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Physical, Emotional/Behavioral, and Neurocognitive Developmental Outcomes From 2 to 4 Years After PICU Admission: A Secondary Analysis of the Early Versus Late Parenteral Nutrition Randomized Controlled Trial Cohort*

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OBJECTIVES: PICU patients face long-term developmental impairments, partially attributable to early parenteral nutrition (PN) versus late-PN. We investigated how this legacy and harm by early-PN evolve over time.

DESIGN: Preplanned secondary analysis of the multicenter PEPaNIC-RCT (ClinicalTrials.gov, NCT01536275) that enrolled 1,440 critically ill children from 2012 to 2015 and its 2- (2014–2018) and 4-year (2016–2019) cross-sectional follow-up studies.

SETTING: PICUs of Leuven (Belgium), Rotterdam (The Netherlands), and Edmonton (Canada).

PATIENTS: Patients and demographically matched healthy control children that underwent longitudinal assessment for physical/emotional/behavioral/neurocognitive functions at both follow-up time points.

INTERVENTIONS: In the PEPaNIC-RCT, patients were randomly allocated to early-PN versus late-PN.

MEASUREMENTS AND MAIN RESULTS: This within-individual longitudinal study investigated changes in physical/emotional/behavioral/neurocognitive functions from 2 to 4 years after PICU admission for 614 patients (297 early-PN and 317 late-PN, tested at mean ± SD age 5.4 ± 4.2 and 7.3 ± 4.3 yr) and for 357 demographically matched healthy children tested at age 5.6 ± 4.3 and 7.5 ± 4.3 years. We determined within-group time-courses, interaction between time and group, and independent impact of critical illness and early-PN on these time-courses. Most deficits in patients versus healthy children remained prominent over the 2 years ($p \leq 0.01$). Deficits further aggravated for height, body mass index, the executive function metacognition, intelligence, motor coordination (alternating/synchronous tapping), and memory learning-index, whereas verbal memory deficits became smaller (working/immediate/delayed memory) ($p \leq 0.05$). Adjustment for risk factors confirmed most findings and revealed that patients "grew-into-deficit" for additional executive functions (flexibility/emotional control/total executive functioning) and "grew-out-of-deficit" for additional memory functions (recognition/pictures) ($p \leq 0.05$). Time-courses were largely unaffected by early-PN versus late-PN, except for weight loss and limited catch-up for visual-motor integration and alertness in early-PN patients ($p \leq 0.05$).

CONCLUSIONS: From 2- to 4-year post-PICU admission, developmental impairments remained prominent. Within that time-window, impaired growth in height, executive functioning and intelligence aggravated, and impaired memory and harm by early-PN only partially recovered. Impact on development into adulthood requires further investigation.

***See also p. 656.**

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RESEARCH IN CONTEXT

- Children who have been critically ill face long-term physical, emotional/behavioral, and neurocognitive developmental problems, which can remain present up to years after hospital discharge, as documented by cross-sectional studies.
- It remained unclear how development of individual patients evolves over time after PICU discharge compared with the normal developmental trajectory of healthy children.
- To assess whether former PICU patients "grow-into" or "grow-out-of" their developmental legacy over time, we performed a within-individual longitudinal study of patients from 2 to 4 years after critical illness, in parallel with similar follow-up of matched healthy children.

KEY WORDS: children; critical illness; neurocognitive development; physical development; pediatric intensive care unit; within-individual longitudinal study

Children who have been critically ill and required PICU admission face long-term physical, emotional/behavioral, and neurocognitive developmental problems (1–5). These deficits can remain up to years after discharge and can have a negative impact on the children's daily and academic functioning. Longitudinal studies on the evolution over time of these impairments are scarce and have focused on small specific subgroups of children who underwent surgery for congenital heart disease or suffered from traumatic brain injury (6–9). These studies yielded apparently conflicting results going from worsening of impairments, no effect over time, to partial catch-up toward performance of healthy children. Part of the long-term legacy of critical illness may be preventable through altering aspects of intensive care, such as omitting early use of parenteral nutrition (PN) (1, 3, 4). Indeed, providing full nutritional intake early with PN to supplement insufficient enteral nutrition ("early-PN") has shown to be clinically inferior to accepting an early macronutrient deficit by postponing PN to beyond the first week in PICU ("late-PN"). Indeed, the Pediatric Early versus Late Parenteral Nutrition in Intensive Care Unit randomized controlled trial (PEPaNIC-RCT) demonstrated that early-PN caused more PICU-acquired infections and delayed recovery from the illness (10). Early-PN patients also showed worse long-term development of executive functions and/or emotional and behavioral problems compared with late-PN patients, with vulnerability depending on age at exposure (3, 4, 11). Aberrant de novo changes in DNA methylation, arising rapidly during PICU stay, were identified as a plausible molecular basis of the long-term effects, as they statistically explained at least part of the adverse effect of critical illness and early-PN on neurocognitive development (12–14).

Although the developmental problems and the impact hereon of in-PICU nutritional management have been documented cross-sectionally at 2 and 4 years after critical illness, it remains unclear how development of individual patients evolves over time compared with the normal developmental trajectory of healthy children. To assess, in a more sensitive manner, whether former PICU patients "grow-into" or "out-of" their physical, emotional/behavioral, and neurocognitive developmental legacy over time, a within-individual longitudinal study of patients and healthy children is required.

MATERIALS AND METHODS

Study Design and Participants

This is a preplanned secondary analysis of the multicenter PEPaNIC-RCT (Leuven-Rotterdam-Edmonton, ClinicalTrials.gov-NCT01536275) that enrolled 1,440 critically ill children from 2012 to 2015 and its 2- (2014–2018) and 4-year (2016–2019) cross-sectional follow-up studies (3, 4, 10). The study protocol has been published (15). Longitudinal assessment at both follow-up time points for anthropometrics, emotional/behavioral problems, and neurocognitive functions allowed analysis of time-courses for 614 patients (297 early-PN and 317 late-PN) and 357 demographically matched healthy children (**Fig. 1**). Information on participants, written informed consent, and institutional review board approval are described in **Supplemental Digital Content Methods S1** (http://links.lww.com/PCC/C63).

In the PEPaNIC-RCT, patients had been randomly allocated to "early-PN" or "late-PN" (10, 15). In the

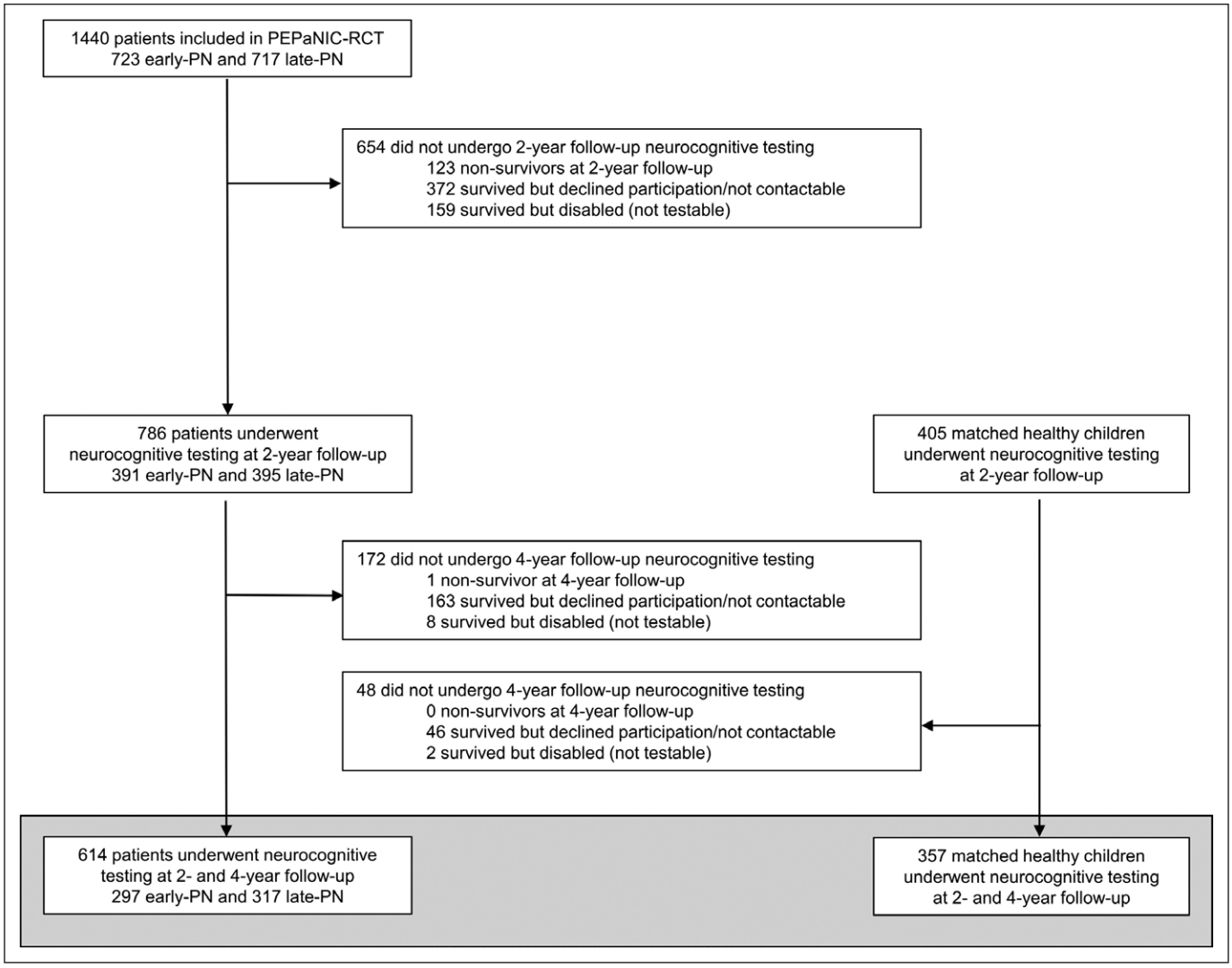

Figure 1. Consort diagram of the study participants. PEPaNIC = pediatric early versus late parenteral nutrition in ICU, PN = parenteral nutrition, RCT = randomized controlled trial.

early-PN group, supplemental PN was initiated within 24 hours after PICU admission to supplement enteral nutrition (oral intake or intake via nasogastric or nasoduodenal tube) whenever 80% of targeted calories per age and weight categories was not yet reached. In the late-PN group, supplemental PN was withheld in the first week of PICU stay (meaning no PN for patients discharged before day 8), and patients parenterally only received a glucose 5%/sodium chloride 0.9% mixture to match fluid intake. After 1 week, for both groups equally, PN could be administered if necessary. When enteral nutrition covered 80% or more of calculated targets, supplemental PN was discontinued. Enteral nutrition was initiated early for both groups equally, and all patients received IV micronutrients.

At follow-up, participants were assessed for developmental outcomes, at the hospital or at home, by physicians and experienced pediatric psychologists who had not been involved in the PICU care of the patients and who were strictly blinded regarding treatment allocation (3, 4). The same psychologists who tested most of the children at the 2-year follow-up also tested most of the children at the 4-year follow-up. Parents had not been masked for treatment allocation during the child's PICU stay and were not actively informed about the findings of the initial PEPaNIC-study or 2-year follow-up study. Parents did receive a report on their child's performance after the neurocognitive testing at both follow-up time points.

Developmental Outcomes

Physical development was assessed via measurement of head circumference, body weight, and height. A

clinical neurologic examination was performed to assess gross neurologic abnormalities. Performance for a broad range of emotional/behavioral and neurocognitive functions was assessed with validated internationally recognized, age-adjusted questionnaires, and clinical tests with adequate normative data. Parents or caregivers completed Behavior Rating Inventory of Executive Function questionnaires (16, 17) on executive functioning and Child Behavior Checklist (18, 19) questionnaires on emotional and behavioral problems of their child. Clinical tests consisted of age-appropriate versions of the Wechsler Intelligence Quotient Scale (20–22) to assess intelligence, the Beery Developmental Test of Visual-Motor Integration (23) to assess visual-motor integration, tasks of the Amsterdam Neuropsychologic Task Battery (24) to assess alertness and motor coordination (for children 4 yr old or older), and the Children's Memory Scale (25) to assess memory (for children aged 5–16 yr). The developmental outcomes and available data are more extensively described in **Supplemental Digital Content Methods S2** and **Table S2** (http://links.lww.com/PCC/C63) (3, 4, 26).

Statistical Analyses

Demographics and medical characteristics of early-PN and late-PN patients and healthy control children were summarized, with differences between groups analyzed with a χ^2, Student *t* test, or Wilcoxon rank-sum test, as appropriate.

First, the within-group evolution over time of physical, emotional/behavioral, and neurocognitive functionings of the former PICU patients and control children and of former early-PN versus late-PN PICU patients was assessed with repeated-measures analysis of variance, and differences in these time-courses between the groups were assessed by univariate significance assessment of the interaction between time and group.

Subsequently, to investigate to what extent the critical illness and use of early-PN versus late-PN in the PICU, independent of other risk factors, was associated with any differences in the time-course of the developmental outcomes, multivariable linear regression analyses were performed adjusted for risk factors. To this end, for each outcome, the difference between the scores at 2- and 4-year follow-up ("delta," 4-yr follow-up minus 2-yr follow-up) was calculated per individual and entered into the model as the dependent variable. Adjustments were done for age, center, gender, race, geographic origin, language, hand preference, history of malignancy, a history of a predefined "syndrome" (**Supplemental Digital Content Methods S3**, http://links.lww.com/PCC/C63), and the educational and occupational statuses of the parents/caregivers (**Supplemental Digital Content Methods S4**, http://links.lww.com/PCC/C63). For the comparison between the early-PN and late-PN groups, additional adjustment was done for admission diagnosis, severity of illness upon PICU admission (PIM3 and PeLOD scores), risk of malnutrition (Screening Tool for Risk on Nutritional Status and Growth), and parental smoking behavior prior to PICU admission.

Data are presented as numbers and proportions, means and SD, or beta-estimates with 95% CIs.

Statistical analyses were performed with JMP15.0.0 (SAS Institute, Cary, NC). Two-sided *p* values of 0.05 or lower were considered statistically significant. As the studied developmental outcomes are not independent, correction for multiple comparisons was not performed (4, 27).

RESULTS

On average, the 4-year follow-up was performed 1.9 years (SD, 0.2 yr) after the 2-year follow-up, for early-PN and late-PN patients ($p = 0.59$) as well as for patients and healthy children ($p = 0.24$). Early-PN patients were tested at mean age 5.5 (4.3) and 7.4 (4.3) years, late-PN patients at mean age 5.3 (4.1) and 7.2 (4.2) years, and demographically matched healthy children at age 5.6 (4.3) and 7.5 (4.3) years. Demographics and medical characteristics of former PICU patients and healthy children are shown in **Table 1** and **Supplemental Digital Content Table S1** (http://links.lww.com/PCC/C63). Total macronutrient doses administered on each of the first 7 days in PICU are shown in **Supplemental Digital Content Figure S1** (http://links.lww.com/PCC/C63).

Evolution of Physical, Emotional/Behavioral, and Neurocognitive Functions of Former PICU Patients Versus Healthy Control Children Over the 2-Year Time-Window

Evolution of the developmental outcomes over time is illustrated in **Figure 2** and **Supplemental Digital Content Figure S2** (http://links.lww.com/PCC/C63).

TABLE 1.
Demographics and Medical Characteristics of Former PICU Patients and Healthy Children Tested at 2- and 4-Year Follow-Up

Demographics of Participants and Medical Characteristics of Patients	Healthy Control Children (*n* = 357)	Former PICU Patients (*n* = 614)	*p*
Age at 2-yr follow-up–median (IQR)/mean (SD), yr	3.6 (2.6–7.4)/5.6 (4.3)	3.1 (2.6–6.5)/5.4 (4.2)	0.40
Age at 4-yr follow-up–median (IQR)/mean (SD), yr	5.5 (4.4–9.2)/7.5 (4.3)	5.1 (4.4–8.5)/7.3 (4.3)	0.31
Male sex–*n* (%)	193 (54.1)	353 (57.5)	0.29
Known non-Caucasian race[a]–*n* (%)	26 (7.3)	48 (7.8)	0.76
Known non-European origin[a]–*n* (%)	44 (12.3)	111 (18.1)	**0.01**
Known not exclusive Dutch or English language–*n* (%)	67 (18.8)	138 (22.5)	0.16
Socioeconomic status[b,c]			
Parental educational level 1–*n* (%)	25 (7.0)	77 (12.5)	**< 0.0001**
Parental educational level 2–*n* (%)	112 (31.4)	261 (42.5)	
Parental educational level 3–*n* (%)	205 (57.4)	176 (28.7)	
Parental educational level unknown–*n* (%)	15 (4.2)	100 (16.3)	
Parental occupational level 1–*n* (%)	20 (5.6)	66 (10.8)	**< 0.0001**
Parental occupational level 2–*n* (%)	65 (18.2)	165 (26.9)	
Parental occupational level 3–*n* (%)	118 (33.1)	164 (26.7)	
Parental occupational level 4–*n* (%)	112 (31.4)	95 (15.5)	
Parental occupational level unknown–*n* (%)	42 (11.8)	124 (20.2)	
Infant (age < 1 yr) at randomization–*n* (%)	NA	294 (47.9)	/
Screening Tool for Risk on Nutritional Status and Growth risk level[d], medium/high–*n* (%)	NA	551 (89.7)/63 (10.3)	/
Pediatric Logistic Organ Dysfunction score, first 24 hr in PICU[e]–mean (SD)	NA	20.0 (11.5)	/
PIM3 score[f]/PIM3 probability of death[g] (%)–mean (SD)	NA	–3.5 (1.3)/6.6 (11.6)	/
Diagnostic category			
Surgical–abdominal–*n* (%)	NA	57 (9.3)	
Surgical–burns–*n* (%)	NA	2 (0.3)	
Surgical–cardiac–*n* (%)	NA	264 (43.0)	
Surgical–neurosurgery-traumatic brain injury–*n* (%)	NA	51 (8.3)	
Surgical–thoracic–*n* (%)	NA	35 (5.7)	
Surgical–transplantation–*n* (%)	NA	10 (1.6)	
Surgical–orthopedic surgery-trauma–*n* (%)	NA	19 (3.1)	
Surgical–other–*n* (%)	NA	21 (3.4)	
Medical–cardiac–*n* (%)	NA	22 (3.6)	
Medical–gastrointestinal-hepatic–*n* (%)	NA	2 (0.3)	
Medical–oncologic-hematologic–*n* (%)	NA	5 (0.8)	
Medical–neurologic–*n* (%)	NA	35 (5.7)	
Medical–renal–*n* (%)	NA	0 (0.0)	
Medical–respiratory–*n* (%)	NA	64 (10.4)	
Medical–other–*n* (%)	NA	27 (4.4)	

(*Continued*)

TABLE 1. (*Continued*).
Demographics and Medical Characteristics of Former PICU Patients and Healthy Children Tested at 2- and 4-Year Follow-Up

Demographics of Participants and Medical Characteristics of Patients	Healthy Control Children (*n* = 357)	Former PICU Patients (*n* = 614)	*p*
Malignancy–*n* (%)	0 (0.0)	36 (5.9)	**< 0.0001**
Diabetes–*n* (%)	0 (0.0)	0 (0.0)	> 0.99
Syndrome[h]–*n* (%)	2 (0.5)	58 (9.5)	**< 0.0001**

IQR = interquartile range; NA = not applicable; PIM3 = Pediatric Index of Mortality 3.
[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 educational level is the average of the paternal and maternal educational levels, which were calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Central Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2), and high (=3) educational level (Supplemental Digital Content Methods S3, http://links.lww.com/PCC/C63).
[c]The occupational level is the average of the paternal and maternal occupational level, which is calculated based on the International ISCO System 4-point scale for professions (Supplemental Digital Content Methods S3, http://links.lww.com/PCC/C63).
[d]Scores on the Screening Tool for Risk on Nutritional Status and Growth range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1–3 indicating medium risk, and a score of 4–5 indicating high risk.
[e]Pediatric Logistic Organ Dysfunction 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]PIM3 probability of death.
[h]A prerandomization syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Supplemental Digital content Methods S2, http://links.lww.com/PCC/C63).
Boldface values indicate a significant difference ($p \leq 0.05$).

At both time points, former PICU patients had inferior scores when compared with healthy children for almost all assessed outcomes ($p \leq 0.01$). The analyses of interaction between time and group (former PICU patients and healthy children), assessing differences in time-course from 2- to 4-year follow-up, revealed that, compared with healthy children, former PICU patients grew less in height though similarly in weight and, thus, showed a relative rise in body mass index. Additionally, former PICU patients deviated further away from the healthy children for the parent- or caregiver-reported executive function metacognition, measures of intelligence (total and verbal intelligence quotient [IQ]), motor coordination (alternating and synchronous tapping) and memory learning-index, either because of a less pronounced improvement or a worsening of the performance. In contrast, patients partially improved over time compared with healthy children for several verbal memory functions (working memory numbers backward, and immediate and delayed memory with regard to word pairs), and hence, for these outcomes, the differences between patients and controls became smaller over time.

Adjusted for other risk factors, prior critical illness was independently associated with less growth in height over the 2 years and with a further impairment of even more parent- or caregiver-reported executive functions than those that were already obvious in the above-reported univariable repeated-measures analyses (flexibility, emotional control, metacognition, and total executive functioning) (**Table 2**). This was also the case for measures of intelligence (total IQ and verbal IQ). In contrast, the deficit decreased over time for alertness as evaluated by reaction time of the right hand and for several memory functions (working memory numbers backward, immediate and delayed memory and recognition with regard to word pairs, and visual memory for pictures).

Evolution of Physical, Emotional/Behavioral, and Neurocognitive Functions of Former Early-PN Versus Late-PN PICU Patients Over the 2-Year Time-Window

The analyses of interaction between time and group (former early-PN and late-PN PICU patients), assessing differences in time-course from 2- to 4-year

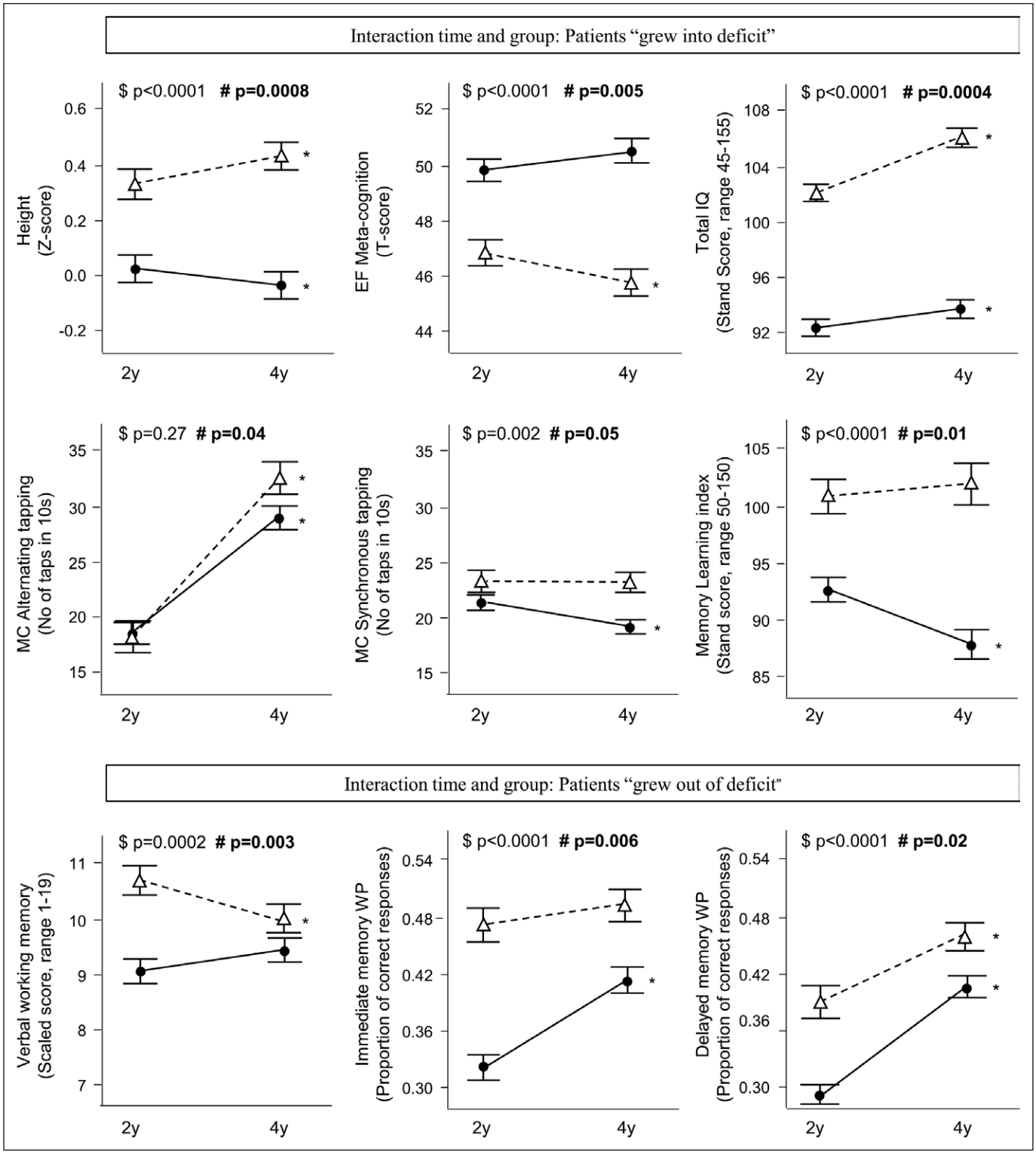

Figure 2. Univariable analyses of the evolution of height, metacognition, and clinically tested neurocognitive functions of PICU patients versus healthy control children over time from 2- to 4-year follow-up. Results are presented as mean and SE. Outcomes are illustrated for which PICU patients (*dots, full line*) significantly worsened ("grew into deficit") or improved ("grew out of deficit") compared with healthy control children (*triangles, dotted line*) from 2- to 4-year follow-up. For height, age- and gender-adjusted *z* scores were calculated with the use of reference data from the World Health Organization Growth Charts. For the parent- or caregiver-reported executive functioning (EF), higher scores reflect worse performance. For intelligence, motor coordination (MC) and memory tests, higher scores reflect better performance. *p value ≤ 0.05 for the univariable comparison of the evolution over time within former PICU patients or within healthy controls separately. $Group p value for the univariable comparison between groups at both time points (former PICU patients and healthy children). #Interaction p value comparing the evolution over time between groups (former PICU patients vs healthy controls). IQ = intelligence quotient, Stand score = Standardized score, WP = word pairs.

TABLE 2.

Multivariable Analyses of the Evolution of Physical, Emotional/Behavioral, and Neurocognitive Functions of Former PICU Patients Versus Healthy Control Children Over Time From 2- to 4-Year Follow-Up

Outcomes Assessed at 2- and 4-Year Follow-Up[a]	No Available Data per Outcome	β-Estimate (95% CI)[b]	*p*
Anthropometrics[c] and physical examination			
Height (*z* score)	941	−0.05 (−0.10 to 0.00)	**0.04**
Weight (*z* score)	941	0.00 (−0.04 to 0.05)	0.89
Body mass index (*z* score)	941	0.05 (−0.01 to 0.11)	0.10
Head circumference (*z* score)	971	−0.02 (−0.08 to 0.04)	0.54
Clinical neurologic evaluation (range, 0–8)	971	−0.01 (−0.02 to 0.01)	0.33
Outcomes reported by parents or caregivers (*T* score)			
Executive functioning–inhibition	941	0.42 (−0.24 to 1.08)	0.21
Executive functioning–flexibility	941	0.66 (0.00–1.33)	**0.05**
Executive functioning–emotional control	941	0.70 (0.03–1.38)	**0.04**
Executive functioning–working memory	941	0.56 (−0.13 to 1.25)	0.10
Executive functioning–planning and organization	941	0.44 (−0.24 to 1.13)	0.20
Executive functioning–metacognition	941	0.90 (0.20–1.60)	**0.01**
Executive functioning–total score	941	0.67 (0.00–1.34)	**0.05**
Emotional/behavioral problems–internalizing problems	941	−0.10 (−0.83 to 0.62)	0.77
Emotional/behavioral problems–externalizing problems	941	0.17 (−0.48 to 0.81)	0.61
Emotional/behavioral problems–total problems	941	0.05 (−0.63 to 0.72)	0.89
Clinical neurocognitive tests			
Intelligence (range, 45–155)–total IQ	971	−0.99 (−1.77 to −0.21)	**0.01**
Intelligence (range, 45–155)–verbal IQ	971	−1.59 (−2.48 to −0.70)	**0.0005**
Intelligence (range, 45–155)–performance IQ	971	0.04 (−0.82 to 0.90)	0.92
Visual-motor integration (range, 0.9–20)	971	0.02 (−0.16 to 0.19)	0.86
Alertness (*z* score)[d]–reaction time right hand	418	−0.26 (−0.50 to −0.01)	***0.03***
Alertness (*z* score)[d]–within subject SD of repeated tests	418	−0.24 (−0.50 to 0.02)	0.07
Alertness (*z* score)[d]–reaction time left hand	418	−0.08 (−0.29 to 0.14)	0.48
Alertness (*z* score)[d]–within-subject SD of repeated tests	418	−0.07 (−0.33 to 0.20)	0.62
Motor coordination (No. of taps in 10s)–No. of taps right hand	418	0.08 (−0.83 to 0.99)	0.86
Motor coordination (No of taps in 10s)–No. of unimanual taps left hand	418	−0.32 (−1.21 to 0.58)	0.49
Motor coordination (No. of taps in 10s)–No. of valid alternating taps	418	−1.02 (−3.01 to 0.96)	0.31
Motor coordination (No. of taps in 10s)–No. of valid synchronous taps	418	−0.55 (−1.69 to 0.60)	0.35
Verbal-auditory memory numbers (range, 1–19)–memory span (forward)	286	0.37 (−0.03 to 0.77)	0.06
Verbal-auditory memory numbers (range, 1–19)–working memory (backward)	286	0.54 (0.14–0.94)	***0.009***

(*Continued*)

TABLE 2. (*Continued*).

Multivariable Analyses of the Evolution of Physical, Emotional/Behavioral, and Neurocognitive Functions of Former PICU Patients Versus Healthy Control Children Over Time From 2- to 4-Year Follow-Up

Outcomes Assessed at 2- and 4-Year Follow-Up[a]	No Available Data per Outcome	β-Estimate (95% CI)[b]	*p*
Memory word pairs[e]—learning	286	−0.01 (−0.03 to 0.02)	0.70
Memory word pairs[e]—immediate memory	286	0.04 (0.02–0.07)	***0.001***
Memory word pairs[e]—delayed memory	286	0.03 (0.01–0.05)	***0.01***
Memory word pairs[e]—recognition	286	0.02 (0.00–0.03)	***0.03***
Nonverbal, visual-spatial memory—pictures[e]	286	0.02 (0.00–0.03)	***0.05***
Nonverbal, visual-spatial memory—dots, learning[e]	286	0.00 (−0.02 to 0.02)	0.70
Nonverbal, visual-spatial memory—dots, immediate memory[e]	286	0.01 (−0.03 to 0.03)	0.75
Nonverbal, visual-spatial memory—dots, delayed memory[e]	286	−0.00 (−0.04 to 0.04)	0.91
Memory learning index (range, 50–150)	286	−2.20 (−4.78 to 0.38)	0.09

IQ = intelligence quotient.

[a]For the clinical neurologic 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 alertness and within 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 difference in scores, "delta" adjusted for risk factors.

[c]Age- and gender-adjusted *z* scores were calculated with the use of reference data from the World Health Organization Growth Charts.

[d]Age-adjusted *z* scores were calculated.

[e]Proportion correct responses.

The "delta" of scores for the different tests was calculated as the score at 4-year follow-up minus the score at 2-year follow-up.

Outcomes with *p* values in boldface and italic font represent an improvement in patients compared with healthy controls over time; outcomes with *p* values in boldface font represent a worsening in patients compared with healthy controls over time.

Boldface values indicate a significant difference ($p \leq 0.05$).

follow-up, revealed that time-courses of physical, emotional/behavioral, and neurocognitive functions were largely unaffected by early-PN versus late-PN. Only for visual-motor integration, alertness, and for one verbal memory function, former early-PN PICU patients partially improved over time compared with former late-PN PICU patients (**Supplemental Digital Content Figure S3**, http://links.lww.com/PCC/C63).

Also, when adjusting for other risk factors, time-courses in physical, emotional/behavioral, and neurocognitive functions were largely unaffected by early-PN versus late-PN, except for the functions that were already obvious in the above-reported univariable repeated-measures analyses (a limited catch-up of early-PN patients toward late-PN patients for visual-motor integration and alertness). Additionally, a relative weight loss in early-PN patients compared with late-PN patients was documented (**Supplemental Digital Content Table S3**, http://links.lww.com/PCC/C63).

DISCUSSION

This within-individual longitudinal study showed that, compared with healthy children, most physical, emotional/behavioral, and neurocognitive deficits observed in former PICU patients did not recover from 2 to 4 years after PICU admission. In contrast, deficits were found to aggravate over time for growth in height (but not weight), the executive function metacognition, intelligence, motor coordination, and memory learning-index, whereas only verbal memory deficits became somewhat smaller. Adjustment for other risk factors largely confirmed that these findings could be attributed independently to the critical illness and revealed that patients "grew-into-deficit" for even more executive functions and "grew-out-of-deficit" for even more memory functions. Time-courses were largely similar for early-PN patients and late-PN patients, except for a relative weight loss in early-PN patients and a limited

WHAT THIS STUDY MEANS

- Most physical, emotional/behavioral, and neurocognitive deficits observed in former PICU patients did not show improvement from 2 to 4 years after PICU discharge, with several deficits even aggravating over time.
- Follow-up of critically ill children should not be limited to the first year(s) after PICU admission and further study of the impact of pediatric critical illness, and the nutritional management in the PICU on development into adulthood is needed.
- Families and caregivers of former PICU patients should be informed about potential longer term consequences, possibly deteriorating over time.

catch-up of these patients toward late-PN patients for visual-motor integration and alertness.

This study, with its within-individual longitudinal design and adjustment for known risk factors, allowed to assess in a sensitive manner whether former PICU patients "grow-into" or "out-of" their physical, emotional/behavioral, and neurocognitive developmental legacies from a mean age of about 5 years to a mean age of about 7 years. The results were rather pessimistic, showing that many developmental deficits remained unaltered or got worse, and only a few memory functions partially improved. Our finding that some developmental outcomes did improve and others deteriorated is in line with the at-first-sight conflicting outcomes of previous smaller studies with variable focus and design (6–9). Also, the observation that the neurocognitive harm evoked by early use of PN in the PICU only showed limited and partial recovery was disappointing. Together, these data suggest that pediatric critical illness and its treatments may have a long-persisting negative impact. A longer within-individual follow-up trajectory is needed to investigate whether there will be permanent consequences for academic and daily functioning of these former PICU patients. Indeed, neurocognitive functions mature throughout development into young adulthood, with gradual further development of the more complex functions. This implies that increasing deficits could emerge later at a time when more complex functions are developing and require brain structures that may have been damaged during earlier stages. As such, cognitive impairments may be somehow latent or less pronounced early in development and become more prominent later (28). This could explain the "growing-into-deficit" phenomenon (29). In contrast, there may also be a certain plasticity of brain areas after an insult, which could allow catch-up development over time that could explain the "growing-out-of-deficit" (30). However, in the current study, with a time interval from 2 towards 4 years after critical illness, any "growing-out-of-deficit" appeared rather limited.

Instead, we observed a "growing-into-deficit" from 2 to 4 years after PICU admission for several executive functions as reported by parents or caregivers, for intelligence and the memory learning-index, in this heterogeneous cohort of critically ill children compared with the normal trajectory of demographically matched healthy children. An executive function that appeared to be affected was metacognition. This represents the ability to control one's own cognitive processes, especially when engaged in learning, and the ability to control the effect of one's own behavior on other people (16). Since parents of PICU children did not report more emotional and behavioral problems over time, the aggravation of metacognition problems for these children is likely attributable to difficulties in the children's ability to control their own cognitive processes over time. The less-developed metacognition may have hampered learning and is, thus, also reflected in an impaired learning-index for memory tasks and a less-pronounced improvement in general and verbal intelligence, compared with healthy children. Earlier smaller longitudinal studies of patients who underwent surgery for congenital heart diseases did not find such a different trajectory in patients and controls for clinically tested executive functions from ±4 to ±7 years after PICU admission (6, 7). This could be due to the underlying pathology or different evaluation methodologies, or could suggest that the deficit stabilized around 4 years post-PICU. For measures of intelligence, both patients and healthy children improved over time, but patients improved much less. A nonsignificant trend toward a growing-into-deficit for intelligence has been observed in children undergoing surgery for transposition of the great arteries

from 5- to 10-year post-PICU (9). In pediatric survivors of Neisseria meningitides-induced septic shock, older age at follow-up combined with younger age at time of illness predicted a lower verbal comprehension-index as IQ subscale, which may indirectly support an aggravation of the IQ deficit with time in a nonlongitudinal design (31). In contrast, IQ showed parallel trajectories in meningitis survivors and controls from 7- to 12-year postillness (32), and children who underwent surgery for congenital heart diseases even showed some growing-out of the IQ deficit from 4 to 7 years after PICU admission (6). Several factors may contribute to differential findings among the studies, including sample size, underlying pathology, and age of the studied children at time of insult and follow-up.

Our study revealed some "growing-out-of" the deficits for several memory functions in patients compared with healthy children over time and one alertness test. The catch-up of memory functions may be explained by the high degree of plasticity of neuronal networks important for memory. After temporal lobe resection for epilepsy, postoperative improvements in memory domains were shown to occur already within 1 year (33, 34), whereas IQ changes are usually seen much later after surgery (35). One could speculate that memory functions recover faster than the more complex functions necessary for executive and intellectual functioning or that patients adapt to their memory deficits over time using compensatory mechanisms. Partial improvement in alertness was also observed from 4 to 7 years after PICU admission in children who underwent surgery for congenital heart diseases (6).

For the other assessed developmental domains, including growth, visual-motor integration, and emotional/behavioral problems, the observed deficits in patients remained stable and important. This is in agreement with previous observations in children from 4 to 7 years after surgery for congenital heart diseases (6). In contrast, two nonlongitudinal studies suggested a "growing-into-deficit" for behavioral problems after traumatic brain injury or brain tumor surgery, based on interaction with time since injury or correlation with age at assessment (36, 37).

The major strength of this study is the longitudinal, parallel developmental follow-up of large groups of former PICU patients and demographically matched developing healthy children with a broad range of validated internationally recognized age-adjusted tests. The study also has some limitations. First, the children were young, and the follow-up focused only on the evolution from 2 to 4 years after PICU admission, a relatively short time period to evaluate development. Our findings can thus not be generalized to further development beyond this timeframe, which needs further investigation. Second, we studied a heterogeneous patient population and, hence, cannot exclude that patients with different underlying illnesses could show a different evolution in the studied outcomes. Third, due to test-age limitations, some functions could not be assessed for all participants. Conclusions for evolution of alertness and motor coordination are based on children who were 2 years or older and those for memory functions on children 3 years or older at the time of PICU admission or recruitment as healthy control. Fourth, we did not have systematic information on access to rehabilitative and follow-up care, though did adjust for socioeconomic status. In addition, potential impact of post-PICU nutritional status or of hospital readmissions within the studied timewindow was not assessed. Fifth, we did not correct for multiple comparisons given the exploratory nature of our study and given that the studied developmental outcomes are not independent, which invalidates the use of a stringent statistical correction. Risk of false-positive findings cannot be completely excluded. Finally, no neuroimaging correlates were investigated.

CONCLUSIONS

From 2 to 4 years after PICU admission, the developmental legacy of former PICU patients remained prominent. Impaired growth in height, executive functioning, and intelligence further aggravated and impaired memory and harm evoked by early-PN only partially recovered. These data emphasize that care for and assessment of critically ill children cannot stop at hospital discharge and stress the importance of following-up the children even beyond the first few years after PICU admission. Thus, the impact of pediatric critical illness and the nutritional management in the PICU on development of these children into adulthood should be further investigated.

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