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# A Systematic Literature Review on the Impact of Different Nutritional Interventions on the Development of Intensive Care Unit-Acquired Weakness

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**Abstract:** *Background:* There is a growing number of intensive care patients who survive from complicated intensive care procedures. However, many of these survivors struggle with muscle weakness, polyneuropathy, and reduced physical function as a result of intensive care unit-acquired weakness (ICUAW). Since nutrition is known to be crucial for the maintenance of muscle, several studies have investigated the effect of nutritional interventions on the development of ICUAW. *Objective:* The aim of this systematic literature review was to investigate the impact of nutrition on the development of ICUAW. *Methods:* This systematic literature review was conducted using the methodological framework described by Booth *et al*. A systematic literature search in CINAHL, MEDLINE, and EMBASE databases was conducted. Randomized controlled trials that investigated the effect of a nutritional intervention administered while the patient was admitted to the ICU were included. The endpoint was ICUAW or outcome measures encompassed by the ICUAW concept, such as muscle weakness, muscle atrophy, or reduced physical function. *Results:* Twenty articles met the inclusion criteria. Different nutritional interventions and different methods for measuring muscle weakness, muscle mass, and physical function were used in the primary studies. Inconsistent results were observed in studies that measured the short-term effects of nutritional interventions. None of the studies that measured ICUAW upon hospital discharge observed a difference in effect between nutritional intervention and the nutrition received by the control group. The samples in several studies were too small to determine the differences in the outcome measures of ICUAW. Some studies were pilot studies, while others had ICUAW as a secondary outcome. *Conclusion:* This literature review cannot determine the role of nutrition in the development of ICUAW. Due to the heterogeneous nature of the intensive care population, patients often have different nutritional needs. Future studies should be designed based on ICU patients' individual nutritional needs. Furthermore, there is a need for standardization of how ICUAW is measured, so that results from future studies can be compared.

**Keywords:** Intensive care nursing; Nutrition; Muscle weakness; Physical function; Systematic literature review

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## 1. Introduction

While an increasing number of people are surviving acute and critical illness requiring intensive care, it has also become apparent that this group struggles with reduced daily function and reduced quality of life as a result of their illness and intensive care treatment [1]. Studies have shown that between 30% and 50% of all intensive care patients experience reduced physical function in the form of intensive care unit-acquired weakness (ICUAW) [2]. ICUAW is a collective term for diagnoses that are due to muscle weakness or neuropathy as a result of intensive care [2]. Critical illness polyneuropathy, critical illness myopathy, muscle atrophy, and reduced muscle cell function are among the conditions covered by ICUAW [3,4]. This diagnosis represents a significant complication for those who are affected. Most require weeks or months of rehabilitation to regain their usual functional level, but in more severe cases, muscle weakness becomes permanent. In the long run, ICUAW is associated with reduced quality of life, reduced cognitive function, difficulty in returning to work, and increased 1-year mortality [4].

ICU nurses have special responsibilities to implement measures to prevent complications such as ICUAW and preserve the patient's strength and physical function [5]. However, preventing ICUAW remains a challenge, as there is a clear correlation between the severity of the disease and the development of the condition. For example, patients with sepsis, acute respiratory distress syndrome (ARDS), and multi-organ failure have a very high risk of developing ICUAW [6]. According to several reviews and primary studies, it is reasonable to assume that adequate nutrition has a preventive effect on ICUAW [7-11]. Nutrition is crucial for limiting muscle wasting, and it is known that prolonged malnutrition or starvation leads to poor outcomes, including increased risk of systemic infection, worsening of disease severity, and increased mortality [12,13]. However, the protective effect of nutrition on muscle function is not as demonstrable in intensive care patients as in other patient groups [7].

Several studies have investigated the association between different nutritional interventions and ICUAW, but their results vary. Both the American Society for Parenteral and Enteral Nutrition (ASPEN) [13] and the European Society for Parenteral and Enteral Nutrition (ESPEN) [12] have recommended increasing protein or amino acid supplementation for intensive care patients, despite the fact that this is based on low-quality studies. However, Puthucheary *et al.* [6] found that increased protein intake is associated with an increased risk of developing ICUAW. This finding has been confirmed by another study that examined the relationship between calorie and protein intake and physical function in 389 intensive care patients [14]. In the latter study, compared with patients who were discharged with better physical function, patients with the worst physical function after intensive care had received more proteins and calories on the third and seventh day of intensive care. The findings applied to both enteral nutrition (EN) and parenteral nutrition (PN). On the other hand, Fetterplace *et al.* [15] found a clear correlation between the degree of energy deficit and the development of ICUAW.

The conflicting results from studies can be partly explained by the fact that too little, too much, or too early nutrition can contribute to muscle weakness and neuropathy [16,17]. The first few days after sepsis or multi-organ failure, the affected patient would develop a neuroendocrine stress response, which reduces the metabolism of supplied nutrients [18]. These nutrients then become a burden that inhibits the cell-sensing mechanism that is crucial for the maintenance of muscle structure. Early full nutrition, therefore, becomes a risk factor of developing ICUAW [19].

The nutritional needs of intensive care patients are complex and depend on interdisciplinary collaboration between doctors, nutritionists, and intensive care nurses [20]. It is the doctor's task to prescribe EN and PN, while the intensive care nurse implements the nutritional measures and follows up with relevant observations. Therefore, whether the patient's nutritional needs are met depends, among other things, on the intensive care nurse's knowledge [20].

The time to initiate nutrition in intensive care patients, as well as the composition and amount of nutrition, remain unclear, as clinical trials have demonstrated conflicting results when investigating ICUAW [1,7]. No systematic literature reviews have been found published or registered in PROSPERO, which investigates nutritional interventions provided during intensive care, and have ICUAW as an endpoint. The systematic reviews published to date have either very limited endpoints, such as muscle volume [8] or sarcopenia [21], or have addressed limited interventions, such as PN [22,23] or protein dosing [24,25]. The aim of this systematic literature review was, therefore, to investigate the relationship between the nutrition patient receives during intensive care and the development of ICUAW on the basis of existing primary studies in this area. The research question was "What is the role of nutrition in the development of ICUAW?".

## 2. Methodology

This study was conducted as a systematic literature review using the framework of Booth *et al.* [26]. This design was suitable as the aim was to compile and critically appraise all suitable evidence, based on specific selection criteria, to answer a specific research question [27]. This systematic review followed the guidelines of the PRISMA statement [28]. No protocol has been published or registered for this study.

### 2.1. Data collection

A systematic literature search in CINAHL, MEDLINE, and EMBASE databases was conducted in November 2020. New hits in the search (alerts) from all three databases were reviewed until May 2021. The design of PICO and search strategy were prepared by the first author with the help of a specialist librarian. The search terms used included "critical care," "intensive care units," "critical illness," "critical care nursing," "ICU," "nutrition therapy," "parenteral nutrition," "enteral nutrition," "nutritional support," "nutrients," "polyneuropathies," "neuromuscular diseases," "muscle weakness," "muscular diseases," "physical functional performance," and "muscular atrophy." Keywords and text words were adapted to the different databases. No restrictions were made on years, as nutritional interventions in intensive care with appropriate outcomes measures will be relevant regardless of the year in which the study was conducted. The language used was restricted to English, Norwegian, Swedish, and Danish. Due to a high number of irrelevant hits in EMBASE, several refinements were made in the search, so that "conference abstract," "conference paper," "conference review," "editorial," "letter," and "note" were filtered out. These publication types were removed manually in CINAHL and MEDLINE. In addition to literature search, handsearching of the included articles was carried out to identify studies that may have been omitted from the search.

### 2.2. Inclusion and exclusion criteria

The inclusion criteria included randomized controlled trials (RCTs) on adult intensive care patients in which the intervention was nutritional intervention provided in the ICU. Studies that included patients up to 16 years of age were also included. The inclusion criteria for outcome measures were muscle wasting or physical function related to ICU stay. Studies were excluded if they combined nutritional interventions with other interventions or if the neuropathy or muscle weakness was attributed to causes other than intensive care. Pilot studies and feasibility studies were excluded if they lacked the sample size necessary to determine the effect on a primary outcome.

### 2.3. Selection process

The hits from the search were transferred to Rayyan [29], a digital tool, to keep the references and for blinding during the selection process. Two authors (ÅØS and SAS, ÅØS and KH) individually assessed the articles for inclusion on the basis of whether the title, abstract, or full text met the inclusion or exclusion criteria. Articles were read in full when it was unclear whether they should be included based on the abstract. When in doubt, a third author was consulted.

### 2.4. Data extraction

Relevant data were entered in a data extraction form based on Fleeman and Dundar's [30] method for data extraction and tabulation. The form was first pilot tested in three studies. Information about the author, year and country, study purpose, population and number of participants, nutritional intervention and control intervention, method for measuring ICUAW, and results that included ICUAW was filled in the data extraction form. Data extraction from the included studies was performed by the first author, while a second author checked the data extraction form against the articles.

### 2.5. Analysis of data

Due to heterogeneity in the intervention and outcome measures of the studies, performing a meta-analysis was not feasible. The results are presented in a narrative form. The findings were categorized according to the endpoints that we aimed to investigate. The results were, therefore, presented according to the outcome measures in the ICUAW-covered studies.

### 2.6. Quality assessment of included studies

The Critical Appraisal Skills Programme (CASP) checklist [31] was used to assess the quality of the primary studies. The criteria for the quality assessment are presented in **Table 1**. The table was designed by the first author based on the CASP checklist for randomized controlled trials and inspired by the table used by Ghouri [32] in his systematic literature review.

**Table 1.** Quality assessment of included studies

| | Does the RCT have a suitable study design? | Is the study methodologically correct? | | | | | What were the results? | | | Are the results helpful in practice? | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Is the research question clear? Was there adequate randomization? Were all the participants accounted for in the analysis? | Were patients blinded? | Were clinicians blinded? | Were the researchers blinded? | Were both groups similar at the start? | Did both groups receive the same treatment outside the intervention? | Was the intervention effect reported comprehensively? | Were the measures of dispersion reported? | Do the benefits of the intervention outweigh the disadvantages? | Can the results be translated to practice? | Does the intervention have greater benefit than any of the existing measures? |
| [51] | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| [48] | Yes | No | No | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | No |
| [34] | Yes | No | No | Yes | Yes | Unclear | Yes | Unclear | Yes | Yes | Yes |
| [37] | Yes | No | No | Yes | No | Yes | Yes | Yes | Yes | No | No |
| [42] | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | No | Yes | No |
| [44] | Yes | No | No | Yes | Yes | Unclear | Yes | Yes | No | Yes | No |
| [45] | Yes | No | No | No | No | Unclear | Yes | Yes | No | Yes | No |
| [40] | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | No | No |
| [41] | Yes | No | No | Yes | No | Unclear | Yes | Yes | Yes | No | No |
| [36] | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| [49] | Yes | No | No | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | No |
| [47] | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| [39] | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Unclear |
| [38] | Yes | No | No | Yes | No | Yes | Yes | Yes | No | Yes | Unclear |
| [43] | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | No | No | No |
| [46] | Yes | Unclear | No | Unclear | Yes | Unclear | Yes | Yes | Yes | No | No |
| [35] | Yes | No | No | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Unclear |
| [53] | Yes | No | No | Unclear | Yes | Unclear | Yes | Yes | Yes | No | No |
| [52] | Yes | No | No | No | Yes | Unclear | No | No | Unclear | No | Unclear |

## 3. Results

The literature search in CINAHL, MEDLINE, and EMBASE yielded a total of 5,211 hits. After duplicates were removed, 4,565 remained. Of these, 4,494 were excluded on the basis of the inclusion and exclusion criteria after reading the title or abstract. The abstract or full text for one reference could not be found, and thus it could not be assessed [33]. Seventy articles were read in full, and 55 of these were excluded. Updates from new hits from the search in the databases yielded two articles that met the inclusion criteria. Further three studies were identified in the reference lists of the included studies. This gave a total of 20 included articles (**Figure 1**).

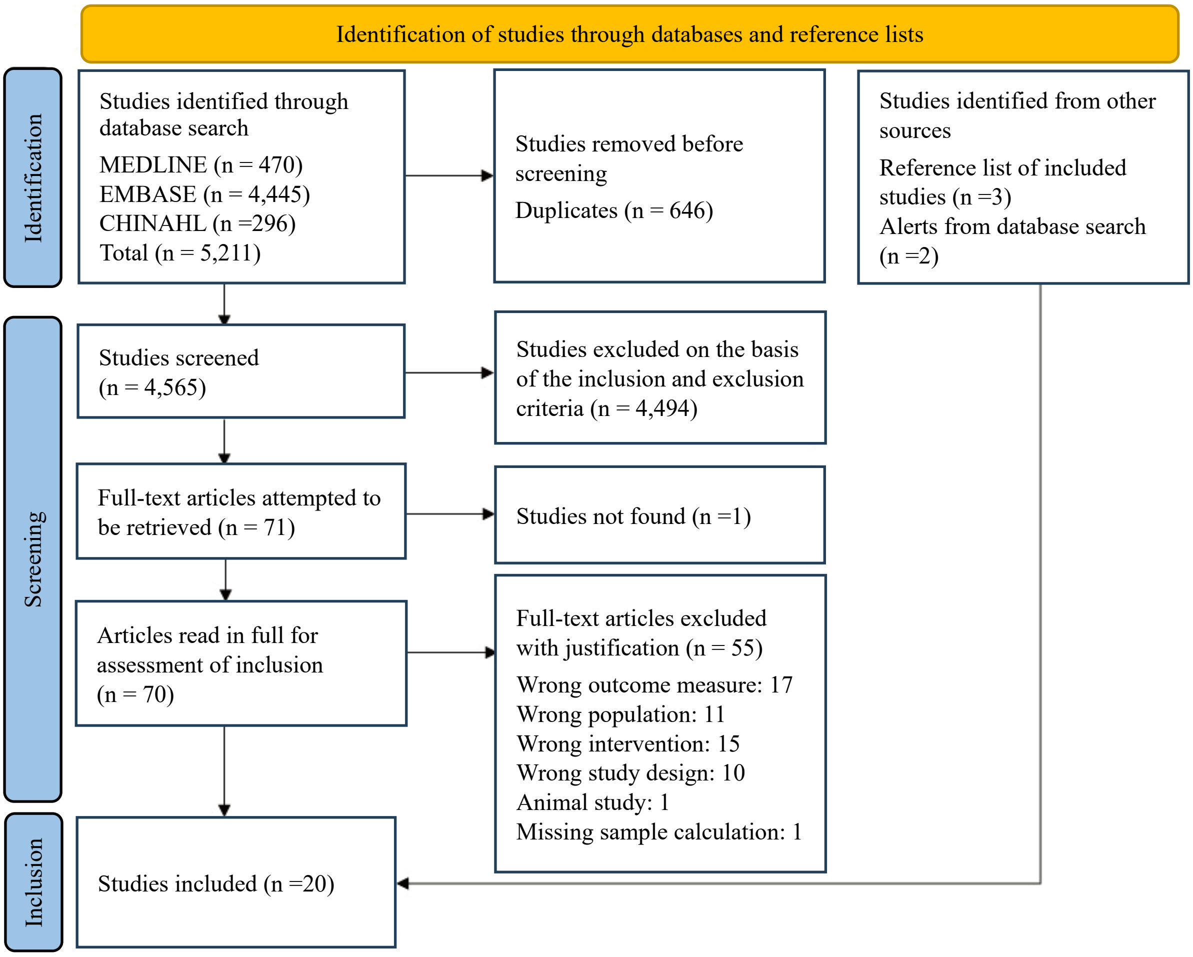


**Figure 1.** PRISMA flow diagram

The 20 included articles were spread across 16 studies. Four articles were from the same multicenter RCT study [34-37], and two of these used the same data material and were, therefore, considered the same study in this systematic literature review [35,36]. Two articles were follow-up studies of the same multicenter RCT study [38,39].

The studies were conducted in Australia (n = 4) [40-43], Australia and New Zealand (n = 3) [44-46], Japan (n = 1) [47], Belgium (n = 4) [34-37], Switzerland (n = 1) [48], England (n = 1) [49], Germany (n = 1) [50], Denmark (n = 1) [51], Philippines (n = 1) [52], USA (n = 2) [38,39], and Canada, France, USA, and Belgium (n = 1) [53]. The number of participants in the studies varied between 15 and 2,492 adult intensive care patients on ventilator. In total, this systematic literature review included 8,604 patients. Eight of the studies were multicenter RCTs [34-36, 38,39,42,44,45], seven were single-center RCTs [37,40, 47-51], three were single-center pilot RCTs [41,46,52], and two were multicenter pilot RCTs [43,53].

In nine studies, the intervention was PN [34-37, 40,44,46,48,53]. Of these, seven investigated the effect of early PN or early supplementary PN [34-37, 44,46,53]. Eight studies investigated the effect of EN [38,39, 41-43, 47,49,52]. Five of the included studies investigated the effect of increased protein or amino acid intake [40,41,45,50,52], while six investigated the effect of increased caloric dose [38,39, 41-43, 48]. One study investigated the effect of supplementation with hydroxymethyl butyrate, a metabolite of an amino acid, which has the property of upregulating muscle protein synthesis [47]. One study investigated the effect of individualized energy and protein dosing measured by indirect calorimetry and nitrogen balance [51]. Although the outcome measures were different, all studies had endpoints that were encompassed by the ICUAW concept.

### 3.1. Physical tests

Nine articles investigated the effect of nutritional interventions on patients' physical function using physical tests [34-36, 38,40,41,46,47,53]. In four of these, physical function was the primary outcome of the studies [35,36,38,40]. The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study [34-37] investigated the effect of early supplemental PN compared with delaying PN until the eighth day of the ICU course. Sub-studies of EPaNIC found that early PN led to a significantly higher risk of ICUAW, as measured by the Medical Research Council sum-score (MRC-SS), compared to late PN [35,36]. At the same time, another EPaNIC study found no difference between the groups in terms of six-minute walk test and activities of daily living (ADL) upon discharge from hospital [34]. However, the latter study found that participants who received late PN were discharged earlier from the intensive care unit and hospital [34].

One study [40] demonstrated that PN with a higher amino acid concentration had a significant positive effect on hand grip strength compared with standard PN. The six other studies that examined grip strength or other physical tests found no difference in effect of nutritional intervention compared with that of the control group [38,41,46,47,49,53].

### 3.2. Measurement of muscles

Five studies used ultrasound to measure the effect of nutritional interventions on muscle mass [40,41, 48-50], which was the primary outcome in two of the studies [49,50]. Two studies found that nutritional intervention has a protective effect on muscle volume. In one of these, the nutritional intervention was an increased dose of amino acids [40], while in the other, the intervention was volume-controlled EN, as compared with the control group that received standard nutritional treatment [41]. The endpoint was measured on day seven [40] and at discharge from intensive care [41]. The three other studies did not find that the effect of nutritional intervention on muscle volume, as measured by ultrasound, was significant [48-50].

Two studies measured muscle volume with computed tomography (CT) and found no effect [34,47]. One of the studies also examined muscle composition and found that early PN reduces the quality of muscle tissue by increasing intramuscular water and fat content [37].

One study measured muscle mass using the Subjective Global Assessment (SGA) and found that early PN led to significantly less muscle wasting compared with standard treatment [44].

### 3.3. Quality of life and physical function

Eight studies investigated the effect of nutritional interventions on self-reported quality-of-life and physical function two, three, six, and twelve months after intensive care [39, 42-46, 51,53]. RAND-36 [44,45], SF-36 [39,43,51,53], EuroQol-5D-3L [39,46], and EuroQol-5D-5L [42,43] questionnaires were used in the studies. One study [44] found a significant difference in general health measured with RAND-36 in favor of the intervention group that received early PN. The outcome measure was measured after 2 months. The other studies found no difference between the intervention and the control groups after discharge from hospital [39,42,43,46,51,53].

### 3.4. Assessment of risk of bias

An overview of the quality assessment of individual studies based on the CASP checklist for RCT studies is presented in **Table 1**. The quality assessment is based on the primary outcomes of the studies. Overall, the quality of the studies was considered good. However, the ICUAW endpoint was a secondary outcome in six of the included studies [34,41, 44-46, 53], and five of the studies were pilot studies [41,43,46,52,53]. Consequently, five of the included studies had inadequate sample size to determine the effect on ICUAW outcome measures [41,43,46,52,53], but this was not reflected in the overview of the quality assessment (**Table 1**). Furthermore, three of the studies were double-blinded, while 15 studies were blinded in their analysis.

In the majority of the studies, it was unclear whether the participants received equal treatment across groups outside the intervention. In 19 studies, the results were reported clearly and comprehensively.

## 4. Discussion

The aim of this systematic literature review was to determine the impact of nutrition on the development of ICUAW. Across the studies, there was considerable heterogeneity in interventions, outcome measures, sample size, and time of measurement, thus making it a challenge when comparing the results. The results of the included studies were contradictory, and there were too few studies of good quality to determine the impact of different nutritional interventions on ICUAW. Even in studies that demonstrated an effect, the effect was fast diminishing. None of the studies that investigated patients' physical function after discharge found an effect.

Across the studies, there was no correlation between the types of interventions that had an effect and those that did not. Good quality studies that investigated the effect of early PN showed varying results. One study found that early PN has a preventive effect on muscle wasting [44], while two other studies found that early PN increases the risk of muscle weakness [35,36]. However, it is worth noting that an effect was observed with delayed PN in studies that measured patients' muscle strength [35,36]. Muscle strength is a more clinically relevant outcome measure compared with muscle wasting, which is a surrogate outcome [17]. One of the included studies also showed that an increase in amount of PN led to an increase in intramuscular water and fat content measured by CT [37]. However, this result must be interpreted with caution, as the study had only 15 participants and the CT scans were only performed on clinical indication. Nevertheless, the study indicates that increased intramuscular volume, without increased muscle fiber size, is a possible explanation for the fact that some studies found an effect of increased nutrition on muscle volume but not on the patients' muscle strength [41,44].

There are too few studies of good quality to determine the effect of protein supplementation on the development of ICUAW. Ferrie *et al*. [40] found a positive effect on muscle volume measured by ultrasound and muscle strength based on grip strength in patients who received a larger amount of protein [40]. Dresen *et al*. [50], on the other hand, found no effect on muscle mass measured by ultrasound with increased protein. Both studies have an adequate sample size, but the interventions were so different that the studies are not comparable. Ferrie *et al*. [40] compared the effect of 0.8 grams of protein/kg/day with that of 1.2 grams of protein/kg/day, while Dresen *et al*. [50] compared 1.2 grams of protein/ kg/day with 1.8 grams of protein/kg/day. The latter study examined the effect of intervention given late during ICU stay and did not include patients before ICU day 13. The study did not report or take into account the nutrition the patients received during the first 13 days of the intensive care course. Vega-Alava *et al*. [52] found that patients who received 18 g of protein enterally per day had less muscle wasting compared with those who received standard EN by measuring their upper arm circumference. The study did not cite any sources on how upper arm circumference correlates with muscle volume. The study also only included 40 participants, while stating that a sample size of 183 patients is needed.

The findings are contradictory among the studies that investigated the effect of interventions to increase calorie and protein intake with EN. In a study by both Fetterplace *et al*. [41] and McNelly *et al*. [49], the intervention group received more of their estimated protein and calorie requirements compared to the control group. Both measured muscle wasting with ultrasound, but muscle wasting was reduced with intervention only in the study by Fetterplace *et al*. [41]. In the latter study, 23% (n = 6) of the participants in the intervention group and 27% (n = 7) of the participants in the control group lacked ultrasound measurements. The groups in this study were dissimilar at baseline.

In most of the studies that found an effect with nutritional interventions [35,36,40,44], the effect ceased rapidly. In three of the studies [36,40,44], the differences ceased before discharge from the ICU. Regardless of the nutritional intervention and choice of endpoint, the time at which the endpoint is measured appears to be important for determining if the intervention has an impact [35,36,40,44]. If the effect of the intervention on different outcome measures of ICUAW is short-term, the clinical relevance will be less, as ICUAW has a major impact on the patient's rehabilitation pathway and often causes reduced physical function over a long period of time [9].

One of the reasons why the effect of nutritional intervention is short-lived may be that the duration of the nutritional intervention is short. In eight of the included studies, the nutritional intervention lasted between five and ten days, or shorter for patients who were discharged earlier from the ICU [36,38,40,43,46,48,49,53]. In other studies, the intervention was designed in such a way that the difference between the intervention group and control group would be balanced out during the intensive care stay. This is the case, for example, in the study by Doig *et al*. [44], where the intervention group and the control group received approximately the same amount of calories and protein by the seventh day in intensive care. The short-term interventions are probably a result of the fact that the patient will have different nutritional needs after approximately five to ten days, when it is assumed that the physiological stress response has passed to some extent.

None of the nine studies that examined patients' physical function after discharge found an effect with nutritional intervention [38,39,42-46,51,53]. However, one of the studies [44] found a significant effect in general health measured with RAND-36, but this did not apply to physical function, which is one of the domains of the instrument. Furthermore, the demonstrated effect of the nutritional intervention was so small that it was not clinically significant.

The results from the primary studies in this systematic literature review suggest that the effect of nutritional interventions given in the ICU is not long enough to affect patients' physical function at three, six, and twelve months later. Any effect might also have been overshadowed by other factors that influence patients' functional level after hospital discharge, such as coping skills, psychosocial conditions, and rehabilitation [54-56]. Studies that measure long-term effects should identify such factors as much as possible in order to avoid risk of bias in the patient sample, which may affect the results. Of the included studies that examine ICUAW after discharge, only two [38,39] have attempted to account for such confounding factors. Needham *et al*. [38,39] included factors such as whether the patients were living at home or an institution, self-reliant, or working before admission to intensive care. In addition, the participants in the study responded to the SF-36 on how their quality of life and level of function were before admission. This information may be important and has been overlooked in other studies. If the groups were dissimilar to begin with, we would not know whether it was the intervention or other factors that led to the result. It is not possible to control all variables that may affect the endpoint. However, when long-term effects in the form of physical function are examined, factors such as previous physical function and social conditions may be of great importance to patient outcomes [9].

A secondary finding in one of the studies by Needham *et al*. [39] was that more people in the group that received trophic nutrition had required rehabilitation after intensive care stay compared with the control group that was under EN. Trophic nutrition refers to a small dose of EN, for example 10 mL/h, with the aim of maintaining intestinal mucosa and intestinal flora, instead of meeting the patient's energy needs [12]. Nevertheless, the studies found no difference in outcome measures between the groups [38,39]. The proportion in work [39], results of the six-minute walk test, and patient's strength measured with MRC-SS [38] were similar in both groups six and twelve months after discharge.

A short-term nutritional intervention alone may not be potent enough to affect the functional level of intensive care patients six and twelve months later [17]. Therefore, it is important to determine how long the effect of the intervention will last in order for it to be of clinical significance. A consensus on which outcome measures are best suited to measure ICUAW and at which time point they should be measured should be developed, so that studies can be compared [17,57].

The results of this systematic review are consistent with two similar systematic reviews that examined specific nutritional interventions [24] and limited outcome measures [8], as mentioned in the introduction. These reviews have indicated that the results from the primary studies are contradictory and that there is too little evidence to draw conclusions on the effect of nutritional interventions on outcomes that can be categorized as ICUAW. Other systematic reviews with meta-analyses that examined the effect of nutritional interventions on other outcomes have shown that nutritional intervention does not have an effect [58,59]. In contrast, systematic reviews that examined the effect of various interventions on muscle mass and physical function have found that physiotherapy and exercise-based interventions have a preventive effect on ICUAW [21,22].

The lack of effect in RCT studies may be a consequence of the fact that intensive care patients may have different responses to the same nutritional intervention. Bear *et al*. [60] pointed out that the heterogeneity of intensive care patients represents a major challenge in nutrition studies because different patients have different nutritional needs. In primary studies, the samples are usually similar in terms of diagnosis, disease severity, gender, age, and body mass index. However, patients differ in body composition and nutritional status prior to admission. Moreover, their metabolism changes during the intensive care period, as the neuroendocrine stress response may be of different durations in each patient [61]. Patient differences imply a possibility that nutritional intervention prevents ICUAW in some but increases the risk of ICUAW in others. The challenge with the heterogeneous ICU population has also been recognized in nutritional guidelines for intensive care patients [12,13]. Both ASPEN [13] and ESPEN [12] have emphasized that the heterogeneity of the ICU population may weaken the external validity of the recommendations, so the needs of each patient should be prioritized ahead of the guidelines.

Many have pointed out that nutrition studies with outcome measures, such as physical function and quality of life, are a relatively new field of research that is still developing [60,62]. Future studies should take greater account of the methodological challenges that have been revealed [60,62]. One example of a study that has done this is the study by Wischmeyer *et al*. [53], which took into account aspects of heterogeneity in the intensive care population and the associated different nutritional needs. Observational studies have shown that underweight and overweight ICU patients benefit from supplemental PN, while normal weight patients do not. In the study by Wischmeyer *et al*. [53], overweight and underweight patients received supplemental PN, while patients of normal weight only received standard EN. The study was a pilot study that did not have a large enough sample size to detect differences in clinical outcome measures, but a non-significant trend toward better outcomes was observed in the intervention group [53].

For ICU nurses in practice, it is important to be aware that the impact of nutrition on the development of ICUAW is still an area with ambiguous evidence, characterized by sparse research and methodological challenges. Therefore, the results of this systematic review cannot be used to change existing guidelines and recommendations. Hopefully, further research will generate new understanding and thus opportunities for changed guidelines and recommendations in nutrition to prevent ICUAW.

## 5. Limitations of the study

In this systematic literature review, a comprehensive literature search was conducted with the aim of including all outcome measures that can be covered by ICUAW. However, there are too few studies that are comparable and of good enough quality to determine the impact of nutritional interventions provided during intensive care on the development of ICUAW. The quality assessment showed that the studies are generally of good quality, owing to the fact that these studies were assessed based on their primary outcome. In several studies, the outcome measures of ICUAW were often secondary or tertiary outcomes. Five of the studies were also pilot studies. This means that some of the studies were not specifically designed to determine the effect on relevant outcome measures of ICUAW [41,43,46,52,53] and thus some of the results of these studies did not have a large enough sample size; it is, therefore, not known whether these findings are due to chance. Due to the design of the interventions in the studies, blinding was a challenge, and only three of the studies were double-blinded [40,42,43]. This means that there were some risks of systematic bias in the studies.

One challenge in this systematic literature review is the variation in the interventions and outcome measures of the primary studies. This heterogeneity made it difficult to compare studies and compile results. A weakness of the present study is that no project description was published in advance. A strength of the present study is that the search was quality assured by a specialist librarian, but studies might have been omitted due to language restrictions.

## 6. Conclusion

This systematic literature review shows that there are conflicting results with regard to the importance of the nutrition patients receive during intensive care on the development of ICUAW. In studies that found an effect with nutritional interventions, the effect declined rapidly, and none of the studies that examined the patients' physical function after discharge found an effect with nutritional interventions. Moreover, there are too few studies of good quality to determine the impact of different nutritional interventions on ICUAW. Future nutritional studies should be designed based on patients' individual needs, as ICU patients will have varying nutritional needs based on their starting point and whether they have an ongoing neuroendocrine stress response or not. It is also necessary to develop a consensus on which endpoints are best suited to measure ICU patients' physical function, so that the endpoints used in studies are clinically relevant and the results from studies can be compared.

## Disclosure statement

The authors declare no conflict of interest.

## References


[1] Bear DE, Wandrag L, Merriweather JL, et al., 2017, The Role of Nutritional Support in the Physical and Functional Recovery of Critically Ill Patients: A Narrative Review. Crit Care, 21(1): 226.

[2] Piva S, Fagoni N, Latronico N, 2019, Intensive Care Unit-Acquired Weakness: Unanswered Questions and Targets for Future Research. F1000 Res, 8: 508. https://doi.org/10.12688/f1000research.17376.1

[3] Stevens RD, Marshall SA, Cornblath DR, et al., 2009, A Framework for Diagnosing and Classifying Intensive Care Unit-Acquired Weakness. Crit Care Med, 37(10): S299–S308. https://doi.org/10.1097/CCM.0b013e3181b6ef67

[4] Hermans G, Van den Berghe G, 2015, Clinical Review: Intensive Care Unit Acquired Weakness. Crit Care, 19(1): 274. https://doi.org/10.1186/s13054-015-0993-7

[5] NSFLIS, 2017, Funksjons- og Ansvarsbeskrivelse for Intensivsykepleier [Functional and Responsibility Description for Intensive Nurse]. Norsk Sykepleierforbund, Oslo.

[6] Puthucheary ZA, Rawal J, McPhail M, et al., 2013, Acute Skeletal Muscle Wasting in Critical Illness. JAMA, 310(15): 1591–1600. https://doi.org/10.1001/jama.2013.278481

[7] Sundström-Rehal M, Tardif N, Rooyackers O, 2019, Can Exercise and Nutrition Stimulate Muscle Protein Gain in the ICU Patient? Curr Opin Clin Nutr Metab Care, 22(2): 146–151. https://doi.org/10.1097/MCO.0000000000000548

[8] Lambell KJ, King SJ, Forsyth AK, et al., 2018, Association of Energy and Protein Delivery on Skeletal Muscle Mass Changes in Critically Ill Adults: A Systematic Review. JPEN J Parenter Enteral Nutr, 42(7): 1112–1122. http://dx.doi.org/10.1002/jpen.1151

[9] Latronico N, Herridge M, Hopkins R, et al., 2017, The ICM Research Agenda on Intensive Care Unit-Acquired Weakness. Intens Care Med, 43(9): 1270–1281. https://doi.org/10.1007/s00134-017-4757-5

[10] Liu Y, Zhao W, Chen W, et al., 2020, Effects of Early Enteral Nutrition on Immune Function and Prognosis of Patients with Sepsis on Mechanical Ventilation. J Intens Care Med, 35(10): 1053–1061. https://doi.org/10.1177/0885066618809893

[11] Yeh DD, Ortiz-Reyes LA, Quraishi SA, et al., 2018, Early Nutritional Inadequacy Is Associated with Psoas Muscle Deterioration and Worse Clinical Outcomes in Critically Ill Surgical Patients. J Crit, 45: 7–13. http://dx.doi.org/10.1016/j.jcrc.2017.12.027

[12] Singer P, Blaser AR, Berger MM, et al., 2019, ESPEN Guideline on Clinical Nutrition in the Intensive Care Unit. Clin Nutr, 38(1): 48–79. https://doi.org/10.1016/j.clnu.2018.08.037

[13] McClave SA, Taylor BE, Martindale RG, et al., 2016, Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). JPEN J Parenter Enter Nutr, 40(2): 159–211. https://doi.org/10.1177/0148607115621863

[14] Yatabe T, Egi M, Sakaguchi M, et al., 2019, Influence of Nutritional Management and Rehabilitation on Physical Outcome in Japanese Intensive Care Unit Patients: A Multicenter Observational Study. Ann Nutr Metab, 74(1): 35–43. https://dx.doi.org/10.1159/000495213

[15] Fetterplace K, Beach LJ, MacIsaac C, et al., 2019, Associations Between Nutritional Energy Delivery, Bioimpedance Spectroscopy and Functional Outcomes in Survivors of Critical Illness. J Hum Nutr Diet, 32(6): 702–712. https://dx.doi.org/10.1111/jhn.12659

[16] Lad H, Saumur TM, Herridge MS, et al., 2020, Intensive Care Unit Acquired Weakness: Not Just Another Muscle Atrophying Condition. Int J Mol Sci, 21(21): 7840. https://doi.org/10.3390/ijms21217840

[17] Fetterplace K, Ridley EJ, Beach L, et al., 2020, Quantifying Response to Nutrition Therapy During Critical Illness: Implications for Clinical Practice and Research? A Narrative Review. JPEN J Parenter Enteral Nutr, 25: 25. https://dx.doi.org/10.1002/jpen.1949

[18] Ingvaldsen B, 2016, Væske, Elektrolytter, Blodgasser og Infusjonsterapi 5 utg. [Fluid, Electrolytes, Blood Gases and Infusion Therapy 5th Ed.], Avdeling for Anestesiologi Oslo Universitetssykehus, Oslo.

[19] García-Martínez MÁ, González JCM, García-de-Lorenzo A, et al., 2019, Muscle Weakness: Understanding the Principles of Myopathy and Neuropathy in the Critically Ill Patient and the Management Options. Clin Nutr, 39(5): 1331–1344. https://doi.org/10.1016/j.clnu.2019.05.027

[20] Guldbrandsen T, Stubberud D-G, (eds) 2016, Intensivsykepleie 3 Utg. [Intensive Care Nursing 3rd Ed.], Cappelen Damm Akademisk, Oslo.

[21] Trethewey SP, Brown N, Gao F, et al., 2019, Interventions for the Management and Prevention of Sarcopenia in the Critically Ill: A Systematic Review. J Critical Care, 50: 287–295. https://dx.doi.org/10.1016/j.jcrc.2019.01.008

[22] Calvo-Ayala E, Khan BA, Farber MO, et al., 2013, Interventions to Improve the Physical Function of ICU Survivors: A Systematic Review. CHEST, 144(5): 1469–1480. https://doi.org/10.1378/chest.13-0779

[23] Bost RB, Tjan DH, van Zanten AR, 2014, Timing of (Supplemental) Parenteral Nutrition in Critically Ill Patients: A Systematic Review. Ann Intensive Care, 4(1): 1–13. https://doi.org/10.1186/s13613-014-0031-y

[24] Fetterplace K, Gill BMT, Chapple LaS, et al., 2020, Systematic Review with Meta-Analysis of Patient-Centered Outcomes, Comparing International Guideline-Recommended Enteral Protein Delivery with Usual Care. JPEN J Parenter Enter Nutr, 44(4): 610–620. https://doi.org/10.1002/jpen.1725

[25] Wandrag L, Brett SJ, Frost G, et al., 2015, Impact of Supplementation with Amino Acids or Their Metabolites on Muscle Wasting in Patients with Critical Illness or Other Muscle Wasting Illness: A Systematic Review. J Hum Nutr Diet, 28(4): 313–330. http://dx.doi.org/10.1111/jhn.12238

[26] Booth A, Sutton A, Papaioannou D, 2016, Systematic Approaches to a Successful Literature Review 2nd Ed., Sage, London.

[27] Grant MJ, Booth A, 2009, A Typology of Reviews: An Analysis of 14 Review Types and Associated Methodologies. J Eur Assoc Health Inf Libr, 26(2): 91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x

[28] Page MJ, McKenzie JE, Bossuyt PM, et al., 2021, The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. BMJ, 2021: 372.

[29] Ouzzani M, Hammady H, Fedorowicz Z, et al., 2016, Rayyan—A Web and Mobile App for Systematic Reviews. Syst Rev, 5(1): 1–10. https://doi.org/10.1186/s13643-016-0384-4

[30] Cherry MG, Boland A, Dickson R, (eds) 2017, Data Extraction: Where Do I Begin?, in Doing a Systematic Review: A Student's Guide 2nd Ed. Sage Publications, California, 93–106.

[31] Critical Appraisal Skills Programme, 2019, CASP Randomised Controlled Trials Checklist, https://casp-uk.net/casp-tools-checklists/

[32] Ghouri F, Hollywood A, Ryan K, 2018, A Systematic Review of Non-Antibiotic Measures for the Prevention of Urinary Tract Infections in Pregnancy. BMC Pregnancy Childbirth, 18(1): 99. https://doi.org/10.1186/s12884-018-1732-2

[33] Brabant GV, Vasilevsky CA, Gardiner PA, 1984, Skeletal Muscle Function and the Nutritional State. Surgical Forum, 35: 90–92.

[34] Casaer MP, Mesotten D, Hermans G, et al., 2011, Early Versus Late Parenteral Nutrition in Critically Ill Adults. N Engl J Med, 365(6): 506–517. https://doi.org/10.1056/NEJMoa1102662

[35] Van Dyck L, Derese I, Vander Perre S, et al., 2019, The GH Axis in Relation to Accepting an Early Macronutrient Deficit and Outcome of Critically Ill Patients. J Clin Endicronol Metabol, 104(11): 5507–5518. https://dx.doi.org/10.1210/jc.2019-00842

[36] Hermans G, Casaer MP, Clerckx B, et al., 2013, Effect of Tolerating Macronutrient Deficit on the Development of Intensive-Care Unit Acquired Weakness: A Subanalysis of the EPaNIC Trial. Lancet Respir Med, 1(8): 621–629. https://dx.doi.org/10.1016/S2213-2600(13)70183-8

[37] Casaer MP, Langouche L, Coudyzer W, et al., 2013, Impact of Early Parenteral Nutrition on Muscle and Adipose Tissue Compartments During Critical Illness. Crit Care Med, 41(10): 2298–2309. https://dx.doi.org/10.1097/CCM.0b013e31828cef02

[38] Needham DM, Dinglas VD, Morris PE, et al., 2013, Physical and Cognitive Performance of Patients with Acute Lung Injury 1 Year After Initial Trophic Versus Full Enteral Feeding EDEN Trial Follow-Up. Am J Respir Crit Care Med, 188(5): 567–576. http://dx.doi.org/10.1164/rccm.201304-0651OC

[39] Needham DM, Dinglas VD, Bienvenu OJ, et al., 2013, One Year Outcomes in Patients with Acute Lung Injury Randomised to Initial Trophic or Full Enteral Feeding: Prospective Follow-Up of EDEN

Randomised Trial. BMJ, 346: f1532. https://dx.doi.org/10.1136/bmj.f1532

[40] Ferrie S, Allman-Farinelli M, Daley M, et al., 2016, Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. JPEN J Parenter Enter Nutr, 40(6): 795–805. https://doi.org/10.1177/0148607115618449

[41] Fetterplace K, Deane AM, Tierney A, et al., 2018, Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial). J Parenter Enter Nutr, 42(8): 1252–1262. http://dx.doi.org/10.1002/jpen.1166

[42] Deane AM, Little L, Bellomo R, et al., 2020, Outcomes Six Months After Delivering 100% or 70% of Enteral Calorie Requirements During Critical Illness (TARGET). A Randomized Controlled Trial. Am J Respir Crit Care Med, 201(7): 814–822. https://doi.org/10.1164/rccm.201909-1810OC

[43] Reid DB, Chapple LS, O'Connor SN, et al., 2016, The Effect of Augmenting Early Nutritional Energy Delivery on Quality of Life and Employment Status One Year After ICU Admission. Anaesth Intens Care, 44(3): 406–412. http://dx.doi.org/10.1177/0310057x1604400309

[44] Doig GS, Simpson F, Sweetman EA, et al., 2013, Early Parenteral Nutrition in Critically Ill Patients with Short-Term Relative Contraindications to Early Enteral Nutrition: A Randomized Controlled Trial. JAMA, 309(20): 2130–2138. https://dx.doi.org/10.1001/jama.2013.5124

[45] Doig GS, Simpson F, Bellomo R, et al., 2015, Intravenous Amino Acid Therapy for Kidney Function in Critically Ill Patients: A Randomized Controlled Trial. Intens Care Med, 41(7): 1197–1208. https://doi.org/10.1007/s00134-015-3827-9

[46] Ridley EJ, Davies AR, Parke R, et al., 2018, Supplemental Parenteral Nutrition Versus Usual Care in Critically Ill Adults: A Pilot Randomized Controlled Study. Crit Care, 22: 1-10. https://doi.org/10.1186/s13054-018-1939-7

[47] Nakamura K, Kihata A, Naraba H, et al., 2020, b-Hydroxy-b-Methylbutyrate, Arginine, and Glutamine Complex on Muscle Volume Loss in Critically Ill Patients: A Randomized Control Trial. JPEN J Parenter Enter Nutr, 44(2): 205–212. https://doi.org/10.1002/jpen.1607

[48] Berger MM, Pantet O, Jacquelin-Ravel N, et al., 2019, Supplemental Parenteral Nutrition Improves Immunity with Unchanged Carbohydrate and Protein Metabolism in Critically Ill Patients: The SPN2 Randomized Tracer Study. Clin Nutr, 38(5): 2408–2416.

[49] McNelly AS, Bear DE, Connolly BA, et al., 2020, Effect of Intermittent or Continuous Feed on Muscle Wasting in Critical Illness: A Phase 2 Clinical Trial. Chest, 158(1): 183–194. https://dx.doi.org/10.1016/j.chest.2020.03.045

[50] Dresen E, Weißbrich C, Fimmers R, et al., 2021, Medical High-Protein Nutrition Therapy and Loss of Muscle Mass in Adult ICU Patients: A Randomized Controlled Trial. Clin Nutr, 40(4): 1562–1570. https://doi.org/10.1016/j.clnu.2021.02.021

[51] Allingstrup MJ, Kondrup J, Wiis J, et al., 2017, Early Goal-Directed Nutrition Versus Standard of Care in Adult Intensive Care Patients: The Single-Centre, Randomised, Outcome Assessor-Blinded EAT-ICU Trial. Intens Care Med, 43(11): 1637–1647. https://doi.org/10.1007/s00134-017-4880-3

[52] Vega-Alava KM, Sy RAG, Domado AM, 2018, The Effect of Whey Protein Supplementation on Duration of Mechanical Ventilation: A Pilot Study. Philipp J Intern Med, 56(2): 71–76.

[53] Wischmeyer PE, Hasselmann M, Kummerlen C, et al., 2017, A Randomized Trial of Supplemental Parenteral Nutrition in Underweight and Overweight Critically Ill Patients: The TOP-UP Pilot Trial. Crit Care, 21: 1–14. https://doi.org/10.1186/s13054-017-1736-8

[54] Coster WJ, 2013, Making the Best Match: Selecting Outcome Measures for Clinical Trials and

Outcome Studies. Am J Occup Ther, 67(2): 162–170. https://doi.org/10.5014/ajot.2013.006015

[55] Aitken LM, Burmeister E, McKinley S, et al., 2015, Physical Recovery in Intensive Care Unit Survivors: A Cohort Analysis. Am J Crit Care, 24(1): 33–40. https://doi.org/10.4037/ajcc2015870

[56] Hashem MD, Nallagangula A, Nalamalapu S, et al., 2016, Patient Outcomes After Critical Illness: A Systematic Review of Qualitative Studies Following Hospital Discharge. Crit Care, 20(1): 345 (2016). http://dx.doi.org/10.1186/s13054-016-1516-x

[57] Taverny G, Lescot T, Pardo E, et al., 2019, Outcomes Used in Randomised Controlled Trials of Nutrition in the Critically Ill: A Systematic Review. Criti Care, 23(1): 12 (2019). http://dx.doi.org/10.1186/s13054-018-2303-7

[58] Marik PE, Hooper MH, 2016, Normocaloric Versus Hypocaloric Feeding on the Outcomes of ICU Patients: A Systematic Review and Meta-Analysis. Intens Care Med, 42(3): 316–323. https://doi.org/10.1007/s00134-015-4131-4

[59] Davies ML, Chapple L-AS, Chapman MJ, et al., 2017, Protein Delivery and Clinical Outcomes in the Critically Ill: A Systematic Review and Meta-Analysis. Crit Care Resusc, 19(2): 117.

[60] Bear DE, Puthucheary Za, 2019, Designing Nutrition-Based Interventional Trials for the Future: Addressing the Known Knowns. Crit Care, 23(1): 53. https://dx.doi.org/10.1186/s13054-019-2345-5

[61] Arabi YM, Casaer MP, Chapman M, et al., 2017, The Intensive Care Medicine Research Agenda in Nutrition and Metabolism. Intens Care Med, 43(9): 1239–1256. https://doi.org/10.1007/s00134-017-4711-6

[62] Chapple LS, Ridley EJ, Chapman MJ, 2020, Trial Design in Critical Care Nutrition: The Past, Present and Future. Nutrients, 12(12): 3694. https://doi.org/10.3390/nu12123694