LIFE AFTER CRITICAL ILLNESS

Neurocognitive functioning and health-related quality of life of children after PICU admission, and the role of late parenteral nutrition

José Hordijk

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Colofon

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Life After Critical Illness:
Neurocognitive Functioning and Health-Related Quality of Life of Children After PICU Admission, and the Role of Late Parenteral Nutrition

Het leven na kritieke ziekte:
neurocognitief functioneren en gezondheidsgerelateerde kwaliteit van leven van kinderen na een intensive care opname en de rol van late parenterale voeding

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CHAPTER 1

General Introduction

Outcomes after critical illness in children

Children surviving critical illness are prone to develop important long-term physical and neurocognitive impairments, which have an impact on quality of life. In the Netherlands, approximately 5,000 critically ill children are admitted every year to the pediatric intensive care unit (PICU).[1] Critically ill children are admitted with various diagnoses, surgical or medical, and half of them with emergency.[2] With regard to the age at PICU admission, infants (<12 months old) had the highest rate of admissions compared to the other age groups.[3] The majority of children older than one year who were admitted to the PICU had preexisting chronic conditions and prior PICU admissions.[4] Length of PICU stay varies, with the majority of children staying less than 24 hours,[3-5] and a minority of patients having a prolonged stay (>28 days) in the PICU (4%).[5,6]

Improvements in pediatric critical care have led to a very low mortality rate of approximately 2%.[1,3,7] Whereas there has been a change in diagnostic categories over the last decades (for example a decrease in infectious diseases), the severity of illness and length of PICU stay have not changed over the last four decades. This means that every year a significant number of children has to live with significant disabilities.[5] This has changed the focus from mortality to disabilities, usually called morbidities, after PICU admission.[8] About one in five children previously admitted to the PICU experience morbidities after discharge.[1] These morbidities interfere with normal development[9] and are described as Post Intensive Care Syndrome (PICS).[10] PICS in children consists of impairments in 4 domains: physical, emotional, social, and cognitive functioning (see **Figure 1**).[10,11]

The resilience to recover from impairments in physical, emotional, social, and cognitive functioning is dependent on factors that already exist before PICU admission, factors related to the admission at the PICU, and factors that exist after PICU discharge, which all influence the outcome (see **Figure 1**). Firstly, pre-existing factors of the child such as medical history (pre-existing comorbidities), psychological and behavioral characteristics, age and environmental characteristics (e.g. family dynamics), moderate the recovery trajectory.[9,12] Furthermore, factors related to the PICU admission such as type of admission (diagnosis), illness severity, number of invasive procedures, length of PICU stay, and medications administered have an influence on recovery trajectory.[9,12] After PICU admission, predictors for the outcome are the child's perceived competence, coping strategies, anxiety and stress, and behavioral changes.[12] Throughout the entire recovery trajectory factors related to the parent(s) and/or caregiver(s) have an influence on the outcomes as well.[9,10] These factors include the parent-child relationship, parental education, socioeconomic status, prior stressful events, family functioning, parental relationship status, social support available for parents, parental coping strategies, separation from the child

during PICU admission, information received from the medical team, and anxiety and stress levels after PICU admission (see **Figure 1**).[9,12,13]

Changes in the four domains of functioning after PICU admission lead to a 'new normal' for the child and the parents (see **Figure 1**) that has been described in the biopsychosocial model of recovery.[14] This means that children and their parents have to adapt to the remaining impairments in order to reach a 'new normal'. The impact of these changes on daily life of the child and parents can be measured objectively or evaluated subjectively.

Physical functioning means the condition of the body, which can be measured objectively by medical devices that assess vital functions such as blood pressure and heart rate. Emotional and social functioning can be complex to assess objectively, but can be assessed subjectively through patient-reported outcomes measures (PROMs) such as interviews and questionnaires.[15] The subjective evaluation of the domains of physical functioning, emotional functioning, and social functioning together is usually measured within one construct, called health-related quality of life (HRQoL). HRQoL gives insight in the impact of health on the broad concept of quality of life and provides information about the subjective evaluation of the first three domains.[16,17] With regard to studies investigating HRQoL, this has been investigated in the first year after PICU admission, but little is known about children's long-term HRQoL.[9]

Cognitive functioning refers to internal mental processes underlying how people perceive stimuli, remember, speak, think, make decisions and solve problems.[18] These mental processes are described in neurocognitive domains such as general intellectual functioning, sensation, attention, memory, and executive functioning. General intellectual functioning, which is usually referred to as intelligence, includes abilities that allow a person to understand and to interact with reality, such as logical reasoning, problem-solving, and learning.[19] In neuropsychology, the model of hierarchy of the other neurocognitive domains has often been used to map developmental problems of the child. In this neurocognitive hierarchy, lower, more basic functions, such as sensation and attention, affect the development of the higher neurocognitive domain memory. Impairments in memory functioning affect, in turn, the development of executive functioning.[20] For example, to reason and make decisions (part of the most complex executive functioning domain), previously stored information is needed (memory), which is obtained by focusing on this information (attention). When impairments exist in the lower domains of the hierarchy, patients will experience more consequences in daily life since it will affect the higher neurocognitive domains.[20] Cognitive functioning can be measured objectively through clinical tests comprising different neurocognitive domains, but also subjectively by using PROMs.[21]

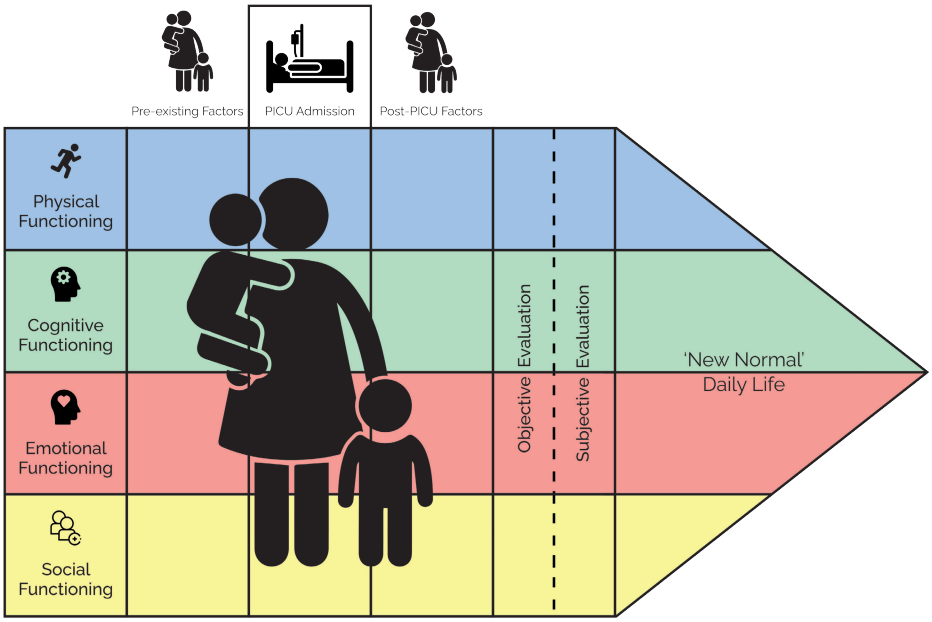

Figure 1. Outcomes after PICU admission, adapted by the biopsychosocial model of recovery[14] and the Post Intensive Care Syndrome in pediatrics (PICS-p) framework[10]. Pre-existing child and parental factors, child and parental factors related to the PICU admission, and child and parental factors that exist after the PICU admission in the recovery phase, all have an influence on the four domains of PICS (physical, cognitive, emotional and social functioning), which can be objectively evaluated and subjectively evaluated. The subjective evaluation reflects the 'new normal' which is the daily life of families.

Modifiable factors during PICU stay

Although various risk factors during PICU admission have been associated with long-term neurocognitive impairment, only few studies have examined modifiable factors.[22] Some factors related to disease management on the PICU can be modified to prevent harm and improve neurocognitive and HRQoL outcomes. A study in children with encephalopathy tried to improve HRQoL outcomes by two different temperature strategies on the PICU, but did not reveal differences between treatment with hypothermia and treatment with normothermia.[23] Different sedation strategies had no effect on HRQoL outcomes in children who required mechanical ventilation and in children with acute respiratory failure.[24,25] A study that investigated two types of surgical techniques to correct congenital heart abnormalities found that the type of surgery affects the neurocognitive outcome of children.[26,27] The type of anesthesia did not affect general intelligence two years later.[28] The development of safer plasticisers, that are used in soft plastic medical devices, might improve neurocognitive outcomes in the long term, as the current plasticisers, phthalates, were associated with attention deficit four years after PICU admission.[29] Lastly, a randomized controlled trial (RCT) that investigated whether tight glucose control was superior to standard glucose

control for neurocognitive functioning 4 years later found that tight glucose control improved motor coordination and cognitive flexibility.[30] Nutrition might also be a possible modifiable risk factor as it is related to the development of brain structures and functions. This makes it a determinant of neurocognitive functioning.[31,32] Especially during critical illness, when most children are unable to eat normally, it is important to know which nutritional strategy predicts the most favorable outcome.

Recently, the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) RCT was conducted to examine the effect of withholding PN (until day 8 of admission), compared with the standard protocol of starting (supplemental) PN early (within the first 24 hour after admission). It was the first trial that examined the clinical outcomes of the timing of PN on the PICU.[33] The PEPaNIC RCT was a multicenter, prospective study with three participating sites.[34] Children were eligible to participate in the study when they were critically ill and admitted to the PICU. The inclusion criterion for age was newborn to 17 years old. In total, a number of 1440 critically ill children admitted were included. This study showed that withholding supplemental PN during the first week in the PICU resulted in better short-term outcomes. Children who were allocated to the Late PN group had a lower incidence of newly acquired infections compared to children allocated to the Early PN group.[2] Furthermore, children in the Late PN group had a shorter stay at both the PICU and the hospital.[2] These favorable outcomes of withholding PN until day 8 were independent of diagnosis, severity of illness, risk of malnutrition, and age of the child. However, another result of withholding PN in the first week of PICU admission was a higher rate of hypoglycemic episodes compared to starting PN early.[2] Hypoglycemic episodes may be associated with worse long-term neurodevelopmental outcomes.[35] Additionally, due to the fact that most children were intolerant to enteral nutrition during the first week, the allocation to the Late PN group resulted in nutritional intakes significantly below recommendations at that time. Therefore, concerns were raised for the long-term health and neurocognitive outcomes of children who were allocated to the Late PN group.[36] To investigate the long-term health and cognitive developmental outcomes, a long-term follow-up study of the PEPaNIC trial was conducted, which is described in this thesis.

Aims and outline thesis

The aim of this thesis is to investigate long-term neurocognitive functioning in critically ill children, and HRQoL in critically ill children and their parents as compared to healthy children (see **Figure 2**). The second aim is to investigate the effect of Late PN as compared with Early PN during PICU admission on the long-term neurocognitive functioning, and on HRQoL of the child and parents. In chapter 2, studies into neurocognitive outcomes and HRQoL outcomes after PICU admission are systematically reviewed. Furthermore, interventions to improve these outcomes

are outlined. In chapter 3, HRQoL outcomes of patients who were admitted to the PICU and their parents are examined 6 months after critical illness. In addition, factors associated with worse HRQoL outcomes are investigated in this chapter. Also the relation between parents' own HRQoL and parent-reported HRQoL of the child is studied. Chapter 4 focuses mainly on the long-term neurocognitive outcomes two years after PICU admission, as well as on the two year outcomes of Late PN compared with Early PN during PICU admission on these outcomes. In chapter 5, the role of age at the time of exposure to Early PN compared with Late PN on long-term developmental outcomes is investigated. Chapter 6 examined HRQoL two years after PICU admission in children and parents, as well as the effects of Late PN compared with Early PN during PICU admission on these outcomes. Chapter 7 covers the assessment of mainly neurocognitive outcomes in the long term, as well as the effect of Late PN compared with Early PN four years after PICU admission. In chapter 8, the general discussion, main results, conclusions, and implications for research and clinical practice are outlined.

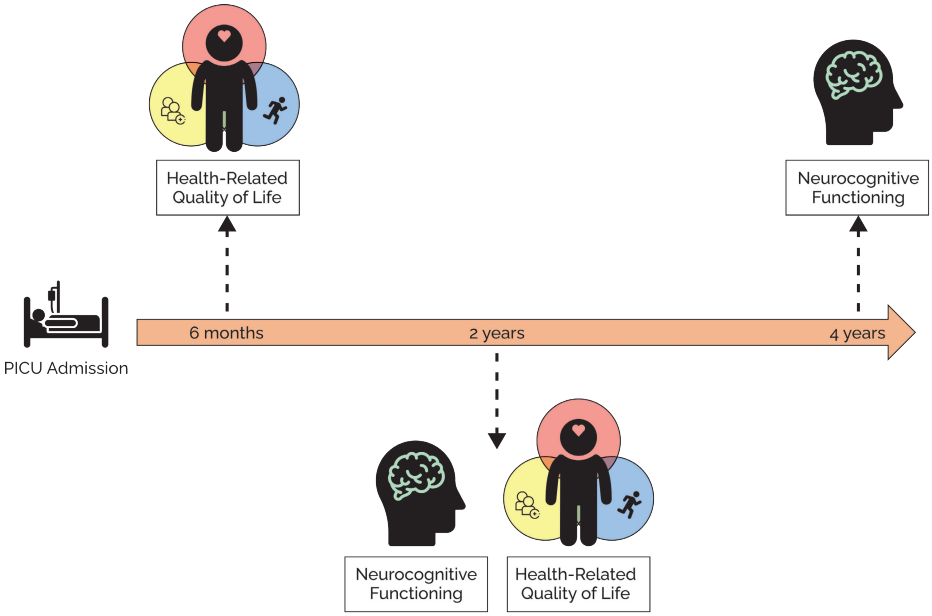

Figure 2. Follow-up time points and outcomes measured of the follow-up study of the PEPaNIC trial, which is described in this thesis

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CHAPTER 2

Neurocognitive functioning and health-related quality of life of children after pediatric intensive care admission: a systematic review

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CHAPTER 3

Health-related quality of life of children and their parents 6 months after children's critical illness

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Abstract

Purpose This study aimed to examine health-related quality of life (HRQoL) of children and their parents, 6 months after the child's admission to the Pediatric Intensive Care Unit (PICU). Associations between parents' reports regarding HRQoL of their child and of themselves were investigated, as well as associations between children's baseline variables and their parent-reported HRQoL outcomes.

Methods This is a secondary analysis of cross-sectional data collected in a group of children who participated in the PEPaNIC trial. Six months after discharge from the PICU, parents of critically ill children completed the Infant–Toddler Quality of Life Questionnaire (ITQOL, for age 0–3 years) or the Child Health Questionnaire-Parent Form 50 (CHQ-PF50, for age 4–18 years), which are parallel questionnaires. Parents completed the Short Form Health Survey (SF-12) regarding their own HRQoL. Results were compared with normative data.

Results At 6 months' follow-up, 86 children of the 1343 (6%) had died which resulted in 1257 eligible children. Parents of 576 surviving children (46%) completed the questionnaires. Children of responding parents had less often an acute reason for admission and differed in diagnosis compared with children of non-responders. PICU children scored lower on most ITQOL (n = 390) scales and CHQ-PF50 (n = 186) scales compared with normative data. Parents reported (n = 570) higher scores on the physical ($p < 0.001$) and lower scores on the mental SF-12 scale ($p < 0.001$) compared with normative data. Parents' mental HRQoL correlated with HRQoL they reported for their child (Pearson Correlations range 0.25–0.57, $p < 0.001$–0.002). Shorter length of stay, lower risk of mortality, younger age, and cardiac diagnosis were associated with higher parent-reported HRQoL outcomes for the child.

Conclusions Six months after PICU discharge, critically ill children have lower HRQoL compared with normative data. The mental component of HRQoL is impaired in parents and is associated with lower overall parent-reported HRQoL of their child.

Introduction

Critical illness is known as the dependency on one or more forms of technology to sustain vital functions or the involvement of persistent multiple vital organ system. Children who are critically ill are admitted to a Pediatric Intensive Care Unit (PICU). PICU admissions are highest within the first year of life and respiratory problems are among the most common reasons for admissions at any age.[1] The majority of critically ill children admitted to the PICU recover rapidly with regard to physical functioning.[2] However, a significant proportion is confronted with prolonged consequences that interfere with normal development, such as psychosocial and neurocognitive deficits.[3] The impact of these prolonged consequences on daily life is highly dependent on the individual perception of the patients and their parents. For example, one patient might perceive hearing problems as a burden, but another patient with a similar problem might not feel this is limiting their quality of life. Therefore, patient-reported outcome measures (PROMs) and parent-reports have gained more interest in assessing patients' health.[4] These PROMs give insight in patients' subjective evaluation of their health status. A frequently used PROM is Health-Related Quality of Life (HRQoL), which comprises multiple domains, such as physical, psychological, and social wellbeing. In other words, HRQoL reflects the impact of health on the broad concept of quality of life and provides insight in what the impairments mean for the daily life of the patient.[5,6] Previous studies in PICU survivors showed that critical illness affects HRQoL after discharge, with lower HRQoL scores 1 to 9 months after critical illness than those of healthy children.[7,8]

Young children are not able to reliably evaluate their own HRQoL. Therefore, parents or caregivers usually assess HRQoL of their child, which is called the proxy report. Parents, who are usually the primary caregivers, are thought to have the most reliable information of the child since they are closely involved in the child's life. Previous studies in parents focused on specific psychological symptoms such as post-traumatic stress, depression, and anxiety.[3] However, studies investigating the relationship between parents' own HRQoL on their proxy-reports are scarce.

Previous studies that examined HRQoL in children who were admitted to the PICU used small sample sizes and focused on groups of patients with a specific diagnosis.[9,10] The present study assessed HRQoL for a large, heterogeneous cohort of children aged 0 to 18 years old, 6 months after critical illness and studied the relationship with parents' HRQoL. The heterogeneity of the cohort adds value to the generalizability of the results to the general population of critically ill children. Insight in the subjective health status of the critically ill child after PICU admission could lead to early identification of impairments and prevention of delays in the development of the child.[2] Furthermore, analyzing the characteristics of children who particularly

have an impaired HRQoL makes it possible to determine which children will benefit from follow-up interventions.

The aims of the current study were therefore threefold. The first aim was to examine HRQoL of children and their parents 6 months after critical illness of the child compared to normative data. The hypothesis was to find lower parent-reported HRQoL scores in critically ill children compared with normative data, especially for physical aspects. This is based on the fact that although the majority of children recover rapidly with regard to functional health, a number of children are seriously impaired in physical functioning.[11] Furthermore, higher self-reported HRQoL regarding physical aspects and lower HRQoL regarding mental aspects were expected for parents' HRQoL, based on a previous study that examined parents HRQoL after PICU admission of their child.[12] The second aim was to investigate the relation between parent-reports regarding their own HRQoL and regarding their child. It was hypothesized to find an association between the parent-reported HRQoL of the child and the self-reported quality of life of parents, since reduced parental physical and psychosocial wellbeing predicts poorer functioning of the child.[3] The third aim was to explore which baseline variables are associated with HRQoL outcomes of the child. Younger age and greater severity of illness were expected to be associated with parent-reported HRQoL outcomes of the child.[2] Overall, a lower HRQoL for patients and their parents compared to the general population was expected on this relatively short-term after PICU admission.

Methods

Participants and procedure

This study included critically ill children who participated in the Pediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) randomized controlled trial (RCT). All children (term newborns—18 years old) who were admitted to one of the participating pediatric ICUs (University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children's Hospital, the Netherlands, and Stollery Children's Hospital Edmonton, Canada) were eligible for inclusion in the PEPaNIC RCT if a stay of 24 h or more in the ICU was expected. The extensive trial protocol and medical outcomes of this RCT have been published previously.[13,14] The institutional review board at each of the 3 participating sites approved the protocol (ML8052; NL49708.078; Pro00038098). The PEPaNIC study enrolled 1440 children who were admitted to the PICU. Participating children were randomly assigned to early (within 24 h) or late (not in the first week) supplementation of insufficient enteral nutrition with parenteral nutrition. The current study is a secondary analysis of cross-sectional data collected in a group of children who participated in the PEPaNIC trial.

At inclusion in the PEPaNIC study, parents had given informed consent for inviting them later for participation in a follow-up with HRQoL questionnaires. Due to logistical reasons only data of children from Belgium and The Netherlands were used in the present study. Participation in the original RCT had ended for the children at the moment they were discharged from the PICU. Six months after PICU discharge, all 1343 children included in the PEPaNIC study in Belgium and the Netherlands were screened for survival status via use of hospital notes, National Registers, and/or contact with the general practitioner or referring pediatrician. After this screening, parents of surviving children were sent HRQoL the questionnaires at home or through email. One of the parents completed the questionnaires. It was unclear whether this was the mother or the father. Results of these questionnaires are presented in this paper.

Instruments

Three internationally validated questionnaires with satisfactory psychometric characteristics were used to measure HRQoL. A higher score reflects better HRQoL for all questionnaires. Parents of patients 0–3 years old completed the Infant–Toddler Quality of Life Questionnaire (ITQOL) about HRQoL of their child.[15] The ITQOL consists of 103 items on 12 scales of HRQoL (for a description of the scales see Online Resource 1). Two scales ("General behavior" and "Getting along") are only relevant for parents of children older than 1 year. The ITQOL has a good internal consistency (Cronbach's alpha > 0.70). Test–retest intraclass correlation coefficients were moderate or adequate (≥ 0.50; $p < 0.001$).[16] Parents of patients 4–18 years old completed the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) about HRQoL of their child.[17] The CHQPF50 consists of 50 items on 13 scales of HRQoL (for a description of the scales see Online Resource 1). The internal consistency for the CHQ-PF50 is good, with Cronbach's alpha for Dutch school children ranging from 0.39 to 0.96 for an average of 0.72 for the subscales.[18] The ITQOL and CHQ-PF50 are parallel forms of the same questionnaire, adapted to the age of the child. This means that nine scales of the questionnaires overlap: physical functioning, bodily pain, general behavior, general health perceptions, parental impact: emotional, parental impact: time, family activities, family cohesion, and change in health (for additional scales of the two forms see Online Resource 1, **Tables 2, 3**).

Parents completed the Short Form Health Survey (SF-12) regarding their own HRQoL. The SF-12 is a short version of the SF-36 which has shown to be an adequate reproduction with a lower burden for the responder. The SF-12 consists of 12 items.[19,20] The "Physical Component Summary" (PCS) and the "Mental Component Summary" (MCS) are reported. The internal consistency of the SF-12 is good, with Cronbach's alpha coefficients of 0.72 to 0.89. Test–retest reliability ranged between 0.73 and 0.86.[21]

For the third aim of the study, regarding the variables associated with HRQoL outcomes of the child, baseline characteristics were collected during admission to the PICU. The baseline variables collected during PICU admission were age at admission, gender, reason for admission (urgent or elective), length of stay, PIM2 (pediatric index of mortality), PELOD (pediatric logistic organ dysfunction), and diagnosis (cardiac surgery, surgery other, neurological, medical other). PIM2 and PELOD scores give an indication of severity of illness.

Norm groups

The Dutch version of HRQoL measurements was used in both Belgium and the Netherlands. Results of both groups were compared using Dutch normative data, since available Belgian normative data consisted of small norm groups. The Dutch norm group of the ITQOL included parents of 410 children.[16] For the CHQ-PF50, the norm group consisted of 353 parents of Dutch school-aged children. No Dutch norms are available for the subscale "Change in health" of the CHQ-PF50.[18] For the SF-12, the norm group consisted of 2301 adults from the general Dutch population.[20]

Statistical analysis

Baseline demographics and clinical variables for surviving children with and without follow-up data at 6 months were compared with Mann–Whitney *U* tests (continuous data) or $\chi 2$ tests (discrete data). Baseline continuous demographical and clinical variables were summarized using median and interquartile range (IQR). Discrete variables were summarized as count and percentage. Following the scoring instructions of the instruments, the scale item scores for the ITQOL and CHQ-PF50 were summed and transformed into 0 (worst possible health state) to 100 (best possible health state) scale scores. Some specific items were recoded to ensure that all items were positively scored and that higher scores indicated better health. Items with an "excellent to poor" response continuum were recalibrated to achieve a better linear fit with corresponding scales and to provide a better estimation of equal interval scaling.[22] The SF-12 "Physical Component Summary" and the SF-12 "Mental Component Summary" were transformed into *T*-scores (mean 50, standard deviation 10). The internal consistency of the ITQoL scales, CHQPF50 scales, and SF-12 scales with 2 or more items per scale were calculated with Cronbach's alpha. Chronbach's alphas > 0.70 were considered good. Mean scale scores of the ITQOL, CHQ-PF50, and SF-12 scores were compared with normative data using Student's t tests and were reported as means and standard deviation. Cohen's *d* effect sizes were calculated by determining the mean difference between the two groups and subsequently dividing this difference by the pooled standard deviation. Effect sizes of smaller than 0.5 were considered small, effect sizes between 0.5 and 0.8 were considered medium and effect sizes greater than 0.8 were considered large. The associations between parents' reports regarding HRQoL of their child and of themselves were analyzed using Pearson Correlations. Correlations of lower than 0.30 (positive or negative) were considered weak, correlations between

0.30 and 0.70 (positive or negative) were considered moderate, and higher than 0.70 (positive or negative) were considered strong.

To assess which baseline variables are associated with subscales of parent-reported HRQoL outcomes of the child, overlapping scales of the ITQOL-97 and CHQ-PF50 were combined to have one score on those scales across all ages. In linear regression analyses (univariate analyses), each baseline variable was associated with each overlapping subscale. When the association had a significance of $p < 0.10$, the variable was inserted into the multiple regression analysis. After multiple regression analysis, baseline variables with $p < 0.10$ were included in the final model, and variables with $p \geq 0.10$ were removed (backward elimination procedure). For the association between the remaining variables and the HRQoL subscale, the total explained variance (R2) was calculated.

Results

Baseline characteristics of the critically ill children

Of the total patient population ($N = 1343$), 86 (6%) children had died within 90 days after PICU admission. Parents of 576 surviving children (46%, 278 of the early parenteral nutrition group and 298 of the late parenteral nutrition group) completed the questionnaires (**Figure 1**). Although the original PEPaNIC study is a randomized controlled trial, too many patients did not have follow-up data at 6 months (343 of the early parenteral nutrition group, 338 of the late parenteral nutrition group) to compare randomization groups.

Therefore, the analyses were conducted on the complete group of critically ill children who participated in this short-term follow-up assessment. Children of responding parents had less often an acute reason for admission than an elective reason for admission, and they differed in type of diagnosis, compared with children of non-responders. When children of both age groups were compared (children aged 0–3 years and children aged 4–18 years), differences were found in age, but also in risk of mortality (lower risk in older children) and diagnosis (**Table 1**).

HRQoL of critically ill children 6 months after PICU admission

As to the internal consistency of the instruments in the current sample, the Cronbach's alphas of the ITQoL scales averaged 0.87 (0.74–0.94), those of the CHQ-PF50 scales averaged 0.85 (0.66–0.98), and those of the SF-12 averaged 0.86 (0.75–0.93). Only the CHQ-PF50 scale 'mental health' ($\alpha = 0.66$) had a Cronbach's alpha < 0.70.

Parents of 390 children between 0-3 years old (44%) completed the ITQOL (**Table 2**). HRQoL of PICU children (0–3 years old) was lower compared with normative data on "Physical functioning", "Growth and development", "Bodily pain", "Temperament

and moods", "General health perceptions", "Parental impact" (Emotional and Time), and "Family activities" ($p < 0.001$). Scores were comparable on "General behavior" ($p = 0.130$) and "Getting along" ($p = 0.936$), which were completed only by parents of children older than 1 year. Parent-reported HRQoL of the child was higher than normative data on "Family cohesion" and "Change in health" ($p < 0.001$). Effect sizes were medium to large except for two scales ("Temperament and moods", and "Family cohesion") on which effect sizes were small. Parents of 186 children between 4 and 18 years old (42%) completed the CHQ-PF50 (**Table 2**). Parent-reported HRQoL of these children was lower compared with normative data on all scales, except for "Family cohesion" ($p = 0.898$). Effect sizes were medium to large except for two scales ("General behavior" and "Self-esteem") for which effect sizes were small.

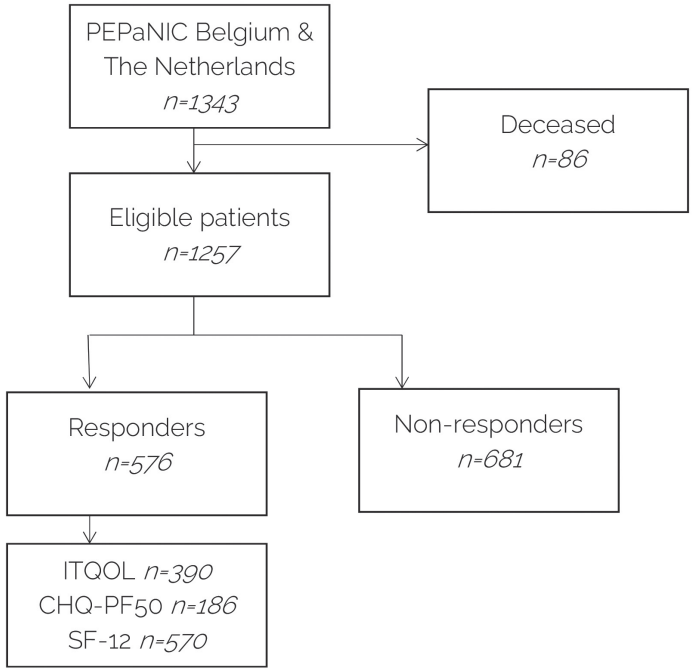

Figure 1. Flowchart of inclusion. ITQOL infant and toddler quality of life questionnaire, CHQ-PF child, health questionnaire-parent form, SF short form health survey

HRQoL of the parents

Parents of 570 children (42%) completed the SF-12 about their own HRQoL. Parents reported significantly higher scores than normative data on the "Physical component summary" of their own HRQoL ($n = 555$, parents of patients 53.7 (SD 7.6) versus norm 50.7 (SD 9.2), $p < 0.001$, Cohen's d 0.35). The effect size was small. Parents scored significantly lower than normative data on the "Mental component summary" of their own HRQoL ($n = 556$, parents of patients 47.2 (SD 12.1) versus norm 50.5 (SD 9.4), $p < 0.001$, Cohen's d .30). Also here, the effect size was small.

Table 1. Baseline characteristics of children from parents who responded and from parents who not responded

Characteristic	Responders (n=576)		Non-responders (n=681)		*p*-value	Children aged 0-3 years (n=390)		Children aged 4-18 years (n=186)		*p*-value
Child characteristics										
Age in years at admission	1.3	(0.2 - 5.6)	1.5	(0.3 - 7.4)	.09	.4	(.09 - 1.5)	8.8	(5.8 - 13.6)	
Gender (male)	330	57.3%	403	59.2%	.50	229	58.7%	101	54.3%	.32
Disease characteristics										
Acute admission	269	46.7%	307	45.1%	.01	187	47.9%	82	44.1%	.39
Length of stay	3.0	(2.0 - 7.0)	4.0	(2.0 - 7.0)	.63	4.0	(2.0 – 7.3)	2.0	(1.0 - 5.0)	.79
PIM2	-3.0	(-3.7 - -1.9)	-2.8	(-3.7 - -1.7)	.31	-2.9	(-3.6 - -1.7)	-3.1	(-3.8 - -2.1)	<.01
PELOD	21.0	(12.0 - 31.0)	21.0	(11.0 - 31.0)	.05	21.0	(12.0 - 31.0)	21.0	(11.0 - 31.0)	.15
Diagnosis					<.01					<.01
Cardiac surgery	264	45.8%	239	35.1%		189	48.5%	75	40.3%	
Surgery other	179	31.1%	222	32.6%		103	26.4%	76	40.9%	
Neurological	30	5.2%	58	8.5%		23	5.9%	7	3.8%	
Medical other	103	17.9%	162	23.8%		75	19.2%	28	15.1%	

Data are presented as number of subjects (%) in the group, except for age, length of stay, PIM2 (Pediatric Index of Mortality 2), and PELOD (Pediatric Logistic Organ Dysfunction) which are presented as median (interquartile range). *p*-values were considered statistically significant with two-tailed *p*-values of less than .05 in which case they are expressed in bold. PIM2 estimates mortalitiy risk (higher score means less probability of mortality, less severe illness), PELOD describes the severity of organ dysfunction (higher score means more severe illness). Diagnostic group was determined by diagnosis at admission and was classified in the following way: cardiac surgery: cardiac surgery, surgery other: abdominal, burns, neurosurgery, thoracic, transplantation, orthopedic surgery-trauma, and other surgery, neurological: medical neurologic, medical other: cardiac medical, gastrointestinal-hepatic, oncologic-hematologic, neurologic, renal, respiratory and medical other.[16]

Table 2. Parent-reported mean scores of Infant Toddler Quality of Life and Child Health Questionnaire – Parent Form 50

	Infant Toddler Quality of Life (ITQOL; 0-3 years)					Child Health Questionnaire – Parent form (CHQ-PF50; 4-18 years)				
Subscale	***n***	**Patients**	**Norm**	***p*-value patients versus norm**	**Effect size Cohen's *d***	***n***	**Patients**	**Norm**	***p*-value patients versus norm**	**Effect size Cohen's *d***
Physical functioning	354	84.8 (22.6)	97.2 (9.8)	<.01	.71	181	73.9 (32.5)	99.1 (4.3)	<.01	1.08
Growth and development	390	79.5 (15.7)	86.5 (10.6)	<.01	.52					
Bodily pain	389	72.8 (22.6)	83.8 (16.8)	<.01	.55	183	71.5 (25.4)	85.7 (17.2)	<.01	.65
Temperament and moods	386	74.8 (12.8)	77.2 (10.5)	<.01	.20					
General behavior*	159	74.6 (15.1)	72.8 (12.7)	.13	.12	181	75.2 (15.1)	78.5 (13.1)	<.01	.23
Getting along*	158	71.5 (10.2)	71.4 (8.8)	.94	.01					
General health perceptions	386	51.3 (20.4)	79.0 (14.5)	<.01	1.56	183	51.3 (24.6)	82.9 (13.4)	<.01	1.59
Parental impact: emotional	387	80.9 (19.9)	92.1(10.5)	<.01	.70	184	62.5 (30.6)	86.3 (15.2)	<.01	.98
Parental impact: time	386	80.8 (21.0)	93.0 (11.0)	<.01	.72	184	73.6 (31.2)	94.0 (13.0)	<.01	.85
Family activities	385	71.2 (24.6)	86.2 (13.5)	<.01	.75	183	72.5 (25.9)	91.5 (11.9)	<.01	.94
Family cohesion	385	79.1 (17.9)	75.3 (18.8)	<.01	.20	183	72.4 (21.6)	72.2 (19.4)	.90	.009
Change in health*	119	70.0 (30.5)	56.1 (18.4)	<.01	.55					
Role functioning emotional/behavioral						179	79.0 (33.8)	97.9 (7.2)	<.01	.77
Role functioning physical						175	71.0 (37.3)	95.8 (15.6)	<.01	.86
Mental health						181	73.0 (14.3)	81.4 (12.1)	<.01	.63
Self-esteem						175	73.2 (17.7)	79.2 (11.0)	<.01	.40

Data are presented as means (standard deviation). A higher score represents a better HRQoL (0 is worst possible health state, 100 is best possible health state). *p*-values were considered statistically significant with two-tailed *p*-values of less than .05 in which case they are expressed in bold. Cohen's *d* effect sizes of <.5 were considered small, <.8 medium and >.8 large. * Scales are only applicable to children aged 1 year or older. For a description of the subscales see Online Resource 1. "Change in health" was assessed in the CHQ-PF 50 as well, but no Dutch normative data are available which explains why this scale was not analyzed. Some parents did not complete all questions of a scale which resulted in differences between sample sizes on the subscales.

Associations between HRQoL of the parents and that of their children

No significant correlations were found between the self-reported SF-12 "Physical component summary" and the scales of the parent-reported ITQOL and CHQ-PF50 regarding the child's HRQoL, except for "Physical functioning" (ITQOL, Pearson Correlation 0.12, $p = 0.028$) and "Bodily pain" (CHQ-PF50, Pearson Correlation .18, $p = 0.021$) (**Table 3**). The self-reported SF-12 "Mental component summary" significantly correlated with all scales of the parent-reported ITQOL and CHQ-PF50 regarding the child's HRQoL (Pearson Correlations ranges 0.25–0.57, $p < 0.001$–0.002) (**Table 3**). These correlations are all positive, which means that when the score on the self-reported SF-12 "Mental component summary" was higher, scores on scales of the parent-reported ITQOL and CHQ-PF50 for the child were also higher. Regarding the strengths of the correlations, most scales of the child's HRQoL were moderately correlated to the mental component of parents HRQoL (**Table 3**).

Baseline PICU variables associated with 6 months' HRQoL of the child

Baseline variables during PICU stay explained the most variance in the following scales (ranging from 12 to 26%): parent-reported physical functioning of the child, change in health of the child, and parental impact emotional, compared with the other six parent-reported HRQoL scales of the child (explained variances lower than 10%) (Online Resource 2 and **Table 4**). Higher age at admission of the child, longer length of PICU stay, a higher PIM2 score (higher risk of mortality), and other diagnoses than cardiac surgery were associated with worse scores for children on parent-reported physical functioning, change in health, and parental impact emotional. Overall as to diagnosis, parents of children with cardiac surgery reported the most favorable scores and parents of children with a neurological diagnosis reported the lowest scores on physical functioning, change in health, and parental impact emotional.

Table 3. Correlations between parent-reported quality of life in children (ITQOL; 0-3 years and CHQ-PF50; 4-18 years) and their own quality of life (SF-12)

	ITQoL				**CHQ-PF50**			
	SF-12 Physical component summary		**SF-12 Mental component summary**		**SF-12 Physical component summary**		**SF-12 Mental component summary**	
Subscale	**Pearson correlation**	***p*-value**	**Pearson correlation**	***p*-value**	**Pearson correlation**	***p*-value**	**Pearson correlation**	***p*-value**
Physical functioning	.12	.028	.29	<.01	.06	.455	.32	<.01
Growth and development	.02	.635	.41	<.01				
Bodily pain	.02	.665	.37	<.01	.18	.021	.25	<.01
Temperament and moods	.07	.192	.37	<.01				
General behavior	.14	.083	.25	<.01	.06	.417	.28	<.01
Getting along	.11	.174	.27	<.01				
General health perceptions	.04	.498	.54	<.01	.13	.089	.36	<.01
Parental impact emotional	.03	.566	.50	<.01	.09	.221	.53	<.01
Parental impact time	.05	.309	.50	<.01	.12	.117	.50	<.01
Family activities	-.004	.933	.57	<.01	.12	.102	.54	<.01
Family cohesion	-.02	.744	.31	<.01	.11	.145	.36	<.01
Change in health	-.13	.181	.35	<.01	.06	.402	.27	<.01
Role functioning emotional/behavior					.15	.050	.39	<.01
Role functioning physical					.02	.833	.42	<.01
Mental health					.11	.154	.43	<.01
Self-esteem					.03	.709	.39	<.01

Correlations were considered statistically significant with two-tailed *p*-values lower than .05 (expressed in bold).

No significant correlations were found between the self-reported SF-12 "Physical component summary" and the scales of the parent-reported ITQOL and CHQ-PF50 regarding the child's HRQoL, except for "Physical functioning" (ITQOL, Pearson Correlation 0.12, p = 0.028) and "Bodily pain" (CHQ-PF50, Pearson Correlation .18, p = 0.021) (**Table 3**). The self-reported SF-12 "Mental component summary" significantly correlated with all scales of the parent-reported ITQOL and CHQ-PF50 regarding the child's HRQoL (Pearson Correlations ranges 0.25–0.57, $p < 0.001$–0.002) (**Table 3**). These correlations are all positive, which means that when the score on the self-reported SF-12 "Mental component summary" was higher, scores on scales of the parent-reported ITQOL and CHQ-PF50 for the child were also higher. Regarding the strengths of the correlations, most scales of the child's HRQoL were moderately correlated to the mental component of parents HRQoL (**Table 3**).

Baseline PICU variables associated with 6 months' HRQoL of the child

Baseline variables during PICU stay explained the most variance in the following scales (ranging from 12 to 26%): parent-reported physical functioning of the child, change in health of the child, and parental impact emotional, compared with the other six parent-reported HRQoL scales of the child (explained variances lower than 10%) (Online Resource 2 and **Table 4**). Higher age at admission of the child, longer length of PICU stay, a higher PIM2 score (higher risk of mortality), and other diagnoses than cardiac surgery were associated with worse scores for children on parent-reported physical functioning, change in health, and parental impact emotional. Overall as to diagnosis, parents of children with cardiac surgery reported the most favorable scores and parents of children with a neurological diagnosis reported the lowest scores on physical functioning, change in health, and parental impact emotional.

Table 4. Final model results of baseline characteristics associated with overlapping scales of the Infant Toddler Quality of Life Questionnaire (ITQOL) and Child Health Questionnaire – Parent Form 50 (CHQ-PF50)

Subscale	*n*	Constant	Unstandardized β	SE	Standardized β	*p*-value	Multiple R^2
Impact on the child							
Physical functioning	535						
Age at admission in years		83.02	-1.13	.23	-.20	<.01	.12
Length of stay			-.33	.12	-.12	<.01	
PIM2			-3.10	.83	-.17	<.01	
Diagnosis – surgery other[a]			-9.66	2.66	-.17	<.01	
Diagnosis- neurological[a]			-15.66	5.04	-.13	<.01	
Diagnosis – medical other[a]			-1.67	3.10	-.02	.59	
Bodily pain	572						
Length of stay		69.47	-.34	.11	-.14	<.01	.05
PIM2			-1.86	.68	-.12	.01	
General behavior							
Diagnosis – surgery other[a]		75.01	-.00	1.86	.00	.99	.02

Table 4. Final model results of baseline characteristics associated with overlapping scales of the Infant Toddler Quality of Life Questionnaire (ITQOL) and Child Health Questionnaire – Parent Form 50 (CHQ-PF50)

Subscale	*n*	Constant	Unstandardized β	SE	Standardized β	*p*-value	Multiple R^2
Diagnosis- neurological[a]			-7.26	3.67	-.11	.05	
Diagnosis – medical other[a]			1.87	2.34	.05	.42	
General health perceptions	569						
Length of stay		49.87	-.27	.10	-.12	<.01	.06
PIM2			-1.75	.67	-.12	<.01	
Diagnosis – surgery other[a]			-1.00	2.15	-.02	.64	
Diagnosis- neurological[a]			-6.02	4.16	-.06	.15	
Diagnosis - medical other[a]			-5.72	2.52	-.10	.02	
Change in health	300						
Age at admission in years		89.85	-1.12	.37	-.16	<.01	.26
Reason for admission[b]			-13.43	5.36	-.19	.01	
Length of stay			-.43	.18	-.12	.02	
Diagnosis – surgery other[a]			-16.39	4.72	-.23	<.01	
Diagnosis – neurological[a]			-23.62	9.18	-.16	.01	
Diagnosis – medical other[a]			-20.92	7.05	-.23	<.01	
Impact on the family							
Parental impact emotional	571						
Age at admission in years		81.35	-1.78	.21	-.33	<.01	.18
Length of stay			-.23	.11	-.09	.03	
PIM2			-2.14	.73	-.13	<.01	
Diagnosis – surgery other[a]			-10.11	2.37	-.18	<.01	
Diagnosis – neurological[a]			-11.95	4.60	-.10	.01	
Diagnosis – medical other[a]			-3.36	2.74	-.05	.22	
Parental impact time	570						
Age at admission in years		75.30	-.85	.22	-.16	<.01	.09
Gender[c]			4.53	2.05	.09	.03	
PIM2			-3.01	.76	-.18	<.01	
Diagnosis – surgery other[a]			-8.87	2.46	-.16	<.01	
Diagnosis – neurological[a]			-9.73	4.86	-.08	.05	
Diagnosis – medical other[a]			.20	2.84	.00	.95	
Family cohesion	568						
Age at admission in years		79.97	-.83	.17	-.20	<.01	.04
Family activity	568						
Length of stay		69.75	-.36	.11	-.14	<.01	.04
PIM2			-1.53	.73	-.09	.04	

a Reference category is diagnosis cardiac surgery
b Elective = 0, acute = 1
c Male = 0, female = 1

Discussion

Overall, HRQoL of children 6 months after critical illness, as reported by parents, appeared to be lower than that of healthy peers of the general population. With regard to parents' own HRQoL, parents reported higher scores on physical aspects of HRQoL and lower scores on mental aspects of HRQoL compared with adults from the general population. Furthermore, parents' own mental HRQoL showed positive associations with scales of HRQoL that they reported for their child.

In line with previous research, parent-reported HRQoL of children in the short-term after critical illness was lower compared with healthy children.[7,8] In the current study, most domains were impaired in PICU survivors as reported by the parent. However, on a few scales PICU survivors scored comparable or even better than healthy children. One of these scales is the family cohesion, indicating that the relationships between family members did not seem to be impaired. Therefore, although critical illness of a child impacts the emotional state of each family member,[23] it does not seem to impact the bonds within the family. Moreover, it may even strengthen bonds as is reflected in results of the ITQOL in the current study. This might probably be due to enhanced awareness of the value of these relationships in burdensome times, shortly after critical illness of the child. This could be a result of a response shift, in which parents value certain aspects of life more as a consequence of the difficult situation they are in.[3,24] It has also been reported that strengths of attachment within the family increase in the short-term after PICU admission of a child.[23]

With regard to behavioral aspects of HRQoL, parents of older PICU survivors (4–18 years) reported worse scores for their children compared to healthy peers on the subscale 'general behavior'. This is in contrast with a study that used the same questionnaire and that examined HRQoL in school aged children 10 years after admission to the PICU for meningococcal disease.[12] Children did not show significant differences with normative data on the subscale 'general behavior' in this study. Possibly, the longer follow-up interval compared to the current study caused the differences between the two studies. This suggests that children on the short-term have to adjust their behavior, but show behavior that is similar to their peers on the longer term.

The role of parents' own HRQoL in their reports of HRQoL of their children

Parents reported that their own HRQoL with regard to physical aspects was better than that of adults from the general population. In a previous study, parents reported that the PICU admission of their child made them appreciate life more fully.[12] Especially when parents have seen the possible poor physical health state a person can be in, their internal standards of physical health may change. This is called a response shift.[12]

With regard to mental aspects of HRQoL, parents reported worse HRQoL for themselves compared with adults from the general population. This appears to reflect the psychosocial burden of critical illness of their child and is in line with previous studies.[3,25] These psychosocial symptoms are common among parents of children previously admitted to the PICU.[26,27] In the short-term, 6 months after admission, parents have to adjust to the psychosocial burden they experienced due to the critical illness in their child.

Parents' own mental HRQoL was positively correlated to the HRQoL they report for their child. This means that when parents' mental HRQoL is better, parent-reported HRQoL of the child is also better. The association between parent-reported HRQoL of children and self-reported HRQoL of parents themselves might be explained by the fact that family characteristics influence children's HRQoL.[3] When parents experience impairments in their mental health as an effect of the PICU admission of their child, this will influence the way the family is functioning. Since the child is dependent on the parents for physical, emotional. and social needs, their HRQoL will be lower as well.[3] However, the found association between the HRQoL of the child and the HRQoL of the parents could also be reflection of the distress that parents experience.[24] This might also explain why parents in previous studies report more problems than the child regarding the child's health status.[28] The phenomenon of these differences between parent-reports and self-reports of the child's HRQoL is called the proxy-problem and has been extensively studied.[29]

Variables during PICU stay associated with HRQoL outcomes

Parents of children who were admitted to the PICU report worse scores for physical functioning and change in health of their child when the child had a higher age at admission, had a longer length of stay and had a more severe illness. Furthermore, when the diagnosis of the child was related to a cardiac surgery, parent-reported physical functioning and change of health was higher for the child. With regard to the emotional impact on the parent we found the same variables that were associated with lower HRQoL outcomes of the child. The associations between length of stay and severity of illness with parent-reported HRQoL of the child are in line with results that have been found in previous reviews.[2,23,30] Age and diagnosis are relatively less studied in these reviews. However, it should be noted that the sample size of children with a neurological condition in the current study was relatively low, which could have influenced the results.

Implications

Considering the impaired HRQoL of children a few months after PICU admission, identifying children most at risk by asking parents to complete HRQoL questionnaires should be part of the follow-up care to intervene early and to prevent problems on the longer term. The self-reported mental wellbeing of parents, which was associated

with their reports on HRQoL outcomes for children, suggests that the focus of follow-up interventions might have to involve the entire family. Furthermore, HRQoL outcomes of critically ill children and the impact of parents' own perceived HRQoL in the longer term after critical illness of the child could be investigated. A study that examined the longer term in the most critically ill children (who needed a prolonged PICU stay) with a mean follow-up of 6 years showed that although some children recover from the HRQoL impairments, almost half of the children were at risk for impaired HRQoL on the longer term,[31] what suggests that research into children who experience impaired HRQoL on the longer term is necessary. Lastly, since a higher age at admission, a longer length of PICU stay, a more severe illness, and another diagnosis than cardiac diagnosis were associated with lower HRQoL of the child, children and parents with these characteristics are of special attention in follow-up programs.

Limitations and strengths

Our study has some limitations that need to be addressed. First, despite the large sample size, the response rate was relatively low. However, other follow-up studies that examined HRQoL on the short-term after critical illness showed similar response rates.[7,32] Due to the relatively low response rates, we decided not to analyze the effects of the RCT, which is a shortcoming of the study as well since withholding parenteral nutrition during the first week of critical illness might have influenced the HRQoL outcomes in a beneficial way as the short-term medical outcomes were positive as well.[13] Another limitation of this study is that no self-reports of children regarding their own HRQoL were reported. Although proxy-reports are valuable instruments since parents are so closely involved in the child's life,[24] some scales are subjective and might be hard to observe by the parents,[29] such as mental health and self-esteem. However, only 12% of the children in our sample was old enough (12 years or older) to be able to report their own HRQoL with the self-report version of the questionnaire. Therefore, proxy reports were unavoidable. Nevertheless, the current results should be interpreted from the perspective of the parent, and therefore with caution. Furthermore, children of responding parents differed in emergency of admission and diagnosis, compared with children of non-responding parents. Lastly, all data of Dutch and Belgian children and parents were compared to Dutch normative data. Differences might exist between the Dutch and Belgian general population. The Dutch normative data show little differences compared to the sample of children in the current study regarding gender (ITQOL norm data 50% girls,[16] study sample 41% girls, CHQ-PF50 norm data 54% girls,[18] study sample 46% girls) and age (ITQOL norm data mean 2.1 years,[16] study sample mean 0.9 years, CHQPF50 norm data mean 8.8 years,[18] study sample mean 9.5 years). In the current sample there are a bit more girls and the children were a little younger. The sample-based internal consistency of the HRQoL instruments used were satisfying and were comparable or even better

than the internal consistency as reported for the normative groups in the concerning manuals. However, the current results should be generalized with caution.

A strength of the current study is that this study is unique in its sample size, which is much larger than most studies on HRQoL of PICU survivors. The added value of this study is that it not only examined HRQoL of children and parents after PICU admission, but also investigated the relation between parent-reports regarding their own HRQoL and regarding their child.

Conclusion

HRQoL seems to be important in evaluating the health status of critically ill children and is usually reported by parents. Six months after discharge from the PICU this HRQoL of the child is lower compared with healthy children from the general population. The current study suggests that parents' own physical health after PICU admission of their child is better than that of the general population of adults, but that their mental HRQoL is lower. These lower scores on mental health of parents seem to be associated with lower HRQoL they report for their children. Therefore, parents should also be targeted in follow-up care for PICU survivors, but more research on this parental role is needed.

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Appendix Chapter 3

Online resource 1

Table 1. ITQOL scales and score interpretation *

Scale	Description low score	Description high score
Physical functioning (PF)	Child is considerably limited in performing physical activities such as eating, sleeping, grasping, and playing due to health problems	Child performs all types of physical activities such as eating, sleeping, grasping, and playing without limitations due to health problems
Growth and development (GD)	Parent is very dissatisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament	Parent is very satisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament
Bodily pain (BP)	Child has extremely severe, frequent and limiting bodily pain/discomfort	Child has no pain or limitations due to pain/discomfort
Temperament and moods (TM)	Child very often has certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness	Child never has certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness
General behavior (BE)	Parent believes child's behavior is poor and likely to get worse	Parent believes child's behavior is excellent and will continue as such
Getting along (GA)	Child very often exhibits behavioral problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behavior, such as ability to cooperate, to appear sorry, and to adjust to new situations is seldom shown	Child never exhibits behavioral problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behavior, such as ability to cooperate, to appear sorry, and to adjust to new situations is frequently shown
General health perceptions (GH)	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue as such
Parental impact: emotional (PE)	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development
Parental impact: time (PT)	Parent experiences a lot of limitations in time avail-able for personal needs due to child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience limitations in time avail-able for personal needs due to child's physical and/or psychosocial health and/or growth and development
Family activities (FA)	The child's health and/or growth and development very often limits and interrupts family activities or is a source of family tension	The child's health and/or growth and development never limits and interrupts family activities or is a source of family tension
Family cohesion (FC)	Family's ability to get along is rated as 'poor'	Family's ability to get along is rated as 'excellent'
Change in health (CH)	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

* Cited by "The CHQ user's manual" [1]

Table 2. CHQ-PF50 supplementary scales of the CHQ-PF50 and score interpretation *

Scale	Description low score	Description high score
Role functioning: Emotional / Behavior (REB)	Child is limited a lot in school work or activities with friends as a result of emotional or behavior problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavior problems
Role functioning: Physical (RF)	Child is limited a lot in school work or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Mental health (MH)	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self-esteem (SE)	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall

* Cited by "The CHQ user's manual": Landgraf JM, Abetz L, Ware JE. Child health questionnaire (CHQ) : a user's manual. Boston, Mass.: Landgraf & Ware; 1999.

Online Resource 2

Table 2. Associations between baseline characteristics and overlapping scales of the Infant Toddler Quality of Life Questionnaire (ITQOL) and Child Health Questionnaire – Parent Form 50 (CHQ-PF50); standardized coefficients b

Subscale	*n*	Age at admission in years	Gender[a]	Reason for admission[b]	Length of stay	PIM2	PELOD	Diagnosis		
								Surgery other[c]	Neurological[c]	Medical other[c]
Physical functioning	535	-.21*	.06	-.002	-.18*	-.15*	.02	-.12*	-.10*	-.00
Bodily pain	572	-.01	.03	-.02	-.18*	-.17*	-.06	-.02	-.04	-.08*
General behavior	340	.08	-.002	.02	.07	-.06	-.03	.00	-.12*	.06
General health perceptions	569	-.02	.001	.02	-.17*	-.18*	-.02	.06	-.05	-.14*
Change in health	300	-.20*	.03	-.42*	-.23*	-.11*	.14*	-.17*	-.14*	-.25*
Parental impact emotional	571	-.35*	.01	-.07*	-.13*	-.08*	.007	-.17*	-.07*	-.01
Parental impact time	570	-.17*	.08*	-.05	-.11*	-.12*	-.02	-.12*	-.06	.02
Family cohesion	568	-.20*	-.02	.01	-.05	-.01	-.01	-.02	-.03	-.02
Family activity	568	.01	.05	-.02	-.17*	-.14*	-.03	-.03	-.06	-.06

a Male = 0, female = 1
b Elective = 0, acute = 1
c Reference category is diagnosis cardiac surgery
* $p < .10$, and thus included in the multiple regression analysis

CHAPTER 4

Long-term developmental effects of withholding parenteral nutrition for 1 week in the pediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomized, controlled trial

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Abstract

Background The Pediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicenter, randomized, controlled trial showed that compared with early parenteral nutrition (Early PN), withholding supplemental parenteral nutrition for 1 week in the pediatric intensive care unit (PICU; Late PN) reduced infections and accelerated recovery from critical illness in children. We aimed to investigate the long-term impact on physical and neurocognitive development of early versus late parenteral nutrition (PN).

Methods In this preplanned 2-year follow-up study, all patients included in the PEPaNIC trial (which was done in University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada) were approached for possible assessment of physical and neurocognitive development compared with healthy children who were matched for age and sex, and who had never been admitted to a neonatal ICU or a PICU. Assessed outcomes comprised anthropometric data; health status; parent/caregiver-reported executive functions, and emotional and behavioral problems; and tests for intelligence, visual-motor integration, alertness, motor coordination, inhibitory control, cognitive flexibility, and memory. To address partial responses among the children tested, we did multiple data imputation by chained equations before univariable and multivariable linear and logistic regression analyses adjusted for risk factors.

Findings At the 2-years follow-up, 60 (8%) of 717 children who received Late PN and 63 (9%) of 723 children who received Early PN had died (p=0.81). 68 (9%) of 717 children who received Late PN and 91 (13%) of 723 children who received Early PN were too disabled for neurocognitive assessment (p=0.059), and 786 patients (395 assigned to Late PN and 391 assigned to Early PN) consented for testing. 786 patients and 405 healthy control children underwent long-term outcomes testing between August 4, 2014, and January 19, 2018, and were included in the imputation model for subsequent multivariable analyses. Late PN did not adversely affect anthropometric data, health status, or neurological functioning, and improved parent/caregiver-reported executive functioning (Late PN vs Early PN β estimate −2.258, 95% CI −4.012 to −0.504; p=0.011), more specifically inhibition (−3.422, −5.171 to −1.673; p=0.0001), working memory (−2.016, −3.761 to −0.270; p=0.023), and meta-cognition (−1.957, −3.694 to −0.220; p=0.027). Externalizing behavioral problems (β estimate −1.715, 95% CI −3.325 to −0.106; p=0.036) and visual-motor integration (0.468, 0.087 to 0.850; p=0.016) were also improved in the Late PN group compared with the Early PN group. After Bonferroni correction for multiple comparisons, the effect on inhibitory control remained significant (p=0.0001).

Interpretation Withholding Early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status, and neurocognitive development, and improved inhibitory control 2 years after PICU admission.

Introduction

The Pediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicenter, randomized, controlled trial revealed that withholding parenteral nutrition (PN) for up to 1 week in the pediatric intensive care unit (PICU), when enteral nutrition (EN) was insufficient, was clinically superior to providing full nutrition up to caloric targets with supplemental PN.[18] Indeed, not giving PN during the first week in PICU and thus, in most patients, accepting low caloric and macronutrient intake reduced the incidence of new infections and accelerated recovery.[18] Despite these short-term clinical benefits, concerns have been raised about potential adverse long-term consequences of low caloric and macronutrient intake for the patients' length, bodyweight, head circumference, health status and neurocognitive development.[75,166] To evaluate long-term value for patients, patient-reported outcomes or rather, in case of children, parent/caregiver-reported outcomes should also be investigated.[167] Any such adverse patient-centered long-term consequences would discourage withholding PN early in the course of pediatric critical illness. Children who have been treated in the PICU tend to have adverse long-term developmental and neurocognitive outcomes.[168] In view of the potential benefits of fasting-induced responses for removal of cell damage and prevention of neurodegeneration,[169,170] we hypothesized that withholding PN early during the course of critical illness in children could also bring about beneficial effects in the long term, in particular for neurocognitive development.

We aimed to investigate whether withholding supplemental PN during the first week in PICU, rather than giving PN to reach nutritional targets as soon as possible, while adequately providing micronutrients, has an impact on survival, health status, and anthropometrics, clinically assessed neurological function, and parent/caregiver-reported and clinically tested neurocognitive outcomes at the 2-year follow-up, compared with matched healthy children.

Methods

Study design and participants

This study is the preplanned 2-year follow-up of the PEPaNIC trial, in which 1440 critically ill children admitted to the participating PICUs (University Hospitals Leuven, Belgium; Erasmus-MC Sophia Children's Hospital, Rotterdam, Netherlands; Stollery Children's Hospital, Edmonton, AB, Canada) had been enrolled between 2012 and 2015. The full study protocol and acute outcome results have been published.[18,129]

Parents or legal guardians had provided written informed consent on admission to the PICU to contact them for long-term follow-up testing of their child. Survival status was determined by assessment of hospital notes, national registers, or contact with

the general practitioner or referring pediatrician. All PICU survivors and their parents or caregivers were first sent a standardized patient information letter. Subsequently, they were contacted by phone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment. Participating patients (see appendix) were assessed either at the hospital or at home; the latter was offered whenever parents or caregivers considered the burden of coming to the hospital too high. Neonates and infants enrolled in the PEPaNIC trial were assessed at the age of 2.5 years because the youngest appropriate age for parent/caregiver-reported executive functioning (with the Behavior Rating Inventory of Executive Function [BRIEF] and a general intelligence test, Wechsler Preschool and Primary Scale of Intelligence [WPPSI]) is 2.5 years.

405 healthy control children were recruited for a medical and neurocognitive assessment similar to that of the PEPaNIC patients. These children were demographically matched to the patients for age and sex. To control as much as possible for genetic, socioeconomic, and environmental background, siblings and relatives of the patients were preferably recruited into this control group besides unrelated children recruited from the same geographical area. Exclusion criteria for the control group were previous admission to a neonatal ICU or a PICU, or hospital admission for at least 7 days with need for an intravenous line, history of suspicious or established inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and history of short bowel syndrome on home PN or other conditions that require home PN.

Written informed consent was obtained from the parents or legal guardians or from the adolescent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098). The protocol is available online.

Procedures, randomization and masking

In the PEPaNIC trial,[18] after having obtained consent, children who were admitted to the PICU were randomly allocated (1:1) to receive Early PN, which was initiating PN within 24 hours of PICU admission to supplement EN whenever 80% of targeted calories per age and bodyweight categories was not reached, or Late PN. Late PN meant that, for up to 1 week, patients received a mixture of glucose 5% and sodium chloride 0.9% without other forms of PN (lipid or protein infusions) being administered, corresponding to no PN in the majority of children. After 1 week, for both groups equally, PN could be administered if necessary. When EN covered 80% or more of calculated targets, supplemental PN was discontinued. Total macronutrient doses administered on each of the first 7 days in PICU are shown in the appendix. EN was initiated early for both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors were physicians and experienced pediatric psychologists who had not been involved in the management of the patients during their stay in the PICU and who were strictly blinded for the randomized allocation to either Late PN or Early PN. Parents had not been masked during the time the child was treated in the PICU and were not actively informed about the initial PEPaNIC study results.

Outcomes

In this 2-year follow-up study, the primary outcomes assessed were growth, physical ability, health status, and clinical, neurological, and neurocognitive outcomes. Death and severe disability precluding neurocognitive testing were a priori defined as safety endpoints. Neurocognitive testability was determined by screening of the medical file or clinical judgment, before the start of the neurocognitive assessment, by the physician or psychologist and confirmed by the parents or caregivers.

For children who were examined at follow-up, head circumferences, bodyweights, and heights were measured. A clinical neurological examination was done to assess gross neurological abnormalities. A structured interview with the parents or caregivers assessed whether the child had been diagnosed with a somatic or psychiatric illness, or had been admitted to a hospital for medical or surgical reasons during the preceding 2 years for healthy control children and during the 2 years following the index PICU admission for patients.

Validated, internationally recognized questionnaires and clinical tests with adequate normative data were used to score performance for a broad range of neurocognitive functions.[20] Patient-reported outcome questionnaires were completed by parents or caregivers. They reported executive functioning in their child with the BRIEF preschool version for children aged 2.5-5 years or BRIEF for patients aged 6-18 years. Overlapping scales of both questionnaires (inhibition, flexibility, emotional control, working memory, and planning and organization), the overlapping index (meta-cognition, comprising the scales working memory and planning and organization), and the total score were reported (T scores, with mean 50 [SD 10]).[171,172] Parents or caregivers completed the Child Behavior Checklist (CBCL 1.5–5 years or CBCL 6–18 years)[173,174] to assess emotional and behavioral problems. Internalizing, externalizing, and total problems were analyzed (T scores, with mean 50 [SD 10]).[173,174]

Clinical tests were used to evaluate neurocognitive functions. General intellectual ability was assessed with use of age-appropriate versions of the Wechsler intelligence quotient (IQ). WPPSI-III-NL[175] was used for children aged between 2.5 years and 5 years 11 months, the Wechsler Intelligence Scale for Children (WISC-III-NL)[176] was used for children aged between 6 years and 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[177] for adolescents or young adults who were 17 years or older. For all of these tests, total IQ, verbal IQ, and performance IQ scores (test

mean 100 [SD 15]) were computed. The Beery Developmental Test of Visual–Motor Integration[178] was used for children aged 2.5 years and older to assess the ability to integrate visual and motor functions (total scaled score, with test mean 10 [SD 3]). The validated computerized Amsterdam Neuropsychological Tasks (ANT) program was used to measure attention, motor coordination, and executive functions in children aged 4 years or older.[179] ANT-Baseline Speed was used to evaluate alertness (reaction time and SD), ANT-Tapping to assess motor coordination (number of taps), and Response Organization Objects to measure inhibitory control and cognitive flexibility (differences in reaction time and in number of errors between tests of increasing demand). Memory was assessed with use of 4 tests from the Children's Memory Scale (CMS) for children aged between 5 years and 16 years 11 months.[180] CMS-Numbers assessed short-term verbal memory span and verbal working memory load (scaled score, with test mean 10 [SD 3]). The CMS-Word Pairs assessed short-term and long-term verbal memory, and recognition; CMS-Picture Locations assessed immediate visual memory; and CMS-Dot Locations assessed immediate and delayed visual memory (proportion of correct responses, ranging from 0 to 1). The CMS-Learning index represents learning abilities of the child (standard score, with mean 100 [SD 15]). The extended description of the parent/caregiver-reported outcome questionnaires and of the clinical and neuropsychological test battery is available in the appendix.

Statistical analysis

After taking into account estimations for the safety endpoints (death and severe disability precluding neurocognitive testing), we estimated that about 30% of the patients among the critically ill patients who had been included in the PEPaNIC trial and who were alive and testable at the 2-year follow-up would be lost to follow-up, on the basis of earlier experience.[20] We calculated that such a sample size had >80% power to detect, with a certainty of >95%, clinically relevant differences between the 2 randomization arms, in the same order of magnitude as those we had previously documented with blood glucose control in the PICU.[20] For the healthy control group, we calculated that with a sample size of 405 children, we would be able to detect, with a power of >80% and certainty of >95%, outcome differences between patients and healthy children of the same order of magnitude as those previously documented.[20]

The inability to fully complete any of the neurocognitive tests would introduce bias in univariable analyses of these test results, because this in itself might suggest poor function. Hence, to correctly address partial responses, multiple data imputation by chained equations was required,[181] with use of all available data per individual (see appendix). For tests validated for a specific age range (alertness, motor coordination, inhibitory control and flexibility in children aged 4 years or older, and memory in children who are between 5 and 16 years old), we imputed data within these age ranges only. To avoid bias and instability in this imputation model, the percentage of missing data per variable could not exceed 30%[181] and to minimize loss of statistical

power, the number of iterative imputations was set at 31.[181] Comparison of the observed and imputed values and the imputation predictor are shown in the appendix.

To analyze the differences in outcomes between PEPaNIC participants and healthy control children, and to investigate the long-term outcome differences between patients randomly allocated to Late PN or Early PN during PICU stay, we did multivariable linear and logistic regression analyses on the 31 imputed datasets with the β estimates or odds ratios reported as pooled results, preceded by a pooled univariable comparison with use of Fisher's exact test, Student's *t* test, or Wilcoxon rank-sum test as appropriate (see appendix). All multivariable analyses were adjusted for the following risk factors: age, center, race,[182] sex, geographic origin,[182] language, hand preference, history of malignancy, diabetes, a predefined syndrome (see appendix), and the educational and occupational status of parents (see appendix). For the comparison between Late PN and Early PN groups, further adjustment was done for diagnosis and severity of illness (with the Pediatric Index of Mortality 3 and pediatric logistic organ dysfunction scores) on PICU admission, risk of malnutrition, and parental smoking behavior before PICU admission. We calculated *p*-values for interaction between age group and randomization to assess whether patients who were infants (aged <1 years) at randomization behaved differently from older children.

We did explanatory statistical analyses with further adjustment to investigate whether any eventual impact of Late PN versus Early PN on the long-term outcomes might have been mediated by its acute effects on new PICU infections and duration of PICU stay, and thus possibly indirectly also number of post-randomization hypoglycemic events or the duration of post-randomization treatments such as mechanical ventilatory support, hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics, and α2-agonists. Data are presented as β estimates and odds ratios with 95% CIs, means and SDs, or numbers and proportions, as appropriate. Statistical analyses were done with R version 3.4.3, MICE version 2.46.0, and JMP version 13.0.0. Two-sided *p*-values of 0.05 or less were considered statistically significant. Bonferroni corrections for the multiple comparisons (n=45) were done as a sensitivity analysis, which altered the required level of *p*-value for significance to 0.001 or less.

Results

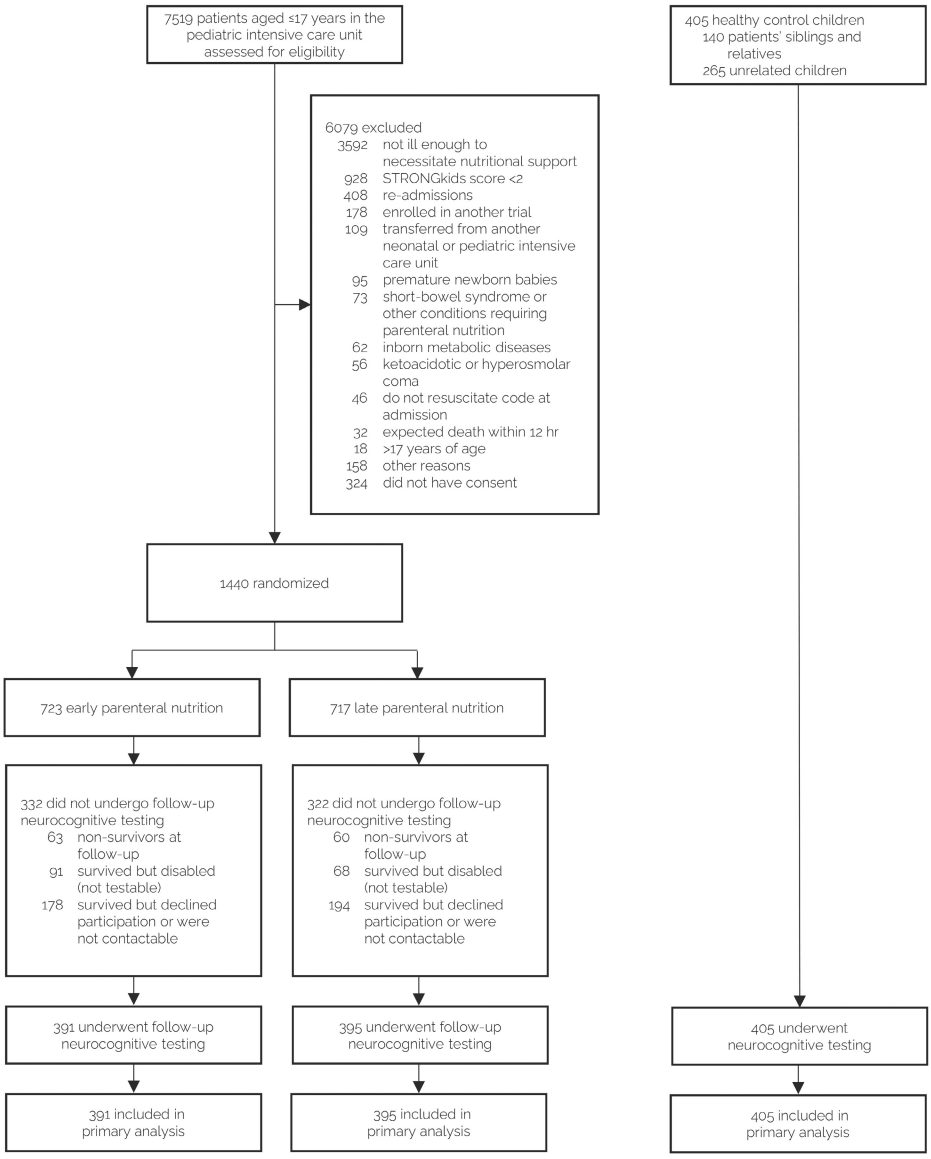

Figure 1. CONSORT flow diagram of the study participants
PN = parenteral nutrition, STRONGkids = Screening Tool for Risk on Nutritional Status and Growth

Of the total patient population (n=1440), 60 (8%) of 717 children in the Late PN group and 63 (9%) of 723 children in the Early PN group had died 2 years after admission to a PICU (p=0.81; **Figure 1**). 68 (9%) patients in the Late PN group and 91 (13%) patients in the Early PN group were identified as too disabled to assess for neurocognitive

development (p=0.059). 372 (26%) patients survived, but declined participation or could not be reached. No differences in reasons for loss to follow-up between randomization groups were observed (p=0.27). 786 patients (395 assigned to Late PN and 391 assigned to Early PN) and 405 healthy controls underwent long-term outcome testing between August 4, 2014 and January 19 2018, and were included in the imputation model for subsequent multivariable analyses. Of the healthy control children, 332 (82%) were assessed at the hospital compared with 502 (64%) PEPaNIC children (p<0.001), with similar proportions for the Early PN 458 (64%) and Late PN 461 (64%) groups being assessed at the hospital (p=0.79). Demographic and medical characteristics of PEPaNIC participants and healthy control children are shown in **Table 1**. Patients who were tested at follow-up were overall comparable to the initial PEPaNIC study population (**Table 1**).

Overall, PEPaNIC participants had worse outcomes at the 2-year follow-up for height, body weight, and head circumference, for health status, clinically assessed neurological functioning, parent/caregiver-reported executive functioning, and emotional and behavioral problems, and for clinical tests for intelligence, visual-motor integration, alertness, and memory than did healthy control children, assessed via univariable and via multivariable comparisons (**Table 2**; **Table 3**).

Patients in the Late PN group and those in the Early PN group were similar in terms of height, bodyweight, body-mass index, and head circumference, and for health status, and clinically assessed neurological functioning in univariable and multivariable analyses (**Table 2**, **Table 3**) However, in the univariable comparisons, patients in the Late PN group performed better than did those in the Early PN group on parent/caregiver-reported inhibitory control, working memory, meta-cognition, and overall executive functioning, and on clinical tests for visual-motor integration, verbal-auditory recognition, and for one motor coordination task (synchronous tapping; **Table 2**). Adjusted for multiple comparisons, the better inhibitory control of patients in the Late PN group than that of patients in the Early PN group remained significant (p=0.0001). After multivariable adjustment for risk factors, parents/caregivers of patients in the Late PN group reported better overall executive functioning than did parents/caregivers of patients in the Early PN group (β estimate –2.258, 95% CI –4.012 to –0.504; p=0.011), more specifically for inhibition (–3.422, –5.171 to –1.673; p=0.0001), working memory (–2.016, –3.761 to –0.270; p=0.023), and metacognition (–1.957, –3.694 to –0.220; p=0.027; **Table 3**; **Figure 2**). Furthermore, patients in the Late PN group had fewer externalizing behavioral problems (–1.715, 95% CI –3.325 to –0.106; p=0.036) as reported by parents/caregivers and scored better on visual-motor integration (0.468, 0.087 to 0.850; p=0.016) than did patients in the Early PN group (**Table 3**; appendix).

For overall executive functioning, inhibition, meta-cognition, and externalizing problems as reported by parents/caregivers, patients in the Late PN group were

not different from healthy control children (*p*-values of ≥0.12; appendix). After further correction for multiple comparisons, the better inhibitory control of patients in the Late PN group than of those in the Early PN group remained significant (p=0.0001; **Table 3**). Sensitivity analyses for the missing-at-random assumption and with imputing worst test scores for the severely disabled and thus non-testable children, as presented in the appendix, further supported the robustness of these results.

The effects of Late PN versus Early PN were more pronounced in the subgroup of patients who were infants at randomization than in older children (interaction *p*-values of ≤0.03): β estimates for Late PN versus Early PN among infants for parent/caregiver-reported overall executive functioning (-3.843, 95% CI -6.361 to -1.325; p=0.0029), meta-cognition (-3.749, -6.244 to -1.254; p=0.0034), and working memory (-3.594, -6.052 to -1.135; p=0.0043; appendix).

The impact of Late PN versus Early PN on long-term outcomes did not appear to be mediated by its acute effects on new PICU infections, duration of PICU stay, exposure to hypoglycemia, or duration of potentially hazardous post-randomization treatments during the PICU stay (appendix). The use of benzodiazepines and of corticosteroids was independently associated with poorer outcomes, whereas treatment with α2 agonists was associated with better overall executive functioning and visual-motor integration (appendix).

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested population[a]		**Total PEPaNIC population**		**Tested PEPaNIC population[b]**	
	Healthy control children (n=405)	**PEPaNIC patients (n=786)**	**Early PN (n=723)**	**Late PN (n=719)**	**Early PN (n=391)**	**Late PN (n=395)**
Demographic						
Age at 2-year follow-up - years	6.0 (4.7)	5.7 (4.5)	NA	NA	5.7 (4.4)	5.6 (4.5)
Sex						
Female	186 (46%)	331 (42%)	331 (42%)	305 (43%)	161 (41%)	170 (43%)
Male	219 (54%)	455 (58%)	415 (57%)	412 (57%)	230 (59%)	225 (57%)
Known non-white race[c]	33 (8%)	63 (8%)	50 (7%)	33 (5%)	38 (10%)	25 (6%)
Known non-European origin[c]	54 (13%)	152 (19%)	161 (22%)	128 (18%)	88 (23%)	64 (16%)
Known not exclusive Dutch or English language	76 (19%5)	184 (23%)	122 (17%)	106 (15%)	95 (24%)	89 (23%)
Socioeconomic status						
Parent[d] educational level 1	13 (3%)	37 (5%)	NA	NA	12 (3%)	25 (6%)
Parent[d] educational level 1.5	23 (6%)	54 (7%)	NA	NA	28 (7%)	26 (7%)

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested population[a]		Total PEPaNIC population		Tested PEPaNIC population[b]	
	Healthy control children (n=405)	PEPaNIC patients (n=786)	Early PN (n=723)	Late PN (n=719)	Early PN (n=391)	Late PN (n=395)
Parent[d] educational level 2	55 (14%)	184 (23%)	NA	NA	96 (25%)	88 (22%)
Parent[d] educational level 2.5	76 (19%)	131 (17%)	NA	NA	60 (15%)	71 (18%)
Parent[d] educational level 3	215 (53%)	200 (26%)	NA	NA	100 (26%)	100 (25%)
Parent[d] educational level unknown	23 (6%)	180 (23%)	NA	NA	95 (24%)	85 (22%)
Parent[e] occupational level 1	2 (<1%)	10 (1%)	NA	NA	2 (<1%)	8 (2%)
Parent[e] occupational level 1.5	25 (6%)	76 (10%)	NA	NA	33 (8%)	43 (11%)
Parent[e] occupational level 2	47 (12%)	127 (16%)	NA	NA	61 (16%)	66 (17%)
Parent[e] occupational level 2.5	26 (6%)	77 (10%)	NA	NA	44 (11%)	33 (8%)
Parent[e] occupational level 3	83 (21%)	121 (15%)	NA	NA	54 (14%)	67 (17%)
Parent[e] occupational level 3.5	40 (10%)	54 (7%)	NA	NA	32 (8%)	22 (6%)
Parent[e] occupational level 4	116 (29%)	108 (14%)	NA	NA	53 (14%)	55 (14%)
Parent[e] occupational level unknown	66 (16%)	213 (27%)	NA	NA	112 (29%)	101 (26%)
Infant (age<1y) at randomization	NA	363 (46%)	328 (45%)	325 (45%)	177 (45%)	186 (47%)
STRONGkids risk level[f]						
Medium	NA	707 (90%)	644 (89%)	644 (90%)	351 (90%)	356 (90%)
High	NA	79 (10%)	79 (11%)	73 (10%)	40 (10%)	39 (10%)
PeLOD score, first 24h in PICU[g]	NA	20.0 (11.6)	19.7 (12.0)	20.1 (12.3)	20.0 (11.6)	20.0 (11.5)
PIM3 score[h]	NA	−3.5 (1.4)	−3.2 (1.6)	−3.2 (1.7)	−3.4 (1.4)	−3.5 (1.3)
PIM3 probability of death, %[h]	NA	6.7 (11.8)	9.4 (15.9)	9.1 (17.4)	6.8 (12.0)	6.5 (11.6)
Diagnostic category						
Surgical: abdominal	NA	70 (9%)	53 (7%)	60 (8%)	34 (9%)	36 (9%)
Surgical: burns	NA	2 (<1%)	5 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)
Surgical: cardiac	NA	339 (43%)	279 (39%)	268 (37%)	173 (44%)	166 (42%)
Surgical: neurosurgery or traumatic brain injury	NA	71 (9%)	63 (9%)	53 (7%)	39 (10%)	32 (8%)
Surgical: thoracic	NA	42 (5%)	34 (5%)	27 (4%)	23 (6%)	19 (5%)
Surgical: transplantation	NA	14 (2%)	7 (1%)	17 (2%)	4 (1%)	10 (3%)
Surgical: orthopedic surgery or trauma	NA	23 (3%)	28 (4%)	26 (4%)	14 (4%)	9 (2%)
Surgical: other	NA	27 (3%)	21 (3%)	27 (4%)	10 (3%)	17 (4%)
Medical: cardiac	NA	26 (3%)	30 (4%)	31 (4%)	10 (3%)	16 (4%)

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested population[a]		Total PEPaNIC population		Tested PEPaNIC population[b]	
	Healthy control children (n=405)	**PEPaNIC patients (n=786)**	**Early PN (n=723)**	**Late PN (n=719)**	**Early PN (n=391)**	**Late PN (n=395)**
Medical: gastrointestinal or hepatic	NA	3 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	2 (<1%)
Medical: oncologic or hematologic	NA	8 (1%)	8 (1%)	7 (1%)	5 (1%)	3 (<1%)
Medical: neurologic	NA	44 (6%)	51 (7%)	52 (7%)	21 (5%)	23 (6%)
Medical: renal	NA	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Medical: respiratory	NA	83 (11%)	99 (14%)	96 (13%)	38 (10%)	45 (11%)
Medical: other	NA	34 (4%)	42 (6%)	43 (6%)	18 (5%)	16 (4%)
Malignancy	0 (0.0)	42 (5%)	51 (7%)	33 (5%)	26 (7%)	16 (4%)
Diabetes	0 (0.0)	1 (<1%)	3 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Syndrome[i]	5 (1.2)	79 (10%)	123 (17%)	118 (16%)	34 (9%)	45 (11%)
Known parental smoking between birth and PICU admission	NA	149 (19%)	NA	NA	72 (18%)	77 (20%)
Acute effect of randomization and post-randomization treatment in PICU						
Duration of stay in the PICU - days	NA	7.4 (15.1)	9.2 (21.3)	6.5 (10.0)	8.4 (18.4)	6.4 (10.8)
Patients who acquired a new infection in PICU	NA	105 (13%)	134 (19%)	77 (11%)	66 (17%)	39 (10%)
Duration of mechanical ventilatory support - days	NA	4.7 (11.0)	6.4 (18.6)	4.4 (7.3)	5.5 (13.9)	3.9 (7.1)
No. of days with hypoglycemia <40mg/dl - days	NA	0.1 (0.5)	0.1 (0.6)	0.2 (0.6)	0.1 (0.5)	0.2 (0.6)
Duration of antibiotic treatment - days	NA	5.1 (13.4)	6.7 (19.0)	4.6 (8.7)	5.8 (16.4)	4.3 (9.5)
Duration of hemodynamic support - days	NA	2.5 (7.2)	3.0 (7.4)	2.4 (6.2)	2.6 (7.6)	2.3 (6.8)
Duration of treatment with opioids - days	NA	4.7 (8.8)	6.1 (16.5)	4.1 (6.2)	5.4 (10.8)	4.1 (6.2)
Duration of treatment with benzodiazepines - days	NA	4.2 (9.8)	5.4 (16.7)	4.0 (8.8)	4.5 (9.9)	3.9 (9.7)
Duration of treatment with hypnotics - days	NA	1.4 (5.6)	1.8 (6.3)	1.3 (3.1)	1.6 (7.4)	1.2 (2.9)
Duration of treatment with α2-agonists - days	NA	1.0 (6.4)	1.1 (8.7)	1.0 (6.0)	0.9 (5.9)	1.1 (6.8)

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested population[a]		Total PEPaNIC population		Tested PEPaNIC population[b]	
	Healthy control children (n=405)	**PEPaNIC patients (n=786)**	**Early PN (n=723)**	**Late PN (n=719)**	**Early PN (n=391)**	**Late PN (n=395)**
Duration of treatment with corticosteroids) - days	NA	1.2 (3.7)	1.6 (4.3)	1.3 (3.9)	1.3 (4.2)	1.0 (3.1)

Data are mean (SD) or n (%). BMI=body mass index; NA=not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD = Pediatric Logistic Organ Dysfunction score; PICU = pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition; SEM = standard error of the mean.
a 708 (59%) of 1191 participating children were tested in Belgium, 463 (39%) in the Netherlands, and 20 (2%) in Canada.
b No differences in demographics, allocation to Late or Early PN, and PICU- or hospital-related primary and secondary study endpoints were observed between the PEPaNIC patients who were tested and those who survived, but declined participation or could not be reached (n=372; all p>0.15).
c Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.
d The education level is the mean of the paternal and maternal educational level, and calculated on the basis of the 3-point scale (1=low, 2=middle, 3-high; appendix) subdivisions as made by the Algemene Directie Statistiek (Belgium) and the Centraal Bureau voor de Statistiek (The Netherlands).
e The occupation level is the mean of the paternal and maternal occupation level, which is calculated on the basis of the International Isco System 4-point scale for professions (appendix).
f STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
g PeLOD scores range from 0 to 71, with higher scores indicating more severe illness.
h PIM3 probability of death, ranging from 0-100% with high percentage indicating a higher probability of death in PICU.
i A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (appendix).

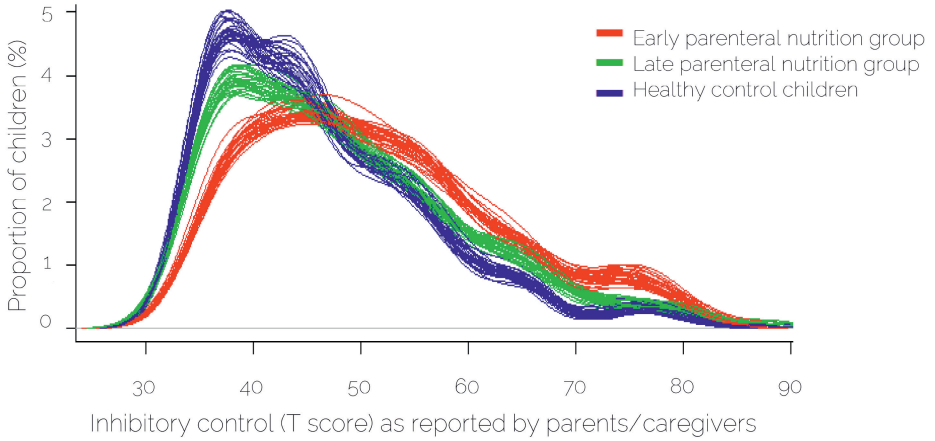

Figure 2. Density estimates for inhibitory function as reported by parents or caregivers
Each line corresponds to an imputed dataset. Densities, which correspond to the proportions of children with a certain score (equivalent to a smoothed histogram), are shown separately for healthy control children and for pediatric early versus late parenteral nutrition in critical illness (PEPaNIC) participants who had been randomly assigned to receive late parenteral nutrition (no parenteral nutrition in the first week after admission to a pediatric intensive care unit [PICU]) or early parenteral nutrition (within 24 h after PICU admission when enteral nutrition alone was insufficient). Higher scores indicate worse functioning.

Discussion

Two years after inclusion in the PEPaNIC multicenter, randomized, controlled trial, PICU survivors had worse developmental outcomes than did healthy control children. However, no adverse effect of withholding PN during the first week in the PICU could be detected for survival, anthropometrics health status, and neurocognitive development. In fact, omitting Early PN in the PICU improved parent/caregiver-reported executive functioning 2 years later compared with Early PN, in particular resulting in a better inhibitory control. Moreover, of the patients who survived, fewer were too disabled to be tested in the Late PN group than in the Early PN group.

The long-term legacy of problems in executive functioning, as reported in this article by parents or caregivers of patients admitted to the PICU, has been described previously, although mostly limited to the results of clinical neurocognitive testing.[20,90]

Table 2. Pooled univariable analyses of the differences assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (n=405)	PEPaNIC patients (n=786)	*p*-value	Early PN (n=391)	Late PN (n=395)	*p*-value
Height – cm	1126 (95%)	114.6 (27.4)	110.6 (26.5)	0.0018[a]	111.2 (25.9)	109.9 (27.0)	0.16
SD score[b]	1126 (95%)	0.370 (1.1)	-0.066 (1.3)	<0.0001[a]	-0.016 (1.2)	-0.115 (1.4)	0.47
Weight – kg	1135 (96%)	24.6 (16.7)	23.0 (16.2)	0.0020	23.0 (15.2)	23.0 (17.0)	0.20
SD score[b]	1135 (96%)	0.425 (0.9)	0.154 (1.2)	<0.0001	0.187 (1.1)	0.122 (1.1)	0.30
Body-mass index – kg/m^3	1126 (95%)	16.9 (2.7)	17.0 (5.1)	0.27	16.9 (3.1)	17.2 (6.5)	0.51
SD score[b]	1126 (95%)	0.306 (1.0)	0.249 (1.2)	0.043	0.259 (1.2)	0.240 (1.2)	0.61
Head circumference – cm	1060 (89%)	51.5 (2.6)	50.9 (2.8)	<0.0001	51.0 (2.8)	50.8 (2.8)	0.14
SD score[b]	1060 (89%)	0.504 (1.1)	0.107 (1.3)	<0.0001	0.139 (1.3)	0.076 (1.3)	0.35
Diagnosed with a somatic illness	957 (81%)	140 (35%)	507 (65%)	<0.0001	259 (66%)	248 (63%)	0.31
Diagnosed with a psychiatric illness	1160 (98%)	16 (4%)	52 (7%)	<0.0001	30 (8%)	22 (6%)	0.23
Admitted to hospital for a medical or surgical reason	1191 (100%)	72 (18%)	425 (54%)	<0.0001	216 (55%)	209 (53%)	0.51
Clinical neurological evaluation score (range 0-8)[c]	1116 (94%)	0.22 (0.6)	0.71 (1.5)	<0.0001	0.81 (1.6)	0.61 (1.3)	0.096
Executive functioning as reported by parents/caregivers - T-score[c]							
Inhibition	850 (72%)	46.3 (11.5)	49.9 (15.2)	<0.0001	51.4 (14.4)	48.4 (13.2)	<0.0001
Flexibility	851 (72%)	46.7 (11.3)	49.9 (15.3)	<0.0001	50.5 (14.3)	49.4 (13.3)	0.12
Emotional control	851 (72%)	47.7 (11.2)	49.7 (13.5)	0.0052	50.0 (12.7)	49.4 (12.4)	0.34
Working memory	845 (71%)	46.7 (12.1)	51.4 (16.7)	<0.0001	52.3 (15.4)	50.6 (14.1)	0.055
Planning and organization	847 (72%)	46.9 (11.9)	50.3 (14.7)	0.0001	50.8 (13.8)	49.8 (12.9)	0.18
Meta-cognition index	842 (71%)	46.8 (12.5)	50.2 (15.2)	<0.0001	51.0 (14.1)	49.5 (13.5)	0.059
Total score	841 (71%)	45.9 (11.6)	50.2 (15.4)	<0.0001	51.1 (14.5)	49.3 (13.7)	0.029
Emotional and behavioral problems as reported by parents/caregivers - T-score[c]							
Internalizing problems	1014 (86%)	46.7 (10.7)	51.1 (13.5)	<0.0001	51.4 (13.3)	50.8 (12.5)	0.53
Externalizing problems	1014 (86%)	46.8 (10.1)	49.8 (13.2)	<0.0001	50.5 (12.7)	49.1 (12.0)	0.11

Table 2. Pooled univariable analyses of the differences assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (n=405)	PEPaNIC patients (n=786)	*p*-value	Early PN (n=391)	Late PN (n=395)	*p*-value
Total problems	1014 (86%)	46.1 (10.4)	50.9 (13.2)	<0.0001	51.6 (13.0)	50.2 (12.3)	0.12
Intelligence (range 45-155)[d]							
Total IQ	1066 (90%)	100.7 (13.0)	90.6 (16.5)	<0.0001	90.3 (16.6)	90.9 (15.8)	0.57
Verbal IQ	1052 (89%)	100.8 (14.1)	92.0 (18.2)	<0.0001	91.6 (18.2)	92.4 (17.3)	0.55
Performance IQ	1071 (90%)	100.7 (13.8)	91.5 (16.4)	<0.0001	91.4 (16.7)	91.7 (15.6)	0.54
Visual-motor integration (range 0.9-20)[d]	1097 (93%)	9.6 (2.4)	8.2 (3.5)	<0.0001	8.0 (3.5)	8.5 (2.9)	0.010
Alertness[c,e]							
Reaction time right hand - ms	413 (78%)	480.8 (290.2)	561.1 (700.4)	0.0064	591.4 (581.8)	527.6 (489.9)	0.082
Within-person SD of repeated tests	413 (78%)	219.3 (176.0)	278.8 (715.0)	0.056	296.3 (559.0)	259.5 (510.8)	0.29
Reaction time left hand - ms	418 (79%)	459.7 (239.2)	536.2 (538.1)	0.038	557.1 (460.6)	513.0 (412.5)	0.11
Within-person SD of repeated tests	418 (79%)	217.3 (222.4)	287.4 (542.7)	0.063	196.0 (454.0)	177.8 (401.8)	0.23
Motor coordination (number of taps in 10 s)[d,e]							
Number of right hand taps	433 (82%)	41.4 (16.1)	37.9 (41.1)	0.095	37.2 (32.6)	38.8 (28.8)	0.29
Number of left hand taps	433 (82%)	36.3 (14.4)	34.9 (36.6)	0.30	33.7 (29.1)	36.2 (25.9)	0.19
Number of valid alternating taps	392 (74%)	18.3 (23.2)	18.6 (63.8)	0.35	17.4 (49.4)	20.0 (45.7)	0.36
Number of valid synchronous taps	392 (74%)	23.9 (15.1)	21.9 (35.8)	0.19	20.4 (27.6)	23.5 (26.5)	0.041
Inhibition and flexibility[c,e]							
Difference in reaction time (inhibition) - ms	383 (72%)	234.5 (411.0)	264.2 (1207.6)	0.24	286.5 (937.0)	239.6 (826.2)	0.17
Difference in no of errors (inhibition)	385 (73%)	2.1 (12.7)	4.1 (38.6)	0.053	4.2 (28..5)	4.0 (27.3)	0.73
Difference in reaction time (flexibility) - ms	369 (70%)	427.9 (445.3)	445.8 (1149.2)	0.31	458.7 936.0)	431.6 (782.9)	0.49
Difference in numbers of errors (flexibility)	370 (70%)	2.4 (10.8)	4.8 (35.7)	0.067	4.6 (26.8)	5.0 (24.8)	0.64

Table 2. Pooled univariable analyses of the differences assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (n=405)	PEPaNIC patients (n=786)	*p*-value	Early PN (n=391)	Late PN (n=395)	*p*-value
Memory[d, e]							
Verbal-auditory							
Numbers (range 1-19)							
Memory span (forward)	331 (83%)	10.2 (2.9)	8.6 (5.7)	<0.0001	8.6 (5.0)	8.7 (4.4)	0.66
Working memory (backward)	318 (80%)	10.3 (3.0)	8.7 (4.5)	<0.0001	8.9 (4.3)	8.4 (3.7)	0.38
Word pairs (% of correct responses)							
Learning	287 (72%)	0.50 (0.2)	0.43 (0.8)	0.047	0.42 (0.7)	0.45 (0.5)	0.26
Immediate memory	285 (72%)	0.47 (0.2)	0.33 (0.6)	<0.0001	0.31 (0.5)	0.35 (0.4)	0.13
Delayed memory	282 (71%)	0.40 (0.3)	0.31 (0.8)	0.0059	0.30 (0.7)	0.32 (0.5)	0.43
Recognition	279 (70%)	0.95 (0.2)	0.87 (0.5)	0.0003	0.85 (0.4)	0.89 (0.3)	0.043
Non-verbal, visual-spatial							
Pictures (% of correct responses)	319 (80%)	0.85 (0.1)	0.789 (0.3)	0.0001	0.77 (0.2)	0.79 (0.2)	0.29
Dots (% of correct responses)							
Learning	305 (77%)	0.86 (0.2)	0.78 (0.5)	0.010	0.79 (0.4)	0.78 (0.4)	0.57
Immediate memory	305 (77%)	0.87 (0.2)	0.80 (0.8)	0.058	0.80 (0.6)	0.80 (0.5)	0.70
Delayed memory	299 (75%)	0.87 (0.2)	0.80 (0.8)	0.094	0.79 (0.6)	0.80 (0.5)	0.59
Learning index (range 50-150)	280 (71%)	100.2 (22.5)	92.2 (85.5)	0.025	91.9 (69.2)	92.5 (54.9)	0.50

Results are the combined number (%) and means (SD) from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. IQ = intelligence quotient; PN = parenteral nutrition.
a Statistically significant after Bonferroni correction for multiple comparisons.
b Age-specific and sex-specific SD scores were calculated with the use of reference data from the WHO Growth Charts. The mean change in Z-scores from admission to a PICU to 2-year follow-up in the tested PEPaNIC population was 0.073 (SD 0.781) for height, 0.533 (1.101) for bodyweight, and 0.673 (1.393) for body-mass index. The mean change in Z-scores from PICU admission to 2-year follow-up for patients who received Late PN versus those who received Early PN in the tested PEPaNIC population was 0.027 (SD 1.899) versus 0.119 (1.656; p=0.84) for height, -0.366 (1.314) versus -0.397 (1.316; p=0.34) for bodyweight, and 0.605 (1.429) versus 0.739 (1.355; p=0.31) for body-mass index.
c Higher scores reflect worse performance.
d Higher scores reflect better performance.
e For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]	*p*-value	Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs Early PN, adjusted for risk factors[b]	*p*-value
Height – cm	1126 (95%)	-1.717 (-2.670;-0.763)	0.0004[c]	-0.538 (-3.358;2.282)	0.70
Weight – kg	1135 (96%)	-0.318 (-1.052;0.417)	0.39	0.278 (-1.639;2.194)	0.77
Body-mass index – kg/m^3	1126 (95%)				
Head circumference – cm	1060 (89%)	-0.461 (-0.701;-0.221)	0.0001[c]	-0.150 (-0.496;0.197)	0.39
Diagnosed with a somatic illness	957 (81%)	2.940 (2.199;3.931)[d]	<0.0001[c]	0.881 (0.625;1.242)[d]	0.74
Diagnosed with a psychiatric illness	1160 (98%)	2.137 (1.104;4.136)[d]	0.024	0.764 (0.403;1.448)[d]	0.40
Admitted to hospital for a medical or surgical reason	1191 (100%)	4.781 (3.485;6.559)[d]	<0.0001[c]	0.867 (0.634;1.186)[d]	0.37
Clinical neurological evaluation score (range 0-8)[e]	1116 (94%)	0.296 (0.154;0.439)	<0.0001[c]	-0.134 (-0.308;0.040)	0.13
Executive functioning as reported by parents/caregivers - T-score[f]					
Inhibition	850 (72%)	2.067 (0.507;3.628)	0.0095	-3.422 (-5.171;-1.673)	0.0001[c]
Flexibility	851 (72%)	1.611 (0.107;3.114)	0.035	-1.146 (-2.841;0.550)	0.18
Emotional control	851 (72%)	0.678 (-0.796;2.152)	0.36	-0.861 (-2.500;0.778)	0.30
Working memory	845 (71%)	2.834 (1.196;4.471)	0.0007[c]	-2.016 (-3.761;-0.270)	0.023
Planning and organization	847 (72%)	2.008 (0.426;3.590)	0.031	-1.139 (-2.807;0.529)	0.18
Meta-cognition index	842 (71%)	1.783 (0.145;3.421)	0.032	-1.957 (-3.694;-0.220)	0.027
Total score	841 (71%)	2.445 (0.882;4.008)	0.0022	-2.258 (-4.012;-0.504)	0.011
Emotional and behavioral problems as reported by parents/caregivers - T-score[e]					
Internalizing problems	1014 (86%)	3.153 (1.705;4.600)	<0.0001[c]	-0.837 (-2.535;0.860)	0.33
Externalizing problems	1014 (86%)	1.675 (0.261;3.088)	0.020	-1.715 (-3.325;-0.106)	0.036
Total problems	1014 (86%)	3.206 (1.757;4.655)	<0.0001[c]	-1.590 (-3.268;0.088)	0.063
Intelligence (range 45-155)[e]					
Total IQ	1066 (90%)	-5.508 (-7.254;-3.761)	<0.0001[c]	0.044 (-1.947;2.034)	0.96
Verbal IQ	1052 (89%)	-4.301 (-6.197;-2.405)	<0.0001[c]	0.237 (-1.980;2.455)	0.83

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]	*p*-value	Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs Early PN, adjusted for risk factors[b]	*p*-value
Performance IQ	1071 (90%)	-5.650 (-7.462;-3.838)	<0.0001[c]	-0.158 (-2.201;1.885)	0.87
Visual-motor integration (range 0.9-20)[f]	1097 (93%)	-0.925 (-1.256;-0.594)	<0.0001[c]	0.468 (0.087;0.850)	0.016
Alertness[e, g]					
Reaction time right hand - ms	413 (78%)	55.695 (6.319;105.071)	0.027	-55.418 (-121.649;10.813)	0.10
Within-person SD of repeated tests	413 (78%)	48.403 (0.632;96.174)	0.047	-34.167 (-91.313;22.978)	0.23
Reaction time left hand - ms	418 (79%)	54.996 (10.192;99.799)	0.016	-40.166 (-106.821;26.488)	0.23
Within-person SD of repeated tests	418 (79%)	49.624 (4.158;95.089)	0.032	-17.296 (-75.374;40.783)	0.55
Motor coordination (number of taps in 10 s)[f, g]					
Number of right hand taps	433 (82%)	-2.429 (-5.171;0.314)	0.081	0.863 (-2.181;3.907)	0.57
Number of left hand taps	433 (82%)	-1.536 (-4.077;1.004)	0.23	1.998 (-0.878;4.874)	0.17
Number of valid alternating taps	392 (74%)	0.707 (-4.391;5.805)	0.78	2.085 (-2.653;6.823)	0.38
Number of valid synchronous taps	418 (79%)	-1.354 (-3.998;1.289)	0.31	2.650 (-0.375;5.675)	0.085
Inhibition and flexibility[e, g]					
Difference in reaction time (inhibition) - ms	383 (72%)	25.177 (-51.033;101.387)	0.51	-53.416 (-125.105;18.274)	0.14
Difference in numbers of errors (inhibition)	385 (73%)	1.422 (-0.788;3.632)	0.20	-0.326 (-2.145;1.492)	0.72
Difference in reaction time (flexibility) - ms	369 (70%)	40.680 (-47.657;129.017)	0.36	-22.794 (-110.737;65.148)	0.60
Difference in numbers of errors (flexibility)	370 (70%)	2.085 (-0.062;4.231)	0.056	0.631 (-1.083;2.344)	0.46
Memory[f, g]					
Verbal-auditory					
Numbers (range 1-19)					
Memory span (forward)	331 (83%)	-1.113 (-1.883;-0.342)	0.0048	0.037 (-0.859;0.933)	0.93
Working memory (backward)	318 (80%)	-0.927 (-1.638;-0.216)	0.010	-0.393 (-1.286;0.500)	0.38
Word pairs (proportion of correct responses)					

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 2-year follow-up between patients and healthy control children and between Late PN and Early PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]	*p*-value	Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs Early PN, adjusted for risk factors[b]	*p*-value
Learning	287 (72%)	-0.065 (-0.121;-0.008)	0.025	0.039 (-0.027;0.104)	0.24
Immediate memory	285 (72%)	-0.110 (-0.165;-0.055)	0.0001[c]	0.047 (-0.014;0.109)	0.13
Delayed memory	282 (71%)	-0.078 (-0.132;-0.025)	0.0046	0.017 (-0.044;0.078)	0.57
Recognition	279 (70%)	-0.058 (-0.096;-0.021)	0.0027	0.035 (-0.013;0.083)	0.14
Non-verbal, visual-spatial					
Pictures (proportion of correct responses)	319 (80%)	-0.056 (-0.088;-0.024)	0.0006[c]	0.009 (-0.033;0.052)	0.66
Dots (proportion of correct responses)					
Learning	305 (77%)	-0.050 (-0.095;-0.005)	0.029	-0.016 (-0.064;0.032)	0.51
Immediate memory	305 (77%)	-0.051 (-0.114;0.012)	0.11	-0.013 (-0.077;0.052)	0.69
Delayed memory	299 (75%)	-0.058 (-0.122;0.006)	0.073	-0.002 (-0.069;0.064)	0.94
Learning index (range 50-150)	280 (71%)	-6.328 (-12.555;-0.101)	0.046	0.487 (-5.590;6.565)	0.87

Results are the combined beta-estimates and odds ratios from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. Sensitivity analyses to the missing-at-random assumption and with imputing worst test-scores for the severely disabled and thus non-testable children, as specified in the appendix, further supported the robustness of these results.
IQ = intelligence quotient; PeLOD score = Pediatric Logistic Organ Dysfunction Score; PICU = pediatric intensive care unit; PIM3 score = Pediatric Index of Mortality 3 score; PN = parenteral nutrition; SD = standard deviation; STRONGkids = Screening Tool Risk On Nutritional Status and Growth.
a Estimates and odds ratios were adjusted for the following risk factors: age, center, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, and the educational and occupational status of parents.
b Estimates and odds ratios were adjusted for the following risk factors: age, center, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behavior prior to PICU admission.
c Statistically significant after Bonferroni correction for multiple comparisons.
d These values are odds ratios.
e Higher scores reflect worse performance.
f Higher scores reflect better performance.
g For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Executive dysfunction comprises problems in complex decision making and goal-oriented behavior with implications for daily life[183] and has been associated with externalizing problems such as antisocial and aggressive behaviour.[171,184] Indeed, poor inhibitory control in children is known to contribute to impulsive and destructive behaviors that upset or harm others.[184] Hence, the possible beneficial effects of delaying PN in pediatric critical illness on the longer-term parent/caregiver-reported inhibitory function, further supported by better scores for other executive functions, externalizing behavior, and visual-motor integration (comparisons that lost significance after Bonferroni correction), are relevant. Indeed, the consequences for daily life and for the social environment are otherwise difficult to quantify by existing clinical neurocognitive tests.

The most robust protection of executive functioning of delayed PN was observed for the ability to suppress immediate responses, as measured by the parent/caregiver-reported inhibition score; this finding suggests potential damage induced by Early PN to frontal lobe areas that coordinate inhibition.[185] The frontal lobe appears to be particularly vulnerable to metabolic insults during critical illness, with inflammation and neuronal damage described, which can be partially prevented by avoiding excessive hyperglycaemia.[186] A previous randomized, controlled trial[20] that documented the long-term neurocognitive impact of preventing hyperglycemia in the PICU also found some improvement of executive functioning. We speculate that harm induced by Early PN to executive functioning might also be a direct metabolic insult on the developing brains of young children, because it was not statistically explained by the acute effects of the intervention, such as increased incidence of new infections or delayed recovery, or by other potentially hazardous post-randomization treatments given during the PICU stay, such as use of benzodiazepines. The larger benefit observed for critically ill infants than for older children provides support for this speculation. Whether other periods of age or development, such as puberty, also represent special vulnerability remains to be investigated.

Unlike our current findings in patients admitted to the PICU early in life, studies in other pediatric settings and otherwise healthy children have shown that insufficient rather than abundant nutritional intake, both prenatally and during childhood, can result in impaired growth and neurocognitive development.[84,187] These differing results could be explained by the context. Indeed, specifically in the context of critical illness, fasting-induced responses brought about during the first days after an insult might generate beneficial effects through (autophagy-induced) cell damage removal and prevention of neuronal loss.[132,186] The early administration of amino acids, the most powerful suppressors of autophagy,[132] rather than glucose or lipids was found to explain the short-term harm by Early PN in critically ill children.[70] However, the exact underlying mechanisms of any long-term effect of not forcefully feeding patients early during critical illness remain speculative. Among others, alterations in DNA

methylation in promoters or bodies of genes involved in neuronal growth, axonal guidance, and signal transduction could play a part,[188] since such epigenetic changes have been previously associated with executive dysfunction.[183] Moreover, the potential involvement of telomere shortening, which has been shown to be accelerated by early initiation of PN during pediatric critical illness, should be further investigated.[126]

This study has limitations. First, the young age of PEPaNIC patients precluded complete and reliable results for certain neurocognitive tests. For these tests, the statistical power and thus the odds of identifying a difference between treatment groups was reduced. Second, neuroimaging studies were not done. Third, information on physiotherapy in the PICU and on the regular ward (i.e., after PICU but before hospital discharge) was not recorded. Fourth, data on follow-up consultations and therapies beyond the study protocol were not systematically available for all centers and all diagnostic subgroups. Fifth, after conservative Bonferroni correction, only the impact of withholding PN early in the PICU on long-term inhibitory control remained significant. However, given that inhibition is an important cognitive function involved in many aspects of daily life, and given the absence of any harm, this finding is relevant for endorsing implementation of withholding Early PN in the PICU.

Conclusions

Patients admitted to the PICU early in life had worse outcomes at the 2-year follow-up for anthropometrics, health status, and neurocognitive development than did healthy control children. Withholding Early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status and neurocognitive development, and improved inhibitory control 2 years later.

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Appendix Chapter 4

Methods S1: Definition of educational and occupational level of parents

Educational level of parents
The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents
The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (http://www.ilo.org/public/english/bureau/stat/isco/). In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Methods S2: Definition of "Syndrome"
A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development, and which is subdivided in the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Pedopsychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré

- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomization
- Severe convulsions or stroke prior to randomization

Methods S3: Detailed description of outcome measures

Medical assessment

Anthropometric data
Height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status
In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 2 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination
In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. An abnormal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing
A broad range of neurocognitive functions, including general intellectual functioning, visual-motor integration, attention, motor coordination, inhibitory control and cognitive flexibility, verbal and visual-spatial learning, and memory were evaluated, as previously reported.[20]

Patient/Parents-reported outcomes (PROs)
Executive functioning was measured with the Behavior Rating Inventory of Executive Function (BRIEF-P 2.5-5 years, BRIEF 6-18 years), filled out by the parents or caregivers of the child. Overlapping scales and indices of both questionnaires (Inhibition, Flexibility, Emotional Control, Working Memory, Planning and Organization, Meta-cognition) and a Total Score were analyzed (T-scores, with mean 50 and SD 10).[171,172] Emotional and behavioral problems were assessed by the parent or caregiver with the Child Behavior Checklist (CBCL 1.5-5 years or CBCL 6-18 years).[173,174] Internalizing,

externalizing, and total problems were analyzed (T-scores, with mean 50 and SD 10).[173,174]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[175] was used for children aged 2.5 years to 5 years 11 months (one version for age range 2 years 6 months to 3 years 11 months, and another version for age range 4 years to 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-III-NL)[176] was used for children aged 6 years to 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[177] for adolescents who were 17 years or older. For all these tests Total IQ, Verbal IQ, and Performance IQ scores (Test-mean 100, SD 15) were computed.

Visual-motor integration

We used the Beery Developmental Test of Visual-Motor Integration, 6th Edition (VMI) to assess the ability to integrate their visual and motor functions (total Scaled Score, Test-mean 10, SD 3). This involves eye-hand coordination.[178]

Alertness, motor-coordination, and executive functions

To measure alertness, motor-coordination and executive function, the validated Amsterdam Neuropsychological Tasks (ANT) program was used.[179] The ANT is a computer-aided assessment battery of reaction time (RT) tasks that allows for the systematic evaluation of information processing capacities.

Children 4 years and older performed ANT-Baseline Speed (BS), ANT-Tapping (TP), and Response Organization Objects (ROO). The ANT-BS evaluated alertness by measuring simple RT to visual stimuli (mean RT and SD of RT were obtained for the right and left hand separately). The ANT-TP assessed motor coordination for the right hand, left hand, bimanual alternating, and bimanual synchronous. The ANT-ROO measured inhibitory control and cognitive flexibility by calculating the differences in RT and the differences in number of errors between tests of increasing demand.

Memory

Auditory/verbal memory and Visual-spatial/non-verbal memory were assessed with use of four tests from the Children's Memory Scale (CMS) for children between 5 and 16 years 11 months. [180] As to verbal memory, CMS-Numbers assessed short-term verbal memory span (forward digit recall) and verbal working memory load (backward digit recall). The CMS-Word Pairs (recall a list of word pairs) assessed short-term and long-term verbal memory, and recognition. As to non-verbal memory, CMS-Picture Locations (remembering and recall of pictures in various locations) assessed immediate visual memory. CMS-Dot Locations (remembering and recall

of the location of dots) assessed immediate and delayed visual memory. For CMS-Numbers, raw scores for verbal memory span, CMS-numbers forward, and verbal working memory load, CMS-numbers backward were reported. For CMS-Word Pairs, CMS-Picture Locations, and CMS-Dot Locations, proportional scores were analyzed (proportion of correct responses ranging from 0 to 1, with higher scores reflecting better performance). The CMS-Learning index is a standardized score of the sum of the three learning trials of the CMS-Word Pairs and the learning trial of the CMS-Dot Locations subtests. The range of the score is 50-150, with a higher score representing a better learning ability.

Methods S4: Imputation

Missing data (excluding the deceased and the severely disabled whereby non-testable children) were handled by ***multiple data imputation with chained equations under a 'missing at random' assumption***. There were no missing data in the baseline variables. Predictors for missing values included all covariates listed below, and were retained in the predictor models with a minimum correlation of 0.1 with the prediction target. Predictive mean matching[189] was used for numeric variables except for factors with two levels (which were imputed based on logistic regression) and factors with more than two levels (for which polytomous (unordered) regression was used). A monotonous visiting scheme was used such that variables for imputation were visited in increasing order of the number of missing data. Imputation convergence was assessed visually and set at 70 iterations (**Figure S1**). Since there were no more than 30% missing observations for all variables, 31 complete imputed datasets were used in the analyses,[181] and pooled results were obtained across datasets using Rubin's rules.[190]

Plausibility of the imputations was assessed visually via the densities of the observed data and that resulting from the imputed values (**Figure S2**). ***Sensitivity of results to the 'missing at random' assumption*** was assessed with use of pattern mixture models [190-192] assuming the original imputed values were either too high or too low by a factor of 0.1 for the main result of inhibition as reported by parents. Under this assumption, the obtained beta-estimates and *p*-values for randomization to Late PN vs. Early PN for the multivariable linear regression analyses performed to determine significant and independent associations between risk factors and inhibition as reported by the parents at two-year follow-up within the tested patient population (**Table S1-1**) ranged from -2.962 ($p<0.0001$) to -2.396 ($p=0.032$). The effect-sizes thus remained of the same order of magnitude, sign, and statistical significance as were observed for the original imputed datasets, which suggested that the analyses were robust against the investigated 'missing at random' violation.

To further evaluate the robustness of the main findings**,** the analyses were repeated after imputing a ***penalized test result for all severely disabled and thus non-testable***

patients**,** defined as the worst result in the observed patients or controls, plus or minus one, as appropriate for each test. In this case, the obtained beta-estimates (*p*-values) for randomization to Late PN vs. Early PN for the multivariable linear regression analyses were respectively: A) -3.382 (p<0.0001) for inhibition as reported by parents; B) -1.928 (p=0.031) for meta-cognition as reported by parents; C) -1.992 (P=0.026) for working memory as reported by parents; D) -2.224 (p=0.014) for overall executive functioning as reported by parents; E) -1.668 (p=0.045) for externalizing emotional and behavioral problems as reported by parents; and F) 0.464 (p=0.017) for visual-motor integration. These sensitivity analyses corresponded closely to the primary results as reported in **Table 2** of the main manuscript.

All multiple data imputation analyses were performed with R version 3.4.3 and MICE version 2.46.0.

List of variables used for multiple data imputation by chained equations

Demographics of patients and control children and patient characteristics upon PICU admission

Centre, randomization for Late PN or Early PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome", educational and occupational status of parents, diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking behavior prior to PICU admission, age at randomization, age group at randomization.

Acute effects of randomization and post-randomization treatments in PICU

Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycemia, duration of treatment with hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and α2-agonists.

At two-year follow-up

Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performance IQ, total IQ, visual motor integration, reaction time left hand, reaction time right hand, within subject SD of reaction time left hand, within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, delta reaction time inhibition, delta number of errors inhibition, delta reaction time flexibility, delta number of errors flexibility, numbers memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs

recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organization, meta-cognition index, and total score), emotional and behavioral problems as reported by parents/caregivers (internalizing problems, externalizing problems, and total problems). Interactions between age group and randomization were not included in the imputation models.

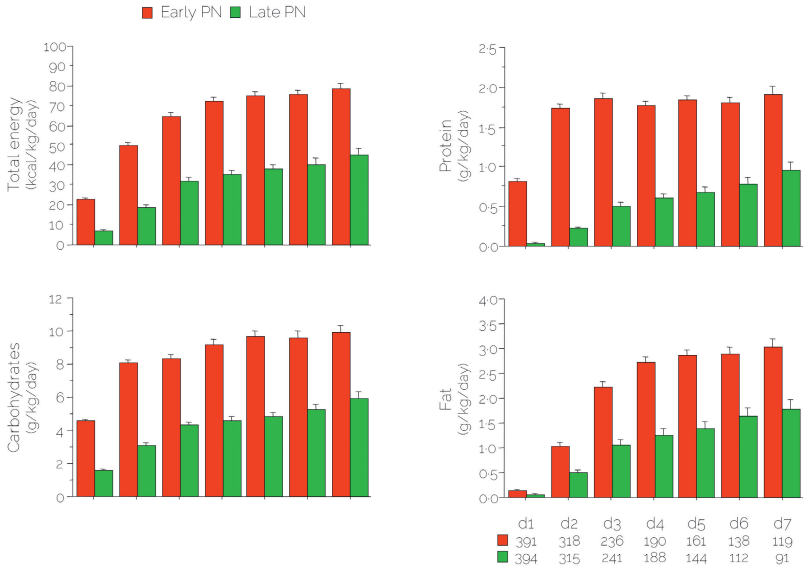

Figure S1. Macronutrient doses during the first week in PICU administered to the tested population
Daily amount of total energy in kcal/kg/day, and the daily amounts of total substrates in g/kg/day are shown for the first 7 days in the pediatric intensive care unit (PICU). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the Early PN group and the green bars represent the Late PN group.

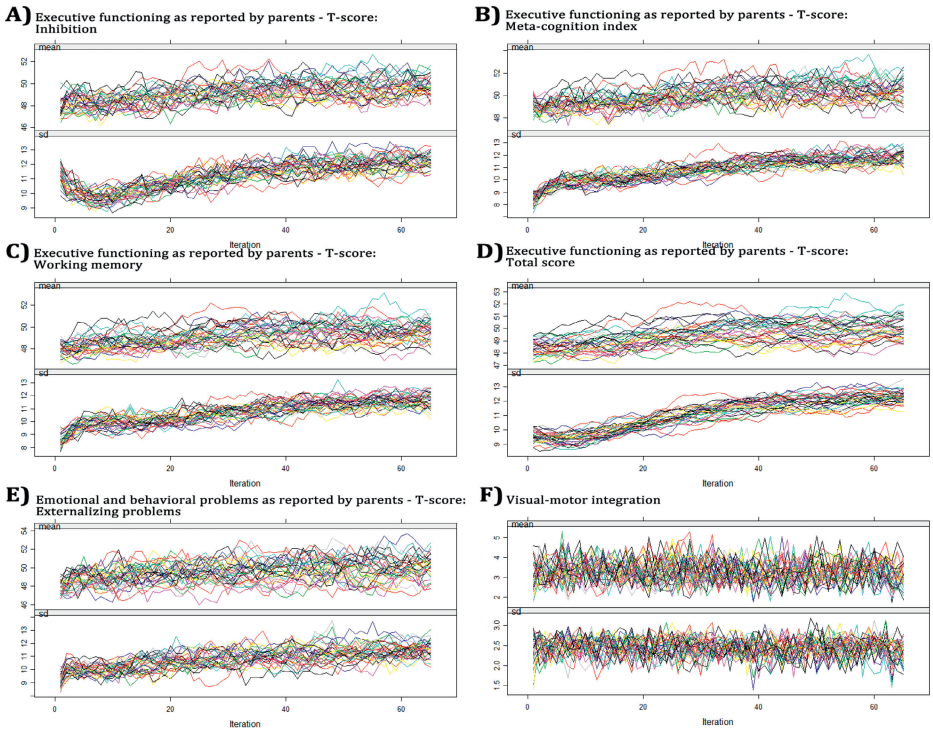

Figure S2. Imputation convergence for selected neurocognitive test results
Mean and standard deviation of imputed values in each of 31 datasets over 70 iterations for

- **A)** Executive functioning as reported by parents/caregivers - T-score: Inhibition;
- **B)** Meta-cognition index;
- **C)** Working memory;
- **D)** Total score;
- **E)** Emotional and behavioral problems as reported by parents/caregivers - T-score: Externalizing problems;
- **F)** Visual-motor integration.

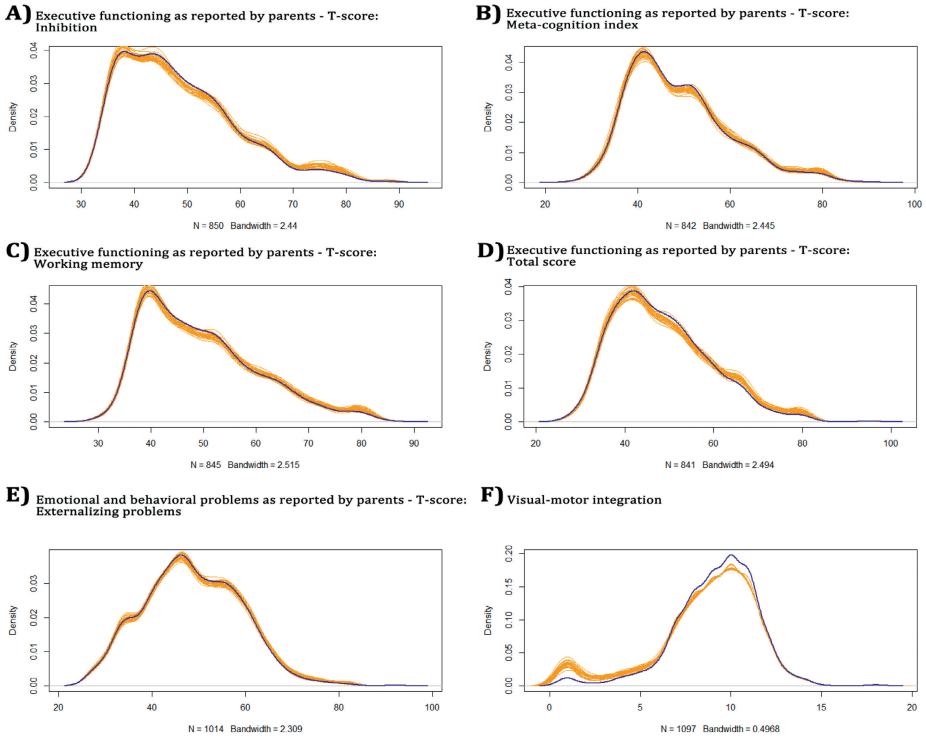

Figure S3. Density estimates of the observed and imputed values for selected neurocognitive test results
Density estimated for observed values (in blue) and for each imputed dataset (in orange) for

- **A)** Executive functioning as reported by parents/caregivers - T-score: Inhibition;
- **B)** Meta-cognition index;
- **C)** Working memory;
- **D)** Total score;
- **E)** Emotional and behavioral problems as reported by parents - T-score: Externalizing problems;
- **F)** Visual-motor integration.

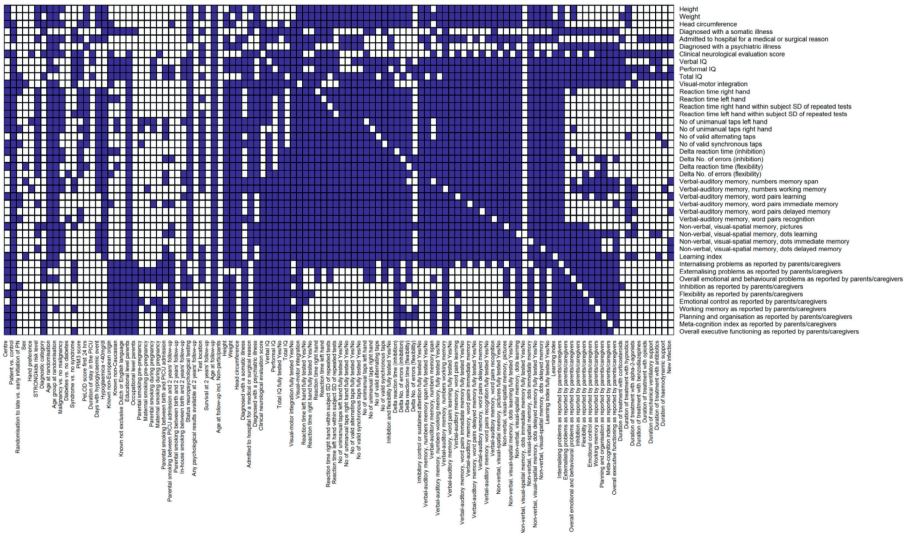

Figure S4. Multiple imputation predictor variables
Missing values for the variables in each row are imputed based on models that use as predictors only the column variables highlighted in blue. The predictor variables are selected as described in Methods S4

Table S1. Multivariable linear regression analyses determining significant and independent associations between risk factors and long-term test results within the tested patient population

Table S1-1. Multivariable linear regression analyses determining significant and independent associations between risk factors and inhibition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***-3.422***	***-5.171***	***-1.673***	***0.00013***	***-3.373***	***-5.140***	***-1.605***	***0.00020***
Centre								
Leuven vs. Edmonton	1.752	-5.864	9.369	0.65	2.306	-5.392	10.004	0.55
Rotterdam vs. Edmonton	1.683	-6.012	9.377	0.66	1.307	-6.456	9.069	0.74
Male vs. female sex	1.098	-0.740	2.937	0.24	1.162	-0.675	2.999	0.21
Right vs. left hand preference	0.280	-2.548	3.109	0.84	0.284	-2.492	3.060	0.83
Medium vs. high STRONGkids risk level[a]	0.592	-2.543	3.726	0.71	0.562	-2.620	3.745	0.72
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-0.800	-4.510	2.911	0.67	-0.634	-4.338	3.070	0.73
Burns	-1.969	-17.860	13.923	0.80	-3.540	-19.912	12.833	0.67
Neurosurgery - traumatic brain injury	1.988	-1.662	5.638	0.28	1.640	-2.005	5.285	0.37
Thoracic	-1.293	-5.670	3.084	0.56	-1.225	-5.650	3.200	0.58
Transplantation	5.434	-2.598	13.465	0.18	3.995	-5.157	13.148	0.38
Orthopedic surgery-trauma	0.485	-5.186	6.157	0.86	0.184	-5.522	5.889	0.94
Other	3.419	-1.470	8.309	0.17	2.611	-2.369	7.591	0.30
Medical								
Cardiac	2.694	-2.638	8.026	0.32	2.291	-3.295	7.877	0.42
Gastrointestinal-hepatic	10.927	-5.325	27.179	0.18	10.591	-5.610	26.792	0.19
Hematologic-oncologic	3.951	-4.925	12.828	0.38	0.637	-8.789	10.063	0.89
Neurologic	0.691	-3.535	4.918	0.74	-0.297	-4.658	4.064	0.89
Respiratory	0.374	-3.370	4.118	0.84	-0.161	-4.032	3.710	0.93

Table S1-1. Multivariable linear regression analyses determining significant and independent associations between risk factors and inhibition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Other	0.096	-4.640	4.832	0.96	-0.307	-5.197	4.582	0.90
Infant (age<1y) vs. child at randomization	0.315	-1.635	2.265	0.75	0.331	-1.719	2.382	0.75
Malignancy vs. no malignancy	-1.620	-5.794	2.554	0.44	-1.907	-6.129	2.314	0.37
Diabetes vs. no diabetes	-5.169	-28.229	17.890	0.65	-3.412	-26.465	19.642	0.77
Syndrome vs. no syndrome[b]	3.447	0.314	6.581	0.031	3.727	0.571	6.884	0.020
PIM3 score (per point added)[c]	0.071	-0.780	0.922	0.87	-0.006	-0.883	0.871	0.98
PeLOD score first 24 hrs (per point added)[d]	0.067	-0.047	0.181	0.24	0.051	-0.064	0.167	0.38
Known non-European origin vs. other[e]	-0.582	-4.367	3.202	0.76	-0.625	-4.407	3.158	0.74
Known non-Caucasian vs. other[e]	-1.931	-6.585	2.724	0.41	-1.560	-6.231	3.112	0.51
Known not exclusive Dutch or English language vs. other	0.359	-2.480	3.198	0.80	0.379	-2.456	3.214	0.79
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.090	-8.471	2.292	0.25	-2.468	-7.907	2.970	0.37
Educational level 2	-2.097	-6.648	2.453	0.36	-1.634	-6.226	2.958	0.48
Educational level 2.5	-3.730	-8.625	1.164	0.13	-3.127	-8.047	1.792	0.21
Educational level 3	-4.590	-9.509	0.329	0.067	-4.043	-8.996	0.909	0.10
Educational level unknown	-0.579	-6.400	5.242	0.84	-0.111	-5.963	5.742	0.97
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	3.634	-4.260	11.527	0.36	3.091	-4.810	10.992	0.44
Occupational level 2	3.086	-4.721	10.893	0.43	2.380	-5.448	10.208	0.55
Occupational level 2.5	3.803	-4.335	11.941	0.35	2.995	-5.176	11.166	0.47
Occupational level 3	3.047	-4.923	11.017	0.45	2.400	-5.583	10.382	0.55
Occupational level 3.5	0.490	-7.969	8.950	0.90	-0.224	-8.701	8.253	0.95
Occupational level 4	4.074	-4.163	12.312	0.33	3.139	-5.147	11.426	0.45

Table S1-1. Multivariable linear regression analyses determining significant and independent associations between risk factors and inhibition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Occupational level unknown	2.458	-5.483	10.399	0.54	1.882	-6.074	9.839	0.64
Parental smoking between birth and PICU admission vs. no smoking	1.530	-0.787	3.847	0.19	1.635	-0.671	3.942	0.16
New infection vs. no new infection					-0.420	-3.898	3.058	0.81
Duration of stay in the PICU (per day added)					0.033	-0.258	0.323	0.82
Days with hypoglycemic event (per day added)					-0.331	-2.299	1.637	0.74
Duration of mechanical ventilatory support (per day added)					-0.089	-0.291	0.113	0.38
Duration of treatment with antibiotics (per day added)					-0.049	-0.321	0.223	0.72
Duration of hemodynamic support (per day added)					-0.100	-0.305	0.104	0.33
Duration of treatment with corticosteroids (per day added)					0.229	-0.101	0.558	0.17
Duration of treatment with opioids (per day added)					-0.082	-0.368	0.204	0.57
Duration of treatment with benzodiazepines (per day added)					0.323	0.056	0.590	0.017
Duration of treatment with hypnotics (per day added)					0.073	-0.211	0.356	0.61
Duration of treatment with α2-agonists (per day added)					-0.186	-0.449	0.078	0.16

PeLOD = pediatric logistic organ dysfunction score; PICU = pediatric intensive care unit; PIM3 = pediatric index of mortality 3 score; PN = parenteral nutrition.
For inhibition as reported by parents, higher scores reflect worse performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2)
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-2. Multivariable linear regression analyses determining significant and independent associations between risk factors and working memory as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***-2.016***	***-3.761***	***-0.270***	***0.023***	***-1.961***	***-3.728***	***-0.194***	***0.029***
Centre								
Leuven vs. Edmonton	0.686	-6.879	8.250	0.85	1.356	-6.400	9.112	0.73
Rotterdam vs. Edmonton	0.107	-7.564	7.779	0.97	-0.082	-7.943	7.778	0.98
Male vs. female sex	1.266	-0.523	3.055	0.16	1.220	-0.564	3.005	0.17
Right vs. left hand preference	0.222	-2.353	2.797	0.86	0.287	-2.274	2.849	0.82
Medium vs. high STRONGkids risk level [a]	-0.120	-3.331	3.092	0.94	0.180	-3.084	3.444	0.91
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.737	-6.574	1.100	0.16	-2.573	-6.423	1.277	0.18
Burns	-1.793	-17.437	13.850	0.82	-2.819	-18.998	13.361	0.73
Neurosurgery - traumatic brain injury	2.159	-1.515	5.833	0.24	1.930	-1.752	5.612	0.30
Thoracic	-3.357	-7.670	0.956	0.12	-3.286	-7.666	1.094	0.14
Transplantation	6.273	-1.387	13.934	0.10	5.872	-2.856	14.599	0.18
Orthopedic surgery-trauma	0.651	-4.851	6.153	0.81	0.536	-4.962	6.034	0.84
Other	4.021	-0.885	8.927	0.10	3.462	-1.543	8.467	0.17
Medical								
Cardiac	3.986	-1.280	9.252	0.13	3.125	-2.477	8.727	0.27
Gastrointestinal-hepatic	13.673	-1.652	28.999	0.080	13.484	-1.816	28.784	0.083
Hematologic-oncologic	-1.926	-10.690	6.838	0.66	-4.287	-13.541	4.967	0.36
Neurologic	0.246	-3.909	4.402	0.90	-0.369	-4.582	3.843	0.86
Respiratory	-2.172	-5.908	1.563	0.25	-2.735	-6.583	1.113	0.16
Other	-1.210	-5.913	3.493	0.61	-1.545	-6.405	3.314	0.53

Table S1-2. Multivariable linear regression analyses determining significant and independent associations between risk factors and working memory as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Infant (age<1y) vs. child at randomization	-0.737	-2.690	1.216	0.45	-0.703	-2.721	1.315	0.49
Malignancy vs. no malignancy	1.704	-2.413	5.821	0.41	1.688	-2.471	5.847	0.42
Diabetes vs. no diabetes	0.527	-22.272	23.326	0.96	1.951	-20.856	24.757	0.86
Syndrome vs. no syndrome[b]	5.298	2.181	8.414	0.00094	5.324	2.167	8.481	0.0010
PIM3 score (per point added)[c]	0.280	-0.614	1.173	0.53	0.191	-0.737	1.120	0.68
PeLOD score first 24 hrs (per point added)[d]	0.011	-0.101	0.124	0.84	-0.004	-0.118	0.110	0.94
Known non-European origin vs. other[e]	1.118	-2.771	5.007	0.57	1.112	-2.781	5.005	0.57
Known non-Caucasian vs. other[e]	-3.969	-9.097	1.158	0.12	-3.744	-8.870	1.382	0.15
Known not exclusive Dutch or English language vs. other	0.316	-2.338	2.970	0.81	0.365	-2.305	3.036	0.78
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.391	-8.554	1.773	0.19	-2.870	-8.119	2.379	0.28
Educational level 2	-2.230	-6.603	2.144	0.31	-1.745	-6.159	2.669	0.43
Educational level 2.5	-3.950	-8.584	0.683	0.094	-3.314	-7.974	1.346	0.16
Educational level 3	-4.174	-8.873	0.524	0.081	-3.631	-8.376	1.114	0.13
Educational level unknown	-1.527	-7.153	4.099	0.59	-1.042	-6.754	4.669	0.71
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.618	-7.159	8.394	0.87	0.162	-7.632	7.956	0.96
Occupational level 2	0.579	-7.203	8.362	0.88	0.055	-7.752	7.863	0.98
Occupational level 2.5	0.286	-7.808	8.381	0.94	-0.453	-8.571	7.665	0.91
Occupational level 3	-0.860	-8.803	7.082	0.83	-1.442	-9.390	6.506	0.72
Occupational level 3.5	-3.143	-11.577	5.292	0.46	-3.740	-12.188	4.708	0.38
Occupational level 4	0.358	-7.869	8.585	0.93	-0.426	-8.692	7.840	0.91
Occupational level unknown	0.378	-7.667	8.422	0.92	-0.162	-8.241	7.918	0.96

Table S1-2. Multivariable linear regression analyses determining significant and independent associations between risk factors and working memory as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Parental smoking between birth and PICU admission vs. no smoking	1.230	-1.255	3.715	0.32	1.315	-1.174	3.803	0.29
New infection vs. no new infection					0.674	-2.783	4.131	0.70
Duration of stay in the PICU (per day added)					0.001	-0.287	0.289	0.99
Days with hypoglycemic event (per day added)					-0.166	-2.167	1.835	0.87
Duration of mechanical ventilatory support (per day added)					-0.103	-0.300	0.095	0.30
Duration of treatment with antibiotics (per day added)					0.034	-0.239	0.307	0.80
Duration of hemodynamic support (per day added)					-0.066	-0.266	0.134	0.51
Duration of treatment with corticosteroids (per day added)					0.095	-0.226	0.415	0.56
Duration of treatment with opioids (per day added)					-0.150	-0.435	0.134	0.29
Duration of treatment with benzodiazepines (per day added)					0.337	0.075	0.598	0.011
Duration of treatment with hypnotics (per day added)					0.066	-0.214	0.346	0.64
Duration of treatment with α2-agonists (per day added)					-0.207	-0.465	0.050	0.11

PeLOD = Pediatric Logistic Organ Dysfunction score; PICU = pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition.
For working memory as reported by parents, higher scores reflect worse performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2)
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-3. Multivariable linear regression analyses determining significant and independent associations between risk factors and meta-cognition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***-1.957***	***-3.694***	***-0.220***	***0.027***	***-1.914***	***-3.668***	***-0.159***	***0.032***
Centre								
Leuven vs. Edmonton	1.562	-5.918	9.041	0.68	2.358	-5.310	10.026	0.54
Rotterdam vs. Edmonton	0.874	-6.632	8.380	0.81	0.959	-6.726	8.644	0.80
Male vs. female sex	0.936	-0.884	2.755	0.31	0.883	-0.934	2.699	0.33
Right vs. left hand preference	0.355	-2.296	3.006	0.79	0.456	-2.136	3.049	0.72
Medium vs. high STRONGkids risk level[a]	-0.073	-3.217	3.071	0.96	0.190	-3.019	3.398	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.385	-6.209	1.438	0.22	-2.290	-6.145	1.565	0.24
Burns	-0.358	-16.758	16.043	0.96	-1.153	-18.197	15.892	0.89
Neurosurgery - traumatic brain injury	1.129	-2.417	4.674	0.53	0.907	-2.639	4.453	0.61
Thoracic	-3.311	-7.540	0.919	0.12	-3.228	-7.490	1.034	0.13
Transplantation	5.501	-2.154	13.157	0.15	5.628	-3.204	14.460	0.20
Orthopedic surgery-trauma	1.015	-4.352	6.381	0.71	0.939	-4.431	6.310	0.73
Other	3.183	-1.648	8.015	0.19	2.623	-2.336	7.581	0.29
Medical								
Cardiac	2.776	-2.502	8.053	0.30	2.040	-3.474	7.553	0.46
Gastrointestinal-hepatic	13.837	-1.403	29.076	0.074	13.620	-1.592	28.832	0.079
Hematologic-oncologic	0.069	-8.634	8.773	0.98	-1.756	-11.000	7.488	0.70
Neurologic	-0.205	-4.378	3.967	0.92	-0.703	-4.941	3.536	0.74
Respiratory	-1.146	-5.067	2.776	0.56	-1.620	-5.670	2.430	0.43
Other	-1.400	-6.082	3.282	0.55	-1.681	-6.540	3.179	0.49

Table S1-3. Multivariable linear regression analyses determining significant and independent associations between risk factors and meta-cognition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Infant (age<1y) vs. child at randomization	-0.047	-1.996	1.901	0.96	-0.008	-2.034	2.017	0.99
Malignancy vs. no malignancy	0.192	-3.858	4.243	0.92	0.267	-3.816	4.350	0.89
Diabetes vs. no diabetes	2.021	-20.625	24.666	0.86	3.172	-19.481	25.826	0.78
Syndrome vs. no syndrome[b]	4.615	1.484	7.746	0.0040	4.650	1.463	7.838	0.0044
PIM3 score (per point added)[c]	0.140	-0.764	1.044	0.76	0.057	-0.887	1.002	0.90
PeLOD score first 24 hrs (per point added)[d]	0.005	-0.111	0.121	0.93	-0.011	-0.128	0.106	0.85
Known non-European origin vs. other [e]	1.902	-2.060	5.864	0.34	1.933	-2.039	5.904	0.33
Known non-Caucasian vs. other[e]	-4.294	-9.338	0.750	0.094	-4.159	-9.193	0.874	0.10
Known not exclusive Dutch or English language vs. other	-0.479	-3.185	2.227	0.72	-0.525	-3.243	2.193	0.70
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.383	-8.510	1.743	0.19	-2.849	-8.040	2.342	0.28
Educational level 2	-2.252	-6.601	2.098	0.30	-1.850	-6.234	2.533	0.40
Educational level 2.5	-3.961	-8.586	0.663	0.092	-3.364	-8.009	1.280	0.15
Educational level 3	-3.754	-8.451	0.943	0.11	-3.251	-7.998	1.496	0.17
Educational level unknown	-2.156	-7.533	3.221	0.42	-1.668	-7.105	3.770	0.54
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	1.617	-6.176	9.410	0.68	1.218	-6.597	9.034	0.75
Occupational level 2	1.903	-5.876	9.682	0.63	1.382	-6.410	9.174	0.72
Occupational level 2.5	1.416	-6.695	9.528	0.73	0.718	-7.412	8.847	0.86
Occupational level 3	0.828	-7.068	8.724	0.83	0.237	-7.661	8.135	0.95
Occupational level 3.5	-2.904	-11.297	5.489	0.49	-3.499	-11.894	4.896	0.41
Occupational level 4	1.026	-7.130	9.183	0.80	0.218	-7.962	8.399	0.95

Table S1-3. Multivariable linear regression analyses determining significant and independent associations between risk factors and meta-cognition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Occupational level unknown	1.409	-6.541	9.359	0.72	0.899	-7.064	8.861	0.82
Parental smoking between birth and PICU admission vs. no smoking	0.770	-1.592	3.131	0.51	0.858	-1.503	3.219	0.47
New infection vs. no new infection					0.261	-3.320	3.843	0.88
Duration of stay in the PICU (per day added)					-0.042	-0.328	0.244	0.77
Days with hypoglycemic event (per day added)					-0.262	-2.237	1.714	0.79
Duration of mechanical ventilatory support (per day added)					-0.090	-0.288	0.108	0.36
Duration of treatment with antibiotics (per day added)					0.070	-0.206	0.346	0.61
Duration of hemodynamic support (per day added)					-0.048	-0.249	0.153	0.63
Duration of treatment with corticosteroids (per day added)					0.053	-0.279	0.386	0.75
Duration of treatment with opioids (per day added)					-0.103	-0.389	0.183	0.48
Duration of treatment with benzodiazepines (per day added)					0.328	0.067	0.590	0.014
Duration of treatment with hypnotics (per day added)					0.032	-0.254	0.319	0.82
Duration of treatment with α2-agonists (per day added)					-0.235	-0.495	0.025	0.076

PeLOD = Pediatric Logistic Organ Dysfunction score; PICU = pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition.
For meta-cognition as reported by parents, higher scores reflect worse performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-4. Multivariable linear regression analyses determining significant and independent associations between risk factors and overall executive functioning as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***-2.258***	***-4.012***	***-0.504***	***0.011***	***-2.181***	***-3.953***	***-0.409***	***0.015***
Centre								
Leuven vs. Edmonton	3.856	-3.580	11.291	0.30	4.479	-3.043	12.001	0.24
Rotterdam vs. Edmonton	3.164	-4.370	10.699	0.40	2.874	-4.744	10.493	0.45
Male vs. female sex	0.990	-0.826	2.806	0.28	0.977	-0.841	2.796	0.29
Right vs. left hand preference	0.295	-2.397	2.986	0.82	0.404	-2.232	3.039	0.76
Medium vs. high STRONGkids risk level[a]	-0.324	-3.425	2.777	0.83	-0.053	-3.211	3.106	0.97
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.051	-5.824	1.722	0.28	-1.943	-5.732	1.847	0.31
Burns	1.883	-14.275	18.041	0.81	0.303	-16.376	16.983	0.97
Neurosurgery - traumatic brain injury	2.165	-1.441	5.770	0.23	1.896	-1.712	5.505	0.30
Thoracic	-1.916	-6.216	2.383	0.38	-1.812	-6.154	2.529	0.41
Transplantation	6.550	-0.796	13.896	0.080	6.490	-1.812	14.793	0.12
Orthopedic surgery-trauma	0.235	-5.239	5.710	0.93	0.026	-5.466	5.517	0.99
Other	4.937	0.015	9.858	0.049	4.123	-0.923	9.168	0.10
Medical								
Cardiac	2.858	-2.373	8.089	0.28	1.891	-3.581	7.362	0.49
Gastrointestinal-hepatic	13.977	-1.084	29.038	0.068	13.632	-1.377	28.640	0.074
Hematologic-oncologic	1.544	-7.245	10.333	0.73	-0.418	-9.711	8.875	0.92
Neurologic	-0.445	-4.596	3.706	0.83	-1.077	-5.314	3.160	0.61
Respiratory	-0.999	-4.628	2.631	0.58	-1.492	-5.206	2.223	0.42
Other	-0.949	-5.599	3.701	0.68	-1.363	-6.189	3.464	0.57

Table S1-4. Multivariable linear regression analyses determining significant and independent associations between risk factors and overall executive functioning as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Infant (age<1y) vs. child at randomization	0.317	-1.608	2.242	0.74	0.386	-1.634	2.406	0.70
Malignancy vs. no malignancy	-0.038	-4.162	4.085	0.98	-0.131	-4.290	4.028	0.95
Diabetes vs. no diabetes	2.475	-20.377	25.328	0.83	4.192	-18.640	27.025	0.71
Syndrome vs. no syndrome[b]	5.082	2.013	8.152	0.0012	5.296	2.202	8.390	0.00086
PIM3 score (per point added)[c]	0.194	-0.695	1.082	0.66	0.121	-0.805	1.048	0.79
PeLOD score first 24 hrs (per point added)[d]	0.026	-0.089	0.140	0.66	0.009	-0.107	0.125	0.88
Known non-European origin vs. other[e]	1.782	-2.000	5.563	0.35	1.779	-2.001	5.559	0.35
Known non-Caucasian vs. other[e]	-4.530	-9.283	0.222	0.061	-4.265	-9.022	0.492	0.078
Known not exclusive Dutch or English language vs. other	0.066	-2.585	2.718	0.96	-0.003	-2.665	2.659	0.99
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.958	-9.112	1.196	0.13	-3.283	-8.492	1.927	0.21
Educational level 2	-2.614	-7.009	1.782	0.24	-2.119	-6.552	2.314	0.34
Educational level 2.5	-4.118	-8.777	0.541	0.083	-3.422	-8.103	1.259	0.15
Educational level 3	-4.625	-9.360	0.111	0.055	-4.032	-8.806	0.742	0.097
Educational level unknown	-0.202	-5.678	5.273	0.94	0.386	-5.139	5.910	0.89
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	2.929	-4.880	10.738	0.46	2.240	-5.573	10.053	0.57
Occupational level 2	3.469	-4.305	11.244	0.38	2.652	-5.129	10.433	0.50
Occupational level 2.5	3.334	-4.693	11.361	0.41	2.298	-5.752	10.348	0.57
Occupational level 3	2.959	-4.955	10.873	0.46	2.159	-5.758	10.077	0.59
Occupational level 3.5	-0.484	-8.917	7.948	0.91	-1.317	-9.760	7.125	0.75
Occupational level 4	3.326	-4.857	11.508	0.42	2.245	-5.979	10.468	0.59

Table S1-4. Multivariable linear regression analyses determining significant and independent associations between risk factors and overall executive functioning as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Occupational level unknown	2.792	-5.114	10.698	0.48	2.085	-5.836	10.006	0.60
Parental smoking between birth and PICU admission vs. no smoking	1.022	-1.242	3.285	0.37	1.144	-1.108	3.396	0.31
New infection vs. no new infection					-0.356	-3.782	3.070	0.83
Duration of stay in the PICU (per day added)					0.045	-0.236	0.326	0.75
Days with hypoglycemic event (per day added)					-0.670	-2.632	1.293	0.50
Duration of mechanical ventilatory support (per day added)					-0.123	-0.323	0.076	0.22
Duration of treatment with antibiotics (per day added)					-0.017	-0.282	0.247	0.89
Duration of hemodynamic support (per day added)					-0.071	-0.272	0.130	0.48
Duration of treatment with corticosteroids (per day added)					0.073	-0.251	0.396	0.65
Duration of treatment with opioids (per day added)					-0.102	-0.381	0.177	0.47
Duration of treatment with benzodiazepines (per day added)					0.368	0.111	0.625	0.0050
Duration of treatment with hypnotics (per day added)					0.078	-0.206	0.363	0.58
Duration of treatment with α2-agonists (per day added)					-0.260	-0.516	-0.003	0.047

PeLOD = Pediatric Logistic Organ Dysfunction score; PICU = pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition.
For overall executive functioning as reported by parents, higher scores reflect worse performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-5. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***-1.715***	***-3.325***	***-0.106***	***0.036***	***-1.810***	***-3.441***	***-0.179***	***0.029***
Centre								
Leuven vs. Edmonton	4.664	-1.959	11.287	0.16	4.377	-2.421	11.175	0.20
Rotterdam vs. Edmonton	3.024	-3.740	9.787	0.37	2.464	-4.455	9.383	0.48
Male vs. female sex	1.483	-0.241	3.207	0.091	1.427	-0.303	3.157	0.10
Right vs. left hand preference	0.103	-2.410	2.616	0.93	0.159	-2.327	2.645	0.89
Medium vs. high STRONGkids risk level[a]	-0.069	-2.880	2.742	0.96	0.170	-2.702	3.042	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.597	-2.874	4.068	0.73	0.672	-2.793	4.138	0.70
Burns	8.641	-6.396	23.679	0.25	8.965	-6.524	24.454	0.25
Neurosurgery - traumatic brain injury	3.809	0.528	7.089	0.022	3.699	0.412	6.985	0.027
Thoracic	-1.001	-5.006	3.004	0.62	-0.765	-4.811	3.280	0.70
Transplantation	7.503	0.677	14.328	0.031	8.683	0.985	16.381	0.027
Orthopedic surgery-trauma	-0.017	-5.137	5.102	0.99	-0.105	-5.263	5.053	0.96
Other	2.924	-1.639	7.487	0.20	2.192	-2.432	6.815	0.35
Medical								
Cardiac	2.955	-2.044	7.954	0.24	2.199	-3.080	7.479	0.41
Gastrointestinal-hepatic	10.723	-4.646	26.091	0.17	10.571	-4.771	25.913	0.17
Hematologic-oncologic	7.972	-0.416	16.361	0.062	7.727	-1.147	16.600	0.087
Neurologic	2.384	-1.535	6.303	0.23	2.119	-1.908	6.146	0.30
Respiratory	1.392	-1.909	4.693	0.40	1.040	-2.386	4.467	0.55
Other	-0.018	-4.367	4.330	0.99	-0.257	-4.787	4.273	0.91

Table S1-5. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Infant (age<1y) vs. child at randomization	1.165	-0.685	3.016	0.21	0.660	-1.293	2.614	0.50
Malignancy vs. no malignancy	-3.056	-7.042	0.931	0.13	-3.143	-7.173	0.887	0.12
Diabetes vs. no diabetes	15.073	-6.806	36.951	0.17	15.892	-5.983	37.767	0.15
Syndrome vs. no syndrome[b]	1.066	-1.763	3.895	0.45	1.180	-1.693	4.052	0.41
PIM3 score (per point added)[c]	0.067	-0.752	0.886	0.87	-0.051	-0.904	0.801	0.90
PeLOD score first 24 hrs (per point added)[d]	0.054	-0.052	0.161	0.31	0.041	-0.067	0.150	0.45
Known non-European origin vs. other[e]	-0.480	-4.171	3.210	0.79	-0.425	-4.123	3.272	0.82
Known non-Caucasian vs. other[e]	-2.054	-6.511	2.404	0.36	-1.933	-6.383	2.517	0.39
Known not exclusive Dutch or English language vs. other	2.015	-0.467	4.496	0.11	1.989	-0.496	4.474	0.11
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-1.008	-5.866	3.851	0.68	-0.433	-5.377	4.510	0.86
Educational level 2	0.382	-3.730	4.494	0.85	0.763	-3.413	4.939	0.71
Educational level 2.5	-1.791	-6.206	2.624	0.42	-1.300	-5.762	3.163	0.56
Educational level 3	-2.165	-6.604	2.274	0.33	-1.684	-6.184	2.815	0.46
Educational level unknown	1.718	-2.986	6.422	0.47	2.140	-2.621	6.900	0.37
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.469	-7.078	8.015	0.90	0.079	-7.465	7.624	0.98
Occupational level 2	2.858	-4.657	10.373	0.45	2.361	-5.147	9.869	0.53
Occupational level 2.5	1.806	-5.933	9.546	0.64	1.312	-6.437	9.060	0.73
Occupational level 3	1.638	-6.002	9.277	0.67	1.398	-6.242	9.039	0.71
Occupational level 3.5	-0.323	-8.366	7.719	0.93	-0.465	-8.512	7.583	0.90
Occupational level 4	0.810	-7.026	8.647	0.83	0.287	-7.581	8.154	0.94

Table S1-5. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Occupational level unknown	0.795	-6.737	8.326	0.83	0.450	-7.064	7.963	0.90
Parental smoking between birth and PICU admission vs. no smoking	2.017	-0.063	4.096	0.057	2.142	0.071	4.214	0.042
New infection vs. no new infection					-0.771	-3.886	2.344	0.62
Duration of stay in the PICU (per day added)					0.112	-0.157	0.381	0.41
Days with hypoglycemic event (per day added)					1.425	-0.477	3.328	0.14
Duration of mechanical ventilatory support (per day added)					-0.113	-0.295	0.070	0.22
Duration of treatment with antibiotics (per day added)					-0.062	-0.314	0.189	0.62
Duration of hemodynamic support (per day added)					-0.101	-0.286	0.084	0.28
Duration of treatment with corticosteroids (per day added)					-0.055	-0.363	0.253	0.72
Duration of treatment with opioids (per day added)					-0.111	-0.371	0.150	0.40
Duration of treatment with benzodiazepines (per day added)					0.304	0.064	0.544	0.013
Duration of treatment with hypnotics (per day added)					0.042	-0.226	0.310	0.76
Duration of treatment with α2-agonists (per day added)					-0.200	-0.446	0.046	0.11

PeLOD = Pediatric Logistic Organ Dysfunction score; PICU = pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition.
For externalizing problems as reported by parents, higher scores reflect worse performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-6. Multivariable linear regression analyses determining significant and independent associations between risk factors and visual-motor integration at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Randomization to late vs. early initiation of PN	***0.468***	***0.087***	***0.850***	***0.016***	***0.422***	***0.037***	***0.807***	***0.031***
Centre								
Leuven vs. Edmonton	5.647	3.729	7.566	<0.0001	5.449	3.506	7.391	<0.0001
Rotterdam vs. Edmonton	4.879	3.032	6.727	<0.0001	4.834	2.961	6.708	<0.0001
Male vs. female sex	-0.789	-1.178	-0.400	<0.0001	-0.794	-1.185	-0.403	<0.0001
Right vs. left hand preference	0.544	-0.091	1.179	0.092	0.542	-0.101	1.185	0.098
Medium vs. high STRONGkids risk level[a]	0.339	-0.334	1.013	0.32	0.270	-0.417	0.958	0.44
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.449	-0.358	1.255	0.27	0.372	-0.436	1.180	0.36
Burns	0.585	-3.065	4.235	0.75	1.054	-2.699	4.807	0.58
Neurosurgery - traumatic brain injury	-0.037	-0.786	0.713	0.92	0.031	-0.717	0.778	0.93
Thoracic	0.630	-0.273	1.533	0.17	0.528	-0.380	1.436	0.25
Transplantation	-1.738	-3.224	-0.253	0.021	-1.099	-2.725	0.527	0.18
Orthopedic surgery-trauma	-2.207	-3.346	-1.069	0.00015	-2.236	-3.378	-1.094	0.00013
Other	0.245	-0.849	1.340	0.65	0.289	-0.817	1.395	0.60
Medical								
Cardiac	0.128	-1.022	1.277	0.82	0.333	-0.894	1.560	0.59
Gastrointestinal-hepatic	0.245	-2.770	3.260	0.87	0.239	-2.761	3.239	0.87
Hematologic-oncologic	1.275	-0.776	3.326	0.22	1.891	-0.263	4.045	0.085
Neurologic	-0.472	-1.371	0.427	0.30	-0.268	-1.189	0.652	0.56
Respiratory	0.506	-0.233	1.246	0.17	0.445	-0.315	1.206	0.25
Other	-0.180	-1.188	0.827	0.72	-0.279	-1.324	0.767	0.60

Table S1-6. Multivariable linear regression analyses determining significant and independent associations between risk factors and visual-motor integration at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				**Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments**			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Infant (age<1y) vs. child at randomization	1.228	0.799	1.657	<0.0001	1.179	0.736	1.622	<0.0001
Malignancy vs. no malignancy	0.014	-0.945	0.972	0.97	0.196	-0.771	1.163	0.69
Diabetes vs. no diabetes	0.511	-4.802	5.823	0.85	-0.090	-5.383	5.204	0.97
Syndrome vs. no syndrome[b]	-1.336	-1.985	-0.687	<0.0001	-1.474	-2.125	-0.823	<0.0001
PIM3 score (per point added)[c]	0.017	-0.169	0.203	0.85	0.028	-0.163	0.219	0.77
PeLOD score first 24 hrs (per point added)[d]	-0.015	-0.039	0.010	0.23	-0.012	-0.037	0.013	0.34
Known non-European origin vs. other[e]	-0.144	-0.901	0.613	0.70	-0.133	-0.888	0.622	0.72
Known non-Caucasian vs. other[e]	-0.278	-1.197	0.642	0.55	-0.333	-1.250	0.585	0.47
Known not exclusive Dutch or English language vs. other	0.350	-0.231	0.932	0.23	0.381	-0.201	0.962	0.19
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	0.121	-1.036	1.279	0.83	0.029	-1.143	1.201	0.96
Educational level 2	0.500	-0.469	1.469	0.31	0.413	-0.565	1.391	0.40
Educational level 2.5	0.419	-0.614	1.451	0.42	0.319	-0.717	1.355	0.54
Educational level 3	0.988	-0.062	2.037	0.062	0.883	-0.173	1.939	0.10
Educational level unknown	0.235	-0.769	1.238	0.64	0.080	-0.931	1.091	0.87
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.643	-1.186	2.472	0.49	0.807	-1.015	2.630	0.38
Occupational level 2	0.687	-1.140	2.515	0.46	0.808	-1.016	2.631	0.38
Occupational level 2.5	0.899	-0.990	2.789	0.35	1.075	-0.812	2.961	0.26
Occupational level 3	1.079	-0.766	2.924	0.25	1.228	-0.610	3.065	0.19
Occupational level 3.5	0.669	-1.295	2.634	0.50	0.766	-1.193	2.725	0.44
Occupational level 4	0.392	-1.520	2.304	0.68	0.625	-1.286	2.536	0.52
Occupational level unknown	0.506	-1.314	2.327	0.58	0.619	-1.196	2.434	0.50

Table S1-6. Multivariable linear regression analyses determining significant and independent associations between risk factors and visual-motor integration at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late PN vs Early PN and for post-randomization treatments			
Variable	**Beta-estimate**	**Confidence interval**		***p*-value**	**Beta-estimate**	**Confidence interval**		***p*-value**
Parental smoking between birth and PICU admission vs. no smoking	-0.247	-0.729	0.235	0.31	-0.293	-0.765	0.180	0.22
New infection vs. no new infection					0.043	-0.672	0.759	0.90
Duration of stay in the PICU (per day added)					-0.026	-0.089	0.037	0.41
Days with hypoglycemic event (per day added)					0.256	-0.175	0.687	0.24
Duration of mechanical ventilatory support (per day added)					0.026	-0.015	0.068	0.21
Duration of treatment with antibiotics (per day added)					0.027	-0.033	0.086	0.37
Duration of hemodynamic support (per day added)					-0.025	-0.068	0.019	0.26
Duration of treatment with corticosteroids (per day added)					-0.078	-0.148	-0.007	0.030
Duration of treatment with opioids (per day added)					0.022	-0.039	0.084	0.47
Duration of treatment with benzodiazepines (per day added)					-0.035	-0.093	0.022	0.22
Duration of treatment with hypnotics (per day added)					-0.053	-0.118	0.011	0.10
Duration of treatment with α2-agonists (per day added)					0.078	0.021	0.134	0.0074

PeLOD = Pediatric Logistic Organ Dysfunction score; PICU= pediatric intensive care unit; PIM3 = Pediatric Index of Mortality 3 score; PN = parenteral nutrition.
For visual-motor integration, higher scores reflect better performance.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
b A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[18]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S2. Comparison of patients randomized to late parenteral nutrition during PICU stay with healthy control children for the tests significantly affected by the randomized intervention

Neurocognitive function	***p*-value**
Visual-motor integration	0.00052
Externalizing problems as reported by parents/caregivers	0.34
Inhibition as reported by parents/caregivers	0.66
Working memory as reported by parents/caregivers	0.032
Meta-cognition index as reported by parents/caregivers	0.34
Overall executive functioning as reported by parents/caregivers	0.12

Table S3. Impact of late versus early parenteral nutrition in infants for tests showing a significant interaction *p*-value with age group

Variable	**Beta-estimate**	**Confidence interval**		***p*-value**
Overall executive functioning	-3.843	-6.361	-1.325	0.0029
Meta-cognition	-3.749	-6.244	-1.254	0.0034
Working memory	-3.594	-6.052	-1.135	0.0043

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CHAPTER 5

Role of age of critically ill children at time of exposure to early or late parenteral nutrition in determining the impact hereof on long-term neurocognitive development

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Abstract

Background and aims Early use of parenteral nutrition (Early PN), as compared with withholding it for one week (Late PN), in the PICU, has shown to slow down recovery from critical illness and impair long-term development of 6 neurocognitive/behavioral/emotional functions assessed 2 years later. Given that key steps in brain maturation occur at different times during childhood, we hypothesized that age at time of exposure determines long-term developmental impact of Early PN.

Methods The 786 children who were neurocognitively tested 2 years after participation in the PEPaNIC-RCT were included in this study. First, for each studied long-term outcome, interaction between randomization to Early PN versus Late PN and age was assessed with multivariable linear regression analysis. Subsequently, for outcomes with an interaction p≤0.15, the impact of Early PN versus Late PN was analyzed, after adjustment for risk factors, for 4 subgroups defined based on developmentally-relevant age at time of exposure [≤28 days (n=121), 29 days to 11 months (n=239), 11 months to <5 years (n=223) and ≥5 years (n=203)].

Results Interaction between randomization and age was present for weight, and parent-reported inhibitory control, cognitive flexibility, working memory, planning/organization, metacognition, total executive functioning, and internalizing and total behavioral/emotional problems. Subgroup analyses revealed that none of the age-groups revealed benefit, whereas children aged 29 days to <11 months were most vulnerable to harm by Early PN for development of inhibitory control (p=0.008), working memory (p=0.009), planning/organization (p=0.004), metacognition (p=0.008), and total executive functioning (p=0.004), and for internalizing (p=0.005) and total behavioral/emotional problems (p=0.01). Children aged 11 months to <5 years revealed harm by Early PN for development of inhibitory control (p=0.003). In contrast, children aged ≥5 years and neonates aged ≤28 days appeared less vulnerable.

Conclusions Critically ill children aged 29 days to 11 months at time of exposure were identified as most vulnerable to developmental harm evoked by Early PN.

Introduction

Children who have been critically ill often suffer from adverse health sequelae that remain present years after hospital discharge.[1-4] Recently, it has been shown that the nutritional management of patients treated in the pediatric intensive care unit (PICU) can modify short-term outcome as well as the long-term legacy.[5-9] The multicenter 'Pediatric Early versus Late Parenteral Nutrition in Critical Illness – PEPaNIC' randomized controlled trial (RCT) has shown that targeting full nutritional intake early by early initiation of supplemental parenteral nutrition when enteral nutrition is insufficient ('Early PN') was clinically inferior to accepting the macronutrient deficit that accumulates by postponing any supplemental PN to beyond the first week in the PICU ('Late PN').[6-8] Early PN was found to increase the risk of infection and to delay recovery from critical illness. Apart from these harmful short-term effects, Early PN also showed to negatively affect the development of 6 neurocognitive and behavioral/emotional functions, as assessed 2 years later, with worse inhibitory control, working memory, metacognition, total executive functioning, more externalizing behavioral problems and worse visual-motor integration.[9] These long-term adverse effects of Early PN were found to be mediated by altered DNA-methylation of genes involved in brain development.[10]

Given that the age-range of children who are admitted to the PICU is wide (0 to 17 years old), it is theoretically possible that exposure to Early PN versus Late PN has a different developmental impact depending on the age at time of exposure. Indeed, it is known that exposure to adverse environmental factors during different time windows of childhood can affect brain development either along or away from the normal trajectory.[11-13] Although stages of brain development are not strictly and uniformly timed for an individual child, it is generally accepted that a major brain growth spurt with a steep rise in synaptogenesis for higher cognitive functions occurs from the age of about 1 month until about 11 to 12 months.[11,14-19] This is followed by a plateau in synaptogenesis and initiation of synapse regression referred to as "pruning" until the age of about 5 years. Thereafter, synaptogenesis tapers off and pruning predominates. Hence, we hypothesized that the age at which children are admitted to the PICU may determine whether exposure to Early PN, as compared with Late PN, evokes long-term developmental harm or benefit. Indeed, although for the total population, Early PN was found to adversely affect development of 6 neurocognitive and behavioral/emotional functions, it is possible that the impact of Early PN depends on the age at exposure and, consequently, a neutral outcome for the total patient population may hide benefit for one and harm for another age-group.

To test this hypothesis, we performed a secondary analysis of the PEPaNIC-RCT, in which interaction between randomization to Early PN versus Late PN and age at time of exposure was first determined for all developmental outcomes assessed at

2-year follow-up, with subsequent subgroup analyses for 4 developmentally-relevant age-groups.

Materials and Methods

Study design and participants

This study is a secondary analysis of the multicenter PEPaNIC-RCT that included 1440 critically ill children (0-17 years) admitted to the PICUs of Leuven (Belgium), Rotterdam (The Netherlands) and Edmonton (Canada).[7] The full study protocol has been published.[6]

From the total PEPaNIC-RCT patient population, 786 patients, 391 from the Early PN group and 395 from the Late PN group, were assessed for physical, neurocognitive and behavioral/emotional functions 2 years later (**Figure 1**).[9] Children who were neonates or infants younger than 6 months old at PICU admission were assessed at the age of 2.5 years, because this is the youngest age for appropriate assessment of parent-reported or caregiver-reported executive functioning (with the Behavior Rating Inventory of Executive Function [BRIEF]) in combination with a general intelligence test (Wechsler Preschool and Primary Scale of Intelligence [WPPSI]). Inclusion date for follow-up of the other children was 2 years after the date of inclusion in the PEPaNIC-RCT, with an ideal window of 3 months and an accepted window of 6 months before or after this follow-up inclusion date. These 786 patients were included in the present secondary analysis.

Study approval by the institutional review boards of the participating centers (ML8052; NL49708.078; Pro00038098) and written informed consent from the parents or legal guardians and from the child when reaching adolescent age were obtained according to local regulations. The study was performed in accordance with the 1964 Declaration of Helsinki and its amendments.

Randomization and masking

Patients had been randomized to Early PN or Late PN.[6,7] In the Early PN group, supplemental PN was initiated within 24 hours after PICU admission when enteral nutrition was insufficient to reach nutritional targets (**Tables S1-2, Figure S1**). In the Late PN group, such supplemental PN was withheld in the first week of PICU stay (which meant no PN for the majority of the patients in view of discharge before day 8) and patients received a mixture of glucose 5% and sodium chloride 0.9% to match fluid intake. After one week, for both groups equally, PN could be administered if necessary. When enteral nutrition covered 80% or more of the calculated targets, supplemental parenteral nutrition was discontinued.

Participants were assessed for developmental outcomes either at the hospital or at home by physicians and experienced pediatric psychologists who were strictly masked for treatment allocation.[9] Parents had not been masked during the time the child was treated in the PICU and were not actively informed about the initial PEPaNIC-study results.

Developmental outcomes

Clinical tests and validated, internationally recognized questionnaires with adequate normative data were used to assess physical, neurocognitive and behavioral/emotional development in the 2-year PEPaNIC follow-up study.[1,9] Studied outcomes available for all ages were growth, performance on clinical neurological examination, executive functions, behavioral and emotional problems, general intellectual functioning and visual-motor integration.[9]

To assess growth, body weight, height, and head circumference were measured. A clinical neurological examination was done to assess signs of major neurologic dysfunction in interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves and special senses (sensory, visual and auditory functions). These domains were all scored normal (score 0) or abnormal (score 1), yielding a total score ranging from 0 to 8. Parents or caregivers completed BRIEF questionnaires on executive functioning of their child. For children aged 2.5-5 years 11 months, the preschool version (BRIEF-P) was used and for children aged 6-18 years the child version (BRIEF) was used.[20,21] Only the overlapping domains of the two questionnaires were analyzed: inhibitory control, cognitive flexibility, emotional control, working memory, planning and organization, metacognition and total executive functioning. All scores of the BRIEF questionnaires were reported as T scores, with mean 50 [SD 10]. Higher scores in this questionnaire represent more problems with everyday executive functioning. Parents or caregivers were also asked to complete the Child Behavior Checklist (CBCL) questionnaires (two versions depending on the age of the child: CBCL 1.5-5 years 11 months or CBCL 6-18 years) to assess behavioral and emotional problems of the children. Internalizing, externalizing and total behavioral and emotional problems were analyzed (T scores with mean 50 [SD 10]).[22,23] Higher scores on this questionnaire represent more problems. General intellectual ability was assessed with use of the age-appropriate versions of the Wechsler intelligence quotient (IQ) scale. The Wechsler Preschool and Primary Scale of Intelligence WPPSI-III-NL[24] was used for children aged between 2.5 and 5 years 11 months, the Wechsler Intelligence Scale for Children (WISC-III-NL)[25] was used for children aged between 6 and 16 year 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[26] was used for adolescents and young adults who were 17 years or older. For all Wechsler tests, total IQ, verbal IQ, and performance IQ scores (test mean 100 [SD 15]) were computed, with higher scores representing better general intellectual ability. The Beery Developmental Test of Visual-Motor

Integration[27] was used to assess the ability to integrate visual and motor functions, involving eye-hand coordination (total scaled score, with test mean 10 [SD 3]). A higher score indicates better visual-motor integration. A detailed description of the outcome measures is available in the appendix.

Statistical analysis

As previously described,[9] multiple data imputation by chained equations was performed to correctly address partial responses.[28] To avoid bias and instability in this imputation model, the percentage of missing data per variable could not exceed 30% and thus the number of iterative imputations was set at 31.[9,28] For each outcome, *p*-values for the interaction between the randomized intervention (Early PN versus Late PN) and age at time of exposure were determined with use of multivariable linear regression analysis. These analyses were adjusted for the risk factors center, sex, race, geographical origin, language, the education and occupational status of the parents (appendix), risk of malnutrition (screening tool for risk on nutritional status and growth [STRONGkids] score), severity of illness upon PICU admission (pediatric index of mortality 3 [PIM3] score and pediatric logistic organ dysfunction scores [PeLOD] score), diagnosis group (surgical-cardiac, surgical-other, neurosurgery/neurology, trauma/burn, transplantation/hematology/oncology, medical-other), history of malignancy, diabetes, a predefined syndrome (appendix), and, parental smoking behavior. Subsequently, for those outcomes that revealed an interaction *p*-value ≤0.15, the effect of Early PN versus Late PN was assessed for 4 *a priori* defined age subgroups separately, with multivariable linear regression analysis adjusted for the same risk factors. These 4 *a priori* defined age subgroups [≤28 days old, 29 days to <11 months old, 11 months to <5 years old, and 5 years or older] were identified based on previously reported timing of cerebral maturation spurts and synaptogenesis of higher cognitive functions[11,14-19] and with the aim to obtain, as much as possible, samples of relatively comparable size.

All multivariable linear regression analyses were performed on the 31 imputed datasets with β-estimates and *p*-values reported as pooled results. In order to correct for multiple comparisons, two-sided *p*-values of 0.01 or less were considered statistically significant. Statistical analyses were performed with use of R version 3.5.3 and JMP© version 14.0.0 (SAS Institute, Inc, Cary, NC).

Results

Among the 786 children who underwent physical, neurocognitive and behavioral/emotional developmental testing 2 years after randomization to Early PN or Late PN, 121 were ≤28 days old (56 Early PN and 65 Late PN), 239 were 29 days to <11 months old (120 Early PN and 119 Late PN), 223 were 11 months to <5 years old (110 Early PN and 113 Late PN) and 203 were 5 years or older (105 Early PN and 98 Late PN) (**Figure**

1). Patient demographics and medical characteristics upon PICU admission are shown in **Table 1**. Total energy intake and blood glucose levels of Early PN versus Late PN patients of each age group are shown in **Figures S1–2** for the first 7 days in PICU.

Interaction between randomization to Early PN versus Late PN and age at time of exposure was identified for 9 developmental outcomes: weight, development of inhibitory control, cognitive flexibility, working memory, planning and organization, metacognition, and total executive functioning, and internalizing and total behavioral and emotional problems (**Table 2**). No interaction between randomization to Early PN versus Late PN and age at exposure was present for height, head circumference, clinical neurological evaluation score, externalizing behavioral problems, verbal IQ, performance IQ and total IQ and visual-motor-integration. Hence, the harmful effect of randomization to Early PN, versus Late PN, previously identified for externalizing behavioral and emotional problems and visual-motor-integration, was not determined by age at time of exposure and was present across all ages.[9]

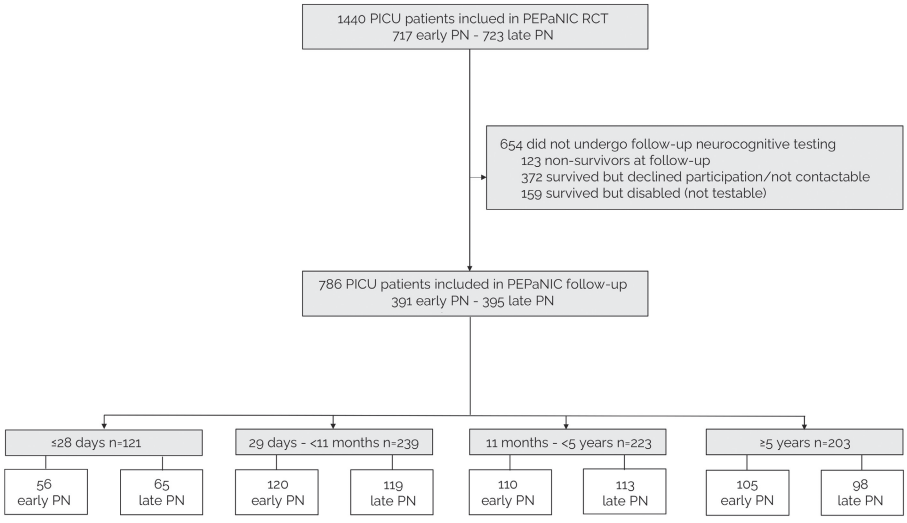

Figure 1. CONSORT diagram of study participants

Table 1. Patient demographics and medical characteristics

	≤28d (n=121)		29d - <11m (n=239)		11m - <5y (n=223)		≥5y (n=203)	
	Early PN (n=56)	**Late PN (n=65)**	**Early PN (n=120)**	**Late PN (n=119)**	**Early PN (n=110)**	**Late PN (n=113)**	**Early PN (n=105)**	**Late PN (n=98)**
Demographics								
Age								
At randomization, years	0.02 (0.02)	0.02 (0.02)	0.38 (0.2)	0.37 (0.2)	2.74 (1.1)	2.59 (1.2)	10.24 (3.5)	10.68 (3.7)
At 2-year follow-up, years	2.57 (0.07)	2.56 (0.06)	2.65 (0.2)	2.65 (0.2)	4.61 (1.2)	4.47 (1.2)	12.14 (3.5)	12.55 (3.7)
Sex								
Female	22 (39%)	28 (43%)	42 (35%)	49 (41%)	50 (45%)	50 (44%)	47 (45%)	43 (44%)
Male	34 (61%)	37 (57%)	78 (65%)	70 (59%)	60 (55%)	63 (56%)	58 (55%)	55 (56%)
Known non-white race‡	7 (12%)	2 (3%)	16 (13%)	8 (7%)	7 (6%)	11 (10%)	8 (8%)	4 (4%)
Known non-European origin‡	10 (18%)	8 (12%)	35 (30%)	19 (16%)	22 (20%)	28 (25%)	21 (20%)	9 (9%)
Known non-exclusive Dutch or English language	13 (23%)	11 (17%)	29 (24%)	29 (24%)	24 (22%)	34 (30%)	29 (28%)	15 (15%)
Socioeconomic status								
Parents educational level 1	6 (11%)	8 (12%)	13 (11%)	17 (14%)	10 (9%)	11 (10%)	11 (10%)	15 (15%)
Parents educational level 2	28 (50%)	27 (42%)	46 (38%)	42 (35%)	53 (39%)	52 (46%)	39 (37%)	38 (38%)
Parents educational level 3	11 (20%)	20 (31%)	33 (28%)	37 (31%)	32 (29%)	19 (17%)	24 (23%)	24 (23%)
Parents educational level unknown	11 (20%)	10 (15%)	28 (23%)	23 (19%)	25 (23%)	31 (27%)	31 (30%)	21 (21%)
Parents occupational level 1	6 (11%)	8 (12%)	11 (9%)	14 (12%)	6 (5%)	16 (14%)	12 (11%)	13 (13%)
Parents occupational level 2	10 (18%)	16 (25%)	32 (27%)	31 (26%)	30 (27%)	16 (14%)	33 (31%)	24 (24%)
Parents occupational level 3	11 (20%)	14 (22%)	29 (24%)	25 (21%)	29 (26%)	28 (25%)	17 (16%)	26 (27%)
Parents occupational level 4	7 (13%)	13 (20%)	16 (13%)	25 (21%)	17 (15%)	24 (22%)	13 (12%)	5 (5%)
Parents occupational level unknown	22 (39%)	14 (22%)	32 (27%)	24 (20%)	28 (25%)	33 (29%)	30 (29%)	30 (31%)
Patient characteristics upon PICU admission								
STRONGkids risk level								

Table 1. Patient demographics and medical characteristics

	≤28d (n=121)		29d - <11m (n=239)		11m - <5y (n=223)		≥5y (n=203)	
	Early PN (n=56)	**Late PN (n=65)**	**Early PN (n=120)**	**Late PN (n=119)**	**Early PN (n=110)**	**Late PN (n=113)**	**Early PN (n=105)**	**Late PN (n=98)**
Medium	39 (70%)	54 (83%)	109 (91%)	105 (88%)	106 (96%)	105 (93%)	97 (92%)	92 (94%)
High	17 (30%)	11 (17%)	11 (9%)	14 (12%)	4 (4%)	8 (7%)	8 (8%)	6 (6%)
PeLOD score. first 24h in PICU	17.8 (11.7)	17.9 (11.0)	20.7 (11.2)	21.9 (11.5)	21.7 (11.8)	19.8 (11.1)	18.5 (11.7)	19.5 (12.1)
PIM3 score	-2.87 (1.3)	-3.1 (1.4)	-3.6 (1.3)	-3.5 (1.2)	-3.4 (1.4)	-3.6 (1.3)	-3.6 (1.5)	-3.7 (1.5)
Diagnostic category								
Surgical-cardiac	20 (36%)	23 (35%)	70 (58%)	60 (50%)	47 (43%)	46 (41%)	36 (34%)	37 (38%)
Surgical-other	25 (45%)	28 (43%)	16 (13%)	17 (14%)	13 (12%)	12 (11%)	13 (12%)	15 (15%)
Neurosurgery/neurology	0 (0%)	0 (0%)	10 (8%)	12 (10%)	21 (19%)	21 (19%)	29 (28%)	22 (22%)
Trauma/burn	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (5%)	3 (2.7%)	10 (10%)	7 (7%)
Transplantation/hematology/oncology	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	2 (2%)	8 (7%)	6 (6%)	5 (5%)
Medical-other	11 (20%)	14 (22%)	23 (19%)	30 (25%)	22 (20%)	23 (20%)	11 (10%)	12 (12%)
History of malignancy	0 (0%)	0 (0%)	1 (0.08%)	0 (0%)	10 (9%)	7 (6%)	15 (14%)	9 (9%)
Diabetes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Predefined syndrome	3 (5%)	5 (8%)	10 (8%)	16 (13%)	12 (11%)	14 (12%)	9 (9%)	10 (10%)
Parental smoking between birth and PICU admission	26 (48%)	22 (34%)	47 (39%)	40 (34%)	54 (49%)	61 (54%)	57 (54%)	47(48%)

Data are mean (SD) or n (%). STRONGkids: screening tool for risk on nutritional status and growth. PeLOD: pediatric logistic organ dysfunction. PIM3: pediatric index of mortality 3. PICU: pediatric intensive care unit. ǂ Participants were classified according to race and geographical origin by the investigators. The educational and occupational level is the mean of the paternal and maternal educational or occupational level (appendix). STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1–3 indicating a medium risk, and a score of 4–5 indicating a high risk. PeLOD scores range from 0 to 71, with higher scores indicating more severe illness. Higher PIM3 scores indicate a higher risk of mortality. 'Surgical-other' includes abdominal, thoracic or, other surgery. 'Medical-other' includes cardiac, gastrointestinal or hepatic, renal, respiratory, or other medical problems. A predefined syndrome is any pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (appendix).

Table 2. Interaction between randomization to Early PN or Late PN and age at time of exposure in determining developmental outcome (physical, neurocognitive and behavioral/emotional functions) two years later

Developmental outcome	Interaction *p*-value
Physical development	
Weight	0.01*
Height	0.93
Head circumference	0.28
Clinical neurological evaluation score	0.86
Parent- or caregiver-reported executive functions	
Inhibitory control	0.10*
Cognitive flexibility	0.15*
Emotional control	0.29
Working memory	0.02*
Planning and organization	0.004*
Metacognition	0.01*
Total executive functioning	0.01*
Parent- or caregiver-reported behavioral/emotional problems	
Internalizing problems	0.15*
Externalizing problems	0.21
Total behavioral and emotional problems	0.07*
IQ	
Verbal IQ	0.99
Performance IQ	0.60
Total IQ	0.72
Visual-motor integration	0.40

For each developmental outcome, *p*-values for interaction between randomization to Early PN or Late PN and age at randomization were determined with multivariable linear regression analyses in which age was entered as a continuous variable. *interaction *p*-value ≤0.15. Results are computed from the 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption. Covariates entered in the multivariable analyses are: center, sex, race, geographical origin, language, the education and occupational status of the parents (appendix), risk of malnutrition (screening tool for risk on nutritional status and growth [STRONGkids] score), severity of illness upon PICU admission (pediatric index of mortality 3 [PIM3] score and pediatric logistic organ dysfunction [PeLOD] score), diagnosis group (surgical-cardiac, surgical-other, neurosurgery/neurology, trauma/burn, transplantation/hematology/oncology, medical-other), history of malignancy, diabetes, a predefined syndrome (appendix), and, parental smoking behavior before PICU admission.

For the 9 outcomes that revealed interaction between randomization to Early PN versus Late PN and age at time of exposure, none of the age subgroups showed benefit from Early PN. Instead, interaction between randomization to Early PN versus Late PN and age at time of exposure revealed that one subgroup was particularly vulnerable to harm evoked by Early PN whereas other subgroups were less vulnerable. More specifically, neonates aged ≤28 days old and children aged 5 years or older at time of exposure did not appear to suffer from harm by Early PN (**Figure 2**). In contrast, for children aged between 29 days and 11 months at time of exposure, patients in the Early PN group performed much worse than those in the Late PN

group for most neurocognitive and behavioral/emotional functions that showed interaction with age, but not for weight (**Figure 2**). More specifically, children aged between 29 and 11 months at time of exposure to Early PN had worse inhibitory control (β-estimate 4.54, 95% CI 1.21 to 7.87; p=0.008), working memory (β-estimate 4.35, 95% CI 1.10 to 7.60; p=0.009), planning and organization (β-estimate 4.49, 95% CI 1.41 to 7.57; p=0.004), metacognition (β-estimate 4.42, 95% CI 1.15 to 7.69; p=0.008) and overall executive functioning (β-estimate 4.84, 95% CI 1.55 to 8.13; p=0.004) than children exposed to Late PN. Parents or caregivers also reported more behavioral and emotional problems for children aged between 29 and 11 months at time of exposure to Early PN, as compared with Late PN, with more internalizing problems (β-estimate 4.23, 95% CI 1.31 to 7.15; p=0.005) and total behavioral and emotional problems (β-estimate 3.98, 95% CI 0.96 to 7; p=0.01) (**Figure 2**). For children aged between 11 months and 5 years at time of exposure, lower scores were observed with Early PN, as compared with Late PN, for inhibitory control (β-estimate 5.29, 95% CI 1.78 to 8.80; p=0.003), but not for any of the other outcomes (**Figure 2**).

Discussion

This secondary analysis of the PEPaNIC-RCT and its 2-year follow-up study revealed that the administration of Early PN as compared with omitting PN for one week had a different impact on 9 long-term developmental outcomes depending on the age at time of exposure. No age group revealed long-term developmental benefit from Early PN, whereas children aged between 29 days and 11 months at time of exposure, as compared with other age subgroups, appeared most vulnerable to the long-term developmental harm evoked by Early PN.

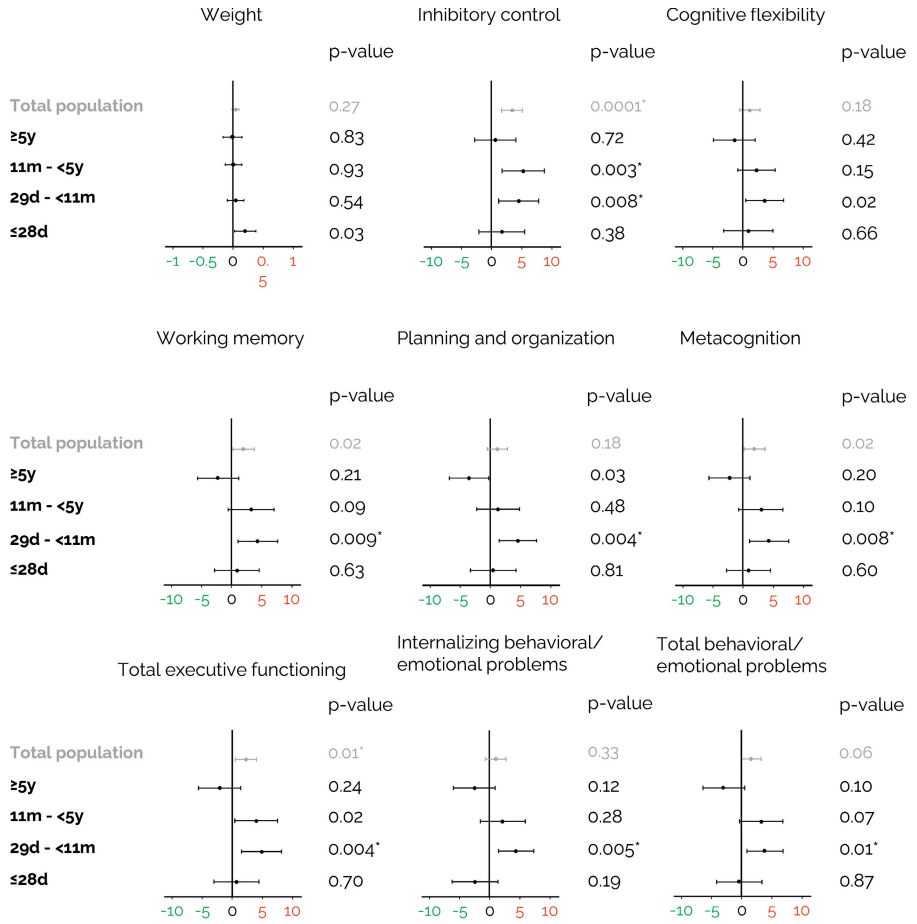

Figure 2. Impact of Early PN, as compared with Late PN, during stay in the PICU on developmental outcome (physical, neurocognitive and behavioral/emotional functions) of children assessed two years later, according to age at time of exposure. Data are presented as β estimate (dot) and 95% CI (line) for the effect of Early PN, versus Late PN, on those outcomes that revealed interaction between randomization and age at time of exposure. Results represent the combined β-estimates and *p*-values from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for 786 PEPaNIC patients divided into 4 a priori defined developmentally-relevant age categories, with data from the total study population, previously published,[9] added for comparison. β-estimates were adjusted for center, sex, race, geographical origin, language, the education and occupational status of the parents (appendix), risk of malnutrition (screening tool for risk on nutritional status and growth [STRONGkids] score), severity of illness upon PICU admission (pediatric index of mortality 3 [PIM3] score and pediatric logistic organ dysfunction [PeLOD] score), diagnosis group (surgical cardiac, surgical-other, neurosurgery/neurology, trauma/burn, transplantation/hematology/oncology, medical-other), history of malignancy, diabetes, a predefined syndrome (appendix), and parental smoking behavior. For the developmental outcomes red indicates worse scores and green indicates better scores. For weight, red indicates 'heavier' and green indicates 'lighter' weight-for-age z-score than the average for that age.

This secondary analysis of the 2-year follow-up of the PEPaNIC RCT revealed that there was interaction between randomization to Early PN versus Late PN and age at time of exposure in determining the long-term developmental consequences of

the use of Early PN. Unlike what we had hypothesized, there was no specific age subgroup that benefited from the use of Early PN that could have been hidden by a neutral outcome in the total PEPaNIC population.[9] Even if not taking into account correction for multiple comparisons, Early PN appeared to affect only a single outcome, i.e. development of planning and organization, in a positive manner. Instead, the interaction between randomization to Early PN versus Late PN and age at time of exposure pointed towards a specific age subgroup that was particularly vulnerable to the long-term developmental harm induced by Early PN, whereas this was less so for the other age subgroups. Indeed, critically ill children exposed to Early PN at an age between 29 and 11 months suffered most, whereas patients who were neonates, aged ≤28 days, and older children aged 5 years or more at time of exposure were least harmed by the use of Early PN, except for the two outcomes previously found to be negatively affected by Early PN in the total population - externalizing behavioral and emotional problems and visual-motor-integration - but for which there was no interaction with age at exposure. Children aged between 29 days and 11 months at time of exposure to Early PN, versus Late PN, had worse scores for the development of 5 higher cognitive functions (inhibitory control, working memory, metacognition, planning and organization, total executive functioning) and suffered more from internalizing and total behavioral and emotional problems as compared with the other age subgroups. The adverse effect of Early PN on development of planning and organization, internalizing and total behavioral and emotional problems documented in this age-group, had not been identified earlier for the total PEPaNIC study population. For development of working memory, metacognition and total executive functioning, the adverse effect of Early PN was larger in this age subgroup than previously identified for the total patient population.[9] Although children aged between 11 months and 5 years at time of exposure to Early PN also suffered from impaired development of inhibitory control, other developmental outcomes were unaffected. Interestingly, both the critically ill term neonates (aged ≤28 days) and the oldest children aged 5 years or more appeared least vulnerable to long-term harm evoked by Early PN during critical illness.

Our finding that patients aged between 29 days and 11 months were most vulnerable to adverse long-term effects of exposure to Early PN in the PICU was in line with the first year of life being critical for brain development and with the known high sensitivity of the brain to environmental disturbances during this time window.[11-19] Indeed, postnatally, a brain growth spurt takes place roughly between 1 and 11 months of postnatal age, a time window during which many "sensitive" and "critical" periods have been identified. Various potentially harmful environmental exposures such as psychological stressors (caregiver insensitivity, violence), malnutrition (under- and overfeeding) and infectious and noninfectious inflammation can have major impact on brain growth and maturation whereby they can affect long-term development leading to increased risk of cognitive, emotional and social deficits.[2,11,29-31] Also children

aged between 11 months and 5 years showed Early PN induced harm in particular for the development of inhibitory control, which may point to an effect on the initiation of the pruning process which is important for normal development of executive functioning.[11,16,17,30]

Our observation that children older than 5 years seemed less vulnerable to the cognitive harm evoked by Early PN during critical illness is in line with the general knowledge that beyond this age, fewer "critical" and "sensitive" windows of brain development occur.[11-19,30,31] Less expected was the observation that patients who were at neonatal age at time of exposure to Early PN in the PICU did not show neurocognitive developmental harm evoked by Early PN except for an increased risk of impaired visual motor integration and disturbed externalizing behavior[9] which did not depend on age of exposure as shown here. This is in contrast with the particularly high vulnerability to the short-term harm evoked by Early PN in this age group, as reported previously.[8] One could speculate about possible explanations. First, during the initial 4 weeks of postnatal life, predominantly sensory functions rather than higher cognitive functions are being developed.[11,16,17,30] Second, in the context of brain damage, it has been suggested that the younger the patient at the time of the insult, the better the recovery.[32] However, specific studies that focus on term neonates are currently lacking. Our finding of protection against harm from Early PN in this youngest age-group may be explained either by a predominant adverse effect of Early PN on synaptogenesis for higher cognitive functions, or it may suggest that neonates can better overcome such a metabolic insult.

This study has some limitations to highlight. By dividing the PEPaNIC patients into developmentally-relevant age subgroups, statistical power was inevitably reduced as compared with the original patient population. However, we based our conclusion on age-dependent vulnerability to harm evoked by Early PN via assessing, in the total patient population, the statistical interaction between randomization to Early PN versus Late PN and age at time of exposure, which circumvented such a power issue. Hypothesis-generating, the visualization of the differences in impact of Early PN versus Late PN per *a priori* defined age subgroup clearly identified one particularly vulnerable age subgroup, despite its smaller sample size. A second limitation is the fact that the sample size of the subgroup of neonates at time of exposure was somewhat smaller than that of the other subgroups. This may have reduced the statistical power to detect vulnerability in this youngest subgroup. However, most of the confidence intervals for the effect of Early PN versus Late PN were symmetrically spanning neutrality. Finally, energy requirements were mostly estimated by standard equations rather than by indirect calorimetry, which has been criticized for risk of overfeeding. However, macronutrient doses administered to patients in the Early PN group were substantially below target.[33] Furthermore, also the use of indirect calorimetry for estimating energy expenditure in critically ill children has been

criticized for accuracy[34] and feasibility,[35] and hence is not frequently used in daily practice.[36] Nevertheless, in hindsight, the children treated with Early PN can be considered overfed in view of the adverse outcomes reported in this group, even with low doses.[7,8,9]

In conclusion, the negative impact of Early PN in critically ill children on development of visual-motor-integration and externalizing behavior, assessed 2 years later, was present across all ages. We could not identify an age subgroup of patients that benefited from Early PN for the long-term physical and neurocognitive development. In contrast, in particular critically ill children aged between 29 days and 11 months at time of exposure to Early PN were identified as most vulnerable to the long-term developmental harm evoked by Early PN. These findings further support de-implementation of the use of Early PN in critically ill children of all ages.

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Appendix Chapter 5

Methods S1. Definition of 'syndrome'

A prerandomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development, and which is subdivided in the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Pedopsychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomization
- Severe convulsions or stroke prior to randomization

Methods S2. Definition of educational and occupational level of parents

Educational level of parents

The educational level is calculated based upon the 3-point scale subdivision as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): low (1), middle (2) and high (3) educational level. The average score of the paternal and maternal educational level was calculated. Categories where than made as followed: average 1 or 1.5 = category 1, average 2 or 2.5 = category 2, average 3 = category 3.

Occupational level of parents

The occupational level is calculated based upon the international Isco System 4-point scale for professions.[1] In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case 'unemployed', 'disabled', 'student', or 'housewife/houseman' was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as 'employee', 'worker',

'liberal profession', or 'retired', they were given an Isco code level of 2. The average score of the paternal and maternal occupational level was calculated. Categories where than made as followed: average 1 or 1.5 = category 1, average 2 or 2.5 = category 2, average 3 or 3.5 = category 3, average 4 = category 4.

Methods S3. Detailed description of outcome measures

Medical assessment

Anthropometric data
At the beginning of the follow-up visit, height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status
In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 2 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination
In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. A normal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing

Patients/Parents-reported outcomes (PROs)
Executive functioning was measured with the Behavior Rating Inventory of Executive Function (BRIEF-P 2.5-5 years, BRIEF 6-18 years), filled out by the parents/caregivers of the child. Overlapping scales and indices of both questionnaires (inhibition, flexibility, emotional control, working memory, panning and organization, metacognition) and a total score were analyzed (T-scores, with mean 50 and SD 10). Inhibitory control refers to the ability to withhold initial responses in contexts where they are not appropriate and emotional control to respond on ongoing experiences with a range of emotions that is socially tolerable and sufficiently flexible to permit spontaneous reactions. Cognitive flexibility is the ability to shift attentional focus between tasks and mental sets. Emotional control is the ability to manage and control your emotions in order

to achieve a goal or complete a task. Panning and organization involves managing current or future tasks by setting goals and establishing the steps needed to complete the task. Working memory is a cognitive system that temporarily maintains and manipulates information. Metacognition is the awareness and understanding of one's own thought processes, 'thinking about thinking'.[2-4]

Behavioral and emotional problems were assessed by the parents/caregivers of the child with the Child behavior checklist (CBCL 1.5-5 years or CBCL 6-18 years). Internalizing, externalizing and total problems were analyzed. Internalizing problems refers to anxious, depressed, withdrawn and over-controlled behavior and externalizing problems to aggressive, hyperactive, noncompliant, and under controlled behavior. In the total score for the behavioral and emotional problems, not only internalizing and externalizing problems, but also sleep abnormalities for younger children and social, thinking and attention abnormalities for older children are included.[5-6]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL[7]) was used for children aged 2.5 years - 5 years 11 months (one version for age range 2 years 6 months - 3 years 11 months, and another version for age range 4 years - 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-II-NL[8]) was used for children aged 6 years - 16 years 11 months, and the Wechsler Adult Intelligence scale (WAIS-IV-NL[9]) for adolescents who were 17 years or older. For all these testes Total IQ, Verbal IQ and Performance IQ scores (test-mean 100, SD 15) were computed.

Visual-motor integration

We used the beery Developmental Test of visual-motor integration 6th Edition to assess the ability to integrate visual and motor functions (total scaled score with test-mean 10, SD 3). This involves eye-hand coordination.[10]

Table S1. Macronutrient and caloric target per centre[11]

Centre	First day	Subsequent stay
Leuven, Belgium	First 10 kg: 100 kcal/kg 10-20 kg: + 50 kcal/kg >20 kg: + 20 kcal/kg (adjusted downward when fluid restriction required)	
Rotterdam, The Netherlands	EN: basal metabolic rate by Schofield-weight[12] PN: ESPGHAN[13]	EN: Recommended Dietary Allowances[14] PN: ESPGHAN[13]
Edmonton, Canada	Resting energy expenditure by indirect calorimetry. If indirect calorimetry impossible: 65% of basal metabolic rate (FAOWHO[15])	Adjusted daily by the dietician based on clinical information

EN=enteral nutrition, PN=parenteral nutrition

Table S2. Average total macronutrient doses administered up to each of the first 7 days in PICU, expressed as percentages of the reference doses for age and weight

	Glucose		Amino acids		Lipids	
Dose up to day [a]	**Early PN**	**Late PN**	**Early PN**	**Late PN**	**Early PN**	**Late PN**
1	60.3 (37.1-81.7)	16.5 (11.7-24.2)	74.0 (0.0-102.2)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
2	70.4 (47.7-86.3)	19.1 (14.3-32.6)	87.4 (45.8-109.2)	0.0 (0.0-6.6)	15.9 (4.6-49.1)	0.0 (0.0-11.2)
3	61.9 (43.1-75.7)	19.9 (14.4-31.8)	80.0 (56.7-99.4)	2.0 (0.0-13.2)	36.6 (21.7-73.7)	3.5 (0.0-28.2)
4	60.1 (42.1-72.1)	20.1 (14.4-31.9)	75.7 (59.1-89.7)	3.2 (0.0-19.5)	49.5 (34.2-79.1)	6.8 (0.0-41.2)
5	59.2 (42.3-70.9)	20.7 (14.8-31.8)	74.1 (59.2-87.9)	4.7 (0.0-27.3)	60.9 (46.2-93.9)	9.6 (0.0-46.8)
6	56.1 (40.8-70.9)	23.7 (15.6-34.5)	75.0 (57.5-85.5)	6.8 (0.5-33.0)	67.9 (51.3-98.7)	14.6 (1.4-54.4)
7	56.8 (41.6-69.5)	24.4 (15.3-36.0)	73.8 (60.1-86.8)	11.7 (1.7-34.3)	73.7 (57.2-106.0)	23.7 (2.3-60.5)

[a] Average daily doses of the 3 macronutrient classes administered up to each of the first seven days in PICU are expressed as percentages of the reference doses for age/weight as described in nutritional guidelines summarized in **Table S1**.[11] Data represent medians and interquartile ranges

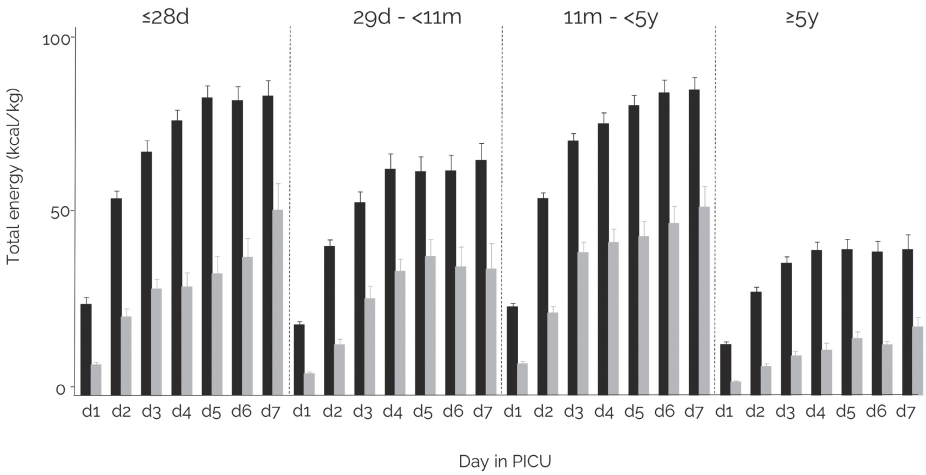

Figure S1. Total energy intake of the Early PN and Late PN patients of each age group for the first 7 days in PICU
Black bars represent the daily total amount of energy (kilocalories per kg) for Early PN patients and grey bars for Late PN patients. Data are presented as means and standard errors.

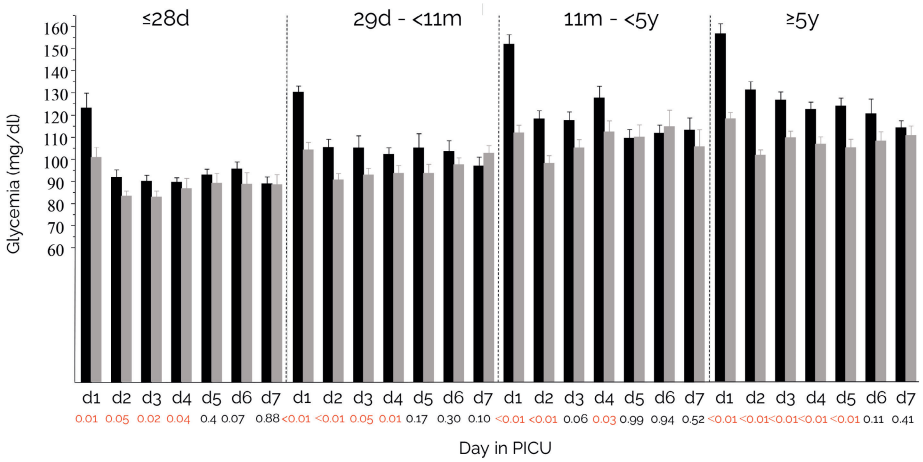

Figure S2. Blood glucose levels of the Early PN and Late PN patients of each age group for the first 7 days in PICU
Black bars represent the average glycaemia (milligram per decilitre) per day for Early PN patients and grey bars for Late PN patients in each age group. Data are presented as means and standard errors.

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CHAPTER 6

Health-related quality of life of children and their parents 2 years after critical illness: pre-planned follow-up of the PEPaNIC international, randomized, controlled trial

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Abstract

Background Pediatric intensive care unit (PICU) survivors are at risk for prolonged morbidities interfering with daily life. The current study examined parent-reported health-related quality of life (HRQoL) in former critically ill children and parents themselves and aimed to determine whether withholding parenteral nutrition (PN) in the first week of critical illness affected children's and parents' HRQoL 2 years later.

Methods Children who participated in the pediatric early versus late parenteral nutrition in critical illness (PEPaNIC) trial and who were testable 2 years later (n = 1158) were included. Their HRQoL outcomes were compared with 405 matched healthy controls. At PICU admission, children had been randomly assigned to Early PN or Late PN. In the Early PN group, PN was initiated within 24 h after PICU admission. In the Late PN group, PN was withheld for up to 1 week in the PICU. Parents completed the Infant Toddler Quality of Life Questionnaire (ITQOL; age 2–3 years) or the Child Health Questionnaire-Parent Form 50 (CHQ-PF50; age 4–18 years). Besides, they completed the Health Utility Index (HUI) and the Short Form Health Survey (SF-12) regarding their child's and their own HRQoL, respectively.

Results For the total age group of 786 post-PICU survivors, parents reported lower scores for almost all HRQoL scales compared to healthy children. Age-specifically, younger critically ill children (2.5 to 3 years old) scored worse for growth and development and older children (4–18 years old) scored worse for role functioning and mental health. Parents' own mental and physical HRQoL was comparable to that of healthy control parents. No HRQoL differences were found between children in the Late PN and those in the Early PN group.

Conclusions Parent-reported HRQoL of children 2 years after critical illness was impaired compared with healthy controls. In relation to their child's HRQoL, parents reported impairments in emotions, personal time, and family activities; however, their own HRQoL was not impaired. Withholding PN in the first week during critical illness had no impact on longer-term HRQoL of the child.

Background

Improvements in care for critically ill children have led to lower mortality rates in our pediatric intensive care units (PICUs).[1] Nevertheless, a significant part of these surviving children will be confronted with increased morbidity after discharge from the hospital.[1,2] Such morbidity carries a major burden on children and their families. Patient-reported outcomes (PROs) are an important source of information to assess these long-term consequences of critical illness on daily life.[3] PROs in the case of young children are reported by the parents and focus on the subjective evaluation of different domains regarding the perceived functioning of the child.[4] Health-related quality of life (HRQoL) is the most common PRO. It reflects the impact of health on the broad concept of quality of life, e.g., physical, mental, and social functioning, and provides insight in what the impairments mean for the daily life of the patient.[5,6]

We recently showed that parents reported lower HRQoL in PICU survivors, 6 months after PICU admission, compared with healthy children. Parents themselves reported better scores for physical HRQoL and worse scores for mental HRQoL compared with the general population.[7] This counterintuitive finding might reflect the short-term emotional impact on the parents/ families of experiencing a life-threatening disease in their child.[8] However, little is known regarding longer-term HRQoL of critically ill children and their parents.[9]

The pediatric early versus late parenteral nutrition in critical illness (PEPaNIC) multicenter, randomized controlled trial (RCT) showed that withholding supplemental parenteral nutrition (PN) during the first week in the PICU resulted in better short-term outcomes, with a reduced incidence of new infections, a shorter stay at the PICU, and reduced direct healthcare costs, compared with initiating parenteral nutrition on the day of admission to the PICU.[10,11] Importantly, withholding PN for 1 week did not negatively affect survival, anthropometrics, health status, and neurocognitive development and even improved a few domains of parent-reported executive functioning, less externalizing behavioral problems, and improved visual-motor integration compared with children in the Early PN group, evaluated 2 years later.[12] In this secondary analysis, we first investigated parent-reported HRQoL of critically ill children as compared with healthy control children at 2-years follow-up and parents' self-reported HRQoL as compared with parents of healthy control children. Secondly, we investigated whether the better long-term neurocognitive outcomes of children in the Late PN group are also reflected in a better HRQoL as compared with children who received Early PN in the PICU.

Methods

Design

This study is part of the pre-planned 2-year follow-up of the PEPaNIC trial that enrolled 1440 critically ill children admitted to the three participating PICUs (Belgium, the Netherlands, and Canada) between June 18, 2012, and July 27, 2015. The full study protocol with sample size calculation, short-term outcomes, and 2-year medical and neurocognitive outcomes have been published.[10,12,13] In summary, at PICU admission, children had been randomly assigned to Early PN or Late PN. In the Early PN group, PN was initiated within 24 h after PICU admission to supplement insufficient enteral caloric intake (whenever 80% of targeted calories per age and weight categories were not yet reached). In the Late PN group, PN was withheld for up to 1 week in the PICU, resulting in no PN in the majority of the children. After 1 week, for both groups equally, PN could be administered if necessary. When enteral nutrition covered ≥ 80% of calculated targets, supplemental PN was discontinued. Enteral nutrition was initiated early for both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Participants at follow-up

Children who had participated in the PEPaNIC trial and who were alive and neurocognitively testable at 2-year follow-up were also eligible for the current study. Four hundred and five healthy control children, who had never been admitted to a neonatal or pediatric ICU, were recruited for a medical and neurocognitive assessment similar to that of the post-PICU patients. These children were demographically matched to the patients for age and gender. To control as much as possible for genetic and socio-economic/environmental background, siblings and relatives of the patients were preferably recruited into this control group, besides unrelated children recruited from the same geographic area.

Procedure

From August 2014 through January 2018, all PICU survivors and their parents were first approached through a standardized patient information letter after screening for survival status was performed. When children's neurocognitive functioning was not testable as determined by the physician and confirmed by the parents, they were not included in the analyses. Children who were neonates (0 to 6 months old) at the time of the PEPaNIC trial were tested at the age of 2.5 years due to the age-limits of the neurocognitive tests. When consent was obtained, they were subsequently contacted by phone to schedule an appointment for the follow-up assessment that was performed either at the hospital or at the patient's home. Parents received the HRQoL measurements along with the confirmation letter of the appointment for follow-up assessment. One of the parents completed the questionnaires at home and handed them over to the researcher on the day of the follow-up assessment. Written informed consent was obtained from the parents or legal guardians and/or from the adolescent according to local regulations. The institutional review boards at each participating site approved this follow-up study.

Health-related quality of life outcomes

The type of validated parent-reported questionnaires assessing the child's HRQoL depended on the age of the child. Parents of patients 2.5–3 years old completed the Infant Toddler Quality of Life Questionnaire (ITQOL) about their child's HRQoL,[14] consisting of 103 items divided over 12 multi-item scales. Parents of patients 4–18 years old completed the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) about their child's HRQoL,[15] consisting of 50 items divided into 11 multi-item scales and 4 single-item scales. The ITQOL and CHQPF50 are parallel forms of the same questionnaire and scores range from 0 (worst) to 100 (best) (see Additional file 1a and Additional file 5 for the psychometric characteristics of the questionnaires and a description of the subscales). Some subscales of these questionnaires are related to the impact of the health status of the child on the parents. Subsequently, all parents completed the Short Form Health Survey (SF-12) for assessment of their own HRQoL, independent of the health status of the child. The SF-12 consists of 12 items[16,17] summarized in the "Physical Component Summary" (PCS) and "Mental Component Summary" (MCS) based on the US-derived summary scores with mean 50 and SD 10 and higher scores representing better HRQoL. Parents who had a child both in the patient group and in the control group completed the SF-12 twice.

The Health Utilities Index Mark 2 and 3 (HUI2 and HUI3) are based on the 15-item HUI questionnaire and are two different classification systems that together provide a combined view of the child's HRQoL and provide a more objective way to measure the health status of the child. The HUI2 and HUI3 comprise respectively 6 or 7 function-attributes based on single items. Scores range from 1 (no functional limitations) to 4, 5, and 6 (severe functional limitations) and 1 weighted multi-attribute utility function with ranges of minus 0.36 (score worse than dead) to 1.00 (perfect health). In the current study, since children were matched with healthy control children, the HUI2 and HUI3 were assessed in children of all ages.

Statistical analyses

The fraction of missing HRQoL data per variable was determined and analyzed to examine whether they were missing at random or not at random. In order to avoid selection bias, multiple imputation by chained equation (MICE) of HRQoL variables was performed when ≥ 70% of the data was available.[18] The number of imputed data sets was set equal to the percentage of missing data plus one. Predictors for missing values are described in Additional file 1b. The pooled estimates that take into account variation across imputations were reported.

To analyze the differences in HRQoL scales available for all ages between post-PICU patients and healthy control children and to investigate differences between patients randomly allocated to Late PN or Early PN during PICU stay, multivariable linear analyses were done on 21 imputed datasets with the beta-estimates reported as pooled results, preceded by a pooled univariable comparison with use of Student

t test or Wilcoxon rank-sum test as appropriate. All multivariable analyses were adjusted for the baseline risk factors described in Additional file 1c and further for the short-term effects of the PEPaNIC trial as described in Additional file 1d. Sub-analyses were conducted for the HRQoL scales that were only available for a specific age range. Data are presented as beta-estimates with 95% confidence intervals (CI), means and standard deviations, or numbers and proportions, as appropriate. Statistical analyses were performed with the use of R version 3.4.3, MICE version 2.46.0, and JMP© version 13.0.0 (SAS Institute, Inc., Cary, NC). Two-sided *p*-values ≤ 0.05 were considered statistically significant. To explore whether the results of the SF-12 were affected by the fact that some parents completed this questionnaire twice for two children participating in the study, one-way analyses of variance were done on three of the 21 imputed datasets as a sensitivity analysis.

Results

Of the 1158 children who were alive and testable 2 years later, a total of 391 children in the Early PN group and 395 children in the Late PN group participated in the 2-year PEPaNIC follow-up study (**Figure 1.**; flow diagram of study participants). Demographic characteristics of the post-PICU children and matched healthy control children are shown in **Table 1** (and Additional file 2). Children who were tested 2-years post-PICU admission were overall comparable to both the initial PICU children (**Table 1**) for demographics and patient characteristics upon PICU admission, as well as to the group of patients who survived, but declined participation or could not be reached (all *p*-values > 0.15).

Overall, critically ill children had worse outcomes at 2-year follow-up for parent-reported HRQoL compared with healthy control children (**Table 2** and Additional File 3). For the total age group, differences between critically ill children and healthy control children were found in multivariable analyses for almost all parent-reported HRQoL multi-item scales, with differences of 5.4 to 27.2 points, with the exception of general behavior and family cohesion (**Table 2**). For the age specific HRQoL scales, younger critically ill children (2.5 to 3 years old) scored worse for growth and development and older children (4–18 years old) scored worse for role functioning due to emotions/behavior and due to physical problems, and mental health compared with healthy control children. Critically ill children also scored worse on the parent-reported multi-attribute utility function on the dead-healthy scale for both HUI2 and HUI3 classifications, compared with healthy control children (**Table 2** and Additional file 3). In multivariable analysis, lower scores were found on the HUI2 and HUI3 single utility scores for sensation, mobility, self- care, speech, and ambulation in patients compared with healthy controls (**Table 2**). Univariable analysis of HRQoL scores of parents of critically ill children reported for themselves a lower physical component score and mental component score compared with parents of healthy control children (Additional file 3). In the multivariable analysis, these differences were

not statistically significant after adjusting for child and parent risk factors (**Table 2**). Sensitivity analyses without the data of n = 111 parents who completed the SF-12 two times or more showed no differences in results (Additional file 4).

Parents of critically ill children in the Late PN group overall reported comparable HRQoL scores as parents of critically ill children in the Early PN group, in univariable and multivariable analyses (**Table 2** and Additional file 3).

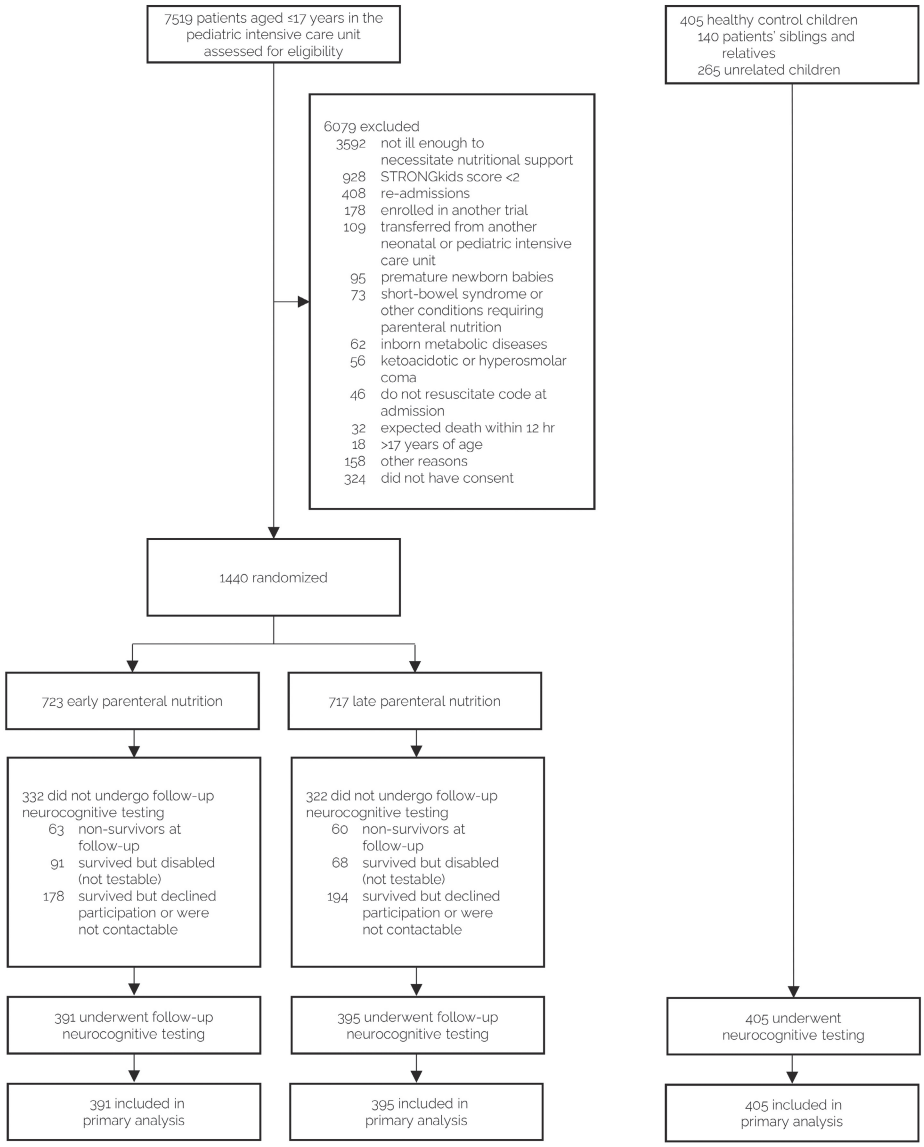

Figure 1. Flow diagram of study participants

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested populations		Total PICU population		Tested post-PICU population[a]	
	Healthy control children N=405	Post-PICU patients N=786	Early PN N=723	Late PN N=717	Early PN N=391	Late PN N=395
Demographics						
Age at 2-years' follow-up (mean±SEM) - years	6.0±0.2	5.7±0.2	NA	NA	5.7±0.2	5.6±0.2
Male gender - no. (%)	219 (54.1)	455 (57.9)	415 (57.4)	412 (57.5)	230 (58.8)	225 (57.0)
Known non-Caucasian race - no. (%)[b]	33 (8.1)	63 (8.0)	50 (6.9)	33 (4.6)	38 (9.7)	25 (6.3)
Known non-European origin - no. (%)[b]	54 (13.3)	152 (19.3)	161 (22.3)	128 (17.9)	88 (22.5)	64 (16.2)
Known not exclusive Dutch or English language - no. (%)	76 (18.8)	184 (23.4)	122 (16.9)	106 (14.8)	95 (24.3)	89 (22.5)
Socioeconomic status - no. (%)						
Educational level parents[c, d]						
Educational level 1	13 (3.2)	37 (4.7)	NA	NA	12 (3.1)	25 (6.3)
Educational level 1.5	23 (5.7)	54 (6.9)	NA	NA	28 (7.2)	26 (6.6)
Educational level 2	55 (13.6)	184 (23.4)	NA	NA	96 (24.6)	88 (22.3)
Educational level 2.5	76 (18.8)	131 (16.7)	NA	NA	60 (15.3)	71 (18.0)
Educational level 3	215 (53.1)	200 (25.4)	NA	NA	100 (25.6)	100 (25.3)
Educational level unknown	23 (5.7)	180 (22.9)	NA	NA	95 (24.3)	85 (21.5)
Patient characteristics upon PICU admission						
Infant (age<1y) at randomization - no. (%)	NA	363 (46.2)	328 (45.4)	325 (45.3)	177 (45.3)	186 (47.1)
STRONGkids risk level - no. (%)[e]						
Medium	NA	707 (89.9)	644 (89.1)	644 (89.8)	351 (89.8)	356 (90.1)
High	NA	79 (10.1)	79 (10.9)	73 (10.2)	40 (10.2)	39 (9.9)
PeLOD score, first 24h in PICU (mean±SEM)[f]	NA	20±0.4	19.7±0.4	20.1±0.5	20±0.6	20±0.6
PIM3 score (mean±SEM)[g]	NA	-3.5±0.0	-3.2±0.1	-3.2±0.1	-3.4±0.1	-3.5±0.1
Diagnostic category - no. (%)[h]						
Surgical						

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested populations		Total PICU population		Tested post-PICU population[a]	
	Healthy control children N=405	**Post-PICU patients N=786**	**Early PN N=723**	**Late PN N=717**	**Early PN N=391**	**Late PN N=395**
Cardiac	NA	339 (43.1)	279 (38.6)	268 (37.4)	173 (44.2)	166 (42.0)
Other	NA	249 (31.7)	211 (29.2)	215 (30.0)	125 (32.0)	124 (31.4)
Medical						
Respiratory	NA	83 (10.6)	99 (13.7)	96 (13.4)	38 (9.7)	45 (11.4)
Other	NA	115 (14.6)	134 (18.5)	138 (19.2)	55 (14.1)	60 (15.2)
Malignancy - no. (%)	0 (0.0)	42 (5.3)	51 (7.1)	33 (4.6)	26 (6.6)	16 (4.1)
Diabetes - no. (%)	0 (0.0)	1 (0.1)	3 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Syndrome - no. (%)[i]	5 (1.2)	79 (10.1)	123 (17.0)	118 (16.5)	34 (8.7)	45 (11.4)
Known parental smoking between birth and PICU admission - no. (%)	NA	354 (45.0)	NA	NA	184 (47.1)	170 (43.0)
Acute effects of randomization and post-randomization treatments in PICU						
Duration of stay in the PICU (mean±SEM) - days	NA	7.4±0.5	9.2±0.8	6.5±0.4	8.4±0.9	6.4±0.5
Patients who acquired a new infection in PICU - no. (%)	NA	105 (13.4)	134 (18.5)	77 (10.7)	66 (16.9)	39 (9.9)
Duration of mechanical ventilatory support (mean±SEM) - days	NA	4.7±0.4	6.4±0.7	4.4±0.3	5.5±0.7	3.9±0.4
Number of days with hypoglycemia <40mg/dl (mean±SEM) - days	NA	0.1±0.0	0.1±0.0	0.2±0.0	0.1±0.0	0.2±0.0
Duration of antibiotic treatment (mean±SEM) - days	NA	5.1±0.5	6.7±0.7	4.6±0.3	5.8±0.8	4.3±0.5
Duration of hemodynamic support (mean±SEM) - days	NA	2.5±0.3	3.0±0.3	2.4±0.2	2.6±0.4	2.3±0.3
Duration of treatment with opioids (mean ±SEM) - days	NA	4.7±0.3	6.1±0.6	4.1±0.2	5.4±0.5	4.1±0.3
Duration of treatment with benzodiazepines (mean±SEM) - days	NA	4.2±0.3	5.4±0.6	4.0±0.3	4.5±0.5	3.9±0.5
Duration of treatment with hypnotics (mean±SEM) - days	NA	1.4±0.2	1.8±0.2	1.3±0.1	1.6±0.4	1.2±0.1

Table 1. Demographics of patients and healthy control children, post-randomization treatments in the PICU, and acute outcomes

	Tested populations		Total PICU population		Tested post-PICU population[a]	
	Healthy control children N=405	**Post-PICU patients N=786**	**Early PN N=723**	**Late PN N=717**	**Early PN N=391**	**Late PN N=395**
Duration of treatment with alpha-2-agonists (mean±SEM) - days	NA	1.0±0.2	1.1±0.3	1.0±0.2	0.9±0.3	1.1±0.3
Duration of treatment with corticosteroids (mean±SEM) - days	NA	1.2±0.1	1.6±0.2	1.3±0.1	1.3±0.2	1.0±0.2

a No differences in demographics, allocation to Late PN or Early PN, and ICU/hospital primary/secondary study endpoints were observed between the tested post-PICU population (N=786) and the group of patients who survived, but declined participation or could not be reached (N=372) (all P>0.15).
b Participants were classified according to race and geographical origin. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity.
c The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Additional file 1f).
d For occupational level see Additional file 2.
e Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
f Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
g Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
h For more detailed information regarding the diagnostic categories see Additional file 2.
i A pre-randomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Additional file 1e).
Abbreviations: BMI, body mass index; NA, not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

Table 2. Multivariable linear and logistic regression analyses of the differences in HRQoL outcomes between study groups

HRQoL outcomes assessed at 2 years' follow-up	No. (%) available data per outcome (N=1191)	Beta-estimate (95% CI) for the comparison patients vs. controls, adjusted for risk factors[a]	*p*-value	Beta-estimate (95% CI) for the comparison Late PN vs. Early PN, adjusted for risk factors[b]	*p*-value
Parent-reported HRQoL in children (ITQOL & CHQ-PF50)					
Physical functioning	960 (81%)	-6.34 (-8.59 - -4.10)	**<0.001**	1.32 (-1.54 – 4.17)	0.36
Bodily pain	967 (81%)	-6.81 (-9.54 - -4.07)	**<0.001**	1.20 (-2.32 – 4.73)	0.50
General behavior	967 (81%)	-1.87 (-3.88 – 0.14)	0.07	2.28 (-0.01 – 4.57)	0.05
General health	961 (81%)	-27.20 (-29.91 - -24.49)	**<0.001**	2.92 (-0.47 – 6.31)	0.09
Change in health	965 (81%)	12.94 (9.93 – 15.95)	**<0.001**	-0.88 (-4.37 - 2.61)	0.62
Parental impact-emotional	964 (81%)	-7.92 (-10.50 - -5.33)	**<0.001**	2.40 (-0.80 – 5.60)	0.14
Parental impact-time	965 (81%)	-5.41 (-8.07 - -2.76)	**<0.001**	3.05 (-0.37 – 6.47)	0.08
Family activity	960 (81%)	-6.18 (-8.78 - -3.58)	**<0.001**	3.58 (0.32 – 6.84)	**0.03**
Family cohesion	962 (81%)	-2.25 (-4.97 – 0.47)	0.10	0.70 (-2.41 – 3.81)	0.66
Parent-reported HRQoL in children 2.5 to 3 years only (ITQOL)					
Temperament and Moods	548 (83%)	-1.14 (-3.46 – 1.17)	0.33	-0.33 (-2.87 – 2.20)	0.80
Growth and Development	547 (83%)	-3.09 (-6.02 - -0.15)	**0.04**	1.56 (-1.52 – 4.65)	0.32
Getting Along	543 (82%)	-0.25 (-2.53 – 2.03)	0.83	1.56 (-0.82 – 3.94)	0.20
Parent-reported HRQoL in children aged 4-18 years only (CHQ-PF50)					
Role functioning emotional/behavior	425 (80%)	-6.73 (-12.86 - -0.60)	**0.03**	-1.26 (-7.30 – 4.79)	0.68
Role functioning due to physical problems	424 (80%)	-7.87 (-14.35 - -1.39)	**0.02**	0.71 (-5.00 – 6.43)	0.81
Mental Health	425 (80%)	-5.28 (-8.45 - -2.11)	**0.001**	0.01 (-3.62 – 3.65)	0.99
Self-esteem	426 (80%)	-2.34 (-6.20 – 1.51)	0.23	1.08 (-2.28 – 4.45)	0.53
Parent-reported HRQoL in children (HUI2; single utility scores)					
Sensation	959 (80%)	-0.03 (-0.06 - -0.00)	**0.03**	0.02 (-0.02 – 0.06)	0.30
Mobility	959 (80%)	-0.02 (-0.04 – 0.01)	**0.007**	0.01 (-0.02 – 0.023)	0.62
Emotions	962 (81%)	-0.01 (-0.02 – 0.00)	0.06	-0.00 (-0.02 – 0.01)	0.43
Cognition	958 (80%)	-0.01 (-0.02 -0.00)	0.13	0.01 (-0.01 – 0.03)	0.26
Self-care	960 (81%)	-0.04 (-0.08 - -0.00)	**0.03**	0.01 (-0.04 – 0.05)	0.83
Pain	961 (81%)	-0.00 (-0.02 – 0.01)	0.56	0.00 (-0.02 – 0.02)	0.66
Multi-attribute utility function on Dead-healthy scale	944 (79%)	-0.04 (-0.06 - -0.02)	**<0.001**	0.01 (-0.01 – 0.03)	0.40
Parent-reported HRQoL in children (HUI3; single utility scores)					
Vision	958 (80%)	0.00 (-0.01 – 0.01)	0.96	-0.00 (-0.02 – 0.01)	0.77
Hearing	961 (81%)	0.00 (-0.02 – 0.02)	0.80	0.01 (-0.02 – 0.03)	0.57
Speech	960 (81%)	-0.04 (-0.07 -0.01)	**0.01**	0.02 (-0.01 – 0.06)	0.21
Ambulation	959 (80%)	-0.04 (-0.06 - -0.01)	**0.002**	0.01 (-0.02 – 0.04)	0.45

Table 2. Multivariable linear and logistic regression analyses of the differences in HRQoL outcomes between study groups

HRQoL outcomes assessed at 2 years' follow-up	No. (%) available data per outcome (N=1191)	Beta-estimate (95% CI) for the comparison patients vs. controls, adjusted for risk factors[a]	*p*-value	Beta-estimate (95% CI) for the comparison Late PN vs. Early PN, adjusted for risk factors[b]	*p*-value
Dexterity	962 (81%)	-0.01 (-0.04 – 0.01)	0.24	0.01 (-0.03 – 0.04)	0.71
Emotions	962 (81%)	-0.007 (-0.01 – 0.00)	0.05	-0.00 (-0.01 – 0.00)	0.41
Cognition	944 (79%)	-0.01 (-0.03 – 0.00)	0.15	0.01 (-0.02 – 0.04)	0.52
Pain	961 (81%)	-0.01 (-0.03 – 0.01)	0.25	0.00 (-0.02 – 0.03)	0.71
Multi-attribute utility function on Dead-healthy scale	931 (78%)	-0.06 (-0.09 - -0.03)	**<0.001**	0.02 (-0.02 – 0.05)	0.33
HRQoL of parents (SF-12)					
Physical component score	938 (79%)	-0.38 (-1.57 – 0.82)	0.53	0.66 (-0.75 – 2.08)	0.36
Mental component score	938 (79%)	-0.88 (-2.22 – 0.45)	0.19	1.12 (-0.47 – 2.71)	0.17

Results are the combined beta estimates (95% confidence interval) from 21 datasets generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 786 post-PICU patients and 405 healthy control children. *p*-values were considered statistically significant with two-tailed *p*-values of less than .05 in which case they are expressed in bold. For a description of the subscales see Additional file 5. Some parents did not complete all questions of a domain which resulted in differences between sample sizes on the subscales

a Estimates were adjusted for the following risk factors: age, center, race, gender, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined "syndrome", and the educational and occupational status of parents.

b Estimates were adjusted for the following risk factors: age, center, race, gender, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined "syndrome", the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behavior prior to PICU admission.

Abbreviations: HRQoL, Health related quality of life; PN, parenteral nutrition; CI, confidence interval; PICU, pediatric intensive care unit; ITQOL, infant toddler quality of life questionnaire; CHQ-PF50, Child Health Questionnaire - Parent Form 50; HUI, healthy utility index; SF-12, short form 12

Discussion

HRQoL of critically ill children versus healthy control children

Two years after children were included in the PEPaNIC trial, significant lower scores were found for post-PICU survivors compared with healthy control children on physical and general health-related HRQoL domains and single HUI scores. Besides, in younger post-PICU children, parent-reported growth and development was impaired. We previously showed that post-PICU children had worse outcomes for height, body weight, and neurocognitive development compared with healthy controls.[12] The present study showed that parents appear to assess these outcomes accurately in their child. Recent publications in short-term outcomes already reported these impairments in growth and development 6 months after critical illness.[7,19]

Impairments in physical HRQoL and in general health were still present in this study but parents reported more positive change in health on the single item scale "change in health" compared to 1year ago. In our previous 6-month PICU follow-up study,[7] parents also reported lower physical HRQoL and also lower scores on psychosocial domains. At 2-year follow-up, only a few psychosocial domains in mainly older children remained impaired, whereas problems in other psychosocial multi-item domains, i.e., temperament and moods, getting along, and self-esteem, and single utility HUI scores emotions and cognition had normalized as compared with healthy control children. This is in line with a recent review that found that parent-reported HRQoL of children improved over time after critical illness.[20] Apparently, after PICU admission, the physical domain remained most impaired on the longer term. A review investigating studies into PICU survivors who experienced a cardiac arrest or acute respiratory distress syndrome also reported lower physical functioning and general health 5 and 10 years after critical illness.[21] This implicates that these problems remain during the development of the child and might interfere with daily life as they may lead to functional disabilities.[9,20] It might be hypothesized that the timing of the follow-up after PICU admission is best within a couple of months to screen for growth and development impairments in younger children and to prevent mental health problems in older children.[8]

HRQoL of parents of critically ill children versus parents of healthy controls

In this study, parents reported that critical illness of their child had a negative impact on emotional wellbeing, personal time, and on activities with the family which is similar to a previous study in parents of children admitted to the PICU for cardiac arrest.[22] Interestingly, in the current study, when parents were asked about their own HRQoL, not directly in relation to the health of their child, they reported no differences compared with parents of healthy control children. Apparently, parents do experience some limitations in personal and family time and activities as a result of the health status of their child, but they do not experience this as an impairment of their own HRQoL. In contrast, in our previous study, 6 months after PICU admission, parents had higher scores on physical health and lower scores on mental health compared with the general population.[7] The higher psychosocial HRQoL in parents of critically ill children over time might be explained by a response shift. This occurs when parents' appraisal of their own health status changes due to the adaptations they make to their child's diminished health status, especially when their child has minor residual symptoms.[9,23]

Late PN versus Early PN during PICU admission

Withholding PN during the first week of critical illness had no impact on parent-reported HRQoL of the child compared with early administration of PN. This contrasts with the favorable outcomes on parent-reported executive functioning, in particular better inhibitory control, in critically ill children of the Late PN group.[12] This may be

explained by the fact that HRQoL is a broader concept of the subjective evaluation of functioning on mental, physical, and social domains of daily life. Parents evaluate their child's executive functioning as less developed compared to healthy peers but appear to retain the subjective feeling that their child is not impaired in overall daily functioning.

Implications

Two years after PICU stay, children showed most impairments in physical HRQoL domains and therefore, follow-up programs should focus on these physical problems after PICU admission.[20] In addition, psychologists should screen on developmental problems in younger children and mental health problems in school aged children. Those children who experience mental problems could be referred to a psychologist to prevent further problems in daily life. It is essential to ask parents to complete HRQoL outcomes after PICU admission to assess which specific needs exist with regard to daily functioning of the child and themselves. As the children included in this study are still relatively young, future research should be done on the longer-term to assess whether impairments remain on the longer term.

Strengths and limitations

A strength of the current study is that the sample size was very large compared with other studies examining HRQoL in PICU survivors. Furthermore, we included the heterogeneous group of PICU patients and extensively adjusted the analyses for baseline and short-term follow-up risk factors for lower HRQoL. Hence, the results are generalizable to the impact of a PICU admission on long-term HRQoL,[9] especially since the outcomes of PICU survivors were compared with those of healthy control children, matched for age and gender.

A limitation of the current study is the dependence on parent-reported outcomes since the majority of the children were too young to be able to assess their own HRQoL. Re-evaluation of the children when they are able to assess their own HRQoL in self-reports will provide further valuable information regarding HRQoL on the longer term after critical illness. Furthermore, children who were too disabled to test were not included in the current analyses. In our opinion, this would have introduced bias and limited the generalizability of the results since questionnaires assess to what extent children are able to participate in society. For example, parents are asked whether their child was limited by their health status in doing their homework or activities with friends in the last 4 weeks.

Conclusions

Two years after critical illness, children showed an impaired parent-reported HRQoL, mainly on physical domains and general health. In relation to the critical illness of their child, parents reported impairments in emotions and personal time. However, parents'

own HRQoL appeared comparable to that of parents of healthy control children. Lastly, withholding PN in the first week during critical illness had no impact on HRQoL of the child on the longer term.

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Appendix Chapter 6

Additional file 1. Psychometric characteristics of the questionnaires and additional information about variables for analyses

1a. Psychometric characteristics of the questionnaires
The ITQOL has shown a good internal consistency (Cronbach's alpha > 0.70) and moderate or adequate test–retest intra-class correlation coefficients (≥0.50; $p < 0.001$).[1] The CHQ-PF50 has shown good internal consistency, with Cronbach's alpha for Dutch school children ranging from 0.39–0.96 for an average of 0.72 for the subscales.[2] The SF-12 has shown good internal consistency, with Cronbach's alpha coefficients of 0.72 to 0.89, and a test-retest reliability range between 0.73-0.86.[3] The Health Utilities Index Mark 2 and 3 (HUI2 and HUI3) has been validated in pediatric populations and is considered to be reliable in children of 5–18 years of age.[4]

1b. List of variables used for multiple data imputation by chained equations
Predictors for missing values were as following:

1) Demographics of patients and control children and patient characteristics upon PICU admission:
Centre, randomization to Late PN or Early PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome" (Additonal file 1e), educational and occupational status of parents (Additional file 1f), diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking behavior prior to PICU admission, age at randomization, age group at randomization.

2) Acute effects of randomization and post-randomization treatments in PICU:
Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycemia, duration of treatment with hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and alpha-2-agonists.

3) Available 2-years neurocognitive and HRQoL variables:
Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performance IQ, total IQ, visual motor integration, reaction time left hand, reaction time right hand, within subject SD of reaction time left hand, within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, delta reaction time inhibition, delta number of errors inhibition, delta reaction time flexibility, delta number of errors flexibility, numbers

memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organization, meta-cognition index, and total score), emotional and behavioral problems as reported by parents/caregivers (internalizing problems, externalizing problems, and total problems). All HRQoL outcomes available for all ages, see **Table 2**. For HRQoL scales validated for a specific age-range (growth and development, temperament and moods, and getting along in children aged 3 years or younger, and role functioning emotional/behavioral, role functioning physical, mental health, and self-esteem in children who are 4 years or older), imputation was performed within these age-ranges only.

1c. List of baseline risk factors for adjusting multivariable analyses
All multivariable analyses were adjusted for the following risk factors: age, center, race, gender, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined "syndrome" (Additional file 1e), and the educational and occupational status of parents (Additional file 1f). For the comparison between Late PN and Early PN groups, further adjustment was done for diagnosis and severity of illness Pediatric Index of Mortality (PIM3) and Pediatric Logistic Organ Dysfunction (PeLOD) upon PICU-admission, risk of malnutrition, and parental smoking behavior prior to PICU-admission.

1d. List of short-term effects for adjusting multivariable analyses
In order to investigate whether any eventual impact of Late PN versus Early PN on the long-term HRQoL outcomes might have been mediated by its acute effects on new PICU-infections and duration of PICU-stay, and thus possibly indirectly also number of post-randomization hypoglycemic events or the duration of post-randomization treatments such as mechanical ventilatory support, hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and alpha-2-agonists, explanatory statistical analyses were performed with further adjustment for these treatments.

1e. Definition of "syndrome"
A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development, and which is subdivided in the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology

- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Psychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation

1f. Definition of educational and occupational level of parents

Educational level of parents

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents

The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions. In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled out, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Additional file 2. Detailed demographic information regarding socioeconomic status and diagnostic category

	Tested populations		Total PICU population		Tested post-PICU population[a]	
	Healthy control children N=405	**Post-PICU patients N=786**	**Early PN N=723**	**Late PN N=717**	**Early PN N=391**	**Late PN N=395**
Demographics						
Socioeconomic status - no. (%)						
Occupational level parents[a]						
Occupational level 1	2 (0.5)	10 (1.3)	NA	NA	2 (0.5)	8 (2.0)
Occupational level 1.5	25 (6.2)	76 (9.7)	NA	NA	33 (8.4)	43 (10.9)
Occupational level 2	47 (11.6)	127 (16.2)	NA	NA	61 (15.6)	66 (16.7)
Occupational level 2.5	26 (6.4)	77 (9.8)	NA	NA	44 (11.3)	33 (8.4)
Occupational level 3	83 (20.5)	121 (15.4)	NA	NA	54 (13.8)	67 (17.0)
Occupational level 3.5	40 (9.9)	54 (6.9)	NA	NA	32 (8.2)	22 (5.6)
Occupational level 4	116 (28.6)	108 (13.7)	NA	NA	53 (13.6)	55 (13.9)
Occupational level unknown	66 (16.3)	213 (27.1)	NA	NA	112 (28.6)	101 (25.6)
Patient characteristics upon PICU admission						
Diagnostic category - no. (%)						
Surgical						
Abdominal	NA	70 (8.9)	53 (7.3)	60 (8.4)	34 (8.7)	36 (9.1)
Burns	NA	2 (0.3)	5 (0.7)	5 (0.7)	1 (0.3)	1 (0.3)
Cardiac	NA	339 (43.1)	279 (38.6)	268 (37.4)	173 (44.2)	166 (42.0)
Neurosurgery-Traumatic brain injury	NA	71 (9.0)	63 (8.7)	53 (7.4)	39 (10.0)	32 (8.1)
Thoracic	NA	42 (5.3)	34 (4.7)	27 (3.8)	23 (5.9)	19 (4.8)
Transplantation	NA	14 (1.8)	7 (1.0)	17 (2.4)	4 (1.0)	10 (2.5)
Orthopedic surgery-Trauma	NA	23 (2.9)	28 (3.9)	26 (3.6)	14 (3.6)	9 (2.3)
Other	NA	27 (3.4)	21 (2.9)	27 (3.8)	10 (2.6)	17 (4.3)
Medical						
Cardiac	NA	26 (3.3)	30 (4.2)	31 (4.3)	10 (2.6)	16 (4.1)
Gastrointestinal-Hepatic	NA	3 (0.4)	2 (0.3)	4 (0.6)	1 (0.3)	2 (0.5)
Oncologic-Hematologic	NA	8 (1.0)	8 (1.1)	7 (1.0)	5 (1.3)	3 (0.8)
Neurologic	NA	44 (5.6)	51 (7.1)	52 (7.3)	21 (5.4)	23 (5.8)
Renal	NA	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Respiratory	NA	83 (10.6)	99 (13.7)	96 (13.4)	38 (9.7)	45 (11.4)
Other	NA	34 (4.3)	42 (5.8)	43 (6.0)	18 (4.6)	16 (4.1)

a The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Additional file 1f)

Additional file 3. Pooled univariable analyses of the differences in HRQoL outcomes between study groups

		Tested populations			Tested post-PICU population		
HRQoL outcomes assessed at 2 years' follow-up	**No. (%) available data per outcome (N=1191)**	**Healthy control children N=405**	**Post-PICU patients N=786**	***p*-value**	**Early PN N=391**	**Late PN N=395**	***p*-value**
Parent-reported HRQoL in children (ITQOL & CHQ-PF50)							
Physical functioning	960 (81%)	100 (100-100)	100 (88.9–100)	**<0.001**	100 (86.7–100)	100 (89.4-100)	0.22
Bodily pain	967 (81%)	91.7 (80-100)	83.3 (66.7-100)	**<0.001**	83.3 (66.7-100)	83.3 (70-100)	0.65
General behavior	967 (81%)	76.7 (66.2-86.5)	70 (56.5-83.3)	**<0.001**	70 (55.8-81.2)	71.9 (58.5-83.5)	0.10
General health	961 (81%)	86.3 (75.8-93.3)	55 (36.3-69.6)	**<0.001**	52.9 (35-68.3)	55.8 (36.3-71.7)	0.33
Change in health	965 (81%)	50 (50-50)	75 (50-100)	**<0.001**	75 (50-100)	75 (50-100)	0.38
Parental impact-emotional	964 (81%)	91.7 (82.1-100)	82.1 (64.3-92.9)	**<0.001**	82.1 (58.3-91.7)	83.3 (66.7-92.9)	0.11
Parental impact-time	965 (81%)	100 (88.9-100)	90.48 (76.2-100)	**<0.001**	88.9 (69.1-100)	90.5 (77.8-100)	**0.05**
Family activity	960 (81%)	91.7 (79.2-100)	87.5 (66.7-100)	**<0.001**	83.3 (66.7-100)	87.5 (70.8-100)	0.08
Family cohesion [a]	962 (81%)	85 (60-85)	85 (60-85)	**0.003**	85 (60-85)	85 (60-85)	0.61
Parent-reported HRQoL in children 2.5 to 3 years only (ITQOL)							
Temperament and Moods	548 (83%)	79.9 (72.6-88.9)	80.6 (70.8-90.3)	0.50	80.6 (70.8-91.7)	80 (70.8-88.9)	0.48
Growth and Development	547 (83%)	90 (77.5-95)	77.5 (67.5-90)	**0.01**	76.3 (60-89.4)	77.5 (67.5-92.5)	0.42
Getting Along	543 (82%)	71.7 (66.2-80)	70 (58.3-77.9)	0.18	68.3 (58.3-76.7)	70 (60-78.3)	0.34
Parent-reported HRQoL in children aged 4-18 years only (CHQ-PF50)							
Role functioning emotional/behavior	425 (80%)	100 (100-100)	100 (89.9-100)	**<0.001**	100 (88.9-100)	100 (88.89-100)	0.61
Role functioning due to physical problems	424 (80%)	100 (100-100)	100 (83.3-100)	**<0.001**	100 (83.3-100)	100 (83.33-100)	0.68
Mental Health	425 (80%)	80 (70-90)	75 (60-85)	**<0.001**	75 (60-85)	75 (60-85)	0.69
Self-esteem	426 (80%)	79.2 (75-95.8)	70.83 (58.3-83.3)	0.06	70.83 (58.3-83.3)	75 (62.5-87.5)	0.40
Parent-reported HRQoL in children (HUI2; single utility scores)							
Sensation	959 (80%)	1 (0.87-1)	0.87 (0.87-1)	**<0.001**	0.87 (0.87-1)	0.87 (0.87-1)	0.51
Mobility	959 (80%)	1 (1-1)	1 (1-1)	**<0.001**	1 (0.92-1)	1 (1-1)	0.07
Emotions	962 (81%)	0.86 (0.86-1)	0.86 (0.86-1)	**0.005**	0.86 (0.86-1)	0.86 (0.86-1)	0.31
Cognition	958 (80%)	1 (1-1)	1 (1-1)	**<0.001**	1 (1-1)	1 (1-1)	0.23

Additional file 3. Pooled univariable analyses of the differences in HRQoL outcomes between study groups

		Tested populations			Tested post-PICU population		
HRQoL outcomes assessed at 2 years' follow-up	**No. (%) available data per outcome (N=1191)**	**Healthy control children N=405**	**Post-PICU patients N=786**	***p*-value**	**Early PN N=391**	**Late PN N=395**	***p*-value**
Self-care	960 (81%)	1 (1-1)	1 (0.85-1)	**<0.001**	1 (0.85-1)	1 (0.85-1)	0.57
Pain	961 (81%)	1 (1-1)	1 (0.95-1)	**<0.001**	1 (0.95-1)	1 (0.95-1)	0.43
Multi-attribute utility function on Dead-healthy scale	944 (79%)	0.93 (0.88-1)	0.87 (0.76-0.93)	**<0.001**	0.85 (0.76-0.93)	0.88 (0.78-0.93)	0.39
Parent-reported HRQoL in children (HUI3; single utility scores)							
Vision	958 (80%)	1 (1-1)	1 (1-1)	**0.02**	1 (1-1)	1 (1-1)	0.57
Hearing	961 (81%)	1 (1-1)	1 (1-1)	**0.001**	1 (1-1)	1 (1-1)	0.56
Speech	960 (81%)	1 (0.67-1)	0.82 (0.67-1)	**<0.001**	1 (0.67-1)	0.82 (0.67-1)	0.63
Ambulation	959 (80%)	1 (1-1)	1 (1-1)	**<0.001**	1 (0.83-1)	1 (1-1)	**0.05**
Dexterity	962 (81%)	1 (1-1)	1 (1-1)	**<0.001**	1 (1-1)	1 (1-1)	0.18
Emotions	962 (81%)	0.91 (0.91-1)	0.91 (0.91-1)	**0.005**	0.91 (0.91-1)	0.91 (0.91-1)	0.31
Cognition	944 (79%)	1 (1-1)	1 (0.86-1)	**<0.001**	1 (0.86-1)	1 (0.86-1)	0.53
Pain	961 (81%)	1 (1-1)	1 (0.92-1)	**<0.001**	1 (0.92-1)	1 (0.92-1)	0.40
Multi-attribute utility function on Dead-healthy scale	931 (78%)	0.92 (0.79-1)	0.79 (0.56-0.93)	**<0.001**	0.79 (0.51-0.89)	0.79 (0.57-0.93)	0.36
HRQoL of parents (SF-12)							
Physical component score	938 (79%)	55.9 (52.6-57.8)	54.4 (48.4-57.2)	**0.01**	54.3 (47.9-57.1)	54.5 (48.6-57.2)	0.20
Mental component score	938 (79%)	55.4 (48.3-60)	53.5 (45.4-57.9)	**0.03**	53.4 (44.5-57.8)	53.49 (46-58.4)	0.32

Results are the combined numbers (%) or medians (IQR) from 21 datasets generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 786 post-PICU patients and 405 healthy control children. *p*-values were considered statistically significant with two-tailed *p*-values of less than .05 in which case they are expressed in bold. A higher score represents a better HRQoL. For ITQOL and CHQ-PF50: 0 is worst possible health state, 100 is best possible health. For the HUI2 and HUI3: scores range from 1 (no functional limitations) to 4, 5, and 6 (severe functional limitations) and 1 weighted multi-attribute utility function with ranges of minus 0.36 (score worse than dead) to 1.00 (perfect health). For SF-12: 50 is average with SD 10. For a description of the subscales see additional file 4. Some parents did not complete all questions of a domain which resulted in differences between sample sizes on the subscales.

a Medians are reported and are similar in the groups, means of the medians are as follows: healthy control children 85, post-PICU patients 77.3, Early PN 77.9, Late PN 76.7

Abbreviations: HRQoL, Health related quality of life; PN, parenteral nutrition; CI, confidence interval; PICU, pediatric intensive care unit; ITQOL, infant toddler quality of life questionnaire; CHQ-PF50, Child Health Questionnaire - Parent Form 50; HUI, healthy utility index; SF-12, short form 12

Additional file 4. Sensitivity analyses of SF-12 outcomes of parents who have only one child in the study

N= 111 parents filled in the SF12 regarding themselves more than one time because they had 2 or more children participating in the follow-up study. Sensitivity analyses were done without the data of these parents (n=251 records) to explore differences between patients and healthy control children for parents' own HRQoL. Three imputed datasets were randomly chosen from the 21 imputed datasets (dataset 1, 4, and 14). As shown below, differences between patients and controls remained statistically significant after excluding parents with 2 or more children in the follow-up study.

Dataset 1:

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
SF12-Physical component score	Control	255	53,22	7,94	,50	52,24	54,20	19,48	65,73
	Patient	704	49,91	10,42	,39	49,14	50,68	14,79	68,47
SF12-Mental component score	Control	255	53,03	9,77	,61	51,82	54,23	19,47	68,78
	Patient	704	49,61	10,57	,40	48,83	50,39	13,15	73,48

Abbreviations: Std. Deviation, Standard Deviation; Std. Error, Standard Error; SF-12, Short Form 12
* *p*-value= <.001

Dataset 4:

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
SF12-Mental component score	Control	255	52,63	9,44	,59	51,47	53,80	15,87	65,73
	Patient	704	47,70	12,61	,48	46,77	48,64	14,79	68,47
SF12-Mental component score	Control	255	53,57	9,50	,59	52,40	54,74	19,47	68,78
	Patient	704	51,31	9,98	,38	50,57	52,04	13,15	73,48

Abbreviations: Std. Deviation, Standard Deviation; Std. Error, Standard Error; SF-12, Short Form 12
* *p*-value= <.001

Dataset 14:

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
SF12-Mental component score	Control	255	52,91	8,45	,53	51,87	53,96	15,87	65,73
	Patient	704	49,52	10,69	,40	48,73	50,31	14,79	68,47
SF12-Mental component score	Control	255	52,14	10,47	,66	50,84	53,43	19,47	68,78
	Patient	704	48,73	11,06	,42	47,91	49,55	13,15	73,48

Abbreviations: Std. Deviation, Standard Deviation; Std. Error, Standard Error; SF-12, Short Form 12
* *p*-value= <.001

Additional file 5. Scales and score interpretation of the questionnaires

Table 5a. ITQOL scales and score interpretation*

Scale	Description low score	Description high score
Physical functioning (PF)	Child is considerably limited in performing physical activities such as eating, sleeping, grasping, and playing due to health problems	Child performs all types of physical activities such as eating, sleeping, grasping, and playing without limitations due to health problems
Growth and development (GD)	Parent is very dissatisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament	Parent is very satisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament
Bodily pain (BP)	Child has extremely severe, frequent and limiting bodily pain/discomfort	Child has no pain or limitations due to pain/discomfort
Temperament and moods (TM)	Child very often has certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness	Child never has certain moods and temperaments, such as sleeping/ eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness
General behavior (BE)	Parent believes child's behavior is poor and likely to get worse	Parent believes child's behavior is excellent and will continue as such
Getting along (GA)	Child very often exhibits behavioral problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behavior, such as ability to cooperate, to appear sorry, and to adjust to new situations is seldom shown	Child never exhibits behavioral problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behavior, such as ability to cooperate, to appear sorry, and to adjust to new situations is frequently shown
General health perceptions (GH)	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue as such
Parental impact: emotional (PE)	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development
Parental impact: time (PT)	Parent experiences a lot of limitations in time avail-able for personal needs due to child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience limitations in time avail-able for personal needs due to child's physical and/or psychosocial health and/or growth and development
Family activities (FA)	The child's health and/or growth and development very often limits and interrupts family activities or is a source of family tension	The child's health and/or growth and development never limits and interrupts family activities or is a source of family tension
Family cohesion (FC)	Family's ability to get along is rated as 'poor'	Family's ability to get along is rated as 'excellent'
Change in health (CH)	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

* Cited by "The ITQOL/CHQ user's manual"[5]

Table 5b. CHQ-PF50 supplementary scales of the CHQ-PF50 and score interpretation*

Scale	Description low score	Description high score
Role functioning: Emotional / Behavior (REB)	Child is limited a lot in school work or activities with friends as a result of emotional or behavior problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavior problems
Role functioning: Physical (RF)	Child is limited a lot in school work or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Mental health (MH)	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self-esteem (SE)	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall

* Cited by "The ITQOL/CHQ user's manual"[5]

References Appendix Chapter 6

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CHAPTER 7

Long-term developmental effect of withholding parenteral nutrition in pediatric intensive care units: a 4-year follow-up of the PEPaNIC randomized controlled trial

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Abstract

Background The PEPaNIC randomized controlled trial, which recruited 1440 critically ill infants and children in 2012–15, showed that withholding parenteral nutrition for 1 week (late-parenteral nutrition), compared with early supplementation within 24 h of admission to the pediatric intensive care unit (early-parenteral nutrition), prevented infections, accelerated recovery, and improved neurocognitive development assessed 2 years later. Because several neurocognitive domains can only be thoroughly assessed from age 4 years onwards, we aimed to determine the effect of late-parenteral nutrition versus early-parenteral nutrition on physical, neurocognitive, and emotional and behavioral development 4 years after randomization.

Methods This is a preplanned, blinded, 4-year follow-up study of participants included in the PEPaNIC trial (done at University Hospitals Leuven, Belgium; Erasmus Medical Centre Sophia Children's Hospital, Rotterdam, Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada) and of matched healthy children. Studied outcomes were anthropometrics; health status; parent-reported or caregiver-reported executive functions, and emotional and behavioral problems; and clinical tests for intelligence, visual-motor integration, alertness, motor coordination, and memory. Through multivariable linear and logistic regression analyses, after imputation for missing values (≤30%) and adjustment for risk factors, we investigated the effect of early-parenteral nutrition versus late-parenteral nutrition.

Findings Between March 8, 2016, and Nov 8, 2019, 684 children from the original PEPaNIC trial (356 from the late parenteral nutrition group and 328 from the early-parenteral nutrition group) were assessed for neurocognitive development at 4-years follow-up. Compared with the control group (369 healthy children), children who had critical illness had lower height (β-estimate −2.11 [95% CI −3.15 to −1.06]; p<0.0001) and head circumference (−0.42 [−0.67 to −0.18]; p=0.00077); and worse health status (e.g., hospital admission odds ratio 4.27 [95% CI 3.12 to 5.84]; p<0.0001), neurocognitive (e.g., parent-reported or caregiver-reported total executive functioning β-estimate 3.57 [95% CI 1.95 to 5.18], p<0.0001; total intelligence quotient −7.35 [−9.31 to −5.39], p<0.0001), and parent-reported or caregiver-reported emotional and behavioral developmental outcomes (internalizing 2.73 [1.19 to 4.28], p=0.00055; externalizing 1.63 [0.19 to 3.08], p=0.027; and total behavioral problems 2.95 [1.44 to 4.46], p=0.00013), adjusted for risk factors. Outcomes were never worse in the late-parenteral nutrition group compared with the early-parenteral nutrition group, but patients in the late-parenteral nutrition group had fewer parent-reported or caregiver-reported internalizing (β-estimate −1.88 [95% CI −3.69 to −0.07]; p=0.042), externalizing (−1.73 [−3.43 to −0.03]; p=0.046), and total emotional and behavioral problems (−2.44 [−4.22 to −0.67]; p=0.0070) than patients who had received early-parenteral nutrition, after adjusting for risk factors, and were no longer different from healthy controls for these outcomes.

Interpretation Omitting early parenteral nutrition use for critically ill children did not adversely affect long-term outcomes 4 years after randomization and protected against emotional and behavioral problems, further supporting the de-implementation of early parenteral nutrition.

Introduction

Critical illness in children is associated with impaired physical, neurocognitive, emotional, and behavioral development, which often persists for years after discharge from the pediatric intensive care unit and hospital.[1,2] Over the past decade, avoidable intensive care-related factors contributing to some long-term effects have been identified; these include hyperglycemia, phthalates leaching into the blood from indwelling medical devices, and the use of early-parenteral nutrition.[3–5] The multicenter randomized controlled PEPaNIC trial6 showed that postponing parenteral nutrition for 1 week in the pediatric intensive care unit (late-parenteral nutrition) has benefits over initiating parenteral nutrition within 24 h after admission to supplement insufficient enteral nutrition (early-parenteral nutrition), such as improved intensive care outcomes,[6] as well as better executive functioning and visual-motor integration and reduced externalizing behavioral problems at 2 years after admission to the intensive care unit.[5] The improvements in neurocognitive development in the late-parenteral nutrition group were found to be mediated by the differential DNA methylation status, in particular of 37 CpG sites related to genes involved in brain development.[7]

A methodological limitation of the 2-year follow-up study of the PEPaNIC trial[5] was the large proportion of patients who were younger than 4 years old when tested neurocognitively. Because of rapid brain development during the first years of life, assessment of most neurocognitive domains is only possible when the child is 4 years of age or older.[8,9] As the child develops, impairments in physical or neurocognitive domains that were observed at 2 years follow-up could persist or disappear and other problems might emerge. Taken together, assessments at a later time point after critical illness are of value. We therefore did a 4-year follow-up study of the children included in the PEPaNIC trial to assess their health status, neurocognitive development, and emotional and behavioral outcomes. We aimed to compare these outcomes with data from matched children who had not had a critical illness, and to investigate the longer term effects of late-parenteral nutrition compared with early-parenteral nutrition.

Methods

Study design and participants

In the PEPaNIC trial,[6] 1440 critically ill infants and children admitted to the participating pediatric intensive care units at University Hospitals Leuven, Leuven, Belgium; Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada were enrolled from 2012 to 2015. The study protocol has been published.10 This study represents the preplanned 4-year follow-up of the original PEPaNIC trial.[6]

As described previously,[5] during admission to a pediatric intensive care unit, parents or legal guardians of the patients provided consent to contact them for long-term follow-up testing. First, survival status was assessed by reviewing hospital notes, obtained through the national register or through contact with the general practitioner or referring pediatrician. After receiving a standardized information letter, survivors and parents or caregivers were contacted by telephone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment, either at the hospital or at the patient's home. For patients who could not be reached by telephone, survival status was reassessed at the end of the study.

For comparison, 369 healthy children, demographically matched to the patients for age and sex, were recruited to a control group and underwent identical medical and neurocognitive assessment. Alongside unrelated children, healthy siblings and relatives of the patients were included to control as much as possible for genetic, socioeconomic, and environmental background. Healthy children were only included if they had not been previously admitted to a neonatal or pediatric intensive care unit, or admitted to hospital with need for an intravenous line for 7 days or more. History of inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and conditions that require home parenteral nutrition, such as short bowel syndrome, were additional exclusion criteria.

Parents, legal guardians, or patients (if they were ≥18 years old), gave written informed consent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098).

Procedures, randomization, and masking

After obtaining informed consent, children in the PEPaNIC trial6 were randomly assigned (1:1) to receive Early parenteral nutrition, with parenteral nutrition initiated within 24 h of admission to the intensive care unit to supplement enteral nutrition whenever 80% of targeted calories per age and weight categories had not been reached, or late-parenteral nutrition, which meant that all parenteral nutrition was withheld for up to 1 week in the intensive care unit. For the late-parenteral nutrition group, this corresponded to no parenteral nutrition in most children. When enteral nutrition covered more than 80% of calculated targets, supplemental parenteral nutrition was discontinued. Total macronutrient doses administered on each of the first 7 days of admission are shown in the appendix. After 1 week in the pediatric intensive care unit, parenteral nutrition could be administered when necessary in both groups. Enteral nutrition was initiated early in both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors of the 4-year follow-up study were physicians and experienced pediatric psychologists who had not been involved in the management of the patients during their stay in the pediatric intensive care unit and who were strictly masked to treatment allocation. Parents and caregivers were not masked while the child was treated in the pediatric intensive care unit and they were not actively informed about the initial PEPaNIC study results or the 2-year outcome results (which only became available near the end of the inclusions in the 4-year follow-up study).[6]

Outcomes

As done in the 2-year follow-up study,[5] at 4-year follow-up, head circumference, body weight, and height were measured. A clinical neurological examination was done to assess gross neurological abnormalities. We used structured interviews with the parents or caregivers to assess whether the children had been diagnosed with a somatic or psychiatric illness, and whether they had been admitted to a hospital for medical or surgical reasons during the past 4 years (for the control group) and during the 4 years following admission to the pediatric intensive care unit (for the PEPaNIC participants). Neurocognitive testability was determined by screening the medical file or on clinical judgement before the start of the neurocognitive assessment by the physician or psychologist and confirmed by the parents or caregivers.

To score performance for a broad range of neurocognitive functions, validated internationally recognized questionnaires and clinical tests with adequate normative data were used. Parent-reported questionnaires included the Behavior Rating Inventory of Executive Function[11,12] (executive functioning, T scores, with mean 50 and SD 10) and the Child Behavior Checklist[13,14] (emotional and behavioral problems, T scores, with mean 50 and SD 10). On both questionnaires, higher scores indicate more problems. Clinical tests consisted of the age-appropriate versions of the Wechsler Intelligence Quotient Scale[15-17] (intelligence, standard scores, with mean 100 and SD 15), the Beery Developmental Test of Visual-Motor Integration[18] (visuomotor integration, scaled score, with mean 10 and SD 3), tasks of the Amsterdam Neuropsychological Task Battery[9] (for children aged 4 years or older), and the Children's Memory Scale[8] (for children aged 5–16 years). Tasks of the Amsterdam Neuropsychological Task Battery consisted of Amsterdam Neuropsychological Task Battery-Baseline Speed (alertness and reaction time) and Amsterdam Neuropsychological Task Battery-Tapping (motor coordination as number of taps). Tasks of the Children's Memory Scale were Children's Memory Scale-Numbers (verbal short-term memory and working memory, scaled scores with mean 10 and SD 3), Children's Memory Scale-Word Pairs (short-term and long-term verbal memory, and recognition, proportion of correct responses ranging from 0 to 1), Children's Memory Scale-Picture Locations (short-term visual memory as the proportion of correct responses), and Children's Memory Scale-Dot Locations (short-term and long-term visual memory proportion of correct responses). The Children's Memory Scale-Learning index represents learning abilities of the

child (standard score, with mean 100 and SD 15). For the clinical tests, a higher score indicates better functioning, with the exception of Amsterdam Neuropsychological Task Battery-Baseline Speed. An extended description of the questionnaires and of the clinical and neuropsychological test battery is reported in the appendix.

Statistical analysis

For patients in the PEPaNIC trial who were alive and testable 4 years later, we estimated a loss to follow-up of about 30%, on the basis of previous studies.[3,5] With this sample size, we calculated that we would have more than 80% statistical power to detect, with a certainty of more than 95%, a minimal clinically relevant four point difference in intelligence quotient (IQ) and clinically relevant differences of a median 5.8% (IQR 3.8–8.0) or mean of 7.6% (SD 7.9) in the other outcomes between patients in the early-parenteral nutrition and late parenteral nutrition groups, based on previous data.[3,5] For the healthy control group, a sample size of 369 allows detection, with a power of more than 80% and certainty of more than 95%, of a difference in IQ of four points with the patients and median differences between patients and the control group of 5.2% (IQR 3.5–7.3) and a mean difference of 7.9% (11.2) in the other outcomes that were studied previously.[3,5]

Inability to fully complete the neurocognitive test battery could indicate poor neurocognitive function and thus introduce bias. Similarly to the 2-year follow-up study.5 missing values were imputed by chained equations, with use of all available data for each individual (see appendix).[19] Imputation of data for age specific tests was only done within the respective age group. Bias and instability of the imputation model was minimized by only including outcomes with no more than 30% missing data.[19] The number of imputation models was set at 31 to avoid the loss of statistical power (see appendix).[19]

Univariable comparison of the pooled data from the imputed models was done with the Fisher exact test, Student *t* test, or Wilcoxon rank-sum test as appropriate. Multivariable linear and logistic regression analyses were done on the 31 imputed datasets with the pooled β-estimates or odds ratios reported to investigate the differences in outcomes between patients and healthy control children, and to analyze the differences between the two groups in PEPaNIC.[5] All multivariable analyses adjusted for covariates, as pre-specified in the statistical analysis plan, and the analyses were done as reported in the 2-year follow-up study.5,10 For the comparison of patients who were critically ill with children in the control group, the analyses adjusted for the baseline risk factors, age, treatment center, sex, race, geographic origin, language, hand preference, history of malignancy, a predefined syndrome (see appendix), and the educational and occupational status of the parents and caregivers (see appendix). Additional adjustment for admission diagnosis, severity of illness upon pediatric intensive care unit-admission (pediatric index of mortality

3 and pediatric logistic organ dysfunction scores), risk of malnutrition (Screening Tool for Risk On Nutritional Status and Growth), and parental smoking behavior before admission to the pediatric intensive care unit was done for the comparison of the late-parenteral nutrition group with the early-parenteral nutrition group. Acute effects of the random allocation on acquisition of new infections and on the duration of hypoglycemia, ventilatory support, and stay in the pediatric intensive care unit could potentially mediate any long-term effect and thus further adjustment for these factors was done in the multivariable models. In addition, further adjustment was done for other post-randomization treatments that could theoretically play a role (duration of hemodynamic support, treatment with antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics, and α2-agonists).

Statistical analyses were done with use of R (version 3.5.3), MICE (versions 3.4.0 and 3.6.0), and JMP (version 14.0.0). Two-sided *p*-values of 0.05 or less were considered statistically significant. As the studied developmental outcomes are not independent (see appendix), correction for multiple comparisons was not done.[7,20]

Results

Of the children included in the original PEPaNIC trial, done between June 18, 2012, and July 27, 2015, 71 (10%) of 723 patients in the early-parenteral nutrition group and 66 (9%) of 717 patients in the late-parenteral nutrition group did not survive to 4 years follow-up (p=0.69; **Figure 1**). For 18 patients survival status was unknown. A total of 247 patients in the early-parenteral nutrition group and 222 patients in the late-parenteral nutrition group survived but declined participation or were not contactable (p=0.47). Hence, loss to follow-up was 34% (487 of 1440). At follow-up, 73 (10%) patients in the early-parenteral nutrition group and 59 (8%) patients in the late parenteral nutrition group were too disabled for neurocognitive testing (p=0.21) and were excluded from the analyses. For transparency, any available clinical data or questionnaire results for these patients are provided in the appendix, (pp 15–17). 684 (48%) children from the original study and 369 healthy controls underwent neurocognitive testing between March 8, 2016, and November 8, 2019, and were included in the imputation models for subsequent multivariable analyses. Neurocognitive testing was done at the hospital for 442 (65%) children who had been critically ill and 301 (82%) children in the control group (p<0.0001), with no differences in the place of assessment between patients in the late-parenteral nutrition and the early-parenteral nutrition groups (p=0.99). Demographics and medical characteristics of children who had been critically ill and children in the control group are shown in **Table 1**. Overall, random assignment and primary and secondary intensive care outcomes of patients who were tested at 4-year follow-up were similar to the initial PEPaNIC study population.

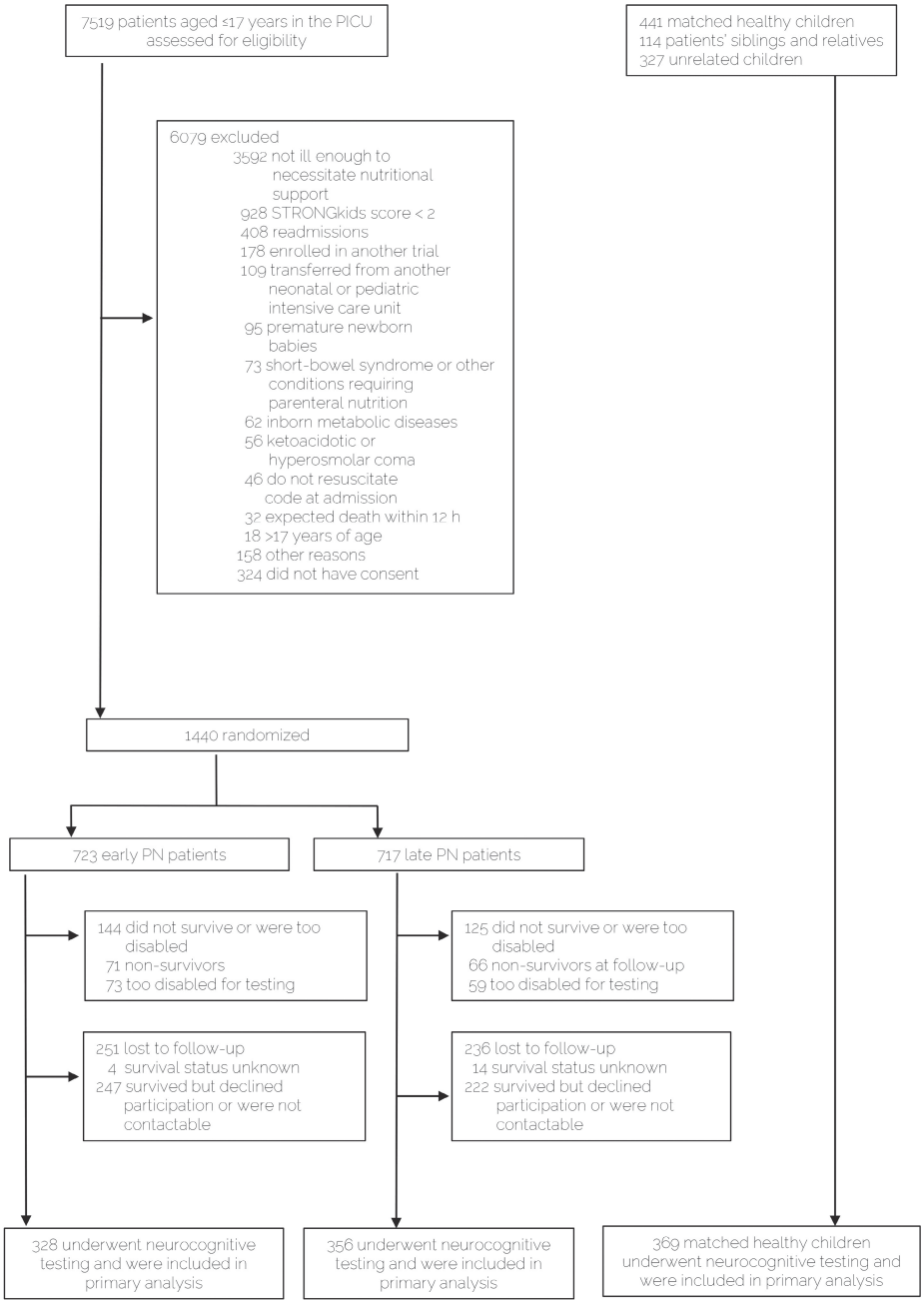

Figure 1. Study profile
PICU: pediatric intensive care unit. STRONGkids: Screening Tool Risk On Nutritional Status and Growth

In univariable and multivariable comparison, at 4-years follow-up children who had been critically ill had worse outcomes for height, weight, head circumference, health status, clinically assessed neurological functioning, parent-reported or caregiver-reported executive functioning and emotional and behavioral problems and clinical tests for intelligence, visual-motor integration, alertness, motor-coordination, and memory than children in the control group (**Table 2 and Table 3**).

Compared with patients who had been allocated to early parenteral nutrition, patients in the late-parenteral nutrition group had similar height, weight, body-mass index, and head circumference, and clinically assessed neurological functioning in univariable and multivariable analysis (**Table 2 and Table 3**). In univariable analyses, fewer patients in the late parenteral nutrition group were admitted to hospital and parents or caregivers of these children reported fewer internalizing, externalizing, and total emotional and behavioral problems and fewer problems regarding flexibility compared with patients who received early parenteral nutrition (**Table 2**; **Figure 2**). After adjustment for risk factors, the finding of fewer internalizing, externalizing, and total emotional and behavioral problems in the late parenteral nutrition group than in the early-parenteral nutrition group remained (**Table 3**; appendix). For internalizing and externalizing problems as well as total emotional and behavioral problems, children in the late parenteral nutrition group were not different from children in the control group (appendix).

Differences in intensive care outcomes of the randomized intervention and other post-randomization factors overall did not explain the observed differences at 4-years follow-up (appendix). Of note, treatment with benzodiazepines was independently associated with worse outcome, whereas α2-agonist treatment was associated with better outcome.

Discussion

4 years after critical illness, children were found to still have a disease legacy characterized by broad abnormalities in all investigated developmental domains, including growth, health status, and neurocognitive, and emotional and behavioral functioning, a finding that confirmed previously reported observations.[3] Our results show that omission of supplemental parenteral nutrition in the first week of the child's time in the intensive care unit did not harm physical and neurocognitive development and that these patients had fewer emotional and behavioral problems compared with children who received early-parenteral nutrition.

Table 1. Demographics, post-randomization treatments in the PICU, and acute outcomes of patients and healthy control children

	Tested populations		Total PICU population		Tested PICU population[i]	
	Healthy control children N=369	**Patients N=684**	**Early PN N=723**	**Late PN N=717**	**Early PN N=328**	**Late PN N=356**
Demographics						
Age at 4-years' follow-up - yr	7.5 (4.3)	7.3 (4.3)	NA	NA	7.4 (4.3)	7.2 (4.2)
Sex						
Male	202 (54.7%)	393 (57.5%)	415 (57.4%)	412 (52.5%)	187 (57.0%)	206 (57.9%)
Female	167 (45.3%)	291 (42.5%)	308 (42.6%)	305 (42.5%)	141 (43.0%)	150 (42.1%)
Known non-Caucasian race[a]	27 (7.3%)	53 (7.8%)	50 (6.9%)	33 (4.6%)	33 (10.1%)	20 (5.6%)
Known non-European origin[a]	45 (12.2%)	129 (18.9%)	161 (22.3%)	128 (17.9%)	73 (22.3%)	56 (15.7%)
Known not exclusive Dutch or English language	71 (19.2%)	158 (23.1%)	122 (16.9%)	106 (14.8%)	78 (23.8%)	80 (22.5%)
Socioeconomic status						
Educational level parents[b]						
Educational level 1	12 (3.3%)	30 (4.4%)	NA	NA	10 (3.1%)	20 (5.6%)
Educational level 1.5	13 (3.5%)	51 (7.5%)	NA	NA	29 (8.5%)	22 (6.2%)
Educational level 2	47 (12.7%)	157 (23.0%)	NA	NA	75 (22.9%)	82 (23.0%)
Educational level 2.5	68 (18.4%)	116 (17.0%)	NA	NA	53 (16.2%)	63 (17.7%)
Educational level 3	207 (56.1%)	183 (26.8%)	NA	NA	86 (26.2%)	97 (27.3%)
Educational level unknown	22 (6.0%)	147 (21.5%)	NA	NA	75 (22.9%)	72 (20.2%)
Occupational level parents[c]						
Occupational level 1	2 (0.5%)	7 (1.0%)	NA	NA	1 (0.3%)	6 (1.7%)
Occupational level 1.5	20 (5.4%)	63 (9.2%)	NA	NA	23 (7.0%)	40 (11.2%)
Occupational level 2	42 (11.4%)	108 (15.8%)	NA	NA	50 (15.2%)	58 (16.3%)
Occupational level 2.5	25 (6.8%)	69 (10.1%)	NA	NA	39 (11.9%)	30 (8.4%)
Occupational level 3	80 (21.7%)	118 (17.3%)	NA	NA	52 (15.9%)	66 (18.5%)
Occupational level 3.5	40 (10.8%)	53 (7.8%)	NA	NA	30 (9.2%)	23 (6.5%)

Table 1. Demographics, post-randomization treatments in the PICU, and acute outcomes of patients and healthy control children

	Tested populations		Total PICU population		Tested PICU population[i]	
	Healthy control children N=369	**Patients N=684**	**Early PN N=723**	**Late PN N=717**	**Early PN N=328**	**Late PN N=356**
Occupational level 4	117 (31.7%)	102 (14.9%)	NA	NA	44 (13.4%)	58 (16.3%)
Occupational level unknown	43 (11.7%)	164 (24.0%)	NA	NA	89 (27.1%)	75 (21.1%)
Patient characteristics upon PICU admission						
Infant (age<1y) at randomization	NA	331 (48.4%)	328 (45.4%)	325 (45.3%)	153 (46.7%)	178 (50.0%)
STRONGkids risk level[d]						
Medium	NA	613 (89.6%)	644 (89.1%)	644 (89.8%)	291 (88.7%)	322 (90.5%)
High	NA	71 (10.4%)	79 (10.9%)	73 (10.2%)	37 (11.3%)	34 (10.0%)
PeLOD score, first 24h in PICU [e]	NA	20.0 (11.6)	19.7 (12.0)	20.1 (12.3)	19.4 (11.6)	20.5 (11.5)
PIM3 score[f]	NA	-3.5 (1.4)	-3.2 (1.6)	-3.2 (1.7)	-3.4 (1.4)	-3.5 (1.3)
PIM3 probability of death - % [g]	NA	6.6 (11.7)	9.4 (15.9)	9.1 (17.4)	6.9 (11.9)	6.4 (11.7)
Diagnostic category						
Surgical						
Abdominal	NA	68 (9.9%)	53 (7.3%)	60 (8.4%)	34 (10.4%)	34 (10.0%)
Burns	NA	3 (0.4%)	5 (0.7%)	5 (0.7%)	2 (0.6%)	1 (0.3%)
Cardiac	NA	291 (42.5%)	279 (38.6%)	268 (37.4%)	137 (41.8%)	154 (43.3%)
Neurosurgery-Traumatic brain injury	NA	58 (8.5%)	63 (8.7%)	53 (7.4%)	31 (9.5%)	27 (7.6%)
Thoracic	NA	38 (5.6%)	34 (4.7%)	27 (3.8%)	21 (6.4%)	17 (4.8%)
Transplantation	NA	11 (1.6%)	7 (1.0%)	17 (2.4%)	3 (0.9%)	8 (2.3%)
Orthopedic surgery-Trauma	NA	19 (2.8%)	28 (3.9%)	26 (3.6%)	12 (3.7%)	7 (2.0%)
Other	NA	25 (3.7%)	21 (2.9%)	27 (3.8%)	11 (3.4%)	14 (3.9%)
Medical						
Cardiac	NA	23 (3.4%)	30 (4.2%)	31 (4.3%)	8 (2.4%)	15 (4.2%)
Gastrointestinal-Hepatic	NA	2 (0.3%)	2 (0.3%)	4 (0.6%)	1 (0.3%)	1 (0.3%)

Table 1. Demographics, post-randomization treatments in the PICU, and acute outcomes of patients and healthy control children

	Tested populations		Total PICU population		Tested PICU population[i]	
	Healthy control children N=369	**Patients N=684**	**Early PN N=723**	**Late PN N=717**	**Early PN N=328**	**Late PN N=356**
Oncologic-Hematologic	NA	6 (0.9%)	8 (1.1%)	7 (1.0%)	2 (0.6%)	4 (1.1%)
Neurologic	NA	42 (6.1%)	51 (7.1%)	52 (7.3%)	19 (5.8%)	23 (6.5%)
Renal	NA	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Respiratory	NA	70 (10.2%)	99 (13.7%)	96 (13.4%)	33 (10.1%)	37 (10.4%)
Other	NA	28 (4.1%)	42 (5.8%)	43 (6.0%)	14 (4.3%)	14 (3.9%)
Malignancy	0 (0.0%)	38 (5.6%)	51 (7.1%)	33 (4.6%)	22 (6.7%)	16 (4.5%)
Diabetes	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syndrome[h]	2 (0.5%)	63 (9.2%)	123 (17.0%)	118 (16.5%)	26 (7.9%)	37 (10.4%)
Known parental smoking between birth and PICU admission	NA	151 (22.1%)	NA	NA	69 (23.1%)	82 (24.5%)
Acute effects of randomization in PICU						
Duration of stay in the PICU – days	NA	7.8 (16.0)	9.2 (21.3)	6.5 (10.0)	9.3 (19.8)	6.5 (11.2)
Patients who acquired a new infection in PICU	NA	96 (14.0%)	134 (18.5%)	77 (10.7%)	59 (18.0%)	37 (10.4%)
Duration of mechanical ventilatory support – days	NA	5.0 (11.7)	6.4 (18.6)	4.4 (7.3)	6.0 (15.0)	4.0 (7.4)
Number of days with hypoglycemia <40 mg/dl – days	NA	0.1 (0.5)	0.1 (0.6)	0.2 (0.6)	0.1 (0.5)	0.2 (0.6)
Post-randomization treatments effects						
Duration of antibiotic treatment – days	NA	5.4 (14.2)	6.7 (19.0)	4.6 (8.7)	6.6 (17.7)	4.4 (9.8)
Duration of hemodynamic support – days	NA	2.7 (7.7)	3.0 (7.4)	2.4 (6.2)	2.9 (8.2)	2.5 (7.3)
Duration of treatment with opioids – days	NA	5.0 (9.3)	6.1 (16.5)	4.1 (6.2)	5.8 (11.5)	4.2 (6.5)
Duration of treatment with benzodiazepines – days	NA	4.4 (10.2)	5.4 (16.7)	4.0 (8.8)	4.9 (10.5)	4.0 (10.0)

Table 1. Demographics, post-randomization treatments in the PICU, and acute outcomes of patients and healthy control children

	Tested populations		Total PICU population		Tested PICU population[i]	
	Healthy control children N=369	**Patients N=684**	**Early PN N=723**	**Late PN N=717**	**Early PN N=328**	**Late PN N=356**
Duration of treatment with hypnotics – days	NA	1.5 (6.0)	1.8 (6.3)	1.3 (3.1)	1.8 (8.1)	1.1 (3.0)
Duration of treatment with alpha-2-agonists – days	NA	1.1 (6.8)	1.1 (8.7)	1.0 (6.0)	1.1 (6.4)	1.1 (7.1)
Duration of treatment with corticosteroids - days	NA	1.2 (3.9)	1.6 (4.3)	1.3 (3.9)	1.4 (4.5)	1.1 (3.3)

Data are n (%) or mean (SD).
a Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.
b The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (**Methods S4**).
c The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (**Methods S4**).
d Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.
e Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.
f Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.
g Pediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU.
h A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (**Methods S3**).
Abbreviations: BMI, body mass index; NA, not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition; SD, standard deviation.
i Overall, demographics upon PICU admission, allocation to late or early parenteral nutrition, and ICU or hospital-related primary and secondary study endpoints were comparable between the PEPaNIC patients who were tested (N=684) and those patients who survived, but declined participation or could not be reached (N=469, **Table S2**).

Table 2. Pooled univariable analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

		Tested populations			Tested PICU population		
Outcomes assessed at 4 years' follow-up[a]	**No. (%) available data per outcome prior to imputation N=1053**	**Healthy control children N=369**	**Patients N=684**	***p*-value**	**Early PN N=328**	**Late PN N=356**	***p*-value**
Height - cm	1012 (96.1%)	124.7 (23.4)	121.1 (23.2)	**0.02**	122.1 (23.1)	120.8 (23.2)	0.26
Z-score[b]	1012 (96.1%)	0.40 (0.99)	-0.03 (1.23)	**<0.0001**	0.04 (1.22)	-0.09 (1.25)	0.16
Weight - kg	1004 (95.3%)	28.0 (16.5)	27.0 (17.1)	0.33	27.2 (16.5)	26.7 (17.5)	0.70
Z-score[b]	1004 (95.3%)	0.32 (0.87)	0.12 (1.17)	**0.005**	0.17 (1.18)	0.08 (1.17)	0.55
BMI - kg/m^2	1003 (95.3%)	16.68 (2.94)	16.86 (3.33)	0.69	16.84 (3.13)	16.89 (3.50)	0.56
Z-score[b]	1003 (95.3%)	0.12 (1.00)	0.21 (1.17)	0.25	0.17 (1.43)	0.09 (1.26)	0.19
Head circumference - cm	1008 (95.7%)	52.5 (2.3)	52.0 (2.7)	**0.001**	52.1 (2.8)	51.8 (2.6)	0.27
Z-score[b]	1008 (95.7%)	0.49 (1.08)	0.13 (1.34)	**<0.0001**	0.17 (1.43)	0.09 (1.26)	0.19
Diagnosed with a somatic illness	840 (79.8%)	120 (32.4)	370 (54.0)	**<0.0001**	180 (54.6)	190 (53.5)	0.70
Diagnosed with a psychiatric illness	960 (91.2%)	16 (4.3)	63 (9.2)	**0.005**	32 (9.5)	31 (8.9)	0.81
Admitted to hospital for a medical or surgical reason	1011 (96.0%)	101 (27.3)	453 (66.2)	**<0.0001**	230 (70.0)	223 (62.7)	**0.05**
Clinical neurological evaluation score (range, 0-8)[a]	970 (92.1%)	0.2 (0.6)	0.6 (1.3)	**<0.0001**	0.7 (1.4)	0.5 (1.2)	0.09
Executive functioning as reported by parents/caregivers - T-score [a c]							
Inhibition	918 (89.9%)	45.7 (9.8)	49.8 (13.2)	**<0.0001**	50.8 (13.3)	49.0 (12.6)	0.07
Flexibility	919 (90.0%)	45.7 (8.5)	49.3 (11.8)	**<0.0001**	50.2 (12.2)	48.5 (11.2)	**0.05**
Emotional control	919 (90.0%)	46.2 (9.4)	48.9 (11.2)	**<0.0001**	49.5 (11.3)	48.4 (11.0)	0.18
Working memory	918 (89.9%)	46.4 (9.6)	51.9 (13.5)	**<0.0001**	52.7 (13.7)	51.1 (12.6)	0.12
Planning and organization	917 (89.8%)	46.3 (9.5)	50.4 (12.8)	**<0.0001**	50.6 (12.8)	50.2 (12.0)	0.60
Meta-cognition index	916 (89.7%)	45.6 (9.8)	50.6 (13.2)	**<0.0001**	50.9 (13.5)	50.2 (12.4)	0.51
Total score	915 (89.6%)	44.8 (9.8)	49.9 (13.2)	**<0.0001**	50.5 (13.3)	49.2 (12.5)	0.18
Emotional and behavioral problems as reported by parents/caregivers - T-score [a c]							
Internalizing problems	940 (92.1%)	46.7 (10.5)	51.0 (12.3)	**<0.0001**	52.1 (12.1)	50.0 (12.2)	**0.02**

Table 2. Pooled univariable analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

		Tested populations			Tested PICU population		
Outcomes assessed at 4 years' follow-up[a]	**No. (%) available data per outcome prior to imputation N=1053**	**Healthy control children N=369**	**Patients N=684**	***p*-value**	**Early PN N=328**	**Late PN N=356**	***p*-value**
Externalizing problems	940 (92.1%)	45.6 (9.7)	48.8 (11.2)	**<0.0001**	49.7 (11.0)	47.9 (11.1)	**0.03**
Total problems	940 (92.1%)	45.4 (9.9)	50.1 (11.9)	**<0.0001**	51.5 (11.6)	48.8 (11.9)	**0.003**
Intelligence (range, 45-155) [a]							
Total IQ	940 (92.1%)	105.7 (13.4)	93.1 (18.2)	**<0.0001**	93.2 (17.0)	93.0 (18.2)	0.89
Verbal IQ	940 (92.1%)	107.5 (14.4)	95.2 (19.0)	**<0.0001**	93.2 (16.0)	92.5 (16.2)	0.56
Performance IQ	940 (92.1%)	102.7 (13.2)	92.9 (16.2)	**<0.0001**	94.8 (18.3)	95.6 (18.6)	0.56
Visual-motor integration (range, 0.9-20) [a]	1025 (97.3%)	10.0 (2.1)	8.7 (3.1)	**<0.0001**	8.7 (3.1)	8.7 (2.7)	0.88
Alertness and motor coordination [a c]							
Alertness[a c d]							
Reaction time right hand – Z-score	739 (72.0%)	0.8 (4.3)	1.7 (12.6)	**0.03**	1.7 (8.9)	1.7 (9.4)	0.65
Within subject SD of repeated tests – Z-score	739 (72.0%)	1.1 (3.4)	2.0 (8.5)	**<0.0001**	2.0 (6.1)	2.0 (6.4)	0.68
Reaction time left hand – Z-score	752 (73.3%)	0.3 (2.5)	1.0 (5.8)	**<0.0001**	1.0 (4.3)	1.1 (4.5)	0.64
Within subject SD of repeated tests – Z-score	752 (73.3%)	1.0 (2.5)	1.7 (4.0)	**<0.0001**	1.6 (3.3)	1.7 (3.2)	0.59
Motor coordination (No of taps in 10s) [a c]							
No of unimanual taps							
Right hand	816 (79.5%)	34.6 (29.6)	32.6 (52.3)	0.12	32.7 (40.0)	32.5 (37.0)	0.76
Left hand	816 (79.5%)	30.5 (32.3)	28.9 (60.4)	0.18	29.1 (46.0)	28.7 (41.7)	0.65
No of valid alternating taps	742 (72.3%)	22.9 (30.0)	19.7 (56.8)	**0.05**	19.6 (43.8)	19.9 (40.7)	0.71
No of valid synchronous taps	785 (76.5%)	16.5 (18.3)	13.2 (27.9)	**<0.0001**	12.9 (21.9)	13.5 (20.5)	0.47
Memory [a c]							
Verbal-auditory							
Numbers (range, 1-19)							

Table 2. Pooled univariable analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

		Tested populations			Tested PICU population		
Outcomes assessed at 4 years' follow-up[a]	**No. (%) available data per outcome prior to imputation N=1053**	**Healthy control children N=369**	**Patients N=684**	***p*-value**	**Early PN N=328**	**Late PN N=356**	***p*-value**
Memory span (forward)	418 (85.1%)	9.9 (3.1)	8.7 (4.3)	**<0.0001**	9.0 (4.0)	8.5 (3.6)	0.18
Working memory (backward)	394 (80.2%)	10.3 (3.1)	9.5 (5.3)	**0.01**	9.7 (4.5)	9.3 (4.3)	0.24
Word pairs (proportion of correct responses)							
Learning	350 (71.2%)	0.5 (0.2)	0.4 (0.4)	**<0.0001**	0.4 (0.4)	0.4 (0.3)	0.67
Immediate memory	346 (70.5%)	0.4 (0.5)	0.4 (1.3)	0.07	0.4 (1.0)	0.4 (0.9)	0.55
Delayed memory	343 (69.9%)	0.4 (0.7)	0.4 (1.6)	0.12	0.4 (1.3)	0.4 (1.1)	0.43
Recognition	343 (69.9%)	0.9 (0.5)	0.9 (1.3)	0.15	0.9 (0.9)	0.9 (0.9)	0.46
Non-verbal, visual-spatial							
Pictures (proportion of correct responses)	404 (82.2%)	0.8 (0.1)	0.8 (0.2)	**<0.0001**	0.8 (0.2)	0.8 (0.2)	0.74
Dots (proportion of correct responses)							
Learning	370 (75.4%)	0.9 (0.2)	0.8 (0.4)	**0.001**	0.8 (0.4)	0.8 (0.3)	0.26
Immediate memory	367 (74.7%)	0.9 (0.3)	0.8 (0.7)	**0.01**	0.8 (0.5)	0.8 (0.5)	0.27
Delayed memory	361 (73.5%)	0.8 (0.4)	0.7 (1.1)	**0.004**	0.7 (0.8)	0.7 (0.8)	0.66
Learning index (range, 50-150)	341 (69.5%)	101.0 (22.6)	88.1 (33.2)	**<0.0001**	88.5 (27.4)	87.7 (25.8)	0.65

Results are presented in numbers with proportions (%) or mean (SD) from the 31 datasets combined generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 684 post-PICU patients and 369 healthy control children.
a For the clinical neurological evaluation score, higher scores reflect worse performance. For parent-reported executive functioning and emotional and behavioral problems, higher scores reflect worse performance. For intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness and within-subject SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For memory tests, higher scores reflect better performance.
b Age- and gender-adjusted Z-scores, were calculated with the use of reference data from the World Health Organization Growth Charts: http://www.bcchildrens.ca/Services/SpecializedPediatrics/EndocrinologyDiabetesUnit/ForProfessionals/AnthropometricCalculators.htm.
c For alertness, motor coordination, executive functions, emotional and behavioral problems and memory, applicable imputation was limited to relevant age-ranges.
d For alertness, age adjusted Z-scores were calculated and imputed in the dataset
Abbreviations: BMI, body mass index; IQ, intelligence quotient; PICU, pediatric intensive care unit; PN, parenteral nutrition; SD, standard deviation.

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

Outcomes assessed at 4 years' follow-up[a]	**No. (%) available data per outcome prior to imputation N=1053**	**Beta-estimate or odds ratio (95% CI) for the comparison patients vs. controls, adjusted for risk factors**[d]	***p*-value**	**Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs. Early PN, adjusted for risk factors**[f]	***p*-value**
Height – cm	1012 (96.1%)	-2.108 (-3.152 to -1.063)	**<0.0001**	-0.814 (-3.448 to 1.820)	0.54
Weight – kg	1004 (95.3%)	-0.091 (-0.966 to 0.785)	0.83	0.129 (-2.047 to 2.304)	0.91
Head circumference – cm	1008 (95.7%)	-0.421 (-0.665 to -0.176)	**0.0007**	-0.113 (-0.461 to 0.234)	0.52
Diagnosed with a somatic illness	840 (79.8%)	2.232 (1.635 to 3.047)[e]	**<0.0001**	0.974 (0.683 to 1.390)[e]	0.88
Diagnosed with a psychiatric illness	960 (91.2%)	2.465 (1.248 to 4.871)[e]	**0.009**	1.035 (0.562 to 1.905)[e]	0.91
Admitted to hospital for a medical or surgical reason	1011 (96.0%)	4.269 (3.120 to 5.842)[e]	**<0.0001**	0.715 (0.501 to 1.020)[e]	0.06
Clinical neurological evaluation score (range, 0-8)[a]	970 (92.1%)	0.237 (0.098 to 0.376)	**0.0008**	-0.098 (-0.275 to 0.079)	0.28
Executive functioning as reported by parents/caregivers - T-score[a b]					
Inhibition	918 (89.9%)	2.685 (1.059 to 4.310)	**0.001**	-1.665 (-3.643 to 0.313)	0.10
Flexibility	919 (90.0%)	2.706 (1.259 to 4.153)	**0.0002**	-1.487 (-3.283 to 0.309)	0.10
Emotional control	919 (90.0%)	2.061 (0.601 to 3.520)	**0.005**	-1.189 (-2.938 to 0.560)	0.18
Working memory	918 (89.9%)	3.695 (2.096 to 5.293)	**<0.0001**	-1.375 (-3.328 to 0.577)	0.17
Planning and organization	917 (89.8%)	2.866 (1.327 to 4.406)	**0.0002**	-0.380 (-2.270 to 1.511)	0.69
Meta-cognition index	916 (89.7%)	3.334 (1.714 to 4.954)	**<0.0001**	-0.610 (-2.580 to 1.359)	0.54
Total score	915 (89.6%)	3.566 (1.950 to 5.183)	**<0.0001**	-1.266 (-3.246 to 0.714)	0.21
Emotional and behavioral problems as reported by parents/caregivers – T-score[a b]					
Internalizing problems	940 (92.1%)	2.730 (1.185 to 4.275)	**0.0005**	-1.880 (-3.690 to -0.071)	**0.042**
Externalizing problems	940 (92.1%)	1.631 (0.185 to 3.076)	**0.02**	-1.731 (-3.433 to -0.028)	**0.046**
Total problems	940 (92.1%)	2.951 (1.443 to 4.459)	**0.0001**	-2.442 (-4.215 to -0.668)	**0.007**
Intelligence (range, 45-155)[a]					
Total IQ	937 (89.0%)	-7.349 (-9.311 to -5.387)	**<0.0001**	-1.100 (-3.399 to 1.198)	0.35
Verbal IQ	931 (88.4%)	-6.955 (-8.986 to -4.924)	**<0.0001**	-0.126 (-2.493 to 2.241)	0.92

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

Outcomes assessed at 4 years' follow-up[a]	No. (%) available data per outcome prior to imputation N=1053	Beta-estimate or odds ratio (95% CI) for the comparison patients vs. controls, adjusted for risk factors[d]	*p*-value	Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs. Early PN, adjusted for risk factors[f]	*p*-value
Performance IQ	943 (89.6%)	-5.968 (-7.905 to -4.030)	**<0.0001**	-1.645 (-3.902 to 0.612)	0.15
Visual-motor integration (range, 0.9-20)[a]	1025 (97.3%)	-0.888 (-1.202 to -0.574)	**<0.0001**	-0.081 (-0.448 to 0.286)	0.66
Alertness and motor coordination [a b]					
Alertness [a b c]					
Reaction time right hand – Z-score	739 (72.0%)	0.668 (0.186 to 1.150)	**0.007**	0.077 (-0.334 to 0.489)	0.71
Within subject SD of repeated tests – Z-score	739 (72.0%)	0.663 (0.254 to 1.071)	**0.001**	0.020 (-0.393 to 0.434)	0.92
Reaction time left hand – Z-score	752 (73.3%)	0.498 (0.177 to 0.819)	**0.002**	0.141 (-0.221 to 0.502)	0.44
Within subject SD of repeated tests – Z-score	752 (73.3%)	0.476 (0.168 to 0.784)	**0.002**	0.173 (-0.166 to 0.512)	0.32
Motor coordination (No of taps in 10s) [a b]					
No of unimanual taps					
Right hand	816 (79.5%)	-1.762 (-3.448 to -0.076)	**0.04**	0.240 (-1.844 to 2.325)	0.82
Left hand	816 (79.5%)	-1.720 (-3.415 to -0.024)	**0.04**	0.094 (-1.893 to 2.081)	0.93
No of valid alternating taps	742 (72.3%)	-2.412 (-4.848 to 0.023)	**0.05**	0.503 (-2.202 to 3.209)	0.71
No of valid synchronous taps	785 (76.5%)	-2.066 (-3.348 to -0.783)	**0.001**	0.354 (-1.192 to 1.901)	0.65
Memory [a b]					
Verbal-auditory					
Numbers (range, 1-19)					
Memory span (forward)	418 (85.1%)	-0.644 (-1.270 to -0.019)	**0.04**	-0.601 (-1.371 to 0.168)	0.12
Working memory (backward)	394 (80.2%)	-0.165 (-0.781 to 0.450)	0.59	-0.323 (-1.047 to 0.400)	0.38
Word pairs (proportion of correct responses)					
Learning	350 (71.3%)	-0.081 (-0.122 to -0.040)	**0.0001**	-0.021 (-0.060 to 0.019)	0.30

Table 3. Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 4 years' follow-up between patients and healthy control children and between Late PN and Early PN patient groups

Outcomes assessed at 4 years' follow-up[a]	No. (%) available data per outcome prior to imputation N=1053	Beta-estimate or odds ratio (95% CI) for the comparison patients vs. controls, adjusted for risk factors[d]	*p*-value	Beta-estimate or odds ratio (95% CI) for the comparison Late PN vs. Early PN, adjusted for risk factors[f]	*p*-value
Immediate memory	346 (70.5%)	-0.040 (-0.101 to 0.021)	0.19	-0.030 (-0.089 to 0.026)	0.31
Delayed memory	343 (70.0%)	-0.034 (-0.098 to 0.029)	0.28	-0.012 (-0.088 to 0.064)	0.76
Recognition	434 (70.0%)	-0.033 (-0.084 to 0.018)	0.20	-0.010 (-0.048 to 0.027)	0.58
Non-verbal, visual-spatial					
Pictures (proportion of correct responses)	404 (82.3%)	-0.029 (-0.056 to -0.003)	**0.02**	0.008 (-0.028 to 0.044)	0.68
Dots (proportion of correct responses)					
Learning	370 (75.4%)	-0.046 (-0.080 to -0.012)	**0.007**	0.007 (-0.040 to 0.054)	0.77
Immediate memory	367 (74.7%)	-0.053 (-0.102 to -0.003)	**0.03**	-0.012 (-0.073 to 0.050)	0.70
Delayed memory	361 (73.5%)	-0.078 (-0.148 to -0.007)	**0.03**	0.005 (-0.071 to 0.080)	0.90
Learning index (range, 50-150)	341 (70.0%)	-10.216 (-13.883 to -6.549)	**<0.0001**	-1.383 (-5.351 to 2.585)	0.49

Results are the combined beta-estimates and odds ratios from 31 datasets generated by multiple data imputation by chained equations under a 'missing at random' assumption for the 684 patients and 369 healthy control children.

a For the clinical neurological evaluation score, higher scores reflect worse performance. For parent-reported executive functioning and emotional and behavioral problems, higher scores reflect worse performance. For intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness and within-subject SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For memory tests, higher scores reflect better performance.

b For alertness, motor coordination, executive functions, emotional and behavioral problems and memory, applicable imputation was limited to relevant age-ranges.

c For alertness, age adjusted Z-scores were calculated and imputed in the dataset

d Estimates and odds ratios were adjusted for the following risk factors: age, center, race, gender, geographic origin, language, hand preference, history of malignancy, a predefined "syndrome", and the educational and occupational status of parents.

e These values are odds ratios.

f Estimates and odds ratios were adjusted for the following risk factors: age, center, race, gender, geographic origin, language, hand preference, history of malignancy, a predefined "syndrome", the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behavior prior to PICU admission.

Abbreviations: IQ, intelligence quotient; PeLOD score, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3 score, pediatric index of mortality 3 score; PN, parenteral nutrition; SD, standard deviation; STRONGkids, Screening Tool Risk On Nutritional Status and Growth.

Sensitivity analyses to the "missing at random' assumption and with imputing worst test-scores for the severely disabled and thus non-testable children, as specified in the Methods S2, further supported the robustness of these results.

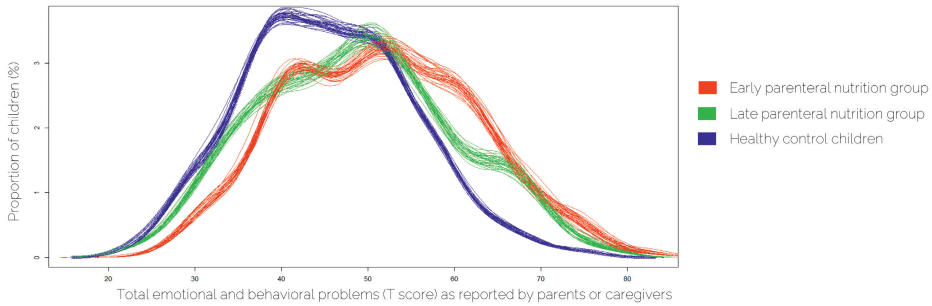

Figure 2. The effect of late-parenteral nutrition versus early parenteral nutrition on the development of long-term emotional and behavioral problems
The figure represents the density estimates for total behavioral and emotional problems reported by parents or caregivers. Each line corresponds to an imputed dataset. Densities correspond to the proportions of children with a certain score (equivalent to a smoothed histogram). Higher scores indicate more total behavioral and emotional problems. PN=parenteral nutrition.

At 4-year follow-up, the legacy of critical illness affected all developmental domains. The extent to which these abnormalities are acquired during intensive care remains debated.22 However, the developmental legacy documented 4 years after critical illness was found to remain present after adjustment for all known baseline risk factors at intensive care unit admission. The documented developmental abnormalities are relevant because they are known to have direct implications for daily life and hamper future societal perspectives.[2,23,24] Moreover, the developmental impairment after pediatric critical illness is at least as pronounced as what has been reported for children who survived cancer[25–27] and for children with chronic diseases such as type 1 diabetes and chronic kidney disease.[28,29]

Of note, the emotional and behavioral problems—such as internalizing, externalizing, and other issues—were preventable by omitting the use of early-parenteral nutrition in the pediatric intensive care unit. Internalizing problems are evidenced by anxious and depressive symptoms, and by social withdrawal,[13,14] which are the consequences of over-controlling behavior. Externalizing problems are externally directed problems that affect the environment and become apparent in aggressive and delinquent behavior, which result in conflicts with others. The total score for the emotional and behavioral problems includes internalizing and externalizing behavioral problems, sleep problems for younger children, and social, thinking, and attention problems for older children. Such issues are thought to be in part a consequence of poor development of executive functions, such as poor inhibitory control.[30,31] This might explain why, at 2-year follow-up, we found that not being exposed to early-parenteral nutrition predominantly reduced abnormal inhibitory control;[5] whereas, 2 years later, the effect on the emotional and behavioral problems became more apparent.

The developing brain of children thus appears vulnerable to metabolic insults during periods of critical illness. We previously showed that tight glycemic control during

intensive care prevented impaired motor coordination 4 years after admission,[3] an impairment that was less apparent in patients of the PEPaNIC trial, who had received at least some form of blood glucose control. In addition to avoiding pronounced hyperglycemia, omitting early-parenteral nutrition during critical illness protected the normal development of other neurobiological pathways that coordinate emotions and behavior. This indicates that the neurocognitive legacy of pediatric critical illness is multifactorial, and improvement can only be expected by a stepwise elimination of various causal factors. The stepwise elimination of harmful factors will need the support of clinical guidelines to help the implementation or de-implementation of certain interventions, such as the latest European Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Clinical Nutrition and Metabolism, European Society for Pediatric Research, and Chinese Society of Parenteral and Enteral Nutrition joint guidelines on pediatric parenteral nutrition.[32] Nevertheless, even though progress has been made, our findings show that children who have been critically ill clearly still face important developmental problems. Thus, the setting up of a structured post critical illness follow-up consultation is necessary for these children, with referral to a specialized health-care professional (e.g., clinical psychologist or psychiatrist) who can initiate an appropriate intervention when warranted.

This study has some limitations to highlight. First, for the clinical tests that assessed inhibition and flexibility, missing data for more than 30% of the population did not allow imputation and thus no information on differences between the groups could be provided. Second, neuroimaging studies were not done because of ethical and practical considerations. Third, we did not correct for multiple comparisons because the studied developmental outcomes are not independent, as shown by the correlations in the outcomes reported, which makes use of the stringent Bonferroni correction inappropriate. Although the risk of false-positive findings cannot be completely excluded, we did find a significant effect of early-parenteral nutrition versus late-parenteral nutrition on caregiver-reported emotional and behavioral problems. The strengths of the study include the limited loss to follow-up compared with other long-term follow-up studies of children with critical illness[33,34] and the broad assessment of the physical, neurocognitive, and emotional and behavioral development of patients and matched control children.

In conclusion, 4 years after critical illness, an important physical, neurocognitive, and emotional and behavioral legacy was reported. The omission of early-parenteral nutrition did not harm any of the developmental domains and protected patients against parent-reported or caregiver-reported emotional and behavioral problems, which were no longer overrepresented in patients in the late parenteral nutrition group compared with healthy controls. These data support de-implementation of the use of parenteral nutrition early during critical illness in infants and children. The findings also open perspectives for future identification of other modifiable risk factors related to intensive care management.

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Appendix Chapter 7

Methods S1. Detailed description of outcome measures

Medical assessment

Anthropometric data

At the beginning of the follow-up visit, height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status

In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 4 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination

In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. An abnormal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing

A broad range of neurocognitive functions, including general intellectual functioning, visual-motor integration, alertness, motor coordination, verbal and visual-spatial learning, and memory were evaluated, as previously reported.[1]

Patient/Parents-reported outcomes (PROs)

Executive functioning was assessed with the Behavior Rating Inventory of Executive Function in children aged years 6 months - 5 years 11 months with BRIEF-P, and in children 6 years – 17 years 11 months with BRIEF, filled out by the parents/caregivers of the child. Overlapping scales and indices of both questionnaires (Inhibition, Flexibility, Emotional Control, Working Memory, Planning and Organization, Meta-cognition) and a Total Score were analyzed (T-scores, with mean 50 and SD 10).[2,3] Emotional and behavioral problems were assessed by the parent/caregiver with the Child behavior Checklist (CBCL 1.5-5 years or CBCL 6-18 years).[4,5] Internalizing, externalizing, and total problems were analyzed (T-scores, with mean 50 and SD 10).[4,5]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[6] was used for children aged 3 years 6 months – 5 years 11 months (one version for age range 3 years 6 months – 3 years 11 months, and another version for age range 4 years – 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-III-NL)[7] was used for children aged 6 years – 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IVNL) [8] for adolescents who were 17 years or older. For all these tests Total IQ, Verbal IQ, and Performance IQ scores (standard scores, with mean 100, SD 15) were computed.

Visual-motor integration

We used the Beery Developmental Test of Visual-Motor Integration, 6th Edition (VMI) to assess the ability to integrate visual and motor functions (scaled score, with mean 10 and SD 3). This involves eye-hand coordination.[9]

Alertness and motor-coordination

To measure alertness and motor coordination, the validated Amsterdam Neuropsychological Tasks (ANT) program was used.[10] The ANT is a computerized assessment battery of reaction time (RT) tasks that allows for the systematic evaluation of information processing capacities. Children aged 4 years and older performed ANT-Baseline Speed (BS) and ANT-Tapping (TP). The ANT-BS evaluated alertness by measuring simple RT to visual stimuli (Z-scores of mean RT and SD of RT with mean 0 and SD 1 were obtained for the right and left hand separately). The ANT-TP assessed motor coordination for the right hand, left hand, bimanual alternating, and bimanual synchronous (number of taps,).

Memory

Auditory/verbal memory and Visual-spatial/non-verbal memory were assessed with use of four tests from the Children's Memory Scale (CMS) for children aged between 5 and 16 years 11 months.[11] As to verbal memory, CMS-Numbers assessed short-term verbal memory span (forward digit recall) and verbal working memory load (backward digit recall). The CMS-Word Pairs (recall a list of word pairs) assessed short-term and long-term verbal memory, and recognition. As to non-verbal memory, CMS-Picture Locations (remembering and recall of pictures in various locations) assessed short-term visual memory. CMS-Dot Locations (remembering and recall of the location of dots) assessed short-term and long-term visual memory. For CMS-Numbers, scaled scores (with mean 10 and SD 3) for verbal memory span, CMS-numbers forward, and verbal working memory load, CMS-numbers backward were reported. For CMS-Word Pairs, CMS-Picture Locations, and CMS-Dot Locations, proportional scores were analyzed (proportion of correct responses ranging from 0 to 1, with higher scores reflecting better performance). The CMS-Learning index is a standardized score of the

sum of the three learning trials of the CMS-Word Pairs and the three learning trials of the CMS-Dot Locations subtests. The range of the score is 50-150, with a higher score representing a better learning ability.

Methods S2. Imputation

Missing data (excluding the deceased and the severely disabled whereby non-testable children) were handled by ***multiple data imputation with chained equations under a 'missing at random' assumption***. There were no missing data in the baseline variables. Predictors for missing values included all covariates listed below, and were retained in the predictor models with a minimum correlation of 0.1 with the prediction target. Predictive mean matching[12] was used for numeric variables except for factors with two levels (which were imputed based on logistic regression) and factors with more than two levels (for which polytomous (unordered) regression was used). A monotonous visiting scheme was used such that variables for imputation were visited in increasing order of the number of missing data. Imputation convergence was assessed visually and set at 100 iterations (**Figure S2**) 31 complete imputed datasets were used in the analyses,[13] and pooled results were obtained across datasets using Rubin's rules.[14]

Plausibility of the imputations was assessed visually via the densities of the observed data and that resulting from the imputed values (**Figure S3**). ***Sensitivity of results to the 'missing at random' assumption*** was assessed with use of pattern mixture models14-16 assuming the original imputed values were either too high by a factor of 0.07 or too low by a factor of 0.1 for the main result of total emotional and behavioral problems as reported by parents/caregivers. Under this assumption, the obtained beta-estimates and *p*-values for randomization to Late PN vs. Early PN for the multivariable linear regression analyses performed to determine significant and independent associations between risk factors and total emotional/behavioral problems as reported by the parents/caregivers at 4 years' follow-up within the tested patient population ranged from -1.98 (P=0.05) to -1.84 (P=0.04). The effect-sizes thus remained of the same order of magnitude, sign, and statistical significance as observed for the original imputed datasets, which suggested that the analyses were robust against the investigated 'missing at random' violation.

To further evaluate the robustness of the main findings, the analyses were repeated after imputing a penalized test result for all severely disabled and thus non-testable patients, defined as the worst result in the observed patients or controls, plus or minus one, as appropriate for each test. In this case, the obtained beta-estimates (*p*-values) for randomization to Late PN vs. Early PN for the multivariable linear regression analyses were respectively: A) -1.80 (P=0.05) for internalizing emotional/behavioral problems as reported by the parents/caregivers B) -1.62 (P=0.06) for externalizing emotional/behavioral problems as reported by the parents/caregivers and C)

-2.36 (P=0.01) for total emotional/behavioral problems as reported by the parents/caregivers. These sensitivity analyses corresponded closely to the primary results as reported in **Table 3** of the main manuscript. All multiple data imputation analyses were performed with R version 3.5.3 and MICE versions 3.4.0 and 3.6.0.

List of variables used for multiple data imputation by chained equations

Demographics of patients and control children and patient characteristics upon PICU admission

Centre, randomization for Late PN or Early PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome", educational and occupational status of parents, diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking before, during and after pregnancy, age at randomization, age group at randomization.

Acute effects of randomization and post-randomization treatments in PICU

Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycemia, duration of treatment with hemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and alpha-2-agonists.

At 4-years' follow-up

Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performance IQ, total IQ, visual motor integration, Z-score reaction time left hand, Z-score reaction time right hand, Z-score within subject SD of reaction time left hand, Z-score within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, numbers memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organization, meta-cognition index, and total score), emotional and behavioral problems as reported by parents/caregivers (internalizing problems, externalizing problems, and total problems).

Methods S3. Definition of "Syndrome"

A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive
development, and which is subdivided in the following categories:[17]

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown etiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumor or tumor with intracranial metastatic disease
- Pediatric psychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity
- disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental
- performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomization
- Severe convulsions or stroke prior to randomization

Methods S4. Definition of educational and occupational level of parents

Educational level of parents[17]

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents[17]

The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions.[18] In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Methods S5. Correlation of physical, neurocognitive and psychosocial outcomes

We computed a correlation matrix to investigate the univariate association between all pairwise combinations of the physical, neurocognitive and psychosocial outcomes evaluated at 4-year follow up. In all cases we used a Pearson correlation of pairwise complete observations. This correlation matrix was then visualized directly with a color-code indicating the sign and strength of the correlation. This analysis was performed with the "Corrr" package version 0.4.0. for R version 3.5.3.

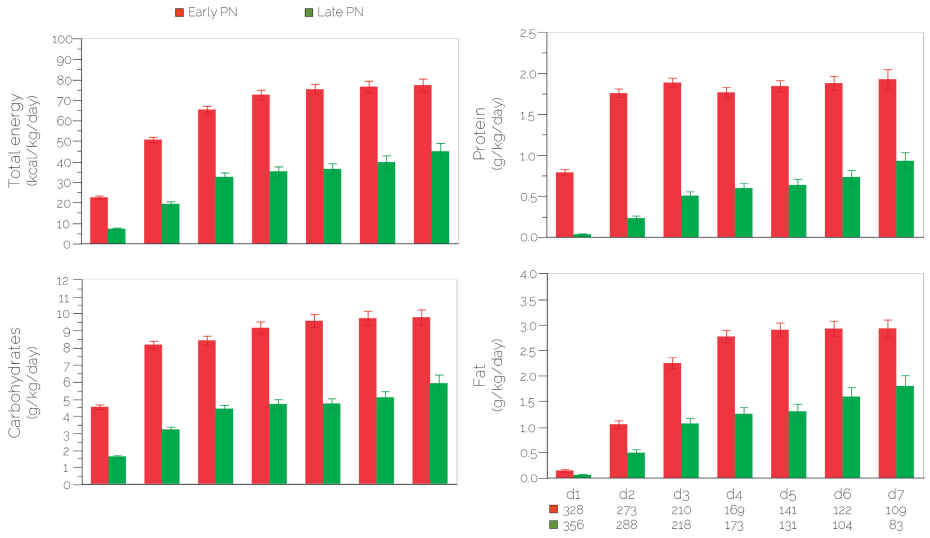

Figure S1. Macronutrient doses during the first week in PICU administered to the tested population
Daily amount of total energy in kcal/kg/day, and the daily amounts of total substrates in g/kg/day are shown for
the first 7 days in the pediatric intensive care unit (PICU). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the Early PN group and the green bars represent the
Late PN group.

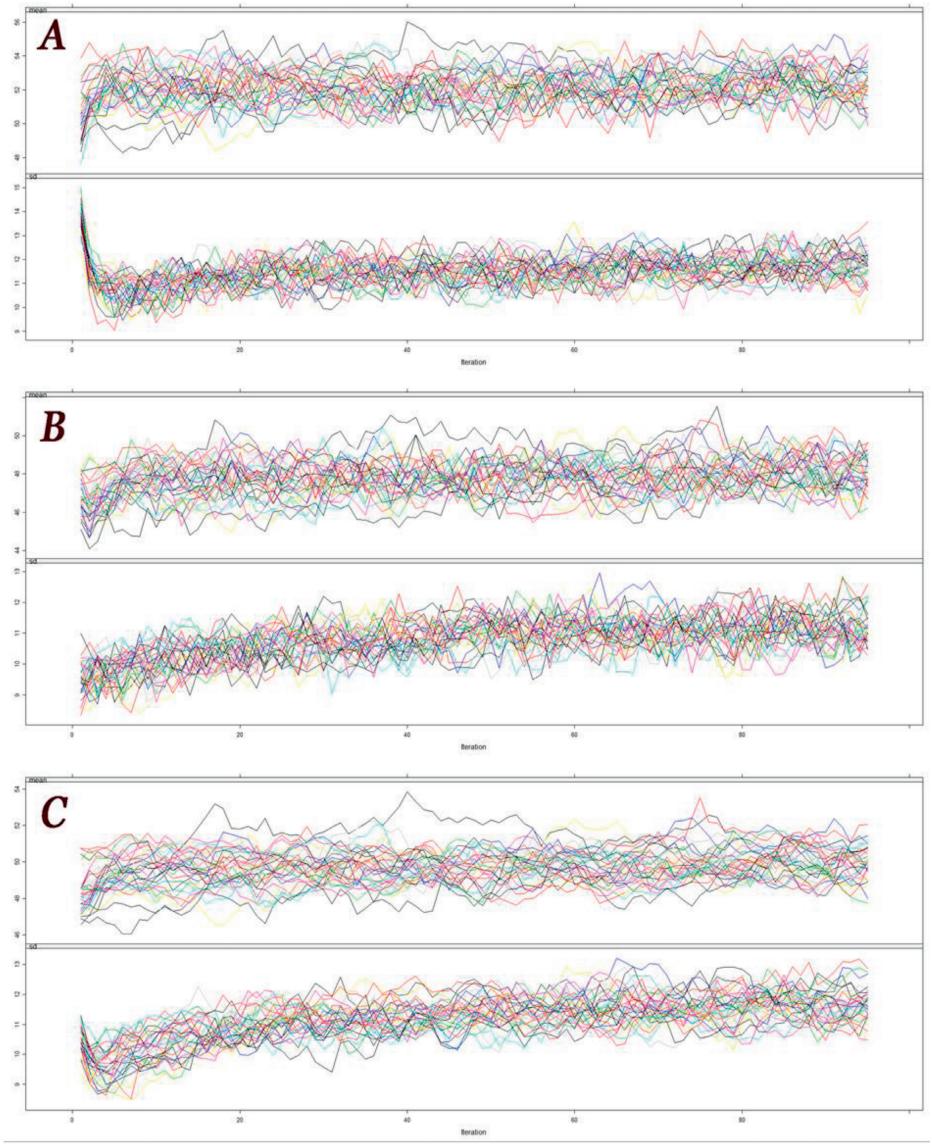

Figure S2. Imputation convergence for selected neurocognitive test results
Mean and standard deviation of imputed values in each of 31 datasets over 100 iterations for **A)** Emotional and behavioral problems as
reported by parents/caregivers — T-score: Internalizing problems **B)** Externalizing problems **C)** Total problems.

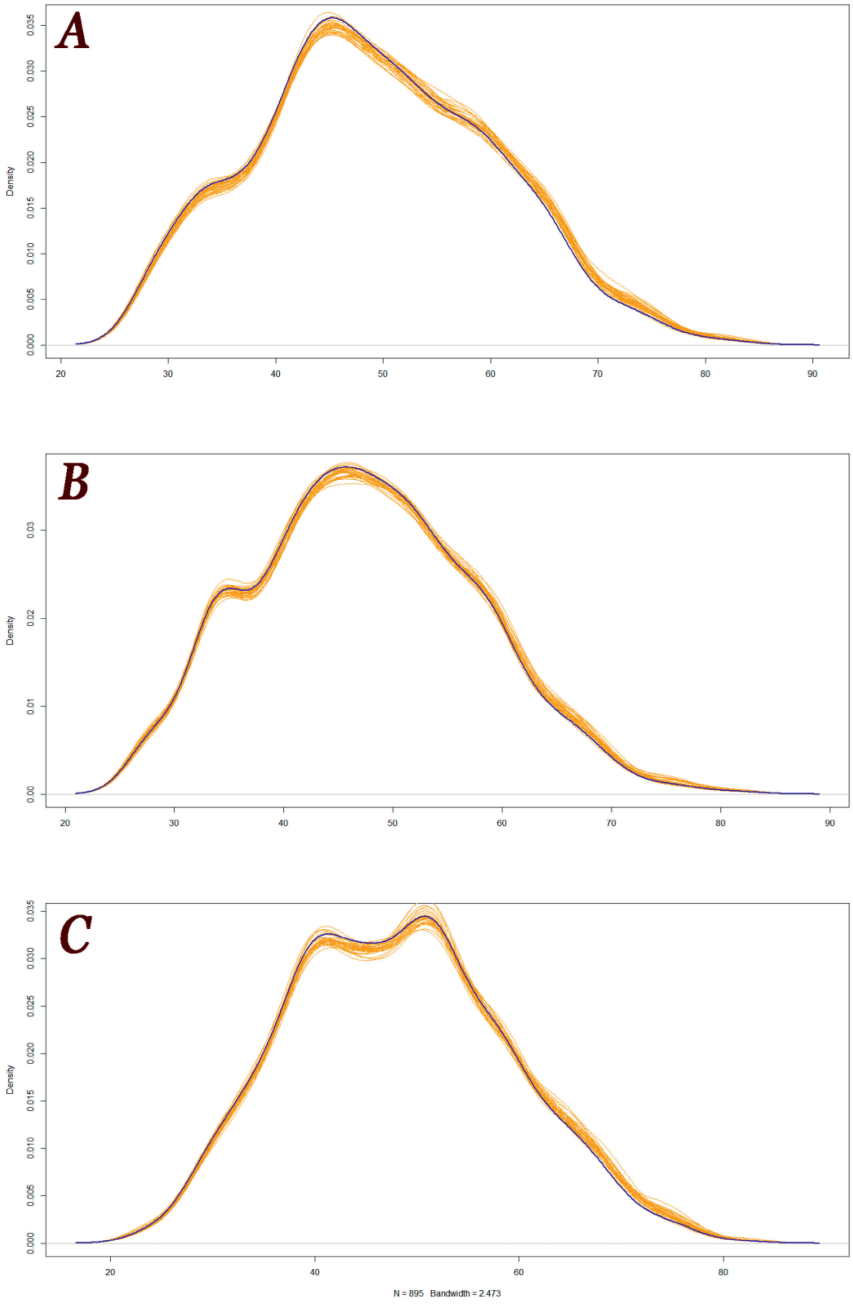

Figure S3. Density estimates of the observed and imputed values for selected neurocognitive test results Density estimated for observed values (in blue) and for each imputed dataset (in orange) for **A)** Emotional and behavioral problems as
reported by parents/caregivers — T-score: Internalizing problems **B)** Externalizing problems **C)** Total problems.

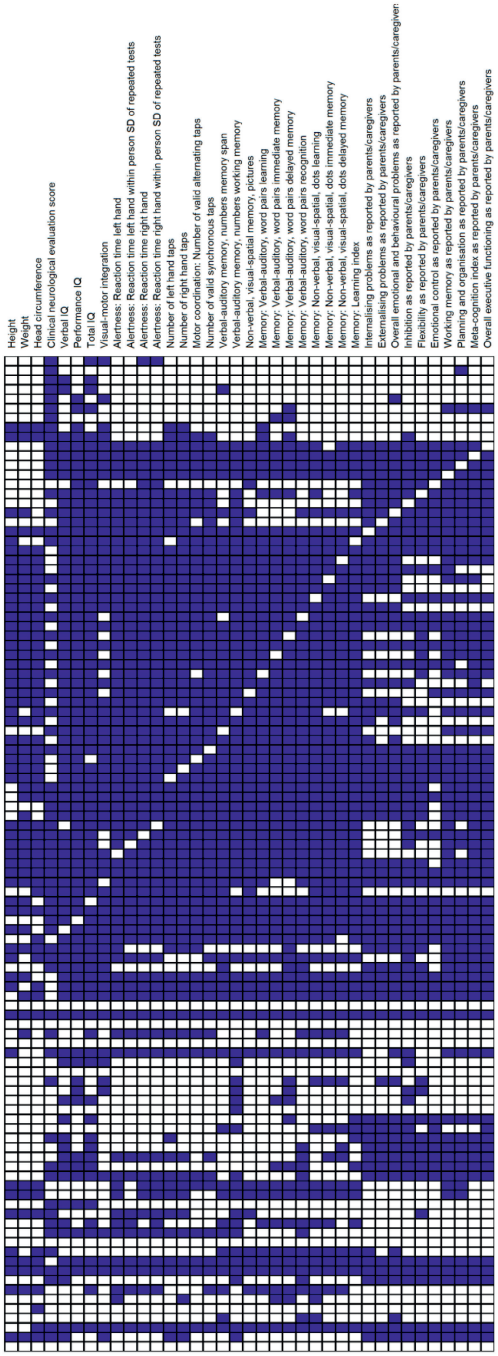

Figure S4. Multiple imputation predictor variables
Missing values for the variables in each row are imputed based on models that use as predictors only the column variables highlighted in blue. The predictor variables are selected as described in **Methods S4.**

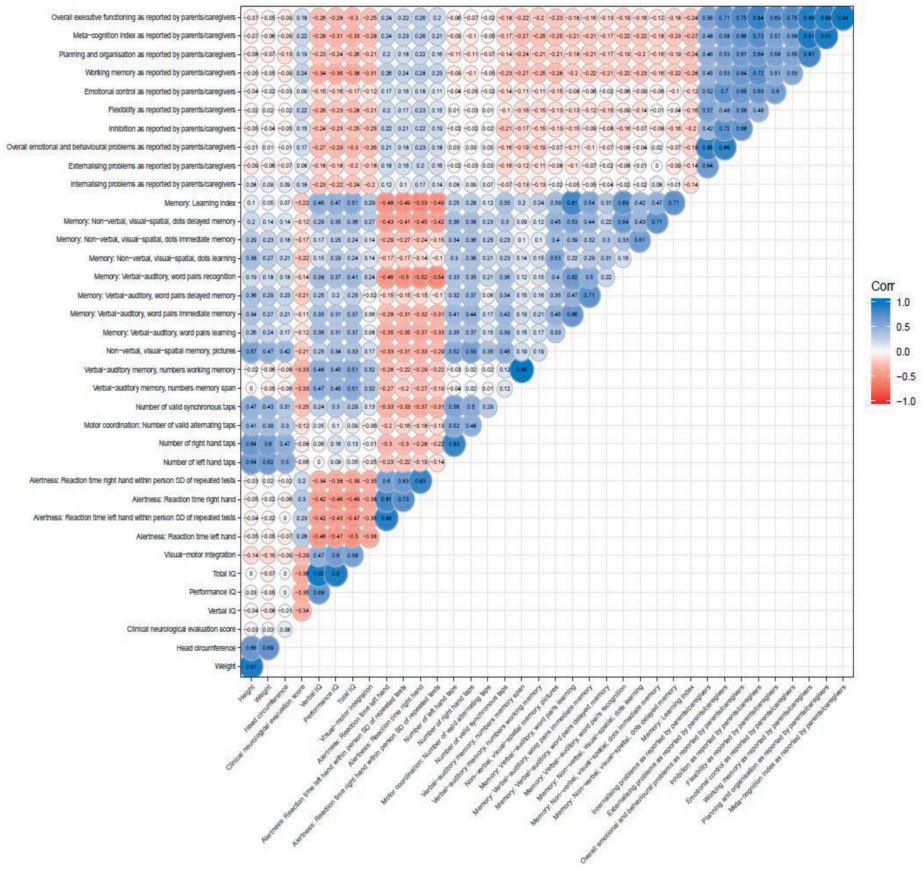

Figure S5. Correlation plot of physical, neurocognitive and psychosocial outcomes
The correlation matrix shows the correlation between all physical, neurocognitive and emotional/behavioral outcomes. Blue shades
represent a positive correlation, red shades represent inverse correlations. Darker colored shading represents a stronger correlation. For
the statistical methodology of this matrix, see **Methods S5**.

Table S1.1. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84	**Neurocognitively tested patients N=684**	***p*-value**
Demographics			
Age at 4-years' follow-up - yr	9.0 (5.6)	7.3 (4.3)	0.008
Sex			
Male	49 (58.3%)	393 (57.5%)	0.87
Female	35 (41.7%)	291 (42.5%)	
Known non-Caucasian race[a]	11 (13.1%)	53 (7.8%)	0.09
Known non-European origin[a]	20 (23.8%)	129 (18.9%)	0.27
Known not exclusive Dutch or English language	20 (23.8%)	158 (23.1%)	0.88
Socioeconomic status			
Educational level parents[b]			0.001
Educational level 1	9 (10.7%)	30 (4.4%)	
Educational level 1.5	4 (4.8%)	51 (7.5%)	
Educational level 2	21 (25.0%)	157 (23.0%)	
Educational level 2.5	11 (13.1%)	116 (17.0%)	
Educational level 3	10 (11.9%)	183 (26.8%)	
Educational level unknown	29 (34.5%)	147 (21.5%)	
Occupational level parents[c]			<0.0001
Occupational level 1	3 (3.6%)	7 (1.0%)	
Occupational level 1.5	6 (7.1%)	63 (9.2%)	
Occupational level 2	19 (22.6%)	108 (15.8%)	
Occupational level 2.5	5 (6.0%)	69 (10.1%)	
Occupational level 3	5 (6.0%)	118 (17.3%)	
Occupational level 3.5	0 (0.0%)	53 (7.8%)	
Occupational level 4	10 (11.9%)	102 (14.9%)	
Occupational level unknown	36 (42.9%)	164 (24.0%)	
Patient characteristics upon PICU admission			
Randomization			0.11
Early PN	48 (57.1%)	328 (48.0%)	
Late PN	36 (42.9%)	356 (52.1%)	
Infant (age<1y) at randomization	36 (42.9%)	331 (48.4%)	0.33
STRONGkids risk level[d]			0.15
Medium	71 (84.5%)	613 (89.6%)	
High	13 (15.5%)	71 (10.4%)	
PeLOD score, first 24h in PICU [e]	22.8 (12.4)	20.0 (11.6)	0.03
PIM3 score[f]	-3.0 (1.5)	-3.5 (1.4)	0.001
PIM3 probability of death - % [g]	9.1 (13.6)	6.6 (11.7)	0.001
Diagnostic category			<0.0001

Table S1.1. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84	**Neurocognitively tested patients N=684**	***p*-value**
Surgical			
Abdominal	1 (1.2%)	68 (9.9%)	
Burns	0 (0.0%)	3 (0.4%)	
Cardiac	28 (33.3%)	291 (42.5%)	
Neurosurgery-Traumatic brain injury	10 (11.9%)	58 (8.5%)	
Thoracic	1 (1.2%)	38 (5.6%)	
Transplantation	1 (1.2%)	11 (1.6%)	
Orthopedic surgery-Trauma	12 (14.3%)	19 (2.8%)	
Other	1 (1.2%)	25 (3.7%)	
Medical			
Cardiac	0 (0.0%)	23 (3.4%)	
Gastrointestinal-Hepatic	2 (2.4%)	2 (0.3%)	
Oncologic-Hematologic	0 (0.0%)	6 (0.9%)	
Neurologic	9 (10.7%)	42 (6.1%)	
Renal	0 (0.0%)	0 (0%)	
Respiratory	11 (13.1%)	70 (10.2%)	
Other	8 (9.5%)	28 (4.1%)	
Malignancy	3 (3.6%)	38 (5.6%)	0.44
Diabetes	0 (0.0%)	0 (0.0%)	>0.99
Syndrome[h]	48 (57.1%)	63 (9.2%)	<0.0001
Known parental smoking between birth and PICU admission	17 (20.2%)	151 (22.1%)	0.70
Acute effects of randomization and post-randomization treatments in PICU			
Duration of stay in the PICU – days	7.5 (14.6)	7.8 (16.0)	0.57
Patients who acquired a new infection in PICU	10 (11.9)	96 (14.0%)	0.59
Duration of mechanical ventilatory support – days	5.2 (10.8)	5.0 (11.7)	0.72
Number of days with hypoglycemia <40mg/dl – days	0.2 (0.8)	0.1 (0.5)	0.97
Duration of antibiotic treatment – days	4.9 (9.6)	5.4 (14.2)	0.81
Duration of hemodynamic support – days	1.9 (3.6)	2.7 (7.7)	0.71
Duration of treatment with opioids – days	3.2 (4.5)	5.0 (9.3)	0.01
Duration of treatment with benzodiazepines – days	4.2 (10.7)	4.4 (10.2)	0.35
Duration of treatment with hypnotics – days	1.0 (1.9)	1.5 (6.0)	0.79

Table S1.1. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84	**Neurocognitively tested patients N=684**	***p*-value**
Duration of treatment with alpha-2-agonists – days	0.9 (6.6)	1.1 (6.8)	0.22
Duration of treatment with corticosteroids - days	1.0 (1.9)	1.2 (3.9)	0.03

Data are n (%) or mean (SD).
a Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.
b The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4).
c The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).
d Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19]
e Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20]
f Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21]
g Pediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU.[21]
h A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3).
Abbreviations: BMI, body mass index; PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

Table S1.2. Physical development and parent-reported outcomes at 4 years' follow-up of participating patients who were too disabled for neurocognitive testing and those who underwent neurocognitive testing

	Participating patients too disabled for neurocognitive testing N=84		**Neurocognitively tested patients N=684**		***p*-value**
	Number (%) of available data per outcome	**Outcome result**	**Number (%) of available data per outcome**	**Outcome result**	
Height - cm	77 (91.7%)	118.1 (24.2)	655 (95.8%)	120.9 (23.1)	0.04
Weight - kg	84 (100.0%)	25.6 (14.0)	647 (94.6%)	27.0 (17.1)	0.45
BMI - kg/m2	77 (91.7%)	17.4 (3.7)	646 (94.4%)	16.9 (3.4)	0.13
Head circumference - cm	83 (98.8%)	50.1 (3.7)	649 (94.9%)	51.9 (2.7)	<0.0001
Diagnosed with a somatic illness	42 (50.0%)	30 (71.4%)	523 (76.5%)	280 (53.5%)	0.02
Diagnosed with a psychiatric illness	76 (90.5%)	11 (14.5%)	609 (89.0%)	53 (8.7%)	0.10
Admitted to hospital for a medical or surgical reason	81 (96.4%)	73 (90.1%)	657 (96.1%)	435 (66.2%)	<0.0001
Clinical neurological evaluation score (range, 0-8)[a]	57 (67.9%)	4.3 (1.8)	616 (90.1%)	0.6 (1.3)	<0.0001
Executive functioning as reported by parents/caregivers - T-score[a]					
Inhibition	36 (42.9%)	61.8 (14.8)	556 (81.3%)	49.6 (11.8)	<0.0001
Flexibility	36 (42.9%)	59.0 (14.8)	557 (81.4%)	49.1 (10.6)	<0.0001
Emotional control	36 (42.9%)	56.1 (15.1)	557 (81.4%)	48.9 (10.5)	0.004
Working memory	35 (41.7%)	67.5 (12.4)	557 (81.4%)	51.5 (11.8)	<0.0001
Planning and organization	35 (41.7%)	62.0 (17.4)	557 (81.4%)	50.2 (11.2)	<0.0001
Meta-cognition index	35 (41.7%)	64.9 (15.7)	556 (81.3%)	50.3 (11.7)	<0.0001
Total score	35 (41.7%)	64.1 (16.8)	555 (81.1%)	49.7 (11.8)	<0.0001
Emotional and behavioral problems as reported by parents/caregivers - T-score[a]					
Internalizing problems	44 (52.4%)	55.7 (10.4)	565 (82.6%)	50.4 (11.2)	0.006
Externalizing problems	44 (52.4%)	53.4 (13.0)	565 (82.6%)	48.5 (10.3)	0.02
Total problems	44 (52.4%)	56.6 (12.2)	565 (82.6%)	49.7 (11.0)	0.0007

a Higher scores reflect worse performance.
Abbreviations: BMI, body mass index; IQ, intelligence quotient; PICU, pediatric intensive care unit; PN, parenteral nutrition; SD, standard deviation

Table S2. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of patients who were tested and those patients who survived, but declined participation or could not be reached.

	Patients who survived, but declined participation or could not be reached N=469	**Neurocognitively tested patients N=684**	***p*-value**
Patient characteristics upon PICU admission			
Randomization			0.11
Early PN	247 (52.7%)	328 (48.0%)	
Late PN	222 (47.3%)	356 (52.1%)	
Sex Male	269 (57.4%)	393 (57.5%)	0.97
Female	200 (42.6%)	291 (42.5%)	
Infant (age<1y) at randomization	193 (41.2%)	331 (48.4%)	0.01
STRONGkids risk level[a]			0.15
Medium	427 (91.0%)	613 (89.6%)	
High	42 (9.0%)	71 (10.4%)	
PeLOD score, first 24h in PICU [b]	17.4 (11.6)	20.0 (11.6)	0.0004
PIM3 score[c]	-3.5 (1.4)	-3.5 (1.4)	0.95
PIM3 probability of death - % [d]	6.5 (11.2)	6.6 (11.7)	0.95
Diagnostic category			0.12
Surgical			
Abdominal	40 (8.5%)	68 (9.9%)	
Burns	7 (1.5%)	3 (0.4%)	
Cardiac	173 (36.9%)	291 (42.5%)	
Neurosurgery-Traumatic brain injury	32 (6.8%)	58 (8.5%)	
Thoracic	19 (4.1%)	38 (5.6%)	
Transplantation	12 (2.6%)	11 (1.6%)	
Orthopedic surgery-Trauma	13 (2.8%)	19 (2.8%)	
Other	18 (3.8%)	25 (3.7%)	
Medical			
Cardiac	23 (4.9%)	23 (3.4%)	
Gastrointestinal-Hepatic	1 (0.2%)	2 (0.3%)	
Oncologic-Hematologic	4 (0.9%)	6 (0.9%)	
Neurologic	32 (6.8%)	42 (6.1%)	
Renal	1 (0.2%)	0 (0%)	
Respiratory	74 (15.8%)	70 (10.2%)	
Other	20 (4.3%)	28 (4.1%)	
Malignancy	17 (3.6%)	38 (5.6%)	0.15
Diabetes	2 (0.4%)	0 (0.0%)	0.16
Syndrome[e]	66 (14.1%)	63 (9.2%)	0.01
Acute effects of randomization and post-randomization treatments in PICU			
Duration of stay in the PICU – days	6.1 (8.2)	7.8 (16.0)	0.66

Table S2. Demographics and other patient characteristics upon PICU admission, acute outcomes and post-randomization treatments in the PICU of patients who were tested and those patients who survived, but declined participation or could not be reached.

	Patients who survived, but declined participation or could not be reached N=469	**Neurocognitively tested patients N=684**	***p*-value**
Patients who acquired a new infection in PICU	51 (10.9)	96 (14.0%)	0.11
Duration of mechanical ventilatory support – days	4.2 (7.1)	5.0 (11.7)	0.59
Number of days with hypoglycemia <40mg/dl – days	0.8 (0.3)	0.1 (0.5)	0.08
Duration of antibiotic treatment – days	4.4 (7.4)	5.4 (14.2)	0.70
Duration of hemodynamic support – days	1.8 (3.8)	2.7 (7.7)	0.13
Duration of treatment with opioids – days	4.1 (6.4)	5.0 (9.3)	0.19
Duration of treatment with benzodiazepines – days	3.5 (6.0)	4.4 (10.2)	0.49
Duration of treatment with hypnotics – days	1.3 (2.1)	1.5 (6.0)	0.001
Duration of treatment with alpha-2-agonists – days	0.5 (2.4)	1.1 (6.8)	0.19
Duration of treatment with corticosteroids - days	1.2 (3.4)	1.2 (3.9)	0.04

Data are n (%) or mean (SD).
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19]
b Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20]
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21]
d Pediatric Index of Mortality 3 (PIM3) probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU.[21]
e A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3).
Abbreviations: BMI, body mass index; PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition; SEM, standard error of the mean.

Table S3. Multivariable linear regression analyses determining significant and independent associations between risk factors and long-term test results within the patient population that underwent neurocognitive testing

Table S3.1. Multivariable linear regression analyses determining significant and independent associations between risk factors and internalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of Late PN vs Early PN**		**Model further adjusted for post-randomization treatments**	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Randomization to late vs. early initiation of PN	***-1.880 (-3.690 to -0.071)***	***0.042***	***-1.702 (-3.541 to 0.173)***	***0.070***	***-1.625 (-3.470 to 0.219)***	***0.084***
Centre						
Leuven vs Edmonton	0.019 (-8.653 to 8.691)	0.997	-0.024 (-8.717 to 8.668)	0.996	0.082 (-8.725 to 8.888)	0.985
Rotterdam vs Edmonton	0.627 (-7.840 to 9.094)	0.884	0.424 (-8.050 to 8.898)	0.922	0.292(-8.316 to 8.899)	0.947
Male vs female sex	1.165 (-0.681 to 3.011)	0.216	1.062 (-0.789 to 2.913)	0.260	1.187(-0.674 to 3.049)	0.211
Right vs left hand preference	-0.130 (-2.867 to 2.608)	0.926	-0.230 (-2.981 to 2.522)	0.870	-0.063 (-2.831 to 2.706)	0.964
Medium vs high STRONGkids risk level[a]	-3.074 (-6.178 to 0.031)	0.052	-2.727 (-5.867 to 0.413)	0.089	-2.667 (-5.893 to 0.559)	0.105
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	0.627 (-3.109 to 4.363)	0.742	0.631 (-3.103 to 4.365)	0.740	0.530 (-3.258 to 4.317)	0.783
Burns	-2.005 (-14.952 to 10.942)	0.761	-2.825 (-15.865 to 10.215)	0.671	-2.919 (-16.09 to 10.255)	0.664
Neurosurgery - traumatic brain injury	1.887 (-1.990 to 5.764)	0.339	1.848 (-2.028 to 5.725)	0.349	1.689 (-2.200 to 5.577)	0.394
Thoracic	-1.197 (-5.380 to 2.986)	0.574	-1.233 (-5.422 to 2.955)	0.563	-0.961 (-5.192 to 3.270)	0.655
Transplantation	-0.617 (-8.396 to 7.162)	0.876	-1.493 (-9.446 to 6.461)	0.712	-1.241 (-10.413 to 7.930)	0.790
Orthopedic surgery-trauma	-0.573 (-6.724 to 5.577)	0.855	-0.821 (-6.987 to 5.346)	0.794	-0.917 (-7.153 to 5.318)	0.772
Other	1.849 (-3.448 to 7.147)	0.761	1.418 (-3.947 to 6.783)	0.604	0.920 (-4.527 to 6.368)	0.740
Medical						
Cardiac	-0.611 (-6.202 to 4.980)	0.830	-1.314 (-6.929 to 4.300)	0.646	-1.436 (-7.200 to 4.328)	0.625
Gastrointestinal-hepatic	-4.742 (-25.519 to 16.035)	0.652	-4.641 (-25.442 to 16.160)	0.659	-4.818 (-25.658 to 16.022)	0.648
Hematologic-oncologic	-2.598 (-12.953 to 7.758)	0.622	-2.529 (-12.915 to 7.857)	0.633	-2.829 (-13.968 to 8.309)	0.618
Neurologic	-2.208 (-6.747 to 2.331)	0.339	-2.106 (-6.655 to 2.444)	0.363	-2.322 (-7.005 to 2.361)	0.330
Respiratory	-1.383 (-4.996 to 2.230)	0.452	-1.414 (-5.059 to 2.231)	0.446	-1.294 (-5.025 to 2.437)	0.496

Table S3.1. Multivariable linear regression analyses determining significant and independent associations between risk factors and internalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatments	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Other	-0.106 (-4.796 to 4.585)	0.965	-0.255 (-4.953 to 4.443)	0.915	0.177 (-4.795 to 5.148)	0.944
Infant (age<1y) vs child at randomization	-4.643 (-6.591 to -2.694)	<0.0001	-4.610 (-6.602 to -2.618)	<0.0001	-4.874 (-6.911 to -2.836)	<0.0001
Malignancy vs no malignancy	2.107 (-2.272 to 6.486)	0.345	2.061 (-2.328 to 6.450)	0.357	2.049 (-2.421 to 6.519)	0.368
Syndrome vs no syndrome[b]	1.699 (-1.521 to 4.919)	0.300	1.520 (-1.732 to 4.772)	0.359	1.906 (-1.400 to 5.211)	0.258
PIM3 score (per point added)[c]	0.526 (-0.364 to 1.416)	0.246	0.401 (-0.529 to 1.330)	0.397	0.326 (-0.607 to 1.260)	0.492
PeLOD score first 24 hrs (per point added)[d]	0.000 (-0.117 to 0.117)	0.995	-0.007 (-0.125 to 0.110)	0.906	-0.014 (-0.133 to 0.105)	0.822
Known non-European origin vs other[e]	0.166 (-3.549 to 3.881)	0.930	0.073 (-3.652 to 3.798)	0.969	0.024 (-3.707 to 3.755)	0.990
Known non-Caucasian vs other[e]	-2.306 (-7.355 to 2.743)	0.368	-2.178 (-7.227 to 2.872)	0.396	-2.025 (-7.097 to 3.047)	0.431
Known not exclusive Dutch or English language vs other	1.709 (-1.020 to 4.438)	0.219	1.922 (-0.830 to 4.673)	0.171	1.794 (-0.968 to 4.555)	0.202
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-2.778 (-8.831 to 3.274)	0.367	-2.491 (-8.585 to 3.603)	0.422	-2.240 (-8.415 to 3.935)	0.476
Educational level 2	-1.811 (-7.261 to 3.639)	0.514	-1.374 (-6.880 to 4.133)	0.624	-1.536 (-7.121 to 4.049)	0.589
Educational level 2.5	-4.396 (-10.040 to 1.248)	0.126	-4.025 (-9.707 to 1.657)	0.164	-3.934 (-9.700 to 1.803)	0.178
Educational level 3	-4.973 (-10.619 to 0.672)	0.084	-4.540 (-10.228 to 1.149)	0.117	-4.629 (-10.387 to 1.128)	0.115
Educational level unknown	-2.630 (-8.386 to 3.125)	0.369	-2.324 (-8.109 to 3.462)	0.429	-2.354 (-8.182 to 3.474)	0.427
Occupational level parents (as compared with level 1)[g]						
Occupational level 1.5	1.679 (-7.871 to 11.229)	0.730	1.529 (-8.054 to 11.113)	0.754	1.092 (-8.523 to 10.706)	0.824
Occupational level 2	0.238 (-9.230 to 9.706)	0.961	0.149 (-9.361 to 9.659)	0.975	-0.395 (-9.928 to 9.138)	0.935
Occupational level 2.5	-2.341 (-12.174 to 7.492)	0.640	-2.473 (-12.346 to 7.400)	0.623	-2.704 (-12.618 to 7.209)	0.592
Occupational level 3	-0.226 (-9.745 to 7.492)	0.963	-0.300 (-9.840 to 9.239)	0.951	-0.660 (-10.210 to 8.890)	0.892
Occupational level 3.5	1.781 (-8.264 to 11.826)	0.728	1.651 (-8.423 to 11.725)	0.747	1.442 (-8.654 to 11.538)	0.779
Occupational level 4	-1.396 (-11.172 to 8.379)	0.779	-1.547 (-11.359 to 8.265)	0.757	-2.074 (-11.907 to 7.759)	0.679

Table S3.1. Multivariable linear regression analyses determining significant and independent associations between risk factors and internalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatments	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Occupational level unknown	1.793 (-7.686 to 11.273)	0.710	1.682 (-7.850 to 11.214)	0.729	1.478 (-8.060 to 11.017)	0.761
Parental smoking between birth and PICU admission vs no smoking	0.827 (-1.321 to 2.974)	0.450	0.863 (-1.290 to 3.016)	0.431	0.950 (-1.203 to 3.103)	0.386
New infection vs no new infection			1.333 (-1.910 to 4.576)	0.420	0.436 (0.802 to -2.972)	3.844
Duration of stay in the PICU (per day added)			0.083 (-0.055 to 0.220)	0.237	0.164 (0.279 to -0.134)	0.461
Days with hypoglycemic event (per day added)			-0.049 (-1.813 to 1.714)	0.956	-0.369 (0.708 to -2.298)	1.561
Duration of mechanical ventilatory support (per day added)			-0.094 (-0.276 to 0.088)	0.310	-0.095 (0.340 to -0.291)	0.101
Duration of treatment with antibiotics (per day added)					-0.127 (0.375 to -0.407)	0.154
Duration of hemodynamic support (per day added)					-0.013 (0.898 to -0.215)	0.188
Duration of treatment with corticosteroids (per day added)					0.020 (0.905 to -0.316)	0.357
Duration of treatment with opioids (per day added)					-0.001 (0.996 to -0.284)	0.282
Duration of treatment with benzodiazepines (per day added)					0.173 (0.227 to -0.108)	0.454
Duration of treatment with hypnotics (per day added)					-0.012 (0.931 to -0.286)	0.262
Duration of treatment with alpha-2-agonists (per day added)					-0.183 (0.153 to -0.434)	0.068

For internalizing problems as reported by parents, higher scores reflect more problems.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19]
b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3)
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21]
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20]
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).[18]
Abbreviations: PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition.

Table S3.2. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of Late PN vs Early PN**		**Model further adjusted for post-randomization treatments**	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Randomization to late vs. early initiation of PN	***-1.731 (-3.433 to -0.028)***	***0.046***	***-1.645 (-3.379 to 0.090)***	***0.063***	***-1.51 (-3.242 to 0.219)***	***0.086***
Centre						
Leuven vs Edmonton	-3.194 (-11.275 to 4.886)	0.438	-3.337 (-11.463 to 4.790)	0.420	-2.708 (-10.865 to 5.449)	0.51
Rotterdam vs Edmonton	-4.080 (-11.970 to 3.811)	0.310	-4.365 (-12.279 to 3.549)	0.279	-4.168 (-12.145 to 3.809)	0.30
Male vs female sex	1.987 (0.306 to 3.667)	0.021	1.922 (0.235 to 3.609)	0.026	2.058 (0.362 to 3.754)	0.017
Right vs left hand preference	0.299 (-2.443 to 3.041)	0.830	0.284 (-2.452 to 3.020)	0.838	0.526 (-2.236 to 3.287)	0.70
Medium vs high STRONGkids risk level[a]	-1.276 (-4.212 to 1.660)	0.394	-1.211 (-4.189 to 1.766)	0.424	-1.380 (-4.461 to 1.700)	0.37
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	-1.137 (-4.542 to 2.268)	0.512	-1.150 (-4.562 to 2.263)	0.508	-1.192 (-4.630 to 4.711)	0.496
Burns	2.862 (-4.331 to 5.632)	0.643	2.764 (9.451 to 14.978)	0.657	1.044 (-11.235 to 13.322)	0.867
Neurosurgery - traumatic brain injury	-0.836 (-9.256 to 14.980)	0.653	-0.807 (-4.459 to 2.846)	0.665	-1.174 (-4.826 to 2.477)	0.527
Thoracic	-0.543 (-4.486 to 2.813)	0.786	-0.545 (-4.479 to 3.390)	0.786	-0.359 (-4.292 to 3.575)	0.857
Transplantation	-4.324 (-4.465 to 3.379)	0.241	-4.343 (-11.742 to 3.056)	0.249	-6.763 (-15.230 to 1.770)	0.119
Orthopedic surgery-trauma	-2.478 (-11.568 to 2.921)	0.385	-2.524 (-8.144 to 3.096)	0.378	-2.685 (-8.333 to -2.964)	0.350
Other	0.650 (-4.331 to 5.632)	0.798	0.453 (-4.575to 5.480)	0.860	-0.359 (-5.428 to 4.711)	0.889
Medical						
Cardiac	0.085 (-5.026 to 5.195)	0.974	-0.210 (-5.378 to 4.957)	0.936	-0.280 (-5.636 to 5.075)	0.918
Gastrointestinal-hepatic	-6.568 (-24.963 to 11.828)	0.482	-6.447 (-24.862 to 11.968)	0.490	-6.618 (-24.971 to 11.734)	0.477
Hematologic-oncologic	-5.302 (-14.848 to 4.245)	0.276	-5.263 (-14.876 to 4.350)	0.283	-7.950 (-18.288 to 2.388)	0.131
Neurologic	-3.142 (-7.219 to 0.934)	0.130	-3.122 (-7.217 to 0.973)	0.135	-3.883 (-8.063 to 0.297)	0.068
Respiratory	-1.308 (-4.669 to 2.052)	0.445	-1.575 (-4.970 to 1.820)	0.362	-1.416 (-4.878 to 2.045)	0.421
Other	-2.207 (-6.608 to 2.195)	0.325	-2.468 (-6.881 to 1.946)	0.273	-2.788 (-7.433 to 1.858)	0.238
Infant (age<1y) vs child at randomization	0.085 (-3.814 to -0.112)	0.038	-1.929 (-3.820 to -0.039)	0.046	-1.930 (-3.864 to 0.003)	0.050

Table S3.2. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatments	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Malignancy vs no malignancy	-1.963 (-1.993 to 6.212)	0.313	2.077 (-2.034 to 6.188)	0.321	1.233 (-2.948 to 5.414)	0.562
Syndrome vs no syndrome[b]	1.045 (-0.206 to 1.471)	0.139	0.861 (-2.032 to 3.754)	0.559	1.754 (-1.173 to 4.682)	0.239
PIM3 score (per point added)[c]	0.632 (-0.118 to 0.098)	0.851	0.567 (-0.303 to 1.438)	0.201	0.497 (-0.373 to 1.367)	0.262
PeLOD score first 24 hrs (per point added)[d]	-0.010 (-5.192 to 1.861)	0.353	-0.010 (-0.119 to 0.099)	0.854	-0.028 (-0.234 to 0.114)	0.498
Known non-European origin vs other[e]	-1.665 (-4.125 to 5.649)	0.758	-1.591 (5.129 to 1.946)	0.377	-3.444 (-8.677 to 1.789)	0.196
Known non-Caucasian vs other[e]	0.762 (-0.483 to 4.868)	0.108	0.824 (-4.064 to 5.713)	0.739	0.165 (-6.148 to 6.479)	0.958
Known not exclusive Dutch or English language vs other	2.192 (-3.814 to -0.112)	0.038	2.243 (-0.441 to 4.926)	0.101	-2.959 (-6.951 to 1.033)	0.146
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-0.738 (-6.223 to 4.747)	0.792	-0.787 (-6.313 to 4.739)	0.780	0.169 (-5.412 to 5.751)	0.952
Educational level 2	0.941 (-3.973 to 5.855)	0.707	1.121 (-3.845 to 6.087)	0.657	1.720 (-3.280 to 6.719)	0.499
Educational level 2.5	-2.784 (-7.912 to 2.345)	0.286	-2.608 (-7.774 to 2.557)	0.321	-2.013 (-7.196 to 3.171)	0.445
Educational level 3	-4.599 (-9.875 to 0.678)	0.087	-4.448 (-9.759 to 0.862)	0.100	-3.841 (-9.179 to 1.497)	0.157
Educational level unknown	-1.506 (-6.824 to 3.813)	0.578	-1.378 (-6.726 to 3.970)	0.612	-0.718 (-6.076 to 4.640)	0.792
Occupational level parents (as compared with level 1)[g]						
Occupational level 1.5	-2.079 (-10.773 to 6.615)	0.639	-2.325 (-11.046 to 6.397)	0.601	-3.048 (-11.746 to 5.650)	0.492
Occupational level 2	0.088 (-8.613 to 8.789)	0.984	-0.177 (-8.922 to 8.568)	0.968	-0.847 (-9.576 to 7.883)	0.848
Occupational level 2.5	-2.387 (-11.413 to 6.639)	0.604	-2.712 (-11.774 to 6.351)	0.557	-3.471 (-12.537 to 5.595)	0.452
Occupational level 3	0.527 (-8.275 to 9.329)	0.906	0.344 (-8.483 to 9.171)	0.939	-0.141 (-8.941 to 8.660)	0.974
Occupational level 3.5	-0.920 (-10.204 to 8.365)	0.846	-1.190 (-10.505 to 8.125)	0.802	-1.568 (-10.882 to 7.746)	0.740
Occupational level 4	-1.592 (-10.639 to 7.454)	0.730	-1.904 (-10.989 to 7.181)	0.681	-2.735 (-11.812 to 6.341)	0.554
Occupational level unknown	-0.963 (-9.764 to 7.838)	0.830	-1.260 (-10.107 to 7.587)	0.780	-1.575 (-10.400 to 7.251)	0.726
Parental smoking between birth and PICU admission vs. no smoking	1.797(-0.309 to 3.903)	0.094	1.781 (-0.332 to 3.893)	0.098	1.895 (-0.203 to 3.993)	0.076

Table S3.2. Multivariable linear regression analyses determining significant and independent associations between risk factors and externalizing problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatments	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
New infection vs no new infection			-0.648 (-3.674 to 2.378)	0.674	-2.044 (-5.248 to 1.160)	0.210
Duration of stay in the PICU (per day added)			0.046 (-0.077 to 0.170)	0.461	0.086 (-0.187 to 0.359)	0.536
Days with hypoglycemic event (per day added)			-0.231 (-1.904 to 1.441)	0.786	-0.449 (-2.265 to 1.367)	0.627
Duration of mechanical ventilatory support (per day added)			-0.008 (-0.174 to 0.158)	0.924	-0.057 (-0.237 to 0.122)	0.527
Duration of treatment with antibiotics (per day added)					-0.096 (-0.355 to 0.163)	0.466
Duration of hemodynamic support (per day added)					0.017 (-0.168 to 0.202)	0.859
Duration of treatment with corticosteroids (per day added)					0.244 (-0.077 to 0.566)	0.135
Duration of treatment with opioids (per day added)					-0.015 (-0.266 to 0.236)	0.906
Duration of treatment with benzodiazepines (per day added)					0.176 (-0.073 to 0.425)	0.646
Duration of treatment with hypnotics (per day added)					0.214 (-0.038 to 0.466)	0.095
Duration of treatment with alpha-2-agonists (per day added)					-0.273 (-0.504 to -0.043)	0.020

For internalizing problems as reported by parents, higher scores reflect more problems.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19]
b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3)
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21]
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20]
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).[18]
Abbreviations: PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition.

Table S3.3. Multivariable linear regression analyses determining significant and independent associations between risk factors and total emotional and behavioral problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		**Model further adjusted for acute effects of Late PN vs Early PN**		**Model further adjusted for post-randomization treatment effects**	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Randomization to late vs early initiation of PN	***-2.442 (-3.433 to -0.028)***	***0.046***	***-2.242 (-4.043 to -0.4043)***	***0.015***	***-2.163 (-3.960 to -0.365)***	***0.019***
Centre						
Leuven vs Edmonton	-2.834 (-11.275 to 4.886)	0.438	-2.687 (-11.115 to 5.742)	0.531	-2.172 (-10.667 6.324)	0.616
Rotterdam vs Edmonton	-2.360 (-11.970 to 3.811)	0.310	-2.476 (-10.732 to 5.742)	0.556	-2.506 (-10.848 to 5.837)	0.555
Male vs female sex	1.483 (0.306 to 3.667)	0.021	1.411 (-0.360 to 3.183)	0.118	1.558 (-0.224 to 3.339)	0.086
Right vs left hand preference	0.019 (-2.443 to 3.041)	0.830	-0.067 (-2.865 to 2.731)	0.962	0.190 (-2.625 to 3.004)	0.894
Medium vs high STRONGkids risk level[a]	-2.630 (-4.212 to 1.660)	0.394	-2.369 (-5.452 to 0.713)	0.132	-2.445 (-5.610 to 0.721)	0.130
Diagnostic category (as compared with cardiac surgery)						
Surgical						
Abdominal	-0.652 (-4.542 to 2.268)	0.512	-0.679 (-4.249 to 2.891)	0.709	-0.703 (-4.301 to 2.895)	0.701
Burns	1.540 (-9.256 to 14.980)	0.643	0.682 (-12.001 to 13.365)	0.916	-0.229 (-12.993 to 12.536)	0.972
Neurosurgery - traumatic brain injury	0.503 (-4.486 to 2.813)	0.653	0.433 (-3.290 to 4.157)	0.819	0.086 (-3.633 to 3.805)	0.964
Thoracic	-1.323 (-4.465 to 3.379)	0.786	-1.354 (-5.435 to 2.727)	0.515	-1.091 (-5.197 to 3.015)	0.602
Transplantation	-2.856 (-11.568 to 2.921)	0.241	-3.506 (-11.188 to 4.176)	0.370	-4.678 (-13.497 to 4.141)	0.298
Orthopedic surgery-trauma	-0.542 (-8.086 to 3.129)	0.385	-0.778 (-6.692 to 5.137)	0.796	-0.892 (-6.840 to 5.056)	0.768
Other	0.705 (-4.331 to 5.632)	0.798	0.379 (-4.881 to 5.640)	0.887	-0.426 (-5.742 to 4.891)	0.875
Medical						
Cardiac	-1.239 (-5.026 to 5.195)	0.974	-1.771 (-7.124 to 3.582)	0.516	-1.964 (-7.501 to 3.573)	0.486
Gastrointestinal-hepatic	-5.844 (-24.963 to 11.828)	0.482	-5.716 (-24.994 to 13.563)	0.559	-5.919 (-25.143 to 13.305)	0.544
Hematologic-oncologic	-5.495 (-14.848 to 4.245)	0.276	-5.668 (-15.844 to 4.507)	0.274	-7.908 (-18.814 to 2.998)	0.155
Neurologic	-4.072 (-7.219 to 0.934)	0.130	-3.963 (-8.229 to 0.303)	0.069	-4.661 (-9.032 to -0.289)	0.037
Respiratory	-2.226 (-4.669 to 2.052)	0.445	-2.311 (-5.835 to 1.214)	0.198	-2.282 (-5.887 to 1.323)	0.214

Table S3.3. Multivariable linear regression analyses determining significant and independent associations between risk factors and total emotional and behavioral problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatment effects	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Other	-2.103 (-6.608 to 2.195)	0.325	-2.285 (-6.863 to 2.293)	0.327	-2.352 (-7.170 to 2.466)	0.338
Infant (age<1y) vs child at randomization	-4.487 (-3.814 to -0.112)	0.038	-4.406 (-6.347 to -2.464)	<0.0001	-4.536 (-6.517 to -2.553)	<0.0001
Malignancy vs no malignancy	3.260 (-1.993 to 6.212)	0.313	3.273 (-0.978 to 7.524)	0.131	2.827 (-1.492 to 7.145)	0.199
Syndrome vs no syndrome[b]	2.110 (-1.819 to 3.909)	0.474	1.892 (-1.198 to 4.983)	0.229	2.610 (-0.519 to 5.738)	0.102
PIM3 score (per point added)[c]	0.582 (-0.206 to 1.471)	0.139	0.450 (-0.451 to 1.351)	0.327	0.375 (-0.527 to 1.276)	0.414
PeLOD score first 24 hrs (per point added)[d]	-0.007 (-0.118 to 0.098)	0.851	-0.014 (-0.128 to 0.100)	0.807	-0.029 (-0.144 to 0.086)	0.615
Known non-European origin vs other[e]	-0.459 (-5.192 to 1.861)	0.353	-0.513 (-4.143 to 3.118)	0.781	-0.575 (-4.201 to 3.050)	0.755
Known non-Caucasian vs other[e]	-0.943 (-4.125 to 5.649)	0.758	-0.850 (-5.866 to 4.166)	0.738	-0.582 (-5.609 to 4.445)	0.819
Known not exclusive Dutch or English language vs other	1.987 (-0.483 to 4.868)	0.108	2.172 (-0.532 to 4.876)	0.115	2.133 (-0.572 to 4.837)	0.122
Socioeconomic status						
Educational level parents (as compared with level 1)[f]						
Educational level 1.5	-1.687 (-6.223 to 4.747)	0.792	-1.543 (-7.337 to 4.252)	0.601	-0.819 (-6.677 to 5.040)	0.784
Educational level 2	-0.445 (-3.973 to 5.855)	0.707	-0.095 (-5.296 to 5.106)	0.971	0.126 (-5.125 to 5.377)	0.962
Educational level 2.5	-4.285 (-7.912 to 2.345)	0.286	-3.979 (-9.365 to 1.407)	0.147	-3.577 (-9.000 to 1.846)	0.195
Educational level 3	-5.469 (-9.875 to 0.678)	0.087	-5.138 (-10.638 to 0.362)	0.067	-4.864 (-10.405 to 0.677)	0.085
Educational level unknown	-2.716 (-6.824 to 3.813)	0.578	-2.467 (-8.024 to 3.091)	0.383	-2.127 (-7.708 to 3.453)	0.453
Occupational level parents (as compared with level 1)[g]						
Occupational level 1.5	1.882 (-10.773 to 6.615)	0.639	1.757 (-7.374 to 10.888)	0.706	1.105 (-8.007 to 10.217)	0.812
Occupational level 2	1.570 (-8.613 to 8.789)	0.984	1.513 (-7.619 to 10.644)	0.745	0.781 (-8.335 to 9.897)	0.866
Occupational level 2.5	-0.537 (-11.413 to 6.639)	0.604	-0.636 (-10.101 to 8.829)	0.895	-1.220 (-10.689 to 8.248)	0.800
Occupational level 3	1.799 (-8.275 to 9.329)	0.906	1.736 (-7.453 to 10.925)	0.711	1.242 (-7.921 to 10.405)	0.790
Occupational level 3.5	1.154 (-10.204 to 8.365)	0.846	1.011 (-8.701 to 10.723)	0.838	0.678 (-9.025 to 10.381)	0.891
Occupational level 4	0.701 (-10.639 to 7.454)	0.730	0.546 (-8.937 to 10.028)	0.910	-0.254 (-9.721 to 9.214)	0.958

Table S3.3. Multivariable linear regression analyses determining significant and independent associations between risk factors and total emotional and behavioral problems as reported by the parents/caregivers at 4 years' follow-up within the patient population that underwent neurocognitive testing

	Model adjusted for risk factors		Model further adjusted for acute effects of Late PN vs Early PN		Model further adjusted for post-randomization treatment effects	
Variable	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**	**β estimate (95% CI)**	***p*-value**
Occupational level unknown	1.571 (-9.764 to 7.838)	0.830	1.481 (-7.699 to 10.661)	0.751	1.142 (-8.012 to 10.296)	0.806
Parental smoking between birth and PICU admission vs. no smoking	1.450 (-0.309 to 3.904)	0.094	1.451 (-0.677 to 3.579)	0.181	1.571 (-0.547 to 3.689)	0.146
New infection vs no new infection			1.215 (-1.941 to 4.370)	0.450	-0.185 (-3.501 to 3.131)	0.913
Duration of stay in the PICU (per day added)			0.057 (-0.071 to 0.186)	0.380	0.105 (-0.180 to 0.389)	0.471
Days with hypoglycemic event (per day added)			-0.343 (-2.051 to 1.366)	0.694	-0.517 (-2.380 to 1.346)	0.586
Duration of mechanical ventilatory support (per day added)			-0.046 (-0.218 to 0.127)	0.601	-0.080 (-0.266 to 0.107)	0.401
Duration of treatment with antibiotics (per day added)					-0.115 (-0.386 to 0.155)	0.402
Duration of hemodynamic support (per day added)					-0.017 (-0.209 to 0.174)	0.858
Duration of treatment with corticosteroids (per day added)					0.166 (-0.161 to 0.493)	0.320
Duration of treatment with opioids (per day added)					-0.054 (-0.317 to 0.210)	0.690
Duration of treatment with benzodiazepines (per day added)					0.277 (0.011 to 0.543)	0.041
Duration of treatment with hypnotics (per day added)					0.134 (-0.129 to 0.398)	0.316
Duration of treatment with alpha-2-agonists (per day added)					-0.281 (-0.523 to -0.039)	0.023

For total emotional and behavioral problems as reported by parents, higher scores reflect more problems.
a Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[19]
b A pre-randomization syndrome or illness *a priori* defined as affecting or possibly affecting neurocognitive development (Methods S3)
c Pediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.[21]
d Pediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.[20]
e Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[22]
f The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods S4).
g The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods S4).[18]
Abbreviations: PeLOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3 score; PN, parenteral nutrition.

Table S4. Comparison of patients randomized to Late PN during PICU stay with healthy control children for the tests significantly affected by the randomized intervention

Neurocognitive testing	***p*-value**
Internalizing problems as reported by parents/caregivers	0.103
Externalizing problems as reported by parents/caregivers	0.313
Total behavioral and emotional problems as reported by parents/caregivers	0.085

References Appendix Chapter 7

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CHAPTER 8

General discussion

The aim of this thesis was to investigate long-term neurocognitive functioning, and HRQoL in critically ill children and their parents, as compared to healthy children. The second aim was to examine the effect of late parenteral nutrition (PN) versus Early PN during PICU admission on the long-term neurocognitive outcomes, and on HRQoL outcomes of the child and parents. Follow-up assessments were six months, two years, and four years after participation in the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) randomized controlled trial (RCT). To avoid repetition of text and to provide a compact overview of the outcomes for patients versus healthy controls, and for children allocated to the Late PN versus Early PN group (both of tests and parent -reports), results of the outcomes are presented in **Table 1**.

Physical, cognitive, emotional, and social outcomes in critically ill children

As a result of the advances in technology, survival rates children admitted to the pediatric intensive care unit (PICU) increased substantially and the focus of post-PICU research shifted from mortality to impairments after discharge (**Chapter 1**). After a PICU admission, children can experience impairments in four different domains: physical, cognitive, emotional, and social functioning, recently described as the post-intensive care syndrome (PICS).[1] Many factors influence the recovery within these four domains after PICU admission: pre-existing factors, factors related to the PICU admission and post-PICU factors. The recovery from impairments in these domains contributes to how children and their families eventually function in daily life, resulting in a 'new normal'.[2] This 'new normal' can be assessed both objectively by the use of (neuro)psychological tests or medical devices, and subjectively through evaluation of the outcome by the patient using instruments (often questionnaires) called patient reported outcome measurements (PROMs)[3] (**Chapter 1**). In young children who are not able to reliably report about their own outcomes, parents and/or caregivers usually complete these measurements.

Physical functioning

Physical functioning can be investigated through objective evaluation of the clinical status of the child (height, weight, head circumference and neurological functioning) and through testing physical condition (e.g. bicycle exercise test). Subjective evaluation can be assessed using questionnaires filled out by children themselves or by the parents/caregivers. In the four-year follow-up of the PEPaNIC trial physical activity of PICU survivors was assessed with a six minute walking test, an activity tracker for seven days at home, and muscle strength with a handgrip strength meter. However, these data have not been analyzed and reported yet. Other outcomes related to physical functioning in critically ill children (height, weight, head circumference, health status, and clinically assessed neurological functioning) were

worse than healthy in control children two and four years after PICU admission, except for weight that showed no significant differences between critically ill children and healthy control children at both time points (**Chapter 4** and **7**).

The subjective evaluation was assessed with use of parent-reported HRQoL measurements six months and two years after PICU admission. Subscales related to the physical functioning domain were 'physical functioning', 'growth and development', 'bodily pain', and 'general health perceptions', 'role functioning physical', and 'change in health'. On all these subscales scores were worse than those of healthy children six months and two years after PICU admission. The only exception was 'change in health', which was better for patients (six months and two years after PICU admission) compared to healthy children. This finding was already expected beforehand, as patients were recovering from a life-threatening condition and the control group was considered stable with regard to their health. The impairments found in physical functioning that remained six months, two years, and four years after PICU admission, are in line with previous research in PICU survivors.[4,5] A systematic review found that these physical impairments decrease over time.[5] However, in meningococcal diseases survivors it was found that physical impairments, assessed with HRQoL measurements, remained after ten years.[6] Some studies even suggested that physical impairments were more severe and persistent than psychosocial impairments over time.[4] Our follow-up study only evaluated whether scores were still lower in patients compared to healthy control children at the different follow-up time points. Additional analyses of differences between patients over time and with a longer follow-up interval will give information whether the impairments decreased, improved or were stable over time in our study sample. Overall it can be concluded that children's physical functioning was impaired both in the short and long term after PICU admission, and that the subjective parent-reported evaluation was in line with the objective evaluation with regard to problems in growth and development that children experience after PICU admission.

Cognitive functioning

Cognitive functioning involves mental processes, which can be assessed objectively (e.g. neuropsychological tests for executive functioning), or subjectively (e.g. parent-reported questionnaires measuring executive functioning).[7] In this thesis, cognitive functioning was assessed at two-year and four-year follow-up, both objectively and subjectively. Results of objective assessment two and four years after PICU admission, by neuropsychological test assessment, showed that children surviving the PICU obtained worse scores for general intelligence, verbal intelligence, performance intelligence, visual-motor integration, alertness, and visual-spatial memory than matched healthy control children (**Chapter 4** and **7**). At the two-year follow-up, patients were not different from healthy control children for a neuropsychological test for inhibition and flexibility (not analyzed at four-year follow-up due to too much

missing data) and for motor coordination (**Chapter 4**). Interestingly, at four-year follow-up, motor coordination was lower in patients compared to healthy control children (**Chapter 7**). This suggests that patients can develop impairments when follow-up time is longer, a concept that is called *growing into deficit*. Growing into deficit means that a deficit in neurocognitive functioning will increase when more complex functions develop during childhood, and when brain structures necessary for this function turn out to be impaired.[8] Possibly, growing into deficit was only applicable to higher neurocognitive functions in the hierarchy,[9] since the parts of motor coordination (alternating and synchronous motor movements, not left and right hand only) that showed a larger difference at the four-year follow-up compared to the two-year follow-up were more complex and required higher cognitive processes of the brain, such as planning of movements.[10] On the other hand, some test scores that were lower in patients versus healthy control children at two-year follow-up, showed no differences between patients and controls at four-year follow-up. More specifically, scores related to verbal memory. Possibly, the group of patients who became old enough to complete the memory tests (minimum age five years), and thus were younger at PICU admission, have more difficulties with verbal memory than children who were older at PICU admission. This was supported by the findings that infants were most vulnerable for the adverse effect of Early PN on subjectively measured neurocognitive functioning at two-year follow-up (**Chapter 5**). However, the majority of infants at time of PICU admission were still not old enough for the memory tests at the four-year follow-up. Therefore, again, future research with a longer follow-up time, to ascertain that all children are old enough for memory testing, including repeated measurements within patients, is needed to give insight in characteristics of patients who score better, worse or similar at the different time points.

As to subjective evaluation of neurocognitive functioning, parents completed a questionnaire regarding executive functioning, which is a more complex domain in the cognitive hierarchy,[9] as more regions of the brain are involved in this neurocognitive domain.[11] Overall, parents reported lower scores for their children than parents of healthy control children for subdomains of executive functioning at both two-year and four-year follow-up (**Chapter 4** and **7**). As to previous research into this field, seven studies described in our systematic review assessed neurocognitive functioning through a subjective evaluation with parent-reported questionnaires (**Chapter 2**).[12-18] Five of these seven studies used the same questionnaire as in our PEPaNIC follow-up study, the Behavior Rating Inventory of Executive Function (BRIEF)[19,20] to assess executive functioning. These studies found overall lower BRIEF scores in PICU survivors compared to healthy peers, which was in line with our findings. We found that although parents reported problems in executive functioning on the BRIEF, the neuropsychological test (inhibition and flexibility) showed no impairments in patients compared to healthy control children at two-year follow-up. This may be explained by the previously described minimum age of some neuropsychological tests that

resulted in a relatively small sample of (older) children that completed this test as compared with the subjective evaluation of executive functioning which was not limited to a specific age range. In future, to be able to reliably compare executive functioning in the complete group of patients versus healthy controls, longer follow-up interval for assessment after PICU admission is necessary. This would also enable the comparison between objective and subjective assessment.

Another consideration to be taken into account is the overall mean scores of patients which fell within the normal range for objective and subjective assessment, both at two-year and four-year follow-up. This means that scores were not below one standard deviation of the general population norm, as was also found previously in international studies (**Chapter 2**). Nonetheless, a group of patients probably do experience cognitive impairments and score below one standard deviation of the norm. Risk factors associated with cognitive impairments were previously found to be younger age at PICU admission, older age at follow-up, lower socio-economic status, requirement of oxygen and mechanical ventilation, and opioids.[21] However, the systematic review reporting these predictors excluded some specific diagnosis groups. Future research in our study sample, consisting of the complete group of critically ill children, is needed to detect early clinical predictors to identify individual children at risk for deteriorating neurocognitive functioning over time (that is; children who will probably grow into deficit).

Emotional functioning

In this thesis, children´s emotional functioning was assessed with subscales of HRQoL measurements (parent reports at six months and two-year follow-up) and with parent-reported questionnaires assessing emotional and behavioral problems (at two and four year follow-up). Six months after PICU admission, younger children aged 0-3 years old were impaired on the parent-reported subscale (of the HRQoL measurement) 'temperament and moods' compared to normative data (**Chapter 3**). The subscale 'general behavior' was not worse than normative data for younger children, but 'general behavior' of older children (aged 4-18 years) was impaired at six months follow-up. Subscales only assessed in older children were 'role functioning emotional/behavioral', 'mental health', and 'self-esteem', which were all lower than normative data, six months after PICU admission. 'Self-esteem' was the only subscale that was still significantly worse in older patients compared to the healthy control children at two-year follow-up (**Chapter 6**). This could be a result of the fact that HRQoL scores usually normalize after a longer period of time,[22] when children have adjusted to the 'new normal'.[2] For younger patients, similar results were found for the subscale 'temperament and moods' that was not significantly different from healthy control children anymore at two-year follow-up. Also 'general behavior' was comparable to patients at two-year follow-up. In contrast, the parent-reported questionnaires concerning emotional and behavioral problems two and four years

after PICU admission showed more internalizing, externalizing, and total emotional and behavioral problems for children compared to healthy control children (**Chapter 4** and **7**). The difference in these findings between comparable outcomes (behavior) could be explained by the difference in questionnaires. On HRQoL questionnaires, subscales comprise five to six questions regarding that domain.[23] In contrast, the Child and Behavior Checklist, used in our follow-up study, consists of 126 items regarding emotional and behavioral problems.[24,25] Therefore, this questionnaire is more sensitive in detecting certain emotional and behavioral problems in contrast with more generic HRQoL measurements that assess overall behavior of children in daily life.

In the current thesis, assessment of emotional functioning did not encompass assessment of posttraumatic stress symptoms (PTSS), which are common in PICU survivors.[26-28] The Child Behavior Checklist (CBCL) could be analyzed in more subdomains than only internalizing and externalizing problems, more specifically PTSS.[29] This was outside the scope of the current follow-up study. However, since PTSS is frequently found in children after critical illness, analyzing this subscale would add information about the emotional wellbeing of children after PICU admission. The sensitivity of this subscale is sometimes debated.[30] Therefore, to further study PTSS more in depth, we recommend a specific measurement of PTSS in follow-up (e.g. Trauma Symptom Checklist for Young Children[31]).

Social functioning

Social functioning of children includes interactions and relationships with peers and family members. In this thesis, social functioning was assessed subjectively through HRQoL measurements six months and two years after PICU admission. Six months after PICU admission, the subscale 'family activities' was worse compared to normative data in children. Two years after PICU admission, 'family activities' were still worse compared to normative data, which might be a result of the impairments in physical functioning, possibly making activities more complicated due to practical barriers. However, impaired family activities might also be related to anxiety of the parents,[32] with parents being afraid that something could happen during generally normal activities with the family. Furthermore, six months after PICU admission, for younger patients aged 0-3 years parent-reported scores as to 'family cohesion' were better compared to normative data. For older patients aged 4-18 years parent-reported scores as to 'family cohesion' were comparable to normative data. Probably, in families with young children, the relationships of children are limited to bonds they have within the family. As in older children, bonds within the family do not have to be strengthened after a stressful event as a consequence of the relationships with peers that are more important than relationships within the family for older children.[33] This is further supported by the fact that two years later, when children were older, 'family cohesion' was comparable to healthy control children. It could also be that social functioning normalized after a longer period of time, what was also found for certain

emotional subscales of HRQoL. However, no age analyses were done at the two-year follow-up. On the last HRQoL subscale into social functioning, 'getting along', patients obtained comparable scores as same-aged healthy peers in social relationships (e.g. with peers and family members), both at six months and two-year follow-up. This is interesting as parents reported both internalizing and externalizing behavioral problems, but this does not seem to impact the social relationships. However, we did not examine the social functioning subscale of the CBCL. To further investigate whether social functioning was not impaired, this subscale should be investigated in future research.

As older children are more focused on their peers, follow-up assessment of social functioning could be enhanced by including peer-reports. Accurately reporting about social functioning can be challenging for parents, since social interactions of their child with peers may be not visible to them and out of their scope. Nevertheless, when interpreting scores of peers, it should be taken into account that peers can be influenced by personal attributes of the person they evaluate, such as physical attractiveness and academic succesfullness.[34] In conclusion, to have a complete view of the child's social functioning, it would be best to use parents, teachers/day care providers, and peers as informant.

Outcomes early parenteral nutrition versus late parenteral nutrition

The follow-up study described in this thesis investigated the long-term outcomes of children who participated in the PEPaNIC RCT. This RCT examined the effects of starting late with supplemental PN (after one week) during PICU admission compared with an early start of supplemental PN (from day 1). As to the first PICS domain, physical functioning, objective measurements showed that children in the Late PN group had comparable scores as children in the Early PN group for survival, height, weight, head circumference, health status, and clinically assessed neurological functioning, both at two-year and four-year follow-up (**Chapter 4** and **7**). Subjectively measured physical functioning showed that at 2 year follow-up Late PN patients scored comparably to Early PN patients (**Chapter 6**). The second PICS domain, cognitive functioning, was also assessed both two and four years after participation in the PEPaNIC trial. Objective neuropsychological tests showed that children who received Late PN scored better than children who received Early PN for visual-motor integration two years after participation in the PEPaNIC trial (**Chapter 4**). As to subjectively measured neurocognitive functioning, children in the Late PN group obtained better parent-reported scores for executive functioning, more specifically for inhibition, working memory and meta-cognition than children in the Early PN group, at two-year follow-up (**Chapter 4**). At four year follow-up, all differences between the Early PN group and the Late PN for parent-reported executive functioning and

visual-motor integration disappeared (**Chapter 7**). In contrast, with regard to emotional functioning, the favorable outcome of the Late PN group showing less externalizing problems at two-year follow-up than the Early PN group was still found four years after PICU admission (**Chapter 4**). Moreover, at four-year follow-up parents in the Late PN group also reported less internalizing problems regarding their child than parents in the Early PN group (**Chapter 7**). In other words, when time elapsed (from two years to four years follow-up), the difference in executive functioning between the Late PN group and the Early PN group disappeared, but in addition to more externalizing problems in the Late PN this group now also experienced more internalizing problems (e.g. anxiety and depression[24,25]) than the Early PN group. These additionally found internalizing problems could be the result of the fact that externalizing problems increase the risk for internalizing problems.[35] Interestingly, previous research showed that executive functioning could explain the shared variance of these two types of behavioral problems.[35] Probably, the problems in executive functioning in the Early PN group were first reflected in externalizing problems as this is related to impulsive behavior and the inability to inhibit initial responses. In the long term these problems regarding inhibition might lead to emotional and behavioral problems as the social environment responds negatively to impulsive behavior. Furthermore, children might develop internalizing problems, as a result of externalizing behavioral problems they had already two years before.[36] This means that when parents or teachers report externalizing behavioral problems for children, also internalizing problems should be monitored and assessed over time as these children are at risk for these problems. As to the fourth domain, social functioning (only assessed at two-year follow-up), parents in the Late PN group reported better scores or 'family activities' than parents in the Early PN group (**Chapter 6**). This means that the health of children in the Late PN group was less often limiting or interrupting family activities than children in the Early PN group.

Lastly, the effect of Late PN compared to Early PN on the outcomes in the four domains of PICS were associated with the age of the child at PICU admission. Infants aged one month to 11 months during PICU admission appeared to be most vulnerable for the impact of Early PN during admission on developing problems in inhibition, working memory, planning and organization, and metacognition, and on emotional and behavioral problems two years later (**Chapter 5**).

In conclusion, although concerns existed regarding the harmful long-term effect of omitting supplemental PN in the first week of critical illness,[37] no adverse effect of Late PN was found for physical functioning, cognitive functioning, emotional functioning, and social functioning. Moreover, although not statistically significant, almost all outcomes on these domains pointed in the same direction, with better scores for children who were allocated to the Late PN group than children allocated to the Early PN group. This further supports the implementation of Late PN in the

protocol at the PICU. With regard to parents of children who participated in the PEPaNIC RCT, overall, no statistically significant differences were found for HRQoL outcomes between parents of children in the Late PN group as compared to parents of children in the Early PN group (**Chapter 6**).

Role of parents

Parents and/or caregivers play a significant role in the developmental outcomes of their child. The psychosocial development of the child is influenced by psychosocial wellbeing of the parents.[38] Posttraumatic stress disorder (PTSD) in parents was previously found to be a strong predictor for posttraumatic stress in children.[28] Additionally, family functioning was also found to be a risk factor for PTSD in children.[39] Previous research found that parents of children with a critical illness are at risk for worse psychosocial wellbeing. A high proportion of parents, up to 84%, experience posttraumatic stress symptoms.[27] Furthermore, it was found that 15% of the parents experienced clinically significant depression symptoms, and 23% of the parents anxiety symptoms after PICU admission of their child.[40] Moreover, a systematic review showed that interaction between parents and children can change, since parents may have difficulties with their role as parent and with maintaining their parenting style after PICU admission of the child.[41]

We assessed health-related quality of life of the parents six months and two years after PICU admission. Six months after PICU admission, HRQoL of parents of PICU survivors was more favorable as to physical domains and less favorable for mental domains compared to adults from the general population (**Chapter 3**). The poorer mental health of parents might be the result of the psychosocial burden that parents experience during and after the critical illness of their child. Our better results on physical functioning in parents of PICU survivors compared to normative data could be the result of a *response shift*, which occurs when certain aspects in life are appreciated more after experiencing a stressful event. In the longer term, after two years, physical HRQoL was no longer better compared to parents of healthy control children. The poorer mental HRQoL of parents that that was present six months after PICU admission, disappeared as well (**Chapter 6**). Parents seem to have adjusted to the burden they experienced and to have adapted to their 'new normal' situation.[2] Although outcomes of parents seemed to normalize over time, parents still report impact of the health status of the child on their personal time and their emotions at six months and two years after PICU admission (**Chapter 3** and **6**). It is important to identify those parents who were not able to adapt to the new situation and who are at risk for psychosocial problems.

In the PEPaNIC follow-up study, parents not only reported about their own HRQoL, they also reported about their child's HRQoL, executive functioning, and emotional

and behavioral problems (**Chapter 3, 4, 5, 6,** and **7**). Probably, parents' own mental health status is reflected in their answers on the questionnaires about their children, as at six months a positive association between parent-reported HRQoL of the child and parents' self-reported HRQoL was found (**Chapter 3**). Besides this shared variance, their own distress might also have influenced family functioning and therefore the child's HRQoL,[42] or the other way around. Irrespective of the underlying mechanism of this association, it raises the question whether proxy-reports are a representation of the true HRQoL of the child or the parent's HRQoL, and whether these reports are reliable. Self-report HRQoL measurements are also available for children, from the age of five years on.[43] Studies that examined both parent-reports and child-reports reported disagreements between parents and their children, which is called the proxy-problem.[44-47] Usually in the PICU population, parents report worse scores for their children than children themselves, which can be (partially) due to overprotection by parents.[38]

As a result of the proxy-problem, the value of proxy-reports for research and clinical practice is often debated. It has been suggested to avoid proxy-reports for domains that are hard to observe by the parents, such as mental health and self-esteem.[45] However, children are usually more likely to give socially desirable answers and their judgements are based on the exact moment of completing the questionnaire instead of a longer period of time.[48] Others suggest that it should not be the question who of the informants is right, as the discrepancies in HRQoL scores between informants are rather a reflection of differences in their perspectives which gives valuable information about the relationship between the parent and the child.[46] As mentioned before, in addition to the parent and the child, the teacher/day care provider, and peers may add value as informants, since they see the child in the context of other children which could serve as a frame of reference in completing the questionnaires.[49]

Parents completed questionnaires about the cognitive functioning of the child as well, more specifically about the neurocognitive domain 'executive functioning. Neurocognitive functioning is usually assessed using neuropsychological tests, and the subjective evaluation of children's neurocognitive function by parents is often debated. In the current follow-up study, a substantial part (48%) of the children was younger than five years old at the four-year follow-up. Although the first year of life is critical for the development of basic structures in the brain required for executive functioning, most executive functions develop throughout childhood (between the age of five and eight years executive functions develop rapidly) and become more stable from the age of nine.[50] This supports the value of parent-reported outcomes in children younger than five years, as these domains are difficult to accurately assess with the use of neuropsychological tests. As previously mentioned, the two types of assessment (objective and subjective evaluation) complement each other and should ideally be used both. Again, teachers/day care providers could have added value

when relying on subjective evaluations as most neurocognitive functions are visible in day care/educational settings.[49]

Strengths and limitations of the current research

The follow-up studies which have been described in this thesis have some limitations to address. First, it would have been interesting to know which patients already had impairments before they were admitted to the PICU. Unfortunately, information about the neurocognitive and psychosocial status of patients before the PICU admission was not available. Although some studies suggested strategies to speculate about the level of functioning prior to the PICU admission, this is well-known problem in research in this field.[51,52]

Second, children who were too disabled to test (which was determined by screening of the medical file by one of the members of the research team and confirmed by the parents), were not included in the analysis in this thesis. This might suggest that the results were not generalizable to the complete group of PICU survivors. However, including these children in the analysis would have influenced the results as they were not able to complete the majority of measurements of the follow-up assessment. Furthermore, as to randomization, in the Late PN group fewer children were too disabled to test than in the Early PN group two years after participation in the PEPaNIC (**Chapter 4**). This suggests that children in the Early PN group were more impaired than children in the Late PN. It would have been informative to assess parents' own HRQoL of children who were too disabled to participate, as they might be more distressed than parents of children who experience (relatively) less impairments.

Third, in the current study no imaging of the brain has been done. One way to validate neuropsychological tests is to measure brain activity while patients are doing these tests. Although brain activity in the expected regions is usually enhanced, activity in other areas of the brain can also enhanced. This implies that the neural networks responsible for cognitive processes are diffuse, and that certain performance on a neurocognitive test does not equal neural anatomy.[53] On the other hand, it is questionable whether this would have added valuable information to our purpose. Furthermore, it would have impacted the follow-up rate, as a group of parents that declined to participate in the follow-up study argued that the assessment lasted already (too) long for their child.

Fourth, a broad range of domains were covered within our test battery (which is also a strength of the study), and consequently most children were not able to finish the complete battery. This resulted in too much missing data for tests that assessed divided attention, focused attention and sustained attention, as these tests were assessed at the end of the follow-up appointment. The test for general intelligence

was completed by almost all children, as this was the first test of the test battery. General intelligence is a more broad indication of cognitive functioning which is less sensitive for differences between groups and over time. For future studies, we recommend not to repeat this IQ test at every follow-up moment to save time and energy for assessing other cognitive domains.

A strength of the two-year and four-year follow-up was the very large number of patients and healthy controls that participated compared to other studies. The majority of previous studies that investigated neurocognitive functioning or HRQoL in PICU survivors included less than 100 children, and for neurocognitive functioning our study sample was the largest in the last five years (**Chapter 2**). Second, the response rate at the two-year and four-year follow-up was high, respectively 74% and 66%. (**Chapter 2**). Third, we compared the patients with a matched healthy control group. In the first place, siblings and relatives of patients were asked to participate to control for genetic and environmental factors. In addition, healthy children from schools in the same geographical area as the corresponding patients came from, were recruited and matched for age and gender. For the six-month follow-up normative data was used, as the control group was not yet recruited at that time. Only very small, negligible differences as to age and gender were found between the studied sample and normative data which makes the comparison of results with normative data reliable (**Chapter 3**).

Conclusions present thesis

1. Children who were critically ill had impairments in physical, cognitive, emotional, and social functioning compared with healthy children, six months, two years, and four years after PICU admission.
2. Parents experienced impaired mental HRQoL, and better physical HRQoL six months after PICU admission of the child, but two years after PICU admission of their child these scores were normalized and comparable to scores of parents with healthy children.
3. Children who received Late PN had better scores compared to children who received Early PN for parent-reported executive functioning and externalizing problems, and for the neuropsychological test for visual-motor integration, two years after PICU admission.
4. Four years after PICU admission, the result of less externalizing problems in the Late PN group compared to the Early PN group was still present. Also less internalizing problems and less total emotional and behavioral problems were found in the Late PN group than the Early PN group.

Future perspectives

As described above, children who survived critical illness perform worse than their healthy peers on different domains of functioning. However, not all children experience impairments in the four domains of PICS, but it is unknown which specific groups (e.g. diagnosis, age, gender) experience which specific problems (e.g. physical activity, memory, getting along with others). Therefore, the next step would be developing and incorporating prediction models for the individual patient in which multiple risk factors are taken into account to predict personalized follow-up trajectories. When these trajectories become clear, treatment could be adapted to individual needs.

Risk factors for group outcomes for HRQoL, as found in the current study, were higher age at PICU admission, longer length of PICU stay, higher severity of illness scores, and a neurological diagnosis, six months after PICU admission (**Chapter 3**). In the PEPaNIC follow-up study, we also found that use of benzodiazepines and corticosteroids during PICU admission, and having a syndrome predicted worse neurocognitive outcomes and more emotional and behavioral problems, two and four years after PICU admission (**Chapter 4** and **7**). When predictors of worse outcomes are known, interventions could be conducted to influence these factors and subsequently improve outcomes. The PEPaNIC RCT is an example of such an intervention study, as it showed that changing the nutritional strategy (by delaying the start of parenteral nutrition during critical illness) had a positive effect on long-term developmental outcomes. Other studies that tried to influence factors associated with worse outcomes focused mainly on disease management and more research into psychosocial interventions aiming to improve factors of the post-PICU phase are needed (**Chapter 2**).

Future studies focusing on parents as predictor for worse outcomes in children could investigate whether empowering parents on the PICU through shared decision making is effective,[41] as this was previously mentioned to improve parental distress.[54] Furthermore, fathers are an understudied population. In the current study, we did not have information whether the mother or the father completed the questionnaires. A systematic review found evidence that mothers experienced more stress than fathers.[33] This implies that studies into the differences between the needs of parents could be valuable. Regardless of the question whom of the parents experience more psychosocial problems, both parents and children experience significant psychosocial problems during and after PICU admission. Problems in emotional functioning of the parents, such as anxiety and stress, may be improved by providing psychosocial help. Since wellbeing of the parents and family functioning are highly correlated with the wellbeing of the child, support for the family members is important.[38] Furthermore, we recommend that psychologists aim to improve outcomes of both the child and parents in family centered care.[41,55]

Electronic technologies can be used (e.g. apps or website) in conducting future interventions as this could enhance communication between the professionals and family members. This was proven to be a helpful tool during psychotherapy for families of after critical illness of the child.[33] Furthermore, use of *virtual reality* to reduce posttraumatic stress by exposure to the traumatic memory (in the virtual environment) has been shown to be effective for traumatic events in adults,[56] and might be effective for children previously admitted to the PICU and their parents.

Finally, it is important that future studies use standardized protocols in examining outcomes across studies. A major problem in literature is the differences between assessment tools, measurements used, type of scores reported, and way of reporting results (**Chapter 2**).[5] The consequence of this heterogeneity between studies is that comparing results is difficult. It would be helpful to organize a standardized (inter) national follow-up program to assure that outcome measurements are similar and also to provide care for the individual patients and family.

Need for structured follow-up: recommendations

The 'Nederlandse Vereniging voor Kindergeneeskunde' guideline 'follow-up of children after admission to intensive care' highlights the importance of structural follow-up of critically ill children after discharge.[57] However, at this moment only a small part of all critically ill children surviving from (inter)national PICUs are invited for a long-term follow-up due to the high costs and long duration of follow-up moments. Besides, the Dutch guidelines do not extensively describe the steps in follow-up care over time, and the guidelines are based on literature investigating acutely admitted children only. To identify those patients and parents who at risk for PICS and to offer more specialized care for patients and families who are at risk for developing more severe impairments, a stepped care model for patients and families is necessary to offer effective follow-up care[58] (see **Figure 1**):

- step one involves prevention of impairments
- step two involves reducing mild impairments and prevention of severe impairments
- step three consists of therapy for severe impairments

Some patients and their families will only need step one, others will need more help. The sequence of the steps of the follow-up program are not fixed and steps could be repeated. Moreover, the steps should be repeated at fixed moments in time, as some patients and parents will have delayed reactions as to the psychosocial symptoms as a result of the PICU admission.[59] Notably, these recommendations are mainly focused on the psychosocial impairments after PICU admission, but a clinician, physiotherapist, and dietician should be incorporated for the physical domain of PICS.

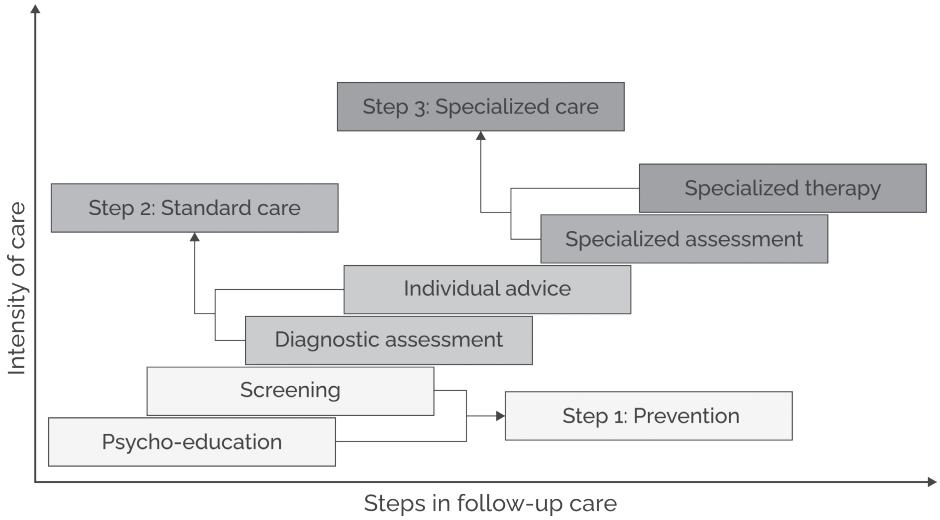

Figure 1. Stepped follow-up care for families after critical illness of the child (adapted from Thambirajah et al., 2011 and Riper et al., 2007 [60,61])

Step 1: Prevention

The first step in follow-up care after PICU admission is to prevent impairments. Psycho-education is helpful in reducing parental stress, improving coping strategies, and preventing overprotection by the parents.[52,62] Psycho-education could be offered in different forms. Information from the medical team or a psychologist who is working at the PICU at time of discharge from the PICU is one way. This psychologist should have a comprehensive understanding of the impairments (PICS) that could exist after PICU admission and of the effects of PICU admission on patients and their families.[63] In other words, families should be informed about what they can expect during the recovery period, and be prepared for the time it will take to reach a situation that feels normal again (new normal).[2] However, transition to the general ward of the hospital is a stressful event for parents.[64] Therefore, information from the medical team at this time point might be lost, and an online patient information portal or mobile app providing information could add value.[65] For some patients and parents, this psycho-education will be enough to continue their daily life without impairments, as it was found that it was sufficient for children with subthreshold symptoms of PTSS.[66] However, to evaluate whether impairments are still present, the following step will be to screen all patients and parents for impairments in their daily functioning. Regularly planned follow-up visits at the clinic to evaluate the health status of the patient could be preceded by the completion of questionnaires (e.g. digitally at home), ideally by the child, parent and teacher/day care provider.[49] To have a broad view of all domains of functioning, HRQoL questionnaires, as well as questionnaires on neurocognitive functioning will give insight in the different domains. For example, the Health Act Questionnaires (Infant Toddler Quality of Life Questionnaire for children

aged 0-3 years, and the Child Health Questionnaire for children aged 4-18 years)[67,68] for HRQoL, the Child Behavior Checklist for emotional and behavioral problems, and the BRIEF for executive functioning. When children are old enough to report about their own outcomes (most questionnaires from the age of twelve, for example the Child Health Questionnaire Child Form), self-reports should be included in the screening instruments. The mode of delivery of these questionnaires can be digital, as a recent study showed that parents' preferences were to complete measurements digitally.[69] Most questionnaires, as well as the three questionnaires mentioned to use for screening, consist of many questions. Therefore, it would be even better to create an adaptive battery of questions, which is easily possible when questionnaires are offered digitally or through a mobile app.[65] Through computer adaptive testing (CAT), patients and parents only have to answer questions that are relevant to them.[70] Furthermore, when finishing the questions, the program will give an overview of domains impaired. This could be shared with the clinician beforehand, to facilitate communication between patients and clinician during follow-up visits. Besides, such an overview might give the clinician information regarding impairments which enables individualized advice during follow-up visits and, if needed, arrange further referral. As it will not take long to complete the questions using CAT, such a mobile app could also be used for monitoring more frequently.[65] When alarming scores are detected, this can be communicated with the clinician, which enables referral in an early phase.

Step 2: Standard care

In this phase, the screening tools direct the diagnostic process to which domains have to be assessed more thoroughly. For example, when emotional problems were reported in step one, these problems will be assessed in more detail (whether this is related to behavior, anxiety, depression) to know which tools can help. This is important as specific impairments for specific groups are not found yet. Although certain groups of PICU survivors were associated with specific problems (such as cognitive problems, mood disturbances, headaches, sleep disturbances and daytime fatigue for patients with traumatic brain injury,[71] and problems with speech, language, visual-spatial skills, executive functions, attention and motor skills for children with a cardiac disease[72]) results varied widely between patients with the same diagnosis and between studies investigating the same subgroup of critically ill patients. With regard to cognitive functioning, a neurocognitive assessment in this phase (step 2, standard care) gives a comprehensive view of the cognitive abilities of the child. This neurocognitive assessment consists ideally of tests for a broad range of relevant domains of the cognitive hierarchy. However, as patients perceived the test battery of the current follow-up study as too long, selection of tests that are easy to administer with good psychometric quality is important. Therefore, it is important that a licensed neuropsychologist is involved in selecting and assessing accurate neuropsychological tests. When the diagnostic assessment results in an extensive overview of the problems, psychosocial tools can be offered to improve

the psychosocial outcome for children. These tools may be advised to parents and class room teachers, such as creating a quiet space in the classroom when children have attentional problems.

Step 3: Specialized care

Some patients and/or parents will experience more severe impairments and/or psychiatric symptoms after PICU admission, such as PTSD or severe attentional problems, and short interventions or tools will not be helpful anymore. These families will be referred for specialized care, which consists of two elements. For some children and/or their parents, additional diagnostic assessment will be necessary to provide more in depth insight and further analyze these problems. For example, if children experience problems in attention, and tools did not improve these attentional problems, more specific tests for attention could be administered, such as tests for alertness, focused attention, divided attention, and sustained attention. For memory, further diagnostic assessment can address short-term and long-term memory problems, working memory and visual-spatial memory or verbal memory. As to executive functioning, inhibition, planning and organization, or flexibility can be impaired. As to psychosocial problems, children could have internalizing problems (e.g. anxiety, depression) or externalizing problems, social, family or school problems. Questionnaires focusing on these specific problems can be assessed to have an extensive view of these problems.

The second element of this third step consists of interventions to reduce the impairments that exist in daily life of the child and/or parents. For cognitive problems, a few interventions exist. Cogmed was one of these interventions and was conducted to improve memory impairments and comprised of training sessions for working memory at home (five weeks, five days a week, 45 minutes each session).[17] This was effective directly after the training, but probably this should be offered for a longer time, as the improvements not remained in the longer time. For psychosocial problems, such as anxious or depressive symptoms, cognitive behavioral therapy (CBT) has been proven the most effective and first line of treatment.[73] Interestingly, a systematic review found that CBT was successful in an internet-based format for children with somatic conditions, which is favorable for the practical implementation of CBT.[74] Moreover, acceptance and commitment therapy and mindfulness based interventions have been proven successful for children with pediatric conditons.[75,76] More specifically, when patients and/or parents experience PTSS, Eye Movement Desensitization Reprocessing (EMDR) is an evidence based psychotherapy that reduces these symptoms.[77] Lastly, improving the psychosocial problems that pediatric patients experience may even improve the physical impairments,[62] which further emphasizes the need of treatment of psychosocial problems in an early phase after PICU admission.

Final overall statement

Children perform worse than healthy children after admission to the PICU. Outcomes can be improved when interventions are conducted that modify factors related to outcomes like withholding parenteral nutrition during the first week of critical illness. To study outcomes it is important to use standardized outcome measurements to identify those children and parents who are at risk for impairments in daily functioning. It is recommended to implement a (inter)nationally organized, stepped care model in follow-up care to prevent and reduce these impairments.

Table 1. Outcome differences of critically ill children versus healthy control children and children allocated to the Late PN group versus Early PN group

		Patients versus healthy control children			Late PN versus Early PN	
	Subscale/test	**6 months * (Chapter 3)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**
Physical functioning	Objective evaluation					
	Height, cm		↓ 2	↓ 2	↔	↔
	Weight, kg		↔	↔	↔	↔
	Head circumference, cm		↓ 0.5	↓ 0.4	↔	↔
	Health status (somatic illness / psychiatric illness / admitted to the hospital), n		↓ (3 / 2 / 5)	↓ (2 / 2 / 4)	↔	↔
	Clinical neurological evaluation score, range 0-8		↓ 0.3	↓ 0.2	↔	↔
	Subjective evaluation					
	Physical functioning (≤18 yr), range 0-100	↓ 12 (≤3 yr)/25 (4-18 yr)	↓ 6		↔	
	Growth and development (<3 yr), range 0-100	↓ 7	↓ 3		↔	
	Bodily pain (≤18 yr), range 0-100	↓ 11	↓ 7		↔	
	General health perceptions (≤18 yr), range 0-100	↓ 28	↓ 27		↔	
	Role functioning physical (4-18 yr), range 0-100	↓ 25	↓ 8		↔	
	Change in health (≤18 yr), range 0-100	↑ 14	↑ 13		↔	
Cognitive functioning	Objective evaluation					
	Total intelligence, standard scores (mean 100, SD 15)		↓ 6	↓ 7	↔	↔
	Verbal intelligence, standard scores (mean 100, SD 15)		↓ 4	↓ 7	↔	↔
	Performance intelligence, standard scores (mean 100, SD 15)		↓ 6	↓ 6	↔	↔
	Visual-motor integration, range 0.9-20		↓ 1	↓ 0.9	↑ 0.5	↔
	Alertness (≥4 yr), ms reaction time		↓ 55 **	↓ 0.6 (z-score) **	↔	↔
	Motor coordination (≥4 yr), number of taps		↔	↓ 2 **	↔	↔
	Inhibition and flexibility (≥4 yr), ms reaction time		↔		↔	↔

Table 1. Outcome differences of critically ill children versus healthy control children and children allocated to the Late PN group versus Early PN group

		Patients versus healthy control children			Late PN versus Early PN	
	Subscale/test	**6 months * (Chapter 3)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**
	Verbal memory (5-16 yr), proportion correct		↓ 0.08 **	↔	↔	↔
	Visual-spatial memory (5-16 yr), proportion correct		↓ 0.05 **	↓ 0.3 **	↔	↔
	Subjective evaluation					
	Inhibition (≤18 yr), T-score (mean 50, SD 10)		↓ 2	↓ 3	↑ 3	↔
	Flexibility (≤18 yr), T-scores (mean 50, SD 10)		↓ 2	↓ 3	↔	↔
	Emotional control (≤18 yr), T-scores (mean 50, SD 10)		↔	↓ 2	↔	↔
	Working memory (≤18 yr), T-scores (mean 50, SD 10)		↓ 3	↓ 4	↑ 2	↔
	Planning and organization (≤18 yr), T-scores (mean 50, SD 10)		↓ 2	↓ 3	↔	↔
	Meta-cognition index (≤18 yr), T-scores (mean 50, SD 10)		↓ 2	↓ 3	↑ 2	↔
	Overall executive functioning (≤18 yr), T-scores (mean 50, SD 10)		↓ 2	↓ 4	↑ 2	↔
Emotional functioning	Subjective evaluation					
	Temperament and moods (≤3 yr), range 0-100	↓ 2	↔	↓ 3	↔	↑ 2
	General behavior (≤18 yr), range 0-100	↔ (≤3 yr)/↓ 3 (4-18 yr)	↔	↓ 2	↔	↑ 2
	Parenteral impact: emotional (≤18 yr), range 0-100	↓ 1 (≤3 yr)/24 (4-18 yr)	↓ 8		↔	
	Parental impact: time (≤18 yr), range 0-100	↓ 12 (≤3 yr)/20 (4-18 yr)	↓ 5	↓ 3	↔	↑ 2
	Role functioning emotional/behavioral (4-18 yr), range 0-100	↓ 19	↓ 7		↔	
	Mental health (4-18 yr), range 0-100	↓ 8	↓ 5		↔	
	Self-esteem (4-18 yr), range 0-100	↓ 6	↔		↔	
	Internalizing problems (≤18 yr), T-scores (mean 50, SD 10)		↓ 3		↔	
	Externalizing problems (≤18 yr), T-scores (mean 50, SD 10)		↓ 2		↑ 2	
	Total emotional & behavioral problems (≤18 yr), T-scores (mean 50, SD 10)		↓ 3		↔	

Table 1. Outcome differences of critically ill children versus healthy control children and children allocated to the Late PN group versus Early PN group

		Patients versus healthy control children			Late PN versus Early PN	
	Subscale/test	**6 months * (Chapter 3)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**	**2 years (Chapter 4 & 6)**	**4 years (Chapter 7)**
Social functioning	Subjective evaluation					
	Family activities (≤18 yr), range 0-100	↓ 15 (≤3 yr)/19 (4-18 yr)	↓ 6		↑ 4	
	Family cohesion (≤18 yr), range 0-100	↑ 4 (≤3 yr)/↔ (4-18 yr)	↔		↔	
	Getting along (≤3 yr), range 0-100	↔	↔		↔	

Main findings are results of the subscales and/or subdomains of outcome measurements and indicated with '↓' when scores were worse (worse functioning and/or more problems) in patients compared to healthy control children/normative data; '↑' when scores were better (better functioning and/or less problems) in patients compared to healthy control children/normative data; '↔' when scores were not significantly different between patients and healthy control children/normative data. Differences between test scores are reported after multivariable linear and logistic regression analyses on the 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption, adjusted for age, center, race, sex, geographical origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, the educational and occupational status of parents, Pediatric Index of Mortality 3 score, and pediatric logistic organ dysfunction score on admission to a pediatric intensive care unit (PICU), screening tool for risk on nutritional status and growth (STRONGkids) risk category, and parental smoking behavior before PICU admission. Numbers indicated are the beta-estimates or odds ratio for the comparison between study groups adjusted for risk factors. Age ranges of tests were reported in case the subscale/test was only available for a specific age group.

* Only univariable regression analyses and comparisons with normative data were available and reported, which means that the numbers in this column are differences in scores on the specific subscale (ranging from 0-100)

** Test/domain exists of more subtests, average scores of these subtests are reported.

Abbreviations: PICU, pediatric intensive care unit; PN, parenteral nutrition; yr, years

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CHAPTER

9

Summary

The Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) multicenter, randomized controlled trial (RCT) was conducted to investigate the effect of withholding parenteral nutrition (PN) during the first week of critical illness compared with the standard protocol of starting (supplemental) PN early from day one of pediatric intensive care unit (PICU) admission. Allocation to the Late PN group resulted in nutritional intakes below recommendations. In total, 1,440 critically ill children admitted to the PICU were included in the study. The short-term outcomes were promising with a lower incidence of newly acquired infections, and a shorter stay at the hospital and PICU in the group of children allocated to the Late PN group compared to the group of children allocated to the Early PN group. The long-term follow-up of the PEPaNIC trial is described in this thesis. Outcome measurements are medical assessment, neurocognitive assessment (including neuropsychological tests for general intelligence, visual-motor integration, alertness, motor-coordination, executive functioning, and memory), and parent-reported outcomes (executive functioning, emotional and behavioral problems, and health-related quality of life (HRQoL)).

Chapter 1

Chapter 1 describes the background of the studies included in this thesis. As a result of the low mortality rates of children admitted to the PICU, the focus of post-PICU research is shifting more towards impairments related to PICS after discharge. During recovery after PICU discharge, changes in the four domains of PICS (physical, cognitive, emotional, and social functioning) can be assessed both objectively and subjectively. The subjective evaluation assesses how changes are appraised in relation to daily life of the patients and their families. Subjective evaluation of physical functioning, emotional functioning, and social functioning could be measured as one construct: HRQoL. This concept indicates whether children and families still struggle with impairments and whether they have been able to create a 'new normal'. Cognitive functioning is usually described in neurocognitive domains and can be assessed objectively through neuropsychological tests and subjectively with questionnaires. The hierarchy of cognitive functions is used to map problems in cognitive functioning of children, with lower functions such as sensation and attention affecting the development of higher functions such as memory and executive functioning. Impairments in functions lower in the hierarchy were expected to result in serious consequences for daily life as the higher functions would be impaired as well. Factors that may influence PICS are pre-existing factors, factors related to the PICU admission, and/or post-PICU factors. Furthermore, both factors related to the child and to the parents will have an impact on the four domains of PICS.

Chapter 1 ends with the aims of this thesis, which were to investigate neurocognitive functioning and HRQoL of PICU patients compared with healthy control children, both

in literature as well as in children who participated in the PEPaNIC trial. Furthermore, long-term effects of Late PN versus Early PN during PICU admission on patients' neurocognitive functioning and on patients' and parents' HRQoL, were examined.

Chapter 2

To give an overview of studies investigating neurocognitive functioning and HRQoL after critical illness in children and adolescents in the past five years, a literature search was conducted. The results of this search are described in chapter 2. A total of 65 studies showed that neurocognitive functioning and HRQoL scores were lower in term neonates and children up to 18 years old who were previously admitted to the PICU, as compared with children from the general population. Overall however, mean scores of the total group of children who survived critical illness were not below one standard deviation of the mean score of the general population, indicating that scores fell in the normal range of corresponding age-scores.

Predictors of worse general intelligence in infants in the short term (≤12 months) were longer length of PICU stay, and in the long term lower weight, lower SES, and older age at time of PICU admission. In children older than one year, the following short-term predictors were associated with lower scores for neurocognitive functioning: higher baseline levels of inattention, higher serum levels of the biomarker neuron-specific enolase, longer length of PICU stay, and longer follow-up time. In the long term (>12 months), longer length of PICU stay, more circulating phthalates, use of benzodiazepines and corticosteroids during PICU admission, and higher premorbid developmental risk were associated with lower scores for neurocognitive functioning in these older children. With regard to interventions, a working memory training improved working memory immediately after participation in the training, which however, disappeared in the longer term. No studies investigated predictive factors associated with short-term HRQoL scores in infants. Studies that investigated long-term HRQoL in infants found the need of mechanical ventilation and neurological complications (intracranial ischemia or hemorrhage) as predictors for lower scores. For children aged one year or older, longer length of PICU stay, older age, and worse disease severity were associated with lower HRQoL in the short term. Whereas in the long term, elective PICU admission and neurological diagnosis were associated with lower HRQoL for older children.

Some studies examined interventions to improve factors related to worse outcomes. These studies were mainly done in the short term after PICU admission. Two intervention studies into modifiable factors during PICU admission, however, found no effect on HRQoL of different sedation procedures and of hypothermia versus normothermia. An intervention study into rehabilitation for children and adolescents during follow-up found that rehabilitation nearby home was superior in improving

HRQoL scores when compared with a program at the hospital. Furthermore, our review showed that early protocolized rehabilitation was not better than care-as-usual. Finally, a working memory training was not effective for improving HRQoL outcomes in older children in the long term after PICU admission.

Chapter 3

Six months after PICU admission, parents of children who participated in the PEPaNIC trial completed HRQoL questionnaires about their child's HRQoL and about their own HRQoL and the results are presented in chapter 3. Parents reported worse HRQoL for their children compared to normative data from same-aged children. Interestingly, family cohesion appeared not to be impaired. Physical HRQoL of parents of PICU survivors was higher (more favorable) than of adults from the general population. On the other hand, their mental HRQoL was lower compared to normative data. Parents' mental HRQoL was associated with the child's HRQoL. This reflects that parents' distress seems to be associated with the HRQoL of the child. However, this finding could also be (partially) explained as a result of shared variance between the two questionnaires completed by the same person. Parents reported worse HRQoL scores on 'change in health' and 'physical functioning' for their children, six months after PICU admission, when the following factors were present: higher age at admission, longer length of PICU stay, and higher risk of mortality. In contrast, cardiac surgery was associated with better scores for these scales. For clinical practice, screening parents and children within a few months after PICU admission to identify those children and parents who are at risk for an impaired HRQoL seems necessary.

Chapter 4

In chapter 4 the developmental outcomes of the two-year follow-up assessment are described. Two years after participation in the PEPaNIC RCT, patients had worse outcomes compared with healthy control children for height, bodyweight, body-mass index, head circumference, health status and clinically assessed neurological functioning. Furthermore, patients scored worse for parent-reported executive functioning and emotional and behavioral problems, and on neuropsychological tests for general intelligence, visual-motor integration, alertness, and memory than healthy control children. Patients in the Late PN group had better parent-reported executive functioning (inhibition, working memory, metacognition, and overall executive functioning) and less externalizing problems compared to the Early PN group, assessed with questionnaires. Furthermore, children allocated to the Late PN group performed better on a neuropsychological test for visual-motor integration compared to patients in the Early PN group. Some biological explanations were discussed (e.g. suppression of autophagy, alternations in DNA methylation or telomere shortening), but further research into these biological explanations is warranted. The young age

of the children limits the completeness and reliability of the results, which stresses the importance of a longer-term follow-up.

Chapter 5

Chapter 5 presents the role of age at time of exposure in the results described in chapter 4. Chapter 4 described that the two-year follow-up of the PEPaNIC trial showed that Late PN resulted in more favorable outcomes regarding parent-reported executive functioning, externalizing problems, and objectively tested visual-motor integration compared to Early PN. These results may be determined by the age at time of exposure, especially since some periods are critical for brain development. Outcomes that were available for all ages at the two-year follow-up were used in this sub-study. Interaction between randomization to Early PN versus Late PN and age at time of exposure was found for weight, parent-reported inhibitory control, cognitive flexibility, working memory, planning and organization, metacognition, total executive functioning, internalizing problems, and total emotional and behavioral problems. This means that problems in externalizing behavior and visual-motor integration in the Early PN group versus the Late PN group were present across all ages. No age group showed a beneficial effect of early administration of PN. Children who were exposed to Early PN as an infant (29 days - 11 months) were found to have worse scores than other age subgroups for parent-reported inhibitory control, working memory, metacognition, planning and organization, total executive functioning, internalizing problems, and total emotional and behavioral problems. A possible reason for this finding is that the first year of life is critical for brain development and the brain is highly sensitive to environmental disturbances such as nutrition. Furthermore, the brain grows significantly during this period. Neonates (≤28 days) and children aged 5 years or older were least vulnerable to long-term harm induced by early administration of PN during PICU admission, which could be explained by stages of brain development, with less adverse effect of Early PN on synaptogenesis in neonates and less sensitive periods in children older than 5 years.

Chapter 6

In chapter 6, a secondary analysis of the two-year follow-up assessment of patients who participated in the PEPaNIC trial investigated whether the better neurocognitive outcomes found in the Late PN group compared to the Early PN group (chapter 4) were also reflected in better HRQoL. Furthermore, the study examined whether the worse HRQoL in patients compared to children from the general population found six months after PICU admission, were still present at two-year follow-up. At the two-year follow-up, parents of patients reported worse scores for HRQoL subscales related to physical functioning and for single health-utilities index (HUI) domains for their child than parents of healthy control children. In young children, up to three years

old, parent-reported growth and development was worse than that of healthy control children, which was in line with the objectively assessed lower height and bodyweight in patients compared with healthy control children. In these young children (< 3 years), when compared with the six-month follow-up assessment, impairments in physical health and general health remained at the two-year follow-up. Worse scores for psychosocial domains were no longer found for the young children. However, in older children lower scores for psychosocial domains remained at the two-year follow-up. On the HRQoL questionnaire, parents reported a mental and physical HRQoL that was comparable to that of healthy control parents. No differences were found between randomization groups (Late PN versus Early PN). Self-reports regarding HRQoL completed by the children themselves to determine possible differences with parent-reported HRQoL could have provided additional information. However, the majority of children were still too young to be able to assess their own HRQoL.

Chapter 7

As shown in chapter 4, the two-year follow-up of the PEPaNIC RCT showed that starting PN late during PICU admission compared with starting supplemental nutrition from day one was beneficial for parent-reported executive functioning, externalizing behavioral problems, and objectively assessed visual-motor integration. However, due to the young age, not all neurocognitive tests could have been done reliably. Therefore, all patients and/or parents who participated in the PEPaNIC RCT were approached for a four-year follow-up, which is described in chapter 7. In addition, the group of healthy control children was also approached for this follow-up assessment. At the four-year follow-up, patients had worse outcomes than healthy control children for height, weight, head circumference, clinically assessed neurological functioning, parent-reported executive functioning, and emotional and behavioral problems, and for neuropsychological tests for general intelligence, visual-motor integration, alertness, motor-coordination, and memory. Children allocated to the Late PN group had less parent-reported internalizing, externalizing, and total emotional and behavioral problems than children allocated to the Early PN group. In these outcomes, children in the Late PN group showed no difference from healthy control children. The reported problems with inhibitory control at two-year follow-up probably led to emotional and behavioral problems at the four-year follow-up.

Chapter 8

In chapter 8, the main findings of this thesis are discussed. It is know that patients, after admission to the PICU, can experience impairments in four domains: physical, cognitive, emotional, and social functioning, described as PICS. The results of this thesis showed that patients who participated in the PEPaNIC study overall experienced impairments in these four domains at six months, two years and four

years follow-up. This was found for objectively measured outcomes (through medical assessment and neuropsychological tests) and subjectively measured outcomes (through patient reported outcome measurements (PROMs), questionnaires) completed by parents. With regard to results of the PEPaNIC randomized controlled trial, although concerns existed regarding the harmful effect of Late PN during PICU admission, children allocated to the Late PN group scored not worse on long-term outcomes than children allocated to the Early PN group, both two years and four years after PICU admission. Moreover, children in the Late PN group scored better on some parent-reported outcomes than children in the Early PN group. Parent-reported outcomes are valuable as parents play an important role in the development of the child, especially when children are young. However, parent-reports might be affected by their own HRQoL. Therefore, subjective measurements and objective measurements should complement each other in scientific research and clinical practice. For the future, a standardized, stepped care, follow-up program should be implemented to identify those patients and parents who are at risk for PICS and to offer more specialized care for patients and families who are at risk for developing more severe impairments.

CHAPTER

10

Samenvatting

Het gerandomiseerde, gecontroleerde onderzoek *vroege versus late parenterale voeding op de intensive care* (PEPaNIC) werd uitgevoerd om te onderzoeken of er een verschil bestaat tussen het laat starten van parenterale voeding (PV, ook wel infuusvoeding) en het vroeg starten van PV tijdens een opname op de intensive care (ic) voor kinderen. Het standaardprotocol was dat PV vroeg gestart wordt, namelijk vanaf de eerste dag dat een kind is opgenomen op de ic. In het PEPaNIC onderzoek werd gekeken of het laat starten van PV, wat betekende dat er geen (aanvullende) infuusvoeding werd gegeven tijdens de eerste week van kritieke ziekte, leidde tot betere uitkomsten. In totaal werden 1440 kritiek zieke kinderen die opgenomen waren op de ic geïncludeerd in het onderzoek. De helft van de kinderen werd toegewezen tot de late PV groep en de andere helft tot de vroege PV groep. De korte termijn resultaten van het PEPaNIC onderzoek waren veelbelovend: kinderen in de late PV groep hadden minder nieuwe infecties en waren korter opgenomen op de ic en in het ziekenhuis dan kinderen in de vroege PV groep. Deze positieve korte termijn resultaten van het laat starten van PV voorspellen mogelijk minder problemen na een ic opname op de lange termijn. De lange termijn uitkomsten van de PEPaNIC-studie zijn beschreven in dit proefschrift. Tijdens de follow-up studie hebben kinderen een medisch onderzoek ondergaan, is er gekeken naar neurocognitief functioneren (door middel van neuropsychologische tests voor algemene intelligentie, visueel-motorische integratie, alertheid, motorische coördinatie, executief functioneren en geheugen) en hebben ouders vragenlijsten ingevuld (over executief functioneren, emotionele- en gedragsproblemen, en gezondheid gerelateerde kwaliteit van leven (*Health Related Quality of Life,* HRQoL)). Er was ook een groep van 405 gematchte gezonde controle kinderen waarbij gekeken werd naar dezelfde uitkomsten.

Hoofdstuk 1

Hoofdstuk 1 beschrijft de achtergrond van de onderzoeken beschreven in dit proefschrift en geeft een overzicht van eerdere studies over neurocognitief functioneren en kwaliteit van leven na een kritieke ziekte bij kinderen. Als gevolg van de lage sterftecijfers van kinderen opgenomen op de ic, is de focus van wetenschappelijk onderzoek de laatste jaren verschoven van mortaliteit naar problemen die kinderen ervaren in het dagelijks leven na kritieke ziekte. Na het doormaken van een kritieke ziekte, kunnen kinderen problemen ervaren in vier domeinen (fysiek-, cognitief-, emotioneel- en sociaal functioneren), wat ook wel het post-intensive care syndroom (PICS) wordt genoemd. Deze problemen kunnen zowel objectief als subjectief worden gemeten. De subjectieve evaluatie meet hoe de problemen worden ervaren in het dagelijks leven van patiënten en hun families. De subjectieve evaluatie van de domeinen fysiek functioneren, emotioneel functioneren en sociaal functioneren kan worden gemeten binnen één concept, namelijk HRQoL. Dit concept geeft aan in hoeverre kinderen en gezinnen beperkingen ervaren na de kritieke ziekte van het kind en of ze een situatie hebben kunnen creëren die voelt als een 'nieuw normaal'.

Cognitief functioneren wordt meestal beschreven in neurocognitieve domeinen en kan objectief worden gemeten door middel van neuropsychologische tests en kan subjectief gemeten worden door middel van vragenlijsten. Om cognitieve problemen in kaart te brengen, kan de hiërarchie van cognitieve functies gebruikt worden. In deze hiërarchie beïnvloeden lagere functies, zoals sensatie en aandacht, de hogere functies, zoals geheugen en executief functioneren. Problemen in de ontwikkeling van functies lager in de hiërarchie hebben naar verwachting ernstigere gevolgen voor het dagelijks leven dan stoornissen in de hogere functies, gezien de lagere functies ook de hogere functies beïnvloeden. Er zijn verschillende factoren die de uitkomsten in de vier domeinen van PICS kunnen beïnvloeden, zoals factoren die aanwezig zijn vóór de opname op de ic, factoren die gerelateerd zijn aan de ic opname en factoren in de periode na de ic opname (als kinderen aan het herstellen zijn van de ic opname). Deze factoren kunnen gerelateerd zijn aan het kind en aan de ouders.

Hoofdstuk 1 eindigt met de doelstellingen van dit proefschrift, namelijk het onderzoeken van neurocognitief functioneren en HRQoL van patiënten (en hun ouders) die opgenomen waren op de ic Kinderen in vergelijking met gezonde controle kinderen, zowel in de literatuur als bij kinderen die eerder deel hebben genomen aan de PEPaNIC-studie. Daarnaast is de doelstelling van het proefschrift om te onderzoeken wat de lange termijn effecten zijn van late PV versus vroege PV tijdens de ic opname op het neurocognitief functioneren van patiënten, en op de HRQoL van patiënten en ouders.

Hoofdstuk 2

Hoofdstuk 2 had als doel een overzicht te geven van de bestaande literatuur over het neurocognitief functioneren en de HRQoL van kinderen en adolescenten na kritieke ziekte. Er werd een literatuuronderzoek uitgevoerd naar studies gepubliceerd in de afgelopen vijf jaar. Er werden 65 studies geïncludeerd in het systematische review, die lieten zien dat het neurocognitief functioneren en de HRQoL slechter waren bij kinderen (a term geboren neonaten – 18 jaar) die opgenomen waren op de ic vergeleken met kinderen van de algemene bevolking. De gemiddelde scores van de totale groep kinderen die een kritieke ziekte overleefden waren echter niet lager dan één standaarddeviatie van de gemiddelde score van de algemene bevolking, oftewel binnen de range van scores die als normaal worden gezien.

Voorspeller voor slechtere scores op de korte termijn voor intelligentie bij kinderen die opgenomen waren toen ze jonger dan een jaar waren, was een langere opname op de ic. Op de langere termijn voorspelden een lager gewicht, een lagere sociaaleconomische status en een oudere leeftijd tijdens de ic opname een minder goede score op intelligentietests. Bij kinderen van één jaar of ouder werden de volgende voorspellers gevonden voor lagere scores op neuropsychologische tests

op de korte termijn: meer aandachtsproblemen voorafgaand aan de ic opname, hogere serumlevels van de bio marker neuron-specifieke enolase, een langere opname op de ic en een langere follow-up tijd. Studies die een langer follow-up interval hadden (> 12 maanden), rapporteerden dat een langere opnameduur op de ic, meer circulerende ftalaten (weekmakers van plastic), het gebruik van medicijnen zoals benzodiazepines en corticosteroïden tijdens de ic opname, en een hoger ontwikkelingsrisico voorafgaand aan de opname op de ic geassocieerd waren met lagere scores op neurocognitief functioneren binnen deze groep oudere kinderen. Wat betreft studies die een interventie onderzochten, werd gevonden dat een werkgeheugentraining het werkgeheugen direct na deelname aan de training verbeterde, maar dat deze positieve resultaten op de langere termijn geen standhielden.

Studies die HRQoL onderzochten, hebben geen voorspellers gerapporteerd voor lagere HRQoL-scores voor kinderen jonger dan een jaar. Studies die HRQoL op lange termijn bij kinderen onder het jaar onderzochten, vonden dat kunstmatige beademing tijdens de opname en neurologische complicaties (herseninfarct of hersenbloeding) lagere scores voorspelden. Voor kinderen van één jaar of ouder waren een langere opnameduur op de ic, een oudere leeftijd op het moment van opname en een hogere ernst van ziekte geassocieerd met een lagere HRQoL, op de korte termijn na de ic opname. Voor oudere kinderen werd gevonden dat een electieve (geplande) opname op de ic en een neurologische diagnose een lagere HRQoL voorspelden op de langere termijn.

Interventiestudies die probeerden factoren te beïnvloeden om zo de uitkomsten na een ic opname te verbeteren, onderzochten vooral de korte termijn uitkomsten. Twee interventies die probeerden HRQoL te verbeteren, keken naar het effect van verschillende sedatieprocedures en naar het effect van het koelen van het lichaam tijdens een ic opname. Zij vonden geen effect van de interventies op de HRQoL. Een studie die de aspecten van fysieke revalidatie onderzocht om zo de uitkomsten na een ic opname te verbeteren, vond dat revalidatie dichtbij huis beter was voor de HRQoL dan wanneer de revalidatie in het ziekenhuis plaatsvond. Een ander onderzoek vond dat vroege, geprotocolleerde revalidatie (fysotherapie, ergotherapie, en spraak- en taaltherapie) niet leidde tot betere uitkomsten dan de reguliere revalidatie. Ten slotte was een training voor het werkgeheugen niet effectief voor het verbeteren van de HRQoL-resultaten bij oudere kinderen op langere termijn na opname op de ic.

Hoofdstuk 3

Zes maanden na de ic opname vulden ouders van kinderen die eerder deel hadden genomen aan de PEPaNIC-studie HRQoL-vragenlijsten in over hun kind en over zichzelf. De resultaten van deze vragenlijsten worden besproken in hoofdstuk 3.

Ouders rapporteerden een slechtere HRQoL voor hun kinderen vergeleken met normatieve data bestaande uit kinderen van dezelfde leeftijd. Interessant is dat de samenhang binnen het gezin (cohesie) niet slechter was binnen families van patiënten in vergelijking met families van leeftijdsgenoten uit de algemene bevolking. Fysieke HRQoL van ouders van kritiek zieke kinderen was hoger (gunstiger) dan van volwassenen uit de algemene bevolking. Aan de andere kant was hun mentale HRQoL lager in vergelijking met gegevens uit de algemene bevolking. De mentale HRQoL van ouders was daarnaast geassocieerd met de HRQoL die de ouders voor het kind rapporteerden. Dit betekent dat de mentale problemen die ouders ervaren na een ic opname van het kind verband houden met de HRQoL van het kind. Deze bevinding kan echter ook (gedeeltelijk) verklaard worden door de gedeelde variantie tussen de twee vragenlijsten die door dezelfde ouder zijn ingevuld. Daarnaast werd gevonden dat een hogere leeftijd van het kind bij opname, langere opnameduur op de ic en een hoger risico op sterfte leidden tot lagere HRQoL-scores van het kind op de subschalen 'verandering in gezondheid' en 'fysiek functioneren', zes maanden na opname op de ic. Daarentegen was een cardiale diagnose geassocieerd met betere scores op deze schalen. Voor de klinische praktijk impliceren de resultaten uit hoofdstuk 3 dat kinderen en ouders binnen een aantal maanden na de ic opname gescreend moeten worden om kinderen en ouders te identificeren die risico lopen op een verminderde HRQoL.

Hoofdstuk 4

In hoofdstuk 4 worden de resultaten van de follow-up studie, twee jaar na ic opname, beschreven. Twee jaar na deelname aan de PEPaNIC-studie hadden patiënten slechtere resultaten voor lengte, lichaamsgewicht, BMI, hoofdomtrek, gezondheidsstatus en klinisch beoordeeld neurologisch functioneren, in vergelijking met gezonde controle kinderen. Bovendien scoorden patiënten slechter dan gezonde controle kinderen op vragenlijsten voor executief functioneren en emotionele- en gedragsproblemen ingevuld door ouders, en op neuropsychologische tests voor algemene intelligentie, visueel-motorische integratie, alertheid en geheugen. Patiënten in de late PV groep hadden betere uitkomsten voor ouder-gerapporteerd executief functioneren (inhibitie, werkgeheugen, metacognitie, totaal executief functioneren) en externaliserende problemen in vergelijking met kinderen in de vroege PV groep. Bovendien presteerden kinderen in de late PV groep beter dan patiënten in de vroege PV groep op een neuropsychologische test voor visueel-motorische integratie. Enkele biologische verklaringen werden in dit hoofdstuk besproken (bv. het verstoren van het zelfreinigend systeem van het lichaam door vroege PV of veranderingen in de structuur van het DNA), maar verder onderzoek naar deze biologische verklaringen is nodig. De jonge leeftijd van de kinderen in de studie beperkte de volledigheid en betrouwbaarheid van de resultaten, wat het belang van een langere termijn follow-up onderstreept.

Hoofdstuk 5

Hoofdstuk 5 beschrijft de mogelijke rol die leeftijd op het moment van ic opname speelt in de resultaten die werden gevonden in hoofdstuk 4. Hoofdstuk 4 beschreef dat twee jaar na PEPaNIC late PV resulteerde in gunstiger resultaten op ouder-gerapporteerde uitkomsten (op executief functioneren en externaliserende problemen) en op objectief geteste visueel-motorische integratie, in vergelijking met vroege PV. Deze resultaten zijn mogelijk beïnvloed door de leeftijd van kinderen op het moment van de ic opname, vooral omdat sommige periodes in de ontwikkeling cruciaal zijn voor de hersenontwikkeling. Onderzoeksresultaten die beschikbaar waren voor alle leeftijden binnen de twee-jaars PEPaNIC follow-up studie werden gebruikt. Interactie tussen randomisatie (late PV of vroege PV) en leeftijd op het moment van ic opname werd gevonden voor gewicht en ouder-gerapporteerde inhibitie, cognitieve flexibiliteit, werkgeheugen, planning en organisatie, metacognitie, totaal executief functioneren, internaliserende problemen en totale emotionele- en gedragsproblemen. Dit betekent dat de problemen in externaliserend gedrag en visueel-motorische integratie in de late PV groep versus de vroege PV groep over alle leeftijden heen aanwezig waren. Vroege PV leidde in geen enkele leeftijdsgroep tot een gunstiger effect dan late PV. Kinderen die werden blootgesteld aan vroege PV als baby (29 dagen - 11 maanden) bleken twee jaar later slechter te scoren dan andere leeftijdsgroepen op ouder-gerapporteerde inhibitie, werkgeheugen, metacognitie, planning en organisatie, totaal executief functioneren, internaliserende problemen, en totale emotionele- en gedragsproblemen. Een mogelijke verklaring voor deze bevinding was dat het eerste levensjaar cruciaal is voor de ontwikkeling van de hersenen en dat de hersenen op dat moment gevoelig zijn voor omgevingsinvloeden zoals voeding. Bovendien groeien de hersenen tijdens deze periode aanzienlijk. Pasgeborenen (≤28 dagen) en kinderen van 5 jaar of ouder waren het minst kwetsbaar voor schade op lange termijn veroorzaakt door vroege PV tijdens de ic opname. Dit kan mogelijk worden verklaard door de verschillende stadia van de hersenontwikkeling, met een minder nadelig effect van vroege PV op de het aanmaken van nieuwe verbindingen in de hersenen bij pasgeborenen en minder gevoelige periodes voor de breinontwikkeling bij kinderen ouder dan 5 jaar.

Hoofdstuk 6

In hoofdstuk 6 werd onderzocht of de gunstigere resultaten op het neurocognitief functioneren die werden gevonden in de late PV groep in vergelijking met de vroege PV groep (hoofdstuk 4) ook werden weerspiegeld in een betere HRQoL twee jaar na deelname aan PEPaNIC. De resultaten lieten zien dat ouders van patiënten slechtere scores rapporteerden dan ouders van gezonde controle kinderen voor HRQoL-subschalen gerelateerd aan fysiek functioneren en de gezondheidsstatus van hun kind. Voor jonge patiënten tot en met drie jaar waren de ouder-gerapporteerde

groei en ontwikkeling (twee jaar na ic opname) slechter dan voor gezonde controle kinderen, wat overeenkwam met de objectief gemeten lagere lengte en lichaamsgewicht van patiënten in vergelijking met gezonde controle kinderen. Bij deze jonge kinderen (≤3 jaar) bleken de problemen in de lichamelijke gezondheid en de algemene gezondheid die gevonden werden bij de zes maanden follow-up, ook aanwezig na twee jaar. Slechtere scores op psychosociale domeinen werden na twee jaar niet meer gevonden voor jonge kinderen. Bij oudere patiënten (≥4 jaar) werden de lagere scores op psychosociale domeinen in vergelijking met gezonde controle kinderen ook na twee jaar gevonden. Op de HRQoL-vragenlijst voor ouders zelf rapporteerden ouders een mentale en fysieke HRQoL die vergelijkbaar was met die van ouders van gezonde controle kinderen. Er werden over het algemeen geen verschillen gevonden tussen randomisatiegroepen (late PV versus vroege PV). Als kinderen zelf ook vragenlijsten hadden ingevuld, had dat aanvullende informatie kunnen bieden bij dit onderzoek. De meerderheid van de kinderen was echter nog te jong om hun eigen HRQoL te kunnen beoordelen.

Hoofdstuk 7

Zoals beschreven in hoofdstuk 4, toonde de follow-up twee jaar na de PEPaNIC-studie aan dat het laat starten van PV tijdens de ic opname, in vergelijking met het starten van aanvullende PV vanaf de eerste dag, gunstig was voor ouder-gerapporteerd executief functioneren, externaliserende gedragsproblemen en objectief gemeten visueel-motorische integratie. Vanwege de jonge leeftijd van kinderen in de PEPaNIC-studie konden echter niet alle neuropsychologische tests (betrouwbaar) worden afgenomen. Daarom werden alle patiënten en/of ouders die eerder deel hadden genomen aan de PEPaNIC-studie benaderd voor een follow-up vier jaar na ic opname. De uitkomsten hiervan worden beschreven in hoofdstuk 7. De groep gezonde controle kinderen werd ook benaderd voor deze follow-up. De resultaten toonden aan dat patiënten slechtere uitkomsten hadden dan gezonde controle kinderen voor lengte, gewicht, hoofdomtrek, klinisch beoordeeld neurologisch functioneren, ouder-gerapporteerd executief functioneren en emotionele- en gedragsproblemen, en voor neuropsychologische tests voor algemene intelligentie, visueel-motorische integratie, alertheid, motorische coördinatie en geheugen. Kinderen in de late PV groep hadden minder ouder-gerapporteerde internaliserende, externaliserende en totale emotionele- en gedragsproblemen dan kinderen in de vroege PV groep. Voor deze uitkomsten werden geen verschillen gevonden tussen kinderen in de late PV groep en gezonde controle kinderen. De door ouders gerapporteerde problemen met inhibitie gevonden bij de follow-up twee jaar na ic opname, leidden waarschijnlijk tot emotionele- en gedragsproblemen die gevonden werden bij de follow-up na vier jaar.

Hoofdstuk 8

In hoofdstuk 8 worden de belangrijkste bevindingen van dit proefschrift bediscussieerd. Uit de literatuur is bekend dat patiënten, na een opname op de ic, problemen kunnen ervaren in vier domeinen: fysiek -, cognitief -, emotioneel - en sociaal functioneren, ook wel beschreven als PICS. Uit de resultaten van dit proefschrift is gebleken dat kinderen die deelnamen aan de PEPaNIC studie over het algemeen problemen ervaarden in alle vier de domeinen, op alle drie de meetmomenten (zes maanden, twee jaar en vier jaar na ic opname). Deze resultaten werden gevonden op objectief gemeten uitkomsten (zoals medisch onderzoek en neuropsychologische tests) en subjectief gemeten uitkomsten (vragenlijsten) ingevuld door ouders. Met betrekking tot de resultaten van de PEPaNIC studie werden ondanks de zorgen die bestonden over de schadelijke effecten van late PV tijdens ic opname, geen slechtere lange termijn resultaten (twee en vier jaar na ic opname) gevonden voor kinderen in de late PV groep vergeleken met kinderen in de vroege PV groep. Ouder-gerapporteerde resultaten zijn waardevol gezien ouders een belangrijke rol spelen in de ontwikkeling van het kind, vooral als kinderen jong zijn. Anderzijds kunnen ouder-gerapporteerde vragenlijsten beïnvloed zijn door hun eigen kwaliteit van leven. Daarom is het belangrijk objectieve en subjectieve uitkomstmaten allebei te gebruiken in de wetenschap en klinische praktijk, zodat het een aanvulling op elkaar is. In de toekomst zou een gestandaardiseerd, stapsgewijs follow-up programma geïmplementeerd moeten worden om de kinderen en ouders te identificeren die mogelijk PICS ontwikkelen en dus extra hulp nodig hebben. Daarnaast kunnen kinderen en families die meer ernstige problemen ervaren dan vroeg hulp krijgen.

APPENDICES

A

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Hordijk J, Verbruggen S, Buysse C, Utens E, Joosten K, and Dulfer K. Neurocognitive functioning and health-related quality of life of children after pediatric intensive care admission: a systematic review. (Submitted)

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Phd Portfolio

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	Year	Workload (ECTS)
General academic skills		
Systematic Literature Retrieval in PubMed and other databases	2017	0.6
Endnote	2017	0.4
CPO Patient Oriented Research: design, conduct & analysis	2017	0.3
Research Integrity	2017	0.3
Research skills		
Regression Analysis	2017	1.9
Biomedical English Writing and Communication	2017	4.0
Presenting skills for junior researchers	2018	1.0
Specific skills		
Neuropsychological testing in children	2017	4.0
Workshops		
Erasmus PhD day	2017/2018	0.3
Theme Sophia Research Day	2018/2019	0.3
TULIPS young researchers day (Culemborg, The Netherlands)	2017	0.1
Presentations		
Research Work Meeting Child & Adolescent Psychiatry/Psychology	2017	0.2
Scientific Café Child & Adolescent Psychiatry/Psychology	2017	0.2
European Pediatric Psychology Conference, Ghent, Belgium	2018	2.0
Intensive Care Children Research Meeting	2018	0.2
Research Working Meeting Child & Adolescent Psychiatry/Psychology	2018	0.2
European Congress of the European Academy of Pediatric Societies, Paris, France	2018	2.0
Intensive Care Children Research Symposium	2018	0.2
Colloquium Child- and Adolescent Psychiatry/Psychology	2018	0.2
Intensive Care Children Research Meeting	2019	0.2
European Congress of the Society of Pediatric and Neonatal Intensive Care, Salzburg, Austria	2019	2.0
Intensive Care Children Symposium	2019	0.2

	Year	Workload (ECTS)
Teaching activities		
Lectures Medical students:		
Oppositional behavior	2017/2018/2019	1.5
Normal development 0-18 years	2017/2018/2019	1.5
Writing a systematic review	2017/2018	1.0
Supervision research interns		
Chantal Kabbedijk	2016	0.5
Eline Kochen (master thesis)	2017/2018	1.5
Lotte Koen (bachelor thesis)	2018	1.0
Floortje Ossentjuk	2017	0.5
Fien Akkersdijk (master thesis)	2019	1.5
Laura Leijen (master thesis)	2019	1.5
Research meetings		
Clinical & Research Meetings Pediatric Psychology	2017/2018/2019	1.0
Intensive Care Children Research Meetings	2017/2018/2019	1.0
Research Work Meetings Child & Adolescent Psychiatry/Psychology	2017/2018/2019	2.0

Curriculum Vitae

José Hordijk was born on 14th of November, 1989 in Oud-Beijerland, the Netherlands, as daughter of Dick and Simone and sister of Karen. In 2008 she completed her pre-university education at the 'Willem van Oranje' in Oud-Beijerland. She started at the college for primary teacher, but after two years she switched to the study Psychology at 'Leiden University'. During the bachelor's program, she also studied at the 'Rutgers State University' in New Brunswick (New Jersey), United States. After finishing her bachelor's program, she started her master Medical Psychology, with a subspecialization of Clinical Neuropsychology at 'Tilburg University'. The first year consisted of medical related courses at the university. The second year, she completed a clinical internship at Yulius GGZ, partly in Barendrecht at the department of Child- and Adolescent Psychiatry and partly in Dordrecht at the Albert Schweitzer Hospital at the department of Pediatrics. Her research internship was also at Yulius GGZ in Dordrecht at the department of autism. After graduating cum laude in 2015, she started working as a neuropsychologist at Yulius GGZ in Barendrecht. In March 2016 she started her PhD project at the department of Pediatric Intensive Care, which resulted in the work described in this thesis. In September 2020, she started her training to become a mental health care specialist at Erasmus MC – Sophia Children's Hospital at the department of Child and Adolescent Psychiatry/Psychology.