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

An Jacobs, Karolijn Dulfer*, Renate D Eveleens*, José Hordijk, Hanna Van Cleemput, Ines Verlinden, Pieter J Wouters, Liese Mebis, Gonzalo Garcia Guerra, Koen Joosten, Sascha C Verbruggen†, Fabian Güiza†, Ilse Vanhorebeek†, Greet Van den Berghe†*

Summary

Background The PEPaNIC randomised 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 paediatric 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 behavioural development 4 years after randomisation.

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 behavioural 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. This trial is registered with ClinicalTrials.gov, NCT01536275.

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 (eg, hospital admission odds ratio 4·27 [95% CI 3·12 to 5·84]; p<0·0001), neurocognitive (eg, 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 behavioural developmental outcomes (internalising 2·73 [1·19 to 4·28], p=0·00055; externalising 1·63 [0·19 to 3·08], p=0·027; and total behavioural 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 internalising (β-estimate –1·88 [95% CI –3·69 to –0·07]; p=0·042), externalising (–1·73 [–3·43 to –0·03]; p=0·046), and total emotional and behavioural 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 randomisation and protected against emotional and behavioural problems, further supporting the deimplementation of early parenteral nutrition.

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*Equal first authors

†Equal last authors

Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, Katholieke Universiteit Leuven, Leuven, Belgium (A Jacobs MD, H Van Cleemput MSc, I Verlinden MD, P J Wouters MSc, L Mebis PhD, F Güiza PhD, Prof I Vanhorebeek PhD, Prof G Van den Berghe MD); **Intensive Care Unit, Department of Paediatrics and Paediatric Surgery, Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, Netherlands** (K Dulfer PhD, R D Eveleens MD, J Hordijk MSc, Prof K Joosten MD, S C Verbruggen MD); **and Department of Paediatrics, Intensive Care Unit, University of Alberta, Stollery Children's Hospital, Edmonton, Canada** (G Garcia Guerra MD)

Correspondence to: Prof Greet Van den Berghe, Clinical Division and Laboratory of Intensive Care Medicine, Katholieke Universiteit Leuven, Leuven B-3000, Belgium **greet.vandenberghe@kuleuven.be**

Introduction

Critical illness in children is associated with impaired physical, neurocognitive, emotional, and behavioural development, which often persists for years after discharge from the paediatric 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 hyperglycaemia, phthalates

Research in context

Evidence before this study

The multicentre PEPaNIC trial showed that omitting supplemental parenteral nutrition during the first week in the paediatric intensive care unit improved short-term outcomes compared with initiating early parenteral nutrition to reach caloric targets when enteral nutrition was insufficient. In view of concerns about potential harm induced by accepting substantial macronutrient deficits affecting long-term growth, health status, clinically assessed neurological functioning, and emotional and behavioural development, a 2-year follow-up study of the PEPaNIC trial was done. This study showed that withholding parenteral nutrition during the first week of critical illness in children did not adversely affect survival, growth, health status, and neurocognitive functioning, and improved parent-reported or caregiver-reported executive functioning (inhibition, working memory, metacognition, and total executive functioning), externalising behavioural problems, and visual–motor integration 2 years after admission to the paediatric intensive care unit. However, specific concerns were raised for the large proportion of participants who were infants at the time of exposure to substantial macronutrient deficits. Although the infants benefitted the most from accepting early macronutrient deficits with regard to short-term outcomes, it remained unknown whether they would be more at risk for adverse effects on long-term clinical, neurocognitive, and emotional and behavioural outcomes. Because of their young age, these children could not be completely assessed neurocognitively at the 2-years follow-up of the PEPaNIC randomised controlled trial.

We searched the Medline Ovid, Embase, Cochrane Central Register of Controlled Trials, and Web of Science databases from their inception to Nov, 30 2019, with no date limits or language restrictions. Different combinations of the search terms "nutritional support", "parenteral nutrition or feeding", "intravenous nutrition or feeding" AND "intensive care unit", "critical care", "critical illness", "intensive care", "ICU", "PICU" AND "long-term", "neurocognitive or child development", "child health or growth" were used. We found only one published long-term follow up study assessing the timing of parenteral nutrition during paediatric critical illness, which was the 2-year follow-up study of the PEPaNIC study.

Added value of this study

As children who were infants at the time of critical illness were too young for complete neurocognitive assessment at the 2-year follow-up of the PEPaNIC randomised controlled trial, a 4-year follow-up study was warranted. In this 4-year follow up study, survivors of paediatric critical illness were still found to have impairments in all investigated developmental domains such as growth, health status, neurocognitive and emotional and behavioural functioning compared with healthy matched children. The omission of supplemental parenteral nutrition during the first week of paediatric intensive care unit admission did not harm any of the physical and neurocognitive development domains and protected children against parent-reported or caregiver-reported emotional and behavioural problems.

Implications of all the available evidence

Omitting the early use of parenteral nutrition in critically ill infants and children has not only been shown to prevent intensive care unit-acquired infections and to accelerate recovery, it also improved long-term neurocognitive development at 2 years and 4 years after admission to the intensive care unit. These short-term and long-term benefits support the deimplementation of administering parenteral nutrition during the first week in the paediatric intensive care unit.

leaching into the blood from indwelling medical devices, and the use of early-parenteral nutrition.[3–5] The multicentre randomised controlled PEPaNIC trial[6] showed that postponing parenteral nutrition for 1 week in the paediatric 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 externalising behavioural 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 timepoint 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 behavioural 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 paediatric 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 paediatric 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 paediatrician. After receiving a standardised 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 paediatric 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, randomisation, and masking

After obtaining informed consent, children in the PEPaNIC trial[6] 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 (p 10). After 1 week in the paediatric 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 paediatric psychologists who had not been involved in the management of the patients during their stay in the paediatric intensive care unit and who were strictly masked to treatment allocation. Parents and caregivers were not masked while the child was treated in the paediatric 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 paediatric 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 recognised questionnaires and clinical tests with adequate normative data were used. Parent-reported questionnaires included the Behaviour Rating Inventory of Executive Function[11,12] (executive functioning, T scores, with mean 50 and SD 10) and the Child Behaviour Checklist[13,14] (emotional and behavioural 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

See Online for appendix

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 (p 3–4).

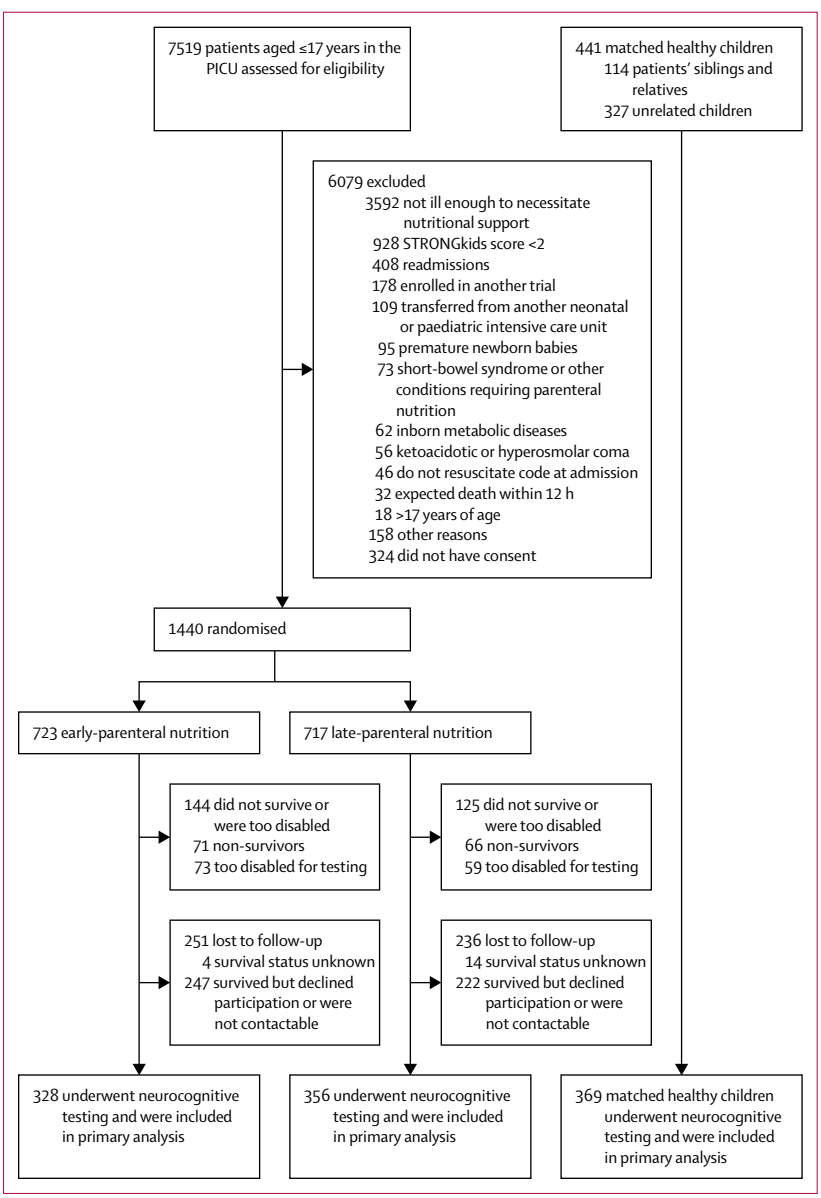

Figure 1: **Study profile**
PICU=paediatric intensive care unit. STRONGkids=Screening Tool Risk On Nutritional Status and Growth.

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 (appendix pp 5–6, 11–13).[19] Imputation of data for age-specific tests was only done within the respective age group. Bias and instability of the imputation model was minimised 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 (appendix pp 5–6, 11–13).[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 analyse the differences between the two groups in PEPaNIC.[5] All multivariable analyses adjusted for covariates, as prespecified 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 centre, sex, race, geographic origin, language, hand preference, history of malignancy, a predefined syndrome (appendix p 7), and the educational and occupational status of the parents and caregivers (appendix p 8). Additional adjustment for admission diagnosis, severity of illness upon paediatric intensive care unit-admission (paediatric index of mortality 3 and paediatric logistic organ dysfunction scores), risk of malnutrition (Screening Tool for Risk On Nutritional Status and Growth), and parental smoking behaviour before admission to the paediatric 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 hypoglycaemia, ventilatory support, and stay in the paediatric intensive care unit could potentially mediate any long-term effect and thus

	Tested populations at 4-years follow-up		Tested PICU population at 4-years follow-up*		Total PICU population recruited to the original trial	
	Control group (n=369)	Patients who have been critically ill (n=684)	Early-parenteral nutrition group (n=328)	Late-parenteral nutrition group (n=356)	Early-parenteral nutrition group (n=723)	Late-parenteral nutrition group (n=717)
Demographics						
Age at 4-years follow-up (years)	7·5 (4·3)	7·3 (4·3)	7·4 (4·3)	7·2 (4·2)	NA	NA
Sex						
Male	202 (55%)	393 (57%)	187 (57%)	206 (58%)	415 (57%)	412 (57%)
Female	167 (45%)	291 (43%)	141 (43%)	150 (42%)	308 (43%)	305 (43%)
Known non-white race†	27 (7%)	53 (8%)	33 (10%)	20 (6%)	50 (7%)	33 (5%)
Known non-European origin†	45 (12%)	129 (19%)	73 (22%)	56 (16%)	161 (22%)	128 (18%)
Known not exclusive Dutch or English language	71 (19%)	158 (23%)	78 (24%)	80 (22%)	122 (17%)	106 (15%)
Socioeconomic status						
Parental educational level‡						
Educational level 1	12 (3%)	30 (4%)	10 (3%)	20 (6%)	NA	NA
Educational level 1·5	13 (4%)	51 (7%)	29 (9%)	22 (6%)	NA	NA
Educational level 2	47 (13%)	157 (23%)	75 (23%)	82 (23%)	NA	NA
Educational level 2·5	68 (18%)	116 (17%)	53 (16%)	63 (18%)	NA	NA
Educational level 3	207 (56%)	183 (27%)	86 (26%)	97 (27%)	NA	NA
Educational level unknown	22 (6%)	147 (21%)	75 (23%)	72 (20%)	NA	NA
Parental occupational level§						
Occupational level 1	2 (0·5%)	7 (1%)	1 (0·3%)	6 (2%)	NA	NA
Occupational level 1·5	20 (5%)	63 (9%)	23 (7%)	40 (11%)	NA	NA
Occupational level 2	42 (11%)	108 (16%)	50 (15%)	58 (16%)	NA	NA
Occupational level 2·5	25 (7%)	69 (10%)	39 (12%)	30 (8%)	NA	NA
Occupational level 3	80 (22%)	118 (17%)	52 (16%)	66 (19%)	NA	NA
Occupational level 3·5	40 (11%)	53 (8%)	30 (9%)	23 (6%)	NA	NA
Occupational level 4	117 (32%)	102 (15%)	44 (13%)	58 (16%)	NA	NA
Occupational level unknown	43 (12%)	164 (24%)	89 (27%)	75 (21%)	NA	NA
Patient characteristics upon admission to the paediatric intensive care unit						
Infants aged less than 1 year at admission	NA	331 (48%)	153 (47%)	178 (50%)	328 (45%)	325 (45%)
STRONGkids risk level¶						
Medium	NA	613 (90%)	291 (89%)	322 (90%)	644 (89%)	644 (90%)
High	NA	71 (10%)	37 (11%)	34 (10%)	79 (11%)	73 (10%)
PeLOD score, first 24 h in PICU‖	NA	20·0 (11·6)	19·4 (11·6)	20·5 (11·5)	19·7 (12·0)	20·1 (12·3)
PIM3 score**	NA	−3·5 (1·4)	−3·4 (1·4)	−3·5 (1·3)	−3·2 (1·6)	−3·2 (1·7)
PIM3 probability of death (%)††	NA	6·6 (11·7)	6·9 (11·9)	6·4 (11·7)	9·4 (15·9)	9·1 (17·4)
Diagnostic category						
Surgical						
Abdominal	NA	68 (10%)	34 (10%)	34 (10·0%)	53 (7%)	60 (8%)
Burns	NA	3 (0·4%)	2 (0·6%)	1 (0·3%)	5 (0·7%)	5 (0·7%)
Cardiac	NA	291 (43%)	137 (42%)	154 (43%)	279 (39%)	268 (37%)
Neurosurgery-traumatic brain injury	NA	58 (8%)	31 (9%)	27 (8%)	63 (9%)	53 (7%)
Thoracic	NA	38 (6%)	21 (6%)	17 (5%)	34 (5%)	27 (4%)
Transplantation	NA	11 (2%)	3 (0·9%)	8 (2%)	7 (1%)	17 (2%)
Orthopaedic surgery-trauma	NA	19 (3%)	12 (4%)	7 (2%)	28 (4%)	26 (4%)
Other	NA	25 (4%)	11 (3%)	14 (4%)	21 (3%)	27 (4%)

(Table 1 continues on next page)

	Tested populations at 4-years follow-up		Tested PICU population at 4-years follow-up*		Total PICU population recruited to the original trial	
	Control group (n=369)	Patients who have been critically ill (n=684)	Early- parenteral nutrition group (n=328)	Late- parenteral nutrition group (n=356)	Early-parenteral nutrition group (n=723)	Late- parenteral nutrition group (n=717)
(Continued from previous page)						
Medical						
Cardiac	NA	23 (3%)	8 (2%)	15 (4%)	30 (4%)	31 (4%)
Gastrointestinal-hepatic	NA	2 (0·3%)	1 (0·3%)	1 (0·3%)	2 (0·3%)	4 (0·6%)
Oncologic-haematologic	NA	6 (0·9%)	2 (0·6%)	4 (1%)	8 (1%)	7 (1%)
Neurologic	NA	42 (6%)	19 (6%)	23 (6%)	51 (7%)	52 (7%)
Renal	NA	0	0	0	1 (0·1%)	1 (0·1%)
Respiratory	NA	70 (10%)	33 (10%)	37 (10%)	99 (14%)	96 (13%)
Other	NA	28 (4%)	14 (4%)	14 (4%)	42 (6%)	43 (6%)
Malignancy	0	38 (6%)	22 (7%)	16 (4%)	51 (7%)	33 (5%)
Diabetes	0	0	0	0	3 (0·4%)	0
Syndrome‡‡	2 (0·5%)	63 (9%)	26 (8%)	37 (10%)	123 (17%)	118 (16%)
Known parental smoking between birth and PICU admission	NA	151 (22%)	69 (21%)	82 (23%)	NA	NA
Acute effects of randomisation in PICU						
Duration of stay in the PICU (days)	NA	7·8 (16·0)	9·3 (19·8)	6·5 (11·2)	9·2 (21·3)	6·5 (10·0)
Patients who acquired a new infection in PICU	NA	96 (14%)	59 (18%)	37 (10%)	134 (19%)	77 (11%)
Duration of mechanical ventilatory support (days)	NA	5·0 (11·7)	6·0 (15·0)	4·0 (7·4)	6·4 (18·6)	4·4 (7·3)
Days with hypoglycaemia <40 mg/dl	NA	0·1 (0·5)	0·1 (0·5)	0·2 (0·6)	0·1 (0·6)	0·2 (0·6)
Duration of postrandomisation treatments (days)						
Duration of antibiotic treatment	NA	5·4 (14·2)	6·6 (17·7)	4·4 (9·8)	6·7 (19·0)	4·6 (8·7)
Duration of haemodynamic support	NA	2·7 (7·7)	2·9 (8·2)	2·5 (7·3)	3·0 (7·4)	2·4 (6·2)
Duration of treatment with opioids	NA	5·0 (9·3)	5·8 (11·5)	4·2 (6·5)	6·1 (16·5)	4·1 (6·2)
Duration of treatment with benzodiazepines	NA	4·4 (10·2)	4·9 (10·5)	4·0 (10·0)	5·4 (16·7)	4·0 (8·8)
Duration of treatment with hypnotics	NA	1·5 (6·0)	1·8 (8·1)	1·1 (3·0)	1·8 (6·3)	1·3 (3·1)
Duration of treatment with α-2-agonists	NA	1·1 (6·8)	1·1 (6·4)	1·1 (7·1)	1·1 (8·7)	1·0 (6·0)
Duration of treatment with corticosteroids	NA	1·2 (3·9)	1·4 (4·5)	1·1 (3·3)	1·6 (4·3)	1·3 (3·9)

Data are n (%) or mean (SD). NA=not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children). STRONGkids=Screening Tool for Risk on Nutritional Status and Growth. PeLOD=paediatric logistic organ dysfunction score. PICU=paediatric intensive care unit. PIM3=paediatric index of mortality 3 score. *Overall, demographics upon admission to the PICU, allocation to the late or early parenteral nutrition groups, and intensive care unit or hospital-related primary and secondary study endpoints were similar in the patients included in the PEPaNIC trial who were tested (n=684) and patients who survived, but declined participation or could not be reached for inclusion in the 4-year follow-up (n=469; appendix pp 18–19). †Participants were classified according to race and geographical origin by the investigators. These classifications were done to capture the ethnical and regional differences in the frequency of consanguinity, which might adversely affect cognitive performance. ‡The education level is the average of the paternal and maternal educational level, and calculated based on the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium) and the Centraal Bureau voor de Statistiek (Netherlands). Low (1), middle (2), and high (3) educational level (appendix p 8). §The occupation level is the average of the paternal and maternal occupation level, which is calculated based on the International ISCO System 4-point scale for professions (appendix p 8). ¶ 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 a medium risk, and a score of 4 to 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. ††PIM3 probability of death, ranging from 0% to 100%, with higher percentages indicating a higher probability of death in PICU. ‡‡A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (appendix p 7).

Table 1: **Demographics, post-randomisation treatments in the paediatric intensive care unit, and acute outcomes of patients and healthy control children**

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further adjustment for these factors was done in the multivariable models. In addition, further adjustment was done for other postrandomisation treatments that could theoretically play a role (duration of haemodynamic 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 (appendix pp 9, 14), correction for multiple comparisons was not done.[7,20] This trial is registered with ClinicalTrials.gov, NCT01536275.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Of the children included in the original PEPaNIC trial, done between June 18, 2012, and July 27, 2015, 71 (10%) of

	Number (%) with available data (n=1053)	Tested populations					Tested PICU population				
		Univariable analysis			Multivariable analysis		Univariable analysis			Multivariable analysis	
		Control children (n=369)	Patients who have been critically ill (n=684)	p value	β-estimate or odds ratio (95% CI)*	p value	Early-parenteral nutrition group (n=328)	Late-parenteral nutrition group (n=356)	p value	β-estimate or odds ratio (95% CI)†	p value
Anthropometrics, n=1053											
Height (cm)	1012 (96%)	124·7 (23·4)	121·1 (23·2)	0·017	−2·11 (−3·15 to −1·06)	<0·0001	122·1 (23·1)	120·8 (23·2)	0·26	−0·81 (−3·45 to 1·82)	0·54
Z score‡	1012 (96%)	0·40 (0·99)	−0·03 (1·23)	<0·0001	..	..	0·04 (1·22)	−0·09 (1·25)	0·16	..	..
Weight (kg)	1004 (95%)	28·0 (16·5)	27·0 (17·1)	0·33	−0·09 (−0·97 to 0·79)	0·83	27·2 (16·5)	26·7 (17·5)	0·70	0·13 (−2·05 to 2·30)	0·91
Z score‡	1004 (95%)	0·32 (0·87)	0·12 (1·17)	0·0056	..	..	0·17 (1·18)	0·08 (1·17)	0·55	..	..
BMI (kg/m²)	1003 (95%)	16·68 (2·94)	16·86 (3·33)	0·69	..	..	16·84 (3·13)	16·89 (3·50)	0·56	..	..
Z score‡	1003 (95%)	0·12 (1·00)	0·21 (1·17)	0·25	..	..	0·17 (1·43)	0·09 (1·26)	0·19	..	..
Head circumference (cm)	1008 (96%)	52·5 (2·3)	52·0 (2·7)	0·0010	−0·42 (−0·67 to −0·18)	0·00077	52·1 (2·8)	51·8 (2·6)	0·27	−0·11 (−0·46 to 0·23)	0·52
Z score‡	1008 (96%)	0·49 (1·08)	0·13 (1·34)	<0·0001	..	..	0·17 (1·43)	0·09 (1·26)	0·19	..	..
Health status, n=1053											
Diagnosed with a somatic illness	840 (80%)	120 (32%)	370 (54%)	<0·0001	2·23 (1·64 to 3·05)§	<0·0001	180 (55%)	190 (53%)	0·70	0·97 (0·68 to 1·39)§	0·88
Diagnosed with a psychiatric illness	960 (91%)	16 (4%)	63 (9%)	0·0058	2·47 (1·25 to 4·87)§	0·0094	32 (10%)	31 (9%)	0·81	1·04 (0·56 to 1·91)§	0·91
Admitted to hospital for a medical or surgical reason	1011 (96%)	101 (27%)	453 (66%)	<0·0001	4·27 (3·12 to 5·84)§	<0·0001	230 (70%)	223 (63%)	0·052	0·72 (0·50 to 1·02)§	0·064
Clinical neurological evaluation score (range 0–8)¶	970 (92%)	0·2 (0·6)	0·6 (1·3)	<0·0001	0·24 (0·10 to 0·38)	0·00083	0·7 (1·4)	0·5 (1·2)	0·093	−0·10 (−0·28 to 0·08)	0·28
Executive functioning as reported by parents or caregivers, n=1021 (T score)¶											
Inhibition	918 (90%)	45·7 (9·8)	49·8 (13·2)	<0·0001	2·69 (1·06 to 4·31)	0·0012	50·8 (13·3)	49·0 (12·6)	0·071	−1·67 (−3·64 to 0·31)	0·10
Flexibility	919 (90%)	45·7 (8·5)	49·3 (11·8)	<0·0001	2·71 (1·26 to 4·15)	0·00025	50·2 (12·2)	48·5 (11·2)	0·054	−1·49 (−3·28 to 0·31)	0·10
Emotional control	919 (90%)	46·2 (9·4)	48·9 (11·2)	<0·0001	2·06 (0·60 to 3·52)	0·0057	49·5 (11·3)	48·4 (11·0)	0·18	−1·19 (−2·94 to 0·56)	0·18
Working memory	918 (90%)	46·4 (9·6)	51·9 (13·5)	<0·0001	3·70 (2·10 to 5·29)	<0·0001	52·7 (13·7)	51·1 (12·6)	0·12	−1·38 (−3·33 to 0·58)	0·17
Planning and organisation	917 (90%)	46·3 (9·5)	50·4 (12·8)	<0·0001	2·87 (1·33 to 4·41)	0·00027	50·6 (12·8)	50·2 (12·0)	0·60	−0·38 (−2·27 to 1·51)	0·69
Meta-cognition index	916 (90%)	45·6 (9·8)	50·6 (13·2)	<0·0001	3·33 (1·71 to 4·95)	<0·0001	50·9 (13·5)	50·2 (12·4)	0·51	−0·61 (−2·58 to 1·36)	0·54
Total score	915 (90%)	44·8 (9·8)	49·9 (13·2)	<0·0001	3·57 (1·95 to 5·18)	<0·0001	50·5 (13·3)	49·2 (12·5)	0·18	−1·27 (−3·25 to 0·71)	0·21
Emotional and behavioural problems as reported by parents or caregivers, n=1020 (T score)¶											
Internalising problems	940 (92%)	46·7 (10·5)	51·0 (12·3)	<0·0001	2·73 (1·19 to 4·28)	0·00055	52·1 (12·1)	50·0 (12·2)	0·024	−1·88 (−3·69 to −0·071)	0·042
Externalising problems	940 (92%)	45·6 (9·7)	48·8 (11·2)	<0·0001	1·63 (0·19 to 3·08)	0·027	49·7 (11·0)	47·9 (11·1)	0·032	−1·73 (−3·43 to −0·03)	0·046
Total problems	940 (92%)	45·4 (9·9)	50·1 (11·9)	<0·0001	2·95 (1·44 to 4·46)	0·00013	51·5 (11·6)	48·8 (11·9)	0·0030	−2·44 (−4·22 to −0·67)	0·0070

(Table 2 continues on next page)

	Number (%) with available data (n=1053)	Tested populations					Tested PICU population				
		Univariable analysis			Multivariable analysis		Univariable analysis			Multivariable analysis	
		Control children (n=369)	Patients who have been critically ill (n=684)	p value	β-estimate or odds ratio (95% CI)*	p value	Early-parenteral nutrition group (n=328)	Late-parenteral nutrition group (n=356)	p value	β-estimate or odds ratio (95% CI)†	p value
(Continued from previous page)											
Clinical neurocognitive tests											
Intelligence (range 45–155)‖, n=1053											
Total IQ	937 (89%)	105·7 (13·4)	93·1 (18·2)	<0·0001	−7·35 (−9·31 to −5·39)	<0·0001	93·2 (17·0)	93·0 (18·2)	0·89	−1·10 (−3·40 to 1·20)	0·35
Verbal IQ	931 (88%)	107·5 (14·4)	95·2 (19·0)	<0·0001	−6·96 (−8·99 to −4·92)	<0·0001	93·2 (16·0)	92·5 (16·2)	0·56	−0·13 (−2·49 to 2·24)	0·92
Performal IQ	943 (90%)	102·7 (13·2)	92·9 (16·2)	<0·0001	−5·97 (−7·91 to −4·03)	<0·0001	94·8 (18·3)	95·6 (18·6)	0·56	−1·65 (−3·90 to 0·61)	0·15
Visual-motor integration (range, 0·9–20)‖, n=1053	1025 (97%)	10·0 (2·1)	8·7 (3·1)	<0·0001	−0·89 (−1·20 to −0·57)	<0·0001	8·7 (3·1)	8·7 (2·7)	0·88	−0·08 (−0·45 to 0·29)	0·66
Alertness¶, n=1026											
Reaction time right hand (Z score)	739 (72%)	0·8 (4·3)	1·7 (12·6)	0·028	0·67 (0·19 to 1·15)	0·0073	1·7 (8·9)	1·7 (9·4)	0·65	0·08 (−0·33 to 0·49)	0·71
Within subject SD of repeated tests (Z score)	739 (72%)	1·1 (3·4)	2·0 (8·5)	<0·0001	0·66 (0·25 to 1·07)	0·0016	2·0 (6·1)	2·0 (6·4)	0·68	0·02 (−0·39 to 0·43)	0·92
Reaction time left hand (Z score)	752 (73%)	0·3 (2·5)	1·0 (5·8)	<0·0001	0·50 (0·18 to 0·82)	0·0025	1·0 (4·3)	1·1 (4·5)	0·64	0·14 (−0·22 to 0·50)	0·44
Within subject SD of repeated tests (Z score)	752 (73%)	1·0 (2·5)	1·7 (4·0)	<0·0001	0·48 (0·17 to 0·78)	0·0025	1·6 (3·3)	1·7 (3·2)	0·59	0·17 (−0·17 to 0·51)	0·32
Motor coordination (Number of taps in 10 s)‖, n=1026											
Number of unimanual taps (right hand)	816 (80%)	34·6 (29·6)	32·6 (52·3)	0·12	−1·76 (−3·45 to −0·076)	0·040	32·7 (40·0)	32·5 (37·0)	0·76	0·24 (−1·84 to 2·33)	0·82
Number of unimanual taps (left hand)	816 (80%)	30·5 (32·3)	28·9 (60·4)	0·18	−1·72 (−3·42 to −0·02)	0·046	29·1 (46·0)	28·7 (41·7)	0·65	0·09 (−1·89 to 2·08)	0·93
Number of valid alternating taps	742 (72%)	22·9 (30·0)	19·7 (56·8)	0·054	−2·41 (−4·85 to 0·02)	0·052	19·6 (43·8)	19·9 (40·7)	0·71	0·50 (−2·20 to 3·21)	0·71
Number of valid synchronous taps	785 (77%)	16·5 (18·3)	13·2 (27·9)	<0·0001	−2·07 (−3·35 to −0·78)	0·0016	12·9 (21·9)	13·5 (20·5)	0·47	0·35 (−1·19 to 1·90)	0·65

(Table 2 continues on next page)

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

	Number (%) with available data (n=1053)	Tested populations					Tested PICU population				
		Univariable analysis			Multivariable analysis		Univariable analysis			Multivariable analysis	
		Control children (n=369)	Patients who have been critically ill (n=684)	p value	β-estimate or odds ratio (95% CI)*	p value	Early-parenteral nutrition group (n=328)	Late-parenteral nutrition group (n=356)	p value	β-estimate or odds ratio (95% CI)†	p value
(Continued from previous page)											
Memory, n=491											
Verbal-auditory memory‖											
Numbers (range, 1–19)											
Memory span (forward)	418 (85%)	9·9 (3·1)	8·7 (4·3)	<0·0001	−0·64 (−1·27 to −0·019)	0·043	9·0 (4·0)	8·5 (3·6)	0·18	−0·60 (−1·37 to 0·17)	0·12
Working memory (backward)	394 (80%)	10·3 (3·1)	9·5 (5·3)	0·013	−0·17 (−0·78 to 0·45)	0·59	9·7 (4·5)	9·3 (4·3)	0·24	−0·32 (−1·05 to 0·40)	0·38
Word pairs (proportion of correct responses)											
Learning	350 (71%)	0·5 (0·2)	0·4 (0·4)	<0·0001	−0·08 (−0·12 to −0·04)	0·00010	0·4 (0·4)	0·4 (0·3)	0·67	−0·02 (−0·06 to 0·02)	0·30
Immediate memory	346 (70%)	0·4 (0·5)	0·4 (1·3)	0·074	−0·04 (−0·10 to 0·02)	0·19	0·4 (1·0)	0·4 (0·9)	0·55	−0·03 (−0·09 to 0·03)	0·31
Delayed memory	343 (70%)	0·4 (0·7)	0·4 (1·6)	0·12	−0·03 (−0·10 to 0·03)	0·28	0·4 (1·3)	0·4 (1·1)	0·43	−0·01 (−0·09 to 0·06)	0·76
Recognition	343 (70%)	0·9 (0·5)	0·9 (1·3)	0·15	−0·03 (−0·08 to 0·02)	0·20	0·9 (0·9)	0·9 (0·9)	0·46	−0·01 (−0·05 to 0·03)	0·58
Non-verbal, visual-spatial											
Pictures (proportion of correct responses)	404 (82%)	0·8 (0·1)	0·8 (0·2)	<0·0001	−0·03 (−0·06 to −0·00)	0·026	0·8 (0·2)	0·8 (0·2)	0·74	0·01 (−0·03 to 0·04)	0·68
Dots (proportion of correct responses)											
Learning	370 (75%)	0·9 (0·2)	0·8 (0·4)	0·0010	−0·05 (−0·08 to −0·01)	0·0074	0·8 (0·4)	0·8 (0·3)	0·26	0·01 (−0·04 to 0·05)	0·77
Immediate memory	367 (75%)	0·9 (0·3)	0·8 (0·7)	0·012	−0·05 (−0·10 to −0·00)	0·038	0·8 (0·5)	0·8 (0·5)	0·27	−0·01 (−0·07 to 0·05)	0·70
Delayed memory	361 (74%)	0·8 (0·4)	0·7 (1·1)	0·0040	−0·08 (−0·15 to −0·01)	0·031	0·7 (0·8)	0·7 (0·8)	0·66	0·01 (−0·07 to 0·08)	0·90
Learning index (range 50–150), n=487	341 (70%)	101·0 (22·6)	88·1 (33·2)	<0·0001	−10·22 (−13·88 to −6·55)	<0·0001	88·5 (27·4)	87·7 (25·8)	0·65	−1·38 (−5·35 to 2·59)	0·49

Results are presented in numbers with proportions (%), mean (SD), β-estimates (95% CI), and odds ratios (95% CI) from the 31 datasets combined generated by multiple data imputation by chained equations under a missing at random assumption for the 684 patients in PEPaNIC and 369 children in the control group. For alertness, motor coordination, executive functions, emotional and behavioural problems and memory, applicable imputation was restricted to relevant age ranges. For alertness, age adjusted Z-scores were calculated and imputed in the dataset. 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 (pp 5–6), further supported the robustness of these results. BMI=body-mass index. IQ=intelligence quotient. PeLOD score=paediatric logistic organ dysfunction score. PICU=paediatric intensive care unit. PIM3=paediatric index of mortality 3 score. STRONGkids=Screening Tool Risk On Nutritional Status and Growth. *Adjusted for age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, a predefined syndrome, and the educational and occupational status of parents or caregivers. †Adjusted for age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, a predefined syndrome, the educational and occupational status of parents or caregivers, admission diagnosis, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behaviour before admission to the PICU. ‡Age–sex-adjusted Z-scores were calculated with the use of reference data from the WHO growth charts.[21] §These values are odds ratios. ¶Higher scores reflect worse performance. ||Higher scores reflect better performance.

Table 2: **Outcomes at 4 years follow-up between patients in PEPaNIC and healthy control children, and between late-parenteral nutrition and early-parenteral nutrition groups in PEPaNIC**

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.

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 behavioural problems and clinical

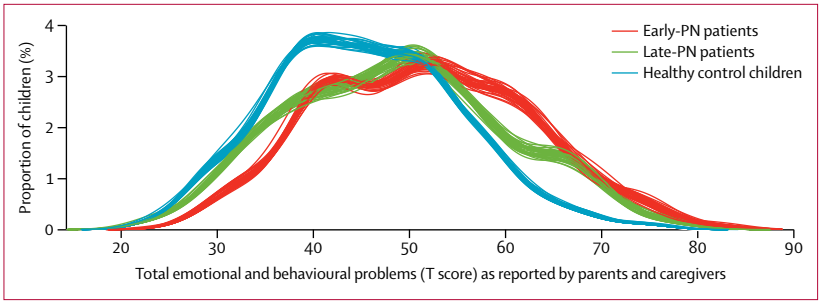

Figure 2: **The effect of late-parenteral nutrition versus early-parenteral nutrition on the development of long-term emotional and behavioural problems**

The figure represents the density estimates for total behavioural 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 behavioural and emotional problems. PN=parenteral nutrition.

tests for intelligence, visual-motor integration, alertness, motor-coordination, and memory than children in the control group (table 2).

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). In univariable analyses, fewer patients in the late-parenteral nutrition group were admitted to hospital and parents or caregivers of these children reported fewer internalising, externalising, and total emotional and behavioural 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 internalising, externalising, and total emotional and behavioural problems in the late-parenteral nutrition group than in the early-parenteral nutrition group remained (table 2; appendix pp 20–29). For internalising and externalising problems as well as total emotional and behavioural problems, children in the late-parenteral nutrition group were not different from children in the control group (appendix p 30).

Differences in intensive care outcomes of the randomised intervention and other postrandomisation factors overall did not explain the observed differences at 4-years follow-up (appendix pp 20–29). 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 characterised by broad abnormalities in all investigated developmental domains, including growth, health status, and neurocognitive, and emotional and behavioural 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 behavioural problems compared with children who received early-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 paediatric 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 behavioural problems—such as internalising, externalising, and other issues—were preventable by omitting the use of early-parenteral nutrition in the paediatric intensive care unit. Internalising problems are evidenced by anxious and depressive symptoms, and by social withdrawal,[13,14] which are the consequences of over-controlling behaviour. Externalising 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 behavioural problems includes internalising and externalising behavioural 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 behavioural 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 glycaemic 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 hyperglycaemia, omitting early-parenteral nutrition during critical illness protected the normal development of other neurobiological pathways that coordinate emotions and behaviour. This indicates that the neurocognitive legacy of paediatric 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 deimplementation of certain interventions, such as the latest European Society for Paediatric Gastroenterology Hepatology and Nutrition, European Society for Clinical Nutrition and Metabolism, European Society for Paediatric Research, and Chinese Society of Parenteral and Enteral Nutrition joint guidelines on paediatric 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 postcritical illness follow-up consultation is necessary for these children, with referral to a specialised health-care professional (eg, 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 behavioural 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 behavioural development of patients and matched control children.

In conclusion, 4 years after critical illness, an important physical, neurocognitive, and emotional and behavioural 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 behavioural problems, which were no longer overrepresented in patients in the late parenteral nutrition group compared with healthy controls. These data support deimplementation 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.

Contributors

GVdB, IVa, SCV, KJ, and KD designed the study. AJ, RDE, JH, IVe, KD, GGG, HVC, LM, and PJW gathered the data. SV, AJ, KD, RE, FG, IVa, and GVdB analysed the data and wrote the manuscript, which was reviewed and approved by all authors. All authors jointly decided to publish. GVdB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Data sharing

Data sharing is offered under the format of collaborative projects. Proposals can be directed to the corresponding author.

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References

1 Verstraete S, Van den Berghe G, Vanhorebeek I. What's new in the long-term neurodevelopmental outcome of critically ill children. *Intensive Care Med* 2018; **44:** 649–51.

2 Kachmar AG, Irving SY, Connolly CA, et al. A systematic review of risk factors associated with cognitive impairment after pediatric critical illness. *Pediatr Crit Care Med* 2018; **19:** e164–71.

3 Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA* 2012; **308:** 1641–50.

4 Verstraete S, Vanhorebeek I, Covaci A, et al. Circulating phthalates during critical illness in children are associated with long-term attention deficit: a study of a development and a validation cohort. *Intensive Care Med* 2016; **42:** 379–92.

5 Verstraete S, Verbruggen SC, Hordijk JA, et al. Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. *Lancet Respir Med* 2019; **7:** 141–53.

6 Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med* 2016; **374:** 1111–22.

7 Güiza F, Vanhorebeek I, Verstraete S, et al. Effect of early parenteral nutrition during paediatric critical illness on DNA methylation as a potential mediator of impaired neurocognitive development: a pre-planned secondary analysis of the PEPaNIC international, randomised, controlled trial. *Lancet Respir Med* 2020; **8:** 288–303.

8 Cohen MJ. Children's memory scale manual. Bloomington, MN: Pearson, 1997.

9 De Sonneville L. Handboek Amsterdamse Neuropsychologische Taken. Amsterdam: Boom test uitgevers. 2014.

10 Fivez T, Kerklaan D, Verbruggen S, et al. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. *Trials* 2015; **16:** 202.

11 Van der Heijden KB, Suurland J, De Sonneville LM, et al. BRIEF-P vragenlijst voor executieve functies voor 2- tot 5-jarigen: handleiding. Amsterdam: Hogrefe, 2013.

12 Huizinga M, Smidts D. BRIEF vragenlijst executieve functies voor 5- tot 18-jarigen: handleiding. Amsterdam: Hogrefe, 2012.

13 Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families, 2000.

14 Verhulst FC, Van der Ende J. Handleiding ASEBA. Vragenlijsten voor leeftijd van 6 tot en met 18 years. Rotterdam: ASEBA Nederland, 2013.

15 Hendriksen J, Hurks P. WPPSI-III-NL Wechsler preschool and primary scale of intelligence: handleiding. Amsterdam: Pearson, 2010.

16 Wechsler D. WISC-III nederlandstalige bewerking. Handleiding. Amsterdam: Pearson, 2005.

17 Wechsler D. WAIS-III nederlandstalige bewerking. Afname en scoringshandleiding. Amsterdam: Pearson, 2012.

18 Beery KE, Buktenica NA, Beery NA. The beery-buktenica developmental test of visual-motor integration, 6th edn (BEERY™ VMI). Amsterdam: Pearson, 2010.

19 Wulff J JL. Multiple imputation by chained equations in praxis: guidelines and review. *Electron J Bus Res Methods* 2017; **15:** 41–56.

20 Reiner A, Yekutieli D, Benjamini Y. Identifying differentially expressed genes using false discovery rate controlling procedures. *Bioinformatics* 2003; **19:** 368–75.

21 BC Childrens hospital. Professional resources. http://www.bcchildrens.ca/health-professionals/clinical-resources/endocrinology-diabetes/professional-resources#Websites (accessed May 18, 2020).

22 Watson RS, Choong K, Colville G, et al. Life after critical illness in children-toward an understanding of pediatric post-intensive care syndrome. *J Pediatr* 2018; **198:** 16–24.

23 Bronner MB, Knoester H, Sol JJ, et al. An explorative study on quality of life and psychological and cognitive function in pediatric survivors of septic shock. *Pediatr Crit Care Med* 2009; **10:** 636–42.

24 Mestrovic J, Kardum G, Sustic A, et al. Neurodevelopmental disabilities and quality of life after intensive care treatment. *J Paediatr Child Health* 2007; **43:** 673–76.

25 Cheung YT, Sabin ND, Reddick WE, et al. Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: a longitudinal analysis. *Lancet Haematol* 2016; **3:** e456–66.

26 Krull KR, Cheung YT, Liu W, et al. Chemotherapy pharmacodynamics and neuroimaging and neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol* 2016; **34:** 2644–53.

27 Robinson KE, Kuttesch JF, Champion JE, et al. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatr Blood Cancer* 2010; **55:** 525–31.

28 Chen K, Didsbury M, van Zwieten A, et al. Neurocognitive and educational outcomes in children and adolescents with ckd: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2018; **13:** 387–97.

29 Naguib JM, Kulinskaya E, Lomax CL, et al. Neuro-cognitive performance in children with type 1 diabetes—a meta-analysis. *J Pediatr Psychol* 2009; **34:** 271–82.

30 Bornstein MH, Hahn CS, Suwalsky JT. Developmental pathways among adaptive functioning and externalizing and internalizing behavioral problems: cascades from childhood into adolescence. *Appl Dev Sci* 2013; **17:** 76-87.

31 Manning JC, Pinto NP, Rennick JE, et al. Conceptualizing post intensive care syndrome in children-the pics-p framework. *Pediatr Crit Care Med* 2018; **19:** 298–300.

32 van Goudoever JB, Carnielli V, Darmaun D, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: amino acids. *Clin Nutr* 2018; **37:** 2315–23.

33 Sadhwani A, Asaro LA, Goldberg C, et al. Impact of tight glycemic control on neurodevelopmental outcomes at 1 year of age for children with congenital heart disease: a randomized controlled trial. *J Pediatr* 2016; **174:** 193–98 e2.

34 Berger JT, Villalobos ME, Clark AE, et al. Cognitive development one year after infantile critical pertussis. *Pediatr Crit Care Med* 2018; **19:** 89–97.