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

Short title: Acute infant bronchiolitis and quality of life

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Abstract

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

Methods: The parents of 209 infants recruited during hospitalisation for bronchiolitis at a mean age of four months, and 206 controls, responded to the generic Infant Toddler Quality of Life Questionnaire nine 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.

Keywords: quality of life, acute bronchiolitis, asthma, risk factors, atopic eczema

Key notes:

- This study investigated if 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 four months, and 206 controls, responded to the Infant Toddler Quality of Life Questionnaire nine months later.
- 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 5,000 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 two to six months after acute bronchiolitis (13). However, it is not known whether the presence of asthma risk factors per se induce a health burden, as reflected by reduced QoL in children

younger than 24 months, or if hospitalisation for acute bronchiolitis influences the susceptibility to reduced QoL.

The main aim of the present study was to investigate if bronchiolitis and common asthma risk factors were associated with later reductions in children's QoL and the possible modification of this association by hospitalisation due to acute bronchiolitis in infancy. Secondly, we aimed to assess the relative impact of each of these risk factors as well as by the sum of risk factors on general health related QoL in early childhood.

METHODS and SUBJECTS

Study design

The present study included 209 of the 404 children hospitalised during 2010-11 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: clinical signs of bronchiolitis, as defined by Court (15), aged 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 Infant Toddler Quality of Life Questionnaire™, version ITQOL-97, (ITQOL) was mailed to the parents of all 644 bronchiolitis patients and controls eight to nine 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 the present 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 re-classified 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 socioeconomic 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 three years and five meaning higher education of more than three years.

Quality of life questionnaire

The ITQOL (copyright holder HealthActCHQ Inc., 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 to one year ago), Parental Impact – Emotions, Parental Impact – Time and Family Cohesion. The domains were scored separately from zero to 100 (best), except for Change in Health, which was scored from one through five (best). With permission from the copyright holder, we recalculated the Change in Health scores into a zero to 100 (best) range. 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 two 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 rhinoconjunctivitis, 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, since the responding parents of the bronchiolitis and control groups did not differ significantly using this variable. All included variables were tested for confounding. Interactions and model assumptions were inspected using jack-knife residuals and Akaike Information Criteria (AIC). The level of significance was set to $p=0.05$ for all analyses.

The 13 domains could not be regarded as independent of each other. Also, an interaction was found between bronchiolitis and some of the other risk factors for three of the domains (data not shown). Thus, the impact of risk factors on the QoL domains were analysed separately for the groups.

Adjustment of p-values for multiple variables was not performed for reasons explained in the discussion.

The SPSS PASW Statistics 18 (IBM Corporation, Armonk, New York USA) and the Number Cruncher Statistical System (NCSS Kaysville, Utah, USA) version 2007 were used in the analyses.

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 to those without bronchiolitis. The mean (95% confidence interval) differences (regression coefficients) in QoL scores was most pronounced for General Health at -11.6 (-14.0 to -9.2), followed by Overall Health at 5.8 (-8.3 to -3.2), whereas a significantly higher score was observed for Change Health at 4.6 (1.0 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 (Figure 1) and six domains in the control group (Figure 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 in 38.9 versus 40.4%, two risk factors in 16.8 versus 23.7% and three in 2.9 versus 2.5%. Overall, the most common risk factor (n, %) was parental 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 to 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 were 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 infant QoL nine months later. A similar effect was seen by an increasing number of asthma risk factors.

Our finding that QoL was reduced nine 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 two to six 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 paper 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 are less than the 33% reduction in QoL observed in five 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 reported a mean reduction of QoL for asthma of 28% (22). 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.

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 nine 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 non-respondents. The respondents from the bronchiolitis group differed less from the control group than the non-respondents 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 quality of life in early childhood.

Abbreviations:

ITQOL - Infant Toddler Quality of Life Questionnaire™

QoL - Quality of life

ns - not significant

SD - standard deviation

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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 Innlandet Hospital Trust's Research Fund.

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

	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 mother, mean (SD)	4.1 (0.9)	4.6 (0.7)	<0.001
Education father, mean (SD)	3.9 (1.0)	4.3 (0.9)	<0.001
Age months at inclusion, mean (SD)	4.1 (2.8)	6.4 (3.4)	<0.001
Age months at QoL, mean (SD)	13.7 (3.1)	14.4 (3.4)	0.02

Table 2 Weighted means¹ of 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 ²	88.0 (86.4, 89.5)	89.3 (87.7, 90.9)
Overall Behaviour ²	88.8 (86.6, 91.0)	88.4 (86.1, 90.6)
Getting Along ²	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 ^{2,3}	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)

¹Means weighted by robust regression by Huber's M method.

²Only for children older than 12 months of age.

³Recoded from scores 1-5 to 0-100.

Figure legend

Figure 1

Significant associations between QoL 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. *0.05 > p>0.01 **0.01> p >0.001 ***0.001> p >0.0001 ****p <0.0001

