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From mortality to morbidity

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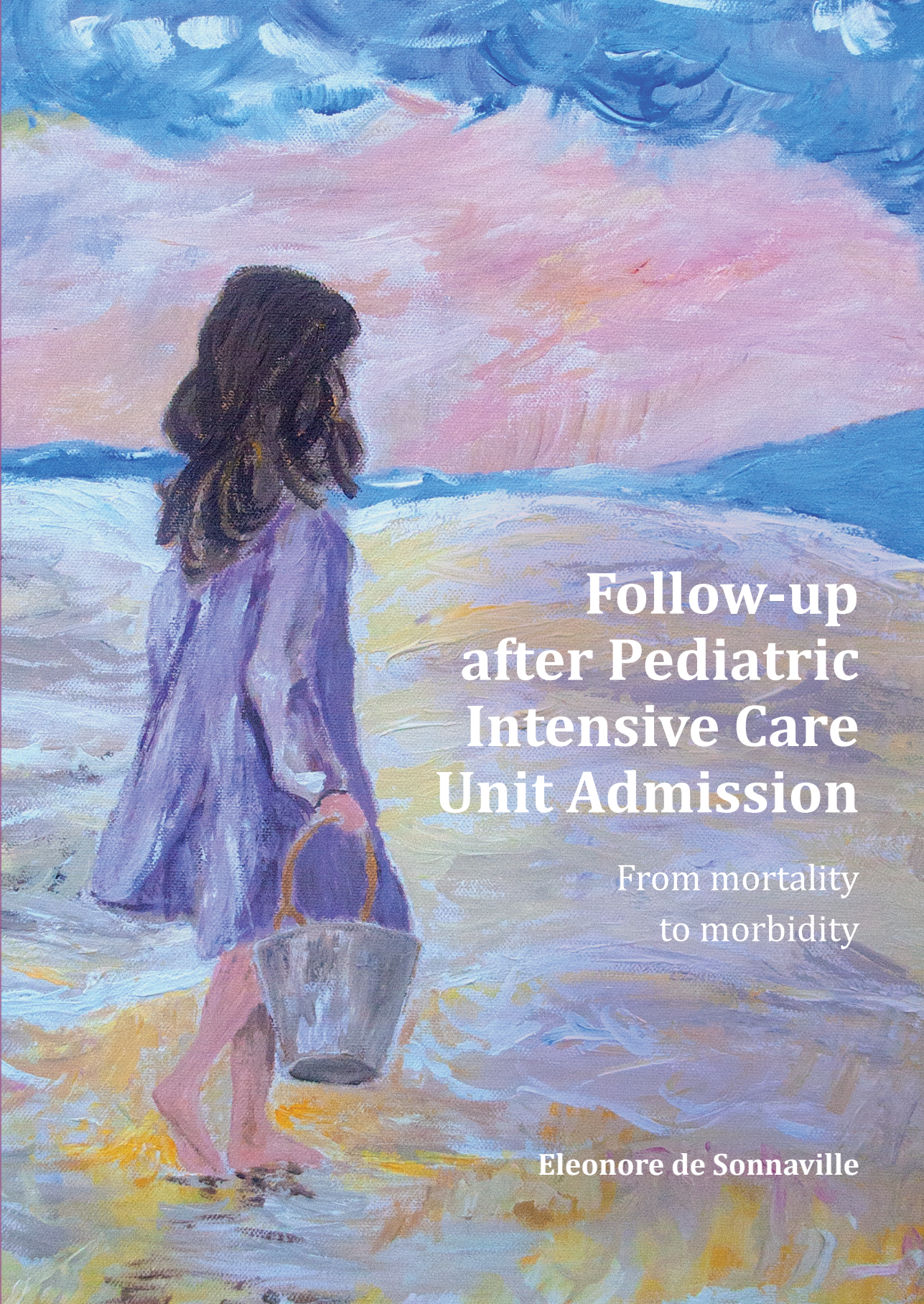

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Eleonore de Sonnaville

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Follow-up after Pediatric Intensive Care Unit Admission
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1 General introduction and outline of this thesis

BACKGROUND AND MAIN OBJECTIVES

Pediatric critical care medicine, a subspecialty of pediatrics and of critical care medicine, represents a small, though vital, component of health care that focuses on vital system surveillance and support for infants, children and adolescents with potential or existing life-threatening illnesses or injuries [1]. Pediatric critical care is usually conducted at the pediatric intensive care unit (PICU), introduced in 1955 in Europe and in 1967 in North America [1]. Specific disorders and developments in neonatology, pediatric general and cardiac surgery, and pediatric cardiology created a growing need for pediatric critical care services [1,2]. In the 1980s, pediatric critical care medicine became a defined, recognized subspecialty [1,2]. Guidelines for organizing, staffing and equipping a PICU were developed, and certification provided clear guidelines for hospital credentialing of pediatric critical care medicine physicians [1-3]. In the 1980s, also the first PICUs in the Netherlands were developed. During the past decades, PICUs have evolved greatly, including e.g. multidisciplinary staffs, full-time critical care and consulting physicians, skilled nursing care and advanced technologies [1,2,4,5]. Currently, approximately 4,500 children are each year admitted to a PICU in the Netherlands [6].

Main reasons for PICU admission include respiratory failure, cardiovascular failure, neurologic disease, metabolic and infectious disorders, trauma and postoperative care [2,4,7,8]. Some diseases are nowadays rarely seen at the PICU, such as epiglottitis due to *Haemophilus influenzae* type b immunization. In contrast, due to improvements in intensive care and advances in pediatric surgery, intensive care is now also offered to some children with complex and chronic diseases who would not have been admitted in the past, and some critically ill children who would previously have died survive [1,2,4,5].

Although the survival rate of children admitted to the PICU has substantially increased during the past decades [4,5], long-term morbidity after PICU admission is a growing concern [9-15]. The underlying disease, critical illness and/or associated treatments at the PICU may impact children's long-term outcomes. An increasing number of studies document adverse outcomes after PICU admission regarding physical, neurocognitive and psychosocial functioning, such as post-thrombotic syndrome, intelligence impairment and post-traumatic stress syndrome [9-15]. Current literature on outcomes after PICU admission is fragmented, mainly comprising small-sized cross-sectional studies often focusing on a specific patient group and/or a limited set of outcomes [15]. Insight into the long-term outcomes after PICU admission is hampered by the distinct heterogeneity of the PICU population and by the potential consequences in a wide range of outcome domains. As a consequence, the long-term prognosis after PICU admission is uncertain, in turn challenging clinical follow-up.

In order to provide targeted clinical follow-up of patients, and to prevent adverse outcomes after PICU admission, it is vital to determine the extent of and identify the

risk factors for poor outcomes of PICU survivors. The current thesis targets two areas of functioning that are of particular importance in PICU survivors: pulmonary and neurocognitive functioning. Respiratory illnesses are the most common reasons for PICU admission [8], but long-term pulmonary outcomes after PICU admission are currently largely unknown, while adverse pulmonary outcomes may have substantial influence on children's daily life. Neurocognitive functioning is associated with important life outcomes [16-19], highlighting neurocognition as an important outcome after PICU admission. However, the extent of and possible risk factors for adverse neurocognitive outcomes after PICU admission remain largely unknown. Furthermore, we describe the process of implementing a structured multidisciplinary follow-up program with the ultimate aim of implementing a cycle of care innovation.

The main objectives of this thesis are to: (1) increase insight into the long-term pulmonary and neurocognitive outcomes of patients after PICU admission; (2) investigate risk factors for adverse pulmonary and neurocognitive outcomes; and (3) design, implement and evaluate a structured multidisciplinary follow-up program for patients and their parents after PICU admission in the Emma Children's Hospital, Amsterdam University Medical Centers (UMC).

OUTLINE OF THIS THESIS

The described study aims translate into six chapters that compose the current thesis.

Structured multidisciplinary follow-up

Currently, a few descriptions of PICU follow-up programs have emerged in the literature [20-26]. Yet, no standardized structure for follow-up care after PICU admission exists. The few existing programs described in the literature [20-26] vary in terms of the included patients (e.g. focused on patients with neurologic diagnoses), involved health care professionals (e.g. physician only), follow-up moment(s), and/or assessed outcomes. Moreover, most PICU follow-up programs lack structured data collection [20], which is essential for health care evaluation and scientific research on outcome and prognosis of patients after PICU admission. **Chapter 2** describes the design and implementation of a structured multidisciplinary follow-up program for patients and their parents after PICU admission in the Emma Children's Hospital, Amsterdam UMC and shows the first results obtained in patients and their parents to illustrate the significance of our program. The follow-up program has been implemented since March 2018 and provides comprehensive and structured follow-up care, tailored to the child's critical illness and received PICU treatments. Our program integrates clinical care, health care evaluation and scientific research to fuel a cycle of care innovation.

Long-term pulmonary outcomes

Respiratory insufficiency is a common indication for PICU admission [4,11]. One of the causes for respiratory insufficiency is acute viral bronchiolitis, a clinical entity of acute viral-induced lower respiratory tract infection in children younger than two years of age [27]. The burden of acute viral bronchiolitis at the PICU has significantly increased during the last two decades [28,29]. In 2000, the annual percentage of PICU admissions for acute viral bronchiolitis was estimated up to 9% of all children 0–2 years old admitted to a European PICU, while this percentage increased up to 23% in 2019 [29]. Although bronchiolitis-associated mortality has been reduced to a minimum in high-income countries, bronchiolitis is associated with long-term pulmonary complications such as recurrent wheeze, asthma and impaired lung function [30-34]. Since hospitalized infants have a higher risk of childhood asthma and impaired lung function as compared to non-hospitalized infants, it is possible that these adverse pulmonary outcomes are associated with bronchiolitis disease severity [30,31]. In addition, mechanical ventilation, although life-saving, can have deleterious effects, such as ventilator induced lung injury, which may lead to irreversible structural and functional changes on the long-term [35,36]. However, up to our knowledge, no studies exist that investigated the long-term pulmonary outcomes, including formally testing of lung function, in children who have been admitted to the PICU for severe bronchiolitis requiring invasive mechanical ventilation. In addition, it is also important to identify predictive risk factors for adverse long-term pulmonary outcomes in this patient group, as identification of risk factors may be useful for more targeted clinical follow-up and for prevention of adverse outcomes. Therefore, the observational cohort study in **chapter 3** investigated the extent, potential explanatory factors, and possible impact on daily life activities of adverse long-term pulmonary outcomes in children with a history of invasive mechanical ventilation for bronchiolitis.

Long-term neurocognitive outcomes

Adverse long-term neurocognitive outcomes are described in PICU survivors and may be caused by complex interaction between factors related to premorbid functioning [37], underlying disease [38], critical illness [39] and intensive care treatment [40], which influence pathophysiological mechanisms involving (a combination of) hypoxia, metabolic derangements such as glucose dysregulation, ischemia, inflammation, hypotension and delirium [41-43]. Neurocognitive functioning is associated with important life outcomes, such as physical and mental health [16,17], academic achievement [18], socioeconomic success [19], and life chances in general [17], highlighting neurocognition as an important outcome after PICU admission. As understanding of the origin of adverse neurocognitive outcomes after PICU admission is a prerequisite for successful prevention and intervention, it is important to unravel the factors that affect the long-term neurocognitive outcome of children after PICU admission.

Intelligence reflects the ability to efficiently process information for goal-directed behavior. Even a small difference in intelligence can have profound effects on life chances [17]. A previous systematic review [44], including 12 studies of which the majority reported on children admitted for sepsis, identified an increased risk of intelligence impairment among PICU survivors. However, meta-analytic quantification of the magnitude of intelligence impairment was not performed, and the available data did not allow to systematically explore predictive factors of intelligence outcome. For successful prevention and more targeted clinical follow-up, it is of great importance to determine intelligence outcome of PICU survivors and identify risk factors for poor intelligence outcome. Therefore, in **chapter 4** a meta-analysis and meta-regression was conducted to quantify intelligence outcome of PICU survivors, and explore risk factors for poor intelligence outcome.

Sedatives, analgesics and anesthetics are routinely used drugs for critically ill children requiring mechanical ventilation at the PICU. Of these drugs, midazolam and morphine are most commonly used and are frequently combined with other sedatives, analgesics or anesthetics [45-47]. Although long considered to be safe, recent research raises concerns about the potential impact of routinely used drugs on brain development in children [48]. Animal studies have indicated that exposure to sedatives [49-51], analgesics [50] and anesthetics [49-51] may cause neurodegeneration, especially in the rapidly developing brain [49-51], co-occurring with neurocognitive impairments [49,50,52-54]. Consequently, the US Food and Drug Administration issued a warning for the potential negative impact of repeated and/or longer use of sedatives and anesthetics on brain development in young children [48]. This raised concerns about the potential impact of routinely used drugs on neurocognitive outcomes of children admitted to the PICU, especially since adverse neurocognitive outcomes are known to interfere with development in other major domains of functioning, such as physical and mental health [16,17], academic achievement [18], socioeconomic success [19], and life chances [17]. However, literature in children is conflicting [55-65] and is challenged by the unknown contribution of the underlying disease in the observed relations between drug exposure and neurocognitive outcomes [60,61]. Consequently, it remains unclear to what extent the worrying findings on exposure to sedatives, analgesics and anesthetics in animals generalize to children after PICU admission. Therefore, in **chapter 5** a cross-sectional observational study was conducted in which we investigated long-term neurocognitive outcomes after PICU admission and explored the relation of neurocognitive outcomes with exposure to the primary choice of drugs (midazolam and morphine). Secondary analyses also explored relations with exposure to the secondary choice of drugs (lorazepam, fentanyl, esketamine and propofol). We specifically focused on children with previous PICU admission for bronchiolitis, because this is a relative homogenous group with single

organ failure that seldom manifests neurologically [66,67] and is therefore not expected to affect neurocognitive functioning in itself.

Digitalization of health care provides increasingly more data that can importantly contribute to better prediction and understanding of long-term outcome after PICU admission. Nevertheless, the increasing wealth of clinical data produced by medical devices, involves very long time series representing a great number of characteristics, with potential complex inter-relations that are relevant for outcome. Therefore, novel data sources challenge conventional statistical methods such as linear regression, which are not suitable to handle larger numbers of predictors and have limited potential to capture complex relations between predictors and outcome. Compared to conventional statistics, machine learning has great potential to capture this complexity thanks to the capability to process vast amounts of data and model nonlinear and highly complex interactions [68]. Machine learning is a rapidly growing field of artificial intelligence that is increasingly applied in health care settings [69-72]. However, the value of machine learning in investigating the relation between PICU admission and long-term neurocognitive outcome has not been investigated thus far and is therefore currently unclear. The observational cohort study in **chapter 6** aimed to elucidate the potential relevance of patient and PICU-related characteristics for long-term neurocognitive outcome after PICU admission as well as to determine the potential of machine learning to improve outcome prediction.

Currently important aspects of daily life functioning after PICU admission remain largely unknown, such as behavioral and emotional functioning, academic performance and health-related quality of life. Neurocognitive functioning has shown to be crucially implicated in daily life functioning. For example, neurocognitive functioning has been related to behavioral and emotional functioning [73,74], academic achievement [18] and a range of other outcomes impacting quality of life [16,17]. Therefore, adverse neurocognitive functioning may underlie the impact of PICU admission on daily life functioning. Better insight in the determinants of daily life functioning in PICU survivors is crucial for early identification, and if possible, prevention of the adverse effects that PICU admission might exert on daily life functioning. The cross-sectional observational study in **chapter 7** investigated the long-term impact of PICU admission on daily life functioning, while exploring the potential mediating role of neurocognitive outcomes.

This thesis concludes with a summary and a general discussion in **chapter 8** and **chapter 9**, respectively. In these chapters, findings from the above outlined studies are summarized and an elaborate discussion of the meaning of our findings for the outcomes of patients after PICU admission is provided, accompanied by a discussion of the methodological considerations that needs to be taken into account whilst interpreting these findings. Finally, a view on future directions for research on long-term outcomes of PICU survivors and the role of structured multidisciplinary follow-up is presented.

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2 Structured multidisciplinary follow-up after pediatric intensive care: a model for continuous data-driven health care innovation

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ABSTRACT

Objective: Morbidity after PICU admission for critical illness is a growing concern. Sequelae may occur in various domains of functioning and can only appropriately be determined through structured follow-up. Here we describe the process of designing and implementing a structured multidisciplinary follow-up program for patients and their parents after PICU admission and show the first results illustrating the significance of our program.

Design: Prospective observational cohort study.

Setting: Outpatient PICU follow-up clinic.

Patients: Patients aged 0-18 years admitted to our PICU.

Interventions: None.

Measurements and main results: In our structured multidisciplinary follow-up program, follow-up care is provided by a pediatric intensivist and psychologist and in addition, depending on patient's critical illness and received PICU treatment(s), by a pediatric pulmonologist, cardiologist, neurologist and/or neuropsychologist. All consultations are scheduled consecutively. Collected data are stored in a hospital-wide data warehouse, and used for yearly health care evaluation sessions as well as scientific research. Challenges in organizing this follow-up program include technological challenges, providing time-efficient care, participation rate, and completeness of questionnaires. In our experience, a dedicated team is essential to tackle these challenges. Our first results, obtained in 307 of 388 referred patients (79.1%), showed the diversity of problems arising after PICU discharge, including physical, neurocognitive and psychosocial sequelae. In addition, our data also reflected the risk of psychosocial problems among parents. Within the limited operation time of our follow-up program, the program has evolved based on our experiences and the data collected.

Conclusions: We successfully developed and implemented a structured multidisciplinary follow-up program for patients and their parents after PICU admission. This program may help to timely initiate appropriate interventions, improve the standard of care during and after PICU admission and facilitate scientific research on outcome and prognosis after PICU admission.

INTRODUCTION

With advances in pediatric intensive care, the mortality of children admitted to the pediatric intensive care unit (PICU) has decreased dramatically during the past decades [1,2]. As a consequence, morbidity after PICU admission is a growing concern, recently acknowledged as the pediatric post-intensive care syndrome [3-7]. Sequelae are described in physical, neurocognitive and psychosocial functioning [3-7] and vary between and within the heterogeneous patient groups that are admitted to the PICU [3]. In addition, admission of a child to the PICU is a major life event for the child's family and may impact family functioning, acknowledged as the post-intensive care syndrome-family [8,9].

Current literature on sequelae after PICU admission is fragmented, mainly comprising small-sized cross-sectional studies often focusing on a specific patient group and/or a limited set of outcomes [10]. Given the distinct heterogeneity of the PICU population and potential consequences in a wide range of outcome domains, the prognosis after PICU admission is uncertain, in turn challenging clinical follow-up. Currently, a few descriptions of PICU follow-up programs have emerged in the literature [11-17]. To our knowledge, no standardized structure for follow-up care after PICU admission exists. The few existing programs described in the literature vary in terms of the included patients (e.g. focused on patients with neurologic diagnoses), involved health care professionals (e.g. physician only), follow-up moment(s), and/or assessed outcomes. Moreover, most PICU follow-up programs lack structured data collection [11], which is essential for health care evaluation and scientific research on outcome and prognosis of patients after PICU admission.

In order to gain more insight in the presence or absence of sequelae in the various domains of functioning in different patient groups and to improve outcomes of patients after PICU admission, we propose that there is a need of structured multidisciplinary follow-up for patients and their parents after PICU admission. Structured follow-up and collection of outcome data within a multidisciplinary follow-up program, can importantly contribute (1) to improve outcomes of individual patients by facilitating timely support and appropriate intervention, if required; (2) to improve the standard of care during and after PICU admission by providing insight in extent and severity of sequelae; and (3) to facilitate scientific research on outcome and prognosis of patients after PICU admission. The objective of this article is to describe the design and implementation of a structured multidisciplinary follow-up program for patients and their parents after PICU admission in our hospital and to show the first results obtained in patients and their parents to illustrate the significance of our program. Our program integrates clinical care, health care evaluation and scientific research to fuel a cycle of care innovation.

METHODS

Setting and patients

Our multidisciplinary follow-up program is provided to patients aged 0 to 18 years admitted to the PICU of the Emma Children's Hospital of the Amsterdam University Medical Centers (UMC), the Netherlands, a tertiary 14-bed PICU, serving the greater Amsterdam area. Detailed information on the inclusion and exclusion criteria for follow-up care is provided in Table 1. Most patients referred to the program are previously healthy children with unplanned PICU admission (> 24 hours), not receiving similar follow-up elsewhere. The PICU follow-up program is part of hospital's follow-up program (Follow Me program) that aims to offer high quality, evidence-based, multidisciplinary follow-up to all level three pediatric patients, improve the standard of care, and facilitate scientific research on outcome and prognosis.

Preparing phase

Prior to implementation of the follow-up program, follow-up protocols were developed based on international [6] and national guidelines [18], consensus statements, systematic reviews, other empirical literature and clinical experience (in order of preference). All protocols were reviewed and approved after several consensus meetings by all members of the follow-up program. A dedicated team was constituted, including a director, project manager, pediatric intensivists, protocol holders (involved health care professionals, i.e. the pediatric psychologist, pediatric pulmonologist, pediatric cardiologist, pediatric neurologist and pediatric neuropsychologist), case managers, a parent counselor, and a PhD student. The follow-up program has been implemented since March 2018.

Structure of the follow-up program

The follow-up program provides comprehensive and structured follow-up care, tailored to the child's critical illness and received PICU treatment(s). The follow-up consultation always comprises consultation with both a pediatric intensivist and a case manager, and a separate consultation with a psychologist (one single psychologist delivers consultations to both patients and parents). Depending on the patient's critical illness and received PICU treatment(s), patients additionally may receive care by the pediatric pulmonologist, pediatric cardiologist, pediatric neurologist and/or pediatric neuropsychologist. Detailed information on the health care professionals involved is provided in Table 1.

The involved case managers are certified PICU nurses who have rotations at the PICU and work as case manager for the follow-up program one day per week. They are the main link between the patient, their parents and the health care professionals involved in the follow-up program. The case manager informs families on the follow-

Table 1. Inclusion and exclusion criteria for follow-up after admission to the Pediatric Intensive Care Unit and involved health care professionals

Inclusion and exclusion criteria for follow-up	Pediatric intensivist	Pediatric psychologist	Pediatric pulmonologist	Pediatric cardiologist	Pediatric neurologist	Pediatric neuropsychologist
Inclusion criteria (irrespective of length of PICU stay)						
Trauma other than traumatic brain injury	X	X				
Sepsis	X	X			X	X
Meningitis	X	X			X	X
Traumatic brain injury	X	X			X	X
Multisystem Inflammatory Syndrome – Children and/or Coronavirus disease-19	X	X			X	X
Cardiopulmonary resuscitation	X	X			X	X
Extracorporeal membrane oxygenation	X	X			X	X
Inclusion criteria (PICU stay ≥ 24 hours)						
Previously healthy and unplanned PICU admission	X	X				
Central venous catheter	X	X				
Traumatic intubation	X	X				
Delirium	X	X			X	X
Status epilepticus	X	X			X	X
Inclusion criteria (PICU stay ≥ 48 hours)						
Bronchiolitis	X	X	X			
≥ 48 hours sedatives/anesthetics	X	X			X	X
(Septic) shock with ≥ 48 hours inotropic agents	X	X		X	X	X
Acute kidney injury during PICU admission*	X	X				
≥ 72 hours (non)invasive mechanical ventilation	X	X	X			
Exclusion criteria	Receives similar follow-up care elsewhere (e.g. diabetic ketoacidosis, supraventricular tachycardia, chronic mechanical ventilation, palliative care, severe neurocognitive and/or motor problems requiring admission to a rehabilitation center) Developmental disorder or social situation precludes follow-up					
Additional exclusion criterion for pediatric neuropsychologist	Developmental disorders known to impact on neurocognitive development; physical conditions and/or behavioral deficits interfering with the ability to adequately perform neurocognitive testing					

Note: * Creatinine elevation > 25% and/or diuresis < 0.5ml/kg/hour for ≥ 8 hours without known kidney disease.

up program during PICU admission, and interfaces with families during consultations. Furthermore, the case manager is responsible for coordinating appointments with different subspecialists.

The first follow-up consultation takes place three to six months after PICU discharge. We identified the three to six month follow-up time frame, because mild problems – not requiring evaluation by the health care professionals – have already resolved spontaneously by that time. For example, the rate of child and parent post-traumatic stress symptoms has shown a sharp decrease in the first months after pediatric injury [19]. Patients and/or parents having concerns prior to consultation are invited to contact the case manager. Our program uses a standardized assessment battery to evaluate neurocognitive function that includes tests appropriate for children aged six years and above, as by that age the full range of neurocognitive functions can be assessed. Therefore, patients younger than six years at first follow-up who meet the inclusion criteria for consultation by the pediatric neurologist and neuropsychologist (including neurocognitive screening) will return for follow-up at the age of six years. Furthermore, in case of prominent neurocognitive and/or motor problems determined during PICU admission or at the first out-patient visit three to six months after PICU discharge, children will be directly referred for neurocognitive assessment and support, either in our hospital or in a rehabilitation center. Patients also return for follow-up at the age of six for consultation by the pediatric pulmonologist, as from that age lung function testing by spirometry can be performed and it is possible to officially diagnose asthma [20]. In addition, the pediatric pulmonologist and the pediatric rehabilitation physician are always present during the multidisciplinary team meeting, and in of case pulmonary problems and/or motor problems, an earlier appointment is scheduled with the pediatric pulmonologist and/or pediatric rehabilitation physician, respectively.

Since the Coronavirus disease-19 (Covid) pandemic, visits to the outpatient clinics were discouraged; patients and parents were therefore first invited for video consultation. If deemed necessary, patients and parents were then invited to the outpatient clinic. Most parents prefer video consultation, as they do not have to travel and consultations are easier to arrange. Therefore, we decided to continue video consultation. In practice, this means that patients who are only scheduled for consultation by the pediatric intensivist and psychologist (majority of the patients), receive video consultation and are only invited to the outpatient clinic if further evaluation is required. Patients who are scheduled for consultation by the pediatric pulmonologist, pediatric cardiologist, pediatric neurologist and/or pediatric neuropsychologist, are always invited to the outpatient clinic.

Consultation time of involved health care professionals is approximately 30 minutes per consultation, spirometry takes approximately 30-60 minutes, and neurocognitive

screening takes approximately 2.5 hours. All consultations are scheduled consecutively in the interest of time-efficiency for patient and parents. In addition, this facilitates multidisciplinary consultations between the health care professionals involved. After the consultations have taken place, a multidisciplinary team meeting is scheduled, in which all monitored outcomes are shared and evaluated and recommendations for further evaluation and treatment are discussed. Parents are approached by phone by the pediatric intensivist or psychologist (depending on the observed problems) to explain recommendations discussed in the multidisciplinary team meeting. If necessary, further follow-up appointments are scheduled or referrals are made. In case patients and/or parents need additional support, this will be either provided by the health care professional who performed consultation (e.g. the psychologist, pediatric pulmonologist) or patients are referred to other health care professionals (e.g. the ear nose and throat physician).

Clinician-reported outcomes are registered in discrete registrations and automatically appear in the standardized written report, which is sent to the general practitioner and other treating physicians, and subsequently stored in the patient's electronic medical record. Health care professionals participating in the follow-up program are responsible for entry of all medical information in the electronic medical files. This is facilitated by the use of pre-coded answer options.

Data collection and outcome measures

Patients (from the age of 8 years) and/or their parents (of patients aged 0-18 years) complete questionnaires online before consultation via a web-based portal (KLIK PROM portal; https://www.hetklikt.nu). Questionnaires pertain to physical and psychosocial functioning (see eTable 1) and are used to prepare the consultation and focus the consultation on the specific issues reported [21]. The physical outcomes are discussed by the pediatric intensivist and the psychosocial outcomes are discussed by the psychologist during the outpatient consultation (both qualified to interpret the results). For some validated questionnaires, a license is required. The KLIK PROM portal has the necessary licenses (see eTable 1).

During the consultations, various outcomes are evaluated, including generic somatic functioning, specific organ functioning, psychosocial and neurodevelopmental functioning, and parental psychosocial well-being. Outcomes are registered in discrete registrations. Each outcome of interest is covered by descriptions (items) in the electronic patient file describing the exact information to be gathered from history taking and physical examination. Some of these items offer follow-up items, depending on the response chosen. eTable 2 displays specific outcome measures assessed by the involved health care professionals, including key references underpinning the importance of involved health care professionals and assessed outcomes.

Database and data warehouse

Data gathered with the patient and parent reported online questionnaires are stored in a local data repository, and clinician-reported outcomes are registered in discrete registrations and stored in the electronic patient record (EPIC Hyperspace). All data from the electronic patient records collected during PICU admission and during follow-up (see eTable 2) are stored in a hospital-wide data warehouse and extracted in a standardized format via an SQL-server. The extracted data are visualized in a real-time available dashboard built in Microsoft PowerBI (see eFigure 1). The databases are available for routine outcome monitoring and research purposes by the involved caregivers and members of the supporting hospital's follow-up program team, if parents and patients from the age of 12 provided informed consent for use of the data collected during PICU admission and during follow-up. The Amsterdam UMC medical ethical committee approved the use of these data for routine outcome monitoring and research purposes (W21_516 # 21.569).

Health care evaluation

Yearly health care evaluation sessions are organized with the multidisciplinary team, representatives of the hospital's follow-up program and management team. In these sessions, process indicators and all assessed outcomes are evaluated at a population level, with the aim to define targets for improvement in the standard of care during and after PICU admission. Process indicators and outcomes are evaluated using the real-time available dashboards. Evaluation of outcome data may also give rise to adjustments in the follow-up protocols and may inspire research questions. Figure 1 shows the data flow in the primary care process and evaluation cycle.

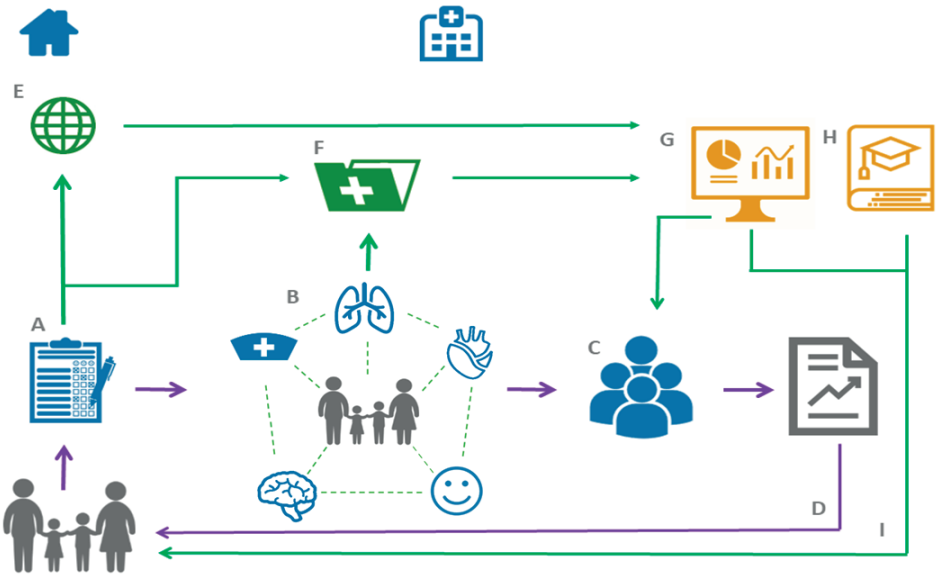


Figure 1. Overview of data collection of patient outcomes and the use of these data for health care evaluation and scientific research

Note: (A) Patients and parents complete online questionnaires; (B) consultations with the assigned health care professionals, with discrete registration of outcomes; (C) multidisciplinary team meeting; (D) standardized written report is sent to the general practitioner and other treating physicians. All collected data are stored in the local data repository (E) or in the electronic patient's record (F) and extracted for the visualization of process and outcome indicators in a dashboard (G) used for health care evaluation and scientific research (H), which in turn contributes to improvements in the standard of care during and after PICU admission (I).

RESULTS

Patients

We here provide a brief overview of selected outcomes obtained during the follow-up care provided to patients discharged from our PICU between October 2017 and April 2021. Of the 1,752 (unique) patients, 388 patients met inclusion criteria for follow-up. Patients not meeting inclusion criteria had elective admission for post-operative care, received similar follow-up care elsewhere, or passed away. A total of 307 patients (79.1% of the patients eligible for follow-up) visited our follow-up clinic between March 2018 and July 2021. Table 2 displays the demographic and clinical characteristics of these patients.

Table 2. Demographic and clinical characteristics of the patients (n = 307) participating in the follow-up program, 3-6 months after PICU admission

Demographic and clinical characteristics	Median (IQR) or n (%)
Male sex, n (%)	178 (58.0)
Age at PICU admission (months), median (IQR)	14.0 (1.0-92.0)
PICU length of stay (days), median (IQR)	4.0 (2.0-7.0)
Mechanical ventilation, n (%)	163 (53.1)
Inotropic agents, n (%)	46 (15.0)
Cardiopulmonary resuscitation, n (%)	13 (4.2)
Extracorporeal membrane oxygenation, n (%)	0 (0.0)
Primary PICU admission indication	
Respiratory, n (%)	
Upper airway obstruction	30 (9.8)
Asthma	33 (10.7)
Bronchiolitis	78 (25.4)
Respiratory insufficiency other than asthma/bronchiolitis	19 (6.2)
Circulatory, n (%)	
Asystole	9 (2.9)
Shock (anaphylactic/cardiogenic/hypovolemic/ septic)	24 (7.8)
Multisystem Inflammatory Syndrome – Children	15 (4.9)
Neurologic, n (%)	
Non-traumatic intracranial hemorrhage	4 (1.3)
Meningitis/encephalitis/empyema/abscess	13 (4.2)
Status epilepticus	17 (5.5)
Trauma, n (%)	
Abdominal trauma	11 (3.6)
Traumatic brain injury with/without other trauma	22 (7.2)
Other trauma	2 (0.7)
Congenital malformation, n (%)	
Congenital gastrointestinal malformation	10 (3.3)
Congenital cor vitium	1 (0.3)
Miscellaneous, n (%)	19 (6.2)

Note: PICU = pediatric intensive care unit, IQR = interquartile range

Outcomes

Figure 2 displays the physical outcomes obtained by the pediatric intensivist. History taking by the pediatric intensivist was performed in all 307 patients, and physical examination was performed in 152 patients, as since the Covid pandemic patients were only invited to the outpatient clinic if necessary. Most frequently revealed problems during history taking were scars (25.1%), sleep problems (18.9%) and shortness of breath (15.3%). Most frequently revealed problems during physical examination were scars (30.3%), rales (5.3%) and wheezing (3.3%) on lung auscultation.

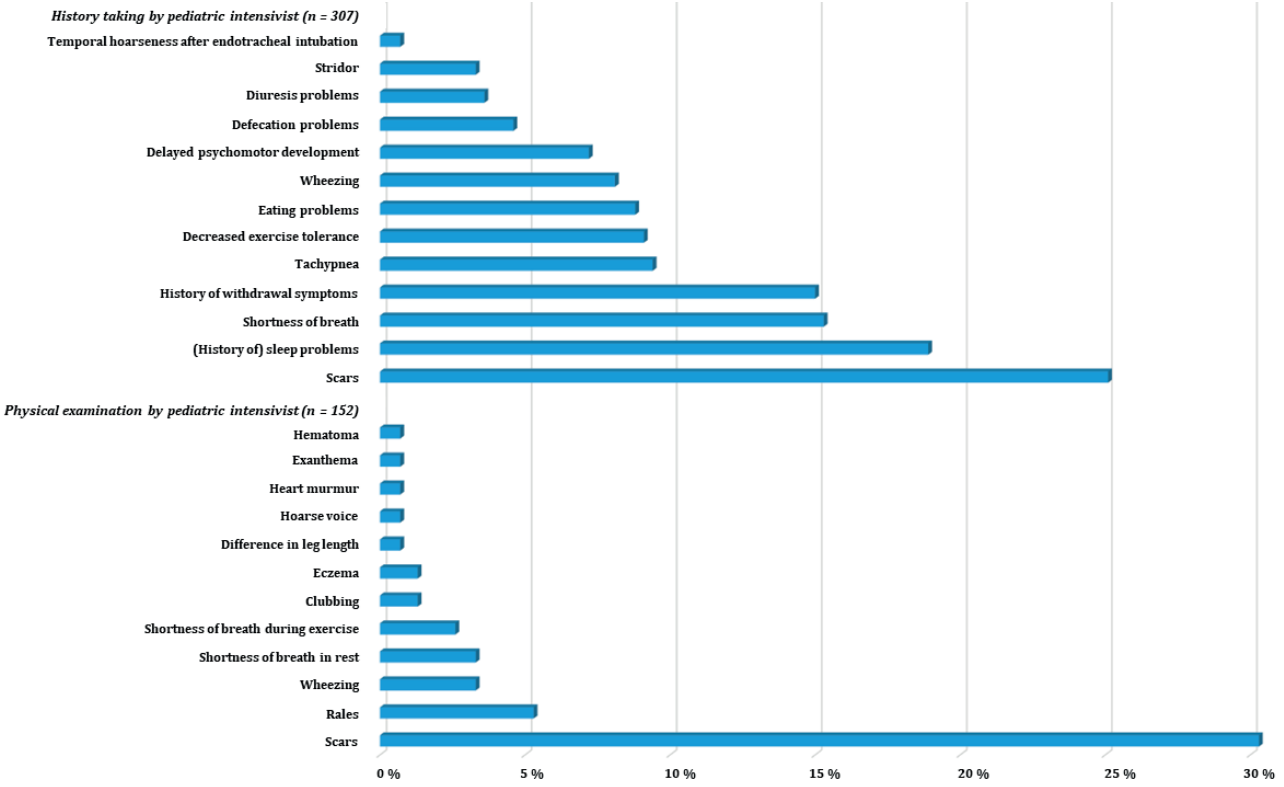
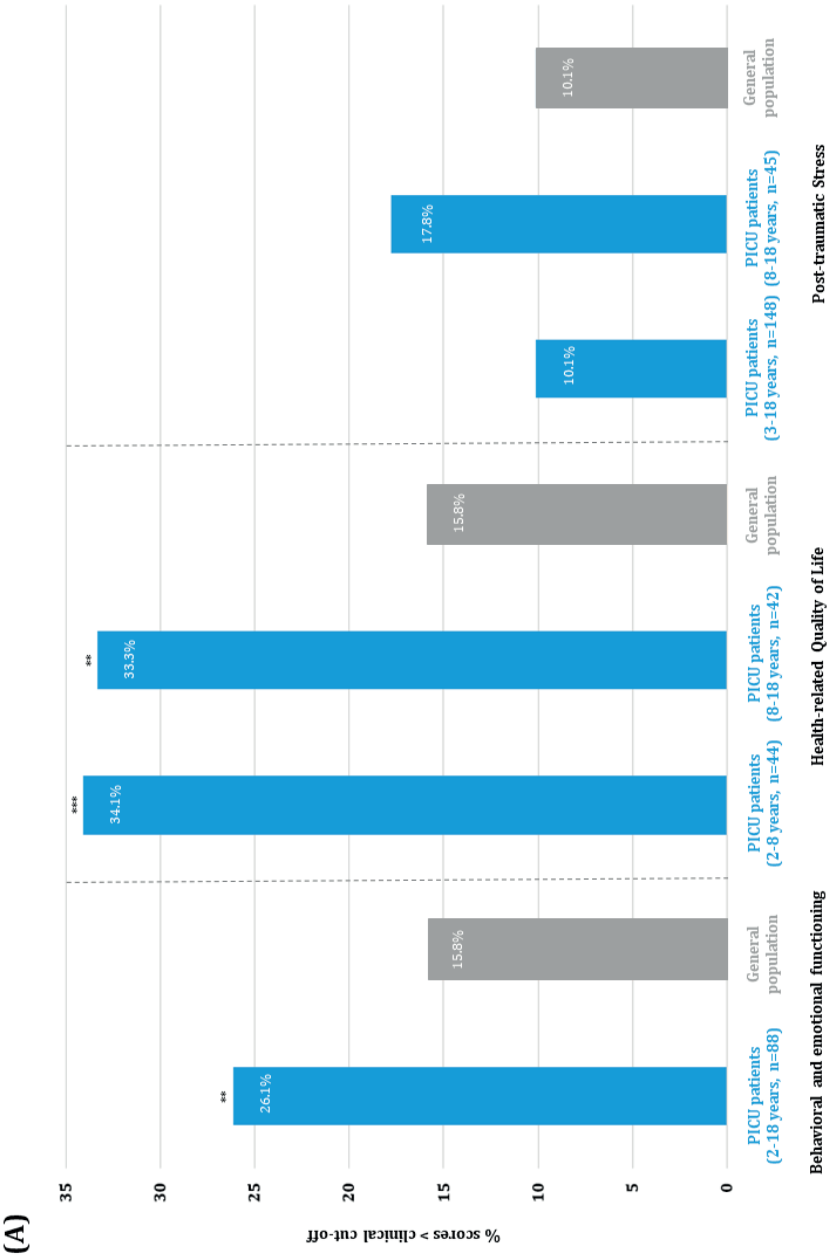


Figure 2. Physical outcomes revealed during history taking (n = 307) and physical examination (n = 152) by the pediatric intensivist at the outpatient follow-up clinic at 3-6 months after PICU discharge.

Note: The pediatric intensivist evaluates whether the outcomes are normal according to patients' age. In case of sleep problems, parents reported their child to have the following problems: problems falling asleep (43.1%), nightmares (17.2%), not wanting to sleep alone (34.5%), sleeps too short (13.8%), and wakes up during the night (41.4%). The majority of the scars (94.8%) had their origin in the period of PICU admission (84.4% due to PICU treatment and 13.0% due to the disease that was reason for PICU admission).


(A)
% scores > clinical cut-off
35
30
25
20
15
10
5
0
**
26.1%
15.8%
***
34.1%
**
33.3%
15.8%
10.1%
17.8%
10.1%
PICU patients (2-18 years, n=88)
General population
PICU patients (2-8 years, n=44)
PICU patients (8-18 years, n=42)
General population
PICU patients (3-18 years, n=148)
PICU patients (8-18 years, n=45)
General population
Behavioral and emotional functioning
Health-related Quality of Life
Post-traumatic Stress

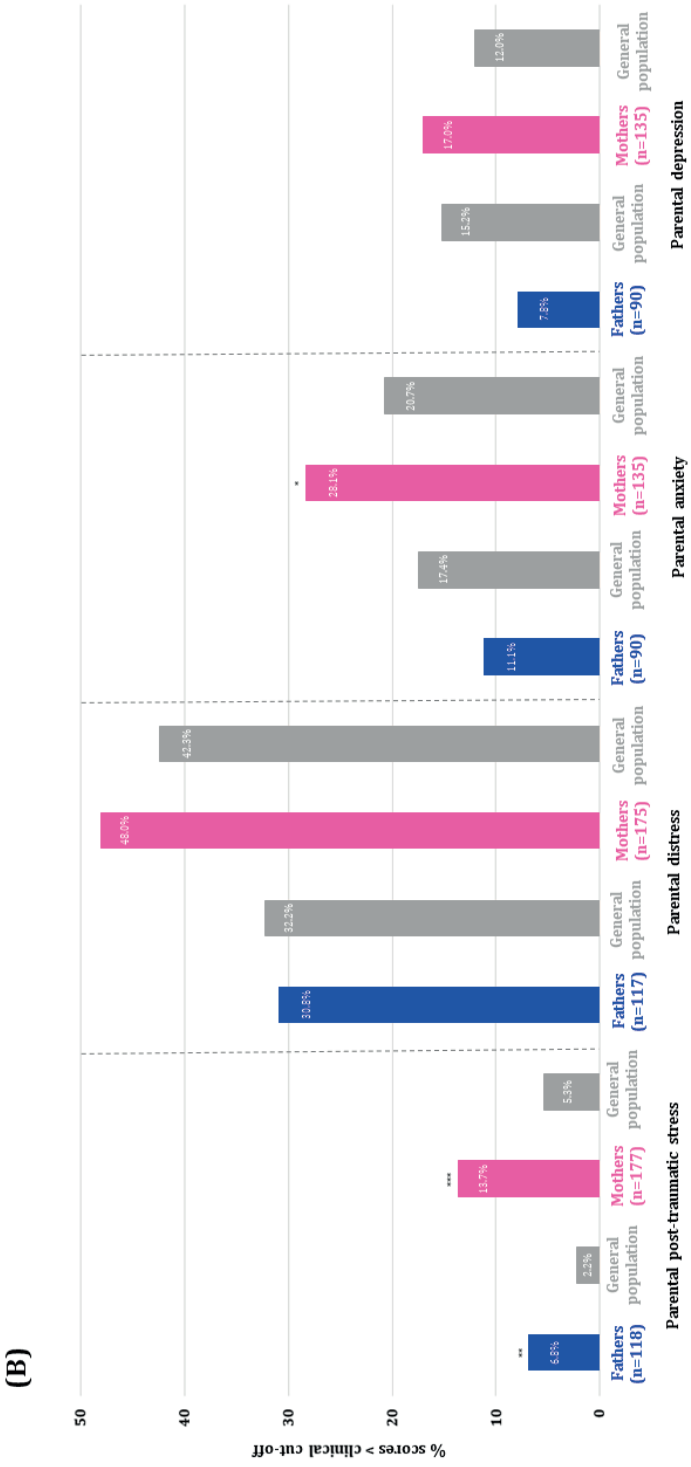


Figure 3. Psychosocial outcomes of (A) PICU patients and (B) parents, compared to the general population.

Figure 3. Psychosocial outcomes of (A) PICU patients and (B) parents, compared to the general population. (*continued*)
Note: * p < .05. ** p < .01. *** p < .001.
Behavioral and emotional functioning assessed by the parent-reported Strengths and Difficulties Questionnaire (SDQ, n = 88). Higher scores indicate greater severity of problems. Percentage of patients with a total score > 1SD and compared to the general population [22].
Health-related Quality of Life assessed by the Pediatric Quality of Life Inventory (PedsQL, 2-8 years parent-reported, n = 44 and 8-18 years patient-reported, n = 42). Higher scores indicate better health-related quality of life. Percentage of patients with a total score < -1SD and compared to the general population [23,24].
Post-traumatic stress assessed by the Children's Revised Impact of Event Scale (CRIES-13, 3-18 years parent-reported, n = 148 and 8-18 years patient-reported, n = 45). Higher scores indicate greater severity of problems. Percentage of patients with "probable PTSD" defined as a total score of ≥ 31 (parent-reported) or ≥ 30 (patient-reported). Patient-reported outcomes compared to the general population [25]. There are no normative data available for the parent reported CRIES-13.
Parental post-traumatic stress disorder (PTSD) assessed until February 2021 by the Self-Rating Scale for Posttraumatic Stress Disorders (SRS-PTSD, assessing DSM-IV symptoms of PTSD, n = 226) and since February 2021 by the PTSD Checklist for DSM-V (PCL-5, assessing DSM-V symptoms of PTSD, n = 69). Higher scores represent more post-traumatic stress symptoms. For the SRS-PTSD, a diagnosis of PTSD is considered likely if one 'Intrusions' symptom, three 'Avoidance' symptoms and two 'Hyperarousal' symptoms are present. For the PCL-5, a diagnosis of PTSD is considered likely if one 'Intrusions' symptom, one 'Avoidance' symptom, two 'Negative Alterations in Cognitions and Mood' symptoms and two 'Arousal and Reactivity' symptoms are present. Percentage of parents for whom the diagnosis of PTSD is considered likely and compared to the general population for the SRS-PTSD [26] only as no normative values are available for the PCL-5.
Parental distress assessed by the Distress Thermometer for Parents (DT-P, n = 292). Higher scores indicate greater severity of distress. Percentage of parents with clinically elevated distress based on a score of ≥ 4 [27] and compared to the general population [27].
Parental anxiety and depression assessed by the Hospital Anxiety and Depression Scale (HADS, n = 225). Higher scores indicate greater severity of anxiety and depression. Percentage of parents with clinically significant anxiety and depression based on a scale score of ≥ 8 and compared to the general population [28].

Figure 3 displays the psychosocial outcomes of patients and parents. Percentages of patients and parents obtaining clinical scores (i.e. scores above cut-off scores defining scores requiring further assessment) were compared to the prevalence observed in the general population. The prevalence of clinical scores with respect to behavioral and emotional functioning and health-related quality of life was higher in patients than observed in the general population. The prevalence of clinical scores for fathers and mothers with respect to parental post-traumatic stress and for mothers with respect to parental anxiety was higher than the prevalence observed in the general population.

Evaluation by the pediatric pulmonologist took place in only four patients, as the great majority of patients was too young (younger than six years) to perform lung function testing. Two out of four patients had complaints during follow-up: one patient had chronic productive cough, and another patient had wheezing complaints during follow-up and received additional follow-up.

Evaluation by the pediatric cardiologist took place in nine patients. Only mild to moderate problems were identified including moderate exercise tolerance (11.1%), shortness of breath (11.1%) and mild tachypnea (33.3%). Electrocardiogram and echocardiogram identified mild hypertrophy of the septum and right ventricle in one

patient, which normalized spontaneously during additional follow-up. Electrocardiogram and echocardiogram revealed no abnormalities in all other patients.

The pediatric neurologist evaluated 27 patients and identified small-fiber polyneuropathy in one patient who was admitted for Multisystem Inflammatory Syndrome - Children (MIS-C). In all other patients no (new) neurologic findings were identified.

Neurocognitive testing was performed in 43 patients. Mean estimated full-scale intelligence quotient (FSIQ) was 98.7 (SD 15.5, range 63.0-131.0). In total, 18.6% of the patients (8/43) had a FSIQ less than -1SD (i.e. < 85), which is not significantly different compared to normative data (p = .61).

DISCUSSION

This article presents the design and implementation of a structured multidisciplinary follow-up program for patients and their parents after PICU admission, including the first results obtained in patients and their parents to illustrate the significance of our program. To our knowledge, no standardized structure for follow-up care after PICU admission exists. Current PICU follow-up programs [11-17] vary widely with respect to, among others, the included patients**,** involved health care professionals, follow-up moment(s) and assessed outcomes. Moreover, most PICU follow-up programs lack structured data collection [11], which is essential for health care evaluation and scientific research on outcome and prognosis of critically ill children. Defining features of our structured multidisciplinary PICU follow-up program include: (1) a multidisciplinary team that is responsible for patient follow-up, (2) structured follow-up using evidence-based protocols and well-defined inclusion and exclusion criteria for follow-up, (3) the use of a one stop shop format for consultations, with consultations of all health care professionals scheduled consecutively, (4) the use of online questionnaires on physical and psychosocial functioning to prepare for the consultations, (5) structured data collection using discrete registrations, (5) yearly health care evaluation sessions aimed at improving the standard of care during and after PICU admission, (6) the use of outcome data for scientific research. Our program integrates clinical care, health care evaluation and scientific research, fueling a cycle of care innovation.

In order to achieve a holistic view on an individual patient's functioning, our structured follow-up protocols include a comprehensive assessment of important outcomes evaluated by a multidisciplinary team. In addition, psychosocial functioning is also assessed in parents. This approach follows the International Classification of Functioning, Disability and Health model of the World Health Organization [29], that

acknowledges that health is a multidimensional construct that is under the influence of personal and environmental factors. Our first results confirm the presence of a diversity of problems arising after PICU admission, including physical, neurocognitive and psychosocial sequelae. In addition, our data also confirm the risk for psychosocial problems among parents [8,9]. These findings underline the importance of structured multidisciplinary follow-up of patients and their parents after PICU admission.

Within the limited operation time of our follow-up program, the program has evolved based on our experiences and the data collected. For example, since the Covid pandemic, patients who are only scheduled for consultation by the pediatric intensivist and psychologist (majority of the patients), receive video consultation and are only invited to the outpatient clinic if further evaluation is required. As most parents prefer video consultation due to time efficiency, we decided to continue video consultation. Furthermore, evaluation of the neurologic exams conducted as part of the consultations by the pediatric neurologist identified new neurological abnormalities in only one patient (3.7%),which were also identified by the pediatric intensivist. Therefore, we have removed the neurologic exam from the structured follow-up, which now only takes place in case of concerns raised by the pediatric intensivist. Furthermore, the collected data can be used to evaluate changes in the protocols used at the PICU. For example, before the introduction of our current follow-up program, we studied the outcomes of children unexpectedly admitted to our PICU three months after discharge. In that study, 7 out of 186 children (3.8%) were diagnosed with post-thrombotic syndrome [30]. This finding has led to the greater awareness of the risk on post-thrombotic syndrome and development of a protocol on central venous catheters, including ultrasound in case of suspected problems and prophylactic anticoagulants during PICU admission. Since then, the prevalence of post-thrombotic syndrome has dropped to 0% as assessed in the patients who visited our structured multidisciplinary follow-up program.

Until now, only few patients were evaluated by the pediatric cardiologist, pediatric pulmonologist and pediatric neuropsychologist, as few patients met the inclusion criteria for evaluation by the pediatric cardiologist and most patients were too young to perform lung function and neurocognitive testing at the time of follow-up. Therefore, based on the current results, we cannot evaluate the beneficial value of these subspecialists to our program. Nevertheless, as part of our follow-up program, we studied a cohort of patients now aged 6-12 years and previously admitted to the PICU for bronchiolitis requiring invasive mechanical ventilation. The results showed that these patients are at risk of adverse long-term pulmonary and neurocognitive outcomes, highlighting the importance of long-term pulmonary and neurocognitive follow-up after PICU admission [31,32]. All children in this cohort with adverse pulmonary outcomes had obstructive lung function, which can only be detected by spirometry and would thus involve a pediatric pulmonologist [31]. The findings of our follow-up program and the existing literature

show a great diversity of adverse outcomes after PICU admission and thus call for a multidisciplinary approach to follow-up of PICU patients.

Currently, our program offers neurocognitive follow-up to children six years of age and older, with younger children receiving delayed neurocognitive follow-up at the age of six years. This approach was chosen as at that age, most neurocognitive functions have been fully formed and a wide range of assessment materials is available [33]. A limitation of this approach is that children younger than six years of age suffering from neurocognitive sequelae might remain undetected and are at risk of delayed support. Assessment tools with established clinimetric properties are available to detect the impact of disease on early neurocognitive development. Although these measures often show limited predictive value for future neurocognitive functioning [34], they provide the best available methods to detect those children in need of intervention and may be helpful in guiding the decisions on adequate support. Recently new and promising assessment methods have become available for young children including methods relying on eye-tracking methodology and applied in babies and infants [35,36] as well as the National Institute of Health Toolbox for the Assessment of Neurological and Behavioral Function [37], suitable for children from three years of age. As the majority of the PICU population is too young for the current neurocognitive tests three to six months after PICU discharge, we consider including neurocognitive tests appropriate for younger children in our program.

A structured approach to multidisciplinary follow-up allows us to create a consecutive cohort, with accumulating patient data, which could be a solution to the challenged literature describing the heterogeneous PICU population with small-sized studies and limited sets of outcomes. Hereby, it allows to create better insight in disease- and treatment-specific outcomes that can contribute to patient education and shared-decision making. Better insight into outcomes will facilitate targeted follow-up of high-risk children and allow further tailoring of the content of follow-up offered to those domains of functioning threatened. The development of personalized prognostic models may importantly facilitate targeted follow-up [38]. The collected patient data will also enhance understanding of risk factors and protective factors for adverse outcomes that may provide targets for health care innovation. At last, structured multidisciplinary follow-up will not only provide answers to scientific questions, but may also support the generation of new research initiatives and easier implementation of research and intervention studies in follow-up practice. For example, since patients were admitted due to MIS-C, we collaborate in outcome research with six other PICUs in the Netherlands [39]. A blueprint of our program has been implemented in these PICUs.

Helpful recommendations for successfully starting and managing PICU follow-up programs have recently been reviewed by Williams and colleagues [11]. Although our program is in line with most of these recommendations, structured multidisciplinary

follow-up faces limitations and challenges. The implementation of new initiatives may come across cautious attitudes among health care professionals and patients and their parents, and may pertain to the clinical usefulness of standardized outcome measures, which potentially has a negative impact on compliance and participation. Another challenge is that our program is labor intensive. Several measures have been taken to improve time-efficiency. The completion of questionnaires on physical and psychosocial functioning before the consultations may help prepare parents for the consultation, save professionals time in history taking, and help focus the consultation on the specific issues reported [21]. Time-efficiency for patients, parents and professionals is promoted by scheduling all consultations consecutively with the multidisciplinary team meeting scheduled after the last consultation. Clinician-reported outcomes are registered in discrete registrations and automatically appear in a standardized written report, which is sent to the general practitioner and other treating physicians. To facilitate health care evaluation sessions, all data from the electronic patient records collected during PICU admission and during follow-up are automatically visualized in a real-time available dashboard built in Microsoft PowerBI (see eFigure 1). Despite aforementioned measures to improve time-efficiency, our program remains labor intensive and therefore the involved health care professionals receive dedicated time. The implementation of a new program also comes with technological challenges, including building questionnaires and registration forms in the electronic patient file for discrete registration, and the building of dashboards to support the health care evaluation sessions. Furthermore, selection bias may occur as patients whose functioning is impaired may be more likely to participate. However, this risk is much lower compared to most cross-sectional studies, as a result of the prospective inclusion of a consecutive cohort in the structured multidisciplinary follow-up program. Finally, a considerable number of patients and parents did not complete all questionnaires sent out before their visit to the outpatient clinic, resulting in inefficient consultations and an incomplete and limited view on their functioning. In our experience, a dedicated team is essential to tackle these challenges.

Future work needs to address the cost-effectiveness of structured multidisciplinary follow-up. The recently published article by Williams and colleagues [11] identified "lack of support", including lack of availability of funding and lack of institutional or departmental support, as the most important barrier with respect to the development and maintenance of PICU follow-up programs. Prior to implementation of our structured multidisciplinary follow-up program, funding was provided by our hospital for the development and implementation of the program. After development of a national guideline on follow-up of PICU patients [18], our structured multidisciplinary follow-up care was acknowledged and reimbursed by insurance companies. Professionals involved in the follow-up programs have been able to attract external funding for scientific research in several of the outcomes targeted. Only a structured follow-up program will provide

insights in potential deleterious consequences of PICU admission, thereby facilitating targeted follow-up and enabling us to know which possible complications we have to focus on during PICU admission in order to prevent these complications and thereby also minimize costs after PICU discharge.

In order to gain a generalizable understanding of sequelae after pediatric critical illness, standardization of outcome assessment is urgently needed. Core outcome set and instrument recommendations have recently been developed by the Pediatric Outcomes STudies after PICU (POST-PICU) Investigators of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) [10,40]. Although our follow-up program was developed well before publication of this core outcome set, the outcomes and instruments of our program largely converge with the recommendations made. Our structured multidisciplinary PICU follow-up program serves as an example of how clinical care, health care evaluation and scientific research can be integrated to continuously provide data-driven health care innovation. Depending on, among others, availability of financial resources, health care professionals, language appropriate questionnaires, electronic patient record and infrastructure to allow structured data collection, other PICUs may adapt this program in order to be applicable in their country and hospital. A strength of our set-up is the flexibility that this program has with regard to outcome measurements. Possible adaptations may arise from, for example, the evaluation sessions, new insights on outcomes, new diseases such as MIS-C requiring monitoring, or new tools or new releases of outcome measurements. Even when adaptations are made, a solid structure and process is preserved in which outcome monitoring is used for the purpose of improvement of patient outcomes, health care evaluation and scientific research.

CONCLUSIONS

We described the process of successful development and implementation of a structured, yet dynamic, multidisciplinary follow-up program for patients and their parents after PICU admission. Structured follow-up and collection of outcome data within a structured multidisciplinary follow-up program, can importantly contribute (1) to improve outcomes of individual patients by facilitating timely support and appropriate intervention, if required; (2) to improve the standard of care during and after PICU admission by providing insight in extent and severity of sequelae; and (3) to facilitate scientific research on outcome and prognosis of patients after PICU admission. Given the distinct heterogeneity of the PICU population and wide range of potential impairments in functioning, we propose that structured multidisciplinary follow-up is required for

patients and their parents after PICU admission. The accumulating outcome data will ultimately provide better insight in disease and treatment specific patient outcomes, thereby facilitating targeted follow-up of high-risk children and allowing further tailoring of the content of follow-up offered to those domains of functioning threatened.

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eTable 1. Overview of patient and parent reported online questionnaires

Outcome measurements	Questionnaire	Informant (parent and/ or child) and ages (years)	License required
Patient outcomes			
Somatic functioning	ISAAC questionnaire [1] Custom-made questionnaire assessing school functioning, medical care after PICU discharge, development, vision and hearing, diuresis, defecation, skin, pain	Parent report (0-17) Patient report (12-17)	No
Demographic characteristics	Custom-made questionnaire assessing parental authority, parental marital status, country of birth of patient and parents, number of children, parental education and work situation	Parent report (0-17)	No
Perinatal history	Custom-made questionnaire assessing pregnancy and labor mother and first weeks of life	Parent report (0-17)	No
Behavioral and emotional functioning	SDQ [2,3]	Parent report (2-17) Patient report (11-17)	Yes [4]
Post-traumatic stress	CRIES-13 [5-7]	Parent report (3-17) Patient report (8-17)	No
Health-related Quality of Life	TAPQOL [8,9]	Parent report (0-1)	No
	PedsQL [10]	Parent report (2-7) Patient report (8-17)	No (only consent of the originator professor J.W. Varni)
Additional patient outcomes in case of neurocognitive screening			
Medical history related to neurocognitive functioning	Custom-made questionnaire assessing general anesthesia, traumatic brain injury, learning disability, neurological disability, psychiatric disability, language and/or speech disorder, developmental coordination disorder, intellectual disability, physical functioning, self-care, social functioning, cognitive abilities, attention, memory, executive functions, visual-spatial skills, motor functioning, school functioning	Parent report (6-17)	No
Behavior and emotional functioning	SWAN [11]	Parent report (6-17)	No

eTable 1. Overview of patient and parent reported online questionnaires (*continued*)

Outcome measurements	Questionnaire	Informant (parent and/ or child) and ages (years)	License required
Parent outcomes			
Parental post-traumatic stress	*Until February 2021:* SRS-PTSD [12] *Since February 2021:* PCL-5 [13]	Parent report (0-17)	SRS-PTSD: No PCL-5: No (free of charge after registration at Center 45: https://www.centrum45.nl/)
Parental distress	DT-P [14]	Parent report (0-17)	No
Parental anxiety and depression	*Until February 2021:* HADS [15,16] *Since February 2021:* PROMIS-CAT Anxiety and Depression [17,18]	Parent report (0-17)	HADS: Yes PROMIS-CAT Anxiety and Depression: Yes [19]

Note: CRIES-13 = Children's Revised Impact of Event Scale; DT-P = Distress Thermometer for Parents; HADS = Hospital Anxiety and Depression Scale; ISAAC = International Study of Asthma and Allergies in Childhood; PCL-5 = PTSD Checklist for DSM-V; PedsQL = Pediatric Quality of Life Inventory; PROMIS-CAT = Parental-Reported Outcomes Measurement Information System Computer Adaptive Test Anxiety and Depression; SDQ = Strengths and Difficulties Questionnaire; SRS-PTSD = Self-Rating Scale for Posttraumatic Stress Disorders; TAPQOL = TNO-AZL Preschool Children Quality of Life Questionnaire; SWAN = Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale.

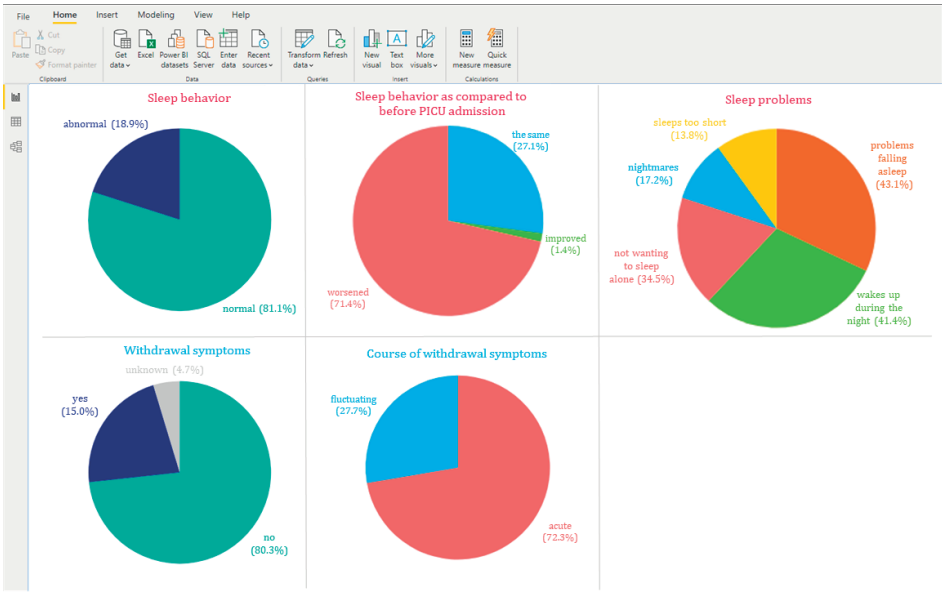
eTable 2. Overview of the clinician-reported outcomes

Involved health care professionals	Key references underpinning the importance of involved health care professionals and assessed outcomes	Clinician-reported outcomes	Details on clinician-reported outcomes
Pediatric intensivist	[20-26]	History taking	Care after PICU discharge; withdrawal symptoms; eating; sleeping; diuresis; defecation; respiratory and cardiac complaints; psychomotor development.
		Physical examination	General impression; head; thorax; airway; respiration; circulation; abdomen; skin; extremities; signs for post-thrombotic syndrome after central venous catheter.
		Diagnostics for kidney function*	Blood: creatinine, ureum and cystatine C. Urine: proteinuria [27-29] and microalbuminuria [25] Blood pressure: measured 3 times after 3 minutes of rest by the oscillometric Mindray VS-600 with the lowest value obtained being used to evaluate hypertension [30].
Pediatric psychologist	[31-35]	Clinical interview with patient and parents	Health-related quality of life; behavior and emotional functioning; post-traumatic stress; parental post-traumatic stress; parental distress; parental anxiety and depression.
Pediatric pulmonologist	[24,36-38]	History taking	Voice; stridor; cyanosis; dyspnea; tachypnea; airway obstruction; exercise tolerance; coughing; breathing; airway infections.
		Physical examination	Head; thorax; respiration; circulation; abdomen; extremities.
		Lung function by spirometry	Spirometry before and after administration of short-acting-βs-mimetic with the calibrated spirometer (Vyntus SPIRO, Vyaire Medical, Inc). Measurements are performed according to the guideline of the American Thoracic Society and the European Respiratory Society [39]. The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximal mid-expiratory flow at 25–75% of FVC (MMEF 75/25) and the Tiffeneau index (FEV1/FVC) are assessed and percentages of predicted values are based on the Global Lung Function Initiative standards [40].

eTable 2. Overview of the clinician-reported outcomes (*continued*)

Involved health care professionals	Key references underpinning the importance of involved health care professionals and assessed outcomes	Clinician-reported outcomes	Details on clinician-reported outcomes
Pediatric cardiologist	[41]	History taking	Exercise tolerance; tachypnea; cyanosis; dyspnea; arrhythmias.
		Physical examination	Respiration; circulation.
		Electrocardiogram	General electrocardiogram.
		Echocardiogram **	1) Biventricular systolic function: left ventricle (LV): LVSF (%), LVEF (%)(triplane en 4D), MAPSE (mm), global longitudinal LV strain (%) (2chamber/3chamber/4chamber), TDI (S' LV free wall en S' septum (cm/s)). Right ventricle (RV): TAPSE (mm), global longitudinal strain (%) (RV free wall), TDI (S' RV free wall (cm/s)). 2) Dimensions left and right ventricle (LVED (mm), LVES (mm), septal, posterior wall, right ventricular wall thickness (mm)). 3) Valve function: gradient (mmHg) over inflow and outflow valves, insufficiency. 4) Anatomy/shunts.
Pediatric neurologist	[20,21]	History taking	Epileptic attacks; headache; sensibility; motor skills.
		Neurologic physical examination	Speech; assessment of cranial nerves; motor skills; coordination; sensibility; reflexes; gait pattern.
Pediatric neuropsychologist	[35,42,43]	Neurocognitive screening	Intelligence: WISC-V-NL short form [44]. Neurocognitive computerized test battery (Emma Toolbox). This test-battery measures a broad range of key neurocognitive domains and contains a composition of child-friendly tests based on well-known neuroscientific paradigms with established validity and reliability, i.e. Attention Network Test,[45] Location Learning Test [46], Rey Auditory Verbal Learning Test [47], Klingberg task [48], Digit Span task [49], and Track & Trace task [50].

Note: *Diagnostics for kidney function in case of PICU admission ≥ 48 hours and acute kidney injury during PICU admission (i.e. creatinine elevation > 25% and/or diuresis < 0.5ml/kg/hour for ≥ 8 hours) without known kidney disease.
** Abbreviations echocardiogram: LV: left ventricle, LVEF: left ventricular ejection fraction, LVSF: left ventricular shortening fraction, MAPSE: mitral annular plane systolic excursion, TAPSE: tricuspid annular plane systolic excursion, RV: right ventricle, TDI: tissue Doppler imaging. WISC-V-NL short form = short version of the Wechsler Intelligence Scale for Children, fifth version in Dutch.



eFigure 1. Example of one of the dashboards used for health care evaluation. The extracted data are visualized in a real time available dashboard built in Microsoft PowerBI.

Note: Each outcome of interest is covered by one or more main items. Some of these items offer follow-up items that require completion depending on the response chosen on the main item(s). The two graphs on the left (dark green, dark blue en grey colors) pertain to main items, while those on the right pertain to follow-up items.

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3 Long-term pulmonary outcomes in children mechanically ventilated for severe bronchiolitis

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ABSTRACT

Objective: Bronchiolitis is a common indication for mechanical ventilation at the Pediatric Intensive Care Unit (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: Out-patient PICU follow-up clinic.

Patients: Children aged 6-12 years with a history of invasive mechanical ventilation for bronchiolitis (age ≤ 1 year).

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 to 36.0] and 1.3 [95%CI 1.0 to 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.

INTRODUCTION

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 at the pediatric intensive care unit (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 non-hospitalized 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 life-saving, 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. Parents and children aged ≥ 12 years 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 ≤ 1 year of age 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.dS.). 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 months), causes of current wheeze, severity of current wheeze (e.g. frequency, difficulty breathing), coughing, and rhinitis symptoms.

Lung function was assessed by spirometry before and after administration of short-acting-β2-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 (MMEF 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 β2-agonist medications were instructed to withhold the medications before lung function assessment (> 12 hours for short-acting- and > 36 hours for long-acting-β2-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 one week after all complaints had disappeared.

Children were referred to a pediatric pulmonologist for further evaluation in 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 (weeks), 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 (months), Pediatric Index of Mortality 2 (PIM 2) score [22], duration of mechanical ventilation (hours), PICU admission duration (hours), 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: fraction of inspired oxygen (FiO_2), oxygen saturation (SpO_2), end-tidal carbon dioxide ($etCO_2$), positive inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), mean airway pressure (MAP) and SpO_2/FiO_2 ratio.

Possible impact of adverse pulmonary outcomes on daily life

Sports performance ≥ 1x/week (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-β2-agonists and inhaled corticosteroids after PICU discharge and during the last 12 months before our follow-up (yes/no).

Statistical analysis

Statistical analysis was 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 (versus no adverse pulmonary outcomes) as dependent variable. Second, we performed multivariable binary logistic regression analysis with asthma (versus 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 case of p-value > .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 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, α was set at .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

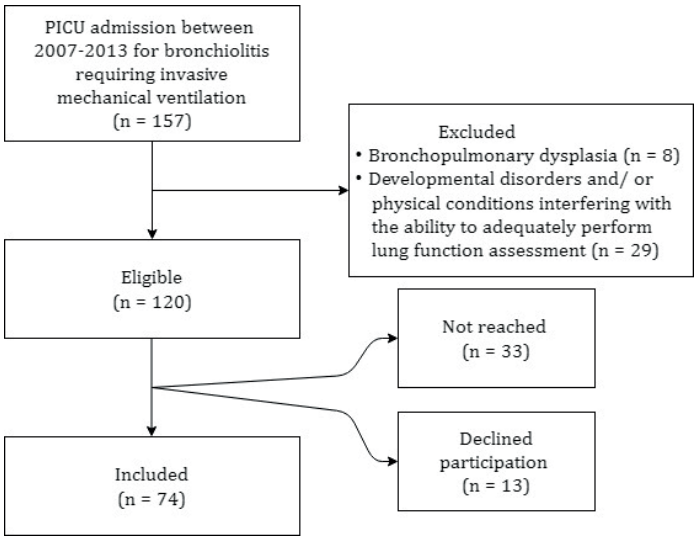

Figure 1. Flowchart of participants.

Table 1. Background characteristics and PICU-related variables

Background characteristics and PICU-related variables (n = 74)	Mean (SD), median (IQR) or n (%)
Sex (boys), n (%)	43 (58)
Age at follow-up (years), mean (SD)	9.2 (1.7)
Socioeconomic status, mean (SD)	5.3 (1.3)
Gestational age (weeks), mean (SD)	37.7 (2.9)
Inhalant allergy, n (%)	6 (8)
Daycare attendance in past, n (%)	66 (89)
Breastfed in past, n (%)	42 (57)
Atopic disease in family, n (%)	48 (65)
Asthma in family, n (%)	19 (26)
Hay fever in family, n (%)	39 (53)
Eczema in family, n (%)	27 (36)
Smoking mother during pregnancy, n (%)	7 (9)
Smoking parents now/past since birth of child, n (%)	22 (30)
Smoking near child now/past, n (%)	7 (9)
Age at PICU admission (months), median (IQR)	1.4 (0.8-2.4)
PIM2 score, median (IQR)	1.5 (1.0-2.1)
Cardiopulmonary resuscitation, n (%)	1 (1)
Invasive mechanical ventilation during first PICU stay (hours), mean (SD)	153.0 (64.3)
Invasive mechanical ventilation during all PICU admissions (hours), mean (SD)	158.0 (73.9)
Non-invasive mechanical ventilation in addition to invasive mechanical ventilation, n (%) *	2 (3)
Need for reintubation, n (%)	3 (4)
Admission duration of first PICU stay (hours), mean (SD)	176.6 (65.1)
Admission duration during all PICU admissions (hours), mean (SD)	185.8 (83.3)
Readmission at PICU, n (%) **	8 (11)
Respiratory syncytial virus, n (%)***	66 (89)
2 or more viral agents, n (%)	9 (12)
Antibiotics during PICU stay, n (%)	63 (85)
FiO_2 (%), mean (SD)	44 (9)
SpO_2 (%), mean (SD)	97 (1)
$etCO_2$ (kPa), mean (SD)	5.2 (0.5)
PIP (cmH_2O), mean (SD)	22 (3)
PEEP (cmH_2O), mean (SD)	5 (1)
Mean airway pressure (cmH_2O), mean (SD)	17 (2)
SpO_2/FiO_2 ratio, mean (SD)	2.4 (0.5)

Note: $etCO_2$ = end-tidal carbon dioxide; FiO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PICU = pediatric intensive care unit; PIM 2 score = Pediatric Index of Mortality 2 score; PIP = positive inspiratory pressure; SpO_2 = oxygen saturation.

* Synchronized intermittent mandatory ventilation via full-face mask.

** Of the children who were readmitted at the PICU (n = 8), 2 children were readmitted due to viral lower respiratory tract infections and 6 children were readmitted because of subglottic stenosis due to upper airway injury by endotracheal intubation.

*** 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%).

to sex, age at PICU admission, duration of invasive mechanical ventilation and PICU admission duration (ps ≥ .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 14/74 (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-β2-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 eTable 1. 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 confirm the pulmonary abnormalities assessed at the

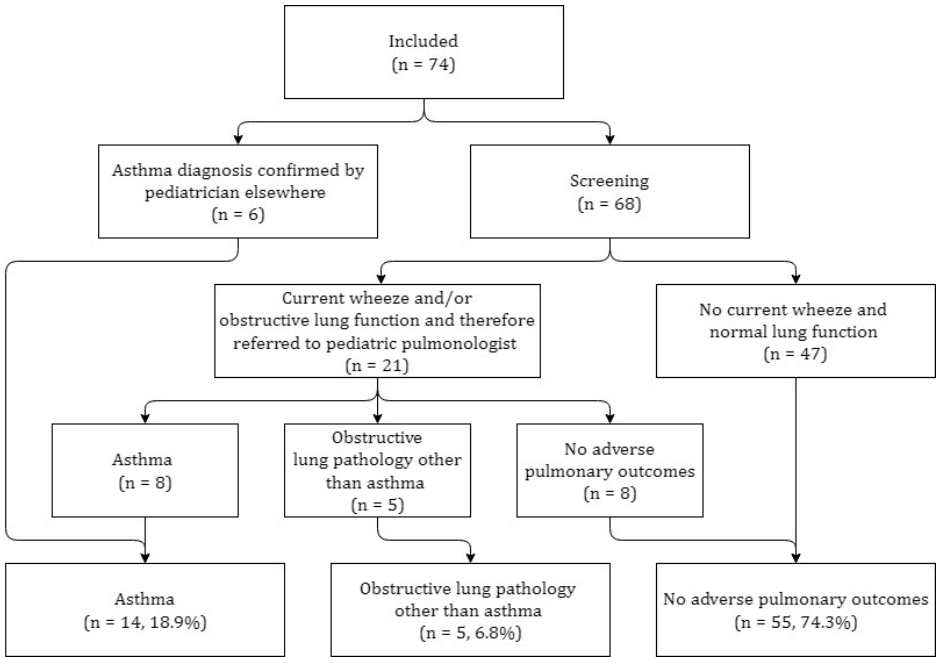

Figure 2. Flowchart of children with and without adverse pulmonary outcomes

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 to 36.0] p = .03 and 1.3 [95% CI 1.0 to 1.7] p = .04, respectively).

Table 2. Risk factors for adverse long-term pulmonary outcomes in general and for asthma

Explanatory factors	Odds Ratio (95% CI)	p-value	Nagelkerke R^2 (%)
Adverse pulmonary outcomes as outcome variable			
Duration of invasive mechanical ventilation (days)	1.2 (1.0-1.4)	.10	5.5
Asthma as outcome variable			
Atopic disease in family	6.4 (1.2- 36.0)	**.03**	20.9
Duration of invasive mechanical ventilation (days)	1.3 (1.0-1.7)	**.04**	

Note: 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 FiO_2. Boldface values indicate $p < .05$.

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 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 (versus 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-β2-agonists and corticosteroids in the period after PICU discharge and 1 year before follow-up.

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 (n = 19)	No adverse pulmonary outcome (n = 55)	p-value *
Sports performance (≥ 1x/week), n (%)	17 (89)	48 (87)	.80
Number of school days missed in last 12 months due to respiratory complaints, median (IQR)	1.0 (0.0-5.0)	0.0 (0.0-0.0)	**.002**
Number of antibiotic treatments after PICU discharge, median (IQR)	4.0 (2.0-9.0)	1.0 (0.0-4.0)	**.002**
Inhaled short-acting-β2-agonists used after PICU discharge, n (%)	18 (95)	31 (56)	**.004**
Inhaled short-acting-β2-agonists used last 12 months before follow-up, n (%)	11 (58)	4 (7)	**< .001**
Inhaled corticosteroids used after PICU discharge, n (%)	14 (74)	18 (33)	**.012**
Inhaled corticosteroids used last 12 months before follow-up, n (%)	5 (26)	2 (4)	**.006**

Note: IQR = interquartile range. Adverse pulmonary outcome = 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 < .05.
* Correction for false discovery rate applied.

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 years of age. 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 years follow-up after pediatric admission – not 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 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, 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 the 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-β2-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-β2-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 aged 0-12 years (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 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 out-patient PICU follow-up clinic, had adverse long-term pulmonary outcomes at 6-12 years of age. 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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ONLINE SUPPLEMENTAL MATERIAL

eTable 1. Lung function results (assessed by spirometry) of children with and without adverse pulmonary outcomes at follow-up

	All children (n = 68)*	**Adverse pulmonary outcome (n = 13)***	**No adverse pulmonary outcome (n = 55)**	**p-value**
Z-scores pre-salbutamol				
FEV1	-0.24 (1.01)	-1.21 (1.03)	-0.01 (0.87)	**< .001**
FVC	-0.00 (1.00)	-0.03 (0.92)	0.00 (1.02)	.92
FEV1/FVC	-0.33 (1.26)	-1.74 (0.86)	0.01 (1.10)	**< .001**
MMEF 75/25	-0.72 (1.14)	-2.28 (0.77)	-0.38 (0.90)	**< .001**
Z-scores post-salbutamol				
FEV1	0.31 (1.08)	-0.16 (1.29)	0.42 (1.00)	.15
FVC	0.19 (1.00)	0.29 (1.12)	0.17 (0.98)	.70
FEV1/FVC	0.19 (1.03)	-0.78 (0.83)	0.42 (0.94)	**< .001**
MMEF 75/25	-0.05 (1.08)	-1.04 (1.02)	0.18 (0.97)	**< .001**
% predicted pre-salbutamol				
FEV1	97.10 (11.91)	85.63 (12.38)	99.81 (10.14)	**< .001**
FVC	100.03 (11.83)	99.84 (10.84)	100.07 (12.15)	.95
FEV1/FVC	96.75 (9.26)	85.27 (9.16)	99.46 (6.97)	**< .001**
MMEF 75/25	85.04 (25.04)	52.78 (16.02)	92.07 (20.79)	**< .001**
% predicted post-salbutamol				
FEV1	103.54 (12.48)	98.22 (15.14)	104.80 (11.57)	.16
FVC	102.33 (11.91)	103.62 (13.29)	102.02 (11.68)	.67
FEV1/FVC	100.63 (6.66)	94.06 (6.71)	102.18 (5.67)	**< .001**
MMEF 75/25	99.97 (25.40)	77.49 (22.14)	105.28 (23.27)	**< .001**
% BDR change				
FEV1	6.88 (6.55)	14.92 (8.96)	4.98 (4.02)	**.002**
FVC	2.40 (4.22)	3.60 (2.89)	2.12 (4.45)	.26
FEV1/FVC	4.46 (6.15)	10.89 (7.74)	2.93 (4.60)	**.003**
MMEF 75/25	21.27 (24.87)	44.90 (30.57)	16.12 (20.37)	**< .001**

Note: All values are expressed as mean (SD). BDR = bronchodilator response; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MMEF 75/25 = maximal mid-expiratory flow at 25–75% of FVC; FEV1/FVC is also known as Tiffeneau index. Boldface values indicate $p < .05$.

*Adverse pulmonary outcome = asthma (n = 14) and obstructive lung pathology other than asthma (n = 5). In six children asthma was already diagnosed by a pediatrician and used inhaled corticosteroids during our follow-up, therefore their spirometry results are not provided in this table.

4 Intelligence outcome of pediatric intensive care unit survivors: a systematic meta-analysis and meta-regression

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ABSTRACT

Background: Long-term morbidity after pediatric intensive care unit (PICU) admission is a growing concern. Both critical illness and accompanying PICU treatments may impact neurocognitive development as assessed by its gold standard measure; intelligence. This meta-analysis and meta-regression quantifies intelligence outcome after PICU admission and explores risk factors for poor intelligence outcome.

Methods: PubMed, Embase, CINAHL and PsycINFO were searched for relevant studies, published from database inception until September 7, 2021. Using random-effects meta-analysis, we calculated the standardized mean difference in full-scale intelligence quotient (FSIQ) between PICU survivors and controls across all included studies and additionally distinguishing between PICU subgroups based on indications for admission. Relation between demographic and clinical risk factors and study's FSIQ effect sizes was investigated using random-effects meta-regression analysis.

Results: A total of 123 articles was included, published between 1973 and 2021, including 8,119 PICU survivors and 1,757 controls. We found 0.47 SD (7.1 IQ-points) lower FSIQ scores in PICU survivors compared to controls (95%CI -0.55 to -0.40, $p < .001$). All studied PICU subgroups had lower FSIQ compared to controls (range 0.38-0.88 SD). Later year of PICU admission (range 1972-2016) and longer PICU stay were related to greater FSIQ impairment (R^2 = 21%, 95%CI -0.021 to -0.007, $p < .001$ and R^2 = 2%, 95%CI -0.027 to -0.002, $p = .03$, respectively), whereas male sex and higher rate of survivors were related to smaller FSIQ impairment (R^2 = 5%, 95%CI 0.001 to 0.014, $p = .03$ and R^2 = 11%, 95%CI 0.006 to 0.022, $p < .001$, respectively). Meta-regression in PICU subgroups showed that later year of PICU admission was related to greater FSIQ impairment in children admitted after cardiac surgery and heart- or heart-lung transplantation. Male sex was related to smaller FSIQ impairment in children admitted after cardiac surgery. Older age at PICU admission and older age at follow-up were related to smaller FSIQ impairment in children admitted after heart- or heart-lung transplantation.

Conclusions: PICU survivors, distinguished in a wide range of subgroups, are at risk of intelligence impairment. Length of PICU stay, female sex and lower rate of survivors were related to greater intelligence impairment. Intelligence outcome has worsened over the years, potentially reflecting the increasing percentage of children surviving PICU admission.

BACKGROUND

Due to major advances in pediatric critical care, the survival rate of children admitted to the pediatric intensive care unit (PICU) has increased dramatically in the past decades [1,2]. Nevertheless, long-term morbidity after PICU admission is a growing concern [2-8]. Both the critical illness and the accompanying PICU treatments may impact neurocognitive development as assessed by its gold standard measure intelligence. Intelligence is associated with important life outcomes, such as physical and mental health [9,10], academic achievement [11], socioeconomic success [12], and life chances in general [10]. These findings highlight intelligence as an important outcome after PICU admission.

Several pathophysiological mechanisms are proposed that may impair long-term intelligence outcome of critically ill patients, including hypoxia, metabolic derangements such as glucose dysregulation, ischemia, inflammation, hypotension and delirium [13-15]. These mechanisms may be influenced by the underlying disease [16], critical illness [17] and associated treatments at the PICU [18]. A previous systematic review [19], including 12 studies of which the majority reported on children admitted for sepsis, identified an increased risk of intelligence impairment among PICU survivors. However, meta-analytic quantification of the magnitude of intelligence impairment was not performed, and the available data did not allow to systematically explore predictive factors of intelligence outcome. Given the distinct heterogeneity in the PICU population (e.g. admission indication, associated treatments and age), it is of great importance to determine intelligence outcome of PICU survivors and identify risk factors for poor intelligence outcome.

The current meta-analysis and meta-regression aims to (1) quantify intelligence outcome of PICU survivors; and (2) explore risk factors for poor intelligence outcome. The results of this study will provide valuable information for prognosis and early identification of children at risk for neurocognitive impairment, facilitating determination of the need for follow-up and/or early intervention after PICU discharge.

METHODS

Study selection

Inclusion criteria for studies were: (1) the study sample consisted of PICU survivors who had been admitted to a general PICU or specialized PICU; (2) full-scale intelligence quotient (FSIQ) was assessed after PICU hospitalization using (short-forms of) standardized and validated tests; and (3) published in a peer-reviewed journal. Exclusion criteria were: (1) the study reported insufficient data to allow calculation of the individual study's effect size; (2) the study sample comprised > 5% patients suffering

from hereditary syndromes with known intelligence impairment (e.g. Down syndrome); (3) part of the sample comprised children hospitalized at other facilities than the PICU; (4) sample size < 10 children; (5) the study was written in Chinese; (6) the study could not be retrieved via our research institutes or via the authors. In case multiple articles reported on (partly) overlapping cohorts, only one article was selected that reported on (in order of importance): (1) the longest follow-up period; (2) the largest sample size; (3) the most extensive set of risk factors for intelligence impairment.

PubMed, Embase, CINAHL and PsycINFO were searched, without language or date restriction (last search September 7, 2021), using combinations of search terms relating to the (1) PICU, (2) children and (3) intelligence. The complete search strategy is provided in Additional file 1. Studies identified by our search were reviewed by two independent authors and disagreements were solved through discussion or by consulting a third author. Reference lists of the included studies were screened. This meta-analysis was conducted according to PRISMA guidelines.[20] The review protocol was registered in the International Prospective Register of Systematic Reviews, PROSPERO (#CRD42020197282) [21].

Outcomes and covariates

We extracted descriptives on FSIQ of the PICU sample (and healthy control sample, if available) and extracted a broad range of demographic and clinical variables as potential risk factors for poor intelligence outcome. The extracted variables were variables reported at least once in the ten most recently published included articles (see Additional file 1: Table S1). In addition, in articles focusing on cardiac surgery and heart- or heart-lung transplantation, we also extracted the percentage of patients receiving cardiopulmonary bypass (CPB) and/or deep-hypothermic circulatory arrest (DHCA) during surgery, CPB duration during surgery, and the percentage of patients with cyanotic heart disease. To be extracted from an article, the reported risk factor was required to be calculated on at least 75% of the PICU sample. In case only median FSIQ was reported, we calculated the mean [22] and standard deviation (SD) [23]. In case SD of FSIQ was not provided, we used the normative SD (i.e. 15). Two reviewers independently extracted data. Any disagreements were solved through discussion or by consulting a third author.

Study quality

Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies [24]. According to the manual, the scale was adapted to fit the goal of this study (see Additional file 1 for more information [24-26]). All included studies were independently rated by two authors and disagreements were solved through discussion or by consulting a third author.-

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis Software version 3.0 [27]. For each individual study, FSIQ differences between PICU survivors and either healthy children or normative data were expressed in terms of standardized mean difference scores (Cohen's *d*) and used as effect size. In case no healthy control group was included in a study, we used normative data for FSIQ (i.e. mean 100 and SD 15) assuming the same sample size as the PICU sample. Cohen's *d* values of 0.2, 0.5 and 0.8, were used to define thresholds for small, medium and large effect sizes, respectively [28].

We calculated a meta-analytic effect size for FSIQ based on all included PICU samples. If a study reported on multiple patient samples separately, one combined effect size was calculated across patient samples before meta-analytic aggregation across studies [29]. In addition, we calculated meta-analytic effect size for a number of PICU subgroup based on the reported indications for PICU admission in the included studies. The available studies allowed to distinguish subgroups of children admitted for: (1) respiratory and/or circulatory insufficiency necessitating ECMO, (2) circulatory insufficiency necessitating CPR (3) traumatic brain injury (4) sepsis and/or meningoencephalitis (5) cardiac surgery (6) heart- or heart-lung transplantation and (7) miscellaneous PICU admission indications. The effect size of each study was weighted by the inverse of its variance to account for sample size and measurement error. Random-effects meta-analysis was performed, recognizing sources of inter-sample variance. Dispersion in effect sizes was quantified using I^2, discriminating between mild (I^2 < 30), moderate (I^2 = 30-50) and strong heterogeneity (I^2 > 50) [30]. Indications for publication bias were evaluated using funnel plots and the Egger's test of asymmetry [31], while the robustness of the meta-analytic effect sizes was calculated by the fail-safe N value, where values > $5k + 10$ were considered robust [32].

In order to determine risk factors for poor intelligence outcome, aggregated effect sizes of PICU subgroups were compared by Cochran's Q to study whether subgroups differ in the risk for poor intelligence outcome. Subsequently, random-effects meta-regression analyses were performed to quantify the association of each of the demographic and clinical risk factors and the study's effect sizes for FSIQ. These analyses were performed in the total sample of selected studies and in each PICU subgroup. Meta-regression analyses with < 10 observations were omitted [33].

RESULTS

Figure 1 shows the study selection process. Full-text examination revealed 123 eligible studies, published between 1973 and 2021 and comprising 8,119 PICU survivors. Thirty-three studies contained a healthy control group, representing 1,757 healthy

control children. Mean year of PICU admission was 2000 (range 1972-2016, *k* = 99), mean percentage of boys was 59.1% (range 27.0-80.8%, *k* = 103), mean gestational age was 39.2 weeks (range 35.7-40.6 weeks, *k* = 46), mean age at PICU admission was 22.4 months (range 0.0-159.6, *k* = 103), mean time to follow-up was 68.8 months (range 0-231.6, *k* = 107) and mean age at follow-up was 92.8 months (range 30.1-307.2 months, *k* = 112). Additional file 1: Table S1 and S2 provide details of all included studies. Inter-rater agreement was 77.4% for study eligibility and 93.3% for quality assessment. The results of quality assessment at the group level are displayed in Figure 2.

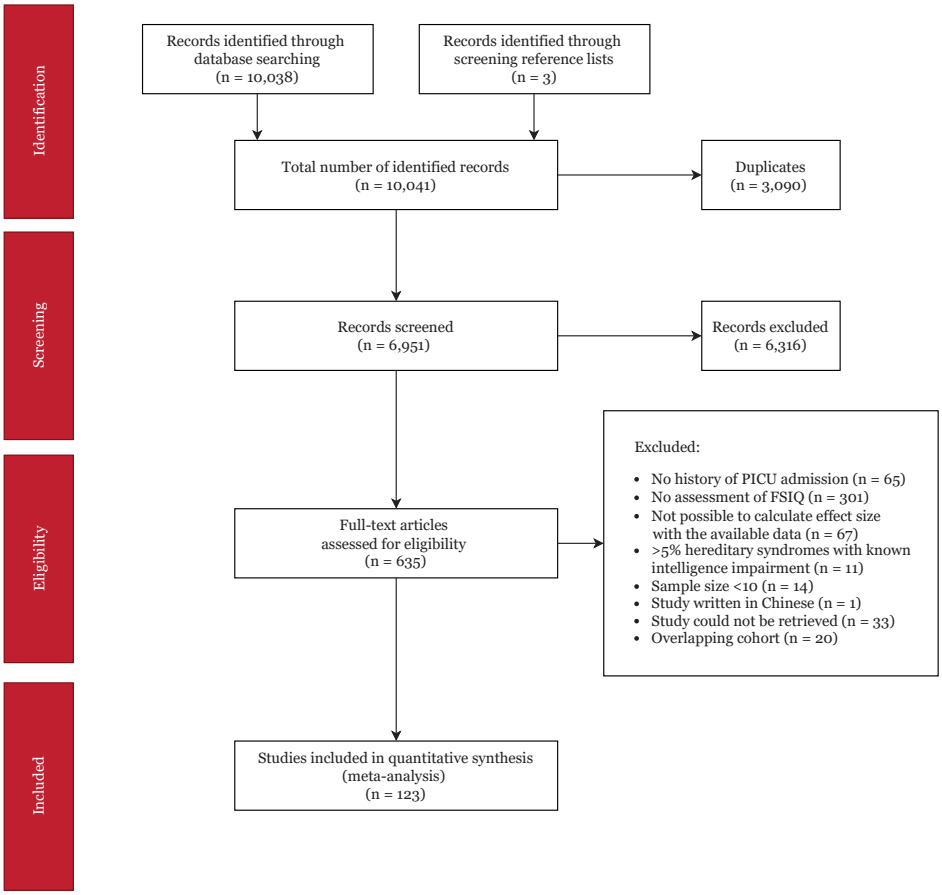

Figure 1. PRISMA flowchart of the study selection procedure.
Note: FSIQ = full-scale intelligence quotient, PICU = pediatric intensive care unit.

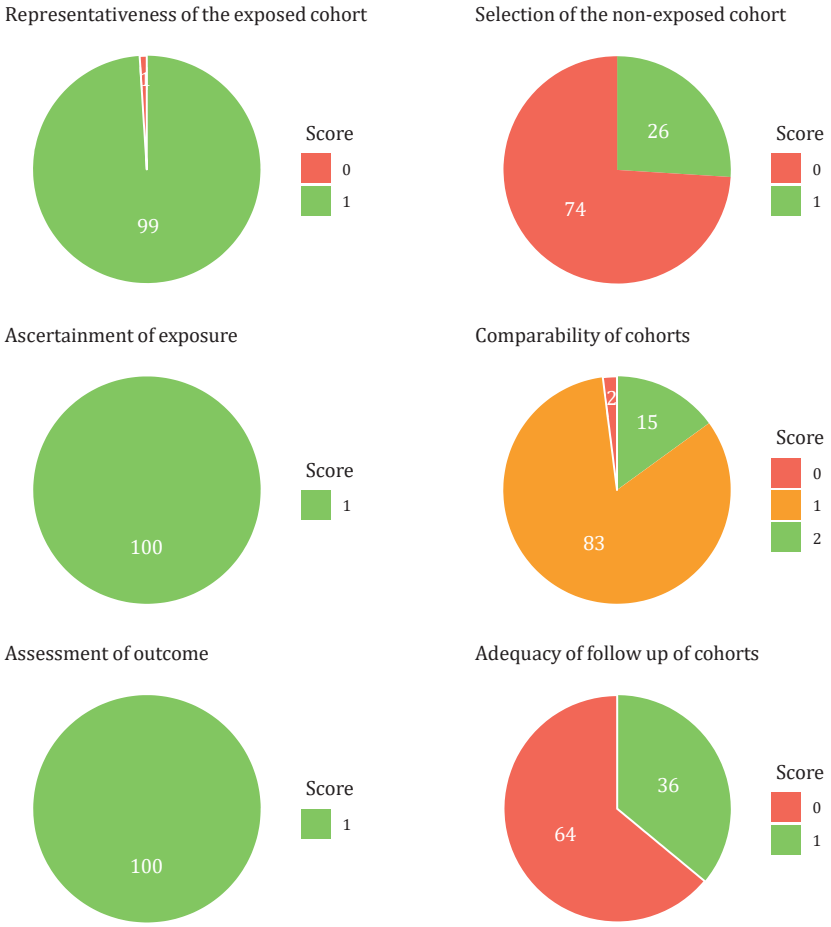

Figure 2. Overview of Quality assessment results.
Note: Labels display percentages. Higher scores indicate higher study quality. See Supplemental Information for more information on the Newcastle Ottawa scale.

FSIQ

The results of meta-analysis aggregating the results of all 123 studies comparing PICU samples to either healthy controls or normative data (further referred to as controls) are displayed in Figure 3. The results reveal a small-sized aggregated effect size of *d* -0.47 (95% CI -0.55 to -0.40, $p < .001$), translating into a FSIQ impairment of on average 7.1 points in PICU survivors. There was strong heterogeneity in the individual study's effect sizes ($I^2 = 71.20$; $p < .001$).

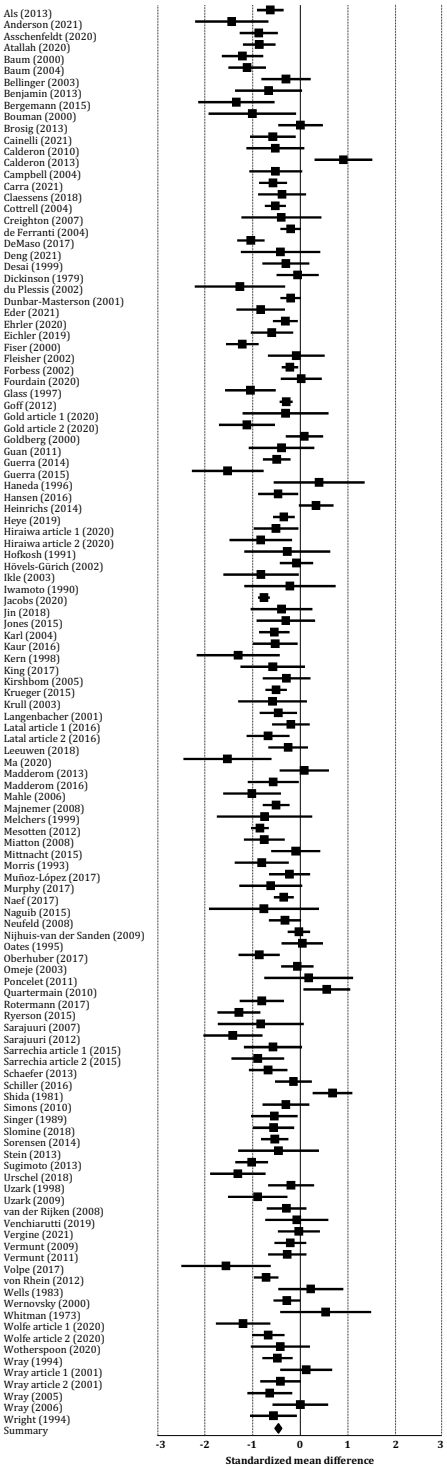

Figure 3. Forest plot showing standardized mean differences and accompanying 95% CI of studies comparing FSIQ of PICU survivors to healthy controls or normative data.

Risk factors

To study possible sources of the heterogeneity in the individual study's effect sizes, we analysed subgroups of children based on the reported reasons for PICU admission. All subgroups had significantly lower FSIQ scores than controls (Table 1 and Additional files 2-8: Figures S1-7). The role of PICU subgroup as risk factor was determined by comparison of the aggregated effect sizes for FSIQ between subgroups. The results indicate that children admitted after heart- or heart-lung transplantation had significantly greater FSIQ impairment (d = -0.80) compared to children admitted after cardiac surgery (d = -0.38, Q = 9.48 , p = .002) and compared to children admitted for sepsis and/or meningoencephalitis (d = -0.39, Q = 5.85, p = .02). Other comparisons between subgroups revealed no significant differences.

The relation between demographic and clinical risk factors and the study's individual effect sizes for FSIQ was investigated using meta-regression in the total sample (Table 2). Later year of PICU admission was significantly related to greater FSIQ impairment (R^2 = 21%, see also Figure 4), indicating that intelligence outcome of PICU survivors dropped with an average of 2.1 IQ-points every decade between 1972-2016. Furthermore, sex was significantly related to FSIQ (R^2 = 5%). This finding indicates that one percentage increase in the percentage of boys in a study was related to an increase of on average 0.1 IQ-points (range studied 27.0-80.8%). In addition, longer PICU stay was significantly related to greater FSIQ impairment (R^2 = 2%), indicating that intelligence outcome of PICU survivors dropped with an average of 1.5 IQ-points every additional week of PICU stay (range studied 0.3-35.4 days). Lower rate of survivors (range studied 38.2-100%) was significantly related to greater FSIQ impairment (R^2 = 11%), which suggests that survivors in samples with higher mortality have poorer intelligence outcome. Last, higher study quality, as rated on the Newcastle-Ottawa Scale (range 3-7), was significantly related to greater FSIQ impairment (R^2 = 7%). No other significant relationships were observed. Of note, no multivariate meta-regression analysis was conducted, because of the low number of studies (k = 29) that reported all risk factors that were found significantly related to FSIQ in the univariate meta-regression analysis, which would lead to biased and underpowered analysis.

Meta-regression in PICU subgroups was possible (i.e. > 10 observations) in the subgroups of children with respiratory and/or circulatory insufficiency necessitating ECMO, cardiac surgery and heart- or heart-lung transplantation (Additional file 1: Table S3). Among children admitted after cardiac surgery, later year of PICU admission (range 1972-2013), lower percentage of boys (range 30.3-79.4%) and higher study quality (range 3-7), were related to greater FSIQ impairment (R^2 = 12%, 6% and 9%, respectively). Among children admitted after heart- or heart-lung transplantation, later year of PICU admission (range 1989-2016), younger age at PICU admission (range 1.6-118.4 months) and younger age at follow-up (range 40.7-166.8 months) were related to

greater FSIQ impairment (R^2 = 65%, 74% and 68%, respectively). None of the other risk factors were related to FSIQ impairment in any of the subgroups.

Table 1. Meta-analytic findings and results of the publication bias analyses for PICU subgroups.

Subgroup	*k*	Cohen's *d*	95% CI	Difference in IQ-points	Egger test of asymmetry (p-value)	Fail-safe N
Respiratory and/or circulatory insufficiency necessitating ECMO	10	-0.52 **	-0.81, -0.22	-7.76	.10	88
Circulatory insufficiency necessitating CPR	3	-0.88 **	-1.39, -0.37	-13.23	.13	19
Traumatic brain injury	3	-0.86 **	-1.48, -0.24	-12.84	.48	8
Sepsis and/or meningoencephalitis[a]	5	-0.39 ***	-0.61, -0.18	-5.88	.43	15
Cardiac surgery	80	-0.38 ***	-0.46, -0.30	-5.75	.59	5077
Heart- or heart-lung transplantation	14	-0.80 ***	-1.06, -0.55	-12.06	.44	368
Miscellaneous PICU admission indications	14	-0.55 ***	-0.75, -0.34	-8.19	.07	426

Note: *k* = number of samples; CPR = cardio-pulmonary resuscitation; ECMO = extra-corporeal membrane oxygenation; PICU = pediatric intensive care unit. Difference in IQ-points compared to healthy controls or normative data.
* p<.05. ** p<.01. *** p<.001.
[a] This subgroup contains one sample with non-neurological sepsis.

Table 2. Results of univariate meta-regression analyses of demographic and clinical risk factors for FSIQ impairment.

Risk factors	*k*	Beta	95% CI	R^2 (%)	Range studied
Year of PICU admission	104	-0.014 ***	-0.021, -0.007	21	1972-2016
Sex (% boys)	107	0.007 *	0.001, 0.014	5	27.0-80.8
Gestational age (weeks)	49	-0.069	-0.188, 0.051	0	35.7-40.6
Age at PICU admission (months)	107	0.000	-0.002, 0.002	1	0.0-159.6
Mechanical ventilation (days)	21	-0.011	-0.030, 0.007	0	0.0-41.5
PICU stay (days)	36	-0.014 *	-0.027, -0.002	2	0.3-35.4
Resuscitation (%)	22	-0.005	-0.011, 0.001	2	0.0-100
ECMO (%)	28	-0.002	-0.005, 0.002	0	0.0-100
Rate of survivors (%)	56	0.014 ***	0.006, 0.022	11	38.2-100
Age at follow-up (months)	117	0.000	-0.001, 0.001	0	30.1-307.2
Time to follow-up (months)	110	-0.000	-0.002, 0.001	0	0.1-231.6
Study quality	129	-0.109 *	-0.198, -0.020	7	3-7

Note: *k* = number of samples; ECMO = extra-corporeal membrane oxygenation; PICU = pediatric intensive care unit; Study quality was assessed by the Newcastle Ottawa Scale for cohort studies, revised to a maximum of 7 points. Unstandardized Beta's are reported.
*p<.05. **p<.01. ***p<.001.

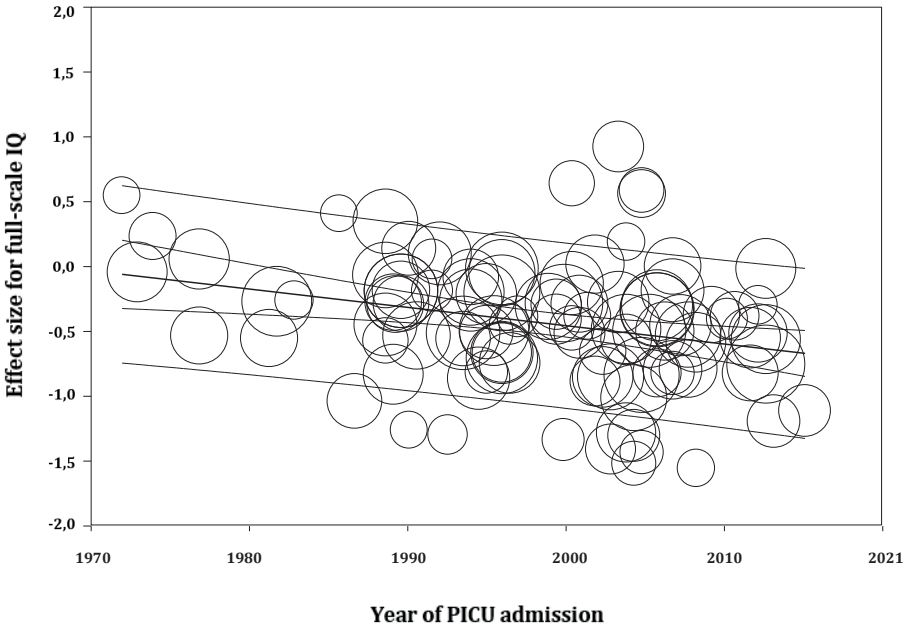

Figure 4. Association between year of PICU admission and study's individual effect sizes for FSIQ.
Note: Plotting characters are proportional to the study weight.

Publication bias

Inspection of the funnel plot in the total sample did not suggest publication bias (Additional file 9: Figure S8), Egger's test of asymmetry was not significant (p = .50) and the fail-safe N (N = 7,559) indicated that the obtained effect size was robust. Similar results were obtained in the PICU subgroups, with the exception that the fail-safe N values did not support the robustness of the effect sizes obtained in the subgroups of children admitted for circulatory insufficiency necessitating CPR, traumatic brain injury and children with sepsis and/or meningoencephalitis (Table 1).

Use of normative data in uncontrolled studies

We explored the validity of using normative data for the calculation of effect sizes in studies not including a healthy control group. Hence, we calculated effect sizes for studies including a healthy control group (k = 31) with two approaches: (1) using data of the healthy control group and (2) using normative data (i.e. mean 100 and SD 15) . Comparisons between the effect sizes retrieved with these two methods revealed a significant difference (Q = 39.5, p < .001), with the approach using healthy control group data resulting in a larger aggregated effect size (healthy control group: d = -0.62, 95% CI -0.74 to -0.51, p < .001 vs. normative data: d = -0.00, 95% CI -0.16 to 0.16, p = .99). This finding was replicated when selecting only those studies with a healthy control group that also tested and confirmed comparability of the PICU and healthy control groups

in terms of sex, age and socioeconomic status (most often defined by parental level of education; k = 14; Q = 35.5, p < .001). These findings indicate that the use of normative data yields conservative estimates of FSIQ impairment in PICU survivors.

DISCUSSION

This meta-analysis and meta-regression aimed to (1) quantify intelligence outcome after PICU admission; and (2) explore risk factors for poor intelligence outcome. Based on 123 studies including 8,119 PICU survivors and 1,757 healthy control children, our results demonstrate 0.47 SD lower intelligence scores in PICU survivors compared to controls (healthy control children or normative data), corresponding to an average difference of 7.1 IQ-points. Accordingly, the prevalence of children with intellectual disability (FSIQ <2 SD [34]) is expected to be threefold higher in PICU survivors (6.4%) than in the general population (2.3%). Intelligence reflects the ability to efficiently process information for goal-directed behavior and is known to be related to physical and mental health [9,10,35], academic achievement [11], socioeconomic success [12] and survival to old age [35]. Even a small difference in intelligence can affect profound effects on life chances [10]. These findings highlight the relevance of intelligence outcome and stress the relevance of structured neurocognitive follow-up of PICU survivors.

The results of our study show intelligence impairment across all PICU subgroups investigated, with effect sizes ranging between -0.38 and -0.88 SD. Children admitted after heart- or heart-lung transplantation had significantly greater intelligence impairment (-0.80 SD) compared to children admitted after cardiac surgery (-0.38 SD), and compared to children admitted for sepsis and/or meningoencephalitis (-0.39 SD). This finding may reflect the greater disease severity, greater intensity of PICU treatments, and/or greater intensity of surgical treatment(s) of children admitted after heart- or heart-lung transplantation. The results on the PICU subgroups in the current study are in line with earlier literature overviews [36-42] and extend these findings by the unique focus on children admitted to the PICU and by providing comprehensive meta-analytic quantification of intelligence impairment.

Meta-regression allowed to study a broad range of demographic and clinical risk factors for intelligence outcome. The results showed that later year of PICU admission (range studied 1972 – 2016) was related to greater intelligence impairment (R^2 = 21%). This finding may reflect the increasing medical attainments that have not only led to increased survival rates of children admitted to the PICU, but also to increasing morbidity rates in those surviving [1,2,43]. This hypothesis does not find direct support by the contrasting observation that lower rate of survivors (range studied: 38.2-100%) was related to greater intelligence impairment (R^2 = 11%). However, differences between

survival rate in this analysis may not only reflect potential trends over time, but also differences in the severity of critical illness between conditions that may influence intelligence outcome. In line with this idea, results showed that longer PICU stay (range studied 0.3-35.4 days) was related to greater intelligence impairment (R^2 = 2%). This finding may reflect the greater disease severity and/or the greater intensity of PICU treatments of children with longer PICU stay, which may have affected their long-term neurocognitive outcome. Our findings are corroborated by a recent systematic review which also showed that length of PICU stay was related to poorer neurocognitive functioning at discharge [44]. Of note, our current findings indicate that boys had on average better intelligence outcome than girls (R^2 = 5%), i.e. every 10 percentage points increase in the amount of boys was related to an increase of on average 1 IQ-point (range studied 27.0-80.8%). No evidence was found for a confounding effect, i.e. girls were not overrepresented in any of the PICU subgroups. The mechanisms underlying sex differences with respect to prevalence and outcome of several neurological conditions are currently not well understood [45]. Sex differences exist in, among others, different states in neuroinflammation [45] and (hormonal) reaction to stress [46-48]. These sex differences may possibly lead to differences in neurocognitive development of PICU survivors. Understanding the mechanisms behind sex differences could help develop more targeted therapy. At last, meta-regression showed that higher study quality was related to greater intelligence impairment (R^2 = 7%). This aligns with the findings of our additional analysis, which showed that the use of the normative mean instead of control group data provides conservative estimates of intelligence impairment.

Regarding subgroups, the meta-regression findings of the total sample were replicated in the subgroup of children admitted after cardiac surgery, with the exception that length of PICU stay and rate of survivors were not significantly related to intelligence in this subgroup. Interestingly, longer CPB duration was not related to greater intelligence impairment. This finding contrasts with existing literature from adults showing that CPB duration is related to length of intensive care unit and hospital stay and in-hospital mortality [49]. Taken together, the potential relation between CPB duration and complication risk may not translate into intelligence outcome in children. The results of this study further show that later year of PICU admission was also related to greater intelligence impairment in children with heart- or heart-lung transplantation. In addition, results indicate that younger age at PICU admission was related to greater intelligence impairment in this subgroup. One possible explanation for this finding may be that the main reasons for heart transplantation differ with age (i.e. < 1 year congenital heart disease, > 1 year cardiomyopathy)[50] and congenital heart disease may impact brain development already before birth [51]. We also found that older age at follow-up was associated with smaller intelligence impairment in this subgroup, suggesting that intelligence outcome after heart- or heart-lung transplantation may improve over time.

Intelligence impairment in PICU survivors may be caused by complex interaction between factors related to premorbid functioning [52], underlying disease [53], critical illness [17] and intensive care treatment [54], which influence pathophysiological mechanisms involving (a combination of) hypoxia, metabolic derangements such as glucose dysregulation, ischemia, inflammation, hypotension, delirium and potential negative effects of sedation [13-15]. We can only speculate about the specific active (combination) of underlying mechanisms that fuel intelligence impairment in critically ill children admitted to the PICU, which is also likely to differ between subgroups. Nevertheless, our study indicates the need for appropriate prospective studies that provide insight into the potential contribution of pathophysiological mechanisms to intelligence outcome. Such studies may expose potential targets for treatment innovations that may benefit outcome of PICU survivors.

One limitation of this study is that a limited number of possible risk factors was assessed in the included studies (e.g. none of the studies assessed medical history prior to or after PICU admission) and the number of missing data for demographic and clinical potential risk factors was considerable. This reduced the power to identify risk factors (particularly in subgroups). Nevertheless, the available data did allow us to study a broad range of risk factors in the total sample of studies. Furthermore, the current study is limited by the availability of studies into intelligence outcome after PICU admission, with the available studies likely not being fully representative of the typical PICU population in terms of reasons for admission. Our study shows that a substantial number of studies is published mainly on the subgroup of children admitted after cardiac surgery, while other subgroups are less well studied or not at all. For example, we were not able to identify studies including children with respiratory insufficiency necessitating mechanical ventilation or renal insufficiency necessitating renal replacement therapy in our broad and extensive systematic search, while these are important indications for PICU admission [1,2] and concerns about neurocognitive development of these PICU subgroups exist [4]. This limits the generalizability of our results to the PICU population as a whole and underscores the need for more follow-up studies on these populations. A strength of our study is that with our broad and extensive systematic search we included a considerable number of studies and we were able to aggregate all existing data on intelligence outcome of PICU survivors, to systematically report on subgroups and to comprehensively study risk factors for intelligence impairment. Second, we showed that the use of normative data might underestimate the estimates of intelligence impairment in PICU survivors. Critical appraisal of the role of control data used is important, as normative data are frequently used in research and this may considerably influence the results and conclusions of studies.

CONCLUSION

In this meta-analysis, robust evidence was found for a risk of intelligence impairment in PICU survivors, applying to a wide range of PICU subgroups. The results further indicate worsening intelligence outcome in the PICU populations over the years (between 1972-2016), potentially reflecting the increasing percentage of children surviving PICU admission with morbidity. In addition, the results indicate that longer length of PICU stay, female sex and lower rate of survivors negatively influence intelligence outcome after PICU admission. The findings of this meta-analysis warrant the need for structured neurocognitive follow-up of PICU survivors.

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ONLINE SUPPLEMENTAL MATERIAL

Search strategy

("Extracorporeal Membrane Oxygenation"[Mesh] OR extracorporeal membrane oxygenation*[tiab] OR ECMO*[tiab] OR extracorporeal life support*[tiab] OR ECLS*[tiab] OR extra corporeal membrane oxygenation*[tiab] OR extracorporeal pump oxygenation*[tiab] OR extrapulmonary oxygenation*[tiab] OR extracorporeal oxygenation*[tiab] OR "Thoracic Surgical Procedures"[Mesh] OR "Thoracic Surgery"[Mesh] OR "Thorax/surgery"[Mesh] OR cardiac surg*[tiab] OR heart surg*[tiab] OR thoracic surg*[tiab] OR cardiac surg*[tiab] OR heart surg*[tiab] OR cardiothoracic surg*[tiab] OR chest surg*[tiab] OR chest wall surg*[tiab] OR thorax surg*[tiab] OR thoracic operation*[tiab] OR "Critical Care"[Mesh] OR "Intensive Care Units, Pediatric"[Mesh] OR "Critical Illness"[Mesh] OR intensive care[tiab] OR PICU*[tiab] OR IC[tiab] OR ICU*[tiab] OR critical ill*[tiab] OR critically ill*[tiab])

AND

("Child"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh:NoExp] OR "Infant, Newborn"[Mesh:NoExp] OR "Pediatrics"[Mesh] OR child*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR infant*[tiab] OR adoles*[tiab] OR teen*[tiab] OR youth*[tiab] OR schoolchild*[tiab] OR preschool[tiab] OR pre-school[tiab] OR kid[tiab] OR kids[tiab] OR toddler*[tiab] OR juvenil*[tiab] OR teen*[tiab] OR pubescen*[tiab] OR puber*[tiab] OR prepubert*[tiab] OR school age*[tiab] OR schoolage*[tiab] OR boy*[tiab] OR girl*[tiab] OR underag*[tiab] OR under ag*[tiab])

AND

("Neurocognitive Disorders"[Mesh] OR "Cognition"[Mesh] OR "Neuropsychology"[Mesh] OR "Intelligence"[Mesh] OR neurocogniti*[tiab] OR cogniti*[tiab] OR neurodevelopment*[tiab] OR neuropsycholog*[tiab] OR intelligence[tiab] OR intellectual[tiab] OR IQ[tiab])

NOT

("fetal growth retardation"[Mesh] OR fetal growth retardat*[tiab] OR fetal growth restrict*[tiab] OR intrauterine growth restrict*[tiab] OR small for gestation*[tiab] OR Intrauterine Growth retardat*[tiab] OR prematur*[tiab] OR preterm[tiab] OR low birth weigh*[tiab] OR SGA[tiab] OR IUGR[tiab])

Table S1. Details on PICU groups studied in the included studies.

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Als (2013)	sepsis and/or meningoencephalitis	UK	NA	NA	NA	NA	120.83	4.10	NA	NA	NA	2008	NA	NA	NA	NA	NA
Als (2013)	miscellaneous	UK	NA	NA	NA	NA	115.75	1.18	NA	NA	NA	2008	NA	NA	NA	NA	NA
Anderson (2021)	heart- or heart-lung tx	Canada	54.3	NA	NA	NA	NA	NA	NA	NA	NA	2005	100	215.8	24.29	NA	80
Asschenfeldt (2020)	cardiac surgery	Denmark	30.3	NA	307.2	231.6	93.6	1.28	NA	NA	NA	1995	100	51.3	0	0	NA
Atallah (2020)	cardiac surgery	Canada	70.60	39.0	56.6	56.3	0.3	25.3	21.4	5.9	1.5	2003	100	113.1	100	100	58
Baum (2000)	heart- or heart-lung tx	USA	NA	NA	84	82.3	1.7	NA	NA	NA	NA	NA	100	NA	100	NA	73
Baum (2004)	heart- or heart-lung tx	USA	58	39.4	76.8	75.16	1.64	NA	NA	NA	NA	NA	100	NA	100	90.9	NA
Bellinger (2003)	cardiac surgery	USA	76.32	39.74	98.37	98.04	0.33	NA	NA	NA	NA	1990	100	108.3	100	100	96
Benjamin (2013)	miscellaneous	USA	68.75	38.5	62.8	62.3	0.5	NA	33.33	NA	25	2003	NA	NA	NA	NA	63
Bergemann (2015)	cardiac surgery	Germany	60.09	NA	95.83	95.52	0.32	NA	NA	12.27	NA	2000	100	88.6	26.32	100	NA
Bouman (2000)	miscellaneous	The Netherlands	54.55	NA	124.83	124.8	0.03	NA	35.77	NA	0	NA	NA	NA	NA	NA	NA
Brosig (2013)	cardiac surgery	USA	64.70	38.20	60	59.79	0.21	NA	NA	NA	11.8	2002	100	328.5	100	100	88
Cainelli (2021)	cardiac surgery	Italy	57	NA	87.12	79.92	15.20	6.60	NA	NA	NA	NA	100	127	NA	NA	NA
Calderon (2010)	cardiac surgery	France	66.67	NA	88	87.5	0.5	NA	NA	0	NA	2001	100	NA	NA	100	NA
Calderon (2013)	cardiac surgery	France	66.67	38.91	65.75	65.52	0.23	6.55	NA	NA	NA	2004	100	130.1	0	100	NA
Campbell (2004)	TBI	Canada	**NA**	40	NA	27	NA	NA	NA	NA	NA	1995		NA	NA	NA	87
Carra (2021)	cardiac surgery	Belgium	64	NA	30.1	24	6.1	7	NA	0	NA	2013	89	77	4	62	95.9

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Claessens (2018)	cardiac surgery	The Netherlands	79.41	39.28	71	70.66	0.34	NA	NA	NA	NA	2010	100	NA	NA	58.82	92
Cottrell (2004)	cardiac surgery	USA	**NA**	NA	48	45	3	NA	NA	NA	NA	1994	100	NA	100	100	NA
Creighton (2007)	cardiac surgery	Canada	68.85	NA	60	59.31	0.69	NA	NA	NA	NA	1997	100	75.8	75.42	100	78
de Ferranti (2004)	cardiac surgery	USA	75	40.04	96	95.73	0.27	NA	NA	NA	NA	1990	100	NA	50.88	100	NA
DeMaso (2017)	cardiac surgery	USA	71.43	39.3	168	**NA**	NA	NA	NA	NA	NA	**NA**	100	NA	NA	100	NA
Deng (2021)	sepsis and/or meningoencephalitis	Australia	54.5	NA	66.61	47	19.59	3	NA	NA	NA	2011	NA	NA	NA	NA	NA
Desai (1999)	ECMO	USA	**NA**	40.55	63.55	63.47	0.08	NA	NA	19.19	100	1989	NA	NA	NA	NA	NA
Dickinson (1979)	cardiac surgery	UK	**NA**	NA	53.42	42.54	10.88	NA	NA	NA	NA	1973	100	NA	100	65.79	64
du Plessis (2002)	cardiac surgery	USA	**NA**	NA	81.6	76.8	4.8	NA	NA	NA	NA	1990	100	83.5	70	70	92
Dunbar-Masterson (2001)	cardiac surgery	USA	76	39.8	100.15	99.88	0.27	6.7	NA	NA	NA	1990	100	108	100	100	96
Eder (2021)	miscellaneous	Germany	54	NA	126	70.3	55.7	19.9	NA	0.0	NA	2012	NA	NA	NA	NA	NA
Ehrler (2020)	cardiac surgery	Switzerland	65	NA	122.4	**NA**	NA	NA	NA	NA	NA	2006	100	NA	NA	36	91
Eichler (2019)	cardiac surgery	Germany	41.03	39	87.6	74.76	12.84	NA	NA	NA	NA	2009	100	NA	NA	0	99
Fiser (2000)	miscellaneous	USA	62	NA	147	0	147	NA	**NA**	NA	NA	NA	NA	NA	NA	NA	NA
Fleisher (2002)	cardiac surgery	USA	73	40	79.19	72	7.19	NA	**NA**	NA	NA	1992	100	102	NA	NA	NA
Fleisher (2002)	heart- or heart-lung tx	USA	44	40	79.52	72	7.52	NA	6.38	NA	NA	1992	100	93	100	NA	NA
Forbess (2002)	cardiac surgery	USA	56.79	NA	67.72	58.63	9.09	5	**NA**	NA	NA	1996	82	133	40	NA	NA

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Fourdain (2020)	cardiac surgery	Canada	46.3	38.7	44.1	43.51	0.59	6.5	NA	NA	NA	NA	67.5	161.9	NA	57.5	NA
Glass (1997)	ECMO	USA	69.16	38.91	60.50	60	0.50	NA	0.10	NA	100	1987	NA	NA	NA	NA	NA
Goff (2012)	cardiac surgery	USA	56.61	38	54	53.61	0.39	NA	**NA**	NA	NA	2000	100	49	57	NA	87
Gold article 1 (2020)	miscellaneous	Canada	42.90	NA	143.16	13.80	129.36	NA	**NA**	NA	NA	2013	NA	NA	NA	NA	NA
Gold article 2 (2020)	heart- or heart-lung tx	Canada	28.0	NA	79.65	69.88	9.77	31.1	NA	NA	8	2016	100	NA	NA	NA	NA
Goldberg (2000)	cardiac surgery	USA	66.67	NA	57.6	20	37.6	NA	**NA**	14.6	NA	1992	100	NA	68.63	100	NA
Guan (2011)	cardiac surgery	China	68.97	NA	NA	NA	NA	NA	**NA**	NA	NA	2002	100	73.6	0	0	NA
Guerra (2014)	cardiac surgery	Canada	61.54	38.9	54	53.62	0.38	16.8	9.9	4	3	2004	100	NA	NA	100	86
Guerra (2015)	CPR	Canada	50.91	NA	52	NA	NA	NA	**NA**	100	100	2005	NA	NA	NA	NA	38.2
Haneda (1996)	cardiac surgery	Japan	NA	NA	NA	0.70	NA	NA	**NA**	NA	NA	1986	100	NA	NA	68.29	NA
Hansen (2016)	cardiac surgery	Germany	65.12	39.7	55.5	55.27	0.23	NA	**NA**	NA	NA	2008	100	385	NA	100	80
Heinrichs (2014)	cardiac surgery	Germany	78.3	NA	202.8	202.57	0.23	NA	**NA**	6.7	NA	1989	100	61.7	100	100	93
Heye (2019)	cardiac surgery	Switzerland	63.64	39.47	75.55	73.98	1.57	16.44	**NA**	NA	NA	2006	100	196	17.48	71	96
Hiraiwa article 1 (2020)	cardiac surgery	Japan	54.3	39.2	89.5	NA	NA	NA	**NA**	8.6	0	2007	100	178	5.7	100	89
Hiraiwa article 2 (2020)	cardiac surgery	Japan	51.9	39.2	113.1	NA	NA	NA	NA	NA	0	2006	100	NA	NA	100	95.7
Hofkosh (1991)	ECMO	USA	69.47	NA	64.14	63.64	0.50	NA	NA	NA	100	1983	NA	NA	NA	NA	NA
Hövels-Gürich (2002)	cardiac surgery	Germany	76.67	NA	126	125.77	0.23	NA	NA	6.7	NA	1989	100	63.4	100	100	91
Ikle (2003)	heart- or heart-lung tx	USA	80.77	NA	NA	NA	NA	NA	NA	NA	NA	1995	100	NA	100	100	70

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Iwamoto (1990)	cardiac surgery	Japan	NA	NA	148	72	76	NA	NA	NA	NA	NA	100	NA	100	1.33	NA
Jacobs (2020)	miscellaneous	Belgium, The Netherlands and Canada	57.46	NA	87.6	48.0	39.6	7.8	5.0	NA	NA	2013	NA	NA	NA	NA	90.5
Jin (2018)	cardiac surgery	China	68.97	NA	NA	NA	NA	NA	NA	NA	NA	2011	100	73.6	NA	0	NA
Jones (2015)	cardiac surgery	Australia	50	NA	79.2	77.5	1.7	NA	NA	NA	NA	2000	100	155	25	NA	NA
Karl (2004)	cardiac surgery	Australia	NA	39.6	109.7	109.18	0.52	3	NA	NA	NA	1991	100	126	100	100	NA
Kaur (2016)	sepsis and/or meningoencephalitis	India	46	NA	93.6	6	87.6	4.9	NA	NA	NA	2013	NA	NA	NA	NA	NA
Kern (1998)	cardiac surgery	USA	58.33	NA	52.8	52.54	0.26	NA	NA	NA	NA	1993	100	188	100	100	NA
King (2017)	cardiac surgery	USA	70.6	NA	213.12	211.2	1.92	NA	NA	NA	NA	NA	100	NA	NA	100	NA
Kirshbom (2005)	cardiac surgery	USA	70	39	136.48	135.33	1.15	8	NA	NA	3.3	1989	100	71	100	100	81
Krueger (2015)	cardiac surgery	Switzerland	64.7	39.3	51.6	48.8	2.8	9.18	5.41	NA	NA	2006	100	165.3	NA	67.3	92
Krull (2003)	miscellaneous	USA	27	NA	81.6	66	15.6	NA	NA	NA	NA	1989	NA	NA	NA	NA	NA
Langenbacher (2001)	ECMO	USA	51.92	39	61	60.94	0.06	NA	NA	NA	100	1989	NA	NA	NA	NA	82
Latal article 1 (2016)	cardiac surgery	Switzerland	65	38.95	51.6	51.06	0.54	21.8	14.22	13.3	1.7	2007	100	NA	NA	70.3	NA
Latal article 2 (2016)	cardiac surgery	Switzerland	43.75	NA	166.36	146.54	19.82	NA	NA	NA	NA	1996	100	91	NA	50	NA
Leeuwen (2018)	ECMO	The Netherlands	54.29	40.29	96	95.50	0.50	27.70	17.61	8.57	100	2007	**NA**	NA	NA	NA	79
Leeuwen (2018)	miscellaneous	The Netherlands	60	38.54	96	95.5	0.5	22.78	10.36	0	0	2007	**NA**	NA	NA	NA	79

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Ma (2020)	cardiac surgery	China	60.0	NA	120.12	94.92	25.20	NA	NA	NA	NA	NA	100	67.75	NA	100	NA
Madderom (2013)	ECMO	The Netherlands	62.5	39.5	96	NA	NA	NA	41.5	NA	100	2001	**NA**	NA	NA	NA	48.6
Madderom (2013)	miscellaneous	The Netherlands	42.11	37.63	96	NA	NA	NA	13.11	NA	0	2001	**NA**	NA	NA	NA	80
Madderom (2016)	ECMO	The Netherlands	47.06	39.89	144.07	144	0.07	NA	12.32	NA	100	1994	**NA**	NA	NA	NA	75
Mahle (2006)	cardiac surgery	USA	68.09	39.50	148.83	148.32	0.51	NA	NA	NA	NA	NA	100	90.5	100	100	NA
Majnemer (2008)	cardiac surgery	Canada		40	64.2	61.5	2.7	11.4	NA	NA	NA	1996	100	152.8	52	68.09	88
Melchers (1999)	TBI	Germany	61.35	NA	**NA**	12	NA	NA	NA	NA	NA	NA	**NA**	NA	NA	NA	NA
Mesotten (2012)	miscellaneous	Belgium	57.24	NA	72.86	47.22	25.64	NA	NA	NA	NA	2005	**NA**	NA	NA	NA	72.1
Miatton (2008)	cardiac surgery	Belgium	51.16	NA	104	98	6	NA	NA	NA	NA	1997	100	NA	NA	55.81	NA
Mittnacht (2015)	cardiac surgery	Germany	50	40	140.57	NA	NA	NA	NA	NA	NA	1994	100	NA	NA	60.7	98
Morris (1993)	CPR	USA	36	NA	67	NA	NA	NA	NA	100	NA	NA	**NA**	NA	NA	NA	NA
Muñoz-López (2017)	cardiac surgery	UK	70	NA	136.8	136.3	0.5	NA	NA	NA	NA	1995	100	NA	NA	100	NA
Murphy (2017)	cardiac surgery	USA	39	NA	193.2	190.13	3.07	NA	NA	NA	NA	NA	100	113.3	NA	100	NA
Naef (2017)	cardiac surgery	Switzerland	61.5	39.19	75.27	70.54	4.73	14.69	NA	NA	NA	2006	100	155.1	NA	63.3	93.2
Naguib (2015)	cardiac surgery	USA	70	NA	36.15	31.70	4.45	2.14	NA	NA	NA	NA	100	119.8	NA	NA	NA
Neufeld (2008)	cardiac surgery	Canada	64.62	39	58	57.64	0.36	NA	9	3	3	1999	100	137	50.77	100	98.5
Nijhuis-van der Sanden (2009)	ECMO	The Netherlands	58.39	39.5	62	61.5	0.5	NA	NA	NA	100	1996	NA	NA	NA	NA	78
Oates (1995)	cardiac surgery	Australia	59.52	NA	126.69	101.20	25.49	NA	NA	NA	NA	1977	100	NA	67.86	48.21	NA

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Oberhuber (2017)	cardiac surgery	Austria	65.12	NA	123.6	123.1	0.5	NA	NA	NA	NA	2003	100	NA	100	100	57
Omeje (2003)	cardiac surgery	Bratislava	62	NA	66.13	63.05	3.08	NA	NA	NA	NA	1996	NA	NA	NA	NA	NA
Poncelet (2011)	cardiac surgery	Belgium	NA	NA	NA	48	NA	NA	NA	NA	2.2	2004	100	NA	NA	NA	95.6
Quartermain (2010)	cardiac surgery	USA	54	NA	147.6	6	141.6	2.1	0	NA	NA	2005	100	46	NA	0	100
Quartermain (2010)	miscellaneous	USA	74	NA	154.8	6	148.8	0.3	0	NA	NA	2005	NA	NA	NA	NA	100
Rotermann (2017)	cardiac surgery	Germany	62.13	39.20	57.18	56.94	0.24	NA	NA	NA	NA	2007	72.63	346.3	NA	72.63	NA
Ryerson (2015)	ECMO	Canada	55.1	NA	52.9	43.4	9.5	NA	NA	NA	100	2004	NA	NA	NA	NA	65
Sarajuuri (2007)	cardiac surgery	Finland	NA	NA	70.10	69.16	0.94	NA	NA	NA	NA	NA	100	121	100	100	NA
Sarajuuri (2012)	cardiac surgery	Finland	NA	NA	61.46	61.16	0.30	NA	NA	NA	NA	2003	100	174.1	NA	100	NA
Sarrechia article 1 (2015)	cardiac surgery	Belgium	41.30	40	106.96	90.78	16.17	2.39	NA	NA	NA	2004	100	NA	NA	0	NA
Sarrechia article 2 (2015)	cardiac surgery	Belgium	33.33	40	110	77	33	NA	NA	NA	NA	NA	100	39.9	NA	0	NA
Schaefer (2013)	cardiac surgery	Switzerland	42.37	NA	164.98	154.18	10.8	NA	NA	NA	NA	1996	100	85.9	NA	51	NA
Schiller (2016)	ECMO	The Netherlands	54.13	40.09	96	95.50	0.50	**NA**	17.22	**NA**	100	2001	NA	NA	NA	NA	73
Shida (1981)	cardiac surgery	Japan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100	NA	100	0	93
Simons (2010)	cardiac surgery	USA	61.29	38.1	72.35	62.25	10.1	2.4	0.02	NA	NA	2001	100	58.5	91	0	NA

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Singer (1989)	miscellaneous	USA	NA	35.7	66	62.7	3.3	NA	NA	NA	NA	1977	NA	NA	NA	NA	71
Slomine (2018)	CPR	USA	60	NA	171.6	12	159.6	35.39	NA	100	NA	2012	NA	NA	NA	NA	NA
Sorensen (2014)	miscellaneous	USA	47.31	NA	102	84.33	17.67	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stein (2013)	heart- or heart-lung tx	USA	70	NA	166.80	65.07	101.73	NA	NA	19.80	9.90	1997	100	NA	100	15.0	NA
Sugimoto (2013)	cardiac surgery	Japan	NA	NA	105.24	79.22	26.02	NA	NA	12.6	NA	2005	100	70.4	69	100	93
Urschel (2018)	heart- or heart-lung tx	Canada	58.18	NA	54.58	38.89	15.69	32.71	17.51	25.46	22	2005	100	NA	100	NA	81
Uzark (1998)	cardiac surgery	USA	46.88	NA	75.6	37.24	38.36	NA	NA	NA	NA	1990	100	129	15.63	100	92
Uzark (2009)	heart- or heart-lung tx	USA	42.86	NA	40.72	14.35	25.4	NA	NA	NA	NA	2002	100	NA	100	NA	NA
van der Rijken (2008)	cardiac surgery	The Netherlands	46.51	NA	151.2	12	139.2	NA	NA	NA	NA	2004	100	207.7	0	34.88	98
Venchiarutti (2019)	cardiac surgery	Italy	52.94	38.6	117.12	NA	NA	NA	NA	NA	NA	NA	100	NA	NA	47.06	NA
Vergine (2021)	cardiac surgery	Italy	57.9	37.9	78	68.4	9.6	7	NA	NA	NA	2013	100	123	NA	68.4	NA
Vermunt (2009)	sepsis and/or meningoencephalitis	The Netherlands	52	NA	132	96	36	5.7	NA	NA	NA	1994	NA	NA	NA	NA	NA
Vermunt (2011)	sepsis and/or meningoencephalitis	The Netherlands	48	NA	256.8	149.76	107.04	NA	NA	NA	NA	1994	NA	NA	NA	NA	NA
Volpe (2017)	TBI	Brazil	56	NA	136.13	66.28	69.85	5.20	3.24	NA	NA	2009	NA	NA	NA	NA	91
von Rhein (2012)	cardiac surgery	Switzerland	56	NA	124.8	107.66	17.14	10.25	NA	8	NA	1996	100	94.5	9	43	NA
Wells (1983)	cardiac surgery	UK	**NA**	NA	68.73	53.37	15.37	NA	NA	NA	NA	1974	100	NA	63.27	57.2	NA
Wernovsky (2000)	cardiac surgery	USA	54.90	NA	169.20	81.60	87.60	NA	NA	NA	NA	1982	100	119.9	NA	100	NA

Table S1. Details on PICU groups studied in the included studies. (*continued*)

Study name	Subgroup	Country	Sex (% boys)	Gestational age (weeks)	Age at follow-up (months)	Time to follow-up (months)	Age at PICU admission (months)	PICU stay (days)	Mechanical ventilation (days)	Resusci-tation (%)	ECMO (%)	Year at PICU (mean)	CPB (%)	CPB duration (minutes)	DHCA (%)	Cyanotic heart disease (%)	Survival rate (%)
Whitman (1973)	cardiac surgery	USA	**NA**	NA	103.33	1.74	101.59	NA	NA	NA	NA	1972	61.11	NA	NA	16.67	NA
Wolfe article 1 (2020)	heart- or heart-lung tx	USA	51.85	NA	111.6	73.92	37.68	NA	NA	NA	22	2014	100	NA	100	NA	NA
Wolfe article 2 (2020)	cardiac surgery	USA	50.0	NA	114.6	NA	NA	NA	NA	NA	NA	NA	100	NA	NA	100	NA
Wotherspoon (2020)	cardiac surgery	Australia	47.6	39.22	184.8	183.26	1.54	NA	NA	NA	NA	2000	100	NA	14.3	71.43	100
Wray (1994)	cardiac surgery	UK and Ireland	NA	NA	74.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wray (1994)	heart- or heart-lung tx	UK and Ireland	NA	NA	112.8	10	102.8	NA	NA	NA	NA	1989	100	NA	100	NA	NA
Wray article 1 (2001)	heart- or heart-lung tx	UK and Ireland	48	NA	154.44	36	118.44	NA	NA	NA	NA	1990	100	NA	100	NA	77
Wray article 2 (2001)	cardiac surgery	UK	42.55	NA	102.3	13.5	88.8	NA	NA	NA	NA	NA	85	NA	NA	36.2	90
Wray (2005)	heart- or heart-lung tx	UK and Ireland	51.06	NA	111.6	12	99.6	NA	NA	NA	NA	NA	100	NA	100	NA	NA
Wray (2006)	heart- or heart-lung tx	UK	52.94	NA	NA	36	NA	NA	NA	NA	NA	NA	100	NA	100	NA	NA
Wright (1994)	cardiac surgery	Australia	68.97	39.3	114	103.37	10.63	NA	NA	NA	NA	1981	100	16.7	100	100	NA

Note: If a study included different subgroups based on reasons of PICU admission, subgroups are displayed in different rows. CPR = cardiopulmonary resuscitation; CPB = cardiopulmonary bypass (during cardiac surgery); DHCA = deep-hypothermic circulatory arrest (during cardiac surgery); ECMO = extra-corporeal membrane oxygenation, heart- or heart-lung tx = heart- or heart-lung transplantation; NA = not available; TBI = traumatic brain injury; UK = United Kingdom; USA = United States of America. Meta-regression was not possible to perform for Pediatric Risk of Mortality (PRISM) score, Pediatric Index of Mortality (PIM) 2 score and Vasopressor score because these variables were reported in less than ten studies (data not shown).

Study quality

Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies, that assesses aspects of participant selection, group comparability and outcome assessment. Two items of the scale ("Demonstration that outcome of interest was not present at the start of study" and "Was follow-up long enough for outcomes to occur?") were not applicable and therefore omitted. Furthermore, the scoring of some items was adjusted to fit the aim of the current meta-analysis. "Selection of the non-exposed cohort" was awarded one point if a healthy control group was included. Comparability was awarded one point if the healthy control group was matched on socioeconomic status since this is known to be an important factor in intelligence, and one point was assigned for comparability if the control group was matched on age and/or sex. If FSIQ was measured in at least 70% of the total sample, one point was awarded for "adequacy of follow up of cohorts". All included studies were independently rated by two authors. Any disagreements were solved through discussion or by consulting a third author.

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls.

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Als (2013)	sepsis and/or meningoencephalitis	control	-0.79	0.25	41	100	5
Als (2013)	miscellaneous	control	-0.53	0.18	44	100	5
Anderson (2021)	heart- or heart-lung tx	normative	-1.44	0.40	54	54	5
Asschenfeldt (2020)	cardiac surgery	control	-0.87	0.21	66	40	5
Atallah (2020)	cardiac surgery	normative	-0.86	0.18	68	68	5
Baum (2000)	heart- or heart-lung tx	normative	-1.21	0.23	46	46	5
Baum (2004)	heart- or heart-lung tx	normative	-1.11	0.20	55	55	4
Bellinger (2003)	cardiac surgery	normative	-0.29	0.27	155	155	5
Benjamin (2013)	miscellaneous	normative	-0.66	0.36	16	16	4
Bergemann (2015)	cardiac surgery	control	-1.34	0.41	38	34	7
Bouman (2000)	miscellaneous	normative	-1.00	0.47	10	10	4
Brosig (2013)	cardiac surgery	normative	0.01	0.24	34	34	4
Cainelli (2021)	cardiac surgery	control	-0.57	0.25	35	33	5
Calderon (2010)	cardiac surgery	control	-0.51	0.31	21	21	6
Calderon (2013)	cardiac surgery	normative	0.92	0.31	45	45	5
Campbell (2004)	TBI	normative	-0.51	0.29	25	25	4
Carra (2021)	cardiac surgery	normative	-0.56	0.16	87	87	4
Claessens (2018)	cardiac surgery	normative	-0.37	0.26	30	30	5
Cottrell (2004)	cardiac surgery	normative	-0.52	0.12	156	156	4
Creighton (2007)	cardiac surgery	normative	-0.39	0.43	53	53	5
de Ferranti (2004)	cardiac surgery	normative	-0.19	0.11	154	154	5
DeMaso (2017)	cardiac surgery	control	-1.03	0.15	91	111	4

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls. (*continued*)

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Deng (2021)	sepsis and/or meningoencephalitis	normative	-0.41	0.43	11	11	4
Desai (1999)	ECMO	normative	-0.29	0.26	62	62	5
Dickinson (1979)	cardiac surgery	normative	-0.05	0.23	38	38	4
du Plessis (2002)	cardiac surgery	normative	-1.26	0.49	10	10	3
Dunbar-Masterson (2001)	cardiac surgery	normative	-0.19	0.11	155	155	5
Eder (2021)	miscellaneous	normative	-0.82	0.27	31	31	5
Ehrler (2020)	cardiac surgery	normative	-0.30	0.14	107	107	4
Eichler (2019)	cardiac surgery	control	-0.59	0.23	39	39	6
Fiser (2000)	miscellaneous	normative	-1.21	0.18	75	75	4
Fleisher (2002)	cardiac surgery	normative	0.05	0.45	10	10	4
Fleisher (2002)	heart- or heart-lung tx	normative	-0.19	0.43	11	11	4
Forbess (2002)	cardiac surgery	normative	-0.21	0.09	243	243	4
Fourdain (2020)	cardiac surgery	normative	0.03	0.22	80	80	4
Glass (1997)	ECMO	control	-1.04	0.28	151	53	6
Goff (2012)	cardiac surgery	normative	-0.29	0.07	378	378	4
Gold article 1 (2020)	miscellaneous	normative	-0.30	0.47	21	21	5
Gold article 2 (2020)	heart- or heart-lung tx	normative	-1.11	0.30	25	25	5
Goldberg (2000)	cardiac surgery	normative	0.10	0.20	48	48	4
Guan (2011)	cardiac surgery	control	-0.38	0.36	16	16	6
Guerra (2014)	cardiac surgery	normative	-0.49	0.15	91	91	5
Guerra (2015)	CPR	normative	-1.52	0.39	17	17	4
Haneda (1996)	cardiac surgery	normative	0.41	0.49	82	82	4

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls. (*continued*)

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Hansen (2016)	cardiac surgery	normative	-0.46	0.22	42	42	5
Heinrichs (2014)	cardiac surgery	normative	0.34	0.19	56	56	4
Heye (2019)	cardiac surgery	normative	-0.33	0.12	143	143	5
Hiraiwa article 1 (2020)	cardiac surgery	normative	-0.50	0.24	35	35	5
Hiraiwa article 2 (2020)	cardiac surgery	control	-0.82	0.34	27	39	5
Hofkosh (1991)	ECMO	Combined	-0.26	0.47	19	19	4
Hövels-Gürich (2002)	cardiac surgery	normative	-0.07	0.18	60	60	4
Ikle (2003)	heart- or heart-lung tx	normative	-0.82	0.41	13	13	4
Iwamoto (1990)	cardiac surgery	normative	-0.21	0.49	75	75	4
Jacobs (2020)	miscellaneous	control	-0.76	0.07	684	369	6
Jin (2018)	cardiac surgery	control	-0.38	0.34	18	18	6
Jones (2015)	cardiac surgery	normative	-0.29	0.32	20	20	4
Karl (2004)	cardiac surgery	control	-0.54	0.17	74	74	6
Kaur (2016)	sepsis and/or meningoencephalitis	control	-0.52	0.24	35	35	6
Kern (1998)	cardiac surgery	normative	-1.30	0.45	12	12	5
King (2017)	cardiac surgery	control	-0.57	0.35	17	17	5
Kirshbom (2005)	cardiac surgery	normative	-0.28	0.26	30	30	4
Krueger (2015)	cardiac surgery	normative	-0.50	0.12	146	146	5
Krull (2003)	miscellaneous	normative	-0.57	0.37	15	15	4
Langenbacher (2001)	ECMO	normative	-0.45	0.20	49	49	4
Latal article 1 (2016)	cardiac surgery	normative	-0.19	0.20	48	48	5
Latal article 2 (2016)	cardiac surgery	control	-0.67	0.23	48	32	6

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls. (*continued*)

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Leeuwen (2018)	ECMO	normative	-0.82	0.40	35	35	5
Leeuwen (2018)	miscellaneous	normative	0.00	0.26	30	30	5
Ma (2020)	cardiac surgery	control	-1.53	0.48	10	13	5
Madderom (2013)	ECMO	normative	-0.48	0.38	14	14	5
Madderom (2013)	miscellaneous	normative	0.64	0.37	15	15	5
Madderom (2016)	ECMO	normative	-0.56	0.28	27	27	4
Mahle (2006)	cardiac surgery	normative	-1.01	0.31	47	47	4
Majnemer (2008)	cardiac surgery	normative	-0.50	0.15	94	94	5
Melchers (1999)	TBI	normative	-0.74	0.52	19	19	4
Mesotten (2012)	miscellaneous	control	-0.84	0.10	456	216	5
Miatton (2008)	cardiac surgery	control	-0.75	0.22	43	43	7
Mittnacht (2015)	cardiac surgery	normative	-0.08	0.27	28	28	5
Morris (1993)	CPR	normative	-0.80	0.29	25	25	4
Muñoz-López (2017)	cardiac surgery	normative	-0.21	0.22	40	40	4
Murphy (2017)	cardiac surgery	control	-0.61	0.34	18	18	6
Naef (2017)	cardiac surgery	normative	-0.34	0.11	169	169	5
Naguib (2015)	cardiac surgery	normative	-0.76	0.60	20	20	4
Neufeld (2008)	cardiac surgery	normative	-0.31	0.18	65	65	4
Nijhuis-van der Sanden (2009)	ECMO	normative	-0.02	0.12	131	131	5
Oates (1995)	cardiac surgery	normative	0.05	0.23	168	168	5
Oberhuber (2017)	cardiac surgery	normative	-0.85	0.23	43	43	4
Omeje (2003)	cardiac surgery	normative	-0.05	0.18	64	64	4

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls. (*continued*)

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Poncelet (2011)	cardiac surgery	normative	0.19	0.48	18	18	4
Quartermain (2010)	cardiac surgery	control	0.56	0.34	32	12	5
Quartermain (2010)	miscellaneous	control	0.59	0.38	18	12	5
Rotermann (2017)	cardiac surgery	normative	-0.61	0.24	95	95	5
Ryerson (2015)	ECMO	normative	-1.28	0.23	44	44	5
Sarajuuri (2007)	cardiac surgery	normative	-0.82	0.47	26	26	5
Sarajuuri (2012)	cardiac surgery	control	-1.41	0.32	36	40	6
Sarrechia article 1 (2015)	cardiac surgery	control	-0.57	0.32	46	46	6
Sarrechia article 2 (2015)	cardiac surgery	control	-0.89	0.29	18	48	6
Schaefer (2013)	cardiac surgery	control	-0.67	0.21	59	40	6
Schiller (2016)	ECMO	normative	-0.13	0.20	178	178	5
Shida (1981)	cardiac surgery	normative	0.69	0.22	45	45	4
Simons (2010)	cardiac surgery	normative	-0.29	0.26	31	31	4
Singer (1989)	miscellaneous	normative	-0.54	0.25	32	32	5
Slomine (2018)	CPR	normative	-0.55	0.23	41	41	5
Sorensen (2014)	miscellaneous	normative	-0.53	0.15	91	91	4
Stein (2013)	heart- or heart-lung tx	control	-1.01	0.46	20	12	6
Sugimoto (2013)	cardiac surgery	normative	-1.01	0.18	70	70	4
Urschel (2018)	heart- or heart-lung tx	normative	-1.31	0.30	55	55	5
Uzark (1998)	cardiac surgery	normative	-0.18	0.25	32	32	4
Uzark (2009)	heart- or heart-lung tx	normative	-0.89	0.32	21	21	5
van der Rijken (2008)	cardiac surgery	control	-0.28	0.22	43	43	6

Table S2. Study characteristics and FSIQ differences (Cohen's *d*) between PICU survivors and controls. (*continued*)

Study name	Subgroup	Comparison	Cohen's *d*	SE	Sample size PICU	Sample size Control	Study quality
Venchiarutti (2019)	cardiac surgery	normative	-0.06	0.34	17	17	4
Vergine (2021)	cardiac surgery	normative	-0.02	0.23	38	38	4
Vermunt (2009)	sepsis and/or meningoencephalitis	normative	-0.20	0.17	66	66	4
Vermunt (2011)	sepsis and/or meningoencephalitis	normative	-0.26	0.21	46	46	4
Volpe (2017)	TBI	normative	-1.56	0.48	25	25	4
von Rhein (2012)	cardiac surgery	normative	-0.68	0.13	117	117	5
Wells (1983)	cardiac surgery	control	-1.31	0.44	49	29	5
Wernovsky (2000)	cardiac surgery	normative	-0.35	0.26	93	93	4
Whitman (1973)	cardiac surgery	normative	0.55	0.49	18	18	4
Wolfe article 1 (2020)	heart- or heart-lung tx	normative	-1.20	0.30	27	27	4
Wolfe article 2 (2020)	cardiac surgery	normative	-0.67	0.18	66	66	4
Wotherspoon (2020)	cardiac surgery	normative	-0.41	0.32	20	20	4
Wray (1994)	cardiac surgery	control	-0.08	0.24	35	35	5
Wray (1994)	heart- or heart-lung tx	control	-0.83	0.23	49	35	5
Wray article 1 (2001)	heart- or heart-lung tx	normative	0.14	0.28	25	25	4
Wray article 2 (2001)	cardiac surgery	control	-0.09	0.22	35	51	7
Wray (2005)	heart- or heart-lung tx	control	-0.63	0.24	35	35	6
Wray (2006)	heart- or heart-lung tx	normative	0.01	0.30	22	22	4
Wright (1994)	cardiac surgery	control	-0.56	0.25	29	36	6

Note: If a study included different subgroups based on reasons of PICU admission, subgroups are displayed in different rows. CPR = cardiopulmonary resuscitation; ECMO = extra-corporeal membrane oxygenation, heart- or heart-lung tx = heart- or heart-lung transplantation; TBI = traumatic brain injury; control = healthy control group; normative = normative data (i.e. mean = 100, SD = 15); Study quality assessed by the Newcastle Ottawa Scale for cohort studies, revised to a maximum of 7 points.

Table S3. Results of univariate meta-regression analyses of risk factors for FSIQ impairment in PICU subgroups.

Risk factors	*k*	Beta	95% CI	R^2 (%)	Range studied
Respiratory and/or circulatory insufficiency necessitating ECMO					
Year of PICU admission	10	-0.012	-0.055, 0.031	0	1983-2007
Age at follow-up (months)	10	0.002	-0.010, 0.014	0	52.9-144.1
Study quality	10	-0.209	-0.734, 0.317	0	4-6
Cardiac surgery					
Year of PICU admission	64	-0.012 **	-0.020, -0.003	12	1972-2013
Sex (% boys)	65	0.008 *	0.000, 0.015	6	30.3-79.4
Gestational age (weeks)	34	-0.134	-0.309, 0.042	0	37.9-40.0
Age at PICU admission (months)	67	0.002	-0.001, 0.004	0	0.2-141.6
PICU stay (days)	22	-0.011	-0.031, 0.009	0	1.3-25.3
Resuscitation (%)	13	0.001	-0.051, 0.052	0	0.0-14.6
Duration of CPB during surgery (minutes)	49	0.000	-0.001, 0.002	0	17-385
DHCA (%)	41	0.001	-0.002, 0.004	0	0.0-100
Cyanotic heart disease (%)	71	-0.002	-0.005, 0.001	0	0.0-100
Rate of survivors (%)	34	0.010	-0.000, 0.020	9	57.0-100
Age at follow-up (months)	75	-0.001	-0.003, 0.001	0	30.1-307.2
Time to follow-up (months)	69	-0.002	-0.004, 0.000	0	0.7-231.6
Study quality	80	-0.148 **	-0.243, -0.053	9	3-7
Heart- or heart-lung transplantation					
Year of PICU admission	10	-0.035 **	-0.061, -0.009	65	1989-2016
Sex (% boys)	12	-0.001	-0.027, 0.025	0	28.0-80.8
Age at PICU admission (months)	11	0.006 **	0.002, 0.011	74	1.6-118.4
Age at follow-up (months)	11	0.008 **	0.002, 0.015	68	40.7-166.8
Time to follow-up (months)	12	-0.006	-0.016, 0.004	8	10.0-82.3
Study quality	14	-0.154	-0.537, 0.228	0	4-6

Note: CPB = cardiopulmonary bypass; DHCA = deep-hypothermic circulatory arrest (during cardiac surgery); ECMO = extra-corporeal membrane oxygenation; PICU = pediatric intensive care unit. Study quality assessed by the Newcastle Ottawa Scale for cohort studies, revised to a maximum of 7 points. Unstandardized Beta's are reported. There was limited variation in percentage use of cardiopulmonary bypass since almost all articles focusing on cardiac surgery reported 100% use of cardiopulmonary bypass and all articles focusing on heart- or heart-lung transplantation reported 100% use of cardiopulmonary bypass. Therefore, this variable was omitted from meta-regression. Furthermore, there was limited variation in percentage use of deep hypothermic circulatory arrest in articles focusing on heart- or heart-lung transplantation and therefore this variable was omitted from meta-regression in this subgroup.
*p<.05. **p<.01. ***p<.001.

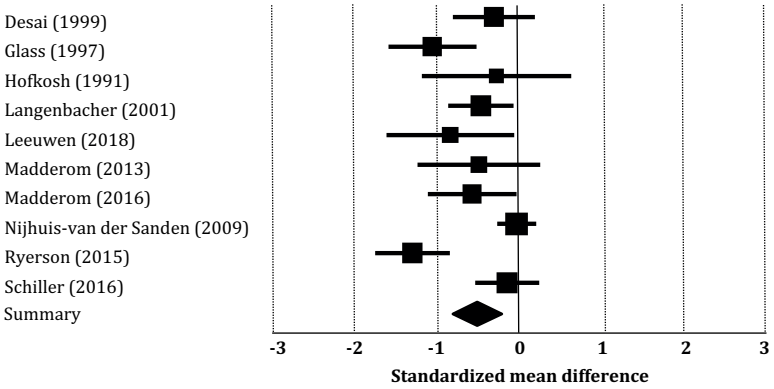

Figure S1. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Respiratory and/or circulatory insufficiency necessitating ECMO, comparing FSIQ of PICU survivors to healthy controls or normative data.

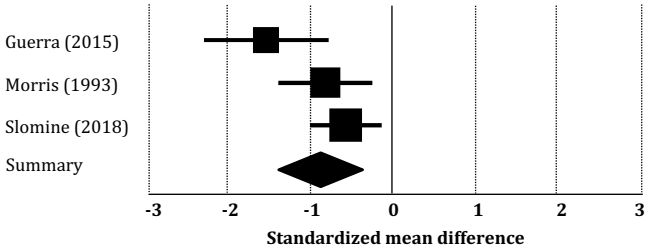

Figure S2. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Circulatory insufficiency necessitating CPR, comparing FSIQ of PICU survivors to healthy controls or normative data.

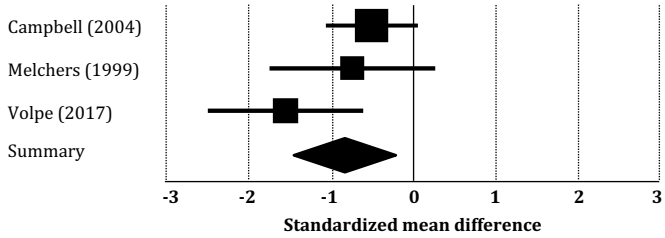

Figure S3. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Traumatic brain injury, comparing FSIQ of PICU survivors to healthy controls or normative data.

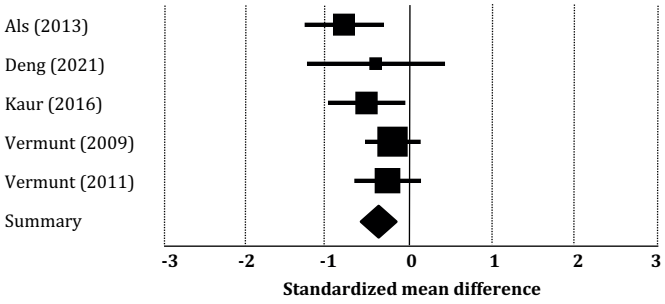

Figure S4. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Sepsis and/or meningoencephalitis, comparing FSIQ of PICU survivors to healthy controls or normative data.

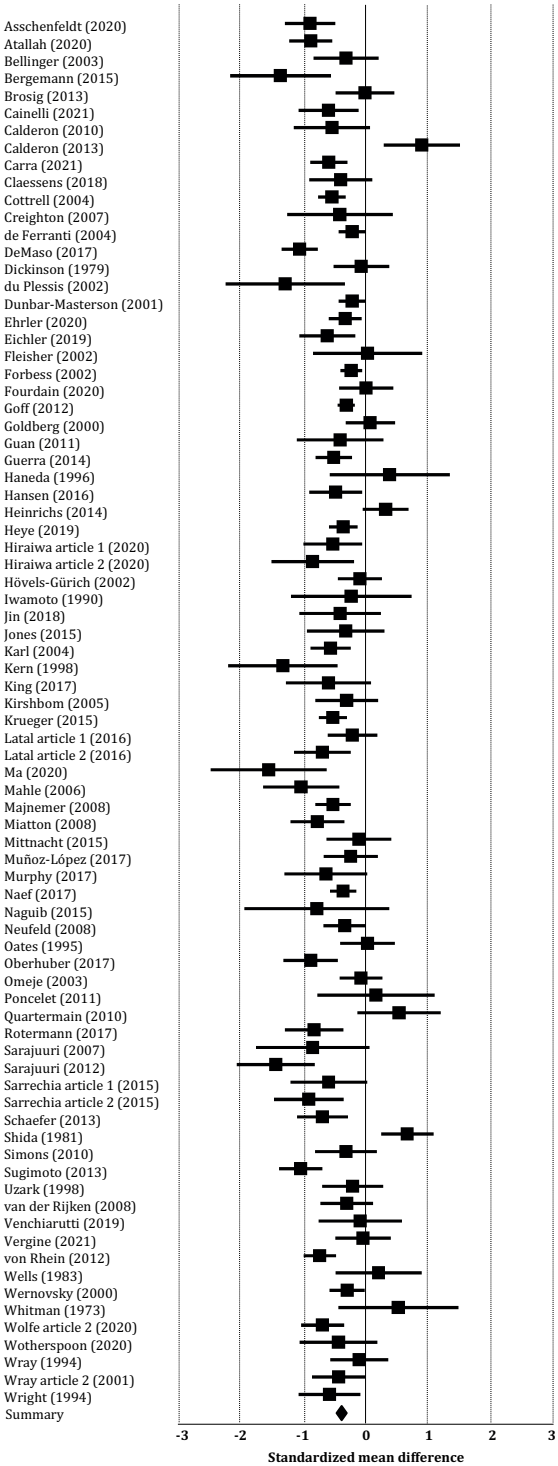

Figure S5. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Cardiac surgery, comparing FSIQ of PICU survivors to healthy controls or normative data.

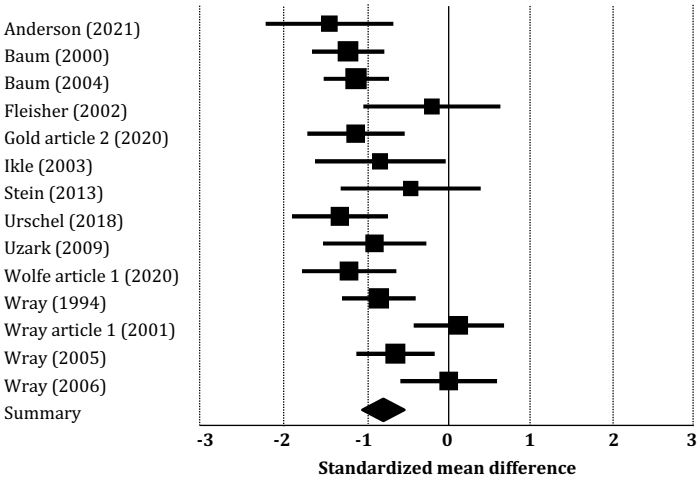

Figure S6. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Heart- or heart-lung transplantation, comparing FSIQ of PICU survivors to healthy controls or normative data.

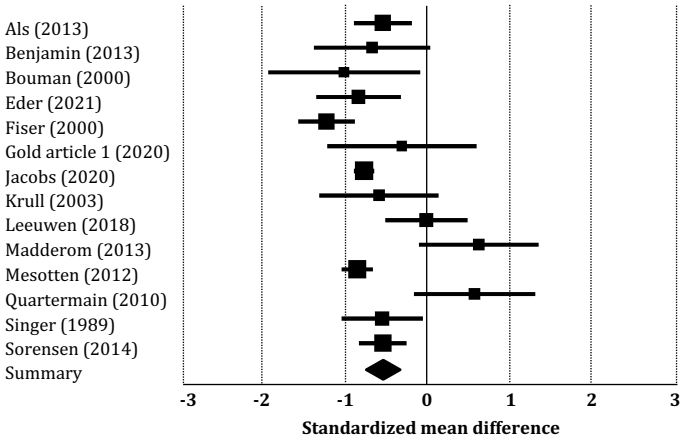

Figure S7. Forest plot showing standardized mean differences and accompanying 95% CI of studies reporting on the subgroup Miscellaneous PICU admission indications, comparing FSIQ of PICU survivors to healthy controls or normative data.

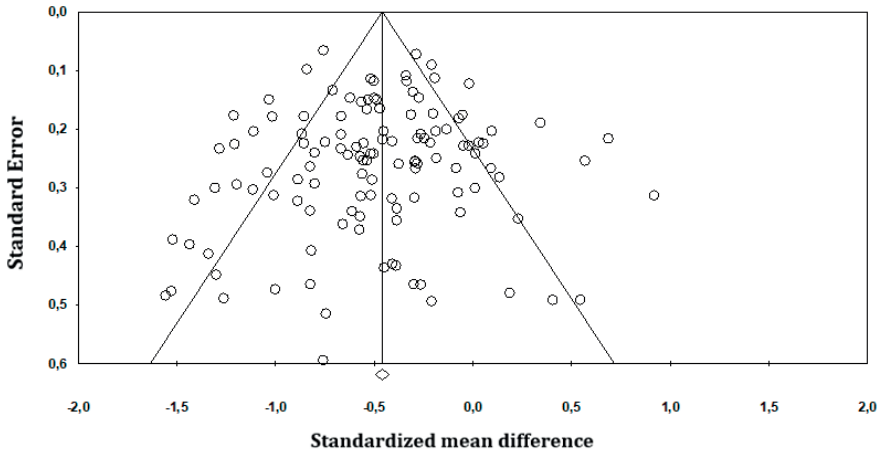

Figure S8. Funnel plot of the study's individual effect sizes for FSIQ plotted against its standard error.

5 Long-term neurocognitive outcomes after pediatric intensive care: exploring the role of drug exposure

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ABSTRACT

Introduction: Concerns exist regarding the impact of widely-used clinical drugs on brain development. This study investigates long-term neurocognitive functioning in relation to frequently used drug exposure at the Pediatric Intensive Care Unit (PICU).

Methods: This study compared children aged 6-12 years with previous PICU admission (age ≤ 1 year) for bronchiolitis requiring mechanical ventilation (patient group, n = 65) to a demographically comparable control group (n = 76) on a broad range of neurocognitive outcomes. The patient group was selected because bronchiolitis seldom manifests neurologically and is therefore not expected to affect neurocognitive functioning in itself. The relation between exposure to sedatives, analgesics and anesthetics and neurocognitive outcomes was assessed by regression analyses.

Results: The patient group had lower intelligence than the control group ($p < .001$, $d = -0.59$) and poorer performance in neurocognitive functions; i.e. speed and attention ($p = .03$, $d = -0.41$) and verbal memory ($p < .001$, $d = -0.60$). Exposure to sedatives, analgesics and anesthetics was not related to neurocognitive outcomes.

Conclusion: Children with PICU admission for bronchiolitis requiring mechanical ventilation are at risk of adverse neurocognitive outcomes. This study found no evidence for a role of exposure to sedatives, analgesics or anesthetics. Findings underline the importance of long-term follow-up after PICU admission, even in absence of disease with neurological manifestation.

INTRODUCTION

Sedatives, analgesics and anesthetics are routinely used drugs for critically ill children requiring mechanical ventilation at the Pediatric Intensive Care Unit (PICU). Of these drugs, midazolam and morphine are most commonly used and are frequently combined with other sedatives, analgesics or anesthetics [1-3]. Although long considered to be safe, recent research raises concerns about the potential impact of routinely used drugs on brain development in children [4].

Animal studies have indicated that exposure to sedatives [5-7], analgesics [6] and anesthetics [5-7] may cause neurodegeneration, especially in the rapidly developing brain [5-7]. Several mechanisms are thought to contribute to the potential neurodegenerative impact, such as impaired neurogenesis, reduced synaptogenesis and elevated neuronal apoptosis during early stages of postnatal brain development [5-11]. Such pathological mechanisms have shown to co-occur with neurocognitive impairments [5,6,8-10]. Consequently, the US Food and Drug Administration issued a warning for the potential negative impact of repeated and/or longer use of sedatives and anesthetics on brain development in young children.[4] This raised concerns about the potential impact of routinely used drugs on neurocognitive outcomes of children admitted to the PICU, especially since neurocognitive impairments are known to interfere with development in other major domains of functioning, such as physical and mental health [12,13], academic achievement [14], socioeconomic success [15], and life chances [13].

A systematic review regarding adult patients presents evidence for a relation between sedative exposure and occurrence of delirium [16], while delirium in turn is related to long-term neurocognitive impairment [17]. Studies directly investigating the relation between exposure to sedatives, analgesics, anesthetics and neurocognitive functioning are scarce. A systematic review [16] identified two studies reporting a relation between sedative exposure and neurocognitive impairment up to three months after Intensive Care Unit (ICU) stay, while this impairment did not persist at 12-month follow-up [18,19]. A recent randomized trial in ICU patients revealed no effects of continuous sedation (as compared to no sedation) on neurocognitive functioning at three months after ICU discharge [20]. Furthermore, some evidence indicates short-term neurocognitive impairment after surgery in adults, although the specific roles of exposure to sedatives, analgesics and anesthetics remain unclear [21,22]. Taken together, the available literature on adults provides mixed evidence with some indications for short-term effects of sedative exposure on neurocognitive functioning, while no evidence is available regarding longer-term effects of exposure to sedatives, analgesics and anesthetics.

Literature in children is conflicting, with studies showing no relation between exposure to sedatives [23], analgesics [23] and anesthetics [24-27] and neurocognitive outcomes, while other studies do report negative relations with exposure to sedatives [28], analgesics

[29] and anesthetics [30-33]. Moreover, the available literature is challenged by the unknown contribution of the underlying disease in the observed relations between drug exposure and neurocognitive outcomes [28,29]. Taken together, it remains unclear to what extent the worrying findings on exposure to sedatives, analgesics and anesthetics in animals - and to some extent in adult patients - generalize to children after PICU admission.

This study investigates long-term neurocognitive outcomes after PICU admission and explores the relation of neurocognitive outcomes with exposure to the primary choice of drugs (midazolam and morphine). Secondary analyses also explore relations with exposure to the secondary choice of drugs (lorazepam, fentanyl, esketamine and propofol). We specifically focused on children with bronchiolitis, because this condition seldom manifests neurologically (i.e. 1-2% [34,35]) and is therefore not expected to affect neurocognitive functioning in itself.

METHODS

Participants

This cross-sectional observational study compared a patient group to a control group of peers. The patient group was retrospectively recruited from a cohort admitted between 2007 and 2013 to the PICU of the Amsterdam University Medical Centers (UMC), the Netherlands. Inclusion criteria for the patient group were: history of PICU admission during infancy or early childhood (age ≤ 1 year) for respiratory insufficiency due to bronchiolitis requiring invasive mechanical ventilation; age at assessment 6-12 years; and proficient in the Dutch language. Exclusion criteria were: clinical signs of neurological complications during PICU admission (e.g. seizure, encephalitis, meningitis); developmental disorders known to impact on neurocognitive development; physical conditions and/or behavioral deficits interfering with the ability to adequately perform neurocognitive testing; presence of family conflict; and living abroad. Family conflict (e.g. child abuse, child being placed under supervision) was ascertained by the pediatric intensivist responsible for the follow-up and was treated as an exclusion criterion to prevent undue burden to be placed on the children and their family. Considering the aim of our study, we specifically focused on children with bronchiolitis since we expect minimal involvement of the central nervous system in the pathophysiology. Bronchiolitis is most commonly caused by respiratory syncytial virus (approximately 70% of children hospitalized for bronchiolitis [36]) that induces cytotoxic injury to lung cells and the subsequent inflammatory response [37]. Although extrapulmonary manifestations of the infection are well-known [38], neurological manifestations are seldom (i.e. 1-2% of cases [34,35]). Nevertheless, we used clinical signs of neurological manifestations during PICU admission (e.g. seizure, encephalitis, meningitis) as an exclusion criterion in this study.

The resulting study sample is relatively well suited for our study aims, since unlike many other diseases treated at the PICU, bronchiolitis in our study sample is not expected to affect neurocognitive functioning in itself.

The control group was recruited using a multichannel approach. Children participating in the patient group were asked to bring a friend or family member. Also, primary schools in the region were contacted for the recruitment of control participants. The inclusion and exclusion criteria for the control group were the same as for the patient group, although children were only included in the control group if they had no history of PICU admission and had not received more than 4 hours sedatives, analgesics and/or anesthetics during their life. We aimed to include at least 64 children in the patient group and 64 children in the control group, in order to achieve sufficient statistical power for the detection of medium-sized effects (Cohen's d = 0.5, assuming power = 80% and alpha = .05). Post-hoc calculation of statistical power indicates that our sample size allows to detect regression effects of medium effect size (r = 0.33 , power = 80%).

Measures

Demographic characteristics

Data on age, sex and socioeconomic status (SES) were collected using a parental questionnaire. SES was estimated by the average level of parental education ranging from 1 (no education) to 8 (postdoctoral education) [39].

Clinical characteristics

Administration of sedatives (midazolam and lorazepam), analgesics (morphine and fentanyl) and anesthetics (esketamine and propofol), and clinical characteristics, related to disease severity and with possible impact on neurocognitive functioning, were extracted from the patient files (Table 1). Exposure to each drug was expressed as the total cumulative dose per kilogram bodyweight obtained during PICU admission. Per local clinical protocol at time of PICU admission, the primary choice of drugs during mechanical ventilation consisted of intravenous midazolam (0.1-0.3 mg/kg/h) and morphine (10-20 mcg/kg/h), while the secondary choice of drugs (lorazepam (0.2-0.4 mg/kg/d), fentanyl (1-8 mcg/kg/h), additional esketamine (0.2-2mg/kg/h) were only administered when required. Propofol (2-4 mg/kg per dose) was only used during (re)intubation and as rescue medication during extreme agitation.

Intelligence

Intelligence was assessed to capture general neurocognitive functioning and was measured by a short form of the Wechsler Intelligence Scale for Children - Third edition (WISC-III) involving the subtests Vocabulary, Arithmetic, Block Design and Picture

Arrangement. Full-scale IQ (FSIQ) estimated with this short form has excellent validity (r = .95) and reliability (r = .90) [40].

Neurocognitive domains

In order to assess specific domains of neurocognitive functioning, a standardized and computerized neurocognitive test-battery was used. This test-battery measures a broad range of key neurocognitive domains and contains a composition of child-friendly tests based on well-known neuroscientific paradigms with established validity and reliability, i.e. Attention Network Test [41], Multisensory Integration Task [42], Tower of London [43], Rey Auditory Verbal Learning Test [44], Digit Span task [45], Klingberg task [46] and Track & Trace task [47]. In order to reduce the number of outcome variables, component analysis was used to construct neurocognitive domain scores out of the performance measures resulting from comprehensive neurocognitive assessment (see Supporting Information and eTable 1). The resulting neurocognitive domains and their descriptions are displayed in Table 2.

Procedure

Participating children underwent neurocognitive testing by trained examiners in a quiet room with an approximate duration of three hours, including breaks. Block randomized order of test administration was applied to counterbalance the systematic influence of fatigue on test performance.

Ethics statement

This study was approved by the medical ethical committee of the Amsterdam UMC (W16_121#16.139) and conducted in accordance with the declaration of Helsinki [48]. Parents and children aged 12 years provided written informed consent for participation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26.0 and R. Group comparability was tested by comparing the patient and control group on demographic characteristics and gestational age, using mixed modeling to account for the presence of sibling pairs in our sample (n = 24). Subsequently, groups were compared on the neurocognitive outcomes. For neurocognitive domains with significant group difference, we investigated their more specific nature by following group comparisons on the related original performance measures from neurocognitive tasks (see eTable 1). Neurocognitive outcomes with significant group difference were subjected to subsequent analyses regarding drug exposure.

The primary analysis regarding the relation between drug exposure and neurocognitive outcomes focused on the primary choice of drugs (midazolam and

morphine), while the secondary analysis focused on the secondary choice of drugs (lorazepam, fentanyl, esketamine and propofol). We performed univariate regression analyses in the patient group with cumulative dose per kilogram bodyweight as independent variable and neurocognitive outcomes as dependent variables. Skewed distributions of cumulative dose were subjected to logarithmic transformation, while severely skewed distributions were dichotomized (i.e. administered yes/no). Lastly, we explored if exposure to a combination of drugs was related to neurocognitive outcomes. Therefore, we ranked exposure to each drug separately in order of cumulative dose per kilogram bodyweight and calculated the sum of ranks across drugs for each individual child in the patient group. The resulting score reflects the combined exposure to sedatives, analgesics and anesthetics. To correct for multiple testing, correction for false discovery rate (FDR correction) was applied. All statistical testing was two-sided, α was set at .05 and effect sizes relating to group differences were expressed as Cohen's *d* [49]. Cohen's *d* values of 0.2, 0.5 and 0.8, were used to define thresholds for small, medium and large effect sizes, respectively [49].

RESULTS

Study groups

Children included in the patient group (n = 65, Figure 1) did not differ from the total recruitment cohort of children satisfying the inclusion criteria (n = 119) with respect to sex, age at PICU admission, duration of mechanical ventilation and length of PICU stay (eTable 2). In addition, comparison between children included in the patient group (n = 65) versus those eligible but not included (n = 54) also showed no significant differences regarding these characteristics (eTable 3), indicating no evidence for selection bias in the study sample. Comparisons between the patient and control group (n = 76) on baseline characteristics are displayed in Table 1. No differences were found in terms of demographics, indicating no evidence for a confounding role of demographic differences between groups. The patient group had lower gestational age than the control group, of which the role in the results will be explored (see confounding analysis).

Table 1. Demographic and clinical characteristics

Demographic and clinical characteristics	Patient group (n = 65)	Control group (n = 76)	Mean (SE) difference	p-value	Cohen's *d*
Demographic characteristics					
Age at time testing (years), mean (SD)	8.1 (1.2)	8.2 (1.4)	-0.10 (0.22)	.64	-0.08
Sex, % boys	60.0	44.7	0.63 (0.35)	.08	
Socioeconomic status, mean (SD)	5.3 (1.2)	5.6 (1.0)	0.01 (0.10)	.92	0.01
Clinical characteristics					
Gestational age (weeks), median (IQR)	38.1 (36.3-39.9)	39.9 (38.1-40.9)	-0.35 (0.12) *	**.004**	-0.35
Born extremely premature (gestational age <32 weeks), n (%)	5 (7.7)	4 (5.3)			
Age at PICU admission (days), median (IQR)	43.0 (23.5-79.5)				
PIM 2 score, median (IQR)	1.4 (1.1-2.1)				
Duration of invasive mechanical ventilation during first PICU stay (hours), mean (SD)	159.3 (67.9)				
Duration of invasive mechanical ventilation during all PICU admissions (hours), mean (SD)	169.5 (88.6)				
Length of first PICU stay (days), median (IQR)	7.4 (5.7-9.0)				
Length of combined PICU stay (days), median (IQR)	7.6 (5.6-9.4)				
Positive respiratory syncytial virus test, n (%)	56 (86.2)				
Reintubation, n (%)	4 (6.2)				
Tracheostomy, n (%)	2 (3.1)				
Extracorporeal membrane oxygenation, n (%)	1 (1.5)				
Cardiopulmonary resuscitation, n (%)	2 (3.1)				
Readmission at the PICU, n (%) **	7 (10.8)				
Withdrawal symptoms, n (%)	23 (35.4)				
Sepsis (during PICU stay), n (%)	1 (1.5)				
Septic shock (during PICU stay), n (%)	0 (0.0)				
Traumatic brain injury after PICU discharge, n (%)	1 (1.5)	1 (1.3)			

Table 1. Demographic and clinical characteristics (*continued*)

Demographic and clinical characteristics	Patient group (n = 65)	Control group (n = 76)	Mean (SE) difference	p-value	Cohen's *d*
Sedatives, analgesics and anesthetics during PICU admission					
Midazolam cumulative mg/kg, median (IQR)	17.6 (10.7-26.4)				
Morphine cumulative mg/kg, median (IQR)	1.5 (1.0-2.2)				
Lorazepam, n (%) ***	17 (26.2)				
Fentanyl, n (%) ***	20 (30.8)				
Esketamine, n (%) ***	20 (30.8)				
Propofol, n (%) ***	16 (24.6)				
Prednisone, n (%) ***	5 (7.7)				
Dexamethasone, n (%) ***	44 (67.7)				

Note: FSIQ = estimated full-scale intelligence quotient; PICU = Pediatric Intensive Care Unit; PIM 2 score = Pediatric Index of Mortality 2 score; SD = standard deviation; SE = standard error.
* Van der Waerden transformation of gestational age to obtain a normal distribution.
** Children were readmitted for viral lower respiratory tract infections and/or subglottic stenosis due to intubation damage.
*** Severely skewed distributions of drug administration, therefore these drugs were dichotomized (i.e. administered yes/no). Boldface values indicate p < .05.

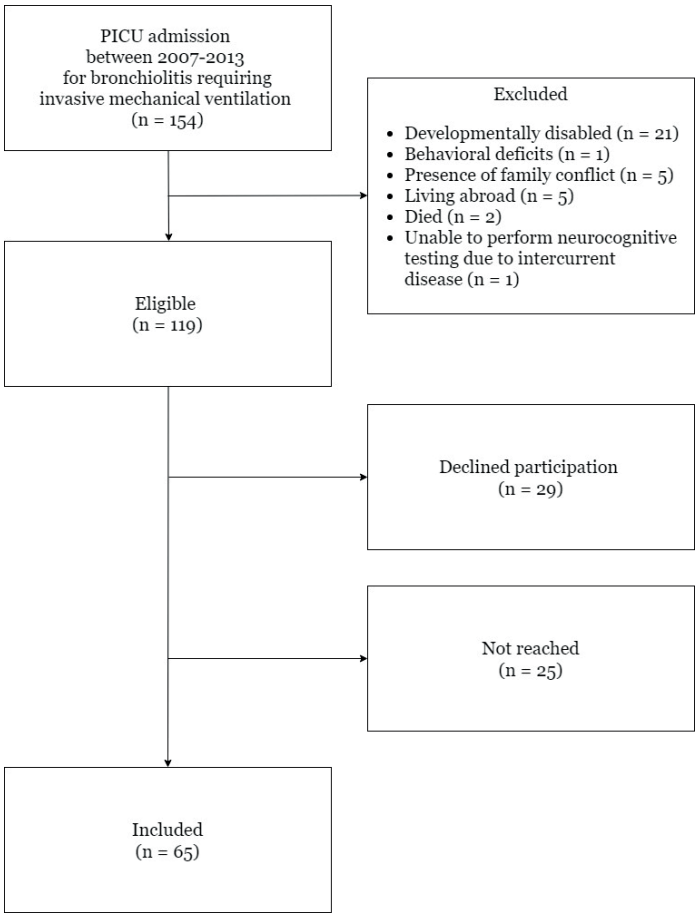

Figure 1. Flowchart of included children in the patient group.
Note: Reasons to decline participation were: not interested (n = 11), no time (n = 10), too high a burden on child (n = 6) or language barrier of parents (n = 2).

Group comparison on neurocognitive outcomes

Results regarding neurocognitive outcomes are shown in Table 2. Compared to the control group, the patient group had a significantly lower FSIQ (medium effect), and significant lower performance on the neurocognitive domains for speed and attention (small effect) and verbal memory (medium effect). Further analysis of the neurocognitive domain scores at the level of the underlying variables revealed that the observed effect of speed and attention was accounted for by lower processing speed ($p = .04$, $d = -0.34$), poorer attention consistency ($p = .019$, $d = -0.39$) and poorer visuomotor accuracy ($p = .04$, $d = -0.29$) in the patient group. The observed effect for verbal memory was found to be accounted for by poorer verbal memory encoding ($p < .001$, $d = -0.61$) and poorer verbal memory retrieval ($p < .001$, $d = -0.60$) in the patient group. While considering impaired verbal memory encoding and retrieval, the patient group had relative better verbal memory consolidation than the control group ($p = .03$, $d = 0.36$).

Drug exposure and neurocognitive outcomes

We investigated the relation between drug exposure and neurocognitive outcomes, focusing on the neurocognitive outcomes with observed group differences (FSIQ and the neurocognitive domains speed and attention and verbal memory). Regarding the relation between drug exposure and neurocognitive outcomes (Table 3 and 4), no significant relations were found in the primary analysis (midazolam and morphine), secondary analysis (lorazepam, fentanyl, esketamine and propofol) and tertiary analysis (combined exposure across all drugs).

Exploratory analysis

As the planned analysis did not reveal relations between drug exposure and neurocognitive outcomes, we performed additional exploratory analysis. In order to exclude the possibility that other aspects of drug exposure than cumulative dose are more important, we additionally performed post-hoc explorations of other aspects of exposure (i.e. duration of administration, mean and highest cumulative day dose), also showing no relations with neurocognitive outcomes (eTable 4). As literature also raised concerns about the potential impact of corticosteroids on neurocognitive functioning in children [50,51], we also explored corticosteroid exposure (short course prednisone and dexamethasone to prevent stridor after extubation), and again found no significant relations with neurocognitive outcomes (eTable 4).

Table 2. Neurocognitive outcomes of children in the patient and control group

Neurocognitive outcomes	Description	Patient group Mean (SD) (n = 65)	Control group Mean (SD) (n = 76)	Mean (SE) difference	p-value *	Cohen's *d*
FSIQ	Intelligence	95.3 (15.9)	105.1 (15.1)	-8.46 (1.98)	**< .001**	-0.59
Neurocognitive domains						
Speed and attention	Speed and variability of information processing and attention	-0.19 (0.95)	0.16 (1.02)	-0.41 (0.15)	**.03**	-0.41
Set shifting	Speed of shifting between response types	-0.03 (1.03)	0.02 (0.98)	-0.08 (0.16)	.75	-0.08
Verbal memory	Learning and memory for verbal information	-0.29 (1.13)	0.24 (0.81)	-0.60 (0.14)	**< .001**	-0.60
Visuomotor integration	Speed and flexibility of visuomotor integration	0.13 (1.06)	-0.11 (0.93)	0.25 (0.17)	.22	0.25
Verbal working memory	Short-term memory and manipulation of verbal information	-0.15 (1.03)	0.13 (0.96)	-0.27 (0.16)	.17	-0.27
Interference control	Speed of suppressing distracting information	0.12 (1.01)	-0.11 (0.98)	0.21 (0.16)	.25	0.21
Visual processing speed	Speed of visual information processing	-0.03 (1.06)	0.02 (0.95)	-0.06 (0.16)	.81	-0.06
Visual working memory	Short-term memory and manipulation of verbal information	-0.16 (1.01)	0.13 (0.98)	-0.29 (0.17)	.17	-0.29
Planning time	Speed and capacity of planning ahead	0.20 (0.99)	-0.17 (0.98)	0.38 (0.16)	.05	0.38
Multisensory integration	Accuracy for integration of information from different sensory modalities	0.02 (1.08)	-0.02 (0.93)	0.04 (0.17)	.82	0.04

Note: FSIQ = estimated full-scale intelligence quotient; SD = standard deviation; SE = standard error. The directionality of neurocognitive variables was adapted so that for all scores, higher values corresponded to better task performance. Boldface values indicate $p < .05$.

* Correction for false discovery rate applied across neurocognitive outcomes.

Table 3. Univariate regression analyses testing the relationship of cumulative doses of midazolam and morphine with selected neurocognitive outcomes

Neurocognitive outcomes	R^2 (%)	Beta (SE)	p-value *
Midazolam, cumulative mg/kg			
FSIQ	0.5	1.82 (3.28)	.85
Speed and attention	0.1	0.04 (0.20)	.85
Verbal memory	0.1	-0.06 (0.23)	.85
Morphine, cumulative mg/kg*			
FSIQ	4.2	8.90 (5.42)	.32
Speed and attention	0.6	-0.21 (0.33)	.71
Verbal memory	0.2	0.15 (0.39)	.71

Note: Beta represents a change of the dependent variable by the independent variable times 10.
* Correction for false discovery rate applied at the level of cumulative dose measure.
** 1 outlier omitted from analysis.

Table 4. Univariate regression analyses testing the relationship of lorazepam, fentanyl, esketamine, propofol and combination of drugs with the selected neurocognitive outcomes

Neurocognitive outcomes	R^2 (%)	Beta (SE)	p-value *
Lorazepam yes/no			
FSIQ	0.2	-1.67 (4.53)	.71
Speed and attention	6.3	-0.54 (0.26)	.13
Verbal memory	2.7	-0.42 (0.32)	.28
Fentanyl yes/no			
FSIQ	3.3	-6.22 (4.24)	.32
Speed and attention	2.5	0.32 (0.25)	.32
Verbal memory	1.3	-0.28 (0.30)	.36
Esketamine yes/no			
FSIQ	0.6	2.56 (4.30)	.55
Speed and attention	4.8	-0.45 (0.25)	.12
Verbal memory	4.8	-0.53 (0.30)	.12
Propofol yes/no			
FSIQ	1.4	-4.37 (4.59)	.52
Speed and attention	3.4	-0.40 (0.27)	.43
Verbal memory	0.7	-0.21 (0.33)	.52
Sedatives, analgesics and anesthetics			
FSIQ	0.3	-0.01 (0.02)	.64
Speed and attention	2.2	-0.00 (0.00)	.45
Verbal memory	1.7	-0.00 (0.00)	.45

Note: Beta represents a change of the dependent variable by the independent variable times 10.
* Correction for false discovery rate applied at the level of exposure measure.

Confounding analysis

As the patient group had significant lower gestational age as compared to the control group, this could theoretically be a confounder in the observed group differences. Therefore, we performed a sensitivity analysis using a subsample of the patient group (n = 60) that was comparable to the control group (n = 67) in terms of gestational age. The results replicate the reported group differences (ps ≤ .003), indicating that the observed evidence for adverse neurocognitive outcomes are not accounted for by premorbid differences in gestational age (see Supporting Information). Various other factors might have accounted for observed group differences. We identified the following relevant factors in the medical history of the patient group: extremely premature birth (gestational age < 32 weeks; n = 5), CPR (n = 2), traumatic brain injury (n = 1), septic shock during PICU admission (n = 0), ECMO (n = 1), and two or more readmissions (n = 4). We excluded children with these factors and compared this relatively 'uncomplicated' patient subgroup (n = 55) to the control subgroup (n = 67; eTable 5). Again, we replicated the reported group differences (ps ≤ .02). Taken together, these findings show that the observed evidence for adverse neurocognitive outcomes in the patient group is not accounted for by a range of potential confounders.

DISCUSSION

This study aimed to investigate the relation between sedatives, analgesics and anesthetics and long-term neurocognitive functioning in children with a history of PICU admission. Therefore, we selected a sample of children admitted to the PICU for bronchiolitis, a condition that seldom manifests neurologically [34,35] and is therefore not expected to affect neurocognitive functioning in itself. The results indicate that children with PICU admission for bronchiolitis have affected neurocognitive functioning, reflected by considerable lower intelligence and poorer performance on specific aspects of neurocognitive functioning (i.e. information processing, attention, verbal memory and visuomotor integration) compared to demographically comparable healthy peers, with effect sizes ranging from -0.41 to -0.60. Contrary to our hypothesis, we found no evidence for a relationship between exposure to sedatives, analgesics, anesthetics or a combination of these drugs and neurocognitive outcomes. The findings of this study indicate that children admitted to the PICU for bronchiolitis requiring mechanical ventilation are at risk of adverse neurocognitive functioning at 6-12 years of age, for which we did not find evidence supporting a role for drug exposure during PICU admission.

In 2016, the US Food and Drug Administration warned that repeated or longer use of general sedatives and anesthetics during procedures in children aged less than three

years may affect children's brain development [4]. As this warning is based on outcomes of animal studies, it remains unclear to what extent these worrying findings could be generalized to children. Studies that reported evidence for potential negative effects of sedatives [28] and analgesics [29], included children in whom the underlying disease is a risk factor for neurocognitive impairment in itself [52,53], and drug exposure may have been linked to disease severity in these studies. The findings of this study suggest that exposure to sedatives, analgesics and anesthetics or a combination of these drugs is unlikely to substantially affect long-term neurocognitive outcomes after PICU admission.

The absence of evidence supporting a role for drug exposure in this study raises the question what factors may have contributed to the observation of adverse neurocognitive outcomes. Other factors may play a role, although we found no evidence for effects of demographic characteristics or medical history (e.g. gestational age, CPR, ECMO). Indeed assuming that bronchiolitis seldom manifests neurologically [34,35], the observed adverse neurocognitive outcomes may suggest that other pathophysiological mechanisms involving (a combination of) secondary consequences of bronchiolitis and/or PICU treatment may negatively affect neurocognitive outcomes, such as hypoxia/hyperoxia, metabolic derangements such as hyponatremia or glucose dysregulation, ischemia, inflammation, hypotension and delirium [38,54-56]. Likewise, (parental) stress is considered to play an important role after PICU admission [57] and may be implicated in the mechanisms affecting neurocognitive outcomes [58,59]. The findings of our study highlight the importance of prospective studies aimed at identifying the combination of factors that may account for adverse neurocognitive outcomes in children admitted to the PICU for bronchiolitis, and for PICU admission in general. Future studies may consider the use of children with mild bronchiolitis not requiring hospitalization as controls, as this would allow the investigation of possible unexpected effects of milder manifestations of bronchiolitis. As neurocognitive impairments are known to interfere with development in crucial outcome domains [12-15], our findings also underline the importance of long-term structured follow-up after PICU admission, even in the absence of underlying disease with neurological manifestation, enabling early identification and appropriate management of adverse outcomes [60].

Limitations and strengths

This study has several limitations. First, a substantial number of eligible children (45.4%) did not participate in our study, mainly because they were not reached despite our maximal and repeated efforts. Nevertheless, important characteristics of the study sample (sex, age at PICU admission, duration of mechanical ventilation and length of PICU stay) did not differ from those of the total recruitment cohort, nor from the specific group of children that were eligible yet not included in the study. These findings indicate no evidence for selection bias in the study sample. Second, the distributions of exposure

to lorazepam, fentanyl, esketamine and propofol followed a highly skewed distribution, necessitating dichotomization. This may have reduced the sensitivity of the relevant analyses, although still sufficiently powered to detect medium-sized effects. A strength of this study is the use of a dedicated control group that was comparable to the patient group in terms of age, sex and SES. A comparable control group allows to account for inflation of intelligence over time (known as the Flynn effect [61,62]) and provides a solution for the inability to correct for SES using standardized norm scores. A second strength is the use of a comprehensive computerized neurocognitive test battery aimed at a broad range of neurocognitive outcomes relevant to daily life functioning. Lastly, we provided a comprehensive analysis of the relation between (combinations of) drug exposure to neurocognitive outcomes.

CONCLUSIONS

This study provides evidence for adverse long-term neurocognitive outcomes among children with a history of PICU admission due to bronchiolitis requiring mechanical ventilation. Contrary to our hypothesis, we found no evidence for a relationship between exposure to sedatives, analgesics, anesthetics or a combination of these drugs and neurocognitive outcomes. Future research should aim at identifying factors that are implicated in the adverse neurocognitive outcomes of children admitted to the PICU for bronchiolitis. The findings also underline the importance of long-term structured follow-up after PICU admission, even in the absence of underlying disease with neurological manifestation, enabling early identification and appropriate management of adverse outcomes.

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ONLINE SUPPLEMENTAL MATERIAL

Pre-processing

Missing values (socioeconomic status: 2.1%, neurocognitive data: 1.9%) were imputed using multiple imputation. The neurocognitive test data were subjected to a pre-processing pipeline to construct neurocognitive domain scores out performance measures resulting from comprehensive neurocognitive assessment. First, the directionality of neurocognitive variables was adapted so that for all scores, higher values corresponded to better task performance. Second, to represent all neurocognitive variables on the same scale and reduce the influence of outliers, all variables were subjected to a Van der Waerden transformation [1]. Third, we reduced the number of outcome variables using Principal Component Analysis with oblique rotation [2,3]. The Kaiser criterion was used to determine the number of neurocognitive domains that were selected for further analysis based on the eigenvalue > 1.0 [4]. Each domain was labeled as a neurocognitive domain based on a selection of variables with the strongest loadings ($-0.5 < r > 0.5$). This procedure resulted in ten neurocognitive domains that explained 78% of the variance contained in the original neurocognitive variables. The neurocognitive domains and the variables corresponding to these domains are displayed in eTable 1.

eTable 1. Overview of the neurocognitive domains, variables, definitions and tasks

Domains & Variables	Description	Definition	Task	Description
Speed and Attention				
Processing Speed	The speed of responding to target appearance	Mean reaction time (ms) on trials with neutral targets	Attention Network Test [5]	Target stimuli pointing left or right are presented on a computer screen. Subjects are instructed to respond as quickly as possible to the direction of a target stimulus by pressing the corresponding button. Performance is influenced by the presentation of cues (central, spatial) and manipulation of target flanker congruency (neutral, congruent, incongruent). The measurement of reaction times is corrected for system latency.
Processing Stability	The variability of responding to target appearance	Standard deviation of the mean reaction time (ms) on trials with neutral targets		
Attention Consistency	Lapses of attention	The average of the exponential component of the fitted ex-Gaussian curve, reflecting the influence of extremely slow responses (lapses of attention) on information processing		
Visuomotor Accuracy	The precision of proactive visuomotor tracking	The mean distance (in pixels) between the target and the mouse cursor in the structured condition across speed levels	Track & Trace task [6]	See ' Visuomotor Integration'
Visuomotor Stability	The variability of proactive visuomotor tracking	The standard deviation of the mean distance (in pixels) between the target and the mouse cursor in the structured condition across speed levels		
Set Shifting				
Speed of set-shifting	The speed of flexibly changing from an automated compatible response to an incompatible response.	The difference in mean reaction time between the set and visual shift trials	Multisensory Integration Task [7]	Measures the ability to flexibly shift between conditions (i.e. set-shifting) and the influence of multisensory integration on set-shifting. In all trials, children were presented with a target in the center of the screen (a penguin) that tilted to the left or to the right, after which a response was required (pressing one of two buttons on a response box). There were three conditions: the *set*, *visual shift* and *audiovisual shift* conditions. In the *set* condition (72% of trials) responses were required to be compatible with the tilt direction of the target. The *visual shift* condition and *audiovisual shift* conditions (14% of trials each) were marked by the presentation of a set-shifting signal at the moment when the target tilted, and required a response that was incompatible with the tilt direction of the target.
Multisensory integration speed	The speed of integrating information from different sensory modalities.	The difference in mean reaction time between the visual shift trials and audiovisual shift trials		

eTable 1. Overview of the neurocognitive domains, variables, definitions and tasks (*continued*)

Domains & Variables	Description	Definition	Task	Description
Verbal Memory				
Verbal Memory Encoding	The ability to encode verbal information in short-term memory	The sum of correct words recalled over the five direct recall trials	Rey Auditory Verbal Learning Test [8]	A list of 15 words is auditorily presented five times. The subject has to reproduce as many words as possible directly after each presentation (direct recall) and after an interval of 15 minutes (delayed recall). Lastly the subject has to select the presented words among 15 distractors (recognition).
Verbal Memory Consolidation	The ability to consolidate verbal information in long-term memory	The difference in the number of correctly recognized words and correctly recalled words in the last direct recall trial		
Verbal Memory Retrieval	The ability to retrieve verbal information from long term memory.	The difference in the number of correctly recognized words and correct words recalled in the delayed recall trial		
Visuomotor Integration				
Visuomotor Speed	The precision of visuomotor tracking at higher speeds	The difference in mean distance (in pixels) at the highest speed and the lowest speed (across the structured and unstructured condition)	Track & Trace task [6]	A moving target stimulus is presented on the screen of an iPad. Subjects are instructed to keep their index finger on the center of the target in a structured condition (predictable, circular path) and in an unstructured condition (unpredictable, random path) at four linearly increasing target speeds. The speed of the moving stimulus is corrected for the system refreshing rate.
Visuomotor Dynamic Integration	The precision of reactive visuomotor tracking	The mean distance (in pixels) between the target and the index finger in the structured condition		
Verbal Working Memory				
Phonological loop	The capacity of encoding visual information in short-term memory.	Performance in the forward condition	Digit Span task [9]	Subjects are required to repeat a sequence of numbers presented auditorily in the order of presentation (forward condition) or reversed order (backward condition). The difficulty increases every other trial, by increasing the length of the sequence of digits. Performance in each condition is defined by the span (the difficulty level of the last correct trial) multiplied by the stability (the total number of correct trials).
Verbal Central Executive	The capacity of the central executive to manipulate verbal information in short-term memory.	The difference in performance between the backward and the forward condition		

eTable 1. Overview of the neurocognitive domains, variables, definitions and tasks (*continued*)

Domains & Variables	Description	Definition	Task	Description
Interference Control				
Orienting Attention	The gain in processing speed by spatially orienting attention	The difference in mean reaction time (ms) between trials with spatial and central cues	Attention Network Test [5]	See 'Speed and Attention'
Interference Control	The speed of suppressing irrelevant information	The difference in mean reaction time (ms) between trials with incongruent and congruent targets		
Visual Processing Speed				
Set Speed	The speed of responding to target appearance	Mean reaction time on set trials	Multisensory Integration Task [7]	See 'Set Shifting'
Multisensory Integration Speed	The speed of integrating information from different sensory modalities.	The difference in mean reaction time between the visual shift trials and audiovisual shift trials		
Visual Working Memory				
Visuo-spatial sketchpad	The capacity of encoding visual information in short-term memory	Performance in the forward condition	Klingberg task [10]	A sequence of yellow dots is presented on a four by four digital grid. Subjects are required to repeat the sequence in the order of presentation (forward) or reversed order (backward) by clicking on the relevant locations in the grid. The difficulty increases every other trial, by increasing the length of the sequence or increasing the difficulty of the virtual trajectory of the yellow dots. Performance in each condition is defined by the span (the difficulty level of the last correct trial) multiplied by the stability (the total number of correct trials).
Visual Central Executive	The capacity of the central executive to manipulate visual information in short-term memory.	The difference in performance between the backward and the forward condition		

eTable 1. Overview of the neurocognitive domains, variables, definitions and tasks (*continued*)

Domains & Variables	Description	Definition	Task	Description
Planning Time				
Alerting Attention	The ability to achieve and maintain an alert state.	The difference in mean reaction time between central cue trials and no cue trials	Attention Network Test [5]	See 'Speed and Attention'
Planning Time	The time taken to plan ahead before responding.	Mean of time to first response in trials with correct answers	Tower of London [11]	Colored discs must be moved one by one from an initial state to match a goal state. Instructions are given to plan the whole sequence of moves that must be carried out mentally, before executing the sequence.
Planning Capacity	The ability to efficiently plan responses in problem solving	Total items correct multiplied by the maximum correct difficulty degree		
Multisensory Integration				
Multisensory Integration Accuracy	The accuracy of integrating information from the different sensory modalities.	The difference in mean accuracy between the visual shift trial and audiovisual shift trial	Multisensory Integration Task [7]	See 'Set Shifting'

Note: Experimental procedures ('Tasks') that have been applied to generate test scores targeting specific neurocognitive functions ('Variables'), which in turn were clustered using component analysis to retrieve overarching scores representing neurocognitive domains ('Domains'). ms = milliseconds

eTable 2. Comparison of included children with the total sample of eligible children

Demographic and clinical characteristics	Patient group (n = 65)	Totale sample of eligible children (n = 119)	p-value
Sex, % boys	60.0	59.7	.96
Age at PICU admission (days), median (IQR)	43.0 (23.5-79.5)	45.0 (27.0-82.0)	.56
Mechanical ventilation (days), mean (SD)	6.6 (2.8)	6.3 (2.7)	.27
PICU stay (days), median (IQR)	7.4 (5.7-9.0)	6.88 (5.0-8.7)	.23

eTable 3. Comparison of included children with eligible children not included

Demographic and clinical characteristics	Patient group (n = 65)	Eligible children not included (n = 54)	p-value
Sex, % boys	60.0	59.3	.94
Age at PICU admission (days), median (IQR)	43.0 (23.5-79.5)	57.5 (28.0-86.3)	.40
Mechanical ventilation (days), mean (SD)	6.6 (2.8)	5.8 (2.5)	.09
PICU stay (days), median (IQR)	7.4 (5.7-9.0)	6.0 (5.0-8.3)	.06

Note: PICU = Pediatric Intensive Care Unit

Confounding analysis

As the patient group had significant lower gestational age as compared to the control group, this could theoretically be a confounder in the observed differences between the patient and control group. Therefore, we assessed whether the neurocognitive variables that were significantly different between the patient and control group, were also related to gestational age. This was the case for FSIQ ($p = .03$) and for verbal memory ($p = .002$), but not for speed and attention ($p = .07$) nor for planning time ($p = .12$). In order to create a patient and control group comparable on gestational age, we excluded 5 children in the patient group with gestational age < 32 weeks en 9 children in the control group with gestational age > 41.5 weeks (median (IQR) respectively 38.36 (36.89-40.11) weeks and 39.57 (38.00-40.43) weeks, $p = .26$). Subsequently, we repeated the group comparisons for FSIQ and verbal memory, which replicated the previously reported significant group differences (mean (SE) difference respectively -8.46 (2.24), $p < .001$ and -0.47 (0.15), $p = .003$). These findings indicate that the observed evidence for adverse neurocognitive outcomes are not accounted for by premorbid differences in gestational age.

eTable 4. Exploratory analysis

Neurocognitive outcomes	R^2 (%)	Beta (SE)	p-value *
Invasive mechanical ventilation duration			
FSIQ	0.2	0.01 (0.02)	.69
Speed and attention	0.3	-0.00 (0.00)	.69
Verbal memory	2.3	-0.00 (0.00)	.69
Midazolam mean cumulative daydose			
FSIQ	0.5	2.10 (3.90)**	.79
Speed and attention	0.3	0.09 (0.23)**	.79
Verbal memory	0.1	0.07 (0.28)**	.79
Midazolam highest cumulative daydose			
FSIQ	1.6	3.90 (4.18)**	.41
Speed and attention	8.5	0.48 (0.22)**	.10
Verbal memory	1.3	0.23 (0.28)**	.41
Morphine mean cumulative daydose			
FSIQ	4.4	10.62 (6.29)**	.25
Speed and attention	0.3	-0.17 (0.38)**	.65
Verbal memory	3.0	0.62 (0.44)**	.25
Morphine highest cumulative daydose			
FSIQ	0.0	0.63 (7.21)**	.93
Speed and attention	1.0	-0.27 (0.39)**	.73
Verbal memory	1.5	-0.42 (0.47)**	.73
Prednisone yes/no			
FSIQ	0.0	0.00 (7.47)	.99
Speed and attention	0.7	0.30 (0.44)	.75
Verbal memory	1.6	-0.52 (0.53)	.75
Dexamethasone yes/no			
FSIQ	2.0	-4.73 (4.22)	.33
Speed and attention	1.6	-0.25 (0.25)	.33
Verbal memory	1.5	0.29 (0.30)	.33
Sedatives, analgesics, anesthetics and corticosteroids			
FSIQ	0.4	-0.01 (0.02)	.60
Speed and attention	1.6	-0.00 (0.00)	.57
Verbal memory	1.2	-0.00 (0.00)	.57

Note: * Correction for false discovery rate applied at the level of exposure measure.
** Beta represents a change of the dependent variable by the independent variable times 10.

eTable 5. Confounding analysis

Demographic and clinical characteristics and neurocognitive outcomes	Mean (SE) difference between patient and control group	p-value
Demographic and clinical characteristics		
Age at time testing (years)	-0.20 (0.24)	.41
Sex (% boys)	0.57 (0.37)	.13
Socioeconomic status	0.01 (0.12)	.96
Gestational age (weeks) *	-0.15 (0.12)	.23
Neurocognitive outcomes		
FSIQ	-7.71 (2.25)	**.001**
Speed and attention	-0.40 (0.17)	**.02**
Verbal memory	-0.44 (0.15)	**.005**

Note: Patient group n = 55, control group n = 67: Excluded in patient group: gestational age < 32 weeks, bronchopulmonary dysplasia, cardiopulmonary resuscitation, traumatic brain injury, septic shock, delirium, Pediatric Index of Mortality 2 score > 10, extra-corporeal membrane oxygenation, more than two PICU admissions. Excluded in control group: gestational age > 41.5 weeks to have a comparable gestational age between patient and control group.
* Van der Waerden transformation of gestational age to obtain a normal distribution. Boldface values indicate $p < .05$.

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6 Predicting long-term neurocognitive outcome after pediatric intensive care unit admission - exploring the potential of machine learning

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ABSTRACT

Purpose: For successful prevention and intervention, it is important to unravel the complex constellation of factors that affect neurocognitive functioning after Pediatric Intensive Care Unit (PICU) admission. This study aims (1) to elucidate the potential relevance of patient and PICU-related characteristics for long-term neurocognitive outcome after PICU admission; and (2) to determine the potential of machine learning to improve outcome prediction.

Methods: In this single-center cohort study we investigated 65 children aged 6-12 years with previous PICU admission for bronchiolitis (age ≤ 1 year). Patient and PICU-related characteristics used for the prediction models were: demographic characteristics, perinatal and disease parameters, laboratory results and intervention characteristics, including hourly validated mechanical ventilation parameters. Neurocognitive outcome was measured by intelligence and computerized neurocognitive testing. Prediction models were developed for each of the neurocognitive outcomes using Regression Trees, k-Nearest Neighbors and conventional Linear Regression analysis.

Results: Lower intelligence was predicted by lower birth weight and lower socioeconomic status (R^2 = 25.9%). Poorer performance on the Speed and Attention domain was predicted by younger age at follow-up (R^2 = 53.5%). Poorer verbal memory was predicted by lower birth weight, younger age at follow-up, and greater exposure to acidotic events (R^2 = 50.6%). The machine learning models did not reveal added value in terms of model performance as compared to Linear Regression.

Conclusions: The findings of this study suggest that in children with previous PICU admission for bronchiolitis: (1) lower birth weight and lower socioeconomic status are associated to poorer neurocognitive outcome; and (2) greater exposure to acidotic events during PICU admission is associated with poorer verbal memory outcome. Findings of this study provide no evidence for added value of machine learning models as compared to linear regression analysis in the prediction of long-term neurocognitive outcome in a relatively small sample of children.

INTRODUCTION

With advances in pediatric intensive care, the survival rate of children admitted to the pediatric intensive care unit (PICU) has increased dramatically in the past decades [1,2]. Yet, long-term morbidity after PICU admission is a growing concern [3,4]. Sequelae are described in physical, neurocognitive and psychosocial health [3-7]. Adverse neurocognitive outcomes are known to interfere with development in other major domains of functioning, such as physical and mental health [8,9], academic achievement [10], and socioeconomic success [11], highlighting neurocognition as an important outcome after PICU admission.

In the literature, multiple pathophysiological mechanisms have been proposed that may contribute to long-term neurocognitive outcome of critically ill patients, including hypoxia, metabolic derangements and ischemia [12-14]. Such mechanisms may be triggered by the underlying disease [15], the critical deterioration [16], and/or the associated treatments at the PICU [17]. As understanding of the origin of difficulties in neurocognitive functioning is a prerequisite for successful prevention and intervention, it is important to unravel the factors that affect neurocognitive functioning after PICU admission.

Digitalization of health care provides increasingly more data that can importantly contribute to better prediction and understanding of long-term outcome after PICU admission. Nevertheless, the increasing wealth of clinical data produced by medical devices, involves very long time series representing a great number of characteristics, with potential complex inter-relations that are relevant for outcome. Therefore, novel data sources challenge conventional statistical methods such as linear regression, which are not suitable to handle larger numbers of predictors and have limited potential to capture complex relations between predictors and outcome. Compared to conventional statistics, machine learning has great potential to capture this complexity thanks to the capability to process vast amounts of data and model nonlinear and highly complex interactions [18]. Machine learning is a rapidly growing field of artificial intelligence that is increasingly applied in health care settings [19-22]. However, the value of machine learning in investigating the relation between PICU admission and long-term neurocognitive outcome has not been investigated thus far and is therefore currently unclear.

This study aims (1) to elucidate the potential relevance of patient and PICU-related characteristics for long-term neurocognitive outcome after PICU admission; and (2) to determine the potential of machine learning to improve outcome prediction. We specifically focused on children with previous PICU admission for bronchiolitis, because this is a relative homogenous group with single organ failure that seldom manifests neurologically [23,24] and is therefore not expected to affect neurocognitive functioning in itself.

MATERIALS AND METHODS

Participants

This observational cohort study assessed children aged 6-12 years with a history of PICU admission during infancy (age ≤ 1 year) for bronchiolitis requiring invasive mechanical ventilation. Children were retrospectively recruited from a consecutive cohort admitted between 2007 and 2013 to the PICU of the Amsterdam University Medical Centers (UMC), the Netherlands. Exclusion criteria were: developmental disorders known to impact on neurocognitive development; physical conditions and/or behavioral deficits interfering with the ability to adequately perform neurocognitive testing; clinical signs of neurological complications during PICU admission (e.g. seizure, encephalitis, meningitis); presence of family conflict interfering with study participation (e.g. child abuse, child being placed under external supervision); and living abroad.

Measures

Patient and PICU-related characteristics

Data on sex, age, and the perinatal characteristics gestational age and birth weight were extracted from the medical files. Data on socioeconomic status, past breastfeeding, mother's smoking and drinking of alcohol during pregnancy were collected using a parental questionnaire. Socioeconomic status was defined as the average level of parental education ranging from 1 (no education) to 8 (postdoctoral education) [25]. Furthermore, we extracted the following patient and PICU-related characteristics from the medical files: age and weight at PICU admission, Pediatric Index of Mortality 2 (PIM 2) score [26], duration of invasive mechanical ventilation, length of PICU stay, need for reintubation, cardiopulmonary resuscitation, use of antibiotics during PICU stay, readmission to the PICU, and the isolation of type(s) of viral agents from the nasopharyngeal aspirate. Furthermore, we extracted the hourly nurse-validated values of the settings of the mechanical ventilator: fraction of inspired oxygen (FiO_2), positive inspiratory pressure (PIP), positive end-expiratory pressure (PEEP). In addition, the following nurse-validated results of mechanical ventilation were recorded: mean airway pressure, oxygen saturation (SpO_2), end-tidal carbon dioxide ($etCO_2$), and SpO_2/FiO_2 ratio. At last, we extracted the laboratory measures serum glucose, pH, partial pressure of carbon dioxide (pCO_2) and lactate. Arterial and/ or capillary (in case patients did not have an arterial line) measures were extracted. Values were compared against clinical cut-offs [27]. All extracted patient and PICU-related characteristics are displayed in Online Resource 1.

Long-term neurocognitive functioning

Neurocognitive functioning was determined by assessment of full-scale intelligence quotient (FSIQ) and specific domains of neurocognitive functioning by a standardized and computerized neurocognitive test-battery. FSIQ was assessed to capture general neurocognitive functioning and was measured by a short form of the Wechsler Intelligence Scale for Children - Third edition (WISC-III) involving the subtests Vocabulary, Arithmetic, Block Design and Picture Arrangement. FSIQ estimated with this short form has excellent validity (r = .95) and reliability (r = .90) [28].

The neurocognitive test-battery measures a broad range of key neurocognitive domains and contains a composition of child-friendly tests based on well-known neuroscientific paradigms with established validity and reliability, i.e. the Attention Network Test [29], Multisensory Integration Task [30], Tower of London [31], Rey Auditory Verbal Learning Test [32], Digit Span task [33], Klingberg task [34] and the Track & Trace task [35]. The neurocognitive data derived from the test-battery were subjected to a pre-processing pipeline to construct neurocognitive domain scores.[36] This procedure resulted in ten neurocognitive domains that explained 78% of the variance contained in the original neurocognitive data derived from the test-battery, i.e. speed and attention, set shifting, verbal memory, visuomotor integration, verbal working memory, interference control, visual processing speed, visual working memory, planning time and multisensory integration. Higher scores on each of the domains, reflect better performance.

In our previous study [36], we compared the same patient group included in the current study to a demographically (age, sex and socioeconomic status) comparable control group (n = 76). For a full description of the findings, see Online Resource 2. Compared to the control group, the patient group had significantly lower FSIQ ($p < .001$, Cohen's $d = -0.59$), and significant poorer performance on the domains Speed and Attention ($p = .03$, $d = -0.41$) and Verbal Memory ($p < .001$, $d = -0.60$). In the current study, these three neurocognitive outcomes were selected as outcome measures.

Pre-processing of patient and PICU-related characteristics

Missing values (≤ 3.1% missing at random in 4 variables) were imputed using multiple imputation [37]. Outliers (mean +/- 3SD) were winsorized. In order to avoid that the final model would be overly sensitive to variables with low prevalence, variables with less than 10 occurrences per event were eliminated. In case of multicollinearity between variables (based on variance inflation factor > 10 and/or Pearson > 0.7 or < -0.7), the variable with the lowest correlation to FSIQ was eliminated.

Statistical analysis

Statistical analysis was conducted using R, RStudio, the car package and the caret package. In order to gain insight in the association between predictor variables (patient

and PICU-related characteristics) and long-term neurocognitive outcomes, we selected two widely adopted machine learning algorithms that provide interpretable outcomes: Regression Trees and k-Nearest Neighbors. We used multivariable linear regression analysis with backward elimination as reference model (p out > .05). With each of the techniques (i.e. Regression Trees, k-Nearest Neighbors, Linear Regression), one model was fitted for each of the neurocognitive outcomes.

The goal of machine learning is to predict an outcome based on patterns present in the input data (training). In order to train a model to predict unseen ("new") data, the original dataset was split into a training set (90% of the data) and a blind test set (10% of the data), which were identical for each model. The training set was then further divided into 10 (folds) for 5-repeated 10-fold cross-validation [38], which was used for performance validation. Each model was trained on data of the training set (9 out of 10 folds), validating training performance on the 10^{th} fold. Based on the results from model training, the mean performance across all folds was reported. Thereafter, the blind test set was used only once for each model, in order to assess model generalizability and model performance on data that were not used for model training. Model generalizability (i.e. stability of model performance on data that were not used to develop the model) was assessed by comparing model performance (the explained variance, R^2) in the training set (average across folds) to the blind test set using 95% bootstrap confidence intervals (95%-CI). In case the mean R^2 of the training set was within the 95%-CI of the R^2 of the blind test set, we concluded that the model had sufficient generalization from the training data to the blind test data. Subsequently, model performance was based on the R^2 in the blind test set. To assess the added value of the machine learning models as compared to our reference model, we compared the R^2 of the blind test set between models, using the 95%-CI of the multivariable linear regression models as reference. For details regarding the machine learning algorithms, see Online Resource 3. All statistical testing was two-sided, α was set at .05.

RESULTS

Participants

A total of 65 of 119 eligible children were included (Figure 1). The included children did not differ from the total sample of eligible children in terms of sex, age at PICU admission, duration of mechanical ventilation and length of PICU stay (ps ≥ .23). Table 1 shows the patient and PICU-related characteristics of the included children that were used for the prediction models.

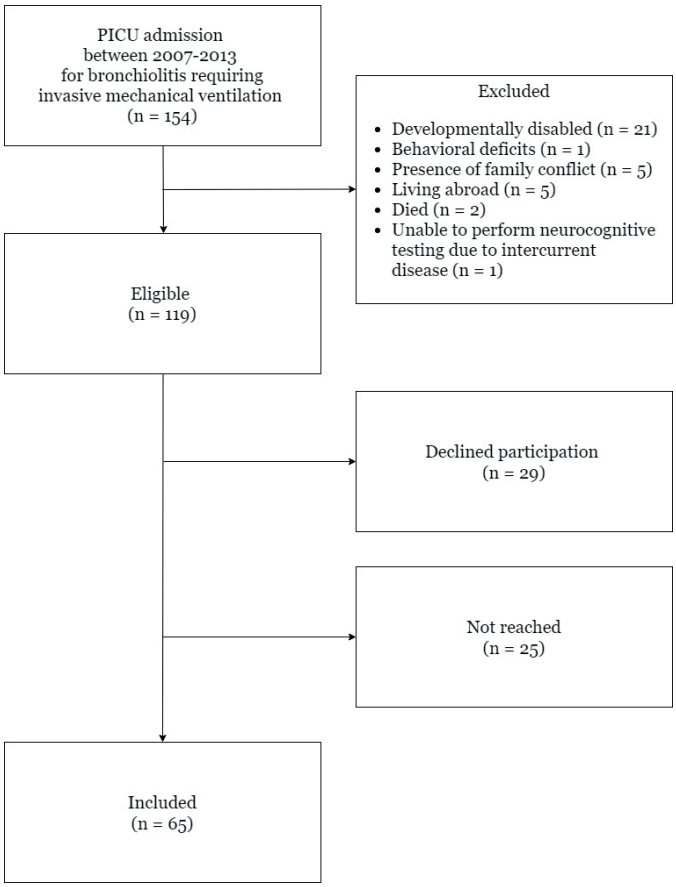

Figure 1. Flowchart of included children in the patient group.
Note: Reasons to decline participation were: not interested (n = 11), no time (n = 10), too high a burden on child (n = 6) or language barrier of parents (n = 2).

Table 1. Patient and PICU-related characteristics that were used for the prediction models.

Patient and PICU-related characteristics	Mean (SD), median (IQR) or number (%)
Age at follow-up (years), mean (SD)	8.1 (1.2)
Sex (female), n (%)	26 (40.0)
Socioeconomic status, mean (SD)	5.3 (1.2)
Gestational age (weeks), median (IQR) *	38.1 (36.3-39.9)
Birth weight (grams), mean (SD)	3083 (968)
Breastfed in past, n (%)	42 (64.6)
Age at PICU admission (days), median (IQR) *	43.0 (23.5-79.5)
Weight at PICU admission (grams), mean (SD)	4634 (1662)
PIM 2 score, median (IQR)	1.4 (1.1-2.1)
Duration of invasive mechanical ventilation (hours), mean (SD)	169.5 (88.6)
Length of PICU stay (days), median (IQR) *	7.4 (5.7-9.0)
Glucose (mmol/L), mean (SD) *	6.1 (0.8)
Number of times glucose > 10 mmol/L, median (IQR)	0.0 (0.0-1.0)
Number of times pCO_2 > 6.4 kPa, median (IQR) *	12.0 (7.5-19.5)
Number of times pCO_2 < 4.7 kPa, median (IQR)	1.0 (0.0-2.0)
Number of times pH > 7.45, median (IQR)	6.0 (4.0-11.5)
Number of times pH < 7.35, median (IQR)	2.0 (0.0-4.0)
Number of times SpO_2 < 90%, median (IQR)	1.0 (0.0-2.0)
Number of times SpO_2 < 85%, median (IQR) *	0.0 (0.0-1.0)
Minimum FiO_2 (%), median (IQR)	26.0 (25.0-30.0)
Maximum FiO_2 (%), mean (SD)	88.6 (17.0)
Mean SpO_2/FiO_2 ratio, mean (SD)	2.5 (0.5)
Minimum SpO_2/FiO_2 ratio, mean (SD) *	1.1 (0.3)
Number of times $etCO_2$ < 3.5 kPa, median (IQR)	1.0 (0.0-4.0)
Number of times $etCO_2$ > 6.5 kPa, median (IQR)	5.0 (1.0-14.0)
Difference between PIP and PEEP (cmH_2O), mean (SD)	15.9 (2.5)
Mean airway pressure (cmH_2O), mean (SD) *	13.4 (1.8)

Note: CPR = cardiopulmonary resuscitation; $etCO_2$ = end-tidal carbon dioxide; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PICU = pediatric intensive care unit; PIP = positive inspiratory pressure; PIM2 score = Pediatric Index of Mortality 2 score; PIP = positive inspiratory pressure; SpO_2 = oxygen saturation.

* Variable eliminated in the Linear Regression and k-Nearest Neighbors models due to multicollinearity.

Value of machine learning

Generalization

Table 2 displays the results regarding generalizability and performance of the models. For the majority of models, we found no significant difference in model performance on blind test data as compared to the training data, suggesting sufficient generalization

of model performance. As exception, the Regression Trees model for Verbal Memory showed significantly higher performance in the blind test data as compared to the training data, suggesting insufficient generalization of model performance. The wide confidence intervals should be noted, with limited sensitivity for comparisons of model generalization.

Performance

The reference Linear Regression models showed predictive value for FSIQ (R^2 = 25.9%, p = .005), performance on the Speed and Attention domain (R^2 = 53.5%, p < .001) and performance on the Verbal Memory domain (R^2 = 50.6%, p < .001). As compared to the reference Linear Regression models, we found no significant differences in performance (on blind test data) for the Regression Trees and k-Nearest Neighbors machine learning models. Again, the wide confidence intervals should be noted, reflecting limited sensitivity for model performance comparisons.

Taken together, the Regression Trees model for Verbal Memory showed poor generalizability of model performance to new data, while both the Regression Trees and k-Nearest Neighbors models did not reveal added value in terms of model performance as compared to Linear Regression. These findings provide no evidence for added value of these machine learning models in the prediction of long-term neurocognitive outcome.

Table 2. Cross-validated results and bootstrapped (R = 1000) test results

Outcome	Algorithm	R^2 (%) Training set	R^2 (%) Blind test set	95% CI of the R^2 (%) Blind test set
FSIQ	Linear Regression	24.1	25.9	0.0 - 97.3
	Regression Trees	19.7	65.3	19.2 – 96.9
	k-Nearest Neighbors	8.9	15.8	0.0 – 58.4
Speed and attention	Linear Regression	43.9	53.5	1.6 - 98.9
	Regression Trees	31.4	70.2	12.2 - 98.9
	k-Nearest Neighbors	7.6	16.9	0.0 – 63.8
Verbal memory	Linear Regression	41.0	50.6	4.0 - 98.5
	Regression Trees	10.8	76.7	23.0 - 99.4
	k-Nearest Neighbors	7.6	16.7	0.0 – 66.5

Note: FSIQ = full-scale intelligence quotient.

Prediction of long-term neurocognitive outcomes

Considering that we did not find evidence for added value of the Regression Trees and k-Nearest Neighbor machine learning models, we used the Linear Regression reference models to provide insight in the variables that contribute to the prediction of long-term neurocognitive outcome (Table 3). The results show that lower FSIQ was predicted by

lower birth weight and lower socioeconomic status (R^2 = 25.9%). Poorer performance on the Speed and Attention domain was solely predicted by younger age at follow-up (R^2 = 53.5%). Poorer performance on the Verbal Memory domain was predicted by lower birth weight, younger age at follow-up, and greater exposure to acidotic events (number of times pH < 7.35; R^2 = 50.6%).

Table 3. Results of the final multivariable linear regression models

Neurocognitive outcomes	Predictors	Standardized Beta	p-value
FSIQ	*Total model*		.005
	Birth weight (grams)	0.24	.047
	Socioeconomic status	0.31	.011
Speed and attention	*Total model*		< .001
	Age at follow-up (years)	0.57	< .001
Verbal memory	*Total model*		< .001
	Birth weight (grams)	0.44	< .001
	Age at follow-up (years)	0.25	.019
	Number of times pH < 7.35	-0.29	.008

Note: FSIQ = full-scale intelligence quotient.

Exploratory analysis

We further explored exposure to acidotic events (number of times pH < 7.35). Acidosis (pH < 7.35) was observed in 47 of 65 patients (72.3%) and regarding acidosis severity, the following pH values were observed: pH 7.25-7.35: 196 observations in 47 patients; pH 7.20-7.25: 36 observations in 16 patients; pH < 7.20: 41 observations in 10 patients. In 247 (90.5%) observations acidosis co-occurred with elevated pCO_2, in 1 observation with elevated lactate, and in 5 observations with a combination of elevated pCO_2 and elevated lactate. In 235 (86%) observations of acidosis, lactate was not measured. The pattern findings suggest a respiratory origin more likely to explain the occurrence of acidosis as compared to a metabolic origin, although a combination cannot be ruled out due to unavailability of lactate measurements for the majority of acidotic events.

The relation between verbal memory outcome and other aspects of acidosis exposure were also explored by multivariable linear regression analysis with backward elimination. The following independent pH variables were used: lowest pH value of each patient, mean pH value of each patient, and exposure to severe acidotic events (pH < 7.20). In addition, we also used exposure to hypercapnia (pCO_2 > 6.4 kPa) as an independent variable. Results are displayed in Table 4. Lower mean pH values and greater exposure to elevated pCO_2 levels were associated with poorer verbal memory outcome (p = .038 and p = .011, respectively).

Table 4. Exploratory analysis regarding acidotic events

Neurocognitive outcome	Predictors	Median (IQR)	Standardized Beta	p-value
Verbal memory	Lowest pH value for each patient	7.29 (7.21-7.36)	0.23	.07
	Mean pH value for each patient	7.42 (7.41-7.44)	0.26	.038
	Number of times pH < 7.20	0 (0-0)	-0.17	.19
	Number of times pCO_2 > 6.4 kPa	12.0 (7.5-19.5)	-0.32	.011

Note: pCO_2 = partial pressure of carbon dioxide

DISCUSSION

This study aimed (1) to elucidate the potential relevance of patient and PICU-related characteristics for long-term neurocognitive outcome after PICU admission, and (2) to determine the potential of machine learning to improve outcome prediction. The results provide no evidence for added value of machine learning models as compared to conventional linear regression analysis in the prediction of long-term neurocognitive outcome after PICU admission. As may be expected, linear regression analysis revealed that neurocognitive outcome was associated with demographic and perinatal characteristics (socioeconomic status, age at follow-up and birth weight). Moreover, children with greater exposure to acidotic events during PICU admission for bronchiolitis had poorer verbal memory outcome. As involvement of the central nervous system in the pathology of bronchiolitis is unlikely [23,24], the relation between acidotic events and neurocognitive outcome may reflect either potentially harmful effects of acidosis itself, or reflect related processes such as hypercapnia, hypoxic and/or ischemic events during PICU admission.

Regarding comparison of prediction models, we found no evidence for added value of the Regression Trees and k-Nearest Neighbors machine learning models as compared to conventional linear regression analysis. The wide confidence intervals, potentially reflecting the small sample size of the blind test set, provided limited sensitivity for model comparisons. Nevertheless, the findings suggest that machine learning models may not have added value in smaller sample sizes. Indeed, machine learning flourishes by large datasets not easily obtained in clinical settings [39]. This further stresses the importance of collaborations between centers to pool clinical data and acquire larger datasets for clinical research into advanced outcome prediction using machine learning.

The results of our study show that lower socioeconomic status was associated with lower intelligence after PICU admission. Abundant research has documented the relation between socioeconomic status and neurocognitive functioning, of which the origin is matter of debate [40]. We also observed that younger age at follow-up was associated with poorer neurocognitive functioning (i.e. poorer speed and attention and verbal memory).

We ascribe this finding to a developmental effect, i.e. reflecting the commonly observed age-related enhancement in neurocognitive functioning [33]. Furthermore, lower birth weight was associated with lower intelligence and poorer verbal memory. This result is in line with literature showing an association between lower birth weight and poorer neurocognitive functioning [41-43].

The findings of our study suggest that greater exposure to acidotic events during PICU admission is associated with poorer verbal memory outcome. In experimental studies several mechanisms have been proposed that may explain a potential negative effect of acidosis on the central nervous system, such as acidosis causing denaturation of proteins and nucleic acids, triggering cell swelling potentially leading to cellular edema and osmolysis, and inhibition of excitatory neurotransmission in the hippocampus, and influencing neuronal vulnerability indirectly by damaging glial cells [44,45]. Although the translation of these findings from the literature to our study findings is unclear, our findings indicate that acidotic events may be implicated in negative effects on the central nervous system, whether or not through other neurotoxic processes such as hypercapnia, hypoxia or ischemia. In our exploratory analyses we found additional evidence indicating that higher pCO_2 measurements, compatible with a respiratory origin of acidosis, were also related to poorer verbal memory outcome. Regardless of the exact mechanisms at play, our findings suggest that children with greater exposure to acidotic events are at risk of adverse long-term neurocognitive outcome after PICU admission, a finding that awaits replication in future prospective studies.

A limitation of our study is that a substantial number of eligible children (45.4%) did not participate in our study, mainly because they were not reached despite our efforts. However, we deem it unlikely that this has caused important selection bias, because the study sample did not differ from the total cohort of eligible children in terms of demographic characteristics and illness severity. Furthermore, we acknowledge that the reported associations between risk factors and outcome may not reflect causal relationships.[46] Important to note, is that the number of acidotic events was determined on blood gas analyses measured based on clinical signs of respiratory distress. Therefore, the number of assessed blood gas analyses varied between patients based on presentation of clinical state. At last, this study has modest sample size and hence had limited statistical power [47]. Consequently, our reported findings await replication in larger future studies that allow for more robust estimation. A strength of our study is that we extensively investigated patient and PICU-related characteristics in the relation between PICU admission and neurocognitive outcome. In addition, we focused on children admitted to the PICU for bronchiolitis, in an attempt to control for the confounding effect of underlying disease on outcome.

CONCLUSION

The findings of this study suggest that in children with previous PICU admission for bronchiolitis: (1) lower birth weight and lower socioeconomic are associated with poorer neurocognitive outcome; and (2) greater exposure to acidotic events during PICU admission is associated with poorer verbal memory outcome. Our study does not provide evidence for added value of machine learning models as compared to conventional linear regression analysis in the prediction of long-term neurocognitive outcome in a relatively small sample of children with PICU admission. This study further highlights the importance of structured follow-up to monitor long-term outcome of children after PICU admission.

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ONLINE SUPPLEMENTAL MATERIAL

eTable 1. Complete list of the extracted patient and PICU-related characteristics of the included children.

Patient and PICU-related characteristics	Mean (SD), median (IQR) or number (%)
Age at follow-up (years), mean (SD)	8.1 (1.2)
Sex (female), n (%)	26 (40.0)
Socioeconomic status, mean (SD)	5.3 (1.2)
Gestational age (weeks), median (IQR) *	38.1 (36.3-39.9)
Birth weight (grams), mean (SD)	3083 (968)
Bronchopulmonary dysplasia, n (%) **	3 (4.6)
Mother cigarette smoking during pregnancy, n (%) **	6 (9.2)
Mother drinking of alcohol during pregnancy, n (%) **	2 (3.1)
Breastfed in past, n (%)	42 (64.6)
Age at PICU admission (days), median (IQR) *	43.0 (23.5-79.5)
Weight at PICU admission (grams), mean (SD)	4634 (1662)
PIM 2 score, median (IQR)	1.4 (1.1-2.1)
Duration of invasive mechanical ventilation (hours), mean (SD)	169.5 (88.6)
Length of PICU stay (days), median (IQR) *	7.4 (5.7-9.0)
Respiratory syncytial virus positive, n (%) **	56 (86.2)
Reintubation, n (%) **	4 (6.2)
Tracheostomy, n (%) **	2 (3.1)
ECMO, n (%) **	1 (1.5)
CPR, n (%) **	2 (3.1)
Readmission at the PICU, n (%) **	7 (10.8)
Nitric oxide, n (%) **	3 (4.6)
Cardiostimulants, n (%) **	5 (7.7)
Antibiotics, n (%) **	56 (86.2)
Sepsis, n (%) **	1 (1.5)
Septic shock, n (%) **	0 (0.0)
Meningitis, n (%) **	0 (0.0)
Glucose (mmol/L), mean (SD) *	6.1 (0.8)
Number of times glucose < 3 mmol/L, median (IQR) **	0.0 (0.0-0.0)
Number of times glucose > 10 mmol/L, median (IQR)	0.0 (0.0-1.0)
Number of times pCO_2 > 6.4 kPa, median (IQR) *	12.0 (7.5-19.5)
Number of times pCO_2 < 4.7 kPa, median (IQR)	1.0 (0.0-2.0)
Number of times pH > 7.45, median (IQR)	6.0 (4.0-11.5)
Number of times pH < 7.35, median (IQR)	2.0 (0.0-4.0)
Number of times lactate > 2.1 mmol/L, median (IQR) **	0.0 (0.0-1.0)
Number of times SpO_2 < 90%, median (IQR)	1.0 (0.0-2.0)

eTable 1. Complete list of the extracted patient and PICU-related characteristics of the included children. (*continued*)

Patient and PICU-related characteristics	Mean (SD), median (IQR) or number (%)
Number of times SpO_2 < 85%, median (IQR) *	0.0 (0.0-1.0)
Minimum FiO_2 (%), median (IQR)	26.0 (25.0-30.0)
Maximum FiO_2 (%), mean (SD)	88.6 (17.0)
Mean SpO_2/FiO_2 ratio, mean (SD)	2.5 (0.5)
Minimum SpO_2/FiO_2 ratio, mean (SD) *	1.1 (0.3)
Number of times $etCO_2$ < 3.5 kPa, median (IQR)	1.0 (0.0-4.0)
Number of times $etCO_2$ > 6.5 kPa, median (IQR)	5.0 (1.0-14.0)
Difference between PIP and PEEP (cmH_2O), mean (SD)	15.9 (2.5)
Mean airway pressure (cmH_2O), mean (SD) *	13.4 (1.8)

Note: CPR = cardiopulmonary resuscitation; $etCO_2$ = end-tidal carbon dioxide; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PICU = pediatric intensive care unit; PIP = positive inspiratory pressure; PIM2 score = Pediatric Index of Mortality 2 score; PIP = positive inspiratory pressure; SpO_2 = oxygen saturation.

There were no missing data except for the variables: mother cigarette smoking during pregnancy, mother drinking of alcohol during pregnancy, birth weight and breastfed in past (≤ 3.1% missing at random).

* Variable eliminated in the Linear Regression and k-Nearest Neighbors models due to multicollinearity.

** Variable eliminated in all models due to less than 10 occurrences per event.

eTable 2. Neurocognitive outcomes of children in the patient and control group

Neurocognitive outcomes	Description	Patient group mean (SD) (n = 65)	Control group mean (SD) (n = 76)	Mean (SE) difference	p-value *	Cohen's *d*
FSIQ	Intelligence	95.3 (15.9)	105.1 (15.1)	-8.46 (1.98)	**< .001**	-0.59
Neurocognitive domains						
Speed and attention	Speed and variability of information processing and attention	-0.19 (0.95)	0.16 (1.02)	-0.41 (0.15)	**.03**	-0.41
Set shifting	Speed of shifting between response types	-0.03 (1.03)	0.02 (0.98)	-0.08 (0.16)	.75	-0.08
Verbal memory	Learning and memory for verbal information	-0.29 (1.13)	0.24 (0.81)	-0.60 (0.14)	**< .001**	-0.60
Visuomotor integration	Speed and flexibility of visuomotor integration	0.13 (1.06)	-0.11 (0.93)	0.25 (0.17)	.22	0.25
Verbal working memory	Short-term memory and manipulation of verbal information	-0.15 (1.03)	0.13 (0.96)	-0.27 (0.16)	.17	-0.27
Interference control	Speed of suppressing distracting information	0.12 (1.01)	-0.11 (0.98)	0.21 (0.16)	.25	0.21
Visual processing speed	Speed of visual information processing	-0.03 (1.06)	0.02 (0.95)	-0.06 (0.16)	.81	-0.06
Visual working memory	Short-term memory and manipulation of verbal information	-0.16 (1.01)	0.13 (0.98)	-0.29 (0.17)	.17	-0.29
Planning time	Speed and capacity of planning ahead	0.20 (0.99)	-0.17 (0.98)	0.38 (0.16)	.05	0.38
Multisensory integration	Accuracy for integration of information from different sensory modalities	0.02 (1.08)	-0.02 (0.93)	0.04 (0.17)	.82	0.04

Note: FSIQ = estimated full-scale intelligence quotient; SD = standard deviation; SE = standard error. The directionality of neurocognitive variables was adapted so that for all scores, higher values corresponded to better task performance.

* Correction for false discovery rate applied across neurocognitive outcomes.

Regression Trees

Regression Trees is a non-parametric machine learning algorithm with high interpretability of outcomes [1]. In order to increase its predictive power and to reduce the risk of overfitting, the bootstrap aggregating (bagging) method was used [2]. The bagging method consists of three steps: (1) generate n bootstrapped samples out of the training dataset; (2) train a regression tree from every sample; (3) take the average predictions from all trained trees. Bagging automatically leaves out 33% of the data within each sample, the out-of-bag sample, which is used for cross-validating the accuracy of the models. A hyperparameter for the bagging method is the optimal number of bagging samples to be generated, which is found by creating a hyper-grid to loop over several different combinations of hyperparameters. It generates 90 models with 10 to 100 bagging samples. Thereafter the error per model is plotted against the number of samples (as increasing the number of samples reduces the error) in order to find the n where the error stabilizes. This n is used as the number of bagging samples. Finally, the models are cross-validated and evaluated based on the performance metrics and the performance of the bagged regression trees is compared to the outcomes of the single tree. The importance of each predictor variable is rated from 0-100% and indicates for how many of the bagging samples this specific variable was used. Variable importance of the bagged Regression Trees in this study is displayed in eTable 3.

eTable 3. Variable importance of the bagged Regression Trees

Neurocognitive outcomes	Predictor variables	Variable importance (%)
FSIQ	Birth weight (grams)	100
	Mean difference between PIP and PEEP (cmH_2O)	89.6
	Socioeconomic status	79.3
	Minimum SpO_2/FiO_2 ratio	69.4
	Mean airway pressure (cmH_2O)	65.6
	Number of times pH > 7.45	65.3
	Mean SpO_2/FiO_2 ratio	64.4
	Glucose (mmol/L)	64.2
	Duration of invasive mechanical ventilation (hours)	63.0
	Gestational age (weeks)	58.7
	Age at follow-up (years)	47.9
	Length of PICU stay (days)	44.8
	Weight at PICU admission (grams)	42.7
	Number of times pCO_2 > 6.4 kPa	34.0
	Number of times $etCO_2$ > 6.5 kPa	33.1
	PIM 2 score	30.8
	Age at PICU admission (days)	26.3
	Number of times $etCO_2$ < 3.5 kPa	15.3
	Number of times pH < 7.35	13.3
	Maximum FiO_2 (%)	12.7
	Sex	12.1
	Number of times SpO_2 < 85%	10.1
	Number of times SpO_2 < 90%	9.2
	Number of times glucose > 10 mmol/L	5.9
	Breastfed in past	0.7
	Number of times pCO_2 < 4.7 kPa	0.5
	Minimum FiO_2 (%)	0.0
Speed and attention	Age at follow-up (years)	100
	Mean airway pressure (cmH_2O)	48.7
	Duration of invasive mechanical ventilation (hours)	47.0
	Birth weight (grams)	45.1
	Mean difference between PIP and PEEP (cmH_2O)	45.1
	PIM 2 score	42.4
	Glucose (mmol/L)	41.4
	Number of times $etCO_2$ > 6.5 kPa	39.4
	Weight at PICU admission (grams)	37.7

eTable 3. Variable importance of the bagged Regression Trees (*continued*)

Neurocognitive outcomes	Predictor variables	Variable importance (%)
	Mean SpO_2/FiO_2 ratio	37.0
	Gestational age (weeks)	31.3
	Age at PICU admission (days)	29.9
	Minimum SpO_2/FiO_2 ratio	29.3
	Number of times pH < 7.35	26.6
	Socioeconomic status	23.8
	Number of times pCO_2 > 6.4 kPa	22.8
	Number of times SpO_2 < 90%	16.4
	Number of times $etCO_2$ < 3.5 kPa	15.9
	Length of PICU stay (days)	13.1
	Maximum FiO_2 (%)	12.3
	Number of times pCO_2 < 4.7 kPa	11.9
	Number of times pH > 7.45	10.0
	Sex	6.6
	Number of times glucose > 10 mmol/L	6.4
	Minimum FiO_2 (%)	4.3
	Number of times SpO_2 < 85%	2.0
	Breastfed in past	0.0
Verbal memory	Birth weight (grams)	100
	Age at follow-up (years)	94.2
	Number of times pCO_2 > 6.4 kPa	91.7
	Weight at PICU admission (grams)	87.1
	Gestational age (weeks)	79.4
	Age at PICU admission (days)	73.0
	Duration of invasive mechanical ventilation (hours)	62.2
	Number of times pH < 7.35	59.1
	Number of times $etCO_2$ > 6.5 kPa	53.5
	Glucose (mmol/L)	53.2
	Mean airway pressure (cmH_2O)	53.1
	Minimum SpO_2/FiO_2 ratio	50.8
	PIM 2 score	38.7
	Mean SpO_2/FiO_2 ratio	38.6
	Mean difference between PIP and PEEP (cmH_2O)	36.7
	Number of times SpO_2 < 90%	35.9
	Socioeconomic status	34.9
	Number of times $etCO_2$ < 3.5 kPa	33.1

eTable 3. Variable importance of the bagged Regression Trees (*continued*)

Neurocognitive outcomes	Predictor variables	Variable importance (%)
	Length of PICU stay (days)	27.1
	Number of times pCO_2 < 4.7 kPa	24.1
	Number of times pH > 7.45	19.3
	Number of times glucose > 10 mmol/L	14.1
	Maximum FiO_2 (%)	13.5
	Breastfed in past	2.7
	Sex	0.4
	Minimum FiO_2 (%)	0.4
	Number of times SpO_2 < 85%	0.0

Note: The importance of each predictor variable is rated from 0-100% and indicates for how many of the bagging samples this specific variable was used.

k-Nearest Neighbors

K-Nearest Neighbor is a proximity based algorithm that uses 'feature similarity' in order to predict the outcomes of new data that is provided to the model. The distance metric used to determine the relative closeness of the datapoint is the euclidean distance. First, the numerical variables were scaled by transformation into z-scores. Second, the categorical variables were converted to dummy coded variables (1 = presence, 0 = absence). Third, the optimal value of the number of neigbors (k) was determined by incorporating a hyperparameter tuner that searches for the optimal value for k out of 20 different values for k. After every increment of k by 1 the model was cross-validated and the performance metrics were calculated.

The outcome value for a new patient is determined by the proximity of its features to that of other patients. For example: a new patient's value for FSIQ is determined by the weighted average of FSIQ values of the k patients whose patient and PICU-related characteristics are most similar. As k-Nearest Neighbors models are never trained, all predictors in the model are equally important to predict an outcome.

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7 Long-term follow-up of daily life functioning after pediatric intensive care unit admission

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ABSTRACT

Objective: To investigate the long-term impact of pediatric intensive care unit (PICU) admission on daily life functioning while exploring the potential mediating role of neurocognitive outcome.

Study design: This cross-sectional observational study compared children aged 6-12 years with previous PICU admission (age ≤ 1 year) for bronchiolitis requiring mechanical ventilation ("patient group", n = 65) to demographically comparable healthy peers ("control group", n=76). The patient group was selected because bronchiolitis is not expected to affect neurocognitive functioning in itself. Assessed daily life outcome domains were behavioral and emotional functioning, academic performance and health-related quality of life (QoL). The role of neurocognitive outcomes in the relationship between PICU admission and daily life functioning was assessed by mediation analysis.

Results: The patient group did not differ from the control group regarding behavioral and emotional functioning, but performed poorer on academic performance and school-related QoL (ps ≤ .04, d = -0.48 to -0.26). Within the patient group, lower full-scale IQ (FSIQ) was associated with poorer academic performance and school-related QoL (ps ≤ .02). Poorer verbal memory was associated with poorer spelling performance (p = .002). FSIQ mediated the observed effects of PICU admission on reading comprehension and arithmetic performance.

Conclusions: Children admitted to the PICU are at risk of long-term adverse daily life outcomes in terms of academic performance and school-related QoL. Findings suggest that lower intelligence may contribute to academic difficulties after PICU admission. Findings underline the importance of monitoring daily life and neurocognitive functioning after PICU admission.

INTRODUCTION

With advances in pediatric critical care, the survival rate of children admitted to the pediatric intensive care unit (PICU) has increased dramatically in the past decades [1,2]. Yet, long-term morbidity after PICU admission is a growing concern, recently acknowledged as the pediatric post-intensive care syndrome, representing a debilitating constellation of impairments in important domains of functioning [3,4]. An increasing number of studies document adverse outcomes after PICU admission regarding physical, neurocognitive, and psychosocial functioning, such as post-thrombotic syndrome, intelligence impairment, and post-traumatic stress syndrome [3-9].

In addition to these reported adverse outcomes, some studies have also documented adverse outcomes in aspects of children's daily life functioning after PICU admission. Nevertheless, currently, important aspects of daily life functioning after PICU admission remain largely unknown, such as behavioral and emotional functioning, academic performance, and health-related quality of life (QoL). These outcomes are known to impact future health and later-life success [10-14]. Studies describing long-term behavioral and emotional functioning and health-related QoL after PICU admission show conflicting results, with some studies reporting similar outcomes compared with controls, while other studies report affected behavioral and emotional functioning and health-related QoL after PICU admission [15-20]. However, comparison between these studies is hampered by variation in factors such as the included patient groups and follow-up intervals. Furthermore, academic performance after PICU admission has only been investigated in one recent study showing that, compared with matched peers, a higher proportion of children admitted to Australian PICUs before the age of 5 did not meet the National Minimum Standard in the standardized primary school assessment at year 3 of primary school [21].

Neurocognitive functioning has shown to be crucially important in daily life functioning. For example, neurocognitive functioning has been related to behavioral and emotional functioning [22,23], academic achievement [24], and a range of other outcomes impacting QoL [25,26]. Therefore, adverse neurocognitive functioning may underlie the impact of PICU admission on daily life functioning. Better insight into the determinants of daily life functioning in PICU survivors is crucial for early identification and, if possible, prevention of the adverse effects that PICU admission might exert on daily life functioning. The current study aims to investigate the long-term impact of PICU admission on daily life functioning while exploring the potential mediating role of neurocognitive performance.

METHODS

Participants

This cross-sectional observational study compared children aged 6-12 years previously (≤ 1 year) admitted to our PICU for bronchiolitis requiring invasive mechanical ventilation ("patient group") with normally developing peers who had not been admitted to the PICU during their life ("control group"). All participants were required to be proficient in the Dutch language. Exclusion criteria were developmental disorders known to impact neurocognitive development, physical conditions and/or behavioral issues interfering with the ability to adequately perform neurocognitive testing, clinical signs of neurological complications during PICU admission (e.g. seizure, encephalitis, meningitis), presence of family conflict interfering with study participation (e.g. child abuse, child being placed under external supervision), and living abroad. We specifically focused on children with PICU admission for bronchiolitis because this is a relatively homogenous group with single organ failure that seldom manifests neurologically [27,28] and is therefore not expected to inherently affect neurocognitive functioning.

The patient group was retrospectively recruited from a consecutive cohort admitted between 2007 and 2013 to the PICU of the Amsterdam University Medical Centers, the Netherlands. All children in the patient group received similar treatment per local clinical protocol at the time of PICU admission, including mode of invasive mechanical ventilation, primary and secondary choice of sedative drugs during mechanical ventilation, oxygen therapy, and nutrition. The control group was recruited through the patient group (friends and relatives) and through primary schools in the Netherlands. We aimed to include at least 64 children in the patient group and 64 children in the control group in order to achieve sufficient statistical power to detect medium-sized group differences (Cohen's d = 0.5, assuming power = 80%, and alpha = .05).

Measures

Demographic characteristics

Data on sex, age, and socioeconomic status (SES) were collected using a parent-reported questionnaire. SES was operationalized by average level of parental education and measured with the Education Categorization Standard developed by the Statistics Netherlands [29]. This standard assesses parental education on an eight-point interval scale (of equal distance apart) ranging from 1 (no education) to 8 (postdoctoral education). We chose to limit SES determination to a single variable because validity of this standard has been established, and the standard is used widely in research [30-32].

Measures of daily life functioning

Behavioral and emotional functioning

Behavioral and emotional functioning was assessed with the parent-reported Child Behavior Checklist (CBCL) and the teacher-reported Teacher Report Form (TRF) [33,34]. The CBCL and TRF are parallel forms and consist of 112 items, rated on a 3-point scale (0 = "not true" to 2 = "very true or often true"). Both questionnaires provide scores on 8 syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior [33,34]. In addition, the questionnaires provide scores on the broad-band scales Internalizing Problems (which combines Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints), Externalizing Problems (which combines Rule-Breaking and Aggressive Behavior), and Total Problems (which combines all syndrome scales). Raw scores can be transformed into T scores (M = 50, SD = 10), standardized for sex and age. Higher scores on the CBCL and TRF indicate greater severity of behavioral and emotional problems. T scores < 65 are regarded in the normal range, T scores 65-69 (93-97 percentile) are regarded in the subclinical range, and T scores ≥ 70 (98 percentile) are regarded in the clinical range. A score in the clinical range has been found associated with referral to a mental health professional [33,34].

To assess symptoms of inattention and hyperactivity/impulsivity in more detail, we used the parent-reported Strength and Weakness of ADHD symptoms and Normal behavior (SWAN) Questionnaire [35]. The SWAN consists of 18 items rated on a 7-point scale (-3 = "far below average" to 3 = "far above average"), assessing symptoms of inattention and hyperactivity/impulsivity. Item scores were reversed, such that higher scores indicate greater severity of symptoms, and mean item scores were computed for Inattention, Hyperactivity/Impulsivity and for the Total score [35].

Academic performance

Academic performance was assessed by the Dutch pupil monitoring system [36], which includes standardized tests to assess spelling, reading comprehension, and arithmetic performance [36,37]. The tests are based on item-response theory. The included children differed in age and primary school grades, requiring assessment with different versions of the Dutch pupil monitoring system. In order to enable comparability across scores, the ability scores were transformed into z scores using the normative sample means and accompanying standard deviations [37]. Higher z scores indicate better academic performance.

Health-related QoL

To evaluate health-related QoL, age-specific versions of the child and parent-reported Pediatric Quality of Life Inventory (PedsQL) were used [38]. The PedsQL consists of 23 items that are rated on a 5-point scale (0 = "never" to 4 = "almost always"). This questionnaire allows calculation of 4 domain scores: the Physical, Emotional, Social, and School domain scores [39]. A Psychosocial domain score (i.e. combined score of Emotional, Social, and School domain) and a Total score (i.e. combined score of all domains) can also be computed. Each item score is reversed and rescaled to a 0-100 scale. Higher scores on the PedsQL indicate better health-related QoL.

Neurocognitive functioning

Neurocognitive functioning was determined by assessment of full-scale intelligence quotient (FSIQ) and specific domains of neurocognitive functioning by a standardized and computerized neurocognitive test battery. FSIQ was assessed to capture general neurocognitive functioning and was measured by a short form of the Wechsler Intelligence Scale for Children - Third edition (WISC-III) involving the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement. FSIQ estimated with this short form has excellent validity (r = .95) and reliability (r = .90) [40].

In order to assess specific domains of neurocognitive functioning, a standardized and computerized neurocognitive test-battery was used. This test-battery measures a broad range of key neurocognitive domains and contains a composition of child-friendly tests based on well-known neuroscientific paradigms with established validity and reliability, i.e. Attention Network Test [41], Multisensory Integration Task [42], Tower of London [43], Rey Auditory Verbal Learning Test [44], Digit Span task [45], Klingberg task [46], and Track & Trace task [47]. In order to reduce the number of outcome variables, the neurocognitive data were subjected to a preprocessing pipeline to construct neurocognitive domain scores out of the performance measures resulting from the comprehensive neurocognitive assessment [48]. This procedure resulted in 10 neurocognitive domains that explained 78% of the variance contained in the original neurocognitive variables, i.e. speed and attention, set shifting, verbal memory, visuomotor integration, verbal working memory, interference control, visual processing speed, visual working memory, planning time, and multisensory integration. Higher scores reflect better performance.

Procedure

Participating children underwent neurocognitive testing by trained examiners using standardized instructions in a quiet room with an approximate duration of 3 hours, including breaks. Block randomized order of test administration was applied to counterbalance the systematic influence of fatigue on test performance. The child-reported PedsQL was filled out by the child, assisted by the trained examiner. Parent-

reported questionnaires were filled out by parents prior to or during neurocognitive testing of their child. Teachers were asked to fill out the TRF and to send the participating child's results of the Dutch pupil monitoring system.

Ethics statement

This study was approved by the medical ethical committee of the Amsterdam University Medical Centers (W16_121#16.139) and conducted in accordance with the Declaration of Helsinki [49]. Parents and children aged 12 years provided written informed consent for participation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26.0. Missing values at random (≤ 5.7%) were imputed using multiple imputation [50]. All children were counted only once in the analyses. In 2 cases, children in the patient group had been admitted twice to the PICU for bronchiolitis. For these children, the first PICU admission was used. One child in the patient group was excluded from the analysis regarding academic performance because this child was in special education where the Dutch pupil monitoring system is not assessed. Comparisons between the PICU and control group were performed using mixed modeling analysis to account for the presence of sibling pairs in our sample (n = 24). Regarding CBCL and TRF, significant group differences on Internalizing, Externalizing, or Total problems were followed up by comparisons on the underlying syndrome scales to guard against type 1 errors.

Within the patient group, multivariable regression analyses tested the relationship between measures of neurocognitive functioning and measures of daily life functioning. Demographic variables (sex, age, and SES) and measures of neurocognitive functioning with observed significant effects of group were entered as independent variables. Outcomes measures of daily life functioning with significant effects of group were entered as dependent variable. Separate multivariable regression analyses with backward selection ($p > .10$) were run for each dependent variable.

Multilevel mediation analysis tested the role of neurocognitive functioning in the relationship between PICU admission and the assessed daily life outcome domains [51]. Neurocognitive outcomes with observed group differences (patient vs. control) and an observed relation to an outcome measure of daily life functioning (assessed by regression analysis), were entered as mediators of the relation between group (patient vs. control) and the relevant daily life outcome measure in mixed modeling analysis. Mediation was assessed by significant decrease in the regression coefficient of the indirect effect (path C'; the effect of group on the outcome, corrected for by the mediator) as compared with the regression coefficient (and 95% CI) of the direct effect (path C; the effect of group on the outcome). All statistical testing was two-sided, α was set at .05 and effect sizes relating

to group differences were expressed as Cohen's *d* [52]. Cohen's *d* values of 0.2, 0.5, and 0.8 were used to define thresholds for small, medium, and large effect sizes, respectively [52].

RESULTS

Participants

Children included in the patient group (n = 65, Figure 1) did not differ from the total recruitment cohort of children satisfying the inclusion criteria (n = 119) with respect to sex, age at PICU admission, duration of mechanical ventilation, and length of PICU stay, indicating no evidence for selection bias in the study sample [48]. Demographic and clinical characteristics of the included children are displayed in Table 1. No differences between the patient and control group (n = 76) were found regarding sex, age, and SES indicating no evidence for a confounding role of demographic differences between groups. The patient group had a lower gestational age than the control group. The possible confounding effects of gestational age on the results were tested in all analyses (see confounding analysis). Results of the analyses on the measures of daily life functioning are reported in Table 2.

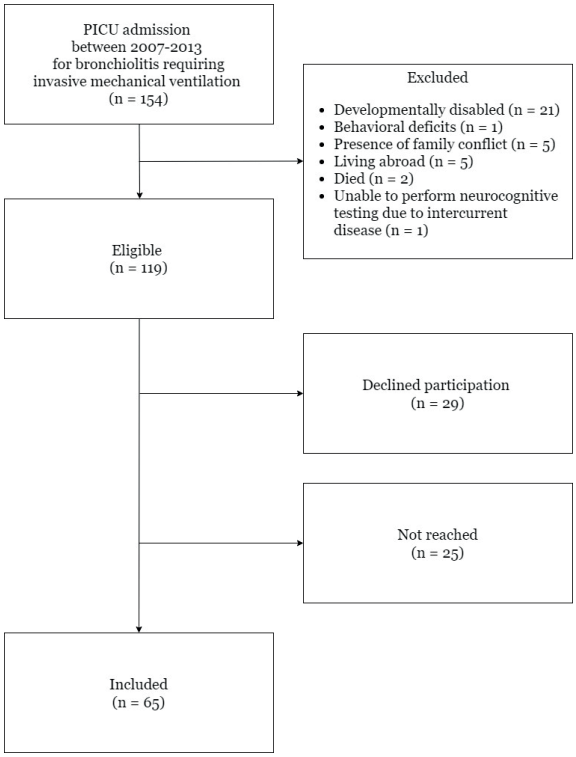

Figure 1. Flowchart of included children in the patient group.

Table 1. Demographic and clinical characteristics of the patient and control group

Demographic and clinical characteristics	Patient group (n = 65)	Control group (n = 76)	Mean (SE) difference	p-value	Cohen's *d*
Demographic characteristics					
Age at time testing (years), mean (SD)	8.1 (1.2)	8.2 (1.4)	-0.10 (0.22)	.64	-0.08
Sex, % boys	60.0	44.7	0.63 (0.35)	.08	
Socioeconomic status, mean (SD)	5.3 (1.2)	5.6 (1.0)	0.01 (0.10)	.92	0.01
Clinical characteristics					
Gestational age (weeks), median (IQR)	38.1 (36.3-39.9)	39.9 (38.1-40.9)	-0.35 (0.12) *	**.004**	-0.35
Gestational age < 32 weeks, n (%)	5 (7.7)	4 (5.3)			
Gestational age 32-37 weeks, n (%)	15 (23.1)	5 (6.6)			
Gestational age ≥ 37 weeks, n (%)	45 (69.2)	67 (88.1)			
Age at PICU admission (days), median (IQR)	43.0 (23.5-79.5)				
PIM 2 score, median (IQR)	1.4 (1.1-2.1)				
Duration of invasive mechanical ventilation during first PICU stay (hours), mean (SD)	159.3 (67.9)				
Duration of invasive mechanical ventilation during all PICU admissions (hours), mean (SD)	169.5 (88.6)				
Length of first PICU stay (days), median (IQR)	7.4 (5.7-9.0)				
Length of combined PICU stay (days), median (IQR)	7.6 (5.6-9.4)				
Positive respiratory syncytial virus test, n (%)	56 (86.2)				
Reintubation, n (%)	4 (6.2)				
Tracheostomy, n (%)	2 (3.1)				
Extracorporeal membrane oxygenation, n (%)	1 (1.5)				
Cardiopulmonary resuscitation, n (%)	2 (3.1)				
Readmission at the PICU, n (%) **	7 (10.8)				
Sepsis (during PICU stay), n (%)	1 (1.5)				
Septic shock (during PICU stay), n (%)	0 (0.0)				
Traumatic brain injury after PICU discharge, n (%)	1 (1.5)	1 (1.3)			

Note: PICU = Pediatric Intensive Care Unit; PIM 2 score = Pediatric Index of Mortality 2 score; SD = standard deviation; SE = standard error. Boldface values indicate p < .05.
* Van der Waerden transformation of gestational age to obtain a normal distribution.
** Children were readmitted for viral lower respiratory tract infections and/or subglottic stenosis due to intubation damage.

Table 2. Long-term daily life functioning of the patient and control group.

Daily life outcome domains	Patient group mean (SD) n = 65	Control group mean (SD) n = 76	Mean (SE) difference	95% CI	p-value	Cohen's *d*
Behavioral and emotional functioning						
CBCL						
Internalizing Problems, T score	49.06 (10.01)	49.85 (9.73)	-0.26 (1.51)	-3.27, 2.74	.86	-0.03
Externalizing Problems, T score	46.84 (10.51)	47.40 (9.56)	0.47 (1.47)	-2.46, 3.40	.75	0.05
Total, T score	47.98 (11.17)	48.22 (9.02)	1.14 (1.46)	-1.77, 4.05	.44	0.12
TRF						
Internalizing Problems, T score	48.81 (8.60)	49.32 (9.29)	-0.51 (1.51)	-3.51, 2.49	.74	-0.06
Externalizing Problems, T score	50.67 (9.16)	49.26 (7.98)	0.98 (1.38)	-1.76, 3.73	.48	0.12
Total, T score	50.58 (9.17)	49.06 (9.07)	1.29 (1.48)	-1.64, 4.23	.38	0.14
SWAN						
Inattention, mean score	-0.96 (0.68)	-0.91 (0.69)	-0.07 (0.11)	-0.29, 0.16	.56	-0.10
Hyperactivity/impulsivity, mean score	-0.89 (0.70)	-0.80 (0.75)	-0.07 (0.11)	-0.30, 0.15	.52	-0.10
Total, mean score	-0.92 (0.62)	-0.85 (0.62)	-0.08 (0.10)	-0.28, 0.11	.38	-0.14
Academic performance						
Dutch pupil monitoring system						
Spelling, z score	-0.11 (1.14)	0.39 (1.02)	-0.48 (0.17)	-0.82, -0.14	**.006**	-0.48
Reading comprehension, z score	-0.12 (0.91)	0.34 (1.10)	-0.41 (0.15)	-0.72, -0.10	**.010**	-0.41
Arithmetic, z score	0.02 (1.16)	0.32 (1.02)	-0.26 (0.12)	-0.51, -0.01	**.04**	-0.26
Health-related quality of life						
PedsQL – child-reported						
Physical functioning	88.34 (10.44)	88.47 (8.32)	-0.13 (1.58)	-3.26, 3.00	.93	-0.01
Emotional functioning	74.16 (18.72)	73.71 (18.18)	1.02 (2.44)	-3.86, 5.90	.68	0.06
Social functioning	86.81 (12.80)	83.64 (15.40)	3.23 (2.35)	-1.44, 7.90	.17	0.23
School functioning	75.93 (17.39)	81.52 (13.16)	-5.47 (2.50)	-10.42, -0.52	**.03**	-0.36
Psychosocial functioning	78.97 (13.18)	79.61 (13.12)	-0.37 (2.04)	-4.42, 3.68	.86	-0.03
Total score	82.23 (11.32)	82.69 (10.64)	-0.21 (1.73)	-3.65, 3.24	.91	-0.02
PedsQL – parent-reported						
Physical functioning	93.18 (10.76)	93.78 (8.36)	-0.73 (1.56)	-3.83, 2.36	.64	-0.08
Emotional functioning	76.43 (18.06)	80.13 (15.43)	-4.37 (2.56)	-9.45, 0.72	.09	-0.27
Social functioning	88.55 (14.91)	89.74 (16.20)	-1.38 (2.53)	-6.40, 3.64	.59	-0.09
School functioning	79.57 (20.07)	86.20 (13.99)	-6.59 (2.81)	-12.17, -1.02	**.02**	-0.39
Psychosocial functioning	81.45 (14.99)	85.32 (12.93)	-4.18 (2.12)	-8.38, 0.02	.05	-0.31
Total score	85.58 (11.75)	88.28 (10.65)	-2.99 (1.73)	-6.43, 0.45	.09	-0.27

Note: CBCL = Child Behavior Checklist; SWAN = Strength and Weakness of ADHD-symptoms and Normal-behavior Questionnaire; TRF = Teacher Report Form. PedsQL = Pediatric Quality of Life Inventory. Higher scores on the CBCL, TRF and SWAN indicate greater severity of problems. Higher scores on the Dutch pupil monitoring system indicate better academic performance. Higher scores on the PedsQL indicate better reported health-related quality of life. Boldface values indicate $p < .05$.

Behavioral and emotional functioning

Group comparisons revealed no significant differences on the CBCL or the TRF regarding Internalizing, Externalizing, or Total problems. In addition, the SWAN showed no significant group differences regarding Inattention, Hyperactivity/Impulsivity, or Total problems.

Academic performance

Children in the patient group had significantly lower performance than the control group on spelling ($p = .006$, $d = -0.48$), reading comprehension ($p = .010$, $d = -0.41$), and arithmetic performance ($p = .04$, $d = -0.26$).

Health-related QoL

Both children in the patient group themselves and their parents reported significantly lower health-related QoL regarding school functioning (further referred to as "school-related QoL") compared with the control group ($p = .03$, $d = -0.36$ and $p = .02$, $d = -0.39$, respectively). All other health-related QoL outcome domains were not significantly different between the 2 groups.

Neurocognitive functioning

Neurocognitive outcomes are fully described elsewhere [48] and summarized in Table 3. In brief, the patient group had a significantly lower FSIQ ($M = 95.3$, $SD = 15.9$) than the control group ($M = 105.1$, $SD = 15.1$; $p < .001$, $d = -0.59$) and significantly poorer performance on the domains Speed and Attention ($p = .03$, $d = -0.41$) and Verbal Memory ($p < .001$, $d = -0.60$).

Table 3. Long-term neurocognitive outcomes of children in the patient and control group

Neurocognitive outcomes	Description	Patient group mean (SD) (n = 65)	Control group mean (SD) (n = 76)	Mean (SE) difference	p-value *	Cohen's *d*
FSIQ	Intelligence	95.3 (15.9)	105.1 (15.1)	-8.46 (1.98)	**< .001**	-0.59
Neurocognitive domains						
Speed and attention	Speed and variability of information processing and attention	-0.19 (0.95)	0.16 (1.02)	-0.41 (0.15)	**.03**	-0.41
Set shifting	Speed of shifting between response types	-0.03 (1.03)	0.02 (0.98)	-0.08 (0.16)	.75	-0.08
Verbal memory	Learning and memory for verbal information	-0.29 (1.13)	0.24 (0.81)	-0.60 (0.14)	**< .001**	-0.60
Visuomotor integration	Speed and flexibility of visuomotor integration	0.13 (1.06)	-0.11 (0.93)	0.25 (0.17)	.22	0.25
Verbal working memory	Short-term memory and manipulation of verbal information	-0.15 (1.03)	0.13 (0.96)	-0.27 (0.16)	.17	-0.27
Interference control	Speed of suppressing distracting information	0.12 (1.01)	-0.11 (0.98)	0.21 (0.16)	.25	0.21
Visual processing speed	Speed of visual information processing	-0.03 (1.06)	0.02 (0.95)	-0.06 (0.16)	.81	-0.06
Visual working memory	Short-term memory and manipulation of verbal information	-0.16 (1.01)	0.13 (0.98)	-0.29 (0.17)	.17	-0.29
Planning time	Speed and capacity of planning ahead	0.20 (0.99)	-0.17 (0.98)	0.38 (0.16)	.05	0.38
Multisensory integration	Accuracy for integration of information from different sensory modalities	0.02 (1.08)	-0.02 (0.93)	0.04 (0.17)	.82	0.04

Note: FSIQ = estimated full-scale intelligence quotient; SD = standard deviation; SE = standard error. The directionality of neurocognitive variables was adapted so that for all scores, higher values corresponded to better task performance. Boldface values indicate $p < .05$.

* Correction for false discovery rate applied across neurocognitive outcomes.

Confounding analysis

As the patient group had a significantly lower gestational age as compared with the control group, the group difference in gestational age might have acted as a confounder in the observed group differences regarding neurocognitive and daily life functioning. Therefore, we performed a sensitivity analysis using a matched patient and control group in terms of gestational age. The results replicate the reported group differences, except for parent-reported school-related QoL (p = .06, Table 4). Nevertheless, the accompanying effect size for parent-reported school-related QoL was highly similar to the effect size obtained with the original sample (*d* = -0.33 vs. -0.39). These findings indicate that the observed evidence for adverse neurocognitive and daily life outcomes is not accounted for by premorbid differences in gestational age (for details, see Appendix).

In addition, we studied the impact of possible confounding disease and treatment characteristics known to be associated with adverse neurocognitive and daily life outcomes.[7,53] To this end, patients with sepsis (n = 1), traumatic brain injury (n = 1), extracorporeal membrane oxygenation (n = 1), and cardiopulmonary resuscitation (n = 2) were excluded from the patient group. These characteristics were collected from all PICU admissions. Comparison of the remaining patients with the control group replicated the reported group differences, except for arithmetic performance and child-reported school-related QoL (ps = .06). Nevertheless, the effect sizes for arithmetic performance and parent-reported school-related QoL were highly similar to those obtained with the full patient sample (*d* = -0.24 vs. -0.26, and *d* = -0.37 vs. -0.39 respectively, Table 5). Taken together, these findings show that the observed evidence for adverse neurocognitive and daily life outcomes in the patient group is not accounted for by a range of potential confounders.

Table 4. Demographic and clinical characteristics, daily life and neurocognitive outcomes of patient and control group matched on gestational age

Demographic and clinical characteristics, daily life and neurocognitive outcomes	Patient group (n = 63)	Control group (n = 63)	Mean (SE) difference	p-value	Cohen's *d*
Demographic and clinical characteristics					
Age at time testing (years), mean (SD)	8.1 (1.2)	8.3 (1.4)	-0.28 (0.23)	.21	-0.22
Sex, % boys	60.3	47.6	0.53 (0.37)	.16	
Socioeconomic status, mean (SD)	5.3 (1.2)	5.6 (1.0)	-0.01 (0.12)	.96	-0.01
Gestational age (weeks), median (IQR)	38.1 (36.4-40.0)	39.4 (37.4-40.1)	-0.06 (0.10) *	.54	-0.08
Daily life outcomes					
Spelling, Z-score, mean (SD) **	-0.09 (1.14)	0.39 (1.04)	-0.45 (0.18)	**.015**	-0.45
Arithmetic, Z-score, mean (SD) **	0.03 (1.18)	0.37 (1.05)	-0.29 (0.14)	**.04**	-0.29
School-related Quality of Life (parent-reported), mean (SD)	79.5 (20.1)	85.3 (14.6)	-5.84 (3.07)	.06	-0.33
Neurocognitive outcomes					
FSIQ, mean (SD)	95.6 (15.8)	105.1 (15.2)	-7.9 (2.2)	**.001**	-0.54
Verbal memory, mean (SD)	-0.25 (1.12)	0.26 (0.84)	-0.55 (0.15)	**.001**	-0.57

Note: FSIQ = estimated full-scale intelligence quotient; SD = standard deviation; SE = standard error. Boldface values indicate $p < .05$.

* Van der Waerden transformation of gestational age to obtain a normal distribution.

** For spelling, reading comprehension and arithmetic performance, one child in the patient group was excluded from the analysis because this child was in special education where the Dutch Pupil Monitoring System is not assessed.. The demographic and clinical characteristics of the matched patient and control group did not significantly differ (ps ≥ .15)

Table 5. Demographic and clinical characteristics, daily life and neurocognitive outcomes of patient and control group excluding patients with sepsis, traumatic brain injury, extracorporeal membrane oxygenation, or cardiopulmonary resuscitation

Demographic and clinical characteristics, daily life and neurocognitive outcomes	Patient group (n = 60)	Control group (n = 76)	Mean (SE) difference	p-value	Cohen's *d*
Demographic and clinical characteristics					
Age at time testing (years), mean (SD)	8.1 (1.1)	8.2 (1.4)	-0.16 (0.22)	.47	-0.13
Sex, % boys	60.0	44.7	0.62 (0.36)	.08	
Socioeconomic status, mean (SD)	5.3 (1.2)	5.6 (1.0)	0.00 (0.11)	.99	0.00
Daily life outcomes					
Spelling, Z-score, mean (SD)	-0.06 (1.16)	0.39 (1.02)	-0.44 (0.18)	**.02**	-0.44
Reading comprehension, Z-score, mean (SD)	-0.04 (0.89)	0.34 (1.10)	-0.32 (0.16)	**.04**	-0.32
Arithmetic, Z-score, mean (SD)	0.09 (1.13)	0.32 (1.02)	-0.24 (0.13)	.06	-0.24
School-related Quality of Life (child-reported), mean (SD)	76.5 (17.7)	81.5 (13.2)	-4.95 (2.58)	.06	-0.33
School-related Quality of Life (parent-reported), mean (SD)	79.9 (20.1)	86.2 (14.0)	-6.31 (2.88)	**.03**	-0.37
Neurocognitive outcomes					
FSIQ, mean (SD)	96.2 (15.6)	105.0 (15.1)	-8.1 (2.1)	**< .001**	-0.56
Speed and Attention, mean (SD)	-0.18 (0.95)	0.16 (1.02)	-0.40 (0.16)	**.01**	-0.41
Verbal memory, mean (SD)	-0.22 (1.12)	0.24 (0.81)	-0.51 (0.14)	**.001**	-0.56

Note: CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; FSIQ = estimated full-scale intelligence quotient; SD = standard deviation; SE = standard error. For spelling, reading comprehension and arithmetic performance, one child in the patient group was excluded from the analysis because this child was in special education where the Dutch Pupil Monitoring System is not assessed. Boldface values indicate $p < .05$.

Relationship between neurocognitive functioning and daily life functioning

Academic performance

Table 6 displays the results of the relationship between measures of neurocognitive functioning and measures of daily life functioning within the patient group, as assessed by multivariable regression analyses. Lower FSIQ and poorer verbal memory were significantly associated with poorer spelling performance (R^2 = 26.4%, p < .001). Lower FSIQ was significantly associated with poorer reading comprehension performance (R^2 = 32.9%, p < .001). Lower FSIQ and female sex were significantly associated with poorer arithmetic performance (R^2 = 47.3%, p < .001). Age, SES, and the neurocognitive domain Speed and Attention were not associated with academic performance.

Table 6. Multivariable regression analyses testing the relationship between neurocognitive functioning and daily life functioning in the patient group

Multivariable regression models	Standardized Beta	Adjusted R^2 (%)	95% CI	p-value
Academic performance assessed by the Dutch pupil monitoring system				
Spelling				
Total model		26.4		**< .001**
FSIQ	0.28		0.003, 0.037	**.02**
Verbal memory	.37		0.136, 0.605	**.002**
Reading comprehension				
Total model		32.9		**< .001**
FSIQ	0.58		0.022, 0.045	**< .001**
Arithmetic				
Total model		47.3		**< .001**
Sex (female)	-0.35		-1.260, -0.394	**< .001**
FSIQ	0.56		0.027, 0.056	**< .001**
Verbal memory	0.18		-0.014, 0.391	.07
Health-related quality of life assessed by the PedsQL				
School functioning, parent-reported				
Total model		9.3		**.008**
FSIQ	0.33		0.112, 0.712	**.008**

Note: Demographic variables (sex, age, SES) and measures of neurocognitive functioning with observed significant effects of group were entered as independent variables. Outcome measures of daily life functioning with significant effects of group were entered as dependent variable. Separate multivariable regression analyses with backward selection (p > .10) were run for each dependent variable. No predictor variables remained after backward elimination for child-reported PedsQL regarding school functioning. FSIQ = full-scale intelligence quotient; SES = socioeconomic status. Boldface values indicate p < .05.

Health-related QoL

Lower FSIQ was significantly associated with poorer school-related QoL as rated by the parents (R^2 = 9.3%, p = .008). Sex, age, SES, and the neurocognitive domain Speed and Attention were not associated with school-related QoL as rated by the parents. None of the studied predictors were associated with school-related QoL as rated by the children.

Mediating role of neurocognitive functioning

With regard to academic performance, no mediating role was found for FSIQ or verbal memory in the analyses for spelling performance. FSIQ significantly mediated the observed group differences on reading comprehension (B of path C': -0.096 > B of path C: -0.41, 95% CI: -0.716 to -0.101) and arithmetic performance (B of path C': -0.010 > B of path C: -0.26, 95% CI: -0.514 to -0.012; Figure 2). For school-related QoL (as reported by parents), no mediating role was found for FSIQ. In summary, group differences (patients vs. controls) for reading comprehension and arithmetic performance were mediated by FSIQ, while other observed group differences (spelling performance and school-related QoL) were not mediated by measures of neurocognitive functioning.

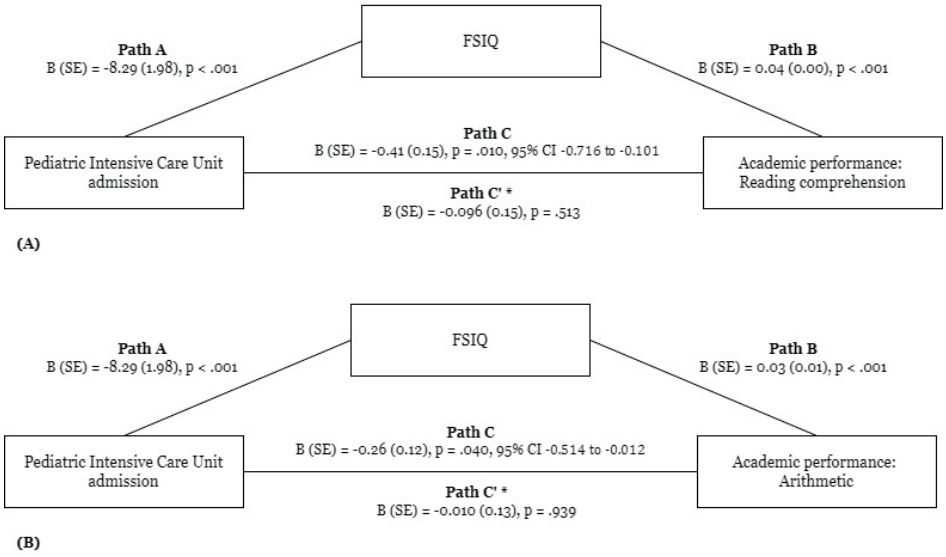

Figure 2. Mediation analysis investigating the role of neurocognitive functioning in the relation between PICU admission and adverse outcomes in daily life functioning (i.e. academic performance).

Note: * FSIQ significantly mediated the observed group differences on reading comprehension (A), and arithmetic performance (B).

DISCUSSION

The findings of this cross-sectional observational study indicate that children admitted to the PICU for bronchiolitis are at risk of long-term adverse outcomes in important aspects of daily life functioning. More specifically, we found adverse outcomes in academic performance and school-related QoL. The observed adverse intelligence outcome in children admitted to the PICU was found to contribute to the observed academic underachievement regarding reading comprehension and arithmetic performance. As neurological manifestations of bronchiolitis are rare [27,28], the findings of this study may reflect potentially harmful effects related to PICU admission.

The present study revealed no evidence for long-term adverse outcomes in behavioral and emotional functioning after PICU admission, but PICU survivors were found to have adverse academic performance with respect to spelling, reading comprehension, and arithmetic performance compared with peers. Furthermore, they were found to have lower school-related QoL (reported by parents and children). Literature regarding long-term behavioral and emotional functioning and health-related QoL in children after PICU admission is scarce and harbors conflicting results [15-20]. In addition, academic performance has only been investigated in one recent article describing affected academic performance in children admitted to the PICU before the age of 5 [21]. The results of the current study indicate the presence of long-term adverse outcomes in specific aspects of daily life functioning, even in the absence of underlying disease with neurological manifestation.

In previous work, we already provided evidence for the existence of long-term adverse neurocognitive outcomes in the current patient sample [48]. The current study demonstrates that lower intelligence is associated with daily life functioning in terms of poorer academic performance and school-related QoL in children after PICU admission. In addition, poorer verbal memory is associated with poorer spelling performance. Moreover, the results identified intelligence as a mediator of the impact of PICU admission on daily life functioning with respect to reading comprehension and arithmetic performance. These findings suggest that long-term adverse neurocognitive outcomes may contribute to academic difficulties after PICU admission.

Indeed assuming that bronchiolitis seldom manifests neurologically [27,28], the observed adverse outcomes may suggest that (a combination of) secondary consequences of bronchiolitis and/or PICU treatment may negatively affect outcomes after PICU admission. Although all children received similar treatment per local clinical protocol during the PICU admission, some diversity in disease and treatment characteristics exists. However, we found no evidence for the possible confounding effects of disease and treatment characteristics known to be associated with adverse neurocognitive and daily life outcomes (i.e. gestational age, extracorporeal membrane oxygenation,

cardiopulmonary resuscitation, sepsis, or traumatic brain injury). Furthermore, in previous work, we investigated the same children as included in the current study and found no evidence for a relationship between exposure to sedatives, analgesics, and anesthetics (per local protocol that was used at that time at our PICU) and a range of neurocognitive outcomes [48]. In addition, duration of invasive mechanical ventilation was also not associated with neurocognitive outcomes [48]. Nevertheless, the absence of evidence of a role of drug exposure on neurocognitive outcomes in that study does not account for variation in sedation practices among different centers and more recent changes in sedation practices. Furthermore, other factors such as hypoxic episodes, hypotension associated with mechanical ventilation, and metabolic derangements may have negatively affected children's neurocognitive and daily life outcomes after PICU admission [54-57]. As understanding of the exact nature and origin of difficulties in daily life functioning is a prerequisite for successful prevention and intervention, the findings of our study highlight the importance of prospective studies aimed at disentangling those factors that operate between the detrimental effects of PICU admission on neurocognitive and daily life functioning.

Our findings also underline the importance of long-term structured follow-up after PICU admission, even in the absence of underlying disease with neurological manifestation, enabling early identification and appropriate management of adverse outcomes. In order to gain a generalizable understanding of sequelae after pediatric critical illness, standardization of outcome assessment is urgently needed. A core outcome set and instrument recommendations have recently been developed by the Pediatric Outcomes STudies after PICU Investigators of the Pediatric Acute Lung Injury and Sepsis Investigators Network and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network [58,59]. These recommendations could be used in follow-up of children after PICU admission. In the current study, we used a comprehensive computerized neurocognitive test battery aimed at a broad range of neurocognitive outcomes relevant to daily life functioning. Nevertheless, for institutions that do not have structured follow-up programs, it may be reasonable to consider the use of measures that are less time-intensive and more accessible, yet exhibit sufficient sensitivity for the detection of neurocognitive impairment.

A limitation of our study is the substantial number of eligible children (45.4%) who did not participate in our study, mainly because they were not reached despite our efforts. Nevertheless, the included children did not differ from the total cohort of eligible children with respect to sex, age at PICU admission, duration of mechanical ventilation, and length of PICU stay, suggesting no evidence for selection bias in the study sample. A second limitation relates to the operationalization of SES as the average level of parental education. The use of parental education is only one attribute

of the multifaceted construct of SES, not accounting for the roles of, for example, income and level of professional functioning [60]. This may limit the generalizability of the study to communities with wide disparities according to race, ethnicity, economic opportunities, insurance status, etc. A third limitation is that due to the lack of pre-PICU neurocognitive assessment, we cannot state whether adverse neurocognitive outcomes were due to the PICU admission or rather reflect pre-PICU levels of neurocognitive functioning. In addition, as recent literature on pediatric post-intensive care syndrome suggests that new morbidities after PICU discharge may improve over time, pre-PICU as well as periodic neurocognitive assessments would have provided a more in-depth understanding of the neurocognitive development of children after PICU discharge. However, as the current patient sample was nonelectively admitted to the PICU and as all children were intubated and sedated when admitted to the PICU, we were unable to assess pre-PICU neurocognitive functioning. A strength of our study is that we focused on children whose reason for PICU admission was bronchiolitis, in an attempt to control for the confounding effect of underlying disease on outcome. A second strength of this study is the use of a control group that was comparable to the patient group in terms of demographic characteristics.

In summary, children admitted to the PICU are at risk of long-term adverse outcomes in daily life functioning in terms of academic performance and school-related QoL. The findings suggest that the adverse intelligence outcomes observed in these children may contribute to the academic difficulties after PICU admission. The results of this study add to a better understanding of long-term morbidity after PICU admission and underline the importance of structured long-term follow-up to allow early identification and support of children after PICU admission.

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ONLINE SUPPLEMENTAL MATERIAL

Confounding analysis

As the patient group had a significantly lower gestational age as compared with the control group, the group difference in gestational age might have acted as a confounder in the observed group differences regarding neurocognitive and daily life functioning. Therefore, we tested whether the outcome measures with observed group difference, were also related to gestational age. This was the case for spelling performance (p = .005), arithmetic performance (p = .025), parent-reported school-related QoL (p = .021), FSIQ (p = .030) and for Verbal Memory (p = .002), but not for reading comprehension (p = .139), child-reported school-related QoL (p = .111), nor for Speed and Attention (p = .071). Subsequently, we matched the patient and control group on gestational age (< 2 weeks difference between a matched pair). For 2 children in the patient group, no matching controls could be found, and these patients were excluded from the confounding analysis. With the matched patient and control group, we repeated the reported group differences, except for parent-reported school-related QoL (p = .06, Table 4). Nevertheless, the accompanying effect size for parent-reported school-related QoL was highly similar to the effect size obtained with the original sample (*d* = -0.33 vs. -0.39). These findings indicate that the observed evidence for adverse neurocognitive and daily life outcomes are not accounted for by premorbid differences in gestational age.

In addition, we studied the impact of possible confounding disease and treatment characteristics known to be associated with adverse neurocognitive and daily life outcomes.[1,2] To this end, patients with sepsis (n = 1), traumatic brain injury (n = 1), extracorporeal membrane oxygenation (n = 1), and cardiopulmonary resuscitation (n = 2) were excluded from the patient group. Comparison of the remaining patients with the control group replicated the reported group differences, except for arithmetic performance and child-reported school-related QoL (ps = .06). Nevertheless, the effect size for arithmetic performance and parent-reported school-related QoL were highly similar to the those obtained with the full patient sample (*d* = -0.24 vs. -0.26, and *d* = -0.37 vs. -0.39 respectively, Table 5). Taken together, these findings show that the observed evidence for adverse neurocognitive and daily life outcomes in the patient group is not accounted for by a range of potential confounders.

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8 Summary

SUMMARY OF MAIN FINDINGS

Chapter 2 describes the process of successful development and implementation of a structured multidisciplinary follow-up program for patients and their parents after PICU admission in the Emma Children's Hospital, Amsterdam UMC, the Netherlands. In addition, we show the first follow-up results obtained in patients and their parents to illustrate the significance of our program. We discuss how structured follow-up and collection of outcome data within a multidisciplinary follow-up program can importantly contribute to (1) improve outcomes of individual patients; (2) improve the standard of care during and after PICU admission; and (3) facilitate scientific research on outcome and prognosis after PICU admission. At last, we discuss challenges and future directions of a structured multidisciplinary follow-up program.

Respiratory insufficiency due to acute viral bronchiolitis is a common indication for mechanical ventilation at the PICU. Both bronchiolitis disease severity and invasive mechanical ventilation may be associated with adverse long-term pulmonary outcomes. The observational cohort study in **chapter 3** investigated children with a history of invasive mechanical ventilation for bronchiolitis addressing the extent, potential explanatory factors, and possible impact on daily life activities of adverse long-term pulmonary outcomes. We found that one-quarter of the included children had adverse long-term pulmonary outcomes at 6-12 years of age. The most frequent diagnosis in these children with morbidity was asthma. In the majority of the children, these adverse pulmonary outcomes had gone previously undetected. The presence of atopic disease in family and/or longer duration of invasive mechanical ventilation were associated with the presence of asthma at follow-up. Furthermore, there was an association between presence of adverse pulmonary outcomes at follow-up and more frequent use of pulmonary medication after PICU discharge. In comparison with those without adverse pulmonary outcomes, we did not identify a difference in frequency of participation in sports or school absenteeism.

In **chapter 4** meta-analytic techniques were used to quantify intelligence outcome after PICU admission and to explore risk factors for poor intelligence outcome, based on a review of the existing literature. A total of 123 articles was included, published between 1973 and 2021, including 8,119 PICU survivors and 1,757 healthy control children. Our results demonstrate 0.47 SD lower intelligence scores in PICU survivors compared to controls (healthy control children or normative data), corresponding to an average difference of 7.1 IQ-points. The available studies allowed to distinguish subgroups of children admitted for: (1) respiratory and/or circulatory insufficiency necessitating ECMO, (2) circulatory insufficiency necessitating CPR, (3) traumatic brain injury, (4) sepsis and/or meningoencephalitis, (5) cardiac surgery, (6) heart- or heart-lung transplantation, and (7) miscellaneous PICU admission indications. All

studied PICU subgroups had lower intelligence compared to controls (range 0.38-0.88 SD). Meta-regression allowed to study a broad range of demographic and clinical risk factors for intelligence outcome. The results show that later year of PICU admission, longer length of PICU stay, female sex and lower survival rates in the studied groups, were related to greater intelligence impairment. Meta-regression in PICU subgroups shows that later year of PICU admission was related to greater intelligence impairment in children admitted after cardiac surgery and heart- or heart-lung transplantation. Female sex and higher study quality were related to greater intelligence impairment in children admitted after cardiac surgery. Younger age at PICU admission and younger age at follow-up were related to greater intelligence impairment in children admitted after heart- or heart-lung transplantation.

The cross-sectional observational study in **chapter 5** aimed to investigate the relation between sedatives, analgesics and anesthetics and long-term neurocognitive functioning in children with a history of PICU admission. The results indicate that children with PICU admission for bronchiolitis requiring mechanical ventilation have affected long-term neurocognitive functioning, reflected by considerable lower intelligence and poorer performance on specific aspects of neurocognitive functioning (i.e. information processing, attention, verbal memory and visuomotor integration) compared to demographically comparable healthy peers, with effect sizes ranging from -0.41 to -0.60. Contrary to our hypothesis, we found no evidence for a relationship between exposure to sedatives, analgesics, anesthetics or a combination of these drugs and neurocognitive outcomes.

The observational cohort study in **chapter 6** aimed to elucidate the potential relevance of patient and PICU-related characteristics for long-term neurocognitive outcome after PICU admission, as well as to determine the potential of machine learning to improve outcome prediction. In this study, we investigated the same patient group as in **chapter 5**. Prediction models were developed for each of the neurocognitive outcomes using Regression Trees, k-Nearest Neighbors and conventional Linear Regression analysis. The findings of this study suggest that in children with previous PICU admission for bronchiolitis: (1) lower birth weight and lower socioeconomic status are associated with poorer neurocognitive outcome, and (2) greater exposure to acidotic events during PICU admission is associated with poorer verbal memory outcome. Findings of this study provide no evidence for added value of machine learning models as compared to linear regression analysis in the prediction of long-term neurocognitive outcome in a relatively small sample of children.

The cross-sectional observational study in **chapter 7** aimed to investigate the long-term impact of PICU admission on daily life functioning, while exploring the potential mediating role of neurocognitive outcomes. In this study, the same patient and control group were investigated as in **chapter 5**. The results indicate that children admitted

to the PICU are at risk of long-term adverse daily life outcome in terms of academic performance and health-related quality of life regarding school functioning. The observed adverse intelligence outcome in children admitted to the PICU was found to contribute to the observed academic underachievement regarding reading comprehension and arithmetic performance. As children admitted to the PICU for bronchiolitis have no primary hit on the central nervous system [1,2], the findings of **chapter 5**, **chapter 6** and **chapter 7** may reflect potentially harmful effects related to PICU admission.

SUMMARY TABLE

Chapter	Study design	Sample	Outcome variables	Methods	Main findings
2	Design paper	307 patients and their parents evaluated 3-6 months after PICU discharge	· Physical outcomes · Full-scale intelligence quotient (FSIQ) · Behavioral and emotional functioning · Health-related Quality of Life · Post-traumatic stress · Parental post-traumatic stress · Parental distress · Parental anxiety and depression	· The design, implementation and evaluation of a structured multidisciplinary follow-up program for patients and their parents after PICU admission in the Emma Children's Hospital, Amsterdam UMC were described. · Outcomes of patients and parents 3-6 months after PICU discharge were compared to normative data by the one-sample Chi square test.	· Structured follow-up and collection of outcome data within a multidisciplinary follow-up program, can importantly contribute (1) to improve outcomes of individual patients by facilitating timely support and appropriate intervention, if required; (2) to improve the standard of care during and after PICU admission by providing insight in extent and severity of sequelae; and (3) to facilitate scientific research on outcome and prognosis of patients after PICU admission. · Our first results showed the diversity of problems arising after PICU discharge, including adverse outcomes in physical, neurocognitive and psychosocial functioning. In addition, our data also reflected the risk of psychosocial problems among parents.

Chapter	Study design	Sample	Outcome variables	Methods	Main findings
3	Observational cohort study	74 children aged 6-12 years with a history of PICU admission for bronchiolitis requiring invasive mechanical ventilation (age ≤ 1 year)	· Adverse long-term pulmonary outcomes were based on pulmonary symptoms and lung function (by spirometry) · Medication use after discharge from the PICU · Sports performance ≥ 1x/ week in last 12 months · Number of school days missed in last 12 months due to respiratory complaints	· Children were referred to a pediatric pulmonologist for further evaluation in case of current wheeze and/ or obstructive lung function. · By logistic regression analysis we assessed whether background characteristics and PICU related variables were associated with adverse long-term pulmonary outcomes.	· One-quarter of the included children had adverse long-term pulmonary outcomes at 6-12 years of age. · The most frequent diagnosis in these children with morbidity was asthma (14 out of 74 children, 19%) · All children with adverse pulmonary outcomes had obstructive lung function, and only 38% of the children who were diagnosed during our follow-up also had current wheeze. · In the majority of the children, these adverse pulmonary outcomes had gone previously undetected. · The presence of atopic disease in family and/or longer duration of invasive mechanical ventilation were associated with the presence of asthma at follow-up. · In comparison with those without adverse pulmonary outcomes, there was more use of pulmonary medication after PICU discharge, but no difference in frequency of sports performance or school absenteeism.

Chapter	Study design	Sample	Outcome variables	Methods	Main findings
4	Meta-analysis and meta-regression	123 studies including 8,119 PICU survivors and 1,757 healthy control children. In case no healthy control group was included in a study, we used normative data for FSIQ (i.e. mean 100 and SD 15) assuming the same sample size as the PICU sample.	FSIQ	· The standardized mean difference in FSIQ between PICU survivors and controls across all included studies and additionally distinguishing between PICU subgroups was calculated by random-effects meta-analysis. · The relation between demographic and clinical risk factors and study's FSIQ effect sizes was investigated using random-effects meta-regression analysis.	· PICU survivors had on average 0.47 SD lower FSIQ compared to controls (healthy control children or normative data), corresponding to an average difference of 7.1 IQ-points. · All studied PICU subgroups had lower FSIQ compared to controls (ps < .01, *d* = -0.38 to -0.88). · Later year of PICU admission, longer length of PICU stay, female sex, lower survival rates and higher study quality were related to greater intelligence impairment. · The use of normative data yields conservative estimates of FSIQ impairment in PICU survivors.
5	Cross-sectional observational study	65 children aged 6-12 years with a history of PICU admission (age ≤ 1 year) for bronchiolitis requiring invasive mechanical ventilation ('patient group') and 76 demographically comparable healthy peers ('control group')	· FSIQ · Standardized and computerized neurocognitive test-battery measuring a broad range of key neurocognitive domains. In order to reduce the number of outcome variables, component analysis was used that resulted in 10 neurocognitive domains that explained 78% of the variance contained in the original neurocognitive variables.	· Comparisons between the patient and control group were performed using mixed modeling analysis. · The relation between exposure to sedatives, analgesics and anesthetics and neurocognitive outcomes was assessed by regression analyses.	· Children with PICU admission for bronchiolitis requiring invasive mechanical ventilation have affected long-term neurocognitive functioning, reflected by considerable lower intelligence and poorer performance on specific aspects of neurocognitive functioning (i.e. information processing, attention, verbal memory and visuomotor integration) compared to demographically comparable healthy peers (ps ≤ .03, *d* = -0.41 to -0.60). · Contrary to our hypothesis, we found no evidence for a relationship between exposure to sedatives, analgesics, anesthetics or a combination of these drugs and neurocognitive outcomes.

Chapter	Study design	Sample	Outcome variables	Methods	Main findings
6	Observational cohort study	The same patient sample as in Chapter 5	FSIQ and the neurocognitive domains Speed and Attention and Verbal Memory (i.e. the affected neurocognitive outcomes of the patient group as described in Chapter 5)	· Patient and PICU-related characteristics used for the prediction models were: demographic characteristics, perinatal and disease parameters, laboratory results and intervention characteristics, including hourly validated mechanical ventilation parameters. · Prediction models were developed for each of the neurocognitive outcomes using Regression Trees, k-Nearest Neighbors and conventional Linear Regression analysis.	· Lower intelligence was predicted by lower birth weight and lower socioeconomic status (R^2 = 25.9%). · Poorer performance on the Speed and Attention domain was predicted by younger age at follow-up (R^2 = 53.5%). · Poorer verbal memory was predicted by lower birth weight, younger age at follow-up, and greater exposure to acidotic events (R^2 = 50.6%). · The machine learning models did not reveal added value in terms of model performance as compared to Linear Regression.
7	Cross-sectional observational study	The same patient and control sample as in Chapter 5	· Behavioral and emotional functioning · Academic performance · Health-related quality of life	· Comparisons between the patient and control group were performed using mixed modeling analysis. · The role of neurocognitive functioning in the relationship between PICU admission and the assessed daily life outcome domains was assessed by multilevel mediation analysis.	· The patient group did not differ from the control group regarding behavioral and emotional functioning, but performed poorer on academic performance and health related quality of life regarding school functioning (ps ≤ .04, d = -0.48 to -0.26). · Within the patient group, lower FSIQ was associated with poorer academic performance and health-related quality of life regarding school functioning (ps ≤ .02). Poorer verbal memory was associated with poorer spelling performance (p = .002). · FSIQ mediated the observed effects of PICU admission on academic performance regarding reading comprehension and arithmetic performance.

9 General discussion

GENERAL DISCUSSION

Long-term pulmonary outcomes

Respiratory insufficiency due to acute viral bronchiolitis, most commonly caused by respiratory syncytial virus (RSV), is a common indication for none-elective PICU admission in children younger than two years of age [3,4]. In this thesis we performed a thorough long-term evaluation of children with a history of invasive mechanical ventilation for bronchiolitis. All children were screened, consisting of a standardized parental questionnaire, history taking, physical examination and spirometry, and if necessary, children were evaluated by a pediatric pulmonologist. We found that one-quarter of the patients had adverse long-term pulmonary outcomes at 6-12 years of age. In the majority of the children these adverse pulmonary outcomes had gone previously undetected. These findings underline the prevalence and importance of screening of long-term pulmonary morbidity after PICU discharge. Our findings are consistent with the results of other studies describing long-term pulmonary outcomes at 6-12 years follow-up after pediatric admission – not requiring invasive mechanical ventilation – during infancy for bronchiolitis [5-7]. 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 in the general pediatric population, being estimated at 8% [8].

Furthermore, we found that the presence of atopic disease in the child's family and longer duration of invasive mechanical ventilation were associated with the presence of asthma at the time of follow-up. The association between atopic disease in the child's family and asthma has been described in literature [9]. However, the association between duration of invasive mechanical ventilation and asthma has not been described previously. This association may reflect greater bronchiolitis disease severity and/or potential harmful effects of invasive mechanical ventilation. In adults, it is well known that higher tidal volume is associated with ventilator-induced lung injury [10,11]. Yet, this association is less well determined 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 [10,12-16]. Studies investigating children with acute hypoxemic respiratory failure or Acute Respiratory Distress Syndrome show conflicting results regarding long-term pulmonary outcomes [13-16]. Some studies [13,14] have failed to demonstrate an association of pulmonary sequelae with mechanical

ventilation, whereas other studies [15,16] did show an association with mechanical ventilation parameters (e.g. FiO_2, PIP). Comparison of these studies with our results is hampered by differences in design and study population.

Another explanation for our finding of adverse long-term pulmonary outcomes after PICU admission for severe bronchiolitis, 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. 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 [17-19]. In addition, also the virus itself may induce airway hyperreactivity and chronic airway inflammation contributing to the risk of adverse pulmonary outcomes [18-20]. Bronchiolitis is most commonly caused by RSV [21,22] and literature suggests that RSV prevention results in a reduction in RSV-related hospitalization and a reduction in wheezing days during the first year of life [23]. In contrast, a systematic review and meta-analysis [24] 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.

In adults, it is well established that mechanical ventilation may have deleterious pulmonary effects [11,25], 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.

Long-term neurocognitive outcomes

The results of our meta-analysis and meta-regression show that PICU survivors, applying to a wide range of PICU subgroups, are at risk of intelligence impairment. PICU survivors had on average 0.47 SD lower FSIQ compared to controls, corresponding to an average difference of 7.1 IQ-points. Accordingly, the prevalence of children with intellectual disability (FSIQ < 2 SD [26]) is expected to be threefold higher in PICU survivors (6.4%) than in the general population (2.3%). Intelligence outcome in the PICU populations has worsened over the years (between 1972-2016). This finding may reflect the increasing medical attainments that have not only led to increased survival rates of children admitted to the PICU, but also to increasing morbidity rates in those surviving [27-29]. Furthermore, lower survival rates in the studied groups and longer PICU stay were related to greater intelligence impairment. These findings may reflect the greater disease severity and/or the greater intensity of - as well as the longer exposure to PICU treatments of children

with longer PICU stay, which may have affected their long-term neurocognitive outcome. Our findings are corroborated by a recent systematic review which also showed that length of PICU stay was related to poorer neurocognitive functioning at discharge.[30] Of note, our findings indicate that boys had on average better intelligence outcome than girls. The mechanisms underlying sex differences with respect to prevalence and outcome of several neurological conditions are currently not well understood [31]. Sex differences exist in, among others, different states in neuroinflammation [31] and (hormonal) reaction to stress [32-34]. These sex differences may possibly lead to differences in neurocognitive development of PICU survivors. Understanding the mechanisms behind sex differences could help develop more targeted therapy. At last, meta-regression showed that higher study quality was related to greater intelligence impairment. This aligns with the findings of our additional analysis, which showed that the use of the normative data instead of control group data might underestimate the estimates of intelligence impairment in PICU survivors. Critical appraisal of the role of control data used is important, as normative data are frequently used in research and this may considerably influence the results and conclusions of studies.

The results of our meta-analysis and meta-regression show intelligence impairment across all PICU subgroups investigated, with effect sizes ranging between -0.38 and -0.88 SD. Children admitted after heart- or heart-lung transplantation had significantly greater intelligence impairment (-0.80 SD) compared to children admitted after cardiac surgery (-0.38 SD), and compared to children admitted for sepsis and/or meningoencephalitis (-0.39 SD). This finding may reflect the greater disease severity, greater intensity of PICU treatments, and/or greater intensity of surgical treatment(s) of children admitted after heart- or heart-lung transplantation. The results on the PICU subgroups in the current study are in line with earlier literature overviews [35-41] and extend these findings by the unique focus on children admitted to the PICU and by providing comprehensive meta-analytic quantification of intelligence impairment. Meta-regression in PICU subgroups was possible for the subgroups of children admitted for respiratory and/or circulatory insufficiency necessitating ECMO, cardiac surgery and heart- or heart-lung transplantation. No risk factors were found in children admitted for respiratory and/or circulatory insufficiency necessitating ECMO. The meta-regression finding of the total sample regarding the relation between later year of PICU admission and intelligence impairment was replicated in the subgroups of children admitted after cardiac surgery and heart- or heart-lung transplantation. In addition, the meta-regression findings in the total sample regarding sex and study quality were replicated in the subgroup of children admitted after cardiac surgery. Younger age at PICU admission was related to greater FSIQ impairment in the subgroup of children admitted after heart- or heart-lung transplantation. One possible explanation for this finding may be that the main reasons for heart transplantation differ with age (i.e. < 1 year congenital heart disease, > 1 year

cardiomyopathy) [42] and congenital heart disease may impact brain development already before birth [43]. We also found that older age at follow-up was related to less intelligence impairment in this subgroup, suggesting that intelligence outcome after heart- or heart-lung transplantation may improve over time.

With our broad and extensive systematic search we included a considerable number of studies and we were able to aggregate all existing data on intelligence outcome of PICU survivors, to systematically report on subgroups and to comprehensively study risk factors for intelligence impairment. Nevertheless, our meta-analysis and meta-regression is hampered by the limited availability of studies into intelligence outcome after PICU admission, with the available studies likely not being fully representative of the typical PICU population in terms of reasons for admission. Results show that a substantial number of studies is published mainly on the subgroup of children admitted after cardiac surgery, while other subgroups are less well studied or not at all. For example, we were not able to identify studies including children with respiratory insufficiency necessitating mechanical ventilation or renal insufficiency necessitating renal replacement therapy in our broad and extensive systematic search, while these are important indications for PICU admission [27,28] and concerns about neurocognitive development of these PICU subgroups exist [44]. This limits the generalizability of our results to the PICU population as a whole and underscores the importance for more follow-up studies on these populations. Furthermore, a limited number of possible risk factors was assessed in the included studies and the number of missing data for demographic and clinical potential risk factors was considerable. This reduced the power to identify risk factors (particularly in subgroups). Nevertheless, the available data did allow us to study a broad range of risk factors in the total sample of studies.

Respiratory insufficiency due to acute viral bronchiolitis is a common indication for none-elective PICU admission in children younger than two years of age [3,4]. In this thesis we specifically focused on this PICU subgroup to study the potential deleterious effects of sedatives, analgesics and anesthetics on neurocognitive outcomes. The group of patients with viral bronchiolitis is a relative homogenous group with single organ failure that seldom manifests neurologically [1,2] and is therefore not expected to affect neurocognitive functioning in itself. We used of a comprehensive computerized neurocognitive test battery aimed at a broad range of neurocognitive outcomes relevant to daily life functioning. The results indicate that these children are at risk of adverse neurocognitive functioning at 6-12 years of age, reflected by considerable lower intelligence and poorer performance on specific aspects of neurocognitive functioning (i.e. information processing, attention, verbal memory and visuomotor integration) compared to demographically comparable healthy peers, with effect sizes ranging from -0.41 to -0.60. Contrary to our hypothesis, we found no evidence supporting a role of exposure to sedatives, analgesics or anesthetics during PICU admission. In 2016,

the US Food and Drug Administration warned that repeated or longer use of general sedatives and anesthetics during procedures in children aged less than three years may affect children's brain development [45]. As this warning is based on outcomes of animal studies, it remains unclear to what extent these worrying findings could be generalized to children. Studies that reported evidence for potential negative effects of sedatives [46] and analgesics [47], included children in whom the underlying disease is a risk factor for neurocognitive impairment in itself [40,48], and drug exposure may have been linked to disease severity in these studies. The findings of this thesis suggest that exposure to sedatives, analgesics and anesthetics or a combination of these drugs is unlikely to substantially affect long-term neurocognitive outcomes after PICU admission.

The absence of evidence supporting a role for drug exposure raises the question what factors may have contributed to the observation of adverse neurocognitive outcomes in patients with acute viral bronchiolitis. Other factors may play a role, although, we found no evidence for the possible confounding effects of disease and treatment characteristics known to be associated with adverse neurocognitive outcomes (i.e. gestational age, ECMO, CPR, sepsis or traumatic brain injury). We extensively investigated patient and PICU-related characteristics in the relation between PICU admission and neurocognitive outcome by conventional linear regression analysis and two machine learning models (Regression Trees and k-Nearest Neighbors). Patient and PICU-related characteristics used for the prediction models were: demographic characteristics, perinatal and disease parameters, laboratory results and intervention characteristics, including hourly validated mechanical ventilation parameters. The results of our study show that lower socioeconomic status was associated with lower intelligence after PICU admission. Abundant research has documented the relation between socioeconomic status and neurocognitive functioning, of which the origin is matter of debate [49]. We also observed that younger age at follow-up was associated with poorer neurocognitive functioning (i.e. poorer speed and attention and verbal memory). We ascribe this finding to a developmental effect, i.e. reflecting the commonly observed age-related enhancement in neurocognitive functioning [50]. Furthermore, lower birth weight was associated with lower intelligence and poorer verbal memory. This result is in line with literature showing an association between lower birth weight and poorer neurocognitive functioning [51-53].

Furthermore, the findings of this thesis suggest that greater exposure to acidotic events during PICU admission is associated with poorer verbal memory outcome. As involvement of the central nervous system in the pathology of bronchiolitis is unlikely [1,2], the relation between acidotic events and neurocognitive outcome may reflect either potentially harmful effects of acidosis itself, or reflect related processes such as hypercapnia, hypoxic and/or ischemic events during PICU admission. In experimental studies, several mechanisms have been proposed that may explain a potential negative

effect of acidosis on the central nervous system, such as acidosis causing denaturation of proteins and nucleic acids, triggering cell swelling potentially leading to cellular edema and osmolysis, and inhibition of excitatory neurotransmission in the hippocampus, and influencing neuronal vulnerability indirectly by damaging glial cells [54,55]. Although the translation of these findings from the literature to our study findings is unclear, our findings indicate that acidotic events may be implicated in negative effects on the central nervous system, whether or not through other neurotoxic processes such as hypercapnia, hypoxia or ischemia. In our exploratory analyses we found additional evidence indicating that higher pCO_2 measurements, compatible with a respiratory origin of acidosis, were also related to poorer verbal memory outcome. Regardless of the exact mechanisms at play, our findings suggest that children with greater exposure to acidotic events are at risk of adverse long-term neurocognitive outcome after PICU admission, a finding that awaits replication in future prospective studies.

Regarding the comparison of prediction models used to investigate risk factors for poor neurocognitive outcomes, we found no evidence for added value of the Regression Trees and k-Nearest Neighbors machine learning models as compared to conventional linear regression analysis. The wide confidence intervals, potentially reflecting the small sample size of the blind test set, provided limited sensitivity for model comparisons. Nevertheless, the findings suggest that machine learning models may not have added value in smaller sample sizes. Indeed, machine learning flourishes by large datasets not easily obtained in clinical settings [56]. This further stresses the importance of collaborations between centers to pool clinical data and acquire larger datasets for clinical research into advanced outcome prediction using machine learning.

Literature regarding long-term behavioral and emotional functioning and health-related quality of life in children after PICU admission is scarce and harbors conflicting results [57-62]. In addition, academic performance has only been investigated in one recent article describing affected academic performance in children admitted to the PICU before the age of five [63]. The results of this thesis revealed no evidence for long-term adverse outcomes in behavioral and emotional functioning after PICU admission for bronchiolitis at 6-12 years of age. Nevertheless, these children were found to be at risk of long-term adverse health-related quality of life regarding school functioning (child-reported: $p = .03$, $d = -0.36$; parent-reported: $p = .02$, $d = -0.39$) and long-term adverse academic performance with respect to spelling ($p = .006$, $d = -0.48$), reading comprehension ($p = .010$, $d = -0.41$), and arithmetic performance ($p = .04$, $d = -0.26$). Moreover, the results identified intelligence as a mediator of the impact of PICU admission on reading comprehension and arithmetic performance. These findings suggest that long-term adverse neurocognitive outcomes may contribute to academic difficulties after PICU admission.

LIMITATIONS AND STRENGTHS

A limitation of our studies regarding the long-term outcomes after PICU admission for bronchiolitis, is that a substantial number of eligible children (40-45%) 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 important patient and disease characteristics (sex, age at PICU admission, duration of mechanical ventilation and length of PICU stay). Furthermore, the sample size allowed to detect medium-sized effects, but the studies are limited in terms of detecting smaller sized effects. A limitation of our study investigating the relation of drug exposure during PICU admission and long-term neurocognitive outcomes, is that the distributions of exposure to lorazepam, fentanyl, esketamine and propofol were highly skewed, necessitating dichotomization. This may have reduced the sensitivity of the relevant analyses, although there was still sufficiently powered to detect medium-sized effects. Lastly, we acknowledge that the reported associations between risk factors and outcome may not reflect causal relationships [64]. 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 the studies regarding neurocognitive and daily life outcomes after PICU admission for bronchiolitis is the use of a dedicated control group that was comparable to the patient group in terms of demographic characteristics (i.e. age, sex and socioeconomic status). A comparable control group allows to account for inflation of intelligence over time (known as the Flynn effect) [65,66] and provides a solution for the inability to correct for socioeconomic status using standardized norm scores.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The results of this thesis add to a better understanding of long-term morbidity after PICU admission, recently acknowledged as the pediatric post-intensive care syndrome [67,68]. In addition, this thesis confirms the impact of PICU admission on family functioning, acknowledged as the post-intensive care syndrome-family [69,70]. The findings underline the importance of structured multidisciplinary follow-up after PICU admission. Structured multidisciplinary follow-up enables early identification and appropriate management of adverse outcomes, hereby improving outcomes of individual patients. Time-efficiency for patients, parents and health care professionals can be promoted by scheduling all consultations of the multidisciplinary team consecutively, with a multidisciplinary team meeting scheduled after the last consultation. In addition,

this thesis shows that structured follow-up, including structured data collection, may improve the standard of care during and after PICU admission by providing insight in extent and severity of sequelae of PICU admission; and to facilitate scientific research on outcome and prognosis of patients after PICU admission.

Our structured multidisciplinary PICU follow-up program serves as an example of how clinical care, health care evaluation and scientific research can be integrated to continuously provide data-driven health care innovation. Depending on, among others, availability of financial resources, health care professionals, language appropriate questionnaires, electronic patient record and infrastructure to allow structured data collection, other PICUs may adapt this program in order to be applicable in their country and hospital. A structured approach to multidisciplinary follow-up allows to create a consecutive cohort, with accumulating patient data, which could be a solution to the challenged literature describing the heterogeneous PICU population with small-sized studies and limited sets of outcomes. Hereby, it allows to create better insight in outcome and prognosis, which can be used to improve patient outcomes, patient education and shared-decision making. At last, structured multidisciplinary follow-up may also support the generation of new research initiatives and easier implementation of research and intervention studies in follow-up practice.

Future work needs to address the cost-effectiveness of structured multidisciplinary follow-up. A recently published article [71] identified "lack of support", including lack of availability of funding and lack of institutional or departmental support, as the most important barrier with respect to the development and maintenance of PICU follow-up programs. Prior to implementation of our structured multidisciplinary follow-up program, funding was provided by the Emma Children's Hospital, Amsterdam UMC for the development and implementation of the program. After development of a national guideline on follow-up of PICU patients [72], our structured multidisciplinary follow-up care was acknowledged and reimbursed by insurance companies. Professionals involved in the follow-up programs have been able to attract external funding for scientific research in several of the outcomes targeted. Only a structured follow-up program will provide insights in potential deleterious consequences of PICU admission, thereby facilitating targeted follow-up and enabling us to know which possible complications we have to focus on during PICU admission in order to prevent these complications and thereby also minimize costs after PICU discharge.

The findings in this thesis show a diversity in adverse outcomes after PICU admission. In order to gain a generalizable understanding of long-term outcomes after pediatric critical illness, standardization of outcome assessment is urgently needed. Core outcome set and instrument recommendations have recently been developed by the Pediatric Outcomes STudies after PICU (POST-PICU) Investigators of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network and the *Eunice Kennedy*

Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) [73,74]. Although our follow-up program was developed well before publication of this core outcome set, the outcomes and instruments of our structured multidisciplinary PICU follow-up program largely converge with the recommendations made.

This thesis identified several risk factors for adverse outcomes after PICU admission that can be useful for more targeted clinical follow-up. Besides demographic and perinatal characteristics that were found to be related to neurocognitive outcomes, observed risk factors for asthma (duration of invasive mechanical ventilation) and for adverse neurocognitive outcome (longer length of PICU stay, lower survival rates, greater exposure to acidotic events) presumably reflect the greater disease severity and/or the greater intensity of - as well as the longer exposure to PICU treatments. Future research should aim to develop more personalized prognostic models and to gain a better understanding of risk factors and protective factors for adverse outcomes after PICU admission, that may provide targets for health care innovation. Digitalization of health care provides increasingly more data that can importantly contribute to better prediction and understanding of long-term outcome of children after PICU admission. Compared to conventional statistics, machine learning has great potential to capture complex inter-relations that are relevant for outcome thanks to the capability to process vast amounts of data and model nonlinear and highly complex interactions [75]. Machine learning is a rapidly growing field of artificial intelligence that is increasingly applied in health care settings [76-79]. However, the results of this thesis suggest that machine learning models may not have added value in smaller sample sizes. Indeed, machine learning flourishes by large datasets not easily obtained in clinical settings [56]. This further stresses the importance of collaborations between centers to pool clinical data and acquire larger datasets for clinical research into advanced outcome prediction using machine learning. Furthermore, collaborations between centers and standardization of interventions and outcomes during and after PICU admission enables monitoring of the effectiveness of the interventions and benchmarking between different hospitals.

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Nederlandse samenvatting
Co-authors
PhD portfolio
International publications
Acknowledgements
About the author

NEDERLANDSE SAMENVATTING

Acute kindergeneeskunde vertegenwoordigt een klein, maar belangrijk onderdeel van de gezondheidszorg dat zich richt op bewaking en ondersteuning van vitale systemen voor zuigelingen, kinderen en adolescenten met potentiële of bestaande levensbedreigende ziekten of verwondingen [1]. Acute kindergeneeskunde wordt meestal uitgevoerd op de Intensive Care voor Kinderen (ICK), welke in 1955 in Europa en in 1967 in Noord-Amerika werd geïntroduceerd [1]. Specifieke aandoeningen en ontwikkelingen in de neonatologie, kinderchirurgie en kindercardiologie creëerden een steeds grotere noodzaak voor acute kindergeneeskunde [1,2]. In de jaren '80 werd acute kindergeneeskunde een gedefinieerd, erkend subspecialisme [1,2]. Er werden richtlijnen ontwikkeld waaraan ICK's moeten voldoen, en certificering zorgde voor duidelijke richtlijnen voor de ziekenhuisaccreditatie van kinderintensivisten [1-3]. In de jaren '80 werden ook de eerste ICK's in Nederland opgericht. In de afgelopen decennia zijn ICK's sterk ontwikkeld, met onder meer een multidisciplinaire staf, full-time kinderintensivisten, geschoolde verpleegkundigen en geavanceerde technologieën [1,2,4,5]. Momenteel worden jaarlijks ongeveer 4500 kinderen op een ICK in Nederland opgenomen [6].

Belangrijkste redenen voor ICK-opname zijn respiratoir falen, cardiovasculair falen, neurologische aandoeningen, metabole en infectieuze aandoeningen, trauma en postoperatieve zorg [2,4,7,8]. Sommige aandoeningen worden tegenwoordig zelden gezien op de ICK, zoals epiglottitis als gevolg van *Haemophilus influenzae* type b immunisatie. Als gevolg van vooruitgang op de ICK en binnen de kinderchirurgie (waaronder ook kinderhartchirurgie) wordt intensieve zorg nu ook geboden aan kinderen met complexe en chronische ziekten die vroeger niet zouden worden opgenomen, en overleven steeds meer kinderen een ICK-opname [1,2,4,5].

Hoewel het overlevingspercentage van kinderen opgenomen op de ICK de afgelopen decennia aanzienlijk is toegenomen [4,5], is de langetermijnmorbiditeit na ICK-opname een steeds groter wordend probleem [9-15]. De onderliggende ziekte, kritieke ziekte en/of bijbehorende ICK-behandelingen kunnen van invloed zijn op de langetermijnuitkomsten van deze kinderen. Een toenemend aantal studies documenteert verminderde langetermijnuitkomsten na ICK-opname met betrekking tot fysiek, neurocognitief en psychosociaal functioneren, zoals post-trombotisch syndroom, verminderde intelligentie en post-traumatisch stress syndroom [9-15]. De huidige literatuur over uitkomsten na ICK-opname is gefragmenteerd en bestaat voornamelijk uit kleinschalige cross-sectionele studies die vaak gericht zijn op een specifieke patiëntengroep en/of een beperkte set uitkomsten [15]. Inzicht in de langetermijnuitkomsten na ICK-opname wordt bemoeilijkt door de heterogeniteit van de ICK-populatie en door de mogelijke gevolgen op een groot aantal uitkomstdomeinen. Als gevolg daarvan is de prognose na ICK-opname onzeker, wat de follow-up bemoeilijkt.

Voor meer gerichte follow-up en ter voorkoming van ongunstige uitkomsten na ICK-opname, is het van belang de omvang van en de risicofactoren voor ongunstige uitkomsten na ICK-opname te identificeren. Dit proefschrift richt zich op twee belangrijke uitkomsten na ICK-opname, namelijk lange termijn long- en neurocognitieve uitkomsten. Respiratoire aandoeningen zijn de meest voorkomende redenen voor ICK-opname [8], maar lange-termijn longuitkomsten na ICK-opname zijn momenteel grotendeels onbekend, terwijl ongunstige longuitkomsten aanzienlijke invloed kunnen hebben op het dagelijks leven van kinderen. Neurocognitief functioneren is geassocieerd met belangrijke levensuitkomsten [16-19], echter de omvang van en mogelijke risicofactoren voor ongunstige neurocognitieve uitkomsten na ICK-opname zijn grotendeels onbekend. Daarnaast beschrijven wij het design van een gestructureerd multidisciplinair follow-up programma met als uiteindelijke doel het implementeren van een zorginnovatiecyclus.

De belangrijkste doelstellingen van dit proefschrift zijn: (1) het vergroten van inzicht in de lange termijn long- en neurocognitieve uitkomsten van kinderen na ICK-opname; (2) het onderzoeken van risicofactoren voor verminderde long- en neurocognitieve uitkomsten; en (3) het ontwerpen, implementeren en evalueren van een gestructureerd multidisciplinair follow-up programma voor kinderen en hun ouders na ICK-opname.

Gestructureerde multidisciplinaire follow-up

Momenteel zijn er enkele ICK follow-up programma's in de literatuur beschreven [20-26]. Toch bestaat er geen gestandaardiseerde structuur voor follow-up na ICK-opname. De bestaande programma's beschreven in de literatuur [20-26] variëren met betrekking tot geïncludeerde patiënten (bijvoorbeeld gericht op patiënten met neurologische diagnoses), betrokken zorgverleners (bijvoorbeeld alleen kinderintensivisten), follow-up moment(en), en/of beoordeelde uitkomsten. Bovendien ontbreekt het de meeste ICK follow-up programma's aan gestructureerde dataverzameling [20], wat essentieel is voor zorgevaluatie en wetenschappelijk onderzoek naar uitkomsten van kinderen na ICK-opname. **Hoofdstuk 2** beschrijft het proces van de ontwikkeling en implementatie van een gestructureerd multidisciplinair follow-up programma voor kinderen en hun ouders na ICK-opname in het Emma Kinderziekenhuis, Amsterdam UMC. Daarnaast beschrijft dit hoofdstuk de eerste follow-up resultaten van kinderen en hun ouders om het belang van ons programma te illustreren. Wij bespreken hoe gestructureerde follow-up en het verzamelen van uitkomstgegevens van patiënten binnen een multidisciplinair follow-up programma een belangrijke bijdrage kan leveren aan (1) het verbeteren van de uitkomsten van individuele patiënten; (2) het verbeteren van de kwaliteit van zorg tijdens en na ICK-opname; en (3) het faciliteren van wetenschappelijk onderzoek naar langetermijnuitkomsten van kinderen na ICK-opname. Ten slotte bespreken wij uitdagingen en aanbevelingen voor de toekomst van een gestructureerd multidisciplinair follow-up programma.

Langetermijn-longuitkomsten

Respiratoire insufficiëntie als gevolg van acute virale bronchiolitis is een veelvoorkomende indicatie voor mechanische beademing op de ICK. Zowel de ernst van bronchiolitis als ook de invasieve mechanische beademing kunnen geassocieerd zijn met verminderde langetermijn-longuitkomsten. In **hoofdstuk 3** onderzochten wij kinderen met een voorgeschiedenis van invasieve mechanische beademing vanwege bronchiolitis, waarbij wij de omvang, mogelijke risicofactoren, en impact op het dagelijkse leven van verminderde langetermijn-longuitkomsten onderzochten. Ongeveer een kwart van de geïncludeerde kinderen had op 6-12 jarige leeftijd verminderde langetermijn-longuitkomsten. Astma was de meest voorkomende diagnose bij deze kinderen. Bij de meerderheid van de kinderen waren deze verminderde langetermijn-longuitkomsten voorheen niet ontdekt. De aanwezigheid van atopische aandoeningen in de familie en/of een langere beademingsduur waren geassocieerd met astma. Er was geen verschil in de frequentie van sportdeelname of schoolverzuim in vergelijking met kinderen met normale langetermijn-longuitkomsten.

Langetermijn-neurocognitieve-uitkomsten

In **hoofdstuk 4** werd een meta-analyse en meta-regressie verricht om, op basis van een review van de bestaande literatuur, intelligentie na ICK-opname te kwantificeren en risicofactoren voor een verminderde intelligentie te onderzoeken. In totaal werden 123 artikelen geïncludeerd, gepubliceerd tussen 1973 en 2021, met in totaal 8119 kinderen na ICK-opname en 1757 gezonde controle kinderen. De resultaten toonden 0,47 SD lagere intelligentiescores bij kinderen na ICK-opname in vergelijking met controle kinderen, wat overeenkomt met een gemiddeld verschil van 7,1 IQ-punten. De beschikbare studies maakten het mogelijk subgroepen te onderscheiden van kinderen opgenomen voor: (1) respiratoire en/of circulatoire insufficiëntie waarvoor Extra Corporale Membraan Oxygenatie (ECMO), (2) circulatoire insufficiëntie waarvoor reanimatie, (3) traumatisch hersenletsel, (4) sepsis en/of meningoencefalitis, (5) hartchirurgie, (6) hart- of hart-longtransplantatie, en (7) overige ICK-indicaties. Alle bestudeerde subgroepen hadden een lagere intelligentie vergeleken met controles (range 0.38-0.88 SD). Met behulp van meta-regressie analyse werd een breed scala aan demografische en klinische risicofactoren voor een verminderde intelligentie onderzocht. De resultaten laten zien dat recenter jaar van ICK-opname, langere ICK-opnameduur, vrouwelijk geslacht, lager overlevingsaantal en hogere studiekwaliteit in de onderzochte groepen samenhingen met een verminderde intelligentie. Meta-regressie in ICK-subgroepen laat zien dat een recenter jaar van ICK-opname verband hield met een verminderde intelligentie bij kinderen die werden opgenomen na hartchirurgie en hart- of hart-longtransplantatie. Vrouwelijk geslacht en hogere studiekwaliteit waren geassocieerd met een verminderde intelligentie bij kinderen opgenomen na hartchirurgie. Jongere leeftijd bij ICK-opname

en jongere leeftijd bij follow-up waren geassocieerd met een verminderde intelligentie bij kinderen opgenomen na hart- of hart-longtransplantatie.

De cross-sectionele observationele studie in **hoofdstuk 5** onderzocht de relatie tussen sedativa, analgetica en anesthetica en langetermijn-neurocognitief-functioneren bij kinderen na ICK-opname. De resultaten laten zien dat kinderen die op de ICK werden beademd vanwege bronchiolitis, een verminderd langetermijn-neurocognitief-functioneren hadden. Zij hadden een substantieel lagere intelligentie en slechtere prestaties op specifieke aspecten van het neurocognitief functioneren (d.w.z. informatieverwerking, aandacht, verbaal geheugen en visueel motorische integratie) in vergelijking met demografisch vergelijkbare gezonde leeftijdsgenoten, met effectgroottes variërend van -0,41 tot -0,60. In tegenstelling tot onze hypothese vonden wij geen bewijs voor een verband tussen blootstelling aan sedativa, analgetica, anesthetica of een combinatie van deze middelen en neurocognitieve uitkomsten.

Machine learning is een onderdeel van kunstmatige intelligentie dat steeds meer wordt toegepast in de gezondheidszorg. De waarde van machine learning bij het onderzoeken van de relatie tussen ICK-opname en langetermijn-neurocognitieve-uitkomsten is echter nog niet onderzocht en is daarom momenteel onduidelijk. **Hoofdstuk 6** had tot doel de potentiële relevantie te onderzoeken van patiënt- en ICK-gerelateerde variabelen voor het langetermijn-neurocognitief-functioneren na ICK-opname, alsmede de potentie van machine learning te onderzoeken. In deze studie onderzochten wij dezelfde patiëntengroep als in **hoofdstuk 5**. Predictiemodellen werden ontwikkeld voor elk van de neurocognitieve uitkomsten met behulp van regressiebomen, k-Nearest Neighbors en conventionele lineaire regressie analyse. De bevindingen van deze studie suggereren dat bij kinderen met een eerdere ICK-opname vanwege bronchiolitis: (1) een lager geboortegewicht en een lagere sociaal-economische status geassocieerd zijn met een slechtere neurocognitieve uitkomst, en (2) een grotere blootstelling aan acidose tijdens de ICK-opname geassocieerd is met een slechter verbaal geheugen. De bevindingen van deze studie laten geen bewijs zien voor toegevoegde waarde van machine learning in vergelijking met lineaire regressie analyse bij de predictie van langetermijn-neurocognitieve-uitkomsten in een relatief kleine patiëntengroep.

In **hoofdstuk 7** onderzochten wij de langetermijnimpact van ICK-opname op het functioneren in het dagelijks leven en de mogelijke mediërende rol van neurocognitief functioneren. In deze studie werden dezelfde patiënten- en controlegroep onderzocht als in **hoofdstuk 5**. De resultaten laten geen aanwijzingen zien voor verminderde langetermijnuitkomsten met betrekking tot gedragsmatig en emotioneel functioneren na ICK-opname vanwege bronchiolitis. Wel bleken deze kinderen een risico te hebben op een verminderde kwaliteit van leven met betrekking schools functioneren en op een verminderd functioneren op school met betrekking tot spelling, begrijpend lezen en rekenen. Bovendien bleek intelligentie een mediator te zijn van het effect van ICK-

opname op begrijpend lezen en rekenen. Deze bevindingen suggereren dat nadelige langetermijn-neurocognitieve-uitkomsten kunnen bijdragen aan een verminderd functioneren op school na ICK-opname. Aangezien kinderen die op de ICK zijn opgenomen vanwege bronchiolitis geen kritieke ziekte hebben die zich neurologisch manifesteert [27,28], kunnen de bevindingen van **hoofdstuk 5**, **hoofdstuk 6** en **hoofdstuk 7** mogelijk schadelijke effecten weerspiegelen die verband houden met de ICK-opname.

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Department:	Pediatric Intensive Care

PhD training

	Year	ECTS
General courses		
Clinical Epidemiology: Evaluation of Medical Tests	2018	0.9
Practical Biostatistics	2018	1.4
Endnote	2018	0.1
Research Data Management	2018	0.9
AMC World of Science	2018	0.7
Clinical Epidemiology: Systematic Reviews	2019	0.7
Scientific Writing in English	2019	1.5
Project Management	2019	0.6
Basiscursus klinisch onderzoekers (eBROK)	2019	1.0
Advanced Topics in Biostatistics	2020	2.1
Clinical Epidemiology: Observational Epidemiology	2021	0.6
Didactical Skills	2021	0.4
Seminars, workshops and master classes		
Two-weekly Research Meeting Emma Neuroscience Group	2017-2021	3.7
Monthly Research Meeting Pediatric Intensive Care	2017-2021	2.0
Coach de Co - Discipline Overstijgend Onderwijs	2020	0.4
Masterclass Amsterdam Kindersymposium	2019	0.3
Oral presentations at scientific conferences		
Amsterdam Kindersymposium, Amsterdam, the Netherlands "The impact of benzodiazepines and opioids on neurocognitive development in children"	2019	0.3
Nederlandse Vereniging voor Kindergeneeskunde (NVK) Congres, Arnhem, the Netherlands Symposium "Lange termijn follow-up als motor achter innovatie in de kindergeneeskunde"	2019	0.3
European Academy of Paediatric Societies (EAPS) Congress (digital) "Cognitive outcomes in children after admission to the paediatric intensive care unit - A systematic review, meta-analysis and meta-regression of IQ findings"	2020	0.3
American Thoracic Society Conference (digital) "Long-term Pulmonary Sequelae in Children Mechanically Ventilated for Severe Bronchiolitis"	2021	0.3

	Year	ECTS
European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Congress (digital) "Long-term Follow-up of Daily Life Functioning after Pediatric Intensive Care Unit Admission"	2021	0.3
Excellence in Pediatrics Conference (digital) "Structured Multidisciplinary Follow-Up of Patients after PICU discharge"	2021	0.3
Amsterdam Kindersymposium, Amsterdam, the Netherlands "Long-term Follow-up of Daily Life Functioning after Pediatric Intensive Care Unit Admission"	2023	0.3
Poster presentations at scientific conferences		
European Academy of Paediatric Societies Congress, Paris, France "The effect of general anaesthetics and sedatives on brain development in children"	2018	0.3
World Federation of Pediatric Intensive and Critical Care Societies (digital) "The impact of benzodiazepines and opioids on neurocognitive development in children"	2020	0.3
(Inter)national conferences		
Amsterdam Kindersymposium, Amsterdam, the Netherlands	2018	0.3
European Academy of Paediatric Societies (EAPS) Congress, Paris, France	2018	1.0
Amsterdam Kindersymposium, Amsterdam, the Netherlands	2019	0.3
Nederlandse Vereniging voor Kindergeneeskunde (NVK) Congres, Arnhem, the Netherlands	2019	0.3
Amsterdam Reproduction and Development PhD Retreat, Ermelo, the Netherlands	2019	1.0
Amsterdam Kindersymposium, Amsterdam, the Netherlands	2020	0.3
European Academy of Paediatric Societies (EAPS) Congress (digital)	2020	1.0
World Federation of Pediatric Intensive and Critical Care Societies Congress (digital)	2020	1.0
Tropen Carrière Dag (digital)	2021	0.3
Amsterdam Kindersymposium (digital)	2021	0.3
American Thoracic Society Conference (digital)	2021	0.3
European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Congress (digital)	2021	0.7
Excellence in Pediatrics Conference (digital)	2021	0.7
Amsterdam Kindersymposium, Amsterdam, the Netherlands	2023	0.3

Teaching

	Year	ECTS
Lecturing		
Onderwijs MSc: Systematic appraisal of systematic review	2020	0.3
Instructor Advanced Paediatric Life Support, Belgium	2018-present	
Supervising		
Karlien Doetjes – Master thesis Brain and Cognition	2017-2018	2.3
Jolee de Jong – Master thesis Brain and Cognition	2017-2018	2.5
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Parameters of esteem

	Year	ECTS
Grants, awards and prizes		
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Other

	Year	ECTS
Organizing committee annual research retreat Amsterdam Reproduction and Development research institute	2019	3.0
Organizing committee Amsterdam Kindersymposium	2019-2021	6.0

INTERNATIONAL PUBLICATIONS

This thesis

Long-term follow-up of daily life functioning after pediatric intensive care unit admission
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The Journal of Pediatrics. 2023 (online ahead of print)

Structured multidisciplinary follow-up after pediatric intensive care: a model for continuous data-driven health care innovation
E.S.V. de Sonnaville, J.B.M. van Woensel, J.B. van Goudoever, M.H. Otten, L. Teela, C.S.H. Aarnoudse-Moens, S.W.J. Terheggen-Lagro, A.E. van der Hulst, M. Engelen, M. Königs, J. Oosterlaan, H. Knoester, the Emma Children's Hospital Amsterdam UMC Follow Me program consortium.
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Molecular Genetics and Metabolism. 2012;107(3):526-33.

Work under review

Predicting long-term neurocognitive outcome after pediatric intensive care unit admission - exploring the potential of machine learning
E.S.V. de Sonnaville, J. Vermeule, K. Oostra, H. Knoester, J.B.M. van Woensel, S. Ben Allouch, J. Oosterlaan, M. Königs.

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ABOUT THE AUTHOR

Eleonore de Sonnaville was born on December 2, 1988 in Amsterdam, the Netherlands. She is a daughter of Jeroen and Marie-Louise de Sonnaville and sister of Catherine, Laurens and Rudolf. Eleonore grew up in Amsterdam, Amstelveen and Bussum. She obtained her high school degree (Gymnasium) in 2007 at the Willem de Zwijger college in Bussum. At the University of Amsterdam she obtained a medical degree in 2015 (cum laude). During her studies she was actively involved in several research projects, which resulted in one national publication and three international peer-reviewed publications. Prior to her clinical rotations (2011-2012), she spent 10 months abroad traveling in Central and South America, New Zealand, Australia, and Southeast Asia. Furthermore, since her studies she was interested in working abroad. She performed her nursing internship (2008) in the Diakonessenhuis in Paramaribo, Suriname, and one of her clinical rotations (2014) at the Intensive Care Unit in Hospital Italiano de Buenos Aires, Argentina. After obtaining her medical degree, she worked voluntarily at the departments of pediatrics, surgery and obstetrics & gynaecology in Haydom Lutheran Hospital, Tanzania. After her work in Tanzania, Eleonore worked as a clinical resident (ANIOS) at the pediatric department of the Spaarne Gasthuis in Haarlem, Maasstad Hospital in Rotterdam and OLVG in Amsterdam. She started her PhD in November 2017 under supervision of prof. dr. Jaap Oosterlaan and prof. dr. Job B.M. van Woensel at the department of Pediatric Intensive Care of the Emma Children's Hospital, Amsterdam University Medical Centers. As part of her PhD she has importantly contributed to the set-up of a newly developed outpatient clinic for children after admission to the Pediatric Intensive Care Unit ("Follow Me program"). Eleonore's current research is embedded in this follow-up program that focuses on the long-term outcomes of children after Pediatric Intensive Care Unit admission. In addition, since 2018 she works as an instructor Advanced Pediatric Life Support in Belgium. In 2022, Eleonore and Rob moved from Amsterdam to Haarlem and became a family of three with their son Eliah.