study included 209 of the 404 children hospitalised during 2010–2011 for acute bronchiolitis at a mean age of 4.2 months (range 0–11 months) (14) in eight counties of the South-East Health Region of Norway. We also included 206 of the 240 control children recruited from a general population of infants of similar age in 2012. Inclusion criteria for the Bronchiolitis ALL-SE study (14) were as follows: clinical signs of bronchiolitis, as defined by Court (15), age below 12 months and a clinical score of four or more on a scale of zero to 10, where 10 was the worst. Exclusion criteria were any severe or chronic disease that might significantly influence the progression of acute bronchiolitis, more than one previous episode of obstructive airway disease or more than four weeks with lower airways disease symptoms and/or use of inhaled corticosteroids in the previous four weeks. The control population was recruited by randomly selecting infants aged up to 12 months from the national population registry who were living in two municipalities close to Oslo University Hospital and Østfold Hospital Trust, Fredrikstad. The exclusion criteria were any severe underlying disease, for example heart, lung, immunological, neurological or oncological disease. A medical history, including socio-economic factors and health-related issues in the subjects and their families, was obtained during enrolment.

The 97-question ITQOL™, version ITQOL-97 (ITQOL), was mailed to the parents of all 644 bronchiolitis patients and controls 8–9 months after enrolment and returned in stamped addressed envelopes.

The study was approved by the regional medical ethics committee and registered in the Norwegian bio bank registry. Informed written consent was obtained from parents of all the children. The clinical trial of the children with acute bronchiolitis (14) was registered with ClinicalTrials.gov number, NCT00817466. EudraCT number 2009-012667-34.

Subjects

The 415 children (57.6% boys) in this study had a mean age of 14.0 months at QoL assessment, with a range of 8.4–23.3 months. These children were largely similar to the 229 whose parents did not return the QoL questionnaire, but were more likely to have Caucasian parents (fathers 92.0% vs. 86.7%, p = 0.001) and a higher mean (SD) educational level [fathers 4.1 (0.9) vs. 3.8 (1.0), p < 0.001]. The parents of the control children had a higher mean educational level, as well as higher rate of allergic rhinoconjunctivitis, than those of the hospitalised children. The control children were exposed to second-hand smoke significantly less often than the hospitalised children, and their mean age at assessment was 0.7 months higher (Table 1). Eight children in the control group were reported to have had previous hospitalisation for acute bronchiolitis and were therefore reclassified as having undergone hospitalisation for acute bronchiolitis.

Parental interview at enrolment

At enrolment, a paediatrician conducted a structured interview with the parents. Information was obtained about parental asthma and allergic rhinoconjunctivitis, previous respiratory symptoms, medications or atopic eczema in the child, indoor smoking in the home, ethnicity and socio-economic factors.

Second-hand smoke exposure was considered positive if the parents reported smoking in the home. Education was scored by the highest level in any of the parents into five categories, with category one denoting no schooling; two meaning primary school; three indicating secondary school; four showing higher education up to 3 years and five meaning higher education of more than 3 years.

Quality of life questionnaire

The ITQOL (copyright holder HealthActCHQ Inc., Boston, MA, USA) includes 13 domains: overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions, overall health, physical abilities, growth and development, bodily pain/ discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions, overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions, overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions, overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions, overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, global behaviour, getting along, general health, change in health (compared with 1 year ago), parental impact – emotions.

Table 1 Comparison of demographic and asthma risk factor data between bronchiolitis and control group responders

| Comparison                                      | Bronchiolitis N = 217 | Controls N = 198 | p-Value for difference |
|------------------------------------------------|------------------------|------------------|------------------------|
| Males, n (%)                                   | 129 (59.4)             | 110 (55.6)       | 0.42                   |
| Parental asthma, n (%)                         | 43 (24.2)              | 54 (27.3)        | 0.49                   |
| Parental allergic rhinoconjunctivitis, n (%)   | 71 (35.3)              | 108 (54.5)       | <0.001                 |
| Atopic eczema, n (%)                           | 23 (11.1)              | 21 (10.6)        | 0.87                   |
| Second-hand smoke, n (%)                       | 32 (16.7)              | 6 (3.1)          | <0.001                 |
| Caucasian mother, n (%)                        | 190 (95.5)             | 189 (95.5)       | 0.99                   |
| Caucasian father, n (%)                        | 190 (96.4)             | 184 (92.9)       | 0.12                   |
| Education of mother, mean (SD)                 | 4.1 (0.9)              | 4.6 (0.7)        | <0.001                 |
| Education of father, mean (SD)                 | 3.9 (1.0)              | 4.3 (0.9)        | <0.001                 |
| Age in months at inclusion, mean (SD)          | 4.1 (2.8)              | 6.4 (3.4)        | <0.001                 |
| Age in months at quality of life, mean (SD)    | 13.7 (3.1)             | 14.4 (3.4)       | 0.02                   |

Significantly differing means with p-values in bold type.
The level of significance was set to \( p = 0.05 \) for all analyses. There was no overall summation score for the ITQOL. A validated Norwegian translation of the ITQOL (provided by the HealthActCHQ) was employed. One postal reminder was distributed after 2 weeks.

**Main outcomes, asthma risk factors and explanatory variables**

The main outcomes were the 13 ITQOL domains. The four risk factors studied in the bronchiolitis and control groups separately were parental asthma, parental allergic rhinitis, conjunctivitis, second-hand smoke exposure and atopic eczema in the child. Gender and age at enrolment were entered as potential explanatory variables for QoL.

**Statistical analyses**

Continuous data are presented by means and standard deviations with differences analysed by Student’s \( t \)-test in case of normal distribution of data. The Welch test was applied for comparison of the means of non-normally distributed data like age at enrolment.

Categorical variables are given as numbers (\( n \)) and percentages, unless otherwise stated, and possible differences were assessed by Pearson’s chi-square test. Due to non-normality of the distribution of the QoL scores and residuals, analyses of QoL data were made by Huber’s M method of robust regression (16).

To estimate the relative impact of each risk factor on the ITQOL domains, we used Hosmer’s manually backward elimination technique in multiple robust regression analysis, retaining age at inclusion and gender in all models (17). Ethnicity was not included in the multiple regression analysis, as the responding parents of the bronchiolitis and control groups did not differ significantly using this analysis, as the responding parents of the bronchiolitis and the 198 controls are control groups did not differ significantly using this analysis, as the responding parents of the bronchiolitis and the 198 controls are

**RESULTS**

Characteristics of the 217 children with previous hospitalisation for acute bronchiolitis and the 198 controls are given in Table 1. The QoL was significantly associated with three domains in children with previous bronchiolitis (Table 2), compared with those without bronchiolitis. The mean (95% confidence interval) differences (regression coefficients) in QoL scores were most pronounced for general health at \(-11.6 (-14.0 \text{ to } -9.2)\), followed by overall health at \(-5.8 (-8.3 \text{ to } -3.2)\), whereas a significantly higher score was observed for change in health at \(4.6 (1.0 \text{ to } 8.3)\) among children with previous bronchiolitis. The other domains were not significantly associated with bronchiolitis.

Atopic eczema had the most widespread negative impact on QoL after adjusting for age and gender, affecting five domains in the bronchiolitis group (Fig. 1) and six domains in the control group (Fig. S1). In both groups, the QoL domains, overall health, physical abilities and temperament and moods, were negatively affected by atopic eczema. Parental asthma negatively affected one domain in the control group. Exposure to second-hand smoke was negatively associated with one domain in the controls and two domains in those with previous bronchiolitis. The most pronounced impact was found in the domain of change in health among children with previous bronchiolitis, with higher scores in those with atopic eczema and lower scores in those with second-hand smoke exposure.

Girls with previous bronchiolitis had significantly higher scores than boys in the domain bodily pain/discomfort. Age at inclusion was negatively associated with general behaviour in the control group.

The number of common asthma risk factors did not differ significantly in the bronchiolitis and the control children, respectively, with no risk factor in 41.3% versus 33.3%, one risk factor in 38.9% versus 40.4%, two risk factors in 16.8% versus 23.7% and three risk factors in 2.9% versus 2.5%. Overall, the most common risk factor (\( n, \% \)) was parental...

| Table 2 | Weighted means* of quality of life (QoL) scores of the two groups (95% confidence intervals); \( p \)-values referring to differences between the groups |
|----------------|---------------------------|---------------------------|
| QoL domain      | Bronchiolitis             | Controls                  |
| Overall health  | \( 85.4 \) (83.6, 87.2)    | \( 91.2 \) (89.4, 93.0)    |
| Physical abilities | 99.5 (99.8, 100.0)  | 100.0 (99.9, 100.1)  |
| Growth and development | 93.9 (92.8, 94.9) | 93.7 (92.7, 94.8) |
| Bodily pain/discomfort | 72.9 (70.7, 75.1) | 74.0 (71.8, 76.3) |
| Temperament and moods | 83.1 (82.0, 84.3) | 83.1 (81.9, 84.3) |
| General behaviour† | 88.0 (86.4, 89.5) | 89.3 (87.7, 90.9) |
| Overall behaviour† | 88.8 (86.6, 91.0) | 88.4 (86.1, 90.6) |
| Getting along† | 80.0 (78.6, 81.3) | 78.4 (77.0, 79.7) |
| General health | \( 70.2 \) (68.5, 71.9) | \( 81.8 \) (80.0, 83.5) |
| Change in health† | \( 56.0 \) (48.9, 53.8) | \( 51.4 \) (48.9, 53.8) |
| Parental emotions | 93.6 (92.7, 94.5) | 93.5 (92.6, 94.4) |
| Parental time | 94.1 (92.9, 95.2) | 94.1 (93.0, 95.3) |
| Family cohesion | 85.0 (85.0, 85.0) | 85.0 (85.0, 85.0) |

*Means weighted by robust regression by Huber’s M method.
†Only for children older than 12 months of age.
‡Recorded from scores 1–5 to 0–100.
Significantly different values in bold type.
allergic rhinoconjunctivitis (179, 43.1%), followed by parental asthma (97, 23.4%), diagnosed atopic eczema in the child (44, 10.6%) and second-hand smoke (38, 9.2%). No subjects had all four risk factors.

Compared with no risk factors, the presence of increasing numbers of asthma risk factors was associated with lower QoL in both groups, as shown in Table S1. In children with previous bronchiolitis, QoL in one and four domains was significantly reduced with the presence of two or three risk factors, respectively. Among the controls, the presence of one risk factor was associated with lower scores in one domain, whereas two or three risk factors were associated with reduced scores in three domains.

The largest reduction in score was seen for family cohesion in children with previous bronchiolitis and three asthma risk factors, followed by bodily pain/discomfort and general health in those with three risk factors in the control group (Table S1).

**DISCUSSION**

Hospitalisation for acute bronchiolitis, particularly in children who also had atopic eczema, was associated with reduced QoL 9 months later. A similar effect was seen by an increasing number of asthma risk factors.

Our finding that QoL was reduced 9 months after hospitalisation for acute bronchiolitis is in line with a previous Dutch study during early childhood by Spuijbroek et al. (13) and Backman et al. (1) in adulthood. In common with the present study, the Dutch study also reported significant reduction in general health 2–6 months after respiratory syncytial virus bronchiolitis in 47 children (13). Wheezing and asthma-like symptoms have previously been associated with reduced QoL (11–13,18) although recurrent wheeze is likely to represent a different entity of obstructive airways disease than the presently reported acute bronchiolitis.

Our study is the first to assess the role of asthma risk factors on generic QoL in early childhood. Atopic eczema at the time of enrolment, included as one of the asthma risk factors, was associated with reduced general health-related QoL in line with findings in older children (19,20) using disease-specific QoL questionnaires (21). In children aged three to 84 months, using the Infants' Dermatitis Quality of Life Index, a negative correlation was found between the presence and degree of atopic eczema and mood and sleep (20). However, this index was only designed and validated for children with atopic eczema. Accordingly, many questions were inappropriate for healthy children. Disease-specific and general health QoL instruments are not directly comparable, possibly explaining some of the discrepancy in magnitude of associations. The presently observed negative impact on QoL by atopic eczema of up to 11 percentage points or score points is less than the 33% reduction in QoL observed in 5 to 16-year-old Scottish children with generalised atopic eczema, but more in line with the 19% reduction in QoL with localised eczema (22). In comparison, Beattie et al. (22) reported a mean reduction of QoL for asthma of 28%. The apparent discrepancy between the Scottish study and our study may be due to our use of the presence or not of atopic eczema recorded at enrolment as a predictor for later QoL, without assessing eczema at the time of completing the QoL questionnaire. We did not distinguish between generalised and localised eczema.

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**Figure 1** Significant associations between quality of life and asthma risk factors are shown in children who were previously hospitalised with acute bronchiolitis. The association with each significant risk factor is given as the regression coefficient (95% confidence interval), adjusted for age and gender in multiple robust regression analyses. Risk factors not shown were excluded by step-down procedure. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.
The other three asthma risk factors – parental asthma, parental allergic rhinoconjunctivitis and second-hand smoke exposure – were to a lesser extent independently associated with QoL.

The present study showed that increasing numbers of asthma risk factors were associated with lower general health-related outcomes. As shown, parental allergic rhinoconjunctivitis was not independently associated with any of the QoL domains, and parental asthma was only associated with one domain. Still, having many risk factors together with rhinoconjunctivitis may reflect a greater untoward health load that influences how well the parents cope with, and perceive, their child’s health as well as their own QoL. Our data suggest that hospitalisation for acute bronchiolitis may modify the association between QoL and common asthma risk factors. Atopic eczema was negatively associated with QoL in the control group, whereas second-hand smoke exposure showed a negative association in the bronchiolitis group. We speculate that having experienced a severe lower respiratory disease leading to hospitalisation during infancy may override a potential limited effect by a common asthma risk factor, as suggested by the impact shown in Figure 1. A large general cohort study including sufficient number of children hospitalised for acute bronchiolitis would be necessary to confirm or contradict our findings.

The present study is strengthened by the prospective assessment of asthma risk factors at enrolment for the two groups of children, thus eliminating the risk of recall bias at the time of reporting QoL 9 months later. The inclusion of a randomly selected control group from a general population of similar age enabled us to study the potential modifying effect of acute bronchiolitis exerted by asthma risk factors on later QoL. To ensure that all children who had experienced acute bronchiolitis were classified correctly in stratified analyses, the eight control subjects who had been hospitalised for bronchiolitis were classified together with the bronchiolitis group. This provided a more stringent opportunity to assess the role of bronchiolitis in later QoL than if they had been classified with the controls. The ITQOL is carefully validated in general infants and child populations (12) as well as for young children with diseases (11,13) relevant for the present study.

The study has limitations that may influence the interpretation of our results. The response rate in the bronchiolitis group was 52%, which appeared to skew the respondents towards native families with higher education than the nonrespondents. The respondents from the bronchiolitis group differed less from the control group than the nonrespondents from the bronchiolitis group did with respect to parents’ education and did not differ significantly from the control group by ethnicity. Our ability to generalise the findings to a truly random population may be restricted. The interpretation of the role of risk factors in reduced QoL may be limited within populations of less highly educated parents or non-Caucasian families.

Adjusting for multiple testing is debated. However, the use of Bonferroni adjustment in multiple regression analyses is designed for outcome variables that are independent of each other, which is not the case with each of the ITQOL domains being measured in the same individual. The negative influence of atopic eczema on ITQOL was found in a high number of domains, thus strengthening the likelihood of statistically as well as clinically significant associations without adjusting for multiple testing.

CONCLUSION

Having acute hospitalised bronchiolitis, atopic dermatitis and three common asthma risk factors during infancy were associated with lower general health-related QoL in early childhood.

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CONFLICTS OF INTERESTS AND FUNDING

None of the authors have reported any conflict of interest related to the present study. The bronchiolitis trial was run in eight paediatric departments without commercial funding. The first author has a 50% fellowship from the Innlandel Hospital Trust’s Research Fund.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

Table S1 The impact on QoL domains by increasing number of the risk factors atopic eczema, parental asthma, parental allergic rhinoconjunctivitis and second-hand smoke as the effect on the change of domain score compared to having no risk factor (0), mean (95% confidence intervals) for children admitted to hospital for acute bronchiolitis (B) and control children (C).

Figure S1 Significant associations between QoL and asthma risk factors are shown in children from the general population sample who were not previously hospitalised with acute bronchiolitis.