

REGULAR ARTICLE

The severity of acute bronchiolitis in infants was associated with quality of life nine months later

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INTRODUCTION

Acute infant bronchiolitis is associated with later wheeze and asthma in children (1–3) and adults (1,4). Bronchodilator treatment of acute bronchiolitis has been found to be ineffective, whereas supportive care such as oxygen supplementation, nasogastric feeding and ventilatory support may be required (5,6). The severity of bronchiolitis has been assessed by inpatient status, length of hospital stay (LOS) (7,8) and by the use of general and ventilatory supportive treatment (9–11). Severity characteristics at the time of hospital admission include the presence of inspiratory retractions, wheezing, respiratory rate and oxygen saturation (12,13), which may predict the length of hospital stay (11).

Health-related quality of life (QoL) measures may quantify the individuals' capability to adapt to illness across social, emotional and physical functioning as well as how much their illness interferes with daily life (14). Hence, measuring QoL is an important supplement to clinical disease assessment.

Infant bronchiolitis has been associated with later reduced QoL in children (15–17) and adults (4). Bont et al. (17) reported that QoL at three years of age was associated with the severity of postbronchiolitis wheezing, but not with age, gender, gestational age or mechanical ventilation

ABSTRACT

Aim: Acute bronchiolitis in infancy increases the risk of later asthma and reduced health-related quality of life (QoL). We aimed to see whether the severity of acute bronchiolitis in the first year of life was associated with QoL nine months later.

Methods: The parents of 209 of 404 of children hospitalised for acute bronchiolitis in eight paediatric departments in south-east Norway at a mean four months of age (range 0–12 months) completed the Infant/Toddler Quality of Life Questionnaire sent by mail nine months after the acute illness. Disease severity was measured by length of stay and the need for supportive treatment. Interactions with gender, inclusion age, prematurity, maternal ethnicity and maternal education were examined.

Results: Reduced QoL in four domains was associated with increased length of stay and need for ventilatory support. Physical abilities and general health were associated with both severity markers, whereas bodily pain and discomfort and change in health were associated with length of stay. Ventilatory support was more negatively associated with QoL than atopic eczema and also associated with reduced parental emotions and parental time.

Conclusion: The severity of acute bronchiolitis in infants was associated with reduced QoL nine months later.

during acute bronchiolitis. Wheezing illness (18) and asthma-like symptoms (19) have been associated with reduced QoL in infants and young children.

Using the 97 question version of the Infant/Toddler Quality of Life Questionnaire (ITQOL-97) (20), we have shown that hospitalisation for acute bronchiolitis as well as asthma risk factors, including atopic eczema in infancy, were associated with reduced general QoL nine months later (21). Apart from Bont's study (17), we were not aware of any studies that had investigated whether the severity of acute bronchiolitis was associated with later QoL. Disease

Key notes

- We explored whether the severity of acute bronchiolitis in the first year of life was later associated with reduced health-related quality of life (QoL).
- The parents of 209 infants completed the Infant/Toddler Quality of Life Questionnaire nine months after they were hospitalised.
- Increasing severity was associated with lower QoL in the domains physical abilities, general health, bodily pain and discomfort, change in health, parental emotions and parental time.

severity during infancy may affect the parents' later perception of health and disease in young children. This has been shown for wheezing illness (18). Therefore, we aimed to investigate whether the severity of acute bronchiolitis in infants was associated with reduced QoL nine months later, primarily by assessing the severity of acute bronchiolitis by LOS and the need for supportive treatment and secondarily by the severity of bronchiolitis assessed upon admission to hospital.

METHODS

Study design

A multicentre, randomised clinical trial, registered as the Bronchiolitis All-Study, south-east Norway (9), compared the effect of inhaled racemic adrenaline versus saline and on demand versus fixed schedule inhalation strategies in infants from January 2010 through May 2011. The infants were recruited from eight paediatric hospital departments in the south-east health region of Norway. The inclusion criteria were that they needed to be less than 12 months of age and have clinical signs of moderate-to-severe bronchiolitis, with a clinical score of at least four on a scale from 0 to 10, with 10 being the worst (Table 1) (9,22). The exclusion criteria were severe underlying disease, more than one episode of previous wheeze, more than four weeks of continuous lower airway symptoms, such as a cough, and the use of corticosteroids in the previous four weeks.

At inclusion, the parents underwent structured paediatrician-guided interviews, including information on the patient and family medical history and sociodemographic factors. Oxygen saturation (SpO₂) was measured transcutaneously with a pulse oximeter. The use of supportive treatment, defined as oxygen supplementation, nasogastric feeding tube or ventilatory support, was recorded daily and verified from patient record reviews. The ITQOL questionnaires were sent by mail to the parents of the bronchiolitis children about nine months after hospitalisation (mean 9.6 months, 95% confidence interval (95% CI) 9.4–9.8 months). Written informed consent was obtained from at least one parent of each child prior to inclusion. If the questionnaires were not returned within two weeks, another questionnaire was sent out once.

The study was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian

Medicines Agency and was registered in the Norwegian Biobank Registry. The study was audited by the Norwegian Medicines Agency in 2011. The trial was registered in ClinicalTrials.gov (NCT00817466) and EudraCT (2009-012667-34).

Subjects

This study included the 209 children whose parents returned the ITQOL, who represented 52% of the 404 included in the randomised clinical trial. The children (60% boys) had a median age of 3.3 months on hospital admission (Table 2), and a median (range) age of 13.0 (8.4–23.3) months at the time of the QoL assessment. The median (range) LOS was 67.4 (2.0–398.1) hours. All 14 children requiring ventilatory support received noninvasive ventilation by continuous positive airways pressure (CPAP), and none received ventilator treatment.

With the exception of more Caucasian mothers and higher parental education among the questionnaire respondents, the baseline characteristics were comparable in the respondents and nonrespondents (Table 2).

Health-related quality of life

The ITQOL-97 consists of 97 questions divided into 13 domains: overall health, physical abilities, growth and development, bodily pain/discomfort, temperament and moods, general behaviour, overall behaviour, getting along, general health, change in health, parental impact (emotions), parental impact (time) and family cohesion. The first ten domains are related to the children, whereas the domains parental impact (emotions) and parental impact (time) are based on questions about the parents' worries and time limitations attributed to their children's health. The three behaviour domains, namely general behaviour, overall behaviour and getting along, and the change in health domain, are only suitable for children older than 12 months of age. The domains are scored from 0 to 100 (best), with no overall score. For the domain change in health, which reflects the parent's perception of their children's health compared to one year ago, the score from 1 to 5 (best) was recoded into 0–100 by permission of the copyright holder (HealthActCHQ Inc, Massachusetts, USA). A score of 50 for change in health indicates unchanged health from one year earlier. A validated translation into Norwegian, provided by the copyright holder, was applied.

Table 1 The clinical score, based on Skjerven et al. (9) and Kristjansson et al. (22)

| | Score 0 | Score 1 | Score 2 |
|--------------------------------|--------------|-----------------------------|------------------------------------------------------|
| Respiratory rate (breaths/min) | <40 | 40–60 | >60 |
| Respiratory chest recessions | None | Moderate costodiaphragmatic | Severe As 1, +rib and jugular retraction |
| Auscultatory breath sounds | Vesicular | Wheeze + rales/rhonchi | Faint ± severe wheeze ± pronounced rales and rhonchi |
| Skin colour | Normal | Pallor | Cyanosis |
| General condition | Not affected | Moderately affected | Severely affected |

Table 2 Baseline characteristics of questionnaire respondents versus nonrespondents

| | Respondents n = 209 | Nonrespondents n = 195 | p Value |
|----------------------------------------------------------|---------------------|------------------------|------------------|
| Boys, n (%) | 125 (59.8%) | 115 (59.0%) | 0.87 |
| Age hospitalised (months), median (range) | 3.3 (0.2–11.9) | 3.9 (0.3–12.0) | 0.47 |
| Moderate or severe bronchiolitis, n (%) | 105 (50.2%) | 100 (51.3%) | 0.83 |
| Length of stay, hours, median (range) | 67.4 (2.0–398.1) | 64.2 (0.5–408.1) | 0.63 |
| Clinical score at inclusion, median (range) [†] | 5.0 (4–9) | 5.0 (4–9) | 0.999 |
| Oxygen saturation <92% at inclusion, n (%) | 16 (8.0%) | 14 (7.4%) | 0.85 |
| Mother Caucasian, n (%) | 198 (94.7%) | 170 (87.2%) | 0.008 |
| Father Caucasian, n (%) | 181 (86.6%) | 158 (81.0%) | 0.13 |
| Maternal education [‡] , median (range) | 4.0 (1–5) | 3.0 (1–5) | <0.001 |
| Paternal education [‡] , median (range) | 4.0 (1–5) | 4.0 (2–5) | 0.028 |
| Birthweight, kg, mean (SD) | 3.5 (0.6) | 3.4 (0.7) | 0.057 |
| Prematurity [§] , n (%) | 19 (9.1%) | 20 (10.3%) | 0.69 |

Characteristics with significant differences in bold.

[†]Clinical score at inclusion – see definition in Table 2.

[‡]The parents' education level was scored by the following categories: 1 = no schooling; 2 = primary school; 3 = secondary school; 4 = higher education up to three years; 5 = higher education more than three years.

[§]Prematurity: Gestational age at birth <37 weeks.

Severity of acute bronchiolitis

The severity of bronchiolitis was assessed by four criteria: LOS, bronchiolitis severity by need for supportive treatment, SpO₂ and clinical score upon inclusion in the study.

LOS was defined as the time from the first study inhalation until discharge from the hospital, as recorded in the medical record for each patient, and given by quintiles, with the lowest representing the shortest LOS.

Bronchiolitis severity was categorised into three discrete groups:

1. No supportive treatment: no nasogastric tube feeding, extra oxygen supply or ventilatory support given,
2. Supportive treatment: supportive treatment, but no ventilatory support given,
3. Ventilatory support: ventilatory support given, regardless of other supportive treatment.

The SpO₂ at study inclusion was reported quantitatively.

The clinical score at study inclusion (Table S1) was reported quantitatively from 4 to 10, as the inclusion criteria required a score of at least four.

Outcomes

The main outcomes were the 13 domains of QoL reported from 1 to 100, with the highest values indicating a better QoL.

Statistical analyses

Groups were compared by Pearson's chi-square tests for categorical data and nonparametric tests for numerical variables unless otherwise stated.

All analyses with QoL as outcomes were analysed by linear robust regression by Huber's M-method (23), due to non-normality of the results and residuals, as well as the logarithms of the results. Data are presented as weighted

means with 95% confidence intervals (95% CI). We calculated the percentage point reductions in scores for the domains that were significantly associated with the severity variables to estimate the relative association with QoL. Possible interactions between the severity measures, gender, age at inclusion, maternal education and ethnicity as well as prematurity were assessed by multiple robust regression, including Hosmer's step-down procedure (24), a priori retaining age and gender in the analyses, and by two-way analysis including variance analysis. After the step-down procedure, we finally selected variables with p values of less than 0.3. Confounding was considered significant if including the variable led to a minimum of a 25% change in the result (24).

Because of non-normality of LOS, quintiles were used in the analysis. The high number of domains, 13, in the QoL questionnaire leads to multiple analyses. The ITQOL domains are not independent from each other and that is why we chose not to adjust the p values for multiple analyses.

The level of statistical significance was set to 0.05 (5%) for all analyses. Analyses were performed with the IBM SPSS Statistics 20 (IBM Corporation, New York, USA) and the version 2007 of the Number Cruncher Statistical System (NCSS Kaysville, Utah, USA).

RESULTS

The LOS varied from 2 to 398 hours, with quintiles of all children ranging from 0.5 to 23.0 hours (lowest) and 124.9 to 408. One hour (highest). No supportive treatment was given to 104 infants, while 91 received oxygen or feeding support and 14 also received ventilatory support. The youngest children were more likely to have more severe disease, with 27 of the 38 children (71.1%) within the highest quintile of LOS and 11 of the 14 children needing

ventilatory support (78.6%) being younger than three months of age. Although prematurity was negatively associated with six domains in bivariate analyses, prematurity did not significantly confound the associations between bronchiolitis severity and QoL (data not shown). Age at hospitalisation was not associated with QoL in bivariate analyses.

LOS and need for supportive treatment

Children with the longest LOS (5th quintile) had significantly reduced QoL in four domains, with a further tendency for reduced QoL in the overall health domain, significant for the 3rd quintile only (Table 3, Fig. 1). The reductions in QoL observed with increasing LOS (Fig. 1) were also significant after adjustment for age at hospitalisation and gender (Table 3) and were significant for the three highest quintiles in relation to the general health and

for two quintiles in the bodily pain and discomfort domains, respectively. The tendency for less improvement in health with increasing LOS compared to the lowest quintile was only significant in the highest quintile.

Children who received ventilatory support had significantly reduced QoL in four domains, while receiving supportive treatment was associated with reduced general health nine months later (Fig. 2), also after adjusting for age at inclusion and gender (Table 4).

The potential modifying effect of having experienced one episode of bronchial obstruction on the associations between acute bronchiolitis and later QoL was analysed by robust regression with and without adjustment for age at inclusion and gender. No significant effect was found for any of the associations, and the results for LOS and the need for supportive treatment are shown in Tables 3 and 4.

Table 3 Significant associations between LOS and QoL domains^{†‡§¶}, adjusted

| QoL domain | | 1st quintile (0.5–23.0 hours) N = 38 | 2nd quintile (23.0–47.9 hours) N = 39 | 3rd quintile (47.9–75.6 hours) N = 51 | 4th quintile (75.6–124.9 hours) N = 43 | 5th quintile (124.9–408.1 hours) N = 38 |
|----------------------------------|----------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------|----------------------------------------------|-----------------------------------------------|
| Overall health | Adjusted for age and gender only | 88.9 (83.9, 94.0) | −4.6 (−11.3, 2.2) | −6.4 (−12.6, −0.1)* | −3.6 (−10.0, 2.8) | −5.6 (−12.5, 1.3) |
| | Adjusted for one previous obstruction [§] | 92.0 (85.7, 98.3) | −6.0 (−12.6, 0.5) | −4.1 (−10.2, 1.9) | −4.0 (−10.2, 2.2) | −4.5 (−11.2, 2.2) |
| Physical abilities ^{††} | Adjusted for age and gender only | 99.8 (99.5, 100.3) | 0.1 (−1.2, 1.5) | −0.5 (−1.8, 0.8) | −0.6 (−2.0, 0.7) | −2.6 (−4.2, −1.0)** |
| | Adjusted for one previous obstruction | 98.6 (97.1, 100.1) | 0.2 (−1.3, 1.8) | −0.4 (−1.9, 1.0) | −0.6 (−2.1, 0.9) | −1.8 (−3.4, −0.1)* |
| Bodily pain/discomfort | Adjusted for age and gender only | 79.9 (74.5, 85.2) | −4.0 (−12.5, 4.5) | −8.3 (−16.2, −0.4)* | −6.3 (−14.5, 1.9) | −9.5 (−18.2, −0.8)* |
| | Adjusted for one previous obstruction | 74.6 (65.8, 83.4) | −2.7 (−11.9, 6.4) | −7.0 (−15.3, 1.3) | −4.3 (−12.9, 4.4) | −5.0 (−14.3, 4.2) |
| General health | Adjusted for age and gender only | 75.3 (70.5, 80.1) | −5.0 (−11.7, 1.8) | −6.6 (−12.8, −0.3)* | −7.0 (−13.6, −0.4)* | −9.9 (−16.9, −3.0)** |
| | Adjusted for one previous obstruction | 76.0 (69.0, 83.0) | −4.8 (−12.1, 2.4) | −5.5 (−12.1, 1.2) | −7.4 (−14.4, −0.4)* | −8.6 (−16.1, −1.1)* |
| Change in health | Adjusted for age and gender only | 73.1 (63.0, 83.1) | −12.1 (−26.1, 1.9) | −12.5 (−25.9, 0.9) | −8.6 (−22.3, 5.2) | −25.7 (−43.3, −8.2)** |
| | Adjusted for one previous obstruction | 81.1 (64.4, 97.8) | −16.5 (−31.7, −1.3)* | −14.5 (−28.6, −0.5)* | −13.4 (−28.4, 0.6) | −27.8 (−46.4, −9.1)** |

*0.01 ≤ p < 0.05 **0.001 ≤ p < 0.01.

†1st quintile as reference category, regression coefficients of 2nd–5th quintiles.

‡We show only domains with results with p < 0.05.

§95% CI in brackets.

¶Lower rows – adjusted for age, gender and one previous episode of obstruction.

††Interaction with prematurity. Including this variable would have made the regression coefficient for the 5th quintile 15.3% more negative.

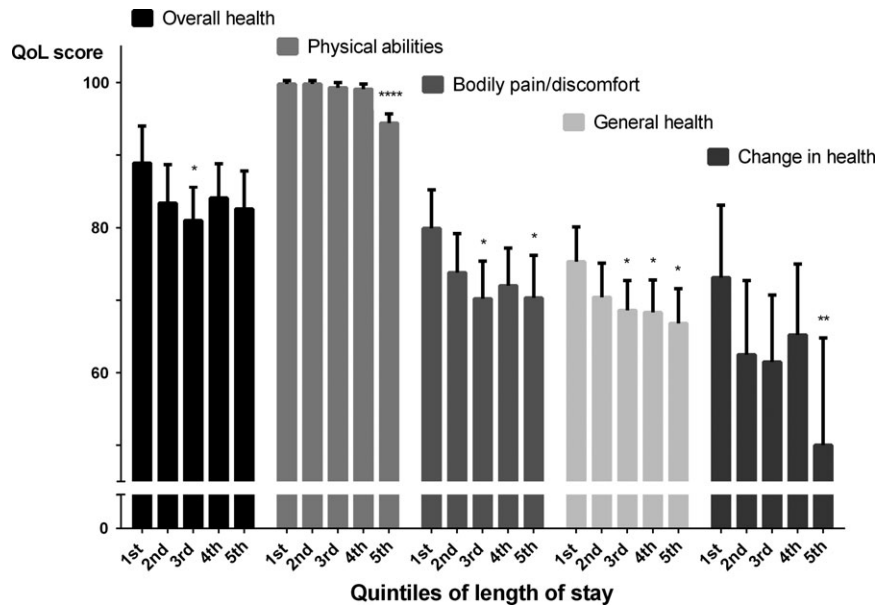


Figure 1 Length of stay and QoL. Quality of life is given by domains with statistically significant associations with bronchiolitis severity based upon the quintiles of length of stay. Weighted mean scores are shown for each quintile. * $p < 0.05$. ** $0.001 < p < 0.01$ **** $p < 0.0001$.

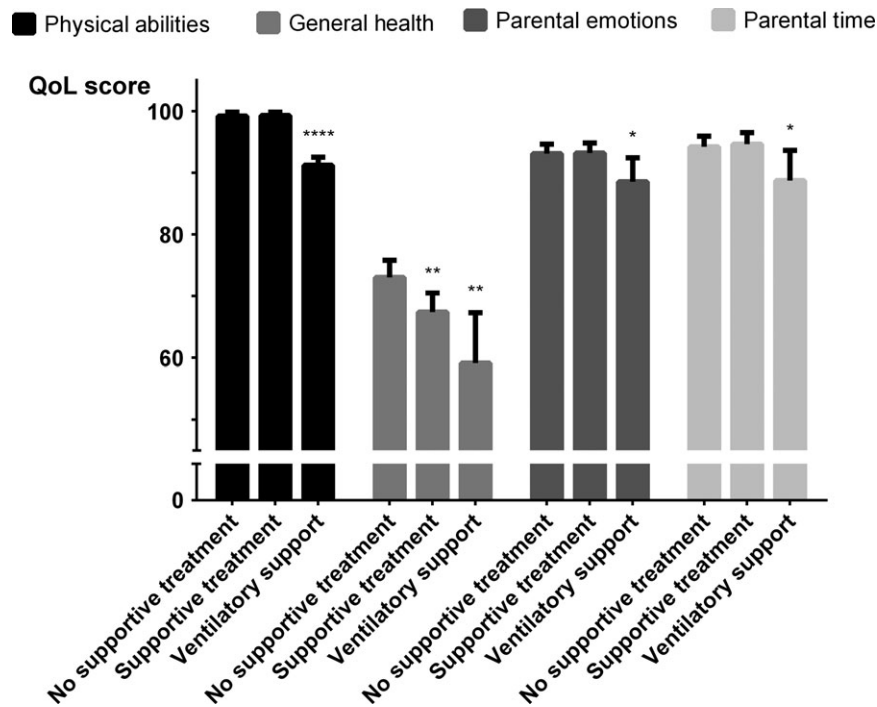


Figure 2 Bronchiolitis severity and QoL. Quality of life is given by domains with statistically significant associations with bronchiolitis severity based upon the need for supportive care. Supportive care: Supplementary oxygen or nasogastric tube feeding, but not ventilatory support. Weighted mean scores are shown for each quintile. * $p < 0.05$. ** $0.001 < p < 0.01$ **** $p < 0.0001$.

Severity of bronchiolitis upon hospital admission

For each increase in the clinical score points at inclusion, a significant reduction of 4.3% points (95% CI 1.9–6.8, $p = 0.0007$) of QoL score in the discomfort and bodily pain domain, the only domain with significant findings in

this respect, was observed, after adjustment for age, gender and maternal ethnicity.

In analyses adjusted for age and gender, SpO2 was associated with the physical abilities domain. A significantly lower score was reported for infants with an SpO2 of

Table 4 Significant associations between severity of acute bronchiolitis and quality of life domains^{†‡§}, adjusted

| QoL domain | | No supportive treatment n = 104 | Supportive treatment (nasogastric tube or O ₂) n = 91 | Ventilatory support n = 14 |
|--------------------------------------|-----------------------------------------------------|------------------------------------|-------------------------------------------------------------------------|-------------------------------|
| Physical abilities [¶] | Age and gender adjusted only | 99.7 (99.4, 100.0) | -0.4 (-1.1, 0.3) | -7.3 (-8.9, -5.7)**** |
| | Adjusted for one previous obstruction ^{††} | 98.9 (97.8, 99.9) | -0.6 (-1.5, 0.3) | -6.2 (-8.1, -4.3)**** |
| General health | Age and gender adjusted only | 75.7 (71.2, 80.1) | -6.0 (-10.1, -1.9)** | -16.1 (-24.6, -7.5)*** |
| | Adjusted for one previous obstruction | 73.9 (68.9, 78.9) | -5.3 (-9.7, -0.9)* | -15.8 (-24.5, -7.0)*** |
| Parental impact – emotions | Age and gender adjusted only | 93.3 (91.9, 94.8) | 0.1 (-2.1, 2.2) | -5.2 (-9.5, -0.9)* |
| | Adjusted for one previous obstruction | 93.9 (91.4, 96.4) | 0.0 (-2.2, 2.2) | -5.2 (-9.4, -1.0)* |
| Parental impact – time ^{‡‡} | Age and gender adjusted only | 94.2 (92.4, 95.9) | 0.3 (-2.1, 2.8) | -6.5 (-11.7, -1.2)* |
| | Adjusted for one previous obstruction | 94.0 (90.9, 97.1) | 0.4 (-2.3, 3.1) | -6.5 (-11.9, -1.0)* |

*0.01 ≤ p < 0.05 **0.001 ≤ p < 0.01 ***0.0001 ≤ p < 0.001 ****p < 0.0001.

[†]Weighted means of no supportive treatment group as reference, regression coefficients of supportive treatment and ventilatory support groups.

[‡]We include only domains showing results with p < 0.05.

[§]95% CI in brackets.

[¶]Interaction with prematurity: Including prematurity in the model would have made the regression coefficient for ventilatory support 10.5% less negative.

^{††}Lower rows – adjusted for age, gender and one previous episode of obstruction.

^{‡‡}Interaction with prematurity: Including prematurity in the model would have made the regression coefficient for ventilatory support 8.9% more negative.

< 92%, with a mean difference of 6.7% points lower (95% CI 4.8–8.5), compared to the mean score reported for infants with an SpO₂ of > 92% of 99.8 (95% CI 99.4–100.2, p < 0.0001).

DISCUSSION

The infants' QoL nine months after hospitalisation for acute bronchiolitis was significantly associated with the severity of the acute illness, mostly in the domain of general health. Infants needing ventilatory support had the poorest QoL nine months later, with significant reductions in four of the 13 domains.

The present study shows, for the first time to our knowledge, that the severity of acute bronchiolitis in hospitalised infants had implications for their QoL almost a year later. We previously showed that, of the asthma risk factors, atopic eczema had the greatest impact on reduced QoL (16), whereas being hospitalised for acute bronchiolitis in infancy was significantly associated with later reduced QoL. The present study extends the previous observations, as it now shows that disease severity appeared to negatively influence the QoL of the infants and the parental perception of the child's health nine months later.

Increased LOS was associated with reduced quality of life in four of the 13 domains, including a considerably less favourable change in health score. Thus, LOS had a greater impact on the change in the health score nine months after hospitalisation than having a diagnosis of atopic dermatitis, as previously shown (16). The impact on QoL reduction by receiving supportive treatment other than ventilatory support was similar to the impact of atopic eczema (16). Similar to our study, a Dutch study in young children (15) showed that having had the respiratory syncytial virus (RSV) infection and a wheezing illness had a significant impact on the general health domain of the ITQOL. Within

this domain, our observed reduction of 16.1% points in infants receiving ventilatory support is similar to the 17% points reduction reported in infants with severe versus no asthma-like symptoms (19) and the 14.7% points reduction in four-year-old children with persistent wheezing compared to the reference group (25). On the other hand, a difference of 22.8% points was reported in infants and preschool children with wheeze and without wheeze (18). Collectively, the reported magnitude of QoL reductions in the presence or severity of respiratory disease is likely to be of clinical relevance.

Reductions in the QoL scores in four domains – physical abilities, general health, parental emotions and parental time – in infants receiving ventilatory support have, to our knowledge, not previously been demonstrated. Our results are in contrast to the study by Bont et al. (17), who did not find associations between mechanical ventilation and QoL two years later in 28 of 128 infants hospitalised with RSV infection. However, they used the TAPQOL questionnaire, assessing 13 scales including the stomach, skin, appetite and liveliness, and their QoL rating took place at three years of age compared to less than one year later, as in the present study. The differences in results may be related to different methods of measuring QoL and the time lapse between exposure and QoL measurement.

This study, and others, report variations in the associations between disease and the different QoL domains. As was found in the present study, reductions in the domain physical abilities were consistently or more strongly associated with several respiratory disease severity characteristics. We found that low SpO₂ at inclusion, or the need for ventilatory support, had a negative impact on this domain, in line with the impact of RSV infection on the domains physical abilities and general health reported in a Dutch study of young children with five health conditions (15). Similarly, a study of four-year-old children with persistent

wheeze showed an association between wheezing and a physical summary score (25). Young age, rendering the infants more prone to severe respiratory viral infections, is unlikely to explain the finding, as the association between ventilatory support and reduced physical abilities remained significant after adjustment for age at inclusion and gender in our study.

The finding that the severity score upon hospital admission was independently associated with later QoL has to our knowledge not previously been shown. Although this association was only found for bodily pain and discomfort, it may indicate that disease severity, already assessed at the time of hospital admission, may have an impact on later disease or health perception.

The present study may be limited by the relatively low rate of QoL answers from the original bronchiolitis group of the randomised controlled trial (52%), leading to an overrepresentation of parents with higher education and Caucasian ethnicity. On the other hand, we found no significant interaction or confounding by maternal education or ethnicity. The respondent and nonrespondent groups were similar in terms of most background characteristics, and the analyses that included maternal ethnicity and education did not reach the confounding criteria in the robust regression analyses. We therefore believe that the effect of selection bias on the associations was limited.

Due to lack of information, we were unable to assess possible influences of severe newborn disease. However, prematurity did not significantly confound the results, and few infants included in the study were expected to have had the need for mechanical ventilation around birth.

CONCLUSION

The severity of acute bronchiolitis, assessed by length of stay in hospital, the need for supportive treatment and the disease severity at hospital admission were all associated with reduced quality of life nine months later. Infants receiving ventilatory support had the poorest QoL almost a year after the acute disease. Our results suggest that infants with severe acute bronchiolitis, judged by increased LOS or the need for supportive care, should be considered for clinical follow-up investigations and for possible management to prevent long-term health consequences.

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CONFLICTS OF INTERESTS

None of the authors have any conflict of interests to report.

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