Harm caused by early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments

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ABSTRACT

Background

Large RCTs have shown harm from early supplemental parenteral nutrition in adult and paediatric ICUs. Overdosing of energy with too little protein was suggested as potential reason. This study analysed which macronutrient was associated with harm caused by early supplemental parenteral nutrition in the randomised PEPaNIC trial.

Methods

Doses of glucose, lipid, and protein/amino acids, administered during the first seven days, were expressed as percentages of reference doses for age/weight. Independent associations between average doses up to each of these days and likelihood of acquiring an infection in the paediatric ICU (PICU), of earlier live weaning from mechanical ventilation, and of earlier live PICU discharge were investigated through multivariable Cox proportional hazard analyses, simultaneously entering the three macronutrients and adjusting for baseline risk factors.

Findings

With increasing doses of amino acids, the likelihood of acquiring a new infection was higher (adjusted hazard ratios (HRs) per ten percent increase between 1·043-1·134 for days one to five, P≤0·029), while that of earlier live weaning from mechanical ventilation (HRs 0·950-0·975 days three to seven, P≤0·045) and earlier live PICU discharge (HRs 0·943-0·972 days one to seven, P≤0·030) was lower. In contrast, more glucose during the first three days was independently associated with fewer infections (HRs 0·870-0·913, P≤0·036), whereas more lipids independently associated with earlier PICU discharge (HRs 1·027-1·050, P≤0·043 days four to seven). Risk of harm with amino acids was already shown for low doses.

Interpretation

These associations suggest that early administration of amino acids, but not glucose or lipid, could explain harm caused by early supplemental parenteral nutrition in critically ill children.

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Key words

Critical illness, paediatrics, glucose, lipids, amino acids, clinical outcome

INTRODUCTION

In critically ill children treated in the paediatric intensive care unit (PICU), macronutrient intake is often very limited because of inability to feed orally and intolerance of feeding administered via nasogastric tubes. The severity of such assumed macronutrient deficit was found to correlate with risk of infections, muscle weakness, prolonged mechanical ventilation, and delayed recovery.[1–3] These associations formed the basis for guidelines recommending initiation of nutritional support early, if necessary via the parenteral route when enteral feeding is insufficient.[4–6] A recent worldwide survey on nutritional practices in PICU revealed that early initiation of parenteral nutrition is a common practice and that 72 percent of the PICUs administer supplemental parenteral nutrition whenever less than 50 percent of the energy goal can be met with enteral nutrition.[7] However, the first multicenter randomised controlled trial (RCT) that investigated whether early supplemental parenteral nutrition (PN) is beneficial for critically ill children, the "Paediatric Early versus Late Parenteral Nutrition In Critical Illness" trial (PEPaNIC), found the opposite. Not giving PN up to one week in the PICU, thus accepting a large macronutrient deficit, was clinically superior to early PN administration.[8,9] This strategy prevented infections and accelerated recovery, with a shorter duration of mechanical ventilation and intensive care. These results corroborated those from an earlier multicenter RCT in adult ICU patients (EPaNIC trial).[10] Also other adult RCTs have questioned benefit from early full-dose nutrition in the ICU.[11–14]

As the results of the EPaNIC and PEPaNIC trials were perceived as unexpected, but could not be attributed to the route of administration,[15] the findings were interpreted as caused by overdosing of energy, in particular glucose, whereas protein/amino acid doses, that were lower than recommended for age/weight, were considered too low to be of any potential benefit.[16,17] In that regard, experts advise higher amino acid doses during critical illness to improve outcome, although high-level evidence in favor of this strategy is lacking.[18,19] In contrast, suspicion has been raised earlier about potential harm by high protein intake early during critical illness.[20] Such potential harm was further supported by *post-hoc* analysis of the EPaNIC trial showing that infusion of amino acids, rather than glucose, delayed

recovery[21] and profoundly increased ureagenesis.[22] However, the use of an all-in-one product precluded assessment of any separate impact of the three macronutrient classes. In the PEPaNIC trial, glucose, lipid, and amino acid doses were titrated separately over a wide range.[8,9] This allowed investigating which macronutrient is associated with harm evoked by early PN.

METHODS

Patients

This is a pre-planned secondary analysis of the multicenter PEPaNIC study (ClinTrials.gov NCT01536275, N=1440) of which the primary results have been published.[8,9] In brief, critically ill children (term-newborn to 17-years old) who had a medium to high risk of malnutrition and who had a central venous line in place for clinical purposes were randomised to early or late PN (supplemental_table_S1). In both patient groups, enteral nutrition was initiated as soon as possible. In patients randomised to the control group (full-feeding with early PN), PN was initiated within 24 hours after PICU admission to supplement any insufficient enteral nutrition to reach the local caloric and macronutrient targets. PN was continued until patients received 80 percent of the caloric target enterally. In patients assigned to the intervention group (restricted-feeding with late PN), PN was withheld during the first week in PICU. In this group, a mixture of dextrose 5 percent and saline was administered to match the fluid intake with that of early PN, taking into account volume of enteral nutrition. For patients from both groups who were still in the PICU on the morning of day eight and who were not yet receiving 80 percent of the caloric target enterally, PN was administered to reach the targets. All patients received intravenous trace elements, minerals, and vitamins early to prevent refeeding syndrome and blood glucose control with insulin according to local target ranges. If the central venous line was no longer in place for clinical purposes, any required parenteral nutrition was delivered via a peripheral line. Outcome assessors and investigators not directly involved in patient care were blinded to randomisation. For a more extensive description of patient characteristics, we refer to the original publication.[9] Written informed consent was obtained from the parents or legal guardians. The institutional/national ethical review boards of the participating centers approved the study protocol. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments.

Clinical endpoints

The clinical endpoints investigated for the current research question were time to the first new infection acquired in the PICU, time to live weaning from mechanical ventilatory support, and time to live discharge from PICU accounting for mortality as a competing risk. Time of discharge from PICU was *a priori* defined as the moment when a patient no longer required, or was no longer at risk of requiring, vital organ support.[10] Plasma urea concentrations were measured from day one to day seven on a routine clinical basis.

Transformation of the given macronutrient doses to a unity that allows comparison between glucose, lipid, and amino acids for children of different ages and weights

Doses of glucose, lipid, and amino acids that were given were transformed from crude grams per day into a percentage of reference doses for age and weight published in nutritional guidelines[4,23] (summarised in supplemental_table_S2 and figure_S1). These reference doses were not necessarily those that were used locally as nutritional targets. They were only used for the current analysis, which required expression of the administered doses of the three macronutrients in an interchangeable and comparable unity for children of different ages and weights, without which the analyses would be flawed.

Statistical analysis of associations between doses of the three macronutrients and the clinical endpoints

As the PEPaNIC RCT investigated the impact on outcome of late versus early PN over the first seven days, with doses that were titrated up differently for each macronutrient, we analysed the independent associations with the clinical outcomes of the average daily total doses of each macronutrient class,

expressed as percentage of reference doses, up to each of the seven days for all patients who were still in PICU on these respective days (supplemental_figure_S1).

Log-rank testing was used for univariable time-to-event analyses, illustrated with Kaplan-Meier plots. Effect sizes of time-to-event analyses [hazard ratios (95 percent confidence intervals)] were estimated with multivariable Cox proportional hazard analysis, censored at 90 days, without and with left-truncation. Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. In a sensitivity analysis accounting for death as competing risk, patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death. In addition, associations with acquisition of a new infection were investigated with multivariable logistic regression analysis. To account for death as competing risk in the analysis of the association with duration of mechanical ventilatory support and duration of PICU stay, non-surviving patients were censored beyond all survivors at 91 days. The multivariable analyses studied associations with the clinical endpoints of doses of the three macronutrients entered together into the model as continuous variables in place of the randomisation group, adjusted for predefined baseline risk factors. These were type of illness (diagnostic groups) and age group (<1 year versus ≥1 year) on which stratification for randomisation was based,[9] severity of malnutrition risk (STRONGkids score dichotomised for "medium risk" (score 2-3) and "high risk" (score 4-5)),[24] severity of illness (Paediatric Index of Mortality-2 (PIM2)[25] score estimating mortality risk and Paediatric Logistic Organ Dysfunction (PELOD)[26] score of the first 24 hours estimating severity of organ dysfunction), and treatment centre. Median PIM2-calculated probability of death in PICU was 5·9 (IQR 2·5-17·7) percent for an observed 4·7 percent PICU mortality. The PIM2 score's univariable aROC for PICU mortality was 0·91. As the PIM2 score was not used in the original PEPaNIC trial, analyses were repeated with omission of PIM2 from the models.[8,9] In sensitivity analyses, we further studied whether any of the previous associations were different for censoring at 28 days, for patients in the Early PN or Late PN groups or for the enteral or parenteral route via which the macronutrients were administered.

To further investigate a possible dose response or threshold for harm, average daily total doses of macronutrients, expressed as percentage of reference doses for age/weight, were subsequently divided into classes, per ten percent increase starting from the lowest dose. For each of these classes, as compared with the lowest dose (0-10 percent class), the likelihood [hazard ratios (95 percent confidence intervals)] of acquiring a new infection in PICU, of live weaning from mechanical ventilation, and of live PICU discharge were determined and visualised as described for the continuous doses.

The time course of plasma urea concentrations was assessed with repeated-measures MANOVA, after square-root transformation to obtain a near-normal distribution.

Analyses were performed with JMP®Pro-12.1.0 (SAS Institute). Two-sided P-values at or below 0.05 were considered significant. No corrections for multiple comparisons were done in this explanatory analysis.

Role of the funding source

The study sponsors had no role in study design; collection, analysis, and interpretation of data; writing of the report, or decision to submit. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Table_1 presents average daily glucose, lipid, and amino acid doses administered up to each of the first seven days in PICU. Total doses given in the early PN group were fairly stable throughout the seven days in PICU for glucose (around 50-60 percent) and amino acids (around 70-80 percent), but were gradually built up from 0 to 70 percent for lipids. Doses of each macronutrient class given to patients in the late PN group were much lower, in line with the RCT protocol.[8,9]

Late PN has been shown to reduce the risk of acquiring a new infection from 18·5 percent to 10·7 percent.[9] The current multivariable Cox proportional hazard analyses showed that the likelihood of acquiring a new infection at any time was significantly lower with late PN than with early PN (adjusted hazard ratio (HR) 0·544 (0·408-0·721), P<0·0001, figure_1A), also when penalising for death as competing risk (HR 0·540 (0·404-0·715), P<0·0001, figure_1B). In the adjusted model, a higher total daily amino acid dose was associated with an increased likelihood of acquiring a new infection for all days up to day five in PICU (HRs per ten percent increase between 1·043-1·134, P≤0·029, figure_2A, supplemental_tables_S3.1-7). In contrast, with a higher daily glucose dose up to day three in PICU, a significantly lower likelihood of acquiring a new infection was found (HRs 0·870-0·913, P≤0·036). This finding was independent of the blood glucose concentration and of the insulin dose administered up to the day of analysis, as shown by a sensitivity analysis further adjusting for these covariates (supplemental_tables_S4, S5.1-6). This further adjusted analysis also revealed that a higher blood glucose concentration was an independent risk factor for infections, whereas the daily glucose dose was protective. There were no significant associations during the first week in PICU between the daily doses of lipids and likelihood of acquiring a new infection. Similar results were obtained with left truncation (only considering new infections beyond the day of analysis), with penalising for death as competing risk, with multivariable logistic regression analysis of the incidence of acquiring a new

infection (rather than time to new infection) (supplemental_figure_S2) and with omission of the PIM2 score from the models (supplemental_figure_S3).

Late PN also accelerated (live) weaning from mechanical ventilatory support (HR 1·203 (1·082-1·337), P=0.0006 and 1·171 (1·052-1·304), P=0·0040, figure_1C,D) and, as reported previously, accelerated PICU discharge.[9] Higher daily amino acid doses during the intervention window were inversely associated with likelihood of earlier live weaning from mechanical ventilatory support (HRs 0·950-0·975, P≤0·045, figure_2B, supplemental_tables_S6.1-7) and earlier live PICU discharge (HRs 0·943-0·972, P≤0·030, figure_2C, supplemental_tables_S7.1-7). Daily glucose doses appeared neutral, whereas a higher daily lipid dose started to favor earlier live PICU discharge from day 4 to day 7 (HRs 1·027-1·050, P≤0·043). Similar results were obtained with omission of the PIM2 score from the models (supplemental_figure_S3).

Similar results were obtained with censoring at 28 days instead of at 90 days (supplemental_figure_S4). Depicting the HRs for the 2 randomisation groups separately also did not reveal any sign of benefit from amino acids (data not shown). The sensitivity analyses for the *enteral and parenteral route of macronutrient delivery separately* (supplemental_figure_S5) showed that findings for the *parenteral* route closely mimicked those observed for *total* daily doses. Also for the macronutrients administered *enterally*, likelihood of acquiring a new infection was higher with increasing doses of amino acids.

For the next sensitivity analysis, performed to identify the dose range from which total amino acids started to be harmful, we focused on day four, as administration of all macronutrients had been initiated in all participating centers by that time. Splitting up the doses in classes of ten percent increments showed that risk of harm by amino acid administration was present already with use of low doses, gradually increased with doses up to an average 40-50 percent of reference doses for age/weight for all studied outcomes and did not further increase with higher doses (figure_3, supplemental_figure_S6). Translating this back to crude grams of amino acids per kg per day up to day four, it was shown that maximal harm was reached with a median daily dose of 1·15 (IQR 1·10-1·22) g/kg for patients weighing

up to ten kg, 0·83 (0·76-1·03) g/kg for patients weighing >10-20 kg, and 0·75 (0·69-0·79) g/kg for patients weighing >20 kg (figure_4). Nevertheless, much smaller doses were already significantly associated with adverse outcome as compared with the lowest dose category (figure_3).

Plasma urea concentrations were higher with early PN than with late PN throughout the first week in PICU (figure_1E).

DISCUSSION

We demonstrated that the dose of amino acids, and not that of glucose or lipid, was associated with more infections and longer dependency on mechanical ventilatory support and other intensive medical care, which could thus offer an explanation for the harm caused by early supplemental PN in critically ill children. Risk of harm with early amino acid administration started with low doses and rose further with increasing amounts up to a median of 1·15 g/kg/day for patients weighing up to ten kg, 0·83 g/kg/day for patients >10-20 kg, and 0·75 g/kg/day for patients >20 kg. In contrast, higher doses of glucose administered very early in the course of illness were independently associated with a lower likelihood of new infections, and higher lipid doses administered beyond the first few days of illness were independently associated with faster live PICU discharge. As early PN, containing protein, glucose and lipids, exerted harm, any benefit by adding glucose or lipids to the intravenous feeding apparently did not suffice to offset the harm by protein.

These findings contradict the conclusions of previous observational studies that feeding critically ill patients a higher protein/amino acid load early during the course of illness would lead to a better outcome.[2,27,28] Already in low doses, much lower than those advised in practice guidelines, we found that the provision of amino acids, and not glucose or lipids, during the first week of critical illness was associated with worse clinical outcomes. A possible reason for the opposite results of this analysis and those of previous observational studies is the fact that the current study was based on an RCT, with amounts of macronutrients being different and covering a very wide range of doses at random, whereas in previous studies, that assessed enteral feeding predominantly, patients who were less sick were more likely to better tolerate nutrition.

One could speculate on the possible explanations for harm by amino acids early during critical illness. First, amino acids are powerful suppressors of autophagy, a crucial pathway for innate immunity and removal of cellular damage (e.g. from myofibers) as shown in patients and in an animal model of critical

illness.[29–33] Second, load of amino acids that exceeds the anabolic capacity may be a burden to liver and kidney, as amino acids are then shuttled towards hepatic production of urea that needs to be excreted via the urine.[34] It was shown in adult ICU patients that early PN containing amino acids was unable to promote anabolism and instead increased nitrogen wasting in urine.[22,30] The here documented increase in plasma urea throughout the seven days intervention time window supports the presence of this phenomenon. Not only absolute amounts, but also suboptimal composition of the amino acid formulations may contribute to the harm of early amino acid administration to critically ill children. Indeed, normal physiological individual amino acid requirements for protein synthesis may not apply to the acute stress response and lead to a relative excess of not required amino acids.[20]

Unlike suggested,[16] we did not observe signs of harm by increasing non-protein calories. A higher early glucose dose was found to associate with a lower likelihood of infection. This may relate to high energy consumption by immune cells in proliferative, biosynthetic, and secretory activities needed to generate an effective immune response, for which glucose is a main fuel source.[35] Higher blood glucose concentrations, however, were found to be associated with an increased risk of infection also in this study, in line with a negative impact of hyperglycaemia on innate immunity.[36] Increasing lipid doses showed a neutral relationship with risk of new infection and possibly a small, late benefit with accelerated recovery.

This study has some strengths and weaknesses. One strength is the wide range of macronutrient doses in the context of an RCT. Another asset is the individual titration of glucose, lipid, and amino acid administration, with use of separate or custom-made solutions rather than all-in-one preparations, and the variability in nutritional management among participating centers.[9] A limitation is the observational design of this secondary analysis of the RCT. Future studies should investigate whether early administration of PN containing less or no amino acids could reduce infections and enhance recovery of critical illness in children.

In conclusion, the observed associations suggest that administration of amino acids, but not glucose or lipid, even in low doses during the first week of critical illness could explain the worse clinical outcome with early PN in critically ill children.

RESEARCH IN CONTEXT

Evidence before this study

We performed a PubMed search without language restriction up to November 2016 with various combinations of the search terms “critical illness”, “critical care”, “intensive care”, “ICU”, “PICU”, “sepsis”, “trauma”, “burn”, “cardiac surgery”, “congenital heart disease”, “children”, “paediatric” and “nutrition or feeding”, “enteral nutrition or feeding”, “parenteral nutrition or feeding”, “intravenous nutrition or feeding”, “caloric intake”, “glucose”, lipid”, “protein”, “amino acid*” and “outcome”, “infection*”, “weaning”, “mechanical ventilation”, “length of stay”, “recovery”.

Macronutrient intake of critically ill children is often insufficient. Guidelines recommend initiation of nutritional support early, parenterally when enteral feeding is insufficient, as observational studies associated macronutrient deficits with risk of infections and delayed recovery. However, the randomised PEPaNIC study demonstrated that accepting a large macronutrient deficit by withholding parenteral nutrition up to one week in the paediatric intensive care unit prevented infections and accelerated recovery, corroborating findings in adults. It has been suggested that overdosing of glucose and insufficient administration of protein/amino acids in patients receiving parenteral nutrition early explains these findings. Observational studies that assessed enteral feeding predominantly suggested that administering a higher protein/amino acid load to critically ill patients would lead to a better outcome, but better tolerance of nutrition in patients who were less sick likely introduced bias. Nevertheless, despite hard evidence, provision of much more protein is advocated. In contrast, suspicion of harm by high protein rather than high glucose intake early during critical illness has been raised, supported by delayed recovery and increased ureagenesis in a *post-hoc* analysis of the adult EPaNIC trial. No studies are available that assessed any separate impact of glucose, lipid and protein/amino acids in critically ill patients.

Added value of this study

The present study investigated the separate impact on outcome of critically ill children of a wide range of glucose, lipid, and amino acid doses, in order to identify which macronutrient was associated with the harmful effects of early parenteral nutrition in paediatric critical illness. As this study was based on a randomised nutritional intervention trial, the bias present in previous observational studies, evoked by less sick patients tolerating more feeding, was circumvented. Our data suggest that the provision of amino acids early during the course of critical illness could explain the worse clinical outcome with early supplemental parenteral nutrition. The risk of harm was already shown for low doses of amino acids, which actually were much lower than those advised in clinical practice guidelines. Unlike previous speculations, we did not observe signs of harm by increasing non-protein calories.

Implications of all the available evidence

In an era where expert opinion has shifted from advising to administer calories to using more protein/amino acids in nutritional formulae during severe illness, despite lack of high-level evidence in favor of such a strategy, the present data call for caution. Indeed, the data are important to generate awareness about potential harm by such a strategy. These data could have major implications for future nutritional intervention studies and clinical practice. In particular, future studies should investigate whether early administration of parenteral nutrition that does not contain (or contains much less) amino acids could reduce infections and enhance recovery of critical illness in children.

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AUTHOR CONTRIBUTIONS

IV, MPC and GVdB designed the protocol for this secondary analysis of the PEPaNIC study. IV and GVdB wrote the statistical analysis plan, performed the statistical analyses and wrote the manuscript. PJW designed the database, supervised and monitored data entry, checked the database for accuracy and exported the data for statistical analysis. Other authors gathered data. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors have no conflicts of interest to report.

FIGURE LEGENDS

Figure 1: Impact of early PN versus late PN on time to new infection, weaning from mechanical ventilation, and urea

Panel A shows the cumulative proportion of patients who acquired a new infection during PICU stay, with patients who did not develop a new infection (N=1229) considered infection-free up to day 90. Panel B depicts the equivalent analysis in which non-surviving patients who did not acquire a new infection while in PICU (N=48) were labeled has having acquired a new infection on the day of death. Panel C shows the cumulative proportion of patients weaned from mechanical ventilation, with data censored at 90 days (dependency on mechanical ventilation was longer than 90 days in four patients) and non-survivors (N=68) censored at the time of death. Panel D depicts the equivalent analysis with non-surviving patients censored beyond all survivors at 91 days to account for death as competing risk. For the sake of clarity, only the first 30 days are shown in panels A-D. Panel E shows the plasma urea concentrations in patients randomised to early or late PN for the first seven days in PICU, with N indicating the number of patients for whom these data were available. Lack of complete 24 hour urine collections for a large proportion of patients precluded assessment of daily urinary excretion of urea. Urea concentrations are expressed in mmol/l (left axis) and in mg/dl (right axis). One mmol/l equals 6.006 mg/dl.

* P-value for randomisation to early PN versus late PN obtained with log rank test; † P-value for randomisation to early PN versus late PN obtained with multivariable Cox proportional hazard analysis adjusting for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center; ‡ P-value for time*randomisation to early PN or late PN obtained with repeated-measures MANOVA, with repeated-measures MANOVA performed for the first 2 days up to the first seven days in PICU, after square root transformation to obtain a near-normal distribution of the data.

Figure 2: Association of average total macronutrient doses with clinical outcome

For each of the first seven days in PICU, the associations of the average total doses of the individual macronutrients up to that day with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals per ten percent added, with macronutrients entered as continuous variables. These were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one. N indicates the number of patients still in PICU on the day of analysis. Harm by increasing doses of amino acids was observed irrespective of baseline risk factors, as analysed by interaction P-values.

Figure 3: Dose relationship per class of ten percent increase in average total macronutrient administration up to day four with clinical outcome

Average total doses up to day four of each macronutrient were split up in classes of absolute ten percent increases, with doses above 90 percent combined in a single class. The associations of the classes of average total doses of the individual macronutrients up to day four with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals as compared with the class of 0-10 percent. These were obtained after adjustment for type of illness, age

group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values and number of patients in each class (N) are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one. The y-axis has been cut to better visualise the dose response. Full-scale figures are given in supplemental_figure_S6.

Figure 4: Average macronutrient administration achieved per class of ten percent increase in average total macronutrient dose up to day four

Doses of the different macronutrients in g/kg body weight corresponding to each class of average total macronutrient administration up to day four is shown for patients weighing up to ten kg, patients weighing >10-20 kg, and patients weighing more than 20 kg for glucose (panel A), amino acids (panel B), and lipids (panel C). Box plots show medians, interquartile ranges, and 10^{th} and 90^{th} percentiles. N indicates the number of patients in each class.

Table 1: Average macronutrient administration for up to each of the first seven days in PICU

			Glucose		Amino acids		Lipids	
Route	Dose up to day [a]	N	Early PN	Late PN	Early PN	Late PN	Early PN	Late PN
Total dose (percent)	1	1440	58·2 (33·8-81·1)	16·8 (11·4-24·6)	62·8 (0·0-99·6)	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)
	2	1188	68·4 (44·2-86·4)	19·2 (14·3-31·6)	81·0 (37·4-109·2)	0·0 (0·0-7·0)	12·0 (4·6-46·1)	0·0 (0·0-11·7)
	3	924	60·9 (41·7-77·6)	19·8 (14·6-31·0)	77·3 (47·8-99·5)	1·4 (0·0-15·9)	34·4 (20·8-64·1)	2·7 (0·0-28·4)
	4	747	58·7 (40·1-72·9)	20·9 (14·7-31·5)	75·0 (48·9-90·8)	3·7 (0·0-23·2)	49·5 (34·2-79·1)	7·3 (0·0-40·4)
	5	611	56·6 (39·5-71·0)	21·8 (14·9-32·6)	73·3 (50·9-88·6)	6·0 (0·0-28·8)	57·2 (42·1-87·2)	11·7 (0·0-45·1)
	6	517	55·2 (39·3-71·6)	24·4 (16·1-35·2)	73·6 (53·1-85·6)	9·9 (1·1-34·5)	64·0 (45·8-92·9)	18·6 (1·6-50·1)
	7	443	54·2 (39·0-70·3)	25·8 (16·3-35·5)	72·6 (55·0-85·4)	14·3 (1·9-37·9)	68·3 (48·0-100·3)	24·3 (3·2-54·4)
Enteral dose (percent)	1	1440	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)
	2	1188	0·0 (0·0-3·5)	0·0 (0·0-4·9)	0·0 (0·0-3·8)	0·0 (0·0-4·9)	0·0 (0·0-7·4)	0·0 (0·0-10·4)
	3	924	0·0 (0·0-8·8)	1·2 (0·0-9·4)	0·0 (0·0-11·7)	1·1 (0·0-13·4)	0·0 (0·0-22·2)	2·1 (0·0-26·5)
	4	747	1·8 (0·0-14·1)	2·6 (0·0-16·4)	2·5 (0·0-19·7)	3·2 (0·0-21·2)	4·3 (0·0-34·4)	6·8 (0·0-39·0)
	5	611	3·3 (0·0-18·4)	4·4 (0·0-18·8)	4·6 (0·0-27·5)	5·5 (0·0-28·3)	8·9 (0·0-44·2)	10·3 (0·0-45·1)
	6	517	4·2 (0·0-19·3)	7·0 (0·9-22·7)	6·2 (0·0-30·7)	8·1 (1·0-34·4)	10·4 (0·0-46·0)	16·6 (1·5-50·1)
	7	443	4·8 (0·0-21·1)	9·2 (0·9-24·2)	7·2 (0·0-32·1)	12·9 (1·0-37·6)	12·9 (0·0-49·5)	23·5 (2·1-54·4)
Parenteral dose (percent)	1	1440	56·6 (32·0-79·7)	16·3 (10·7-23·6)	59·7 (0·0-99·4)	0·0 (0·0-0·0)	0·0 (0·0-0·0)	0·0 (0·0-0·0)
	2	1188	63·9 (34·5-81·3)	16·9 (12·5-23·4)	75·1 (22·4-107·6)	0·0 (0·0-0·0)	4·7 (0·0-29·1)	0·0 (0·0-0·0)
	3	924	55·3 (29·4-71·8)	15·1 (11·2-20·2)	67·2 (22·4-94·7)	0·0 (0·0-0·0)	21·6 (4·2-39·5)	0·0 (0·0-0·0)
	4	747	47·8 (25·5-68·7)	13·4 (10·3-18·9)	65·2 (21·4-85·3)	0·0 (0·0-0·0)	35·2 (9·2-49·7)	0·0 (0·0-0·0)
	5	611	42·6 (22·5-66·8)	12·8 (9·4-17·4)	62·1 (20·6-80·7)	0·0 (0·0-0·0)	37·9 (10·0-54·1)	0·0 (0·0-0·0)
	6	517	39·6 (20·9-67·0)	12·1 (8·1-16·9)	62·0 (23·2-77·7)	0·0 (0·0-0·0)	40·9 (11·2-60·9)	0·0 (0·0-0·0)
	7	443	38·2 (19·3-66·1)	11·8 (7·7-16·2)	57·4 (22·2-75·4)	0·0 (0·0-0·0)	40·4 (11·7-65·6)	0·0 (0·0-0·0)

[a] Average daily doses of the 3 macronutrient classes administered up to each of the first seven days in PICU, in total, via the enteral or via the parenteral route, are expressed as percentages of the reference doses for age/weight as described in nutritional guidelines summarised in supplemental_table_S2.[4,23] These reference doses for age/weight were not necessarily those that were used locally as nutritional targets, but were used only for the current analysis that required expression of the administered doses of the three macronutrients in an interchangeable and comparable unity for children of different ages and weights. Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses, of glucose, amino acids, and lipids were significantly different for patients in the early PN and late PN groups. N indicates the number of patients still in PICU on the day of analysis.

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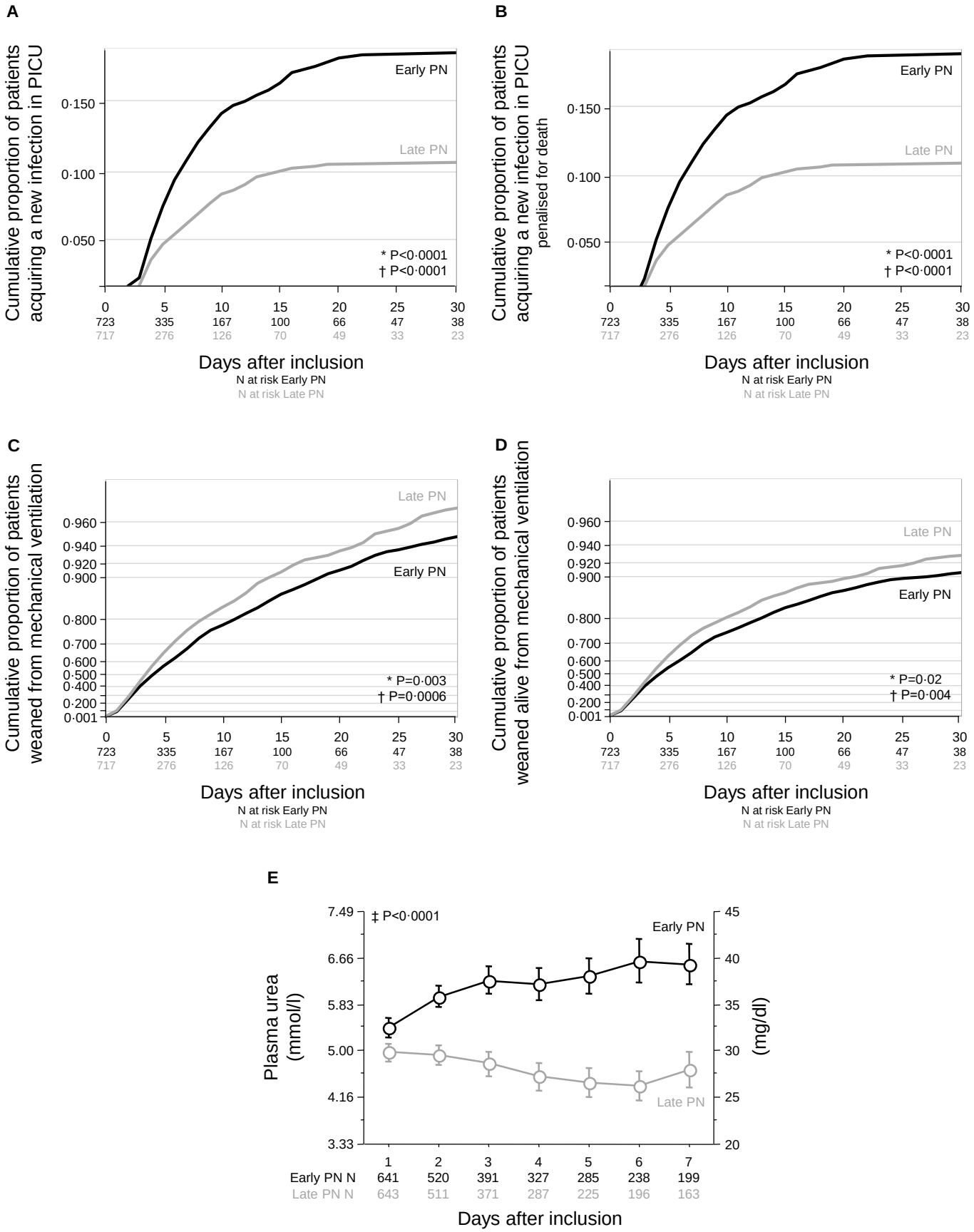
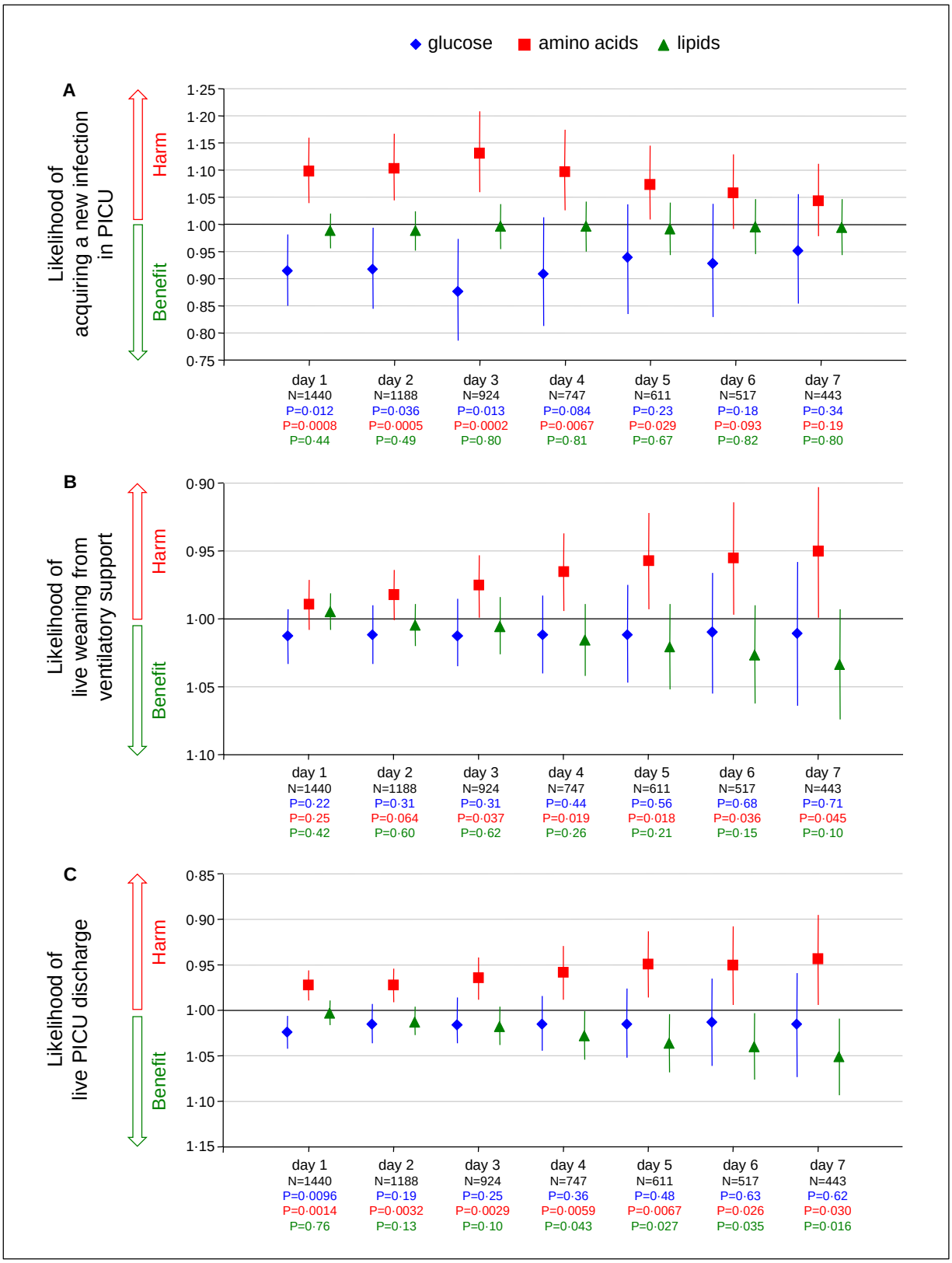
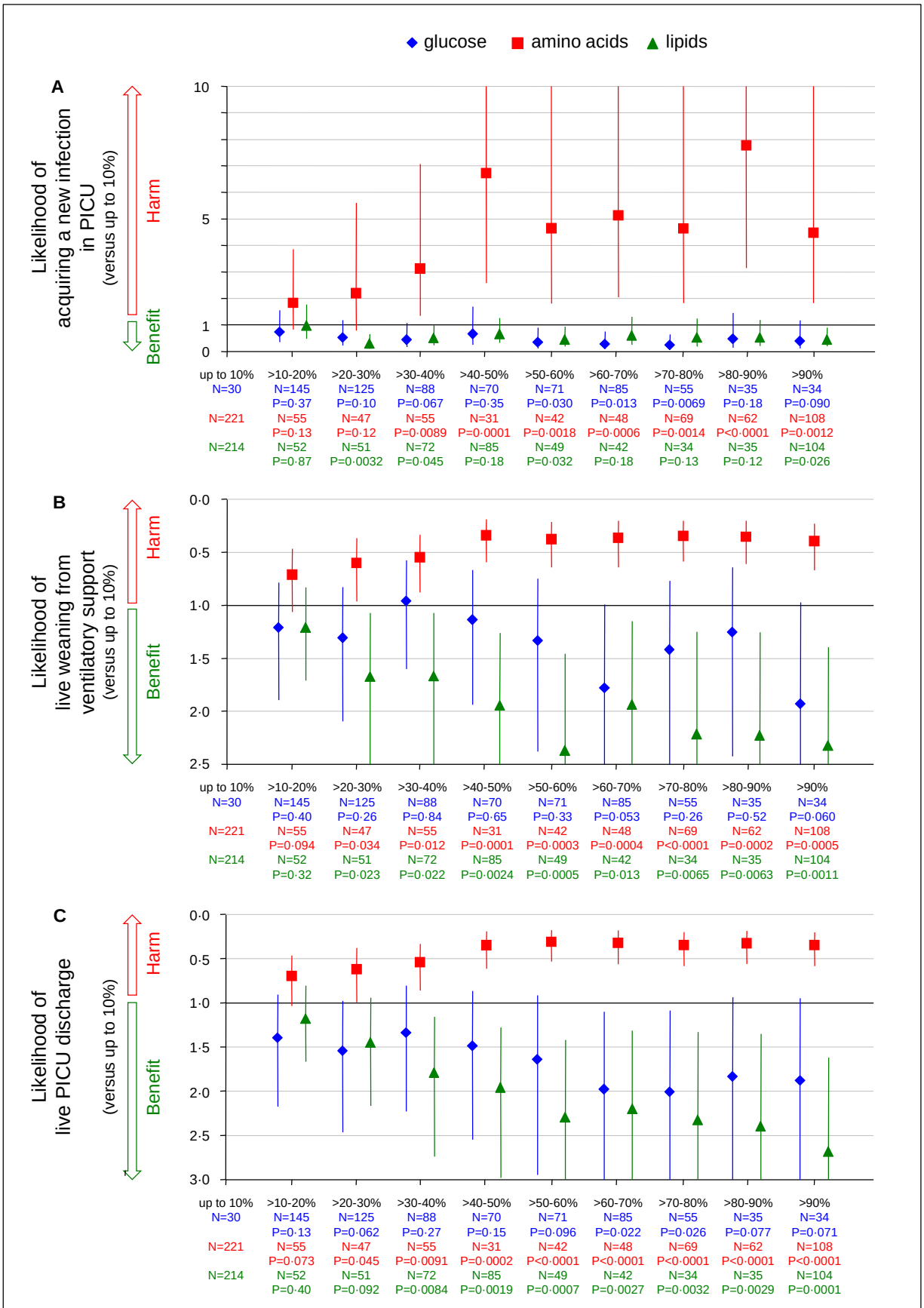
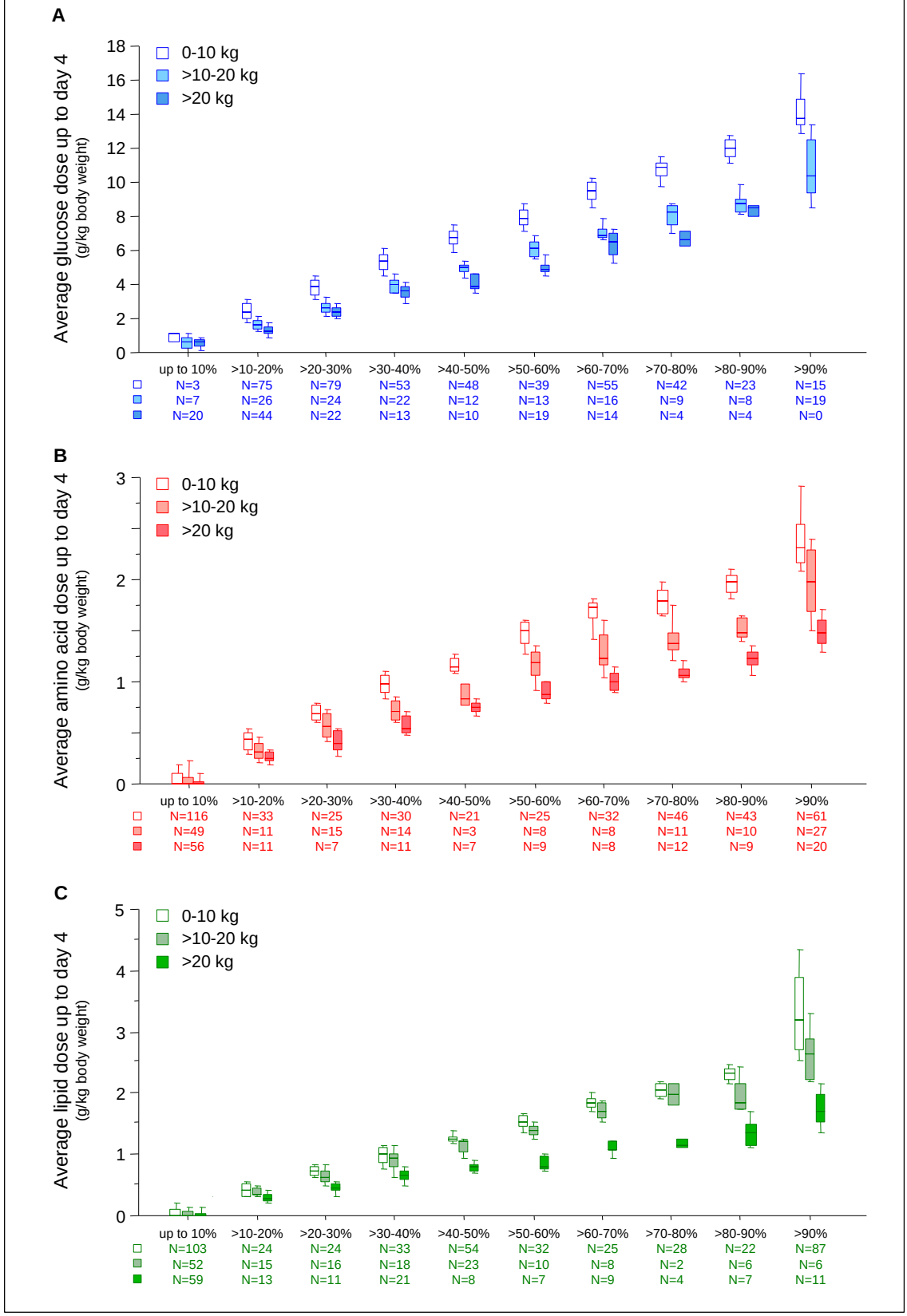

A
Cumulative proportion of patients acquiring a new infection in PICU
Early PN
Late PN
* P<0·0001
† P<0·0001
0·150
0·100
0·050
0 5 10 15 20 25 30
723 335 167 100 66 47 38
717 276 126 70 49 33 23
Days after inclusion
N at risk Early PN
N at risk Late PN
B
Cumulative proportion of patients acquiring a new infection in PICU
penalised for death
Early PN
Late PN
* P<0·0001
† P<0·0001
0·150
0·100
0·050
0 5 10 15 20 25 30
723 335 167 100 66 47 38
717 276 126 70 49 33 23
Days after inclusion
N at risk Early PN
N at risk Late PN
C
Cumulative proportion of patients weaned from mechanical ventilation
Late PN
Early PN
* P=0·003
† P=0·0006
0·960
0·940
0·920
0·900
0·800
0·700
0·600
0·500
0·400
0·200
0·001
0 5 10 15 20 25 30
723 335 167 100 66 47 38
717 276 126 70 49 33 23
Days after inclusion
N at risk Early PN
N at risk Late PN
D
Cumulative proportion of patients weaned alive from mechanical ventilation
Late PN
Early PN
* P=0·02
† P=0·004
0·960
0·940
0·920
0·900
0·800
0·700
0·600
0·500
0·400
0·200
0·001
0 5 10 15 20 25 30
723 335 167 100 66 47 38
717 276 126 70 49 33 23
Days after inclusion
N at risk Early PN
N at risk Late PN
E
‡ P<0·0001
Early PN
Late PN
Plasma urea (mmol/l)
(mg/dl)
7.49
6.66
5.83
5.00
4.16
3.33
45
40
35
30
25
20
1 2 3 4 5 6 7
Early PN N 641 520 391 327 285 238 199
Late PN N 643 511 371 287 225 196 163
Days after inclusion


glucose
amino acids
lipids
A
Likelihood of acquiring a new infection in PICU
Harm
Benefit
1·25
1·20
1·15
1·10
1·05
1·00
0·95
0·90
0·85
0·80
0·75
day 1 N=1440 P=0·012 P=0·0008 P=0·44
day 2 N=1188 P=0·036 P=0·0005 P=0·49
day 3 N=924 P=0·013 P=0·0002 P=0·80
day 4 N=747 P=0·084 P=0·0067 P=0·81
day 5 N=611 P=0·23 P=0·029 P=0·67
day 6 N=517 P=0·18 P=0·093 P=0·82
day 7 N=443 P=0·34 P=0·19 P=0·80
B
Likelihood of live weaning from ventilatory support
Harm
Benefit
0·90
0·95
1·00
1·05
1·10
day 1 N=1440 P=0·22 P=0·25 P=0·42
day 2 N=1188 P=0·31 P=0·064 P=0·60
day 3 N=924 P=0·31 P=0·037 P=0·62
day 4 N=747 P=0·44 P=0·019 P=0·26
day 5 N=611 P=0·56 P=0·018 P=0·21
day 6 N=517 P=0·68 P=0·036 P=0·15
day 7 N=443 P=0·71 P=0·045 P=0·10
C
Likelihood of live PICU discharge
Harm
Benefit
0·85
0·90
0·95
1·00
1·05
1·10
1·15
day 1 N=1440 P=0·0096 P=0·0014 P=0·76
day 2 N=1188 P=0·19 P=0·0032 P=0·13
day 3 N=924 P=0·25 P=0·0029 P=0·10
day 4 N=747 P=0·36 P=0·0059 P=0·043
day 5 N=611 P=0·48 P=0·0067 P=0·027
day 6 N=517 P=0·63 P=0·026 P=0·035
day 7 N=443 P=0·62 P=0·030 P=0·016


glucose
amino acids
lipids
A
Likelihood of acquiring a new infection in PICU
(versus up to 10%)
Harm
Benefit
10
5
1
0
up to 10%
N=30
N=221
N=214
>10-20%
N=145
P=0·37
N=55
P=0·13
N=52
P=0·87
>20-30%
N=125
P=0·10
N=47
P=0·12
N=51
P=0·0032
>30-40%
N=88
P=0·067
N=55
P=0·0089
N=72
P=0·045
>40-50%
N=70
P=0·35
N=31
P=0·0001
N=85
P=0·18
>50-60%
N=71
P=0·030
N=42
P=0·0018
N=49
P=0·032
>60-70%
N=85
P=0·013
N=48
P=0·0006
N=42
P=0·18
>70-80%
N=55
P=0·0069
N=69
P=0·0014
N=34
P=0·13
>80-90%
N=35
P=0·18
N=62
P<0·0001
N=35
P=0·12
>90%
N=34
P=0·090
N=108
P=0·0012
N=104
P=0·026
B
Likelihood of live weaning from ventilatory support
(versus up to 10%)
Harm
Benefit
0·0
0·5
1·0
1·5
2·0
2·5
up to 10%
N=30
N=221
N=214
>10-20%
N=145
P=0·40
N=55
P=0·094
N=52
P=0·32
>20-30%
N=125
P=0·26
N=47
P=0·034
N=51
P=0·023
>30-40%
N=88
P=0·84
N=55
P=0·012
N=72
P=0·022
>40-50%
N=70
P=0·65
N=31
P=0·0001
N=85
P=0·0024
>50-60%
N=71
P=0·33
N=42
P=0·0003
N=49
P=0·0005
>60-70%
N=85
P=0·053
N=48
P=0·0004
N=42
P=0·013
>70-80%
N=55
P=0·26
N=69
P<0·0001
N=34
P=0·0065
>80-90%
N=35
P=0·52
N=62
P=0·0002
N=35
P=0·0063
>90%
N=34
P=0·060
N=108
P=0·0005
N=104
P=0·0011
C
Likelihood of live PICU discharge
(versus up to 10%)
Harm
Benefit
0·0
0·5
1·0
1·5
2·0
2·5
3·0
up to 10%
N=30
N=221
N=214
>10-20%
N=145
P=0·13
N=55
P=0·073
N=52
P=0·40
>20-30%
N=125
P=0·062
N=47
P=0·045
N=51
P=0·092
>30-40%
N=88
P=0·27
N=55
P=0·0091
N=72
P=0·0084
>40-50%
N=70
P=0·15
N=31
P=0·0002
N=85
P=0·0019
>50-60%
N=71
P=0·096
N=42
P<0·0001
N=49
P=0·0007
>60-70%
N=85
P=0·022
N=48
P<0·0001
N=42
P=0·0027
>70-80%
N=55
P=0·026
N=69
P<0·0001
N=34
P=0·0032
>80-90%
N=35
P=0·077
N=62
P<0·0001
N=35
P=0·0029
>90%
N=34
P=0·071
N=108
P<0·0001
N=104
P=0·0001


A
Average glucose dose up to day 4
(g/kg body weight)
0-10 kg
>10-20 kg
>20 kg
0
2
4
6
8
10
12
14
16
18
up to 10% >10-20% >20-30% >30-40% >40-50% >50-60% >60-70% >70-80% >80-90% >90%
N=3 N=75 N=79 N=53 N=48 N=39 N=55 N=42 N=23 N=15
N=7 N=26 N=24 N=22 N=12 N=13 N=16 N=9 N=8 N=19
N=20 N=44 N=22 N=13 N=10 N=19 N=14 N=4 N=4 N=0
B
Average amino acid dose up to day 4
(g/kg body weight)
0-10 kg
>10-20 kg
>20 kg
0
1
2
3
up to 10% >10-20% >20-30% >30-40% >40-50% >50-60% >60-70% >70-80% >80-90% >90%
N=116 N=33 N=25 N=30 N=21 N=25 N=32 N=46 N=43 N=61
N=49 N=11 N=15 N=14 N=3 N=8 N=8 N=11 N=10 N=27
N=56 N=11 N=7 N=11 N=7 N=9 N=8 N=12 N=9 N=20
C
Average lipid dose up to day 4
(g/kg body weight)
0-10 kg
>10-20 kg
>20 kg
0
1
2
3
4
5
up to 10% >10-20% >20-30% >30-40% >40-50% >50-60% >60-70% >70-80% >80-90% >90%
N=103 N=24 N=24 N=33 N=54 N=32 N=25 N=28 N=22 N=87
N=52 N=15 N=16 N=18 N=23 N=10 N=8 N=2 N=6 N=6
N=59 N=13 N=11 N=21 N=8 N=7 N=9 N=4 N=7 N=11

SUPPLEMENTARY APPENDIX

Harm caused by early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments

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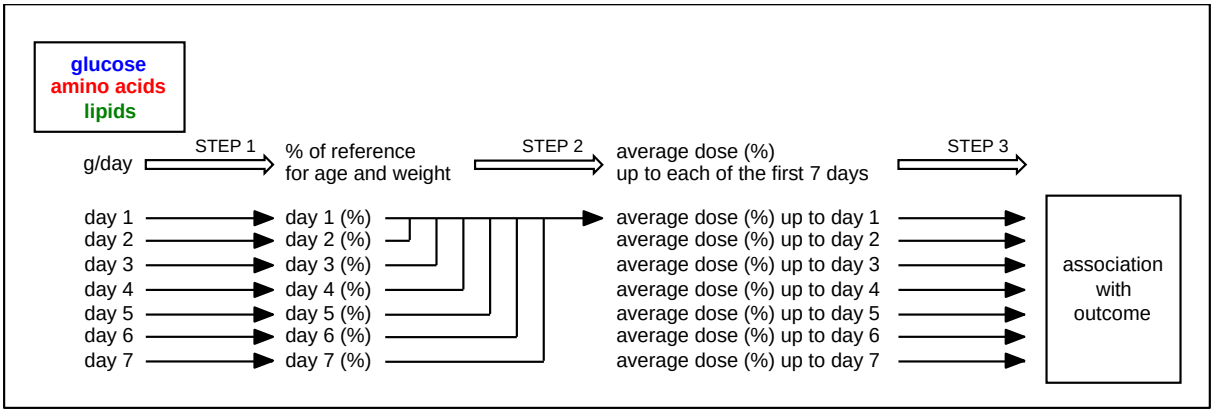
Dirk Vlasselaers MD, Koen Joosten MD, Greet Van den Berghe MD

CONTENTS

SUPPLEMENTARY FIGURES

Figure S1: **Stepwise transformation of the given doses of glucose, lipid, and amino acids to a unity that allows comparison for children of different ages and weights and association with clinical outcome**



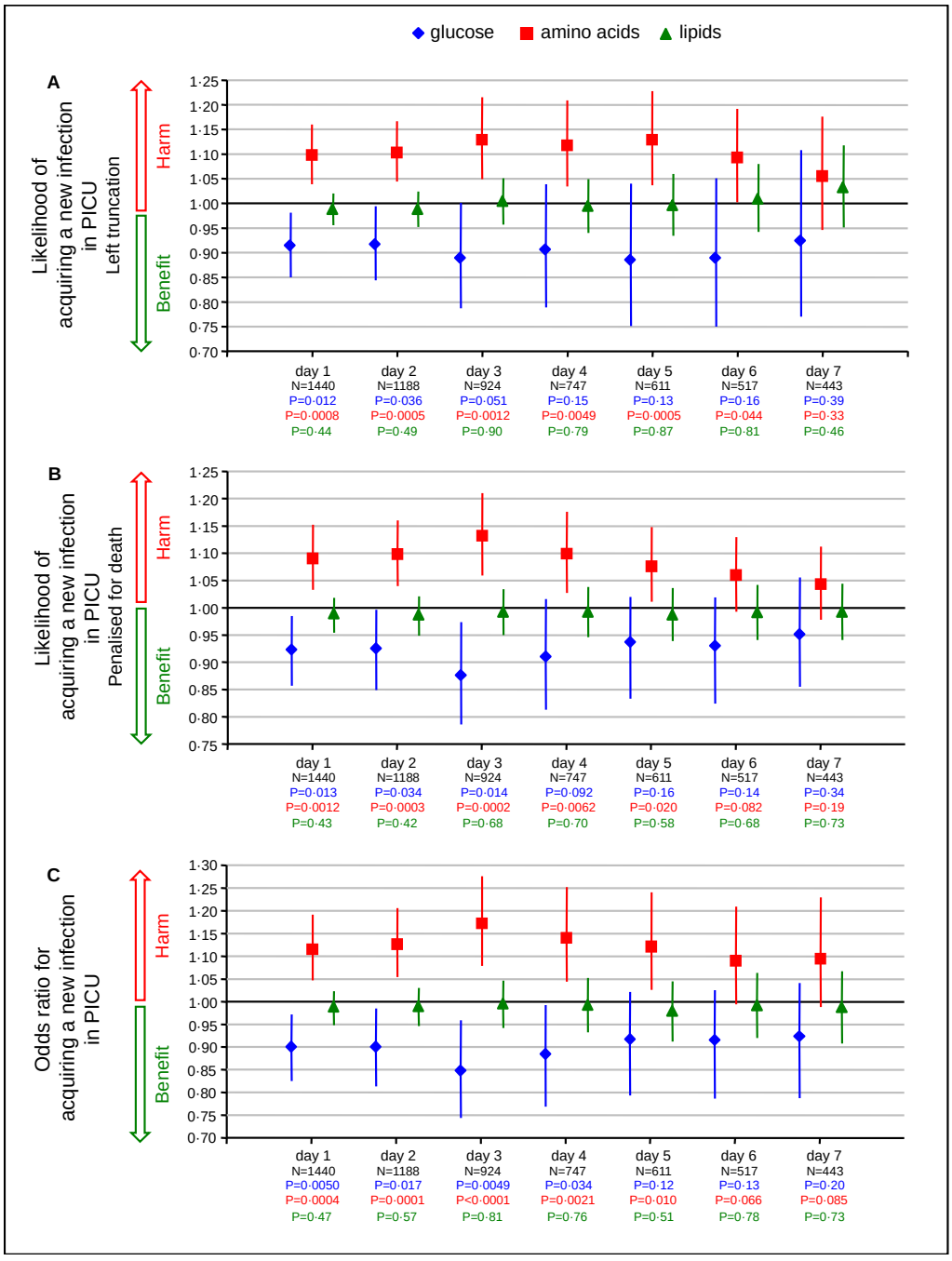
In a first step, doses of glucose, lipid, and amino acids that were given on each of the first seven days in PICU were transformed from the crude grams per day into a percentage of the reference doses for age/weight described in published nutritional guidelines[S1,S2] (summarised in supplemental_table_S2). These doses were not necessarily those that were used locally as nutritional targets. They were only used for the current analysis, which required expression of the administered doses of the three macronutrients in an interchangeable and comparable unity for children of different ages and weights.

In a second step, the transformed doses were used to calculate average doses of glucose, lipid, and amino acids administered up to each of the first seven days in PICU for all patients who were still in PICU on these respective days.

In a third step, associations of these average doses up to each of the first seven days in PICU with the clinical endpoints (time to the first new infection acquired in the PICU, the time to live weaning from mechanical ventilatory support, and the time to live discharge from PICU accounting for mortality as a competing risk) were determined with Cox proportional hazard analyses, adjusting for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center.

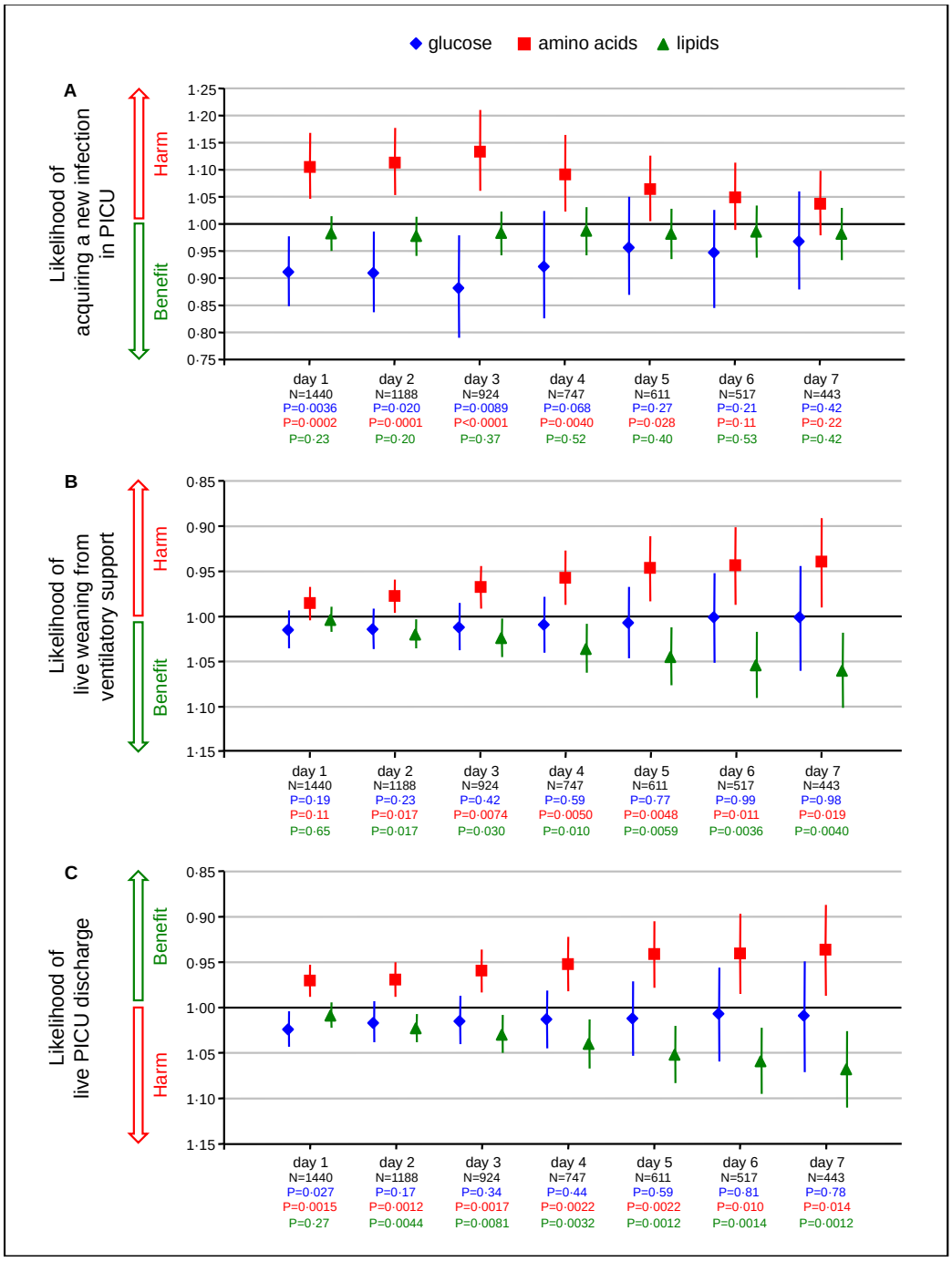
This procedure was performed for total doses and repeated for enteral doses and parenteral doses of glucose, lipid, and amino acids.

Figure S2: **Association of average total macronutrient administration with likelihood of acquiring a new infection: sensitivity analysis with left truncation and accounting for death as a competing risk**



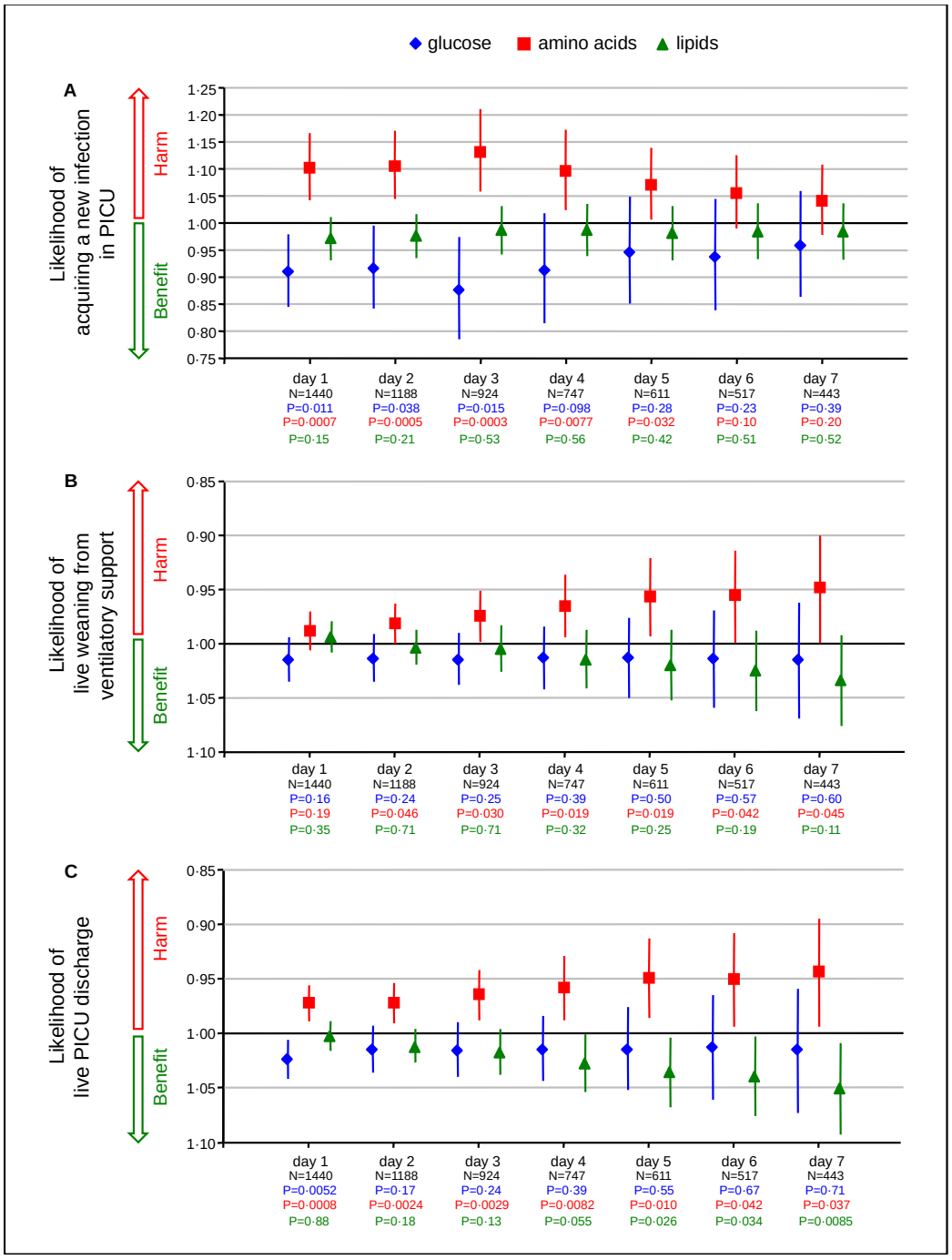
For each of the first seven days in PICU, the associations of the average total administration of the individual macronutrients up to that day with likelihood of acquiring a new infection in PICU are shown as hazard ratios or odds ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals per ten percent added, with macronutrients entered as continuous variables. Panel A shows the analyses when only taking into account development of infections after the day of analysis ("left truncation"). In panel B non-surviving patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death to penalise for death. Panel C shows odds ratios for acquiring a new infection in PICU. Hazard ratios and odds ratios were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio or odds ratio above one is indicative of a detrimental effect, whereas a hazard ratio below one points to a beneficial effect. N indicates the number of patients still in PICU on the day of analysis.

Figure S3: **Association of average total macronutrient doses with clinical outcome, with omission of the PIM2 score from the models**



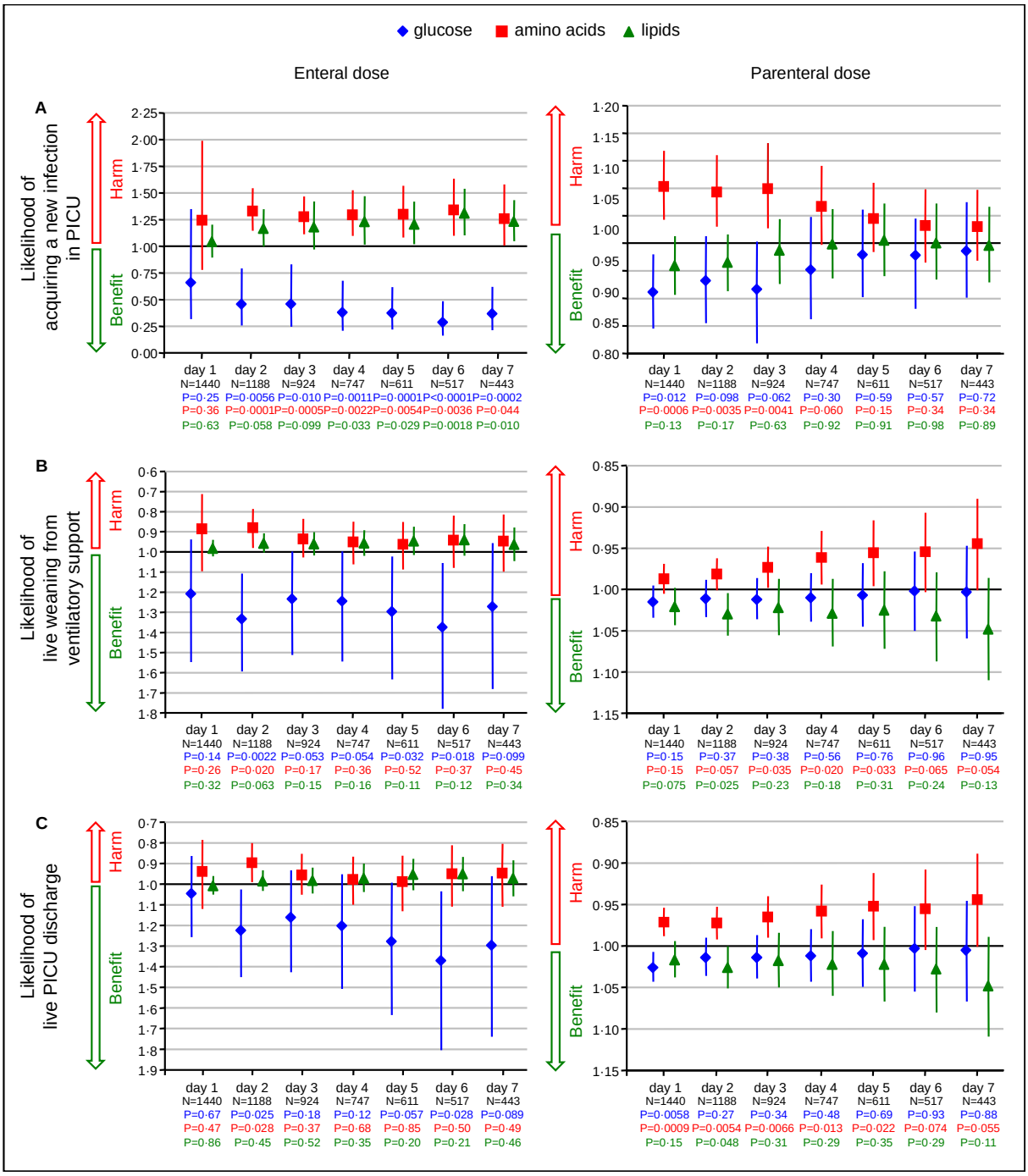
For each of the first seven days in PICU, the associations of the average total doses of the individual macronutrients up to that day with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals per ten percent added, with macronutrients entered as continuous variables. These were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one. N indicates the number of patients still in PICU on the day of analysis.

Figure S4: **Association of average total macronutrient doses with clinical outcome, with censoring at 28 days**



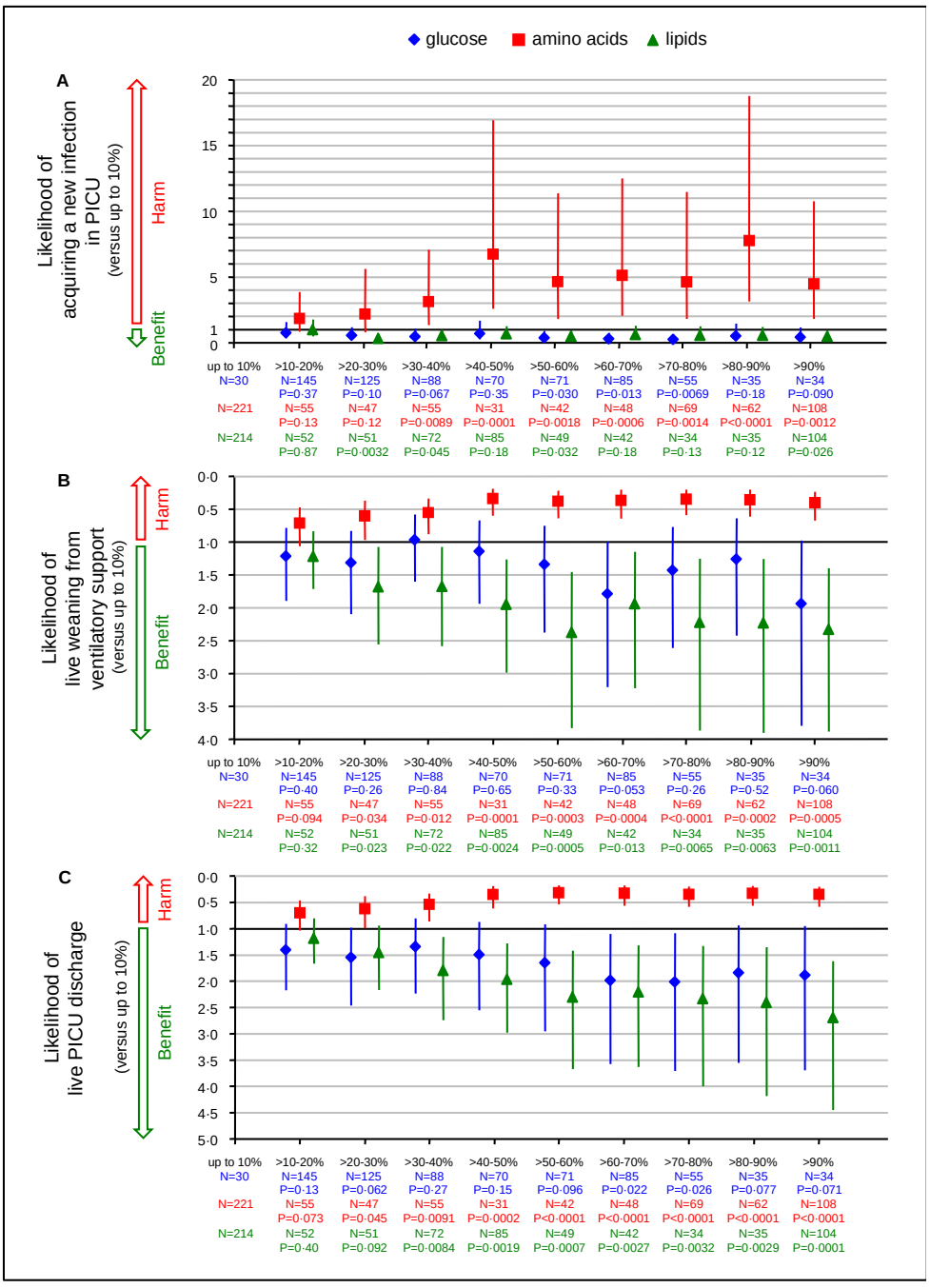
For each of the first seven days in PICU, the associations of the average total doses of the individual macronutrients up to that day with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals per ten percent added, with macronutrients entered as continuous variables. These were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one. N indicates the number of patients still in PICU on the day of analysis.

Figure S5: **Association of average enteral and parenteral macronutrient administration with clinical outcome**



For each of the first seven days in PICU, the associations of the average enteral (left panels) and parenteral doses (right panels) of the individual macronutrients up to that day with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals per ten percent added, with macronutrients entered as continuous variables. These were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one. N indicates the number of patients still in PICU on the day of analysis.

Figure S6: **Dose relationship per class of ten percent increase in average total macronutrient administration up to day four with clinical outcome**



Average total doses up to day four of each macronutrient were split up in classes of ten percent increases, with doses above 90 percent combined in a single class. The associations of the classes of average total doses of the individual macronutrients up to day four with likelihood of acquiring a new infection in PICU (panel A), of live weaning from mechanical ventilation (panel B), and of live PICU discharge (panel C) are shown as hazard ratios (blue diamonds for glucose, red squares for amino acids, and green triangles for lipid doses) and corresponding 95 percent confidence intervals as compared with the class of 0-10 percent. These were obtained after adjustment for type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. Corresponding P-values and number of patients in each class (N) are indicated in blue for glucose dose, in red for amino acid dose, and in green for lipid dose. A hazard ratio higher than one indicates a detrimental effect for likelihood of acquiring a new infection, but a beneficial effect for likelihood of live weaning from mechanical ventilation and of live PICU discharge, and vice versa for a hazard ratio below one.

SUPPLEMENTARY TABLES

Table S1: **Patient baseline characteristics and outcome**

Baseline characteristics	N=1440
Age (years), median (IQR)	1·5 (0·2 – 6·3)
Age <1 year, N (%)	653 (45·3)
Male gender, N (%)	830 (57·6)
Weight (kg), median (IQR)	10·0 (4·7 – 20·3)
Standard deviation score, median (IQR)	-0·5 (-1·4 – 0·5)
Height (cm), median (IQR)	80 (57 – 116)
Standard deviation score, median (IQR)	-0·3 (-1·4 – 0·8)
STRONGkids risk level, N (%)	
Medium	1288 (89·4)
High	152 (10·6)
PELOD score, first 24 hours in PICU, median (IQR)	21 (11 – 31)
PIM2 score, median (IQR)	-2·8 (-3·7 – -1·5)
PIM2-calculated risk of death (%), median (IQR)	5·9 (2·5 – 17·7)
Emergency admission, N (%)	783 (54·4)
Diagnostic group, N (%)	
Type of illness	
Surgical	
Abdominal	113 (7·8)
Burns	10 (0·7)
Cardiac	547 (38·0)
Neurosurgery-traumatic brain injury	116 (8·1)
Thoracic	61 (4·2)
Transplantation	24 (1·7)
Orthopaedic surgery-trauma	54 (3·8)
Other	48 (3·3)
Medical	
Cardiac	61 (4·2)
Gastrointestinal-hepatic	6 (0·4)
Oncologic-hematologic	15 (1·0)
Neurologic	103 (7·2)
Renal	2 (0·1)
Respiratory	195 (13·5)
Other	85 (5·9)
Condition on admission, N (%)	
Mechanical ventilation required	1261 (87·6)
ECMO or other assist device required	44 (3·1)
Infection	558 (38·8)
Outcome	
New infections, N (%)	211 (14·7)
Duration of mechanical ventilatory support (days), mean ± SE	5·4 ± 0·4
Total duration of stay in PICU (days), mean ± SE	7·9 ± 0·4
Death in PICU, N (%)	68 (4·7)
Death within 90 days after enrolment, N (%)	87 (6·0)

BMI: body mass index; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; PELOD: Paediatric Logistic Organ Dysfunction score;[S3] PICU: paediatric intensive care unit; PIM2: Paediatric Risk of Mortality 2 score;[S4] STRONGkids: Screening Tool for Risk On Nutritional Status and Growth (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).[S5]

Table S2: **Reference doses for macronutrients according to weight class used to transform the given doses of macronutrients to a unity that allows comparison for children of different ages and weights**

	Day 1	Day 2	Day 3	Day 4 - …
Glucose (g/kg/day)				
neonate	10	12	20	20
≤10 kg	10	10	20	20
>10 - 15 kg	5	10	15	15
>15 - 20 kg	5	10	15	15
>20 - 30 kg	5	10	15	15
> 30 kg	5	10	10	10
Amino acids (g/kg/day)				
neonate	1·5	2	3	3
≤10 kg	1·5	2	3	3
>10 - 15 kg	1	1·5	3	3
>15 - 20 kg	1	1·5	2	2
>20 - 30 kg	1	1	2	2
> 30 kg	1	1	2	2
Lipids (g/kg/day)				
neonate	1	2	3	3
≤10 kg	1	2	3	3
>10 - 15 kg	1	2	3	3
>15 - 20 kg	1	2	2	3
>20 - 30 kg	1	1	2	2·5
> 30 kg	1	1	2	2

The numbers indicate the upper limit of the reference doses of glucose, amino acids, and lipids for age/weight described in published nutritional guidelines.[S1,S2] The doses of these macronutrients that were administered to the critically ill patients were expressed as percentage relative to these reference doses. These doses were not necessarily those that were used locally as nutritional targets. They were only used for the current analysis, which required expression of the administered doses of the three macronutrients in an interchangeable and comparable unity for children of different ages and weights.

Table S3.1: **Association of average total macronutrient administration up to DAY 1 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·03 (0·55-1·83)	0·91
Burns	**5·95 (1·75-15·30)**	**0·0074**
Neurosurgery-traumatic brain injury	1·31 (0·70-2·31)	0·38
Thoracic	1·27 (0·57-2·50)	0·52
Transplantation	1·64 (0·61-3·67)	0·29
Orthopaedic surgery-trauma	1·12 (0·38-2·59)	0·81
Other	0·79 (0·19-2·18)	0·67
Medical		
Cardiac	1·15 (0·60-2·06)	0·66
Gastrointestinal-hepatic	0·81 (0·04-4·02)	0·83
Oncologic-hematologic	1·67 (0·64-3·79)	0·27
Neurologic	0·57 (0·26-1·11)	0·10
Renal	4·48 (0·25-21·05)	0·23
Respiratory	0·77 (0·46-1·24)	0·28
Other	**0·52 (0·25-1·00)**	**0·050**
Age, younger versus older than 1 year	1·13 (0·83-1·54)	0·44
High versus medium risk of malnutrition	**1·53 (1·01-2·26)**	**0·043**
PeLOD score first 24 hours per point added	**1·02 (1·00-1·04)**	**0·013**
PIM2 score per point added	**1·25 (1·14-1·38)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·94 (1·24-3·06)**	**0·0037**
Edmonton	**3·29 (1·84-5·71)**	**0·0001**
Average glucose dose per ten percent added	**0·91 (0·85-0·98)**	**0·012**
Average amino acid dose per ten percent added	**1·10 (1·04-1·16)**	**0·0008**
Average lipid dose per ten percent added	0·99 (0·96-1·02)	0·44

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.2: **Association of average total macronutrient administration up to DAY 2 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·01 (0·54-1·80)	0·96
Burns	**4·83 (1·41-12·52)**	**0·015**
Neurosurgery-traumatic brain injury	1·23 (0·65-2·20)	0·51
Thoracic	1·29 (0·58-2·57)	0·50
Transplantation	1·45 (0·54-3·25)	0·43
Orthopaedic surgery-trauma	1·14 (0·39-2·68)	0·78
Other	0·74 (0·18-2·09)	0·60
Medical		
Cardiac	1·14 (0·61-2·03)	0·66
Gastrointestinal-hepatic	0·74 (0·04-3·64)	0·76
Oncologic-hematologic	1·67 (0·65-3·76)	0·26
Neurologic	0·55 (0·25-1·09)	0·089
Renal	3·50 (0·20-16·44)	0·30
Respiratory	0·68 (0·41-1·10)	0·11
Other	0·57 (0·28-1·08)	0·088
Age, younger versus older than 1 year	1·06 (0·77-1·47)	0·71
High versus medium risk of malnutrition	1·41 (0·93-2·08)	0·10
PeLOD score first 24 hours per point added	**1·02 (1·01-1·04)**	**0·0053**
PIM2 score per point added	**1·22 (1·11-1·34)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·82 (1·17-2·85)**	**0·0081**
Edmonton	**2·75 (1·55-4·70)**	**0·0008**
Average glucose dose per ten percent added	**0·92 (0·84-0·99)**	**0·036**
Average amino acid dose per ten percent added	**1·10 (1·04-1·17)**	**0·0005**
Average lipid dose per ten percent added	0·99 (0·95-1·02)	0·49

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.3: **Association of average total macronutrient administration up to DAY 3 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·09 (0·58-1·94)	0·78
Burns	**4·44 (1·29-11·58)**	**0·021**
Neurosurgery-traumatic brain injury	1·06 (0·54-1·94)	0·86
Thoracic	1·17 (0·52-2·34)	0·68
Transplantation	1·13 (0·42-2·57)	0·78
Orthopaedic surgery-trauma	1·06 (0·36-2·51)	0·90
Other	0·63 (0·15-1·81)	0·42
Medical		
Cardiac	1·08 (0·58-1·91)	0·79
Gastrointestinal-hepatic	0·82 (0·04-4·39)	0·85
Oncologic-hematologic	1·55 (0·60-3·49)	0·33
Neurologic	0·60 (0·27-1·18)	0·14
Renal	2·53 (0·14-12·01)	0·42
Respiratory	**0·56 (0·34-0·92)**	**0·020**
Other	0·63 (0·32-1·16)	0·14
Age, younger versus older than 1 year	1·00 (0·72-1·40)	0·99
High versus medium risk of malnutrition	1·21 (0·80-1·80)	0·35
PeLOD score first 24 hours per point added	**1·02 (1·00-1·03)**	**0·031**
PIM2 score per point added	**1·23 (1·11-1·37)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·58 (1·03-2·42)**	**0·035**
Edmonton	**2·07 (1·17-3·50)**	**0·013**
Average glucose dose per ten percent added	**0·87 (0·79-0·97)**	**0·013**
Average amino acid dose per ten percent added	**1·13 (1·06-1·21)**	**0·0002**
Average lipid dose per ten percent added	0·99 (0·95-1·04)	0·80

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.4: **Association of average total macronutrient administration up to DAY 4 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·09 (0·59-1·95)	0·76
Burns	**3·93 (1·15-10·21)**	**0·031**
Neurosurgery-traumatic brain injury	1·00 (0·51-1·85)	0·99
Thoracic	1·17 (0·50-2·41)	0·70
Transplantation	1·03 (0·38-2·34)	0·94
Orthopaedic surgery-trauma	1·03 (0·35-2·44)	0·95
Other	0·56 (0·13-1·62)	0·31
Medical		
Cardiac	0·89 (0·48-1·55)	0·68
Gastrointestinal-hepatic	0·82 (0·04-4·29)	0·84
Oncologic-hematologic	1·27 (0·50-2·83)	0·59
Neurologic	0·56 (0·25-1·10)	0·094
Renal	4·13 (0·23-19·86)	0·25
Respiratory	**0·54 (0·33-0·86)**	**0·0096**
Other	0·71 (0·37-1·29)	0·27
Age, younger versus older than 1 year	0·92 (0·66-1·30)	0·63
High versus medium risk of malnutrition	1·34 (0·88-1·99)	0·17
PeLOD score first 24 hours per point added	**1·02 (1·00-1·03)**	**0·046**
PIM2 score per point added	**1·20 (1·08-1·34)**	**0·0006**
Treatment centre, as compared with Leuven		
Rotterdam	1·34 (0·88-2·03)	0·16
Edmonton	1·61 (0·90-2·75)	0·10
Average glucose dose per ten percent added	0·91 (0·81-1·01)	0·084
Average amino acid dose per ten percent added	**1·10 (1·03-1·17)**	**0·0067**
Average lipid dose per ten percent added	0·99 (0·95-1·04)	0·81

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.5: **Association of average total macronutrient administration up to DAY 5 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·98 (0·52-1·75)	0·94
Burns	**3·87 (1·13-10·04)**	**0·033**
Neurosurgery-traumatic brain injury	0·94 (0·47-1·79)	0·85
Thoracic	1·12 (0·48-2·31)	0·77
Transplantation	0·77 (0·28-1·75)	0·55
Orthopaedic surgery-trauma	0·99 (0·34-2·36)	0·98
Other	0·61 (0·14-1·81)	0·40
Medical		
Cardiac	0·66 (0·35-1·17)	0·16
Gastrointestinal-hepatic	0·71 (0·04-3·53)	0·73
Oncologic-hematologic	1·08 (0·42-2·42)	0·85
Neurologic	0·62 (0·28-1·21)	0·16
Renal	3·16 (0·18-15·34)	0·34
Respiratory	**0·46 (0·28-0·75)**	**0·0015**
Other	0·62 (0·32-1·12)	0·11
Age, younger versus older than 1 year	0·92 (0·65-1·30)	0·63
High versus medium risk of malnutrition	1·26 (0·82-1·89)	0·28
PeLOD score first 24 hours per point added	1·01 (0·99-1·03)	0·19
PIM2 score per point added	**1·22 (1·09-1·36)**	**0·0004**
Treatment centre, as compared with Leuven		
Rotterdam	1·26 (0·82-1·91)	0·29
Edmonton	1·46 (0·81-2·52)	0·19
Average glucose dose per ten percent added	0·94 (0·84-1·04)	0·23
Average amino acid dose per ten percent added	**1·07 (1·01-1·14)**	**0·029**
Average lipid dose per ten percent added	0·99 (0·94-1·04)	0·67

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.6: **Association of average total macronutrient administration up to DAY 6 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·04 (0·55-1·87)	0·90
Burns	**3·77 (1·08-10·16)**	**0·039**
Neurosurgery-traumatic brain injury	0·79 (0·39-1·52)	0·49
Thoracic	0·95 (0·38-2·04)	0·89
Transplantation	0·50 (0·16-1·22)	0·13
Orthopaedic surgery-trauma	0·95 (0·32-2·28)	0·91
Other	0·68 (0·16-1·98)	0·51
Medical		
Cardiac	0·58 (0·31-1·03)	0·063
Gastrointestinal-hepatic	0·65 (0·04-3·13)	0·65
Oncologic-hematologic	0·95 (0·37-2·14)	0·90
Neurologic	**0·48 (0·21-0·95)**	**0·035**
Renal	2·85 (0·16-13·92)	0·38
Respiratory	**0·40 (0·24-0·66)**	**0·0003**
Other	**0·51 (0·27-0·94)**	**0·029**
Age, younger versus older than 1 year	0·77 (0·54-1·11)	0·16
High versus medium risk of malnutrition	1·09 (0·70-1·66)	0·69
PeLOD score first 24 hours per point added	1·00 (0·99-1·02)	0·69
PIM2 score per point added	**1·20 (1·08-1·35)**	**0·0012**
Treatment centre, as compared with Leuven		
Rotterdam	1·15 (0·74-1·77)	0·52
Edmonton	1·33 (0·72-2·35)	0·34
Average glucose dose per ten percent added	0·93 (0·83-1·04)	0·18
Average amino acid dose per ten percent added	1·06 (0·99-1·13)	0·093
Average lipid dose per ten percent added	0·99 (0·95-1·05)	0·82

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S3.7: **Association of average total macronutrient administration up to DAY 7 with likelihood of acquiring a new infection**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·93 (0·50-1·68)	0·82
Burns	**7·69 (2·22-20·47)**	**0·0031**
Neurosurgery-traumatic brain injury	0·94 (0·46-1·81)	0·86
Thoracic	0·60 (0·20-1·44)	0·27
Transplantation	**0·40 (0·13-1·00)**	**0·050**
Orthopaedic surgery-trauma	0·72 (0·21-1·88)	0·53
Other	0·37 (0·06-1·27)	0·12
Medical		
Cardiac	**0·47 (0·25-0·85)**	**0·011**
Gastrointestinal-hepatic	0·49 (0·03-2·34)	0·44
Oncologic-hematologic	0·74 (0·29-1·68)	0·48
Neurologic	**0·38 (0·16-0·79)**	**0·0076**
Renal	2·34 (0·13-11·50)	0·46
Respiratory	**0·37 (0·22-0·61)**	**<0·0001**
Other	**0·42 (0·21-0·76)**	**0·0039**
Age, younger versus older than 1 year	0·78 (0·54-1·14)	0·20
High versus medium risk of malnutrition	1·13 (0·72-1·74)	0·58
PeLOD score first 24 hours per point added	1·00 (0·98-1·02)	0·98
PIM2 score per point added	**1·23 (1·09-1·39)**	**0·0006**
Treatment centre, as compared with Leuven		
Rotterdam	1·15 (0·74-1·78)	0·52
Edmonton	1·35 (0·73-2·40)	0·33
Average glucose dose per ten percent added	0·95 (0·85-1·06)	0·34
Average amino acid dose per ten percent added	1·04 (0·98-1·11)	0·19
Average lipid dose per ten percent added	0·99 (0·94-1·05)	0·80

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S4: **Association of average total macronutrient administration with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis: summary**

	Not penalised for death		Penalised for death [a]	
	HR (95 percent CI)	**P**	**HR (95 percent CI)**	**P**
Analysis up to day 1				
Average glucose dose per ten percent added	0·92 (0·86-0·99)	0·031	0·93 (0·86-1·00)	0·049
Average amino acid dose per ten percent added	1·10 (1·04-1·17)	0·0005	1·09 (1·03-1·15)	0·0039
Average lipid dose per ten percent added	0·98 (0·95-1·02)	0·30	0·99 (0·96-1·02)	0·45
Average glycaemia per ten mg/dl added	1·00 (0·97-1·03)	0·83	1·03 (1·00-1·06)	0·068
Average insulin dose per ten IU added	0·84 (0·71-1·00)	0·045	0·90 (0·78-1·05)	0·17
Analysis up to day 2				
Average glucose dose per ten percent added	0·93 (0·85-1·02)	0·10	0·94 (0·86-1·03)	0·20
Average amino acid dose per ten percent added	1·09 (1·02-1·15)	0·0057	1·07 (1·01-1·14)	0·027
Average lipid dose per ten percent added	0·98 (0·94-1·02)	0·35	0·98 (0·94-1·02)	0·37
Average glycaemia per ten mg/dl added	1·03 (0·99-1·09)	0·17	1·05 (1·01-1·10)	0·022
Average insulin dose per ten IU added	0·94 (0·87-1·02)	0·14	0·98 (0·92-1·04)	0·48
Analysis up to day 3				
Average glucose dose per ten percent added	0·89 (0·79-1·00)	0·057	0·89 (0·79-1·00)	0·058
Average amino acid dose per ten percent added	1·10 (1·02-1·19)	0·014	1·10 (1·02-1·19)	0·015
Average lipid dose per ten percent added	0·98 (0·94-1·03)	0·42	0·98 (0·93-1·03)	0·34
Average glycaemia per ten mg/dl added	1·09 (1·03-1·16)	0·0027	1·09 (1·03-1·16)	0·0023
Average insulin dose per ten IU added	0·96 (0·89-1·03)	0·28	0·98 (0·92-1·04)	0·46

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment center. [a] In a sensitivity analysis accounting for death as competing risk, patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death. CI: confidence interval, HR: hazard ratio, PICU: paediatric intensive care unit. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight. Tables S5.1-6 show the full models with all covariates included.

Table S5.1: **Association of average total macronutrient administration up to DAY 1 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis NOT PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·91 (0·48-1·63)	0·74
Burns	**5·11 (1·49-13·25)**	**0·013**
Neurosurgery-traumatic brain injury	1·12 (0·57-2·06)	0·72
Thoracic	1·04 (0·45-2·11)	0·92
Transplantation	1·91 (0·71-4·35)	0·18
Orthopaedic surgery-trauma	1·20 (0·41-2·80)	0·70
Other	0·55 (0·09-1·81)	0·36
Medical		
Cardiac	1·19 (0·62-2·19)	0·58
Gastrointestinal-hepatic	0·74 (0·04-3·69)	0·76
Oncologic-hematologic	1·67 (0·64-3·82)	0·27
Neurologic	**0·44 (0·18-0·92)**	**0·028**
Renal	3·94 (0·22-18·57)	0·26
Respiratory	0·67 (0·39-1·13)	0·13
Other	0·56 (0·27-1·09)	0·088
Age, younger versus older than 1 year	1·12 (0·80-1·55)	0·51
High versus medium risk of malnutrition	1·49 (0·98-2·22)	0·063
PeLOD score first 24 hours per point added	1·02 (1·00-1·03)	0·057
PIM2 score per point added	**1·27 (1·15-1·41)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·86 (1·16-3·00)**	**0·0096**
Edmonton	**2·42 (1·12-4·86)**	**0·026**
Average glucose dose per ten percent added	**0·92 (0·86-0·99)**	**0·031**
Average amino acid dose per ten percent added	**1·10 (1·04-1·17)**	**0·0005**
Average lipid dose per ten percent added	0·98 (0·95-1·02)	0·30
Average glycaemia per ten mg/dl added	1·00 (0·97-1·03)	0·83
Average insulin dose per ten IU added	**0·84 (0·71-1·00)**	**0·045**

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S5.2: **Association of average total macronutrient administration up to DAY 2 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis NOT PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·09 (0·58-1·97)	0·78
Burns	**4·39 (1·28-11·49)**	**0·022**
Neurosurgery-traumatic brain injury	1·12 (0·56-2·07)	0·73
Thoracic	1·11 (0·45-2·34)	0·81
Transplantation	1·60 (0·59-3·66)	0·32
Orthopaedic surgery-trauma	1·27 (0·43-2·98)	0·63
Other	0·66 (0·11-2·20)	0·55
Medical		
Cardiac	1·28 (0·67-2·32)	0·44
Gastrointestinal-hepatic	0·83 (0·05-4·07)	0·85
Oncologic-hematologic	1·68 (0·65-3·84)	0·26
Neurologic	**0·45 (0·18-0·94)**	**0·032**
Renal	3·14 (0·18-14·79)	0·34
Respiratory	0·68 (0·39-1·14)	0·14
Other	0·63 (0·31-1·21)	0·17
Age, younger versus older than 1 year	1·12 (0·79-1·58)	0·53
High versus medium risk of malnutrition	1·44 (0·94-2·16)	0·093
PeLOD score first 24 hours per point added	**1·02 (1·00-1·04)**	**0·033**
PIM2 score per point added	**1·21 (1·09-1·34)**	**0·0004**
Treatment centre, as compared with Leuven		
Rotterdam	**1·66 (1·02-2·71)**	**0·041**
Edmonton	1·86 (0·84-3·86)	0·12
Average glucose dose per ten percent added	0·93 (0·85-1·02)	0·10
Average amino acid dose per ten percent added	**1·09 (1·02-1·15)**	**0·0057**
Average lipid dose per ten percent added	0·98 (0·94-1·02)	0·35
Average glycaemia per ten mg/dl added	1·03 (0·99-1·09)	0·17
Average insulin dose per ten IU added	0·94 (0·87-1·02)	0·14

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S5.3: **Association of average total macronutrient administration up to DAY 3 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis NOT PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·23 (0·64-2·24)	0·52
Burns	**4·33 (1·24-11·62)**	**0·025**
Neurosurgery-traumatic brain injury	0·98 (0·48-1·85)	0·94
Thoracic	1·14 (0·46-2·41)	0·76
Transplantation	1·13 (0·42-2·60)	0·79
Orthopaedic surgery-trauma	1·14 (0·39-2·72)	0·78
Other	0·87 (0·14-2·94)	0·84
Medical		
Cardiac	1·26 (0·67-2·24)	0·46
Gastrointestinal-hepatic	1·14 (0·06-5·80)	0·90
Oncologic-hematologic	1·49 (0·57-3·39)	0·38
Neurologic	0·53 (0·22-1·12)	0·10
Renal	3·73 (0·21-17·96)	0·28
Respiratory	**0·59 (0·34-0·99)**	**0·044**
Other	0·69 (0·34-1·29)	0·24
Age, younger versus older than 1 year	1·15 (0·81-1·65)	0·43
High versus medium risk of malnutrition	1·27 (0·82-1·91)	0·27
PeLOD score first 24 hours per point added	1·01 (1·00-1·03)	0·13
PIM2 score per point added	**1·19 (1·07-1·33)**	**0·0016**
Treatment centre, as compared with Leuven		
Rotterdam	1·38 (0·84-2·26)	0·20
Edmonton	1·12 (0·47-2·45)	0·79
Average glucose dose per ten percent added	0·89 (0·79-1·00)	0·057
Average amino acid dose per ten percent added	**1·10 (1·02-1·19)**	**0·014**
Average lipid dose per ten percent added	0·98 (0·94-1·03)	0·42
Average glycaemia per ten mg/dl added	**1·09 (1·03-1·16)**	**0·0027**
Average insulin dose per ten IU added	0·96 (0·89-1·03)	0·28

Patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S5.4: **Association of average total macronutrient administration up to DAY 1 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·06 (0·56-1·92)	0·84
Burns	**5·72 (1·66-14·97)**	**0·0089**
Neurosurgery-traumatic brain injury	1·23 (0·62-2·26)	0·53
Thoracic	1·22 (0·52-2·50)	0·61
Transplantation	1·85 (0·68-4·21)	0·20
Orthopaedic surgery-trauma	1·32 (0·45-3·09)	0·57
Other	0·65 (0·11-2·16)	0·53
Medical		
Cardiac	1·14 (0·59-2·09)	0·69
Gastrointestinal-hepatic	0·86 (0·05-4·40)	0·88
Oncologic-hematologic	1·66 (0·64-3·76)	0·27
Neurologic	0·50 (0·20-1·06)	0·073
Renal	3·76 (0·21-17·75)	0·28
Respiratory	0·67 (0·39-1·13)	0·13
Other	0·78 (0·40-1·45)	0·44
Age, younger versus older than 1 year	1·27 (0·91-1·77)	0·15
High versus medium risk of malnutrition	1·43 (0·94-2·14)	0·094
PeLOD score first 24 hours per point added	**1·02 (1·00-1·04)**	**0·028**
PIM2 score per point added	**1·35 (1·22-1·50)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·92 (1·19-2·11)**	**0·0075**
Edmonton	**2·32 (1·07-4·66)**	**0·034**
Average glucose dose per ten percent added	**0·93 (0·86-1·00)**	**0·049**
Average amino acid dose per ten percent added	**1·09 (1·03-1·15)**	**0·0039**
Average lipid dose per ten percent added	0·99 (0·96-1·02)	0·45
Average glycaemia per ten mg/dl added	1·03 (1·00-1·06)	0·068
Average insulin dose per ten IU added	0·90 (0·78-1·05)	0·17

Patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death. Other patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S5.5: **Association of average total macronutrient administration up to DAY 2 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·20 (0·63-2·18)	0·55
Burns	**4·59 (1·33-12·06)**	**0·019**
Neurosurgery-traumatic brain injury	1·14 (0·57-2·11)	0·69
Thoracic	1·23 (0·50-2·61)	0·62
Transplantation	1·46 (0·54-3·34)	0·42
Orthopaedic surgery-trauma	1·35 (0·46-3·19)	0·55
Other	0·76 (0·12-2·55)	0·70
Medical		
Cardiac	1·28 (0·68-2·30)	0·42
Gastrointestinal-hepatic	0·96 (0·05-4·74)	0·97
Oncologic-hematologic	1·39 (0·54-3·17)	0·47
Neurologic	0·49 (0·20-1·02)	0·056
Renal	2·94 (0·16-13·82)	0·36
Respiratory	0·66 (0·38-1·10)	0·11
Other	0·74 (0·37-1·37)	0·34
Age, younger versus older than 1 year	1·24 (0·88-1·75)	0·22
High versus medium risk of malnutrition	1·40 (0·91-2·09)	0·12
PeLOD score first 24 hours per point added	**1·02 (1·00-1·04)**	**0·025**
PIM2 score per point added	**1·29 (1·16-1·44)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**1·75 (1·07-2·86)**	**0·025**
Edmonton	1·80 (0·81-3·72)	0·14
Average glucose dose per ten percent added	0·94 (0·86-1·03)	0·20
Average amino acid dose per ten percent added	**1·07 (1·01-1·14)**	**0·027**
Average lipid dose per ten percent added	0·98 (0·94-1·02)	0·37
Average glycaemia per ten mg/dl added	**1·05 (1·01-1·10)**	**0·022**
Average insulin dose per ten IU added	0·98 (0·92-1·04)	0·48

Patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death. Other patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S5.6: **Association of average total macronutrient administration up to DAY 3 with likelihood of acquiring a new infection: sensitivity analysis adjusting for average glycaemia and average insulin dose up to the day of analysis PENALISED for death**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	1·21 (0·63-2·22)	0·54
Burns	**4·50 (1·29-12·10)**	**0·021**
Neurosurgery-traumatic brain injury	0·98 (0·48-1·85)	0·94
Thoracic	1·15 (0·47-2·44)	0·73
Transplantation	1·08 (0·40-2·47)	0·87
Orthopaedic surgery-trauma	1·13 (0·38-2·69)	0·80
Other	0·93 (0·15-3·16)	0·92
Medical		
Cardiac	1·20 (0·64-2·14)	0·55
Gastrointestinal-hepatic	1·29 (0·07-6·70)	0·81
Oncologic-hematologic	1·39 (0·54-3·16)	0·47
Neurologic	0·60 (0·24-1·26)	0·18
Renal	3·53 (0·20-16·98)	0·30
Respiratory	**0·59 (0·34-0·99)**	**0·045**
Other	0·75 (0·38-1·39)	0·37
Age, younger versus older than 1 year	1·19 (0·83-1·70)	0·34
High versus medium risk of malnutrition	1·34 (0·87-2·01)	0·18
PeLOD score first 24 hours per point added	1·02 (1·00-1·03)	0·087
PIM2 score per point added	**1·22 (1·09-1·37)**	**0·0004**
Treatment centre, as compared with Leuven		
Rotterdam	1·45 (0·88-2·38)	0·14
Edmonton	1·19 (0·50-2·60)	0·68
Average glucose dose per ten percent added	0·89 (0·79-1·00)	0·058
Average amino acid dose per ten percent added	**1·10 (1·02-1·19)**	**0·015**
Average lipid dose per ten percent added	0·98 (0·93-1·03)	0·34
Average glycaemia per ten mg/dl added	**1·09 (1·03-1·16)**	**0·0023**
Average insulin dose per ten IU added	0·98 (0·92-1·04)	0·46

Patients who died before acquiring any new infection in the PICU were labeled as having acquired a new infection on the day of death. Other patients who did not acquire a new infection during PICU stay were considered infection-free up to day 90. Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.1: **Association of average total macronutrient administration up to DAY 1 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·87 (0·69-1·09)	0·22
Burns	**0·40 (0·20-0·72)**	**0·0012**
Neurosurgery-traumatic brain injury	**0·75 (0·60-0·93)**	**0·0087**
Thoracic	1·03 (0·78-1·34)	0·84
Transplantation	1·06 (0·67-1·59)	0·80
Orthopaedic surgery-trauma	0·94 (0·69-1·24)	0·65
Other	**0·63 (0·46-0·86)**	**0·0027**
Medical		
Cardiac	0·75 (0·55-1·01)	0·056
Gastrointestinal-hepatic	0·77 (0·27-1·71)	0·56
Oncologic-hematologic	0·81 (0·44-1·36)	0·44
Neurologic	0·81 (0·64-1·02)	0·072
Renal	0·56 (0·03-2·51)	0·52
Respiratory	**0·56 (0·46-0·67)**	**<0·0001**
Other	**0·74 (0·56-0·96)**	**0·024**
Age, younger versus older than 1 year	**0·69 (0·61-0·78)**	**<0·0001**
High versus medium risk of malnutrition	**0·81 (0·67-0·97)**	**0·020**
PeLOD score first 24 hours per point added	**0·97 (0·97-0·98)**	**<0·0001**
PIM2 score per point added	**0·72 (0·69-0·75)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·48 (0·40-0·57)**	**<0·0001**
Edmonton	**0·42 (0·33-0·54)**	**<0·0001**
Average glucose dose per ten percent added	1·01 (0·99-1·03)	0·22
Average amino acid dose per ten percent added	0·99 (0·97-1·01)	0·25
Average lipid dose per ten percent added	0·99 (0·98-1·01)	0·42

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.2: **Association of average total macronutrient administration up to DAY 2 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·81 (0·63-1·04)	0·10
Burns	**0·39 (0·19-0·72)**	**0·0015**
Neurosurgery-traumatic brain injury	**0·69 (0·53-0·90)**	**0·0050**
Thoracic	1·07 (0·77-1·46)	0·66
Transplantation	1·07 (0·67-1·63)	0·76
Orthopaedic surgery-trauma	0·78 (0·52-1·13)	0·19
Other	**0·59 (0·40-0·84)**	**0·0031**
Medical		
Cardiac	**0·74 (0·54-1·00)**	**0·049**
Gastrointestinal-hepatic	0·75 (0·26-1·66)	0·50
Oncologic-hematologic	0·81 (0·44-1·37)	0·45
Neurologic	**0·74 (0·57-0·95)**	**0·018**
Renal	0·55 (0·03-2·45)	0·50
Respiratory	**0·56 (0·45-0·69)**	**<0·0001**
Other	**0·68 (0·50-0·91)**	**0·0084**
Age, younger versus older than 1 year	**0·70 (0·61-0·80)**	**<0·0001**
High versus medium risk of malnutrition	**0·79 (0·65-0·96)**	**0·016**
PeLOD score first 24 hours per point added	**0·98 (0·97-0·99)**	**<0·0001**
PIM2 score per point added	**0·73 (0·70-0·77)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·49 (0·41-0·59)**	**<0·0001**
Edmonton	**0·45 (0·34-0·58)**	**<0·0001**
Average glucose dose per ten percent added	1·01 (0·99-1·03)	0·31
Average amino acid dose per ten percent added	0·98 (0·96-1·00)	0·064
Average lipid dose per ten percent added	1·00 (0·99-1·02)	0·60

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.3: **Association of average total macronutrient administration up to DAY 3 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·80 (0·59-1·06)	0·12
Burns	**0·44 (0·20-0·84)**	**0·010**
Neurosurgery-traumatic brain injury	**0·69 (0·50-0·94)**	**0·019**
Thoracic	1·33 (0·92-1·87)	0·12
Transplantation	1·22 (0·74-1·92)	0·41
Orthopaedic surgery-trauma	0·84 (0·52-1·29)	0·43
Other	0·75 (0·48-1·12)	0·16
Medical		
Cardiac	0·79 (0·56-1·09)	0·16
Gastrointestinal-hepatic	0·42 (0·07-1·34)	0·16
Oncologic-hematologic	0·82 (0·44-1·42)	0·50
Neurologic	**0·72 (0·53-0·96)**	**0·027**
Renal	0·54 (0·03-2·43)	0·49
Respiratory	**0·62 (0·49-0·78)**	**<0·0001**
Other	0·75 (0·54-1·02)	0·071
Age, younger versus older than 1 year	**0·74 (0·62-0·87)**	**0·0004**
High versus medium risk of malnutrition	**0·81 (0·65-1·00)**	**0·044**
PeLOD score first 24 hours per point added	**0·98 (0·97-0·99)**	**<0·0001**
PIM2 score per point added	**0·74 (0·70-0·79)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·53 (0·43-0·66)**	**<0·0001**
Edmonton	**0·49 (0·36-0·64)**	**<0·0001**
Average glucose dose per ten percent added	1·01 (0·99-1·04)	0·31
Average amino acid dose per ten percent added	**0·98 (0·95-1·00)**	**0·037**
Average lipid dose per ten percent added	1·01 (0·98-1·03)	0·62

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.4: **Association of average total macronutrient administration up to DAY 4 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·82 (0·59-1·14)	0·24
Burns	0·51 (0·21-1·01)	0·055
Neurosurgery-traumatic brain injury	0·71 (0·49-1·00)	0·053
Thoracic	1·54 (0·99-2·31)	0·057
Transplantation	1·32 (0·75-2·18)	0·31
Orthopaedic surgery-trauma	0·91 (0·53-1·49)	0·72
Other	1·03 (0·63-1·61)	0·91
Medical		
Cardiac	0·86 (0·60-1·21)	0·39
Gastrointestinal-hepatic	0·23 (0·01-1·09)	0·067
Oncologic-hematologic	0·86 (0·44-1·52)	0·62
Neurologic	0·74 (0·52-1·03)	0·078
Renal	0·00 (0·00-1·14)	0·066
Respiratory	**0·66 (0·51-0·85)**	**0·0014**
Other	0·83 (0·58-1·17)	0·30
Age, younger versus older than 1 year	**0·76 (0·63-0·93)**	**0·0061**
High versus medium risk of malnutrition	0·81 (0·64-1·02)	0·075
PeLOD score first 24 hours per point added	**0·99 (0·98-1·00)**	**0·011**
PIM2 score per point added	**0·75 (0·70-0·80)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·58 (0·46-0·73)**	**<0·0001**
Edmonton	**0·56 (0·41-0·77)**	**0·0002**
Average glucose dose per ten percent added	1·01 (0·98-1·04)	0·44
Average amino acid dose per ten percent added	**0·97 (0·94-0·99)**	**0·019**
Average lipid dose per ten percent added	1·01 (0·99-1·04)	0·26

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.5: **Association of average total macronutrient administration up to DAY 5 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·87 (0·60-1·25)	0·45
Burns	0·59 (0·23-1·26)	0·18
Neurosurgery-traumatic brain injury	0·71 (0·46-1·06)	0·095
Thoracic	**2·03 (1·24-3·17)**	**0·0055**
Transplantation	**1·80 (1·01-3·03)**	**0·046**
Orthopaedic surgery-trauma	1·02 (0·56-1·75)	0·94
Other	1·33 (0·77-2·21)	0·29
Medical		
Cardiac	0·93 (0·63-1·33)	0·69
Gastrointestinal-hepatic	0·23 (0·01-1·07)	0·063
Oncologic-hematologic	0·92 (0·46-1·68)	0·79
Neurologic	0·77 (0·52-1·13)	0·18
Renal	0·00 (0·00-1·17)	0·069
Respiratory	**0·74 (0·56-0·98)**	**0·033**
Other	0·90 (0·60-1·30)	0·57
Age, younger versus older than 1 year	0·83 (0·66-1·04)	0·098
High versus medium risk of malnutrition	0·84 (0·65-1·07)	0·16
PeLOD score first 24 hours per point added	1·00 (0·99-1·01)	0·40
PIM2 score per point added	**0·74 (0·69-0·79)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·65 (0·49-0·84)**	**0·0012**
Edmonton	**0·66 (0·46-0·93)**	**0·015**
Average glucose dose per ten percent added	1·01 (0·98-1·05)	0·56
Average amino acid dose per ten percent added	**0·96 (0·92-0·99)**	**0·018**
Average lipid dose per ten percent added	1·02 (0·99-1·05)	0·21

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.6: **Association of average total macronutrient administration up to DAY 6 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·77 (0·50-1·16)	0·20
Burns	0·64 (0·22-1·45)	0·31
Neurosurgery-traumatic brain injury	0·75 (0·47-1·17)	0·21
Thoracic	**2·55 (1·48-4·19)**	**0·0012**
Transplantation	**2·08 (1·09-3·73)**	**0·028**
Orthopaedic surgery-trauma	1·04 (0·53-1·90)	0·89
Other	1·40 (0·71-2·54)	0·31
Medical		
Cardiac	0·95 (0·63-1·39)	0·79
Gastrointestinal-hepatic	**0·21 (0·01-1·00)**	**0·049**
Oncologic-hematologic	0·92 (0·44-1·74)	0·80
Neurologic	0·87 (0·56-1·30)	0·48
Renal	0·00 (0·00-1·18)	0·070
Respiratory	0·78 (0·57-1·06)	0·11
Other	0·96 (0·63-1·44)	0·85
Age, younger versus older than 1 year	0·89 (0·69-1·14)	0·35
High versus medium risk of malnutrition	0·87 (0·66-1·13)	0·29
PeLOD score first 24 hours per point added	1·00 (0·99-1·01)	0·85
PIM2 score per point added	**0·75 (0·69-0·81)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·70 (0·53-0·93)**	**0·014**
Edmonton	0·76 (0·51-1·10)	0·14
Average glucose dose per ten percent added	1·01 (0·97-1·06)	0·68
Average amino acid dose per ten percent added	**0·95 (0·91-1·00)**	**0·036**
Average lipid dose per ten percent added	1·03 (0·99-1·06)	0·15

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S6.7: **Association of average total macronutrient administration up to DAY 7 with early live weaning from mechanical ventilation**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·77 (0·48-1·21)	0·26
Burns	0·61 (0·18-1·52)	0·31
Neurosurgery-traumatic brain injury	0·68 (0·40-1·12)	0·13
Thoracic	**3·16 (1·70-5·54)**	**0·0006**
Transplantation	**2·24 (1·12-4·18)**	**0·024**
Orthopaedic surgery-trauma	1·07 (0·50-2·07)	0·84
Other	1·75 (0·85-3·31)	0·12
Medical		
Cardiac	0·97 (0·63-1·46)	0·89
Gastrointestinal-hepatic	**0·21 (0·01-0·99)**	**0·048**
Oncologic-hematologic	0·96 (0·45-1·85)	0·91
Neurologic	0·86 (0·53-1·34)	0·50
Renal	0·00 (0·00-1·25)	0·078
Respiratory	0·83 (0·59-1·16)	0·27
Other	0·94 (0·60-1·45)	0·79
Age, younger versus older than 1 year	0·83 (0·63-1·11)	0·21
High versus medium risk of malnutrition	0·87 (0·64-1·16)	0·34
PeLOD score first 24 hours per point added	1·00 (0·99-1·01)	0·72
PIM2 score per point added	**0·76 (0·70-0·83)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	0·74 (0·54-1·01)	0·056
Edmonton	0·83 (0·55-1·25)	0·38
Average glucose dose per ten percent added	1·01 (0·96-1·06)	0·71
Average amino acid dose per ten percent added	**0·95 (0·90-1·00)**	**0·045**
Average lipid dose per ten percent added	1·03 (0·99-1·07)	0·10

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.1: **Association of average total macronutrient administration up to DAY 1 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	**0·79 (0·63-0·99)**	**0·038**
Burns	**0·44 (0·22-0·78)**	**0·0038**
Neurosurgery-traumatic brain injury	**0·72 (0·57-0·89)**	**0·0020**
Thoracic	**0·75 (0·56-0·99)**	**0·039**
Transplantation	**0·63 (0·40-0·95)**	**0·026**
Orthopaedic surgery-trauma	0·77 (0·57-1·03)	0·077
Other	**0·47 (0·34-0·64)**	**<0·0001**
Medical		
Cardiac	**0·54 (0·39-0·74)**	**<0·0001**
Gastrointestinal-hepatic	0·76 (0·27-1·68)	0·52
Oncologic-hematologic	0·65 (0·36-1·08)	0·10
Neurologic	**0·73 (0·58-0·92)**	**0·0071**
Renal	0·32 (0·02-1·42)	0·16
Respiratory	**0·62 (0·51-0·75)**	**<0·0001**
Other	**0·58 (0·44-0·76)**	**<0·0001**
Age, younger versus older than 1 year	**0·72 (0·64-0·82)**	**<0·0001**
High versus medium risk of malnutrition	**0·80 (0·67-0·96)**	**0·018**
PeLOD score first 24 hours per point added	**0·99 (0·98-0·99)**	**0·0002**
PIM2 score per point added	**0·74 (0·71-0·78)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·57 (0·48-0·67)**	**<0·0001**
Edmonton	**0·55 (0·43-0·70)**	**<0·0001**
Average glucose dose per ten percent added	**1·02 (1·01-1·04)**	**0·0096**
Average amino acid dose per ten percent added	**0·97 (0·96-0·99)**	**0·0014**
Average lipid dose per ten percent added	1·00 (0·99-1·02)	0·76

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.2: **Association of average total macronutrient administration up to DAY 2 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	**0·78 (0·60-1·00)**	**0·047**
Burns	**0·49 (0·23-0·89)**	**0·018**
Neurosurgery-traumatic brain injury	**0·70 (0·53-0·90)**	**0·0055**
Thoracic	0·75 (0·54-1·02)	0·069
Transplantation	0·66 (0·41-1·01)	0·055
Orthopaedic surgery-trauma	**0·68 (0·45-0·98)**	**0·039**
Other	**0·46 (0·31-0·66)**	**<0·0001**
Medical		
Cardiac	**0·57 (0·41-0·78)**	**0·0003**
Gastrointestinal-hepatic	0·77 (0·27-1·72)	0·55
Oncologic-hematologic	0·71 (039-1·20)	0·21
Neurologic	**0·74 (0·57-0·95)**	**0·016**
Renal	0·36 (0·02-1·59)	0·21
Respiratory	**0·66 (0·54-0·81)**	**<0·0001**
Other	**0·58 (0·43-0·78)**	**0·0002**
Age, younger versus older than 1 year	**0·78 (0·68-0·90)**	**0·0006**
High versus medium risk of malnutrition	**0·78 (0·64-0·95)**	**0·012**
PeLOD score first 24 hours per point added	**0·99 (0·98-1·00)**	**0·0014**
PIM2 score per point added	**0·76 (0·73-0·80)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·60 (0·50-0·72)**	**<0·0001**
Edmonton	**0·63 (0·49-0·81)**	**0·0003**
Average glucose dose per ten percent added	1·01 (0·99-1·04)	0·19
Average amino acid dose per ten percent added	**0·97 (0·95-0·99)**	**0·0032**
Average lipid dose per ten percent added	1·01 (1·00-1·03)	0·13

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.3: **Association of average total macronutrient administration up to DAY 3 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·81 (0·60-1·08)	0·15
Burns	0·58 (0·26-1·11)	0·10
Neurosurgery-traumatic brain injury	0·77 (0·56-1·04)	0·092
Thoracic	0·93 (0·64-1·32)	0·69
Transplantation	0·76 (0·46-1·19)	0·23
Orthopaedic surgery-trauma	0·78 (0·49-1·20)	0·26
Other	**0·56 (0·36-0·85)**	**0·0057**
Medical		
Cardiac	**0·66 (0·46-0·91)**	**0·010**
Gastrointestinal-hepatic	0·39 (0·06-1·26)	0·12
Oncologic-hematologic	0·78 (0·41-1·34)	0·37
Neurologic	0·77 (0·56-1·03)	0·081
Renal	0·44 (0·03-1·99)	0·35
Respiratory	**0·77 (0·61-0·96)**	**0·021**
Other	**0·67 (0·48-0·91)**	**0·010**
Age, younger versus older than 1 year	**0·84 (0·72-1·00)**	**0·044**
High versus medium risk of malnutrition	**0·80 (0·64-0·99)**	**0·036**
PeLOD score first 24 hours per point added	**0·99 (0·98-1·00)**	**0·029**
PIM2 score per point added	**0·79 (0·74-0·83)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·62 (0·50-0·76)**	**<0·0001**
Edmonton	**0·69 (0·52-0·91)**	**0·0080**
Average glucose dose per ten percent added	1·01 (0·99-1·04)	0·25
Average amino acid dose per ten percent added	**0·96 (0·94-0·99)**	**0·0029**
Average lipid dose per ten percent added	1·02 (1·00-1·04)	0·10

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.4: **Association of average total macronutrient administration up to DAY 4 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·82 (0·59-1·14)	0·24
Burns	0·65 (0·28-1·31)	0·25
Neurosurgery-traumatic brain injury	0·79 (0·55-1·12)	0·18
Thoracic	0·94 (0·60-1·41)	0·76
Transplantation	0·77 (0·44-1·27)	0·31
Orthopaedic surgery-trauma	0·84 (0·49-1·36)	0·49
Other	0·66 (0·40-1·04)	0·075
Medical		
Cardiac	0·73 (0·51-1·02)	0·069
Gastrointestinal-hepatic	**0·20 (0·01-0·94)**	**0·039**
Oncologic-hematologic	0·80 (0·41-1·42)	0·47
Neurologic	0·81 (0·57-1·13)	0·22
Renal	0·00 (0·00-1·07)	0·057
Respiratory	0·82 (0·64-1·05)	0·11
Other	0·73 (0·51-1·03)	0·074
Age, younger versus older than 1 year	0·85 (0·70-1·03)	0·091
High versus medium risk of malnutrition	**0·78 (0·61-0·99)**	**0·038**
PeLOD score first 24 hours per point added	0·99 (0·98-1·00)	0·18
PIM2 score per point added	**0·79 (0·74-0·84)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·67 (0·53-0·85)**	**0·0009**
Edmonton	0·82 (0·60-1·11)	0·20
Average glucose dose per ten percent added	1·01 (0·98-1·04)	0·36
Average amino acid dose per ten percent added	**0·96 (0·93-0·99)**	**0·0059**
Average lipid dose per ten percent added	**1·03 (1·00-1·05)**	**0·043**

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.5: **Association of average total macronutrient administration up to DAY 5 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·88 (0·60-1·27)	0·49
Burns	0·73 (0·28-1·55)	0·44
Neurosurgery-traumatic brain injury	0·76 (0·50-1·14)	0·19
Thoracic	1·12 (0·68-1·75)	0·64
Transplantation	0·97 (0·55-1·63)	0·92
Orthopaedic surgery-trauma	0·95 (0·52-1·62)	0·85
Other	0·73 (0·42-1·22)	0·23
Medical		
Cardiac	0·78 (0·53-1·13)	0·19
Gastrointestinal-hepatic	**0·20 (0·01-0·93)**	**0·037**
Oncologic-hematologic	0·88 (0·44-1·60)	0·68
Neurologic	0·86 (0·57-1·26)	0·43
Renal	0·00 (0·00-1·16)	0·068
Respiratory	0·89 (0·67-1·17)	0·40
Other	0·77 (0·51-1·12)	0·17
Age, younger versus older than 1 year	0·90 (0·72-1·12)	0·32
High versus medium risk of malnutrition	0·80 (0·62-1·03)	0·085
PeLOD score first 24 hours per point added	1·00 (0·99-1·01)	0·93
PIM2 score per point added	**0·78 (0·73-0·84)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	**0·72 (0·55-0·94)**	**0·014**
Edmonton	0·98 (0·69-1·38)	0·92
Average glucose dose per ten percent added	1·01 (0·98-1·05)	0·48
Average amino acid dose per ten percent added	**0·95 (0·91-0·99)**	**0·0067**
Average lipid dose per ten percent added	**1·04 (1·00-1·07)**	**0·027**

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.6: **Association of average total macronutrient administration up to DAY 6 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·79 (0·51-1·20)	0·27
Burns	0·77 (0·27-1·74)	0·55
Neurosurgery-traumatic brain injury	0·80 (0·50-1·23)	0·31
Thoracic	1·25 (0·72-2·06)	0·40
Transplantation	0·97 (0·51-1·71)	0·90
Orthopaedic surgery-trauma	0·98 (0·50-1·79)	0·96
Other	0·62 (0·31-1·15)	0·13
Medical		
Cardiac	0·80 (0·53-1·18)	0·26
Gastrointestinal-hepatic	**0·19 (0·01-0·91)**	**0·034**
Oncologic-hematologic	0·90 (0·43-1·71)	0·77
Neurologic	1·00 (0·65-1·50)	0·99
Renal	0·00 (0·00-1·18)	0·071
Respiratory	0·92 (0·68-1·25)	0·59
Other	0·81 (0·52-1·21)	0·30
Age, younger versus older than 1 year	0·95 (0·74-1·22)	0·67
High versus medium risk of malnutrition	0·83 (0·63-1·09)	0·18
PeLOD score first 24 hours per point added	1·00 (0·99-1·02)	0·42
PIM2 score per point added	**0·79 (0·73-0·86)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	0·75 (0·56-1·01)	0·060
Edmonton	1·17 (0·80-1·70)	0·40
Average glucose dose per ten percent added	1·01 (0·96-1·06)	0·63
Average amino acid dose per ten percent added	**0·95 (0·91-0·99)**	**0·026**
Average lipid dose per ten percent added	**1·04 (1·00-1·08)**	**0·035**

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

Table S7.7: **Association of average total macronutrient administration up to DAY 7 with early live PICU discharge**

	HR (95 percent CI)	P
Type of illness, as compared with cardiac surgery		
Surgical		
Abdominal	0·81 (0·50-1·27)	0·36
Burns	0·71 (0·21-1·75)	0·49
Neurosurgery-traumatic brain injury	0·72 (0·43-1·18)	0·19
Thoracic	1·57 (0·84-2·75)	0·15
Transplantation	0·96 (0·49-1·76)	0·90
Orthopaedic surgery-trauma	1·00 (0·47-1·92)	0·99
Other	0·72 (0·34-1·37)	0·32
Medical		
Cardiac	0·81 (0·52-1·22)	0·31
Gastrointestinal-hepatic	**0·19 (0·01-0·91)**	**0·034**
Oncologic-hematologic	0·94 (0·44-1·80)	0·85
Neurologic	1·00 (0·63-1·57)	0·99
Renal	0·00 (0·00-1·32)	0·086
Respiratory	0·93 (0·66-1·30)	0·68
Other	0·79 (0·49-1·22)	0·29
Age, younger versus older than 1 year	0·88 (0·66-1·17)	0·38
High versus medium risk of malnutrition	0·82 (0·60-1·10)	0·19
PeLOD score first 24 hours per point added	1·00 (0·99-1·02)	0·44
PIM2 score per point added	**0·81 (0·75-0·89)**	**<0·0001**
Treatment centre, as compared with Leuven		
Rotterdam	0·76 (0·55-1·06)	0·10
Edmonton	1·36 (0·90-2·03)	0·14
Average glucose dose per ten percent added	1·01 (0·96-1·07)	0·62
Average amino acid dose per ten percent added	**0·94 (0·90-0·99)**	**0·030**
Average lipid dose per ten percent added	**1·05 (1·01-1·09)**	**0·016**

Multivariable analyses adjusted for the predefined baseline risk factors type of illness, age group, severity of risk of malnutrition, severity of illness, and treatment centre. CI: confidence interval, HR: hazard ratio, PeLOD: paediatric logistic organ dysfunction score, PICU: paediatric intensive care unit, PIM2: paediatric index of mortality 2 score. Glucose, amino acid, and lipid doses were expressed as percentage of published reference doses for age/weight.

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