## REVIEW



# Energy and protein nutrition adequacy in general wards among intensive care unit survivors: A systematic review and meta-analysis

Zenzi Rosseel MPharm<sup>1,2,3</sup> I Pieter-Jan Cortoos MPharm. PhD<sup>1,3,4</sup> Lynn Leemans PhD<sup>2,3,5</sup> | Arthur R. H. van Zanten MD, PhD<sup>6,7</sup> Claudine Ligneel MPharm<sup>1,3</sup> | Elisabeth De Waele MD, PhD<sup>2,3,4,8</sup>

<sup>1</sup>Department of Pharmacy, Universitair Ziekenhuis Brussel (UZ Brussel), Jette, Belgium

<sup>2</sup>Department of Clinical Nutrition, Universitair Ziekenhuis Brussel (UZ Brussel), Jette, Belgium

<sup>3</sup>Vitality Research Group, Vrije Universiteit Brussel (VUB), Jette, Belgium

<sup>4</sup>Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), Jette, Belgium

<sup>5</sup>Rehabilitation Research Department, Vrije Universiteit Brussel (VUB), Jette, Belgium

<sup>6</sup>Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, The Netherlands

<sup>7</sup>Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands

<sup>8</sup>Department of Intensive Care, Universitair Ziekenhuis Brussel (UZ Brussel), Jette, Belgium

#### Correspondence

Zenzi Rosseel, MPharm, Department of Pharmacy, Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Jette, Brussel, Belgium. Email: zenzi.rosseel@uzbrussel.be

## Abstract

Background: Adequate energy and protein provision is mandatory to optimize survival chances in critical illness, prevent loss of muscle mass, and reduce length of stay. Data are available concerning feeding adequacy in intensive care unit (ICU) participants, but little is known about the adequacy in post-ICU participants. This systematic review aimed to evaluate feeding adequacy in post-ICU participants and addressed causes of feeding interruption leading to suboptimal adequacy.

Methods: For this systematic review, a bibliographic search was performed in PubMed, Scopus, and Web of Science. Randomized controlled studies, non-randomized controlled studies, and observational studies conducted between January 1990 and November 2023 fulfilling the inclusion criteria were withheld.

Results: Eight studies were included. Outcomes reported were energy and protein adequacy, barriers, and feeding routes. Energy and protein requirements were determined in various ways, including indirect calorimetry and standardized and weight-based formulas. Energy adequacy ranged from 52% to 102% and protein adequacy between 63% and 86%. Participants were mainly fed with enteral nutrition (EN) or a combination of oral nutrition and EN. The main barrier reported for inadequate nutrition intake was feeding tube removal.

**Conclusion:** Next to different ways in calculating targets and reporting results, a wide range in energy and protein adequacy was observed, but with constant protein underfeeding. Participants fed with EN or a combination of EN and oral nutrition had the best adequacy; inappropriate tube removal is a common barrier leading to inadequate therapy. Standardized reporting and larger studies are needed to guide nutrition care for post-ICU participants.

#### **KEYWORDS**

energy, enteral nutrition, feeding adequacy, parenteral nutrition, protein, survivors

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# INTRODUCTION

Recovery from critical illness can take months to years. In the first year following hospital discharge, more than half of critical illness survivors are unable to resume work, with 38% experiencing muscle weakness.<sup>1,2</sup> Aside from the human impact, healthcare economics are negatively impacted. A comparison of healthcare expenditures between post-intensive care unit (ICU) participants and a control group (general population) revealed that chronic problems, such as malnutrition, led to a three to five times increase in expenses over the year following ICU discharge.<sup>3</sup> Malnutrition can be present before and during the ICU admission and can be caused by several factors, such as loss of body weight (BW), loss of muscle mass, and the presence of a hyper metabolic-catabolic stress response.<sup>4</sup> Therefore, ensuring participants receive adequate nutrition post-ICU discharge is vital to facilitate faster recovery, increase muscle regrowth, and lower the financial burden on healthcare.<sup>3</sup>

In the ICU, a sufficient nutrition intake reduces the possibility of both underfeeding and overfeeding, which are associated with higher mortality, a prolonged length of stay (LOS), and a longer time to recovery.<sup>5-7</sup> On the ward, a trial involving 2088 participants revealed that personalized nutrition support, compared with the hospital's standard diet, resulted in fewer adverse outcomes and all-cause mortality.<sup>8</sup> Guidance is available for optimal nutrition therapy. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that it is crucial to use indirect calorimetry (IC) and schedule regular dietitian consultations to optimize intake and achieve feeding adequacy between 80% and 100%.<sup>4,9-11</sup> Despite these recommendations, achieving such a level of feeding adequacy is challenging in clinical practice because of the additional barriers that must be addressed. The primary objective of this systematic review is to assess energy and protein adequacy in adult post-ICU participants. The second goal is to outline methods of measuring intake, describe data collection procedures, address the main barriers of disruptions in nutrition intake, and explore which combination of feeding routes results in the best level of adequacy.

## MATERIALS AND METHODS

#### Research question and eligibility criteria

This systematic review was registered on PROSPERO, the international Prospective Register of Systematic Reviews (CRD42022369579) on October 31, 2022, and followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).<sup>12</sup>

This systematic review aimed to evaluate the nutrition adequacy (outcome) in adult post-ICU participants (population) who were fed with oral nutrition, enteral nutrition (EN), and/or parenteral nutrition (PN) (exposure). Eligible studies concerned adult ICU participants initially admitted to the ICU who were clinically stable, transferred to the ward (during the consecutive hospitalization period) for recovery and further treatment, and assessed for nutrition adequacy. Participants could receive any combination of PN/EN or oral nutrition. Nutrition adequacy (energy and protein) is expressed as a percentage. If nutrition adequacy was not directly reported, the authors calculated it using the intake divided by the energy and protein targets.<sup>9</sup> Intake and target can be expressed as kcal/kg/day or kcal/day for energy and in g/kg/day or g/day for protein. All abstracts/full-text articles selected had outcomes defined as "feeding adequacy," "nutritional adequacy," "caloric adequacy," "caloric intake," "protein intake," "energy intake," "energy balance," "protein delivery," "energy delivery," and/or "caloric delivery."

The inclusion criteria were randomized controlled trials (RCTs) or observational studies (non-RCTs) of any sample size, written in English or Dutch, and published between 1990 and 2023 with hospitalized adult (≥16 years) post-ICU participants. Our exposures of interest were PN, EN, oral nutrition supplements, and/or oral nutrition. Our outcomes of interest were those studies reporting nutrition (feeding) adequacy (%), intake/requirement (energy) (%), intake/ requirement (protein) (%), intake/requirement (energy) (kcal/kg/day), intake/requirement (protein) (g/kg/day), energy balance, or administered energy/resting energy expenditure (REE) (%).

#### Search strategy

A systematic search was performed in PubMed, Scopus, and Web of Science until January 31, 2023, using Medical Subject Headings and free terms combined with Boolean operators (OR/AND). Additional systematic searches were performed on July 14, 2023, and November 3. 2023, revealing no additional eligible papers. Keywords for the search were "post," "discharge," "survivor," "intensive care unit," "ICU," "critical illness." and "critical care" for patients: "parenteral." "enteral." "oral." "supplemental parenteral," and "nutrition" for exposure; and "calor\*," "protein," "energy," "feeding," "nutritional," "intake," "delivery," "adeguacy," and "balance" for the outcomes. The search terms were selected based on a combination of relevant keywords from preliminary literature, domain knowledge, and input from experts in the field. The complete search strategies for each database are provided in the supplementary files. Mendeley was used as the reference manager (version v1.19.8), and the web application RAYYAN was used for eligibility checks and removing duplicates. Additionally, manual searches of reference lists of selected articles were performed.

## Selection process

Initial title and abstract screening were done by two independent blinded researchers (Z.R. and P.J.C.), followed by an equally blinded screening of full-text articles in the second phase. In case of conflicts, a third researcher (E.D.W.) made the final decision, and, if necessary, the original publication author was consulted for clarification. Using individual assessment of the full text, if the data were present in the title/abstract, enabled us to calculate the adequacy; for example, papers with "energy intake in kcal/day" or "metabolic need" were withheld.

## Data collection and extraction

Data on the study population, study design, sample size, and outcomes of interest were also extracted in a blinded manner (Z.R. and P.J.C.) using a data extraction form. In the case of disagreement, the third researcher (E.D.W.) was consulted, and the disagreement was solved through discussion. In the case of missing data, the original author was contacted. To improve data comparability, data reported as median and interquartile range (IQR) was converted into an estimated mean ± SD using the formula of Wan et al.<sup>13</sup> Converted medians (IQRs) are marked in the tables. Information regarding energy/protein target/intake/adequacy was recorded. In case one value was missing, the authors calculated the value by themselves with the following formulas:

- Target: intake/(adequacy/100)
- Intake: target × (adequacy/100)
- Adequacy: (intake/target) × 100<sup>14,15</sup>

If the authors calculated values, this is indicated in the tables as well. When the energy/protein target or intake was reported as kcal/day or as g/day, it was converted into kcal/kg/day or g/kg/day by using the median/mean weight of the study population in case this conversion was necessary. A meta-analysis on the studies' averages, for energy and protein adequacy, was performed using a random effect to account for the heterogeneity and fit with restricted maximum likelihood. To enable a visual comparison across studies while accounting for varying sample sizes, forest plots were created in R using the "metafor" package.<sup>16</sup>

## Outcomes

The primary outcome is energy and protein feeding adequacy. Secondary outcomes are ICU LOS, ward LOS, hospital LOS, requirements of energy and protein, intake of energy and protein, feeding adequacy, in-hospital mortality, routes of nutrition, and barriers toward adequate nutrition intake.

## RESULTS

## Study selection and characteristics

The initial literature search identified 4516 articles, with 3959 remaining after removing duplicates. Fifty-two articles were screened based on full text. Six articles were included for final analysis supplemented with two additional articles found by backward reference screening of the original six articles, already included. In 94% of cases, there was an agreement between the independent authors. Finally, eight articles were included for final analysis (Figure 1).<sup>11,17-23</sup> Six articles were found in the initial search<sup>11,19-22,24</sup> and two<sup>23,25</sup> by citation searching. One study had a retrospective design,<sup>19</sup> five studies were prospective observational,<sup>11,20,21,24,25</sup> one study was prospective interventional,<sup>22</sup> and one was an RCT<sup>23</sup> (Table 1).

The selected studies included 217 post-ICU participants, accounting for at least 3172 ward observation days (two studies did not mention the number of observation days). Five studies were

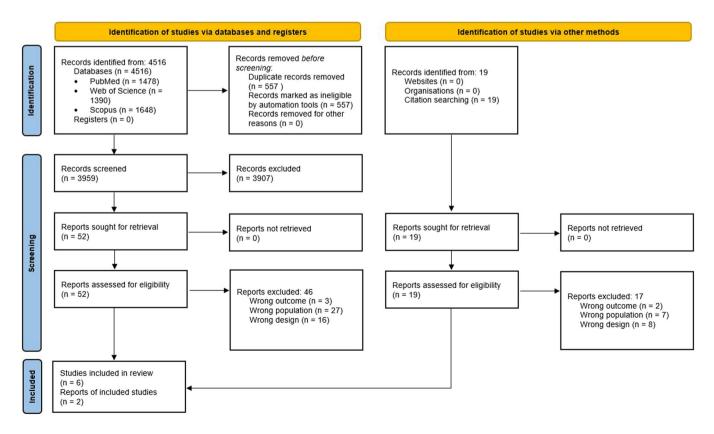


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the literature search process.

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Author, year (country)	Study design	Participants (n), women (%); inclusion criteria	Type of ICU	Age, mean ± SD or median (IQR), y	BMI, mean ± SD or median (IQR), kg/m <sup>2</sup>	LOS ICU, mean ± SD or median (IQR), days
Balasu bramanian et al., 2021 <sup>17</sup> (USA)	RC: single center, university associated	<ul> <li>16 (62)</li> <li>Survivors of critical illness receiving prolonged mechanical ventilation (≥21 consecutive days of mechanical ventilation for ≥6 h/day in an LTACH</li> </ul>	General	61.5 ± 3.2	27.5 ± 2.5 (ward)	56.5 (16–211) = ventilator days – incomplete data
		<ul><li>Age ND</li><li>Random 24-h urine collection</li></ul>				94.5 ± 147.7 <sup>a</sup>
Chapple et al., 2016 <sup>18</sup> (Australia)	PO: single center university hospital	<ul> <li>37 (13)</li> <li>Moderate or severe TBI (GCS 9-12 or 3-8, respectively)</li> </ul>	Neuro-trauma	45.3 ± 15.8	26.7 (19.8–39.5) range (ICU)	13.4 (6.4–17.9)
		<ul><li>Age ≥18 years</li><li>ICU stay of ≥48 h</li></ul>				12.6 ± 8.6 <sup>a</sup>
Hoyois et al., 2021 <sup>19</sup> (Belgium)	PO: single center university hospital	15 (33)	General COVID	60 (55-67)	25.7 (24-31) (ICU)	33 (26-39)
		<ul> <li>Participants infected with COVID-19</li> <li>Age ≥18 years</li> <li>&gt;2 weeks ICU stay with mechanical ventilation requiring endotracheal intubation</li> <li>≥7 days at the post-ICU ward</li> </ul>		60.7 ± 9.1 <sup>a</sup>	26.9 ± 5.3 <sup>a</sup>	32.7 ± 9.9ª
Nematy et al., 2006 (UK) <sup>20</sup>	Pl: single center university hospital	<ul> <li>16 (ND)</li> <li>Age 18-85 years</li> <li>&gt;3 days ICU LOS</li> <li>HIV or hepatitis B surface antigen positive</li> <li>Participants who were already enrolled in a therapeutic study</li> </ul>	General	60 ± 5	28.1 ± 1.7 (ICU)	12.9 ± 2.2
Ridley et al., 2019 <sup>11</sup> (Australia)	PO: 2 sites, not defined	<ul> <li>32 (25)</li> <li>ICU LOS between 48 and 72 h</li> <li>Mechanically ventilated at the time of enrollment and expected to remain ventilated until the day after tomorrow</li> <li>Age ≥16 years</li> <li>Central venous access suitable for PN</li> <li>≥1 organ system failure related to acute illness</li> </ul>	General	56 ± 18	30 ± 8 (ward)	12 (6-17) 11.7 ± 8.2 <sup>a</sup>
Salisbury et al., 2010 <sup>21</sup> (UK)	2 parts: Part A: PO	32 (39)	General	A: 62.5 (54–69)	ND	A: 18 (7-36)
(,	Part B: Pl	Age ND		B: 57.5 (52.8-70)		B: 16.5 (10.5-25)

## TABLE 1 Demographical data.

LOS ward, mean ± SD or median (IQR), days	LOS hospital, mean ± SD or median (IQR), days	APACHE II score, mean ± SD or median (IQR)	Observation days, <i>n</i>	Data collection done by	Outcome after ICU	Mortality, %
ND	26.5 [6-221]	ND	ND	Dietitians	ND	ND
	84.5 ± 162.9 <sup>a</sup>					
19.9 (9.6-32)	37.8 (19.4–52.4)	18 (14-22)	Total: 1512; ICU: 530; ward: 982	Trained dietitians and dietetic investigators	11% hospitalized	0 at day 90
20.5 ± 16.8 <sup>a</sup>	36.5 ± 24.7 <sup>a</sup>	18 ± 6ª			At day 90	
19 (12-23) post-ICU	83.8	ND	Ward: 900	ND	7% hospitalized	0 at day 60
38 (26–51) rehabilitation ward					at day 60	
18 ± 8.3 <sup>a</sup>						
Post-ICU						
38.3 ± 19 <sup>a</sup>						
Rehabilitation ward						
27.4 ± 20.7	40.3 ± 6.6	18.9 ± 6.5	ICU: 207 Ward: 438 Total: 645	Nurses and dietitians	ND	25 (during the whole study period)
10 (7-18) 11.7 ± 8.2ª	24 (18-33) 25 ± 11.2 <sup>a</sup>	18 ± 7	Ward: 227	Study dietitians Nursing staff	ND	0 (whole study period)
A: 26 (13-42)	ND	A: 19.5 (15.3-23.8) B: 26 (19.3-39)	ND	Dietitian Research nurse Ward-based staff	A 63% home	A: ND B: 13 at day 90
B: 15 (11.5-19.8)		D. 20 (17.3-37)		งงลาน-มลรชน รเสท		D. 13 at uay 70

(Continues)

#### TABLE 1 (Continued)

Author, year (country)	Study design	Participants (n), women (%); inclusion criteria	Type of ICU	Age, mean ± SD or median (IQR), y	BMI, mean ± SD or median (IQR), kg/m <sup>2</sup>	LOS ICU, mean ± SD or median (IQR), days
		<ul> <li>Part A (n = 24)</li> <li>≥4 days ICU LOS and</li> <li>Discharged to ward</li> </ul>				
	University hospital	<ul> <li>Part B: control group (n = 8)</li> <li>O Mechanical ventilation ≥4 days</li> </ul>		A: 61.8 ± 11.2 <sup>a</sup>		A: 20.3 ± 21.7 <sup>a</sup>
				B 60.1 ± 13 <sup>a</sup>		B 17.3 ± 10.9 <sup>a</sup>
Slingerland-	PO: single center,	41 (54)	Mixed	70.8 ± 11.4	26.7 ± 6.0 (ward)	9 (5-22)
Boot et al., 2022 <sup>23</sup> (the	nonuniversity hospital	<ul> <li>Age ≥18 years</li> </ul>				12 ± 12.7 <sup>a</sup>
Netherlands)		• ICU LOS ≥72 h				
		<ul> <li>PN/EN ≥24 h during ICU stay</li> </ul>				
Wittholz	PO: single center; ND	28 (25)	Trauma	50 ± 22.5	26	10.6 ± 6.7
et al., 2020 <sup>22</sup> (Australia)		<ul> <li>Age ≥18 years</li> </ul>			(25-32) (ward)	
		<ul> <li>Mechanically ventilated for ≥48h</li> </ul>				
		• TBI			27.7 ± 5.3ª	

Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation II; BMI, body mass index; COVID-19, coronavirus disease 2019; EN, enteral nutrition; GCS, Glasgow coma scale; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LTACH, long-term acute

conducted in a university hospital setting,<sup>17-21</sup> one study in a nonuniversity hospital,<sup>23</sup> and two studies did not report the setting.<sup>11,22</sup> Six of eight studies were single center,<sup>17–20,22,23</sup> one trial was conducted at two sites,<sup>11</sup> and in one trial the number of sites was not described.<sup>21</sup> All study cohorts were relatively small, consisting of <50 participants. Participants were initially admitted to a general ICU, whereas Hoyois et al. included only participants with coronavirus disease 2019.<sup>19</sup> In five of eight studies, participants had to have mechanical ventilation (MV) to be included.<sup>11,17,19,21,22</sup> Ridley et al. included participants aged ≥16 years,<sup>11</sup> two studies did not mention the minimal age of participants but did not mention that pediatric participants were included,<sup>17,21</sup> and all other studies included only adult (>18 years) participants. The required LOS in the ICU was comparable enough to be included except for two studies, which required MV of at least 21 days<sup>17</sup> and at least 14 days, respectively.<sup>19</sup> The Acute Physiology And Chronic Health Evaluation II severity score was reported in six studies ranging from 15 to 26. In most studies, the mean body mass index (BMI) exceeded 25 kg/m<sup>2</sup>.<sup>11,17-20,22,23</sup> The LOS on the ward ranged from 10 to 28 days after an ICU stay, which ranged between 9 and 57 days. The mean age ranged between 45 and 71 years.

The data collection methods were comparable across the studies with dietitians recording food intake and related nutrition information encompassing dietary routes, targets, and adequacy. In the study conducted by Chapple et al., meals were weighed by dietitians to ascertain intake levels, whereas elsewhere this involved dietitians assessing handgrip strength. In five of the eight studies examined, nurses played a pivotal role in completing food charts,<sup>11,20-22</sup> measuring intake,<sup>11,21</sup> and taking after meal photographs.<sup>23</sup> In some studies, ward-based staff,<sup>21,23</sup> participants,<sup>22,23</sup> and family members<sup>23</sup> were involved in completing intake charts. IC measurements were executed by trained staff (not further specified) by Ridley et al.,<sup>11</sup> whereas Hoyois et al.<sup>19</sup> did not specify who did the data collection at all. Ridley et al.<sup>11</sup> described two groups, one group in which requirements were determined by the use of an IC and another group where an IC was not possible. Registration of intake showed important differences: Salisbury et al. did not reveal if the intake was recorded daily or at other time points<sup>23</sup> and four studies recorded intake daily.<sup>11,20,22,23</sup> Chapple et al. recorded EN/PN intake daily in contrast to the oral intake that was documented only 3 days a week.<sup>18</sup> Hoyois et al. recorded intake on days 0, 7, 14, 21, 30, and 60.<sup>19</sup> and the trial of Balasubramanian et al. recorded the intake for only 24 h.17

Mortality was relatively low in most studies except for Nematy et al.  $(4/16, 25\%)^{20}$  and for part B of the study of Salisbury et al. (13/32, 40%).<sup>21</sup> Five of eight studies did not mention the percentage of the participants that were still hospitalized at the end of the trial.<sup>11,17,20,23</sup> Between 7% and 37% of the participants were still

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LOS ward, mean ± SD or median (IQR), days	LOS hospital, mean ± SD or median (IQR), days	APACHE II score, mean ± SD or median (IQR)	Observation days, <i>n</i>	Data collection done by	Outcome after ICU	Mortality, %
A 27 ± 21.7ª		A 19.5 ± 6.4ª				
B 15.4 ± 6.2 <sup>a</sup>		B 28.1 ± 14.7 <sup>a</sup>			37% hospitalized	
12 (8-15)	21 (16-37)	20.4 ± 6.7	Ward: 484	Dietitians	43.9% home	5 (hospital)
11.7 ± 5.2 <sup>a</sup>	24.7 ± 15.7ª			Nurses and food service assistants	51.2% revalidation and 2.4% psychiatric unit	15 at day 90
				Patient and family	ND % hospitalized	17 at day 180
10.9 ± 9.2	21.6 ± 11.8	15 ± 6	Ward: 141	Dietitians	ND	ND
				Nursing staff (completing food charts)		

<sup>a</sup>Median (IQR) converted into mean ± SD with formula of Wan et al. (2014).<sup>13</sup>

hospitalized at the end of the studies.<sup>18,19,21</sup> Participants were either still hospitalized or discharged to home, a revalidation unit, or a psychiatric unit.<sup>21,23</sup>

## Energy adequacy

Intake varied between 14.5 and 33.5 kcal/kg/day.<sup>17,18,21-23</sup> Within the category of predictive equations, including BW and height, energy adequacy was 64%-102%. In the group relying on predictive equations using BW alone, energy adequacy ranged from 79% to 83%. Ridley et al. used IC and demonstrated an energy adequacy of 95%, whereas the study conducted by Nematy et al. reported a notably lower energy adequacy of 52% (Tables 2 and 3; Figure S1).<sup>20</sup> Figure 2 shows a pooled average of energy adequacies (79.10%) (Figure 2) excluding Hoyois et al., Balasubramanian et al., and Ridley et al. (IC subgroup) from the forest plot because of the absence of a reported SD.

Four studies used predictive equations including BW and height<sup>19,23-25</sup>: the Schofield, Penn State 2003b and the Food and Agriculture Organization (FAO formula). Hoyois et al. used a predictive equation solely based on BW.<sup>19</sup> The sixth trial used IC, and in case this was not feasible, they used a predictive equation based on BW.<sup>11</sup> Chapple et al. differentiated between participants receiving MV and the ones who did not to determine energy requirements. In participants receiving MV, a predictive equation including BW was used, and in participants who did not receive MV, a predictive equation including BW and height was used.<sup>18</sup> Nematy et al. did not mention the method used to determine energy requirements.<sup>20</sup> Either actual BW (ABW) was used or adjusted BW (AdjBW) or ideal BW (IBW). All but Ridley et al. used AdjBW/IBW in case of BMI >30 kg/m<sup>2</sup>, with the remaining using a BMI >25 kg/m<sup>2</sup> as a threshold<sup>11</sup> (Table 2).

Energy targets in the group combining BW and height ranged between 25 and 27.8 kcal/kg/day,<sup>17,23</sup> whereas two studies did not define a target.<sup>21,22</sup> In the group that determined energy requirements on BW alone, targets ranged from 23 to 30 kcal/kg/day.<sup>11,19</sup> The only trial, from Ridley et al., with IC measurements revealed a target of 22.9 kcal/kg/day.<sup>11</sup> Chapple et al. combined two strategies depending on MV resulting in a target of 30 kcal/kg/day,<sup>18</sup> whereas the trial of Nematy et al. did not mention the method to calculate intake and could therefore not be compared with the other results.<sup>20</sup>

## Protein adequacy

The protein target varied between 1.2 and 1.5 g/kg/day with the use of BW equations<sup>17,19,22,23</sup> and when energy requirements were

17	IC performed	Calculation of energy requirements
Balasubramanian et al., 2021 <sup>17</sup>		
	No	Penn State 2003b
Chapple et al., 2016 <sup>18</sup>	No	Participants with no MV: (28% of calculations) Schofield: BMI >30 kg/m <sup>2</sup> AdjBW
	No	Participants with MV (72% of calculations): 25 kcal/kg BW/day
Salisbury et al., 2010 <sup>21</sup>	No	Schofield: BMI >30 kg/m <sup>2</sup> AdjBW
Slingerland-Boot et al., 2022 <sup>23</sup>	No	FAO (height)
Wittholz et al., 2020 <sup>22</sup>	Yes (at ICU [not published])	Schofield: BMI >30 kg/m <sup>2</sup> AdjBW
Hoyois et al., 2021 <sup>19</sup>	No	30 kcal/kg/day (or AdjBW if BMI ≥30kg/m²)
Ridley et al., 2019 <sup>11</sup>	No (20/32)	25–30 kcal/kg AdjBW/day (ABW if BMI <25kg/m <sup>2</sup> or AdjBW if BMI ≥25kg/m <sup>2</sup> ) if the patient was receiving RRT or ECMO on that day of ICU stay
	Yes (12/32 patients) REE: IC attempts 2×/week	IC
Nematy et al., 2006 <sup>20</sup>	No	ND

 TABLE 2
 Methods used for the determination of energy requirements.

Abbreviations: ABW, actual body weight; AdjBW, adjusted body weight; BMI, body mass index; ECMO, extracorporal membrane oxygenation; FAO, Food and Agricultural Organization; IC, indirect calorimetry; ICU, intensive care unit; MV, Mechanial Ventilation; ND, not defined; REE, resting energy expenditure; RRT, renal replacement therapy.

calculated based on IC measurements.<sup>11</sup> The Elia equation trial did not mention anything about protein targets<sup>21</sup> nor did Nematy et al.<sup>20</sup>

Intake ranged between 0.7 and 1.6 g/kg/day<sup>11,17,19,22,23</sup> with two studies not reporting intake.<sup>20,21</sup> The adequacy ranges varied considerably among studies using predictive equations based on BW alone (63%–83%). Salisbury et al. using the Elia equation had an adequacy of 85% and 63% for parts A and B, respectively. The trial using IC had an adequacy of 72%,<sup>11</sup> whereas adequacy could not be determined in the trial of Nematy et al.<sup>20</sup> (Tables 3 and 4; and Figure S2). Figure 3 shows a pooled average of protein adequacies (78.13%) (Figure 3) excluding Hoyois et al. and Balasubramanian et al. from the forest plot because of the absence of a reported SD.

Among the selected studies, Salisbury et al.<sup>21</sup> used a predictive equation (Elia equation), whereas the remaining studies relied on BW formulas. Nematy et al. did not specify the applied methodology to assess participants' protein requirements.<sup>20</sup> Two studies used AdjBW when BMI exceeded 25 kg/m<sup>2</sup>,<sup>11,18</sup> Slingerland-Boot et al.<sup>23</sup> when BMI was  $\geq$ 27 kg/m<sup>2</sup> and two studies when BMI was  $\geq$ 30 kg/m<sup>2</sup>.<sup>19,22</sup> The trial of Balasubramanian et al. did not mention anything regarding BW adjustments based on BMI.<sup>17</sup>

## **Routes and barriers**

Regarding feeding routes at ICU discharge, EN (4/8) and oral nutrition (3/9) were the most common routes. Salisbury et al. did not mention feeding routes,<sup>21</sup> and Nematy et al. recorded routes at ICU but not at ICU discharge,<sup>20</sup> resulting in a higher percentage of PN (Table 5). Routes at ICU discharge were all reported as the precentage of participants except for one trial, which was reported as the percentage of days<sup>11</sup> (Figure S3). The removal of the feeding tube was most frequently mentioned as a barrier  $(3/8)^{18,21,23}$  followed by poor registration of nutrition intake by staff  $(2/8)^{21,23}$  Two studies reported dietitian visits on a weekly basis. Participants were visited once or twice a week<sup>18,21</sup> (Table 5).

## DISCUSSION

In this systematic review, our primary objective was to comprehensively synthesize existing literature on the nutrition adequacy of post-ICU populations during their stay in general hospital wards. The scarcity of knowledge in this domain led to the inclusion of only eight eligible studies. Although patient cohorts were generally comparable, two studies by Balasubramanian et al. and Hoyois et al. exclusively focused on individuals with prolonged ICU stays. Our key findings revealed a concerning pattern of poor nutrition adequacy among post-ICU participants in general wards, particularly when relying solely on oral nutrition. Notably, consistently larger protein deficits compared with energy deficits were observed, and the removal of feeding tubes posed a significant risk of nutrition inadequacy.

Regarding the determination of nutrition needs, studies used various methods, such as predictive equations, BW calculations, or IC to calculate/measure energy and protein requirements. Energy and protein targets/intake were reported in kcal/g per kg BW per day or as kcal/g per day. In studies in which the weight of the study cohort population was reported, the conversion to kcal/g per kg BW per day was straightforward. However, not all studies reported weight, making switching to the alternative unit impossible. If participants exceeded a preselected BMI range, BW was recalculated to AdjBW or IBW, although the specific range varied across studies. Body composition is an essential factor to consider, as a bodybuilder and an

TABLE 9 Energy requirements and adequacy:	
Author, year	Energy (target/intake/adequacy [%]) Mean ± SD and/or median (IQR)
Balasubramanian et al., 2021 <sup>17</sup>	Target: 25 ± 1.9 kcal/kg/day; ~1835 kcal/day Converted weight: 2087 kcal/day <sup>a</sup> Intake: 21.7 ± 2.9 kcal/kg/day; ~1593 kcal/day Converted weight: 1812 kcal/day <sup>a</sup> Adequacy: 86%
Chapple et al., 2016 <sup>18</sup>	No MV • Target: 2457 ± 457 kcal/day; ~30 kcal/kg/day • Intake: 1980 ± 915 kcal/day; ~21.7 ± 7.5 kcal/kg/day • Adequacy: 81% ± 35% MV • Target: 2457 ± 457 kcal/day; ~30 kcal/kg/day • Intake: 1980 ± 915 kcal/day; ~21.7 ± 7.5 kcal/kg/day • Adequacy: 81% ± 35%
Salisbury et al., 2010 <sup>21</sup>	A • Target: ND • Intake: ND • Adequacy: • Admission ward 95% (53%-105%); 84.3% <sup>b</sup> ± 39% • Discharge: 87% (60%-105%); 84% <sup>b</sup> ± 33.7% B • Target: ND • Intake: ND • Intake: ND • Adequacy: weekly average 102.3% (83.4%-153.8%); (n = 6) 113.2% <sup>b</sup> ± 52.8 %
Slingerland-Boot et al., 2022 <sup>23</sup>	Target: 27.8 (26.3–29.3) kcal/kg/day; ~27.8 <sup>b</sup> ± 2.2 kcal/kg/day; 2143 kcal/day Intake: 24.7 ± 7.5 kcal/kg/day; ~1904 kcal/day Adequacy: 82% ± 18%
Wittholz et al., 2020 <sup>22</sup>	Target: 2309 <sup>c</sup> kcal/day; ~26.7 kcal/kg/day Intake: 1478 ± 651 kcal/day; ~17.1 kcal/kg/day Adequacy: 64% ± 28%
Hoyois et al., 2021 <sup>19</sup>	<ul> <li>Target:</li> <li>30 kcal/kg/day; ~2610 kcal/day</li> <li>Converted weight: 2520 kcal/day</li> <li>Intake:</li> <li>28-33.5 kcal/kg/day; ~2436-2915 kcal/day</li> <li>Converted weight: 2352-2814 kcal/day</li> <li>Adequacy:</li> <li>83.3%</li> <li>(Compliance checked at days 0, 7, 14, 21, 30, and 60; no daily follow-up)</li> </ul>
Ridley et al., 2019 <sup>11</sup>	Predictive equation • Target: • 2000 ( $1650-2550$ ) kcal/day; ~21.9 kcal/kg/day • $2067 \pm 675^{b}$ kcal/day; ~23 kcal/kg/day • Intake: • $1238 (869-1813)$ kcal/day; ~14 kcal/kg/day • $1307 \pm 708^{b}$ kcal/day; ~14.5 kcal/kg/day • Adequacy: • $79\% (41\%-108\%); 76\% \pm 50\%^{b}$ IC • Target: • $1982 (1843-2345)$ kcal/day; ~22.5 kcal/kg/day • $2057 \pm 376^{b}$ kcal/day; ~22.9 kcal/kg/day <sup>a</sup> • $Vs$ predicted 2000 ( $1725-2880$ ) kcal/day; ~22.2 kcal/kg/day • $2202 \pm 866^{b}$ kcal/day; ~24.5 kcal/kg/day in the same group • Intake: • $1890 (921-2348)$ kcal/day; ~21.4 kcal/kg/day • $1720 \pm 1070^{b}$ kcal/day; ~19.1 kcal/kg/day • $Adequacy$ : • $95\%^{c}$
	(Continues)

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#### TABLE 3 (Continued)

Author, year	Energy (target/intake/adequacy [%]) Mean ± SD and/or median (IQR)
Nematy et al., 2006 <sup>20</sup>	Target: 1687 ± 40 kcal/day Intake: 873.4 ± 215.7 kcal/day Adequacy: 52% <sup>c</sup>

Abbreviations: IC, indirect calorimetry; IQR, interquartile range; MV, mechanical ventilation; ND, not defined.

<sup>a</sup>Recalculated median weight to mean weight to calculate energy target/intake.

<sup>b</sup>Median (IQR) was converted into mean  $\pm$  SD with the formula of Wan et al., 2014.<sup>13</sup>

<sup>c</sup>Not mentioned, calculated following the next formula: (energy intake/energy target) × 100 or energy intake/(adequacy/100).

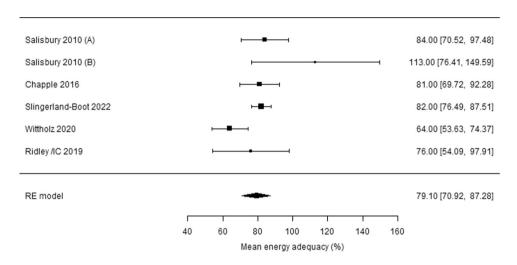


FIGURE 2 Forest plot of the mean energy adequacy (%) with 95% CI and black boxes representing the size of the study cohort. This is the average of the averages over studies, accounting for their SD and sample size. IC, indirect calorimetry; RE, Random Effect.

obese patient can have the same BMI considering that muscles are using up to three times more energy compared with adipocyte tissue (13 vs 4.5 kcal/kg/day).<sup>25</sup> The ESPEN guidelines for ICUs recommend using the AdjBW in participants with a BMI up to 30 kg/m<sup>2</sup> and IBW in participants with a BMI exceeding 30 kg/m<sup>2</sup>.<sup>24</sup> There is no consensus on when to use AdjBW, ABW, or IBW, so IC is the first choice. The prevalence of obesity (BMI >30 kg/m<sup>2</sup>) in hospital wards is very widespread: 37% in the United States, 19% in Europe, and 7% in Asian and Pacific regions, as recorded by NutritionDay.<sup>26</sup> As BW adjustments are based on BMI range and not on body composition, this may result in muscular people receiving less nutrition. Therefore, these adjustments must be used judiciously.

Only two articles<sup>11,25</sup> used IC to determine energy requirements, with only Ridley et al.<sup>11</sup> reporting it during the post-ICU phase. The Wittholz et al. study data<sup>22</sup> were not included in the IC group because those measurements took place during the ICU phase. All other studies used various formulas to estimate the energy needs. The use of IC in predicting energy requirements has already proven its benefit in several studies, including in ICU participants. It was associated with lower mortality, but there was no effect on MV and LOS duration in the ICU and hospitals.<sup>5,10</sup> The use of predictive equations leads to overestimation and underestimation of REE, already proven by several studies and reported earlier by several

research teams.<sup>9,27-31</sup> Considering the risks associated with undernutrition and overnutrition, IC is the gold standard and the most accurate prediction. Two studies did not report the method for calculating nutrition adequacy.<sup>11,20</sup> In two studies,<sup>11,18</sup> energy requirements were calculated using two different methods. Unlike Ridley et al., Chapple et al. did not segregate groups based on the method used; instead, they analyzed energy requirements independently of the methodology.<sup>18</sup> Consequently, the retrieved results are challenging to analyze regarding the accuracy and adequacy of each method.

The approach to data collection intake varied among studies. EN/PN and oral intake were recorded daily except for two studies. Not only was data collection done by different persons, but the intake measurement was planned at different time points. All studies measured intake daily. On the other hand, one trial assessed every 7 days, and another study measured EN/PN daily but oral intake only at three time points every week. The potential of overestimation and underestimation of intake increases as results are extrapolated.

In the included studies, the focus was not on reporting post-ICU nutrition barriers. Nevertheless, a comprehensive exploration of diverse obstacles through interviews with nursing staff, participants, and their families can yield valuable insights. Noncompletion of food charts was reported in two studies.<sup>21,23</sup> Recording oral intake appears

Author, year	Protein requirements	Protein (target/intake/adequacy [%]) Mean ± SD and/or median (IQR)				
Protein requirements determined by equations						
Salisbury et al., 2010 <sup>21</sup>	Elia equation	Part A • Target: ND • Intake: ND • Adequacy: • Ward admission 85% (52%-99%) • 78.7% <sup>a</sup> $\pm$ 35.2% • Ward discharge 83% (62%-99%) • 81.3% <sup>a</sup> $\pm$ 27.7% Part B • Target: ND • Intake: ND • Intake: ND • Adequacy: • Weekly average: 62.8% (50.7%-91.8%) (n = 6) • 68.4% <sup>a</sup> $\pm$ 30.8%				
Protein requirements calculated b	ased on body weight					
Balasubramanian et al., 2021 <sup>17</sup>	1.2g/kg/day (BMI ranges and/or IBW/AdjBW not reported)	<ul> <li>Target:</li> <li>1.2 ± 0.1 g/kg/day; ~88.1 g/day<sup>b</sup></li> <li>Converted weight: 100.2 g/day<sup>b</sup></li> <li>Intake:</li> <li>1.1 ± 0.1 g/kg/day; ~80.7 g/day</li> <li>Converted weight: 91.9 g/day<sup>b</sup>Adequacy: 86%</li> </ul>				
Chapple et al., 2016 <sup>18</sup>	1.2–2.2 g/kg/day (AdjBW for BMI >25 kg/m <sup>2</sup> )	Target: $118 \pm 27 \text{ g/day} \sim 1.44 \text{ g/kg/day}$ Intake: $89 \pm 41 \text{ g/day} \sim 1.0 \pm 0.4 \text{ g/kg/day}$ Adequacy: $77\% \pm 35\%$				
Hoyois et al., 2021 <sup>19</sup>	1.5 g/kg/day (AdjBW BMI ≥30 kg/m²)	<ul> <li>Target:</li> <li>1.5 g/kg/day; ~130 g/day</li> <li>Converted weight: 126 g/day<sup>b</sup></li> <li>Intake:</li> <li>1-1.6 g/kg/day; ~87-139.2 g/day</li> <li>Converted weight: 84-134.4 g/day<sup>b</sup></li> <li>Adequacy:</li> <li>63.3% (NB compliance checked at days 1, 7, 21, 30, and 60; no daily follow-up)</li> </ul>				
Ridley et al., 2019 <sup>11</sup>	1.2 g/kg/day (ABW BMI <25kg/m <sup>2</sup> or IBW if BMI >25kg/m <sup>2</sup> ) if the patient was receiving RRT or ECMO on that day of ICU stay	Target: • 112 (84-129) g/day; ~1.2 g/kg/day • 108.3 ± 33.7 <sup>a</sup> g/day; ~1.2 g/kg/day Intake: • 60 (35-89.5) g/day; ~0.6 g/kg/day • 61.5 ± 40.9 <sup>a</sup> g/day; ~0.7 g/kg/day Adequacy: • 73% (44%-98%) • 71.7% <sup>a</sup> ± 40.5%				
Slingerland-Boot et al., 2022 <sup>23</sup>	<ul> <li>BMI ≤27: 1.5 g/kg of ABW</li> <li>BMI 27-30: 1.5 g/kg, weight corrected to BMI 27</li> <li>BMI 30-40: 2.0 g/kg IBW (male BMI 22.5; female BMI 21)</li> <li>BMI ≥40: 2.5 g/kg IBW (male BMI 22.5; female BMI 21)</li> </ul>	Target: 1.2 or 1.2–1.5 or 1.5 g/kg/day Intake: 1.25 ± 0.38 g/kg/day ~ 96.4 g/day Adequacy: 83% ± 20%				
Wittholz et al., 2020 <sup>22</sup>	<ul> <li>1.2-1.5 g/kg/day</li> <li>BMI &gt;30 kg/m<sup>2</sup> AdjBW</li> </ul>	Target: 104.2 <sup>c</sup> g/day; ~1.25 g/kg/day Intake: 75 ± 37 g/day; ~0.9 g/kg/day Adequacy: 72% ± 32%				

Protein requirements calculated with input of indirect calorimetry

Ridley et al., 2019<sup>11</sup>

1.2 g/kg/day

Target: • 112 (84–129) g/day; ~1.2 g/kg/day

## TABLE 4 (Continued)

Author, year	Protein requirements	Protein (target/intake/adequacy [%]) Mean ± SD and/or median (IQR)
	(ABW BMI <25kg/m <sup>2</sup> or IBW if BMI >25kg/m <sup>2</sup> ) if the patient was receiving RRT or ECMO on that day of ICU stay	<ul> <li>108.3<sup>a</sup> ± 33.7 g/day; ~1.2 g/kg/day Intake:</li> <li>85 (35-121) g/day; ~1 g/kg/day</li> <li>80.3<sup>a</sup> ± 64.5 g/day; ~0.9 g/kg/day</li> <li>Adequacy:</li> <li>73% (44%-98%)</li> <li>71.7%<sup>a</sup> ± 40.5%</li> </ul>
Protein requirements not determin	ned	
Nematy et al., 2006 <sup>20</sup>	ND	Target: ND Intake: ND Adequacy: ND

Abbreviations: ABW, actual body weight; AdjBW, adjusted body weight; BMI, body mass index; ECMO, extracorporal membrane oxygenation; IBW, ideal body weight; ICU, intensive care unit; IQR, interquartile range; NB, Nota Bene; ND, not defined; RRT, renal replacement therapy.

<sup>a</sup>Median (IQR) was converted into mean ± SD with the formula of Wan et al., 2014.<sup>13</sup>

<sup>b</sup>Recalculated median weight to mean weight to calculate protein target/intake.

<sup>c</sup>Not mentioned but calculated following the next formula: protein intake/(adequacy/100).

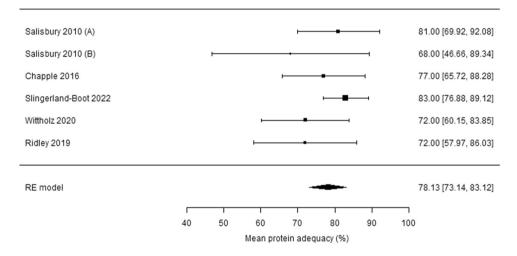


FIGURE 3 Forest plot of the mean protein adequacy (%) with 95% CI and black boxes representing the size of the study cohort. This is the average of the averages over studies, accounting for their SD and sample size. RE, Random Effect.

to be challenging compared with registering EN and/or PN intake. The amount of EN and/or PN administrated is automatically recorded in many hospital systems. For oral intake registration, researchers count on the nursing staff, participants, or their family members.<sup>11</sup> Only one trial reported poor appetite,<sup>20</sup> in accordance with an Australian trial that included 51 post-ICU participants. This study revealed that 79% of post-ICU participants experienced diminished appetite persisting for up to 3 months after ICU admission.<sup>32,33</sup> Swallowing disorders or dysphagia after tracheotomy removal, a common issue after ICU discharge,<sup>34</sup> were only explicitly addressed by Hoyois et al.<sup>19</sup> despite being prevalent among many participants<sup>35</sup> as well as fasting for surgery, procedures, and patient-related factors.<sup>20</sup>

Barriers encountered covering IC measurements were confused participants or measurement refusal by the patient. Three studies

documented inappropriate early feeding tube removal.<sup>11,20,24</sup> Pulling out feeding tubes by confused or agitated participants or the inappropriate early removal are another hurdle to take after ICU discharge.<sup>18</sup> Owing to the presence of dysphagia and reduced appetite, participants are often unable or have limited capacity to meet their nutrition needs after surviving a critical illness.<sup>40</sup> Keeping the feeding tube in place, even if the patient has some oral intake, is a significant requirement to reach nutrition adequacy. Nevertheless, a retrospective trial reported tube dislodgement in 16% of the ICU participants.<sup>36</sup> Also, removing feeding tubes as soon as possible is frequently used to encourage the participants to eat orally and to allow the "diet to grow."<sup>35</sup> Such practices should be discouraged, and nurses' and physicians' awareness of this topic must be increased.

Ensuring the fulfillment of participants' energy and protein requirements often involves a combination of feeding routes. This

#### TABLE 5 Barriers and outcomes.

Author, year	Routes at ICU discharge	Dietary visits/week	Barriers
Balasubramanian et al., 2021 <sup>17</sup>	EN (100%)	ND	ND
Chapple et al., 2016 <sup>18</sup>	Oral nutrition (12, 32%) Oral nutrition + EN (7, 19%) EN (18, 48%)	2.2 ± 1.0	EN interrupted on 58% of days (surgery and procedures) Inadvertent tube removal 83 times Oral interrupted on 234 of 639 days (65% = agitation/refusal; 21% = surgery/procedural fasting)
Hoyois et al., 2021 <sup>19</sup>	EN (14 of 15, 93%) PN (1 of 15, 7%)	ND	Swallowing disorders (60%)
Nematy et al., 2006 <sup>20</sup>	Routes in ICU: Oral nutrition (4 of 16, 25%) EN (10 of 16, 63%) PN (2 of 16, 13%)	ND	Poor appetite Nausea Satiety
Ridley et al., 2019 <sup>11</sup>	Oral nutrition (55% days) Oral nutrition + EN (42% days) EN (3% days) No nutrition (0.5% days)	ND	No IC measurement possibly because of • patient declining (26%) • patient confused (22%)
Salisbury et al., 2010 <sup>21</sup>	ND	A: 0.8 (0.6-2.2) 1.2 <sup>a</sup> ± 1.2 B: 1.2 (0.6-2.1) 1.3 <sup>a</sup> ± 1.1	Untimely removal of enteral feeding tubes Noncompletion by ward-based staff
Slingerland-Boot et al., 2022 <sup>23</sup>	Oral nutrition ( <i>n</i> = 8, 24%) Oral nutrition + EN ( <i>n</i> = 11, 32%) EN ( <i>n</i> = 13, 38%) SPN ( <i>n</i> = 2, 6%)	ND	Poor registration by staff Inadvertent removal of feeding tube (13%)
Wittholz et al., 2020 <sup>22</sup>	Oral nutrition (68%) Oral nutrition + EN (18%) EN (11%) EN + PN (4%)	ND	ND

Abbreviations: EN, enteral nutrition; IC, indirect calorimetry; ICU, intensive care unit; ND, not defined; PN, parenteral nutrition; SPN, supplemental parenteral nutrition.

<sup>a</sup>Median (IQR) was converted into mean  $\pm$  SD with the formula of Wan et al., 2014.<sup>13</sup>

review showed that adequacy is highest when participants receive EN or a combination of oral nutrition and EN. Adequacy decreases when participants receive oral nutrition alone owing to several causes like dysphagia, taste changes, and the presence of a nasogastric tube.<sup>34</sup> Although oral nutrition is still the first choice, when this is insufficient to meet nutrition targets EN and PN are other options. If combining oral intake and EN intake is insufficient, several studies and guidelines recommend adding (supplemental) PN.<sup>37</sup> A review addressed a decrease in adequacy from 62% (combining oral and EN) to 40% on oral nutrition in energy and protein adequacy, it would be expected that more supplemental PN would be used to seek better adequacy.

In recent years, there has been considerable focus on nutrition in intensive care settings,<sup>10,31,39</sup> but this should not be overlooked when participants are transferred to general wards. Recovery from a critical illness can take several months, so participants must be well-nourished on the ward to facilitate optimal recovery. Providing

scientific data can address this issue, but, in addition to the scientific aspect, attention must also be given to the education of healthcare providers because participants who survive critical illness might differ in metabolism and nutrition needs from their ward-only counterparts.

#### Strengths and limitations

The fact that this is the first review on nutrition adequacy in post-ICU participants adds to its strength, but this review has some major limitations. Our literature search was limited to three databases with the risk of missing relevant papers. Besides this, there is a lack of uniform terminology, and nutrition adequacy is not always the primary outcome, leading to underreporting or only partial reporting. Because there has not been much literature in this specific field area, there was only a limited number of publications, exacerbating the impact of outliers, which might lead to incorrect conclusions. Further, to improve comparability and allow conclusions, several medians

were converted to an estimated mean using a validated method, which still potentially impacted our results. Several studies had a lot of missing data, and additional calculations had to be made to allow comparisons, with the risk of misinterpretation and erroneous results. All studies had small (<50 participants) sample sizes, had different study designs, and used a different method of collecting data regarding intake, making it difficult to draw general conclusions. Finally, the included studies used ICU energy and protein targets (20-25 kcal/kg/day for energy and 1.3g/kg/day for protein) in a post-ICU population to calculate the energy and protein adequacy. No post-ICU nutrition guidelines are currently available, but Van Zanten et al. refers to a possible higher energy and protein need in the post-ICU phase compared with the ICU phase, possibly leading to an underestimation or overestimation of the observed adequacies.<sup>38</sup>

# CONCLUSIONS

Only a few studies have examined nutrition adequacy in general wards among participants who have survived critical illness. Many different methods were used in calculating targets and reporting results. Energy adequacy was between 52% and 102%, and protein adequacy was between 63% and 83%. Although IC is the gold standard in international nutrition guidelines, its application in clinical practice is poor, and the need for education is high. There is a need for more extensive studies, standardized reporting, and clear recommendations to guide nutrition screening and follow-up of post-ICU participants in general hospital wards.

#### AUTHOR CONTRIBUTIONS

Zenzi Rosseel, Pieter-Jan Cortoos, Lynn Leemans, and Elisabeth De Waele contributed to the conceptualization of the study; Zenzi Rosseel, Lynn Leemans, and Pieter-Jan Cortoos contributed to the methodology; Zenzi Rosseel and Pieter-Jan Cortoos contributed to the validation; Zenzi Rosseel wrote and prepared the original draft; and Lynn Leemans, Pieter-Jan Cortoos, Claudine Ligneel, Arthur R. H. van Zanten, and Elisabeth De Waele reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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#### CONFLICT OF INTEREST STATEMENT

Elisabeth De Waele reported receiving honoraria for advisory board meetings, lectures, and travel expenses from Baxter Healthcare, Danone-Nutricia, Cardinal Health, Fresenius Kabi, GE Healthcare, ART Medical, and Ferring Pharmaceuticals. Arthur R. H. van Zanten reported receiving honoraria for advisory board meetings, lectures, research grants, and travel expenses from Abbott, AOP Pharma, Baxter, Danone-Nutricia, Dutch Medical Food, Fresenius Kabi, GE Healthcare, Medcaptain, Nestlé, PAION, and Rousselot. The other authors have nothing to declare.

#### ORCID

Zenzi Rosseel D http://orcid.org/0000-0002-0182-6440 Pieter-Jan Cortoos D https://orcid.org/0000-0003-3998-6586 Lynn Leemans D https://orcid.org/0000-0001-5440-6506 Arthur R. H. van Zanten D http://orcid.org/0000-0001-6276-7192 Elisabeth De Waele D https://orcid.org/0000-0002-5126-3500

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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