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# Long-Term Pulmonary Outcomes in Children Mechanically Ventilated for Severe Bronchiolitis\*

**OBJECTIVES:** Bronchiolitis is a common indication for mechanical ventilation in the PICU. Both bronchiolitis and invasive mechanical ventilation may cause adverse long-term pulmonary outcomes. This study investigates children with a history of invasive mechanical ventilation for bronchiolitis, addressing: 1) the extent, 2) potential explanatory factors, and 3) possible impact on daily life activities of adverse long-term pulmonary outcomes.

**DESIGN:** Single-center cohort study.

**SETTING:** Outpatient PICU follow-up clinic.

**PATIENTS:** Children 6–12 years old with a history of invasive mechanical ventilation for bronchiolitis (age <2 yr).

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Long-term pulmonary outcomes were assessed by a standardized questionnaire and by spirometry. Nineteen out of 74 included children (26%) had adverse long-term pulmonary outcomes, of whom the majority had asthma (14/74, 19%). By logistic regression analysis, we assessed whether background characteristics and PICU-related variables were associated with long-term pulmonary outcomes. In general, we failed to identify any explanatory factors associated with adverse long-term pulmonary outcomes. Nonetheless, atopic disease in family and longer duration of invasive mechanical ventilation (days) were associated with greater odds of having asthma at follow-up (odds ratio, 6.4 [95% CI, 1.2–36.0] and 1.3 [95% CI, 1.0–1.7], respectively). Adverse pulmonary outcome at follow-up was associated with more frequent use of pulmonary medication after PICU discharge. In comparison with those without adverse pulmonary outcomes, we did not identify any difference in frequency of sports performance or school absenteeism.

**CONCLUSIONS:** In this single-center cohort, one-quarter of the children attending follow-up with a history of invasive mechanical ventilation for bronchiolitis had adverse, mostly previously undetected, long-term pulmonary outcomes at 6–12 years. Atopic disease in family and longer duration of invasive mechanical ventilation were associated with presence of asthma. The presence of adverse pulmonary outcomes was associated with more frequent use of pulmonary medication after PICU discharge.

**KEY WORDS:** artificial; asthma; bronchiolitis; child; lung; respiration; respiratory function tests; respiratory syncytial viruses; respiratory tract infections

Acute viral bronchiolitis, most commonly caused by respiratory syncytial virus (RSV), is a common cause of hospital admission in infants (1, 2). Up to 5% of such infants who are hospitalized receive respiratory support by invasive mechanical ventilation in the PICU (3, 4). Several studies show that bronchiolitis is associated with long-term complications such as recurrent wheeze, asthma, and impaired lung function (5–9). Since hospitalized infants have a higher risk of childhood asthma and impaired lung function compared with

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## RESEARCH IN CONTEXT

- Bronchiolitis is associated with long-term complications such as recurrent wheeze, asthma, and impaired lung function, with hospitalized infants with bronchiolitis having a higher risk compared with nonhospitalized infants.
- Little is known about such long-term outcomes in infants with severe bronchiolitis receiving invasive mechanical ventilation. Mechanical ventilation, although lifesaving, may also have deleterious pulmonary effects.
- In this study, one-quarter of children with a history of invasive mechanical ventilation for bronchiolitis have adverse long-term pulmonary outcomes. Results suggest that atopic disease in family and/or longer duration of invasive mechanical ventilation are associated with presence of asthma.

nonhospitalized infants, it is possible that these adverse pulmonary outcomes are associated with bronchiolitis disease severity (5, 6). However, little is known about such long-term outcomes in infants with severe bronchiolitis admitted to the PICU for invasive mechanical ventilation. Mechanical ventilation, although lifesaving, can have deleterious effects, such as ventilator-induced lung injury, which may lead to irreversible structural and functional changes on the long term (10, 11).

The primary aim of this study was to investigate the extent of adverse long-term pulmonary outcomes in children with a history of invasive mechanical ventilation for bronchiolitis. In addition, we aimed to assess whether background characteristics and PICU-related variables were associated with greater odds of adverse long-term pulmonary outcomes within this study group and to study the possible impact of adverse long-term pulmonary outcomes on daily life functioning (i.e., sports performance, number of schooldays missed due to respiratory complaints, and medication use after PICU discharge).

## MATERIALS AND METHODS

### Ethics Statement

The medical research ethics committee of the Amsterdam University Medical Centers (UMC)

approved the study (reference number W19\_072#19.110). The work was executed according to Good Clinical Practice guidelines. We included children between 6-12 years. Children 12 years old and parents of younger children provided informed consent for participation.

### Participants

Study participants received structured outpatient follow-up after discharge from our PICU as part of routine care of the Emma Children's Hospital Amsterdam UMC Follow-Me program. For this study, we included children admitted to the PICU of the Emma Children's Hospital, Amsterdam UMC (a tertiary referral center) between 2007 and 2013. All assessments were performed at the Emma Children's Hospital, Amsterdam UMC between March and December 2019. Inclusion criteria were: 1) PICU admission younger than 2 years old for respiratory insufficiency due to severe bronchiolitis, 2) treatment with invasive mechanical ventilation during PICU admission, and 3) age at follow-up 6–12 years. Exclusion criteria were: 1) bronchopulmonary dysplasia and 2) developmental disorders and/or physical conditions interfering with the ability to adequately perform lung function assessment (e.g., Down syndrome).

### Measures

**Long-Term Pulmonary Outcomes.** Long-term pulmonary outcomes were based on pulmonary symptoms and lung function. All children were screened by one of the authors (E.S.V.d.S.). Pulmonary symptoms at follow-up were evaluated by history taking, physical examination, and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (12). This validated questionnaire provides information on wheezing in the past (i.e., wheezing or whistling in the chest in the past), current wheeze (i.e., wheezing or whistling in the chest in the last 12 mo), causes of current wheeze, severity of current wheeze (e.g., frequency and difficulty breathing), coughing, and rhinitis symptoms.

Lung function was assessed by spirometry before and after administration of short-acting- $\beta$ 2-agonist with a calibrated spirometer (Vyntus SPIRO; Vyaire Medical, Mettawa, IL). Spirometry measurements were performed according to the guidelines of the American Thoracic Society and the European

Respiratory Society (13). The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximal mid-expiratory flow at 25–75% of FVC (75/25), and the Tiffeneau index (FEV1/FVC) were selected as outcome measures and transformed into  $z$  scores according to the Global Lung Function Initiative standards (14). All children using  $\beta$ 2-agonist medications were instructed to withhold the medications before lung function assessment (>12 hr for short-acting- and > 36 hr for long-acting- $\beta$ 2-agonist) to allow complete washout (13). If the child suffered from a respiratory tract infection in the week before lung function was tested, testing was postponed to at least 1 week after all complaints had disappeared.

Children were referred to a pediatric pulmonologist for further evaluation in the case of current wheeze (as assessed by the ISAAC questionnaire) and/or obstructive lung function (15). The pediatric pulmonologist repeated history taking, physical examination, and spirometry. Children were consecutively diagnosed with: 1) no adverse pulmonary outcomes, 2) asthma, or 3) obstructive lung pathology other than asthma. “No adverse pulmonary outcomes” was defined as no current wheeze and normal lung function either at screening or if any abnormalities assessed at the initial screening could not be confirmed by the pulmonologist (14, 15). “Asthma” was defined according to the Global Initiative for Asthma (15). “Obstructive lung pathology other than asthma” was defined as obstructive lung function that did not meet the criteria for asthma (14, 15).

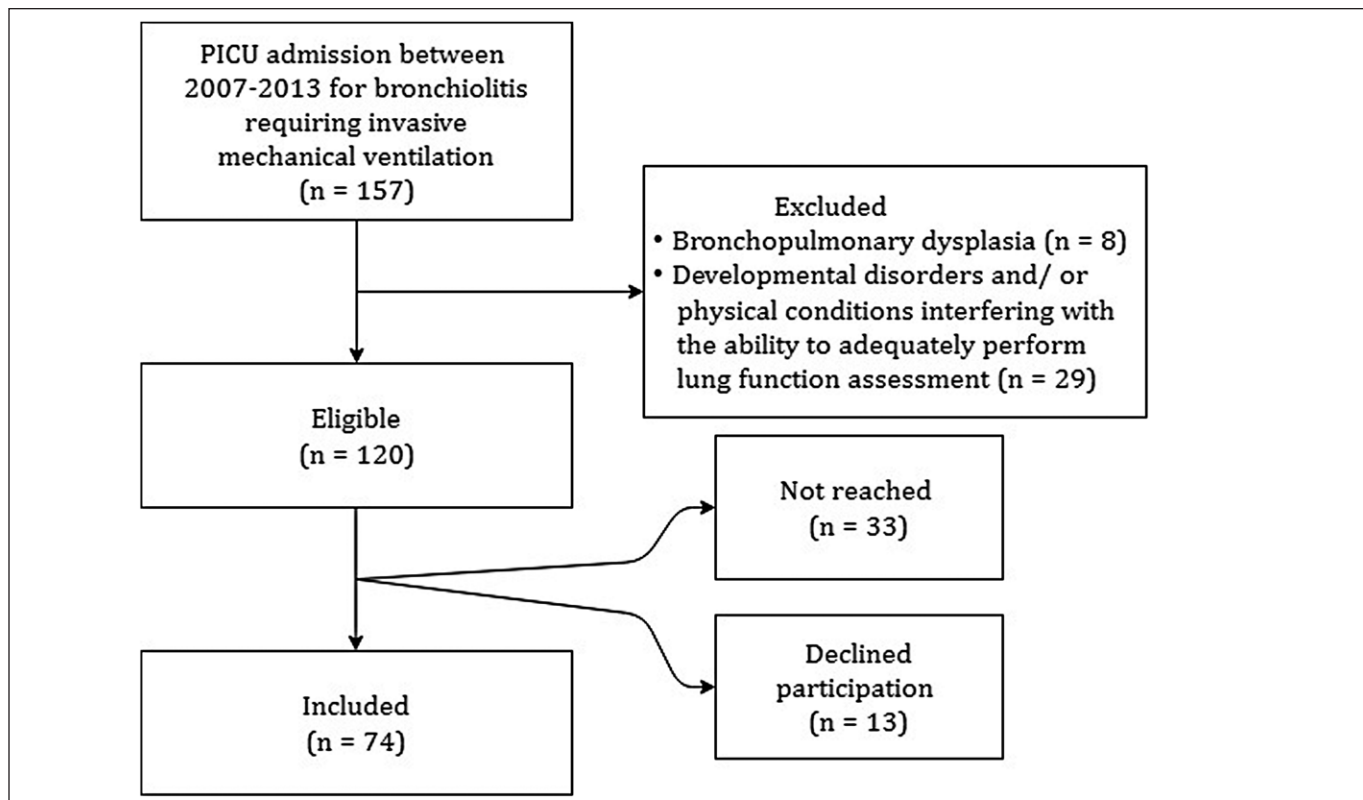
**Risk Factors.** We collected data on known risk factors for asthma using a structured questionnaire and by extraction from the patient medical file. Risk factors that were analyzed included sex, socioeconomic status, gestational age (wk), ethnicity, inhalant allergies (yes/no), daycare attendance in past (yes/no), breastfed in past (yes/no), atopic disease in family (yes/no), and tobacco smoke exposure (yes/no) (16–20). Socioeconomic status was defined as the average level of parental education and was divided in the following eight categories: 1) no education; 2) education to toddlers; 3) primary school, special education; 4) high school, first phase; 5) high school, second phase; 6) bachelor’s degree; 7) master’s degree; and 8) postdoctoral education (21). Atopic disease in the family was defined as asthma, hay fever, and/or eczema in parent(s) and/or sibling(s).

In addition, we extracted the following PICU-related variables associated with disease severity

from the medical files: age at PICU admission (mo), Pediatric Index of Mortality 2 score (22), duration of mechanical ventilation (hr), PICU admission duration (hr), need for reintubation (yes/no), cardiopulmonary resuscitation (yes/no), use of antibiotics during PICU stay (yes/no), readmission to the PICU (yes/no), and the isolation of viral agents from the nasopharyngeal aspirate. Furthermore, we extracted the hourly recorded validated values of the following variables related to mechanical ventilation and calculated the means:  $FiO_2$ ,  $SpO_2$ , end-tidal carbon dioxide, positive inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), mean airway pressure, and  $SpO_2/FiO_2$  ratio.

**Possible Impact of Adverse Pulmonary Outcomes on Daily Life.** Sports performance greater than or equal to  $1\times/wk$  (yes/no) and number of school days missed in last 12 months due to respiratory complaints were evaluated by the ISAAC questionnaire. Furthermore, medication use after discharge from the PICU was collected by electronic patient data from the hospital and local pharmacy, covering hospital, urgency, and primary-care prescriptions. We evaluated the number of antibiotic treatments, use of inhaled short-acting- $\beta$ 2-agonists, and inhaled corticosteroids after PICU discharge and during the last 12 months before our follow-up (yes/no).

**Statistical Analysis.** Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM, Armonk, NY). Missing values (breastfed in past and daycare attendance in past: 2.7%) were imputed using multiple imputation. After analysis of the adverse long-term pulmonary outcomes (i.e., asthma or obstructive lung pathology other than asthma), we explored possible risk factors. First, we performed multivariable binary logistic regression analysis with the adverse pulmonary outcomes (vs no adverse pulmonary outcomes) as dependent variable. Second, we performed multivariable binary logistic regression analysis with asthma (vs no asthma) as dependent variable. Background characteristics and PICU-related variables with at least 10 occurrences per event were entered as independent variables. By backward elimination, independent variables were excluded from the final model in the case of  $p$  value greater than 0.10. At last, we assessed the possible impact of adverse pulmonary outcomes on daily life functioning by comparison of children with and without adverse pulmonary outcomes on their sports performance, the number of school days missed due to



**Figure 1.** Flowchart of participants.

respiratory complaints, and medication use after PICU discharge, using independent *t* tests, chi-square tests, or Mann-Whitney *U* tests, where appropriate. To correct for multiple testing, correction for false discovery rate was applied. All statistical testing was two-sided, and  $\alpha$  was set at 0.05.

## RESULTS

### Participants

**Figure 1** shows the inclusion of children in this study. Of the 120 children admitted to our PICU between 2007 and 2013 that were eligible for inclusion, 33 were not reached and 13 declined participation. Reasons for declining participation were either “not interested” ( $n = 6$ ) or “no time” ( $n = 7$ ). The final cohort of 74 children (61.7% of eligible children) did not differ from the total cohort of eligible children ( $n = 120$ ) with respect to sex, age at PICU admission, duration of invasive mechanical ventilation, and PICU admission duration ( $p \geq 0.12$ ). **Table 1** shows the characteristics of the included children regarding background characteristics and PICU-related variables.

### Long-Term Pulmonary Outcomes

Forty out of 74 children (54%) had wheezing in the past, and 14 of 74 (19%) had current wheeze. In six of 74 children (8%), there was already a diagnosis of asthma, and these children used inhaled corticosteroids and short-acting- $\beta$ 2-agonists (on an as needed basis) at the time of follow-up. Lung function test results of these six children were requested from the local pediatrician, and in all cases, the diagnosis of asthma was confirmed by our pediatric pulmonologist. Except for lung function assessment during our follow-up, these six children underwent the same study procedures as the other included children. The lung function test results obtained at screening of the remaining 68 children are displayed in **e-Table 1** (<http://links.lww.com/PCC/C131>). Based on the screening, 21 of 68 children (31%) had current wheeze and/or obstructive lung function, and were referred to the pediatric pulmonologist for further evaluation. Eight of these 21 referred children (38%) were diagnosed with asthma, and five of 21 children (24%) were diagnosed with obstructive lung pathology other than asthma. In the remaining eight of 21 children, the pediatric pulmonologist could not



**TABLE 1.**  
**Background Characteristics and PICU-Related Variables**

Background Characteristics and PICU-Related Variables	All Included Children ( <i>n</i> = 74)
Sex (boys), <i>n</i> (%)	43 (58)
Age at follow-up (yr), mean (SD)	9.2 (1.7)
Socioeconomic status, mean (SD)	5.3 (1.3)
Gestational age (wk), mean (SD)	37.7 (2.9)
Inhalant allergy, <i>n</i> (%)	6 (8)
Daycare attendance in past, <i>n</i> (%)	66 (89)
Breastfed in past, <i>n</i> (%)	42 (57)
Atopic disease in family, <i>n</i> (%)	48 (65)
Asthma in family	19 (26)
Hay fever in family	39 (53)
Eczema in family	27 (36)
Smoking mother during pregnancy, <i>n</i> (%)	7 (9)
Smoking parents now/past since birth of child, <i>n</i> (%)	22 (30)
Smoking near child now/past, <i>n</i> (%)	7 (9)
Age at PICU admission (mo), median (IQR)	1.4 (0.8–2.4)
Pediatric Index of Mortality 2 score, median (IQR)	1.5 (1.0–2.1)
Cardiopulmonary resuscitation, <i>n</i> (%)	1 (1)
Invasive mechanical ventilation during first PICU stay (hr), mean (SD)	153.0 (64.3)
Invasive mechanical ventilation during all PICU admissions (hr), mean (SD)	158.0 (73.9)
Noninvasive mechanical ventilation in addition to invasive mechanical ventilation, <i>n</i> (%) <sup>a</sup>	2 (3)
Need for reintubation, <i>n</i> (%)	3 (4)
Admission duration of first PICU stay (hr), mean (SD)	176.6 (65.1)
Admission duration during all PICU admissions (hr), mean (SD)	185.8 (83.3)
Readmission at PICU, <i>n</i> (%) <sup>b</sup>	8 (11)
Respiratory syncytial virus, <i>n</i> (%) <sup>c</sup>	66 (89)
Two or more viral agents, <i>n</i> (%)	9 (12)
Antibiotics during PICU stay, <i>n</i> (%)	63 (85)
FiO <sub>2</sub> (%), mean (SD)	44 (9)
SPO <sub>2</sub> (%), mean (SD)	97 (1)
End-tidal carbon dioxide (kPa), mean (SD)	5.2 (0.5)
Positive inspiratory pressure (cm H <sub>2</sub> O), mean (SD)	22 (3)
Positive end-expiratory pressure (cm H <sub>2</sub> O), mean (SD)	5 (1)
Mean airway pressure (cm H <sub>2</sub> O), mean (SD)	17 (2)
SPO <sub>2</sub> /FiO <sub>2</sub> ratio, mean (SD)	2.4 (0.5)

IQR = interquartile range.

<sup>a</sup>Synchronized intermittent mandatory ventilation via full-face mask.

<sup>b</sup> Of the children who were readmitted in the PICU (*n* = 8), two children were readmitted due to viral lower respiratory tract infections, and six children were readmitted because of subglottic stenosis due to upper airway injury by endotracheal intubation.

<sup>c</sup>Viral agents = respiratory syncytial virus, *n* = 66 (89.2%); rhinovirus, *n* = 6 (8.1%); influenza A virus, *n* = 2 (2.7%); coronavirus, *n* = 2 (2.7%); human metapneumovirus, *n* = 1 (1.4%); human Bocavirus, *n* = 2 (2.7%).

confirm the pulmonary abnormalities assessed at the screening; they had no (or transient) current wheeze, and lung function was normal. Of the 13 children with adverse long-term pulmonary outcomes who were diagnosed during our follow-up, five of 13 children (38%) had both current wheeze and obstructive lung function, and eight of 13 children (62%) only had obstructive lung function. **Figure 2** displays the final diagnoses as assessed by the pediatric pulmonologist. A total of 19 of 74 children (26%) had adverse long-term pulmonary outcomes, comprising 14 of 74 children (19%) with asthma and five of 74 children (7%) with obstructive lung pathology other than asthma. The remaining 55 of 74 children (74%) had no adverse pulmonary outcomes.

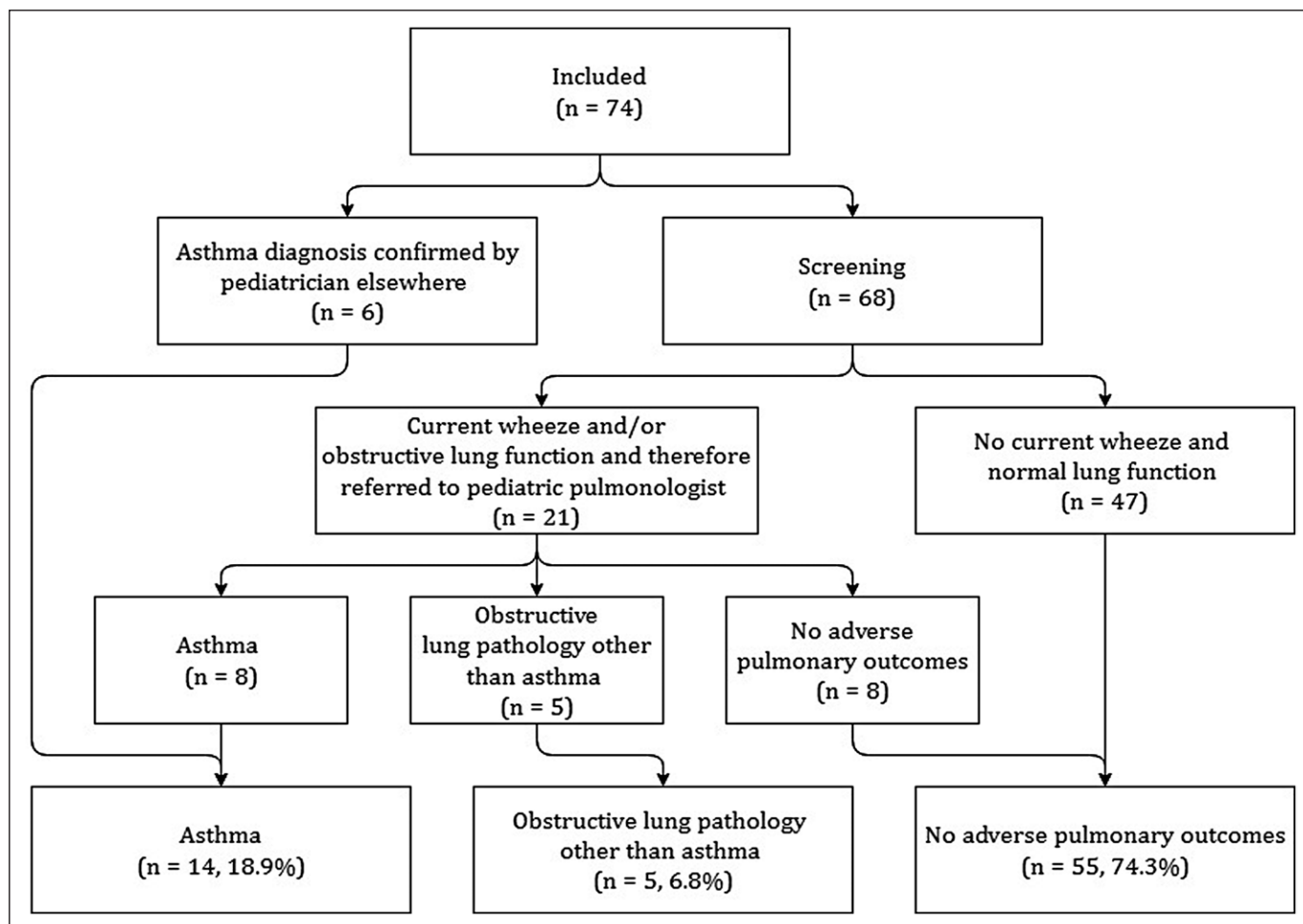
### Risk Factors

In order to identify potential explanatory risk factors associated with adverse long-term pulmonary

outcomes, we conducted multivariable binary logistic regression analysis. We failed to identify an association between increased duration of invasive mechanical ventilation and odds of developing adverse long-term pulmonary outcomes at follow-up (**Table 2**). In a secondary exploratory analysis, focusing on the diagnosis asthma alone, our data suggest that the presence of atopic disease in family and longer duration of invasive mechanical ventilation are associated with greater odds of having asthma at the time of follow-up (odds ratio, 6.4 [95% CI, 1.2–36.0];  $p = 0.03$  and 1.3 [95% CI, 1.0–1.7];  $p = 0.04$ , respectively).

### Potential Impact of Adverse Pulmonary Outcomes on Daily Life Functioning

In order to assess the possible impact of adverse pulmonary outcomes on daily life functioning, we compared children with and without adverse pulmonary outcomes by their sports performance, the number



**Figure 2.** Flowchart of children with and without adverse pulmonary outcomes.

**TABLE 2.**  
**Risk Factors for Adverse Long-Term Pulmonary Outcomes in General and for Asthma**

Explanatory Factors	OR (95% CI)	<i>p</i>	Nagelkerke <i>R</i> <sup>2</sup> (%)
Adverse pulmonary outcomes as outcome variable			
Duration of invasive mechanical ventilation (d)	1.2 (1.0–1.4)	0.10	5.5
Asthma as outcome variable			
Atopic disease in family	6.4 (1.2–36.0)	<b>0.03</b>	20.9
Duration of invasive mechanical ventilation (d)	1.3 (1.0–1.7)	<b>0.04</b>	

OR = odds ratio.

Socioeconomic status was captured as nonsignificant predictor in the model. Predictor variables eliminated due to multicollinearity: invasive mechanical ventilation during all PICU admissions, admission duration of first PICU stay, admission duration during all PICU admissions, and mean  $F_{iO_2}$ .

Boldface values indicate  $p < 0.05$ .

of school days missed due to respiratory complaints, and medication use after discharge from the PICU (Table 3). We failed to identify an association between presence of adverse pulmonary outcomes (vs not) and sports performance. There were associations found in regard to the following variables: missed 1 day school in the last 12 months due to respiratory complaints, increased number of antibiotic treatments after PICU discharge, and more often use of inhaled

short-acting- $\beta$ 2-agonists and corticosteroids in the period after PICU discharge and 1 year before follow-up.

## DISCUSSION

In this single-center follow-up study, we found that one-quarter of the children with a history of invasive mechanical ventilation for bronchiolitis during infancy have adverse long-term pulmonary outcomes at 6–12

**TABLE 3.**  
**Comparison of Possible Consequences for Daily Life in Children With and Without Adverse Pulmonary Outcomes at Follow-Up**

Possible Consequences for Daily Life	Adverse Pulmonary Outcome ( <i>n</i> = 19)	No Adverse Pulmonary Outcome ( <i>n</i> = 55)	<i>p</i>	<i>p</i> After Correction for False Discovery Rate
Sports performance ( $\geq 1 \times/wk$ ), <i>n</i> (%)	17 (89)	48 (87)	0.80	0.80
Number of school days missed in last 12 mo due to respiratory complaints, median (IQR)	1.0 (0.0–5.0)	0.0 (0.0–0.0)	<b>&lt; 0.001</b>	<b>0.002</b>
Number of antibiotic treatments after PICU discharge, median (IQR)	4.0 (2.0–9.0)	1.0 (0.0–4.0)	<b>0.001</b>	<b>0.002</b>
Inhaled short-acting- $\beta$ 2-agonists used after PICU discharge, <i>n</i> (%)	18 (95)	31 (56)	<b>0.002</b>	<b>0.004</b>
Inhaled short-acting- $\beta$ 2-agonists used last 12 mo before follow-up, <i>n</i> (%)	11 (58)	4 (7)	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
Inhaled corticosteroids used after PICU discharge, <i>n</i> (%)	14 (74)	18 (33)	<b>0.010</b>	<b>0.012</b>
Inhaled corticosteroids used last 12 mo before follow-up, <i>n</i> (%)	5 (26)	2 (4)	<b>0.004</b>	<b>0.006</b>

IQR = interquartile range.

Pulmonary sequelae = asthma ( $n = 14$ ) and obstructive lung pathology other than asthma ( $n = 5$ ). Sports performance could be any kind of sport, such as swimming, football, ballet, or horseback riding.

Boldface values indicate  $p < 0.05$ .



## AT THE BEDSIDE

- One-quarter of children with a history of invasive mechanical ventilation for bronchiolitis have adverse long-term pulmonary outcomes, with asthma as most frequent diagnosis. In the majority of the children, these adverse pulmonary outcomes had previously gone undetected.
- Presence of atopic disease in family and/or longer duration of invasive mechanical ventilation are associated with the presence of asthma.
- These findings underline the importance of long-term follow-up of children mechanically ventilated for bronchiolitis, enabling early identification and appropriate management of adverse outcomes.

years old. The most frequent diagnosis in these children with morbidity was asthma, and in the majority of the children, these adverse pulmonary outcomes had gone previously undetected. Our exploratory analyses suggest that the presence of atopic disease in family and/or longer duration of invasive mechanical ventilation are associated with the presence of asthma at follow-up. Furthermore, there was an association between more frequent use of pulmonary medication after PICU discharge and presence of adverse pulmonary outcomes at follow-up.

Our findings are consistent with the results of other studies describing long-term pulmonary outcomes at 6–12 year follow-up after pediatric admission—without requiring invasive mechanical ventilation—during infancy for bronchiolitis (6, 23, 24). However, a direct comparison between these studies and our results is hampered by the different definitions of long-term pulmonary outcomes used. As a consequence, based on our results, we cannot conclude whether the proportion of children with adverse long-term pulmonary outcomes differs between children with and without a history of invasive mechanical ventilation for bronchiolitis. Close to one-fifth of our children were diagnosed with asthma, which demonstrates that the proportion of children with asthma is higher in children with a history of invasive mechanical ventilation

for bronchiolitis than that in the general pediatric population, being estimated at 8% (25). We found that a small number of five children had obstructive lung pathology other than asthma. These children had an obstructive pattern on lung function without significant (>12%) improvement of FEV1 after salbutamol, and none of these children experienced current wheeze. None of these children suffered from subglottic stenosis due to upper airway injury by endotracheal intubation. Most likely, they experience mild, transient obstructive lung function that will improve over time, but this should be evaluated during further follow-up. Another, less likely, explanation is that the finding fits with the rare diagnosis postinfectious bronchiolitis obliterans. This is a chronic obstructive pulmonary disease that develops after severe viral lower respiratory tract infections with irreversible injury of the bronchiolar microenvironment most commonly linked to adenovirus (26–28), a virus that none of the five children suffered from.

We also aimed to identify any explanatory variables associated with adverse long-term pulmonary outcomes (i.e., combination of asthma and obstructive lung pathology other than asthma) and for asthma alone. We assessed background characteristics that have been described previously as risk factors for asthma (16–20), PICU-related variables that are associated with disease severity, and mechanical ventilation parameters. We failed to identify any association between these variables and adverse long-term pulmonary outcomes. Nonetheless, the presence of atopic disease in family and longer duration of invasive mechanical ventilation were associated with the presence of asthma at the time of follow-up. In adults, it is well known that higher tidal volume is associated with ventilator-induced lung injury (10, 29). Yet, this association is less well described in children due to small sample sizes, conflicting results between studies and heterogeneous patient populations with respect to age, PICU admission indications, and disease severity (10, 11, 30–33). Studies investigating children with acute hypoxemic respiratory failure or acute respiratory distress syndrome show conflicting results regarding long-term pulmonary outcomes (30–33). Some studies (30, 31) have failed to demonstrate an association with mechanical ventilation, and other studies (32, 33) have shown an association with mechanical ventilation parameters (e.g.,  $FiO_2$  and PIP). Comparison of these



studies with our results is hampered by differences in design and study population. In our study, we are also limited by sample size—and perhaps bias in follow-up—but there may be an indication that duration of invasive mechanical ventilation is associated with subsequent development of asthma, with each 1 day increase in duration of mechanical ventilation associated with 30% greater odds in having asthma.

Another explanation is that infants that will go on to develop asthma are also more at risk of severe bronchiolitis, instead of severe bronchiolitis causing asthma. Yet, the exact association between bronchiolitis and long-term pulmonary outcomes is still not fully understood. A systematic review and meta-analysis (8) did not find support for the assumption that prevention of RSV lower respiratory tract infections reduces recurrent chronic wheezing illnesses, although the authors reported a high risk of bias in the included studies. Host factors such as genetic, pulmonary, cardiac, and immunologic factors seem to be associated with increased susceptibility to develop severe bronchiolitis, recurrent wheeze, and asthma (9, 34, 35). In addition, also the virus itself may induce airway hyperreactivity and chronic airway inflammation contributing to the risk of adverse pulmonary outcomes (34–36). In adults, it is well established that mechanical ventilation may have deleterious pulmonary effects (29, 37), and thus, mechanical ventilation may have contributed to our observation of asthma-like symptoms later in life in our cohort of children with severe bronchiolitis. Unfortunately, our study does not allow us to make statements regarding the causative role of either bronchiolitis or mechanical ventilation on the long-term deleterious effects, and the exact association between bronchiolitis and adverse long-term pulmonary outcomes remains to be determined.

Regarding the possible impact of adverse pulmonary outcomes on daily life, we found that children with adverse pulmonary outcomes had missed, on average, 1 day of school in the last 12 months due to respiratory complaints, whereas the children without adverse pulmonary outcomes had not missed any schooldays. Although statistically significant, this difference was too small to be clinically relevant. Although the majority of children performed sports and hardly any missed any school days due to respiratory complaints; it is possible that children with adverse pulmonary outcomes

may be unaware that their performance could improve with optimal treatment. As expected, children with adverse pulmonary outcomes more often received antibiotic treatments, inhaled short-acting- $\beta$ 2-agonists, and corticosteroids in the period between PICU discharge and follow-up compared with the children without adverse pulmonary outcomes. Interestingly, a proportion of the children without adverse pulmonary outcomes was also treated with inhaled short-acting- $\beta$ 2-agonists and corticosteroids after PICU discharge. Almost half of these children had wheezing in the past, which appears higher than the general European population of children 0–12 year old (estimated between 4% and 25%) (38).

In the current study, 8% of the children had a previous diagnosis of asthma, and an additional 18% of the children were diagnosed as having adverse long-term pulmonary outcomes during our follow-up for which we started treatment. This finding highlights the importance of structured pulmonary follow-up of children mechanically ventilated for bronchiolitis. All children with adverse pulmonary outcomes had obstructive lung function, and only five of the children who were diagnosed during our follow-up also had current wheeze. As a questionnaire alone is insufficient to detect adverse pulmonary outcomes, we consider that there is also a need for assessing lung function by spirometry. In eight out of 21 children who were referred to a pediatric pulmonologist, the pulmonary abnormalities assessed at the screening could not be confirmed; they had no (or experienced transient) current wheeze, and lung function results were normal. This observation not only highlights the importance of follow-up but also the value of reevaluation of symptoms and lung function in children. Furthermore, as it is unclear whether adverse pulmonary outcomes change later in life, we also wonder about using ongoing pulmonary follow-up at older ages, even into adulthood.

A limitation of our study is that some 40% of eligible children were not included in our analysis, mainly because they could not be reached despite our efforts. However, we deem it unlikely that this has caused important selection bias because the children included in the final analysis did not differ from the total cohort of eligible children in terms of patient and disease characteristics. Another limitation is that we did not include a control group of children hospitalized

for bronchiolitis without mechanical ventilation. Furthermore, this study has modest sample size and limited statistical power (39). Consequently, we consider the reported findings as exploratory, awaiting replication in larger future studies that allow for more robust estimation. Finally, we acknowledge that the reported associations between risk factors and outcome may not reflect causal relationships (40). At the same time, robustly identified predictive risk factors can be useful for more targeted clinical follow-up, also in the absence of causal grounds for the relation between predictor and outcome. A strength of our study is the thorough evaluation of all children by first screening consisting of a standardized parental questionnaire, history taking, physical examination and spirometry, and, if necessary, evaluation by a pediatric pulmonologist.

## CONCLUSIONS

In this single-center study, one-quarter of children with a history of invasive mechanical ventilation for bronchiolitis during infancy, subsequently seen in our outpatient PICU follow-up clinic, had adverse long-term pulmonary outcomes at 6–12 years old. The diagnosis of asthma was most frequent, occurring in one-fifth of the children, and in the majority of the children, these adverse pulmonary outcomes had gone previously undetected. The presence of atopic disease in family and longer duration of invasive mechanical ventilation were associated with the presence of asthma. Furthermore, adverse pulmonary outcome was associated with more frequent administration of pulmonary medication after PICU discharge. Taken together, these findings underline the prevalence and importance of long-term pulmonary morbidity after PICU discharge. Long-term structured follow-up of children mechanically ventilated for bronchiolitis is necessary, enabling early identification and appropriate management of adverse outcomes.

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