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Original article

Calorie intake and short-term survival of critically ill patients

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SUMMARY

Background & aims: The association between calorie supply and outcome of critically ill patients is unclear. Results from observational studies contradict findings of randomized studies, and have been questioned because of unrecognized confounding by indication. The present study wanted to re-examine the associations between the daily amount of calorie intake and short-term survival of critically ill patients using several novel statistical approaches.

Methods: 9661 critically ill patients from 451 ICUs were extracted from an international database. We examined associations between survival time and three pragmatic nutritional categories (I: <30% of target, II: 30–70%, III: >70%) reflecting different amounts of total daily calorie intake. We compared hazard ratios for the 30-day risk of dying estimated for different hypothetical nutrition support plans (different categories of daily calorie intake during the first 11 days after ICU admission). To minimize indication bias, we used a lag time between nutrition and outcome, we particularly considered daily amounts of calorie intake, and we adjusted results to the route of calorie supply (enteral, parenteral, oral).

Results: 1974 patients (20.4%) died in hospital before day 30. Median of daily artificial calorie intake was 1.0 kcal/kg [IQR 0.0–4.1] in category I, 12.3 kcal/kg [9.4–15.4] in category II, and 23.5 kcal/kg [19.5–27.8] in category III. When compared to a plan providing daily minimal amounts of calories (category I), the adjusted minimal hazard ratios for a delayed (from day 5–11) or an early (from day 1–11) mildly hypocaloric nutrition (category II) were 0.71 (95% confidence interval [CI], 0.54 to 0.94) and 0.56 (95% CI, 0.38 to 0.82), respectively. No substantial hazard change could be detected, when a delayed or an early, near target calorie intake (category III) was compared to an early, mildly hypocaloric nutrition.

Conclusions: Compared to a severely hypocaloric nutrition, a mildly hypocaloric nutrition is associated with a decreased risk of death. In unselected critically ill patients, this risk cannot be reduced further by providing amounts of calories close to the calculated target.

Study registration: ID number ISRCTN17829198, website http://www.isrctn.org.

1. Introduction

Patients requiring acute organ support after ICU admission are candidates for artificial nutrition. Appropriate nutrition delivery in the acute phase of critical illness, however, is currently highly controversial. Results of controlled studies have been conflicting, and two major studies have suggested that even a severe energy deficit (daily intake < 600 kcal) may be tolerated during the first week of critical illness [1,2]. These results have been heavily criticized being possibly valid only for highly selected subgroups of critically ill patients [3]. Observational studies, which may be less

Abbreviations: ICU, Intensive Care Unit; HR, Hazard Ratio; CI, Confidence Interval; BMI, Body Mass Index; kg, Kilogram; OI, Oral Intake; EN, Enteral Nutrition; PN, Parenteral Nutrition; MV, Mechanical Ventilation.

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selective in terms of patient inclusion criteria have yielded contradictory results, and have also been subject to substantial criticism because of inherent methodological weaknesses (e.g., confounding by indication) [4,5]. Correspondingly, active treatment strategies currently recommended in specific guidelines differ to the extent that, during the acute phase of a disease, a higher energy supply is recommended in Europe and Canada, whereas U.S. guidelines and recent international sepsis guidelines largely favor a hypocaloric nutrition [6–9].

To better understand the importance of different levels of calorie intake for short-term survival we analyzed a large international database. Novel statistical techniques were used to minimize limitations of conventional ways of assessing nutritional effectiveness in observational studies (indication bias).

2. Methods

2.1. Study overview

2.1.1. Database

The present study is an analysis of a subset of a large international point prevalence survey of nutrition practice in ICUs (www.criticalcarenutrition.com/ins) conducted in 2007, 2008, 2009 and 2012. Details of the survey are provided in the Supplementary Appendix and elsewhere [10].

Participating ICUs were recruited by disseminating of study information to membership registries of critical care and clinical nutrition societies, and by e-mailing individual health care providers. Each year participating ICUs were asked to enroll 20 consecutive intubated adult (≥18) patients who were ventilated within the first 48 h in the ICU and remained in the ICU for at least 72 h. In total, 12,565 patients from 451 ICUs had been included into the database. 9661 critically ill patients could be identified as fulfilling the inclusion criteria for the current analysis.

Clinical management of study patients was left to the discretion of the treating physician. Shortly after ICU admission, a daily caloric target was determined. Ways to calculate this target were also left to the judgment of the individual provider. The local institutional review boards approved the retrospective anonymous data analysis.

2.1.2. Data collection

Using a secure web-based data collection tool, the following information was collected: date of ICU admission, admission category (elective surgery, emergency surgery, medical), primary admission diagnosis, sex, age, BMI, duration of mechanical ventilation, and Apache II score on admission day. Treating physicians recorded daily the type (oral, enteral, parenteral) and amount of calories, amino acids or protein received from parenteral nutrition (PN), enteral nutrition (EN) or propofol. Daily nutritional variables were collected from the day of ICU admission (partial day) to a maximum of additional 11 days after admission date. In the current analysis, we ignored nutrition received on the day of ICU admission and refer to the subsequent discrete calendar days as "*nutrition days 1 to 11*", while a patient's continuous survival time was calculated as "*days after ICU admission*", where each day described a 24 h period starting on the exact date and time of ICU admission. Registering of calorie intake was stopped before nutrition day 11, if a patient died or was discharged from the ICU before that day. For the first three nutrition days, we registered the number of days on which a patient had been mechanically ventilated, had received PN or propofol, or had been fed orally. Patients were followed for a maximum of 60 days. In this study, we investigate short term survival of 30 days. Patients alive for more than 30 days were censored.

2.2. Patients

2.2.1. Inclusion and exclusion criteria

Patients extracted from the database were ≥18 years of age. They had been treated in an ICU for at least 96 h and had, therefore, a higher chance of benefiting from specific metabolic interventions [11]. In addition, on at least one day during the first 96 h of their ICU stay, patients had to have received artificial (enteral or parenteral) nutrition.

2.2.2. Quantifying calorie intake

To account for unquantified, additional energy intake through oral feeding, total daily calorie intake was classified by using a pragmatic approach defining three different categories based on the amount of received calories. For categorization, we first calculated daily artificial energy intake by summing up calories from enteral nutrition, parenteral nutrition or pharmacological (propofol) supply. If patients had not been fed orally on a certain nutrition day, their total daily energy intake was then expressed as a fraction of the daily caloric target calculated at ICU admission. Finally, a specific nutritional category was assigned to this fraction (category I: <30% of target, category II: 30–70% of target, category III: >70% of target).

If there had been additional oral energy intake on a certain nutrition day, classification of total daily energy intake considered both oral and artificial nutrition in a qualitative manner: first, artificial energy intake was categorized as described above. If there had been any oral intake on a certain day, and if patients had simultaneously received <30% of calculated caloric target by artificial (enteral and/or parenteral) nutrition on that day, total daily energy intake was then classified as belonging to category II; if patients had received 30–70% of calculated caloric target on that day in combination with oral intake, total daily energy intake was assumed to be in category III. Total calorie intake remained in category III, if there had been oral intake in combination with >70% of caloric target. Furthermore, we assumed that patients, who had been discharged alive from the ICU before nutrition day 11, subsequently (up to nutrition day 11) had a daily calorie intake in the range of category III.

2.3. Statistics

Full details of the statistical methods are provided in the Supplementary Appendix and in a separate publication [12]. We performed a survival analysis based on a novel combination of generalized additive models and piecewise exponential models to estimate hazard rates for death beyond day 4 after ICU admission [13]. Our model included several confounder variables, including the use of oral, enteral or parenteral nutrition. For the primary analysis, we assumed that daily oral intake had contained a relevant amount of calories, and that patients discharged from the hospital before day 30 after ICU admission had survived up to this day (best case scenario). Two sensitivity analyses checked the validity of these assumptions. When analyzing associations with survival we also used a time lag of 4 days (*lag-time*) to minimize the indication bias originating from possible changes of calorie intake just prior to death.

To facilitate the interpretation of the associations between caloric supply and outcome, we constructed five different hypothetical nutrition support plans reflecting different levels of daily energy intake during nutrition days 1–11 (Table 1). We designed six different pairwise comparisons of these plans analyzing the time-varying mortality hazard ratios associated with these nutrition support plans in comparison to each other (Figs. 1 and 2, graphs shown on the left). These nutrition support plans represent

hypothetical/possible concepts similar to established nutrition protocols, and they do not reflect different patient populations.

We also performed explorative analyses of several subgroups (Apache II Score > 25; BMI ≥ 25 and <25; medical and surgical (elective + emergency) patients).

The statistical programming environment R [14] was used for visualization and data analysis. The models were estimated using the R package mgcv.

3. Results

3.1. Study participants

Nutritional therapies were assessed in 9661 patients who met our inclusion criteria. Of these patients, 1974 patients (20.4%) died in hospital after 96 h but within 30 days of ICU admission. Demographic and clinical characteristics of the patients are listed in Tables 2 and 3. After 30 days, 2981 (30.9%) of the patients were still hospitalized. Discharged patients spent 10 days (Median) (IQR 6.6–15.0 days) in the ICU, 16.3 days (IQR 11.3–22.3 days) in the hospital, and received mechanical ventilation for 6.8 days (Median).

3.2. Nutritional therapy

On at least one nutrition day, 7015 of 9661 patients (72.6%) received very low amounts of calories (<30% of target and no additional oral intake, category I). 7111 patients (73.6%) could not be fed orally during day 1–11 of their ICU stay. Initially, records for 90,898 days of nutritional therapy had been available for the analysis (on average, 9.4 days per patient). Including assumptions on calorie intake after ICU discharge, 102,686 days of nutritional therapy were included into the analysis. On 18,757 nutrition days (18.3%), patients had received less than 30% of the caloric target calculated at ICU admission, and had no additional oral intake; on 21,634 nutrition days (21,1%) calorie intake had been in the range of category II (<30% of target with additional oral intake, or 30–70% of target with no additional oral intake), and on 62,295 nutrition days (60.1%) calorie intake had been in the range of category III (>70% of target regardless of oral intake, or 30–70% of target with additional oral intake).

On the basis of data from nutrition days on which patients had not been fed orally, it was possible to calculate the achieved percentages of daily caloric targets for categories I, II and III, and the precise amount of enteral and/or parenteral calories administered daily (category I: median 4.3% of target [IQR, 0.0–17.8], 1.0 kcal/kg day [0.0–4.1]; category II: 52.3% [41.7–62.0], 12.3 kcal/kg day [9.4–15.4]; category III: 100.0% [88.4–107.2], 23.5 kcal/kg day [19.5–27.8]). There was a strong correlation (r = 0.89) between the daily amount of calories and of protein/amino acids provided during artificial nutrition.

3.3. Association of nutrition with the 30-day risk of dying

The associations of the variables in the confounder model with short-term survival are presented in Fig. S1–S3, and in Table S2 of the Supplementary Appendix. There was no evidence that the number of nutrition days with parenteral nutrition or with oral intake (during the first three nutrition days) was connected with the risk of dying (HR 1.03, 95% CI 0.98 to 1.09 and 0.87, 95% CI 0.73 to 1.03, respectively). We could, however, identify time-varying associations between daily energy intake and outcome. Figures 1 and 2 show the results of the six comparisons of the five, different hypothetical nutrition support plans.

3.3.1. Comparison of a mildly hypocaloric with a severely hypocaloric nutrition (Fig. 1, and Table S3 of the Supplementary Appendix)

We compared three different hypothetical nutrition support plans: a complete (nutrition days 1 to day 11), severely hypocaloric nutrition support plan (plan #1, daily feeding of calories in the order of category I, about 1 kcal/kg); a delayed mildly hypocaloric nutrition support plan (plan #2, daily feeding of calories in the order of category I on nutrition days 1–4, and of category II on nutrition days 5–11); an early, mildly hypocaloric nutrition support plan (plan #3, daily feeding of calories in the order of category II, about 12 kcal/kg).

The key finding was that, when compared with the complete, severely hypocaloric nutrition support plan #1, the early, mildly hypocaloric nutrition support plan #3 was strongly associated with a better short term outcome (Fig. 1a). The hazard ratio began decreasing below 1 (favoring more nutrition) immediately after the 4 day lag-time reaching full effect by day 14 and remaining at 0.59 (95% CI, 0.37 to 0.93) thereafter (see Table S3 of the Supplementary Appendix).

Figure 1b depicts the daily hazard ratio comparing the support plan that starts severely hypocaloric for the first 5 days but thereafter remains mildly hypocaloric (plan # 2) to the nutrition support plan that remained severely hypocaloric (plan #1). In this comparison, a mortality benefit for plan #2 begins to appear after day 9 hitting a minimal hazard ratio by day 14 (HR = 0.70, 95% CI, 0.51 to 0.96) and remaining fairly constant thereafter (see Table S3 of the Supplementary Appendix).

Compared to nutrition support plan #2, early, mildly hypocaloric nutrition support plan #3 provided some evidence in favor of plan #3, albeit the null effect (HR = 1) was contained within the CIs over the entire follow-up period (Fig. 1c and Table S3, minimal hazard ratio 0.83, 95% CI 0.68 to 1.01).

3.3.2. Comparison of a near target caloric supply with hypocaloric nutrition (Fig. 2, and Table S4 of the Supplementary Appendix)

Comparisons of hypothetical nutrition support plans additionally included those which were either partially close to the caloric

Table 1
Definition of hypothetical nutrition support plans; categories I–III of daily nutritional intake (oral + artificial) correspond to different fractions of the caloric target calculated at ICU admission to guide artificial nutrition; (I: <30% of target + no oral intake; II: 30–70% of target, or <30% of target + additional oral intake; III: >70% of target ± additional oral intake, or 30–70% of target + additional oral intake).

	Plan	Definition
#1	Complete, severely hypocaloric nutrition support plan	Feeding of calories in the order of category I on nutrition days 1–11
#2	Delayed, mildly hypocaloric nutrition support plan	Feeding of calories in the order of category I on nutrition days 1–4, and of category II on nutrition days 5–11
#3	Early, mildly hypocaloric nutrition support plan	Feeding of calories in the order of category II on nutrition days 1–11
#4	Delayed, near target nutrition support plan	Feeding of calories in the order of category II on nutrition days 1–4, and of category III on nutrition days 5–11
#5	Early, near target nutrition support plan	Feeding of calories in the order of category III on nutrition days 1–11

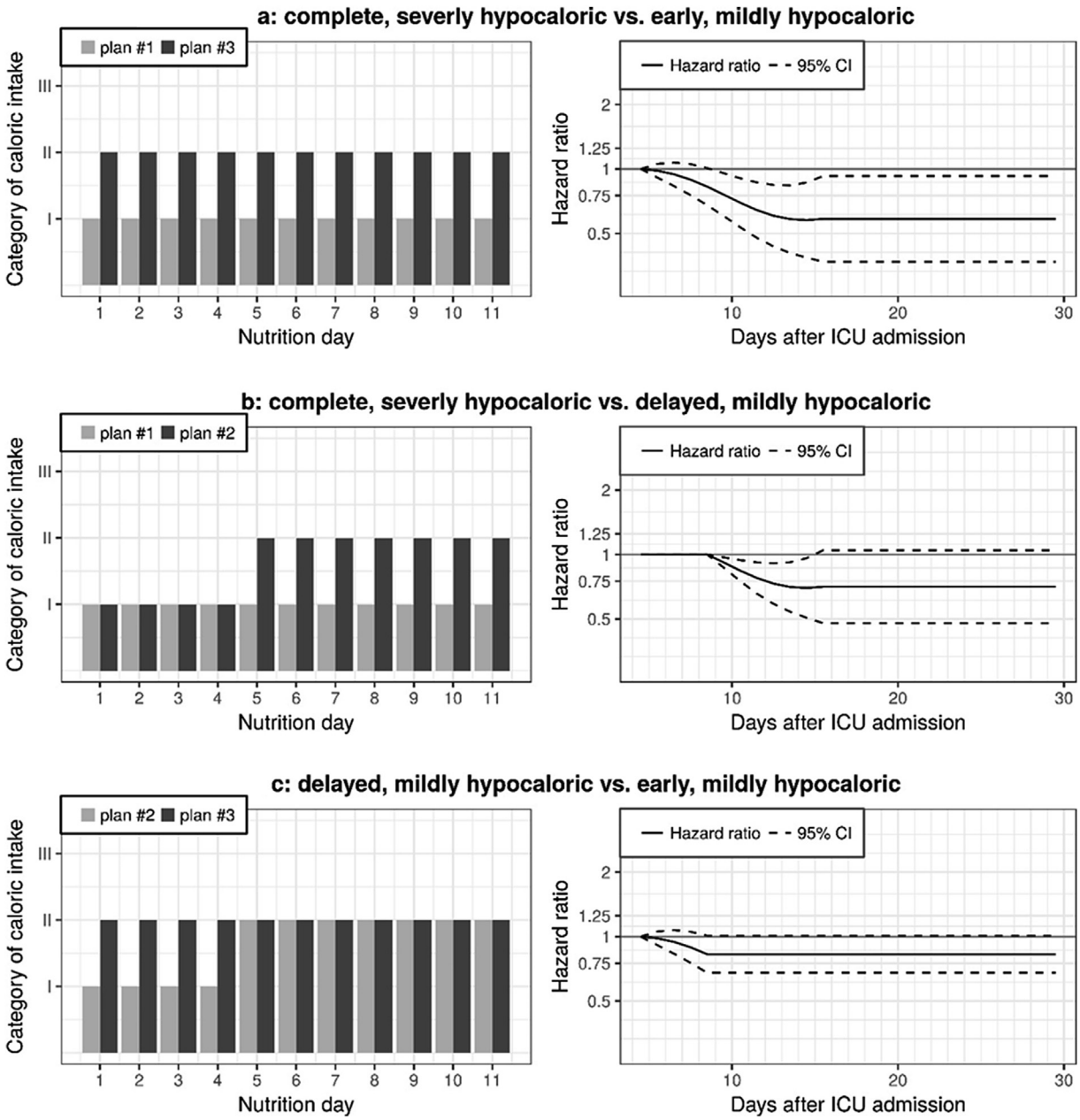

Fig. 1. Comparison of a mildly hypocaloric (category II) with a severely hypocaloric (category I) nutrition. Graphs shown on the left: design of plan comparisons analyzing different hypothetical nutrition support plans (Table 1). Categories of calorie intake were: C I, <30% of target for artificial nutrition (+no oral intake), about 1 kcal/kg day; C II, 30–70% of target, or <30% of target + additional oral intake, about 12 kcal/kg day. Graphs shown on the right: corresponding time-varying associations of different hypothetical nutrition support plans with the risk of dying. Solid lines indicate hazard ratios (HR), hatched lines indicate corresponding 95% confidence intervals (CI) (HRs and CIs for specific time intervals after ICU admission are presented in Table S3 of the Supplementary Appendix). Reference plan is that which provides fewer calories (e.g., an HR (and 95% CI) < 1 would indicate that the risk associated with the plan providing more calories was smaller). Please note that HRs (and corresponding 95% CIs) must be 1 for the first three time intervals (due to the specification of the lag time), and also for time intervals, in which nutritional categories of both hypothetical plans are identical.

target (daily feeding of calories in the order of category II (about 12 kcal/kg) on nutrition days 1–4, and of category III (plan #4, about 24 kcal/kg day) on nutrition days 5–11), or completely close to the target (plan #5, daily feeding of calories in the order of category III on nutrition days 1–11). The main analysis revealed that the early, near target nutrition support plan #5 was strongly associated with a reduced short-term risk when compared with the complete, severely hypocaloric nutrition support plan #1 (Fig. 2a, minimal hazard ratio 0.50, 95% CI 0.35 to 0.69 after the second week after ICU admission, Table S4 of the Supplementary Appendix).

There was no evidence, however, that both the delayed and the early, near target nutrition support plans #4 and #5 were associated with a lower 30-day risk of dying when compared with the early, mildly hypocaloric nutrition support plan #3 (category II) (Fig. 2b and c).

The findings of the main analysis were qualitatively compatible with the results of the sensitivity analyses performed to test the robustness of results with regard to different assumptions about survival after hospital discharge, or amount of oral calories (results for specific plan comparisons are presented in Figs. S5 and S6 of the Supplementary Appendix).

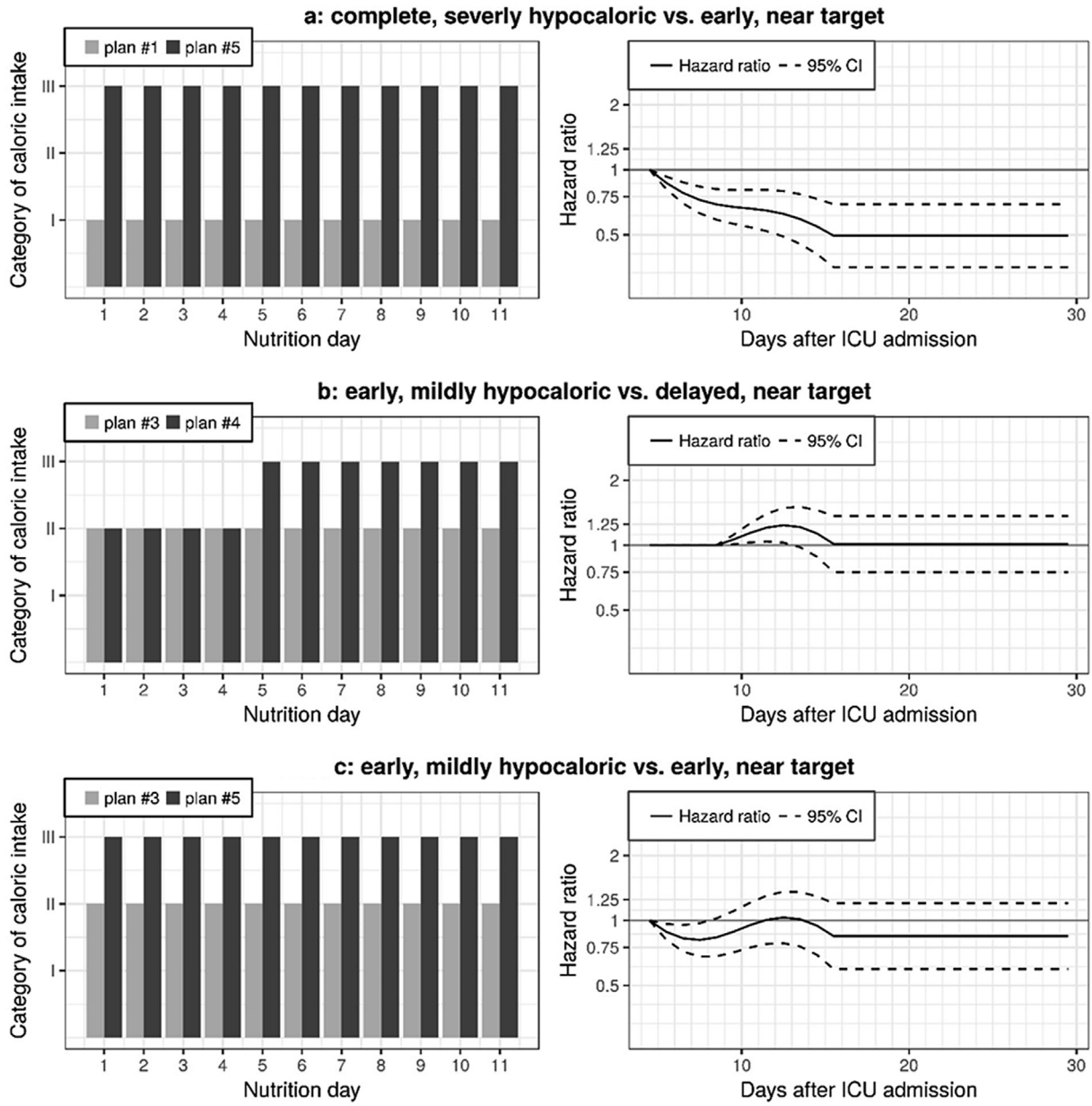

Fig. 2. Comparison of a near target (category III) with a hypocaloric (category I and II) nutrition. Graphs shown on the left: design of plan comparisons analyzing different hypothetical nutrition support plans (Table 1). Categories of calorie intake were: C I, <30% of target for artificial nutrition (+no oral intake) (about 1 kcal/kg day); C II, 30–70% of target, or <30% of target + additional oral intake (about 12 kcal/kg day); CIII >70% of target ± additional oral intake, or 30–70% of target + additional oral intake (about 24 kcal/kg day). Graphs shown on the right: corresponding time-varying associations of different hypothetical nutrition support plans with the risk of dying. Solid lines indicate hazard ratios (HR), hatched lines indicate corresponding 95% confidence intervals (CI) (HRs and CIs for specific time intervals after ICU admission are presented in Table S4 of the Supplementary Appendix). Reference plan is the one which provides fewer calories (e.g., an HR (and 95% CI) < 1 would indicate that the risk associated with the plan providing more calories was smaller). Please note that HRs (and corresponding 95% CIs) must be 1 for the first three time intervals (according to the specification of lag time), and for time intervals, in which nutritional categories of both hypothetical plans are identical.

3.3.3. Association of nutritional intake with the risk of dying in subgroups

Due to comparatively low patient numbers, 95% confidence intervals were wide emphasizing the clearly hypothesis-generating character of the results. In patients with Apache II score values > 25 (n = 3200) associations between different amounts of calories and mortality generally appeared to be somewhat weaker (e.g., hazard ratios closer to 1) than in the whole cohort (Fig. S7). Associations appeared to differ between medical (n = 6181) and surgical patients (n = 3480) (Figs. S8 and S9), and between patients being overweight (BMI ≥ 25, n = 5332) or not (n = 4329) (Figs. S10 and S11). Results of medical or overweight patients were qualitatively comparable to that found in the whole cohort, whereas surgical patients appeared to have been largely insensitive to variations of daily caloric intake. In patients with a BMI < 25 (including underweight patients), an early, near target nutrition support plan #5 (Category III) was associated with a reduced short-term risk when compared with an early, mildly hypocaloric nutrition support plan #3 (category II), whereas no such association could be found when comparing an early, mildly hypocaloric nutrition support plan with a complete, severely hypocaloric nutrition support plan #1 (category I).

Table 2
Demographic and clinical characteristics (categorical variables) of the patients (MV, mechanical ventilation; OI, oral intake; EN, enteral nutrition; PN, parenteral nutrition, PF, propofol; the duration/number of days were calculated up to nutrition day 3).

		All		Outcome	
		n	Percent	Surviving[a]	Surviving (%)
Year	2007	2122	22.0	1686	79.5
	2008	2056	21.3	1606	78.1
	2009	2308	23.9	1860	80.6
	2011	3175	32.9	2535	79.8
Gender	Female	3847	39.8	3033	78.8
	Male	5814	60.2	4654	80.0
Duration of MV	<1 h	48	0.5	44	91.7
	1–24 h	232	2.4	213	91.8
	25–48 h	474	4.9	415	87.6
	>48 h	8907	92.2	7015	78.8
Number of days with OI	0	9179	95.0	7274	79.2
	1	308	3.2	261	84.7
	2	134	1.4	113	84.3
	3	40	0.4	39	97.5
Number of days with PF therapy	0	5807	60.1	4495	77.4
	1	989	10.2	801	81.0
	2	998	10.3	834	83.6
	3	1867	19.3	1557	83.4
Duration of PN	<1 h	7860	81.4	6255	79.6
	1–24 h	302	3.1	238	78.8
	25–48 h	444	4.6	356	80.2
	>48 h	1055	10.9	838	83.7
Duration of EN	<1 h	1914	19.8	1489	77.8
	1–24 h	924	9.6	742	80.3
	25–48 h	1933	20.0	1519	78.6
	>48 h	4890	50.6	3937	80.5
Admission category	Surgical/Elective	1073	11.1	913	85.1
	Medical	6181	64.0	4748	76.8
	Surgical/Emergency	2407	24.9	2026	84.2
Admission diagnosis	Gastrointestinal	1465	15.2	1183	80.8
	Cardio-Vascular	1440	14.9	1080	75.0
	Other	476	4.9	384	80.7
	Metabolic	199	2.1	182	91.5
	Neurologic	1269	13.1	1029	81.1
	Orthopedic/Trauma	1117	11.6	995	89.1
	Renal	104	1.1	77	74.0
	Respiratory	2618	27.1	2051	78.3
	Sepsis	974	10.1	706	72.5

[a] Surviving patients were those either surviving until discharge from the hospital, or until day 30 while still being hospitalized.

Table 3
Demographic and clinical characteristics (quantitative variables) of the patients.

	Age (years)	Apache II Score	Body mass index (kg/m^2)
Min.	18.0	0.0	13.1
1st Qu.	48.0	17.0	22.6
Median	62.0	22.0	25.7
Mean	59.5	22.5	27.3
3rd Qu.	73.0	28.0	30.1
Max.	100.0	71.0	104.8

4. Discussion

The results of our study suggest that in a sample of heterogeneous critically ill patients remaining in the ICU for at least 96 h, provision of only minimal amounts of calories (category I, <30% of target, about 1 kcal/kg day) throughout the first 11 nutrition days is associated with an increased risk of dying during the first 30 days after ICU admission. Compared to such an extremely low calorie intake, a mildly hypocaloric nutrition (category II, 30–70% of target, about 12 kcal/kg day) was strongly associated with a mortality risk reduction.

The precise minimum caloric requirement, however, is disputable. There were associations between a gradually increasing number of nutrition days with a mildly hypocaloric nutrition and a better outcome. This leaves open the possibility of an unchanged 30-day mortality risk if minimal amounts of calories (<30% of target) were provided on only one or two nutrition days.

A second key finding of our study was that, compared to a baseline supply of mildly hypocaloric amounts of calories (category II), a delayed (on days 5–11) or an early (on days 1–11) supply of calories in the range of category III (>70% of target, about 24 kcal/kg day) was not associated with further short-term mortality benefits.

It is currently highly controversial whether a near target caloric supply is beneficial or not. Strong associations between a near target calorie intake and a lower mortality have only been identified by some observational studies [5,15,16]. These findings were not universal, however, and other observational studies found beneficial associations only in subjects who were severely overweight (BMI > 35), malnourished (BMI < 25) [10], or at a high nutritional risk [17], or even presented contradictory results (an association of a near target intake with a higher mortality) [18–22]. Interpretation of these results is extremely difficult since none of these studies specifically considered reverse causation phenomena, or adjusted for duration, type and daily variation of energy intake.

Our study attempts to address several analytical limitations (such as indication bias) inherent in the design of older observational studies, specifically by adjusting for multiple sources of confounding and taking into account the time-dependent nature of

caloric intake. Instead of using average calorie intake during the observation period, associations with outcome were based on daily amounts of calorie intake. Additionally, we adjusted associations of calorie intake with outcome to the use of additional parenteral or oral nutrition.

To corroborate our analytical strategy, we performed a sensitivity analysis testing the importance of additional oral calorie intake on a specific nutrition day for outcome. Since we found that oral intake was unimportant for outcome (Fig. S8), we can be reasonably certain that our analytical strategy largely eliminated bias resulting from variations in the route by which calories had been supplied. Furthermore, these results suggest that further investigations of similar data could ignore oral intake and focus on the continuous effect of artificial calorie intake.

Based on that novel analytical strategy, our study yielded results, which are largely in line with the findings of the randomized studies. Randomized studies were analyzed recently by nine meta-analyses comparing a) a severely (<30% of target, <8 kcal/kg day) with a mildly hypocaloric energy intake (30–60% of target, ≈8–16 kcal/kg day) [23], b) a mildly hypocaloric energy intake with the provision of slightly hypocaloric amounts of calories (70–80% of target, ≈16–21 kcal/kg day) [24–30] or c) a mildly hypocaloric with an isocaloric energy intake (100% of target, ≈24 kcal/kg day) [9]. Corresponding to our findings, two meta-analyses showed that providing only minimal amounts of calories (e.g., <33% of target) is detrimental and that giving 30–60% of target calories will decrease mortality [26,28]. Compared to a mildly hypocaloric nutrition, however, provision of more calories either did not affect mortality [23–25,27,29,30] or even worsened it [26,28].

Altogether, it is likely that in the early phase after an insult (day 1–11) daily provision of 30–70% of the daily caloric target (according to our study, about 10–15 kcal/kg day) would be sufficient to minimize 30-day mortality, and that provision of more calories would not convey a further risk reduction, but may even be detrimental. Our subgroup analyses suggest that interactions between selected covariates and nutrition might be important for the absence or presence of effects. Thus, surgical patients and patients with a high risk (Apache II Score values > 25) were generally less responsive to different amounts of calories than the whole cohort, whereas body weight might modify nutrition effects in a way that overweight patients require less and underweight patients more calories.

4.1. Limitations and strengths

Our study has certain limitations. Calorie intake in our study was rarely guided by indirect calorimetry. Equations to estimate energy expenditure may overestimate the energy needs in up to 70% of patients [31].

We do not know whether associations between caloric supply and short-term mortality would also hold for morbidity. According to the meta-analyses, however, effects on morbidity may also parallel those on mortality. Thus, a severely hypocaloric nutrition was found to increase the infection rate [23], and – compared to a mildly hypocaloric nutrition – provision of more calories did not alter morbidity (rates of new infections, duration of mechanical ventilation, length of stay) in five meta-analyses [9,25,26,30]. Three meta-analyses, however, reported an increased morbidity [24,27,29], thereby largely excluding the possibility that – in unselected critically ill patients - the provision of isocaloric or nearly isocaloric amounts of calories might be beneficial during the acute phase of the disease.

We also could not separately analyze the contribution of energy versus protein intake to mortality. Finally, due to the observational nature of the study, we cannot entirely exclude the possibility that our results are – at least partially – affected by unmeasured confounding or residual indication bias. Indication bias may originate from the phenomenon that a better health is associated with a gastrointestinal tract working more efficiently thereby allowing the supply of more enteral/oral calories. Thereby, a higher calorie intake may be associated with a better outcome without being the true cause. Similarly, bias could result from possible changes of calorie intake just prior to death. The 4-day lag between nutrition and its' effect on the outcome, as used in our analyses, should avoid the most severe effects from such indication bias, as, for example, hypocaloric nutrition just prior to death would not enter the analysis.

The strengths of our study are its size, allowing an in-depth examination of the association between caloric supply and short-term survival, and its statistical strategies. We used novel statistical techniques designed to estimate the time-dependent association of caloric intake and outcome. By including a wide variety of diagnoses and diseases this study also overcomes the criticisms expressed by the opponents of randomized studies. Furthermore, for the first time we could calculate the effect of an extreme scenario, namely the provision of extremely low amounts of calories during the first 11 days after ICU admission. The large number of events and of participating ICUs from many countries may help support the generalizability of the findings.

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Authors' contributions

WH, FS, AB and HK developed the statistical analysis strategy. AB and FS performed the statistical modeling and inference. AB and AD were responsible for data management and created descriptive statistics and visualizations. WH and DK did the literature search and drafted the manuscript. All authors contributed to interpretation of the data and critical revision of the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.04.005.

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