NUTRITION IN SURVIVORS OF CRITICAL ILLNESS

An exploration of the effect of nutrition therapy on muscle mass, nutritional status and clinical outcomes after critical illness with a focus on patients with a traumatic brain injury

Lee-anne Chapple

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Faculty of Health Sciences
University of Adelaide

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Abstract:

Critical illness affects ~130,000 Australians each year, costing the health-care system nearly $3 billion. For intensive care unit (ICU) survivors, quality of life and functional recovery are compromised, with symptoms persisting five years post-discharge. Patients admitted to ICU with traumatic brain injury (TBI) are at particular risk. Accordingly, interventions that enhance recovery will improve patients' quality of life and are also likely to be cost-effective.

Nutrition therapy, ingested or delivered artificially, is an essential component of clinical practice in ICU and post-ICU. In this thesis I reviewed the extent of nutrition research in a hospitalised TBI population (*Chapter 1*) to establish insufficient data reporting intake post-ICU.

In heterogeneous cohorts of critically ill patients, nutrient delivery during ICU admission is below prescribed targets. From a large international cohort, I determined that energy and protein delivery to ICU patients with TBI is below targets, and deficits in the first 12 days are associated with longer time to discharge alive from ICU and hospital, and prolonged mechanical ventilation (*Chapter 4*).

In a methodologically-rigorous single-centre observational study I established that energy and protein deficits exist in ICU. Perhaps of more concern, these deficits increase post-ICU leading to cumulative deficits throughout hospitalisation (*Chapter 1*). These observations highlighted methodological issues, particularly with weighed food records to measure oral intake of hospitalised individuals (Chapter 2). Logistical and attitudinal barriers impede nutrition delivery. Interviews with medical and nursing practitioners provided insight into why these occur (*Chapter 1*). Additionally, TBI patients have marked changes in ultrasound-derived quadriceps muscle thickness. I established that this novel methodology, while challenging, is feasible and may correlate with total lean mass and long-term function (*Chapter 3*).

To provide context beyond the cohort of TBI patients I explored relationships between nutritional intake during critical illness and long-term function. In a blinded pilot trial of critically ill patients, those randomised to augmented enteral nutrition to deliver greater energy, were more likely to return to work after 12-months than those receiving standard nutrition (*Chapter 4*).

In addition, there is considerable interest within the critical care community on the effect of protein delivery on outcomes. I conducted a meta-analysis of randomised controlled trials (RCTs) with greater or lesser amounts of protein delivered to critically ill patients and did not observe any effect of greater protein dose on clinical outcomes. However even the cohort receiving greater protein had amounts lower than recommended in international guidelines.

Lastly, because a frequent criticism of the role of nutritional therapy in the critically ill is the lack of effect on mortality, I undertook a systematic review and identified that nutrition intervention studies in critical care with the primary outcome of mortality have utilised sample size calculations that require a large, and possibly implausible, effect on mortality. The implications are that investigators should incorporate more realistic estimates of effect size in the future and that previous RCTs may have failed to detect an effect on mortality even if there was such an effect (*Chapter 5*).

Declaration:

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Lee-anne Chapple

25th January 2017

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Completing this thesis over the last three and a half years has been a huge undertaking in what has been a tumultuous period in my life, including an interstate move and subsequent change in environment and supervisory panel. This thesis is a result of an incredible amount of hard work, long hours, and dedication to research. None of this could have been possible, however, without the input of a few key individuals.

Firstly, I would like to thank my four supervisors, each of whom made a valuable and distinct contribution to this thesis.

Professor Marianne Chapman took me on with my relocation to the University of Adelaide after one phone call, and has been a steady and considered influence on my progress over the last three years. I have greatly appreciated Marianne’s immense wealth of knowledge, and generous and unwavering support that made this body of work possible, as well as her encouragement for me to develop into a more independent researcher. I am greatly appreciative and excited to have the opportunity to continue the beginnings of my research career under her tutelage.

Associate Professor Adam Deane has played an integral role in the final product of my PhD program. The volume of work in this thesis is a direct result of Adam’s frustratingly quick manuscript turnarounds and persistent ‘encouragement’ to work beyond my perceived abilities. For an at times awkward communicator Adam has an astounding ability to know when to push and when to support. He looked beyond the thesis and the supervisory role, and demonstrated a commitment both to my future success as a researcher and to my personal well-being throughout this process, for which I am extremely grateful. Adam’s own work ethic, ability to produce, and innovative mind are admirable and I am greatly appreciative that he took me under his wing.

Professor Lauren Williams was there from the start, initially as my primary supervisor at the University of Canberra, and then as an external supervisor. Despite my lack of research experience and only the beginnings of a very rough plan stemming from my clinical frustrations, Lauren encouraged me in the PhD direction and shaped my plan into an achievable and succinct proposal. As the only non-medical supervisor on my panel, Lauren provided a unique perspective and kept my plans grounded and realistic. I am appreciative of her attention to detail and ongoing support.

Professor Daren Heyland is one of the leading critical care nutrition researchers internationally and I am so fortunate to have had his expert input into this research. Despite the distance, Daren has been a generous and enthusiastic collaborator, and I have valued his intuitive research ideas, insightful comments, forward thinking, and support of novice researchers.

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It is also important to acknowledge the tireless and often under-recognised work of hospital staff across a number of clinical units and sites that assisted with this research, all co-investigators that contributed to the enclosed manuscripts, and the financial support I received from the Neurosurgical Research Foundation, Australasian Society of Parenteral and Enteral Nutrition, Royal Adelaide Hospital Research Foundation, and the University of Adelaide Discipline of Medicine that made this research possible.

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Finally, I would like to thank the generous and selfless support of the patients and their families for their willingness to be involved in research in what could only be one of the most physically and emotionally challenging situations an individual could experience. I hope that this work, in some way, can improve the care of patients in the future.

Rationale for research:

The purposes of this research program were to:

1.) Provide a greater understanding of longitudinal nutrition support practices in critically ill patients, particularly those with a traumatic brain injury, throughout the entire hospitalisation;

2.) Detail anthropometric changes that occur during hospitalisation in this population and their relationship to longitudinal functional outcomes;

3.) Evaluate novel methodologies to measure nutritional intake and changes in anthropometry, particularly muscle size, in survivors of critical illness and traumatic brain injury; and

4.) Evaluate associations between nutritional therapy and clinical outcomes, including mortality, in critically ill patients, particularly those with a traumatic brain injury.

Format of thesis:

This thesis is by publication, supplemented by narrative, as per University of Adelaide guidelines. This thesis comprises two distinct but complementary sections. Section one encompasses three chapters and section two contains two chapters. Each section of this thesis is preceded by a narrative introduction and followed by a conclusion of the major findings and future directions.

In total, the thesis comprises nine manuscripts: three reviews of the literature and six manuscripts resulting from a series of original clinical and observational studies. At the time of submission of this body of work, all nine of these manuscripts have been published or accepted for publication. None of these manuscripts were solicited by the journals. All of these manuscripts were submitted to appropriate nutrition, neurotrauma, or intensive care journals. The nine manuscripts are presented in the style of the publication to which they were submitted, accounting for the variance in manuscript structure. For consistency, manuscripts are presented in UK English and references for the nine publications are combined and included at the end of this thesis.

The format of this thesis is as follows:

Section One: Nutritional intake and anthropometry in traumatic brain injured patients during and after intensive care stay

Section one incorporates three chapters that describe the current nutrition delivery practices and anthropometric measurements in patients admitted to intensive care, with a focus on those patients admitted with a traumatic brain injury.

<u>Chapter 1: Nutrition support practices in critical illness and traumatic brain injury</u>

Chapter one includes a summary of the literature relevant to nutrition delivery to critically ill patients and three manuscripts.

Manuscript 1[1] is a scoping review of the nutrition and traumatic brain injury (TBI) literature and was published in the *Journal of Neurotrauma*. This provides a broad overview of the extent of nutrition research in a TBI population, including a description of the types of interventions and outcome measures existing in the literature.

Manuscript 2[2] was published in *Clinical Nutrition*. This manuscript is the first of three that resulted from a labour-intensive 12-month prospective observational study that formed a major component of my candidature. Using a rigorous methodology I detailed nutritional intake, and barriers to intake, throughout the entire hospital admission of patients admitted to ICU with a moderate-severe TBI. The novelty of this study is that it is the first study to accurately quantify longitudinal nutrition intake in a patient group initially admitted to the ICU then discharged to the general hospital ward. The study involved quantification of oral nutrition intake as well as liquid nutrient administered via enteral-tube feeding.

Manuscript 3 addresses the views and attitudes on nutrition support of medical and nursing staff working with TBI patients in the critical care and acute care settings. This qualitative study provides context for delivery of care and explores the reasons behind inadequate nutrition support to head injured patients. It was accepted for publication without revisions in the *Journal of Parenteral and Enteral Nutrition.*

<u>Chapter 2: Methodology and measurement of nutritional intake</u>

This chapter evaluates methodologies used to quantify nutritional intake in a hospitalised population, with a particular focus on the challenges associated with recording accurate oral intake data in those patients discharged from ICU to the general hospital ward.

The manuscript[3] presented in this chapter was published in the *Journal of Human Nutrition and Dietetics*. This methodological paper, using data from the 12-month observational study described above, contributes to our understanding of how to accurately quantify ingested nutrients in a hospitalised population.

Chapter 3: Measurement of anthropometric changes over time in critically ill patients admitted with a traumatic brain injury

Chapter three is a summary of anthropometric measurements in critically ill patients. The manuscript in this chapter has been accepted in *Critical Care and Resuscitation*. This manuscript provides a description of the anthropometric changes in patients admitted to ICU with a TBI, including changes in quadriceps muscle thickness using an ultrasonography technique. This paper is the first to report changes in body composition measures in a sub-set of ICU survivors, and provides incremental evidence that the non-invasive technique of ultrasonography is a valid means to measure changes in muscle size in critically ill patients.

Section Two: Influence of nutritional intake on outcomes in critical illness and TBI

Section two encompasses two chapters that explore relationships between nutritional intake in the critically ill, particularly those with TBI, and clinical outcomes.

Chapter 4: Influence of nutritional intake on mortality and clinical outcomes in intensive care and after traumatic brain injury

This chapter includes three manuscripts. The first of these evaluates the association between energy and protein provision and patient-centred outcomes in a critically ill cohort with TBI. The subsequent manuscripts evaluate the relationship between nutrient provision and outcomes, including mortality, in a general intensive care population. There is considerable controversy regarding the optimal amount of energy and protein to deliver to critically ill patients and the manuscripts that comprise this chapter provide important data that contributes to an improved understanding of patient needs.

The first manuscript that comprises chapter four was published in *Critical Care*[4]. Using international data I was able to identify relationships between calorie and protein intake, nutrition support practices, and clinical outcomes in this group of patients.

The second manuscript is a systematic review and meta-analysis of protein delivery to critically ill patients and has been accepted for publication in *Critical Care and Resuscitation*. All RCTs of nutrition interventions in critically ill patients that reported a difference in protein delivery between the two study arms were included, and a meta-analysis of the effect of protein dose on clinical outcomes was conducted.

The third manuscript[5] is a longitudinal follow-up of patients enrolled in a blinded, randomised controlled trial and was published in *Anaesthesia and Intensive Care*. This study evaluated the impact of augmenting early calorie delivery on patient's quality of life and employment status one year after ICU admission.

While I am listed as second author on the two preceding publications, I contributed substantially to the study design, conduct and data interpretation for these studies and drafting/editing of subsequent manuscripts. Based on my contribution my supervisors are of the opinion that inclusion of these papers in this thesis is justified.

Chapter 5: Alternative outcome measures for nutritional studies in intensive care

Chapter five proposes an alternate view to the current orthodoxy when using mortality as the primary outcome in trials of nutrition therapy in the critically ill. This chapter includes a systematic review[6] of randomised controlled trials of nutrition interventions in intensive care with the primary outcome powered for mortality. Specifically, I explored the appropriateness of the sample size calculations presented in these randomised controlled trials and provide suggestions for future directions in my arena of research, i.e. nutritional therapy in the critically ill. The manuscript was published in the *American Journal of*

Clinical Nutrition and based on this publication I have been invited to give a presentation at the 2017 Clinical Nutrition Week, the annual meeting of the American Society for Parenteral and Enteral Nutrition (ASPEN), which will be held in Florida, USA.

Publications included in this thesis are as follows, in order of appearance:

Costello LS, Lithander FE, Gruen RL, Williams LT. *Nutrition therapy in the optimisation of health outcomes in adult patients with moderate to severe traumatic brain injury: Findings from a scoping review.* Injury 2014;45(12):1834-41.

Chapple LS, Deane AM, Heyland DK, Lange K, Kranz AJ, Williams LT, Chapman MJ. *Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury*. Clin Nutr 2016;35:1315-22.

Chapple LS, Deane AM, Williams LT, Strickland R, Schultz C, Lange K, Heyland DK, Chapman MJ. *Longitudinal changes in anthropometry and impact on self-reported physical function following traumatic brain injury.* Crit Care Resusc 2017;19:29-36.

Chapple LS, Deane AM, Williams LT, Lange K, Kranz A, Heyland DK, Chapman MJ. *Weekend days are not required to accurately measure oral intake in hospitalised patients.* J Human Nutr Diet 2016, (E-pub ahead of print, DOI: 10.1111/jhn.12432).

Chapple LS, Chapman MJ, Shalit N, Udy A, Deane AM, Williams LT. *Barriers to nutrition intervention for patients with a traumatic brain injury: Views and attitudes of medical and nursing practitioners in the acute care setting*. JPEN 2017; (e-pub ahead of print), DOI:10.1177/0148607116687498.

Chapple LS, Chapman MJ, Lange K, Deane AM, Heyland DK. *Nutrition support practices in critically ill head-injured patients: A global perspective.* Crit Care 2016;20:6.

Davies M, **Chapple L,** Peake S, Moran J, Chapman M. *Protein delivery and clinical outcomes in the critically ill: A systematic review and meta-analysis.* Crit Care Resusc (in press, accepted Nov 2016).

Reid D, **Chapple L**, O'Connor S, Bellomo R, Buhr H, Chapman M, Davies A, Eastwood G, Ferrie S, Lange K, McIntyre J, Needham D, Peake S, Rai S, Ridley E, Rodgers H, Deane A. *The effect of augmenting early nutritional energy delivery on quality of life and employment status one year after ICU admission.* Anaesth Intensive Care 2016;44(3):406-12.

Summers MJ,* **Chapple LS*,** McClave SA, Deane AM. *Event-rate and delta inflation when evaluating mortality as a primary outcome from randomized controlled trials of nutritional interventions during critical illness: A systematic review.* AJCN 2016; 103(4): 1083-90. (*Contributed equally to manuscript).

Section One:

Nutritional intake and anthropometry in patients with a traumatic brain injury during and after intensive care stay

Section One

Introduction:

Critical illness affects approximately 130,000 Australians each year, with a cost to the health care system of nearly $3 billion per annum[7]. While these patients receive sophisticated, and in some cases expensive, interventions many patients still die from their illness. For those patients that do survive, health-related quality of life and functional recovery are compromised, with symptoms persisting even five years later[8,9]. Therefore, interventions to enhance the rate and degree of recovery after critical illness are required.

Nutrition support is an essential component of clinical practice in the intensive care setting. This is most frequently delivered through artificial means, usually as enteral nutrition (via a nasogastric tube), particularly in patients that are mechanically ventilated[10,11]. There is a considerable body of work evaluating nutrition support practices in general intensive care patients. In general these observational studies consistently report that there is a disconnect between the estimated expenditure and nutrient delivery to critically ill patients, with current standard practice providing approximately 60 % of individual patient's prescribed caloric needs[12-14].

Patients are admitted to the intensive care unit (ICU) with a variety of illnesses and injuries. Those patients admitted with a traumatic brain injury (TBI) represent a large sub-group of critically ill patients who are a particularly vulnerable cohort. TBI is associated with devastating health and socioeconomic consequences[15,16]. Patients with a TBI may experience permanent physical, cognitive, and behavioural impairments, frequently requiring long-term care. In Australia around 2500 new cases of moderate-severe TBI occur each year, with the lifetime cost of incident TBI estimated at $8.6 billion per year[17]. Globally, the incidence of TBI is increasing, such that if the trajectory of incident TBI is maintained it will be the most prevalent cause of death and disability globally by 2020[18]. Finding means to decrease the burden of TBI is clearly a high priority.

TBI is frequently associated with increased metabolism and catabolism, hence the estimated nutritional requirements of these patients are often higher than prior to the injury[19]. However, patients with a TBI frequently have features or complications that may impede delivery of prescribed amounts of nutrition; these include dysphagia, delayed gastric emptying, and fasting for procedures, especially in the setting of multi-trauma[20-23]. Following extubation, barriers to adequate nutrition delivery may be intensified as a result of the confusion and agitation associated with the TBI and/or its treatment. During my clinical practice I noted that these patients frequently refused or were poorly compliant with oral intake, and this was associated with weight loss, delayed wound healing, and fatigue with the potential to impede participation in rehabilitation. It was for these reasons that the research questions for this thesis were developed.

My scoping review (chapter one) identified several key gaps in the literature that formed the foundations for the studies presented in this section. These included the need for: a greater understanding of the current nutrition delivery practices in TBI patients across the continuum of care, both in ICU and the post-ICU ward, including barriers to adequate nutrition delivery; and a description of the changes in body composition that occur over this time period. Given that reduced physical function is a major issue for patients recovering from a TBI, nutritional support has the capacity to accelerate or improve recovery. Perhaps more importantly, this review highlighted the need to develop and validate appropriate methodologies to accurately measure nutritional intake and nutritional status in this patient group in order to progress both research and clinical practice in this area. While nutrition support encompasses a multitude of interventions; including but not limited to delivery of specific nutrients, route of delivery, and timing of delivery, this thesis primarily focuses on the provision of energy and protein.

My clinical experience is that much of the decision-making around nutrition support is at the discretion of the managing medical team, whereas adequate delivery of the prescribed nutrition is reliant on the nursing staff present. Accordingly, an understanding of the views and attitudes of these health professionals on nutrition support to patients with a TBI was necessary in order to identify potential opportunities for change to ultimately improve nutrient delivery in this population.

Section one of this doctoral program aims to contribute to the literature on current nutrition practices in critically ill patients and, specifically, those patients with a TBI, and to enhance future research initiatives to improve nutritional management of these patients.

Chapter 1:

Nutrition support practices in critical illness and traumatic brain injury

Energy and protein targets:

At present there are several sets of guidelines to assist in the management of nutrition support to critically ill patients. However, controversy remains as to what constitutes the 'optimal' amount of energy and protein to be delivered during critical illness.

In the recently updated American Society of Parenteral and Enteral Nutrition guidelines for feeding of critically ill patients[24] it is recommended that energy requirements be determined by predictive equations or weight-based equation (25 - 30 kcal/kg/day) in the absence of indirect calorimetry. Protein requirements are recommended to be calculated at 1.2 - 2.0 g/kg/day, with greater amounts suggested for patients with major burn or multiple injuries from trauma. It is recommended that patients deemed to be at low nutritional risk do not require specialised nutrition therapy during the first week in the ICU, however, patients at 'high nutritional risk', or who are severely malnourished, should be provided with > 80 % of their energy and protein goals within 48 - 72 hours of hospitalisation. These recommendations are all based on expert consensus or on an evidence-base classified as being of 'very low' quality.

Meanwhile, the European Society of Parenteral and Enteral Nutrition ICU feeding guidelines[25] recommend providing no more than 20 - 25 kcal/kg/day during the acute (i.e. initial) phase after injury and 25 - 30 kcal/kg/day during recovery; however, the guidelines also state that no general amount can be recommended, as the prescription should be adjusted according to the progression/course of disease and gut tolerance. No recommendation is provided as to the optimal amount of protein that should be administered to critically ill patients.

In contrast, the Canadian Critical Care Practice guidelines[26], which only incorporate data from randomised controlled trials, state there are insufficient data to make a recommendation on the estimation of energy requirements. While the consideration of intentional ‘underfeeding’ of calories (but not protein) to patients at low nutritional risk is advocated, no set energy or protein recommendations are provided.

Given this sparse, and at times conflicting, evidence base, the prescription and provision of nutrition therapy by intensive care health practitioners is controversial with some divergent and firmly held opinions. There is therefore a clear need for future research to determine the ideal delivery of calories and protein to intensive care patients to improve clinically relevant outcomes.

Table: Energy and protein prescriptions in commonly used guidelines

	Canadian Critical Care Practice guidelines	**ESPEN Guidelines**	**ASPEN Guidelines**
Estimating energy requirements	No recommendation	No recommendation	Predictive equations or weight-based equation (25-30 kcal/kg/day) in the absence of indirect calorimetry
Estimating protein	No recommendation	No recommendation	1.2-2.0 g/kg/day
Feeding targets	That intentional underfeeding of calories (not protein) be considered in patients at low nutritional risk	Acute/initial phase of injury: ≤ 20-25 kcal/kg/day Recovery: 25-30 kcal/kg/day	Low nutritional risk: Do not require specialised nutrition therapy during the first week in the ICU High nutritional risk or who are severely malnourished should receive > 80 % energy and protein goals within 48-72 hrs

MREE: Measured resting energy expenditure, EAST: Eastern Association for the Surgery of Trauma, ASPEN: American Society of Parenteral and Enteral Nutrition, ESPEN: European Society of Parenteral and Enteral Nutrition

Barriers to feeding:

Regardless of the ultimate energy and protein targets used, delivery of nutrition support in the ICU is well below prescribed amounts. There are a number of factors that may contribute to 'under-feeding' in a critically ill population.

The delivery of energy and protein may be diminished by delayed gastric emptying, which occurs frequently in the critically ill[13,14,27]. In addition, interruptions to nutrient delivery are commonplace, and these are primarily due to withholding nutrient delivery for proposed airway management (intubation/extubation of the trachea), fasting for diagnostic or surgical procedures, and inability to deliver nutrition due to tube displacement[13,14,28].

While the current nutrition support practices, including barriers associated with achieving nutritional adequacy, to a general ICU population are generally well documented, there is a paucity of data related specifically to patients with a TBI, particularly in the post-ICU phase. The following three manuscripts provide insight; firstly into the current standing of the nutrition and TBI literature, and secondly into current practices and barriers to nutrient delivery in this population.

Manuscript 1:

Nutrition therapy in the optimisation of health outcomes in adult patients with moderate to severe traumatic brain injury: Findings from a scoping review

Authors:

Lee-anne S Costello[1], Fiona E Lithander[1], Russell L Gruen[2], Lauren T Williams[1,3]

[1]Nutrition and Dietetics, Faculty of Health, The University of Canberra, Bruce, Australian Capital Territory, 2601, Australia

[2]National Trauma Research Institute, The Alfred Hospital and Monash University, Melbourne, Victoria, 3004, Australia

[3]Nutrition and Dietetics, Faculty of Health, Griffith University, Southport, Queensland, 4217, Australia

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Conceptualisation of work, wrote manuscript, and acted as corresponding author		
Overall percentage (%)	70		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor Fiona Lithander		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	15/12/16

Name of Co-Author	Professor Russell Gruen		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Professor Lauren Williams		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Abstract

Introduction: Patients who have sustained traumatic brain injury (TBI) have increased nutritional requirements yet are often unable to eat normally, and adequate nutritional therapy is needed to optimise recovery. The aim of the current scoping review was to describe the existing evidence for improved outcomes with optimal nutrition therapy in adult patients with moderate to severe TBI, and to identify gaps in the literature to inform future research.

Methods: Using an exploratory scoping study approach, Medline, Cinahl, Embase, CENTRAL, the Neurotrauma reviews in the Global Evidence Mapping (GEM) Initiative, and Evidence Reviews in Acquired Brain Injury (ERABI) were searched from 2003 to 14 November 2013 using variations of the search terms 'traumatic brain injury' and 'nutrition'. Articles were included if they reported mortality, morbidity, or length of stay outcomes, and were classified according to the nature of nutrition intervention and study design.

Results: Twenty relevant articles were identified of which: 12 were original research articles; two were systematic reviews; one a meta-analysis; and five were narrative reviews. Of these, eleven explored timing of feed provision, eight explored route of administration of feeding, nine examined the provision of specific nutrients, and none examined feeding environment. Some explored more than one intervention. Three sets of guidelines which contain feeding recommendations were also identified.

Discussion: Inconsistency within nutrition intervention methods and outcome measures means that the present evidence base is inadequate for the construction of best practice guidelines for nutrition and TBI. Further research is necessary to elucidate the optimal nutrition therapy for adults with TBI with respect to the timing, route of administration, nutrient provision and feeding environment. A consensus on the ideal outcome measure and the most appropriate method and timing of its measurement is required as a foundation for this evidence base.

Keywords: Brain injury, nutrition intervention, trauma

Introduction

Traumatic brain injury (TBI), defined as an alteration in brain function or brain pathology resulting from an external force, is a pressing public health issue, with the World Health Organisation estimating that TBI will be the most prevalent cause of death and disability globally by 2020[15,16,18]. An estimated 10 million cases of moderate to severe TBI (leading to mortality or hospitalisation), occur worldwide each year[18]. Interventions that aim to enhance and improve the speed and extent of recovery from head injury are needed.

Nutrition-based interventions have the potential to enhance recovery and was identified by the Brain Trauma Foundation in 2007 as a priority research area and one of 15 key intervention types likely to influence outcomes in TBI patients[29]. *Nutrition support* is defined as the provision of additional nutrition via the parenteral (non-gastrointestinal route direct to the blood stream), or enteral route (via the nasal route using a nasogastric, nasoduodenal, or nasojejunal tube, or directly through the abdomen using a gastrostomy, gastrojejunostomy, or jejunostomy feeding tube)[30]. *Nutrition therapy*, which also includes the oral route, goes beyond nutrition support as a component of medical treatment aimed at maintaining or restoring optimal nutrition status and health[30]. In addition to the usual difficulties associated with the provision of nutrition therapy to critically-ill patients, optimal nutrition therapy in patients with moderate to severe TBI is made more complex by some unique physiological challenges.

Unique post-TBI metabolic changes result in an increase in energy requirements that can vary between 87% to 200% above usual values, extending up to 30 days post-injury[19]. This hypermetabolic response is thought to result from an increased production of corticosteroids, counter-regulatory hormones such as epinephrine, norepinephrine and cortisol, and pro-inflammatory mediators and cytokines such as interleukin-1 (IL-1), IL-6, IL-12, tumour necrosis factor-alpha (TNF-α), and interferon-gamma[31-34]. Whether these inflammatory markers can be used diagnostically to predict the influence of specific interventions on long-term outcomes is yet to be determined, but markers that correlate with the severity of disease and demonstrate prognosis are being sought[32,35]. Hypermetabolism can lead to the hypercatabolism of macronutrients, resulting in negative nitrogen balance, and substantially increased energy and protein requirements[19,36,37]. Hypercatabolism coupled with immobility can lead to an increased risk of malnutrition in the severely ill[38]. Nutritional requirements are further elevated by wound healing in cases of TBI with multi-trauma[39]. In one of the few studies on this topic, Krakau and colleagues demonstrated that approximately 68% of patients show signs of malnutrition within two months of head injury[40]. Dhandapani and colleagues showed that malnutrition has undesirable consequences with poor Glasgow Outcome Scale (GOS) at six months post-injury[41].

The difficulties in meeting increased nutrition requirements in TBI may be compounded further by dysphagia, gastrointestinal intolerance due to gastroparesis, fasting pre-surgery, and medication complications[19,23,42]. Post-traumatic amnesia, a state of altered consciousness associated with the recovery process, often results in inadvertent removal of feeding tubes and food refusal[36]. In many hospitals, nursing staff lack the capacity to provide the amount of assistance sufficient to ensure that the most difficult TBI patients get the nutrition they need[43,44].

Although it is clear that increased nutrition is required following TBI, it is less evident which aspects of nutrition therapy lead to better outcomes. A systematic review of publications between 1993 to 2003[22] examined the evidence for effects of different timing, content, and method of administration of nutritional treatment on early and long-term clinical outcomes in patients with moderate to severe TBI. The reviewers concluded that the evidence base for determining the effect of nutrition support is insufficient, particularly in the post-injury phase[45,46]. Three other systematic reviews[46-48] on nutrition therapy in TBI were published in 1996, 2000, and 2002 however these have since been updated[49,50], but not synthesised. Since these reviews were published (the last in 2007), the influence of nutrient delivery in TBI, specifically immunonutrients, has emerged as an area of scientific interest. The extent of research and best practice with regards to nutrient provision in TBI is unknown, and questions regarding optimal timing of introduction of feeding, rate of achievement of nutrient targets, method of nutrient delivery, and feeding environment, remain.

The aim of the current scoping review was to summarise the current literature in the area of nutrition therapy and TBI, and to investigate the influence of nutrition therapy on outcome measures of mortality, morbidity (measured using Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Acute Physiology And Chronic Health Evaluation II (APACHE II)), and length of hospital/Intensive Care Unit (ICU) stay, most commonly collected in the moderate to severe TBI population. The objective of the scoping review was to address the impact of four areas of nutrition therapy: 1) timing of feed provision; 2) route of administration of feeding; 3) the type of nutrients provided, including immunonutrients; and 4) the feeding environment.

Methods

Scoping reviews aim to identify and describe evidence in broad topic areas, such as nutrition therapy following TBI, that encompass a range of interventions and outcome measures. Like systematic reviews, they should include a comprehensive search and reproducible transparent methods for inclusion, evaluation, analysis and reporting. However, unlike systematic reviews, they usually focus on breadth of research activity and reported findings, rather than detailed independent quality appraisal and meta-analysis that are features of high quality systematic reviews of much more focused questions[51].

The current review focuses on moderate to severe TBI in adults given the highest prevalence rates in the adult population[18]. The causes, complications, and management associated with brain injury tend to differ between adult and paediatric patients, and much of the published research has been conducted separately on these populations, hence data reviewed included adult populations only[52]. Mild traumatic brain injuries do not always result in hospitilisation so studies which focused on this condition have less relevance for nutrition therapy and are therefore not included here. Given the unique needs of the traumatic brain injured patient we have excluded studies exploring other injuries that influence metabolism such as burns[53].

Search Strategy:

Articles were identified through a search of the following databases from 2003 to November 14, 2013: Medline and Cinahl via Ebsco, Embase via Scopas, and Cochrane Central Register of Controlled trials (CENTRAL). The search terms used combined two strings to include either TBI or brain injur* or brain damage* or brain trauma* or head injur* or head trauma* or craniocerebral trauma* or craniocerebral injur* or craniocerebral damage* or neurotrauma* or neuroinjur* AND nutri* or diet* or feed or feeding* or food* or cataboli*. Articles including the following search terms were excluded: stroke, paediatric*, pediatri*, infant*, and animal*. Appropriate truncation was used to account for plural words. The Neurotrauma reviews of the Global Evidence Mapping (GEM) Initiative and Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI) databases were also searched for nutrition and traumatic brain injuries[54,55]. Databases were only searched for articles published from 2003 onwards given a systematic review conducted at this time provided a comprehensive review of the evidence[45], and several prior systematic reviews have been updated since 2003[46-48]. Reference lists of all included articles were also searched.

Selection Process:

Abstracts of articles identified in the search were screened according to inclusion/exclusion criteria. Inclusion criteria were: (1) studies of adults (aged

≥16 years); (2) moderate or severe traumatic brain injury as defined as GCS score 3-13; (3) description of a type of nutrition support or therapy; (4) at least one of the following defined outcome measures of TBI: mortality, change in GCS, GOS, or APACHE II score, or ICU or hospital length of stay (LOS). Studies were excluded if: (1) they were published in a language other than English; (2) the intervention was in children or animals; (3) they had a sample size of one patient; (4) other injuries included a direct insult to gastrointestinal tract or other conditions resulting in increased systemic response e.g. burns; (5) they were published prior to 2003; (6) they did not include at least one of the stated outcomes; or (7) results for TBI patients were not separated from those of other patients. Several reviews were also identified. These were only included if the main focus was nutrition therapy for TBI to demonstrate the breadth of published research. Duplicates were removed at the abstract review stage. In cases where the relevance of the article was unclear from the abstract, the full text article was retrieved. Articles investigating increased metabolism and gastrointestinal intolerance were excluded as they did not demonstrate the effect of nutrition therapy on the defined outcome measures (Figure 1).

Data was extracted from articles according to: (i) timing of feed provision; (ii) route of administration of feeding; (iii) type of nutrients provided including kilojoules, macronutrient, micronutrient, or immunonutrient provided; and (iv) feeding environment using a standardised form adapted from a combination of scoping review methodology papers and published scoping reviews[51,56-59]. A different data extraction criterion was used for the included narrative reviews developed from the previous form. Guidelines for nutrition therapy were collected through reference checks and web searches using the same search terms, and analysed separately in order to extract the most relevant information. Articles were classified according to the Australian National Health and Medical Research Council (NHMRC) levels of evidence criteria, which are similar to international classifications[60].

Results:

The initial database search identified 1,574 unique articles within individual databases. After 142 duplicates across databases were removed, 1,432 articles remained. Title and abstract screening led to the retrieval of 230 potentially-relevant articles for assessment. One article was identified from a previous Google search and included in the analyses. Separate searches of the GEM and ERABI databases found two studies that met inclusion criteria. Seven articles were identified for retrieval from a search of reference lists, however these were all excluded after the abstract review stage as they did not meet the inclusion criteria for the population group. After full text review, 20 articles (two systematic reviews, one meta-analysis, five narrative reviews, and the remainder original research articles) were included in the scoping review. A narrative review was defined as an article that reviewed the literature without the use of specific systematic collection or collation of data and was mainly descriptive in nature. The most common reason for excluding articles was the lack of a clear description of the nutrition prescription (Figure 1). Other excluded articles contained only a small section on TBI, did not present data separately from other conditions, or did not report the defined outcome measures. No other scoping review published in the area of nutrition therapy following TBI was identified.

The number of articles on each topic are shown in Figure 2. ‘Timing of feed provision’ included articles exploring early versus delayed initiation of feeding; ‘Route of administration of feeding’ included articles discussing the route of delivery of nutrition therapy (e.g. enteral versus parenteral, gastric versus jejunal); studies that examined the provision of specific nutrients on TBI (energy, protein, fatty acids, probiotics, micronutrients, and immunonutrients) were categorised under the heading of ‘Type of nutrients provided’. Some articles addressed more than one topic and were included under more than one heading. Feeding environment, defined as the setting in which provision of nutrition therapy takes place, was an aim of this search however no articles meeting the criteria were revealed in the search.

Of the 20 identified papers, eight were classified as review articles: two were systematic reviews; one a meta-analysis; and five were narrative reviews, that is, they reviewed the literature without the use of specific systematic collection or collation of data and were mainly descriptive in nature.

Primary Research Articles:

Timing of feed provision:

The five primary research studies that examined the impact of timing of initiation of feeding on the defined outcome measures are summarised in Table 1. One was an RCT[61], three were cohort studies[62-64], and one a case series[65]. Early versus delayed feeding was defined in each article as: within 48 hours[61,63]; by day three[65]; three versus four to seven versus greater than seven days[62]; and five versus seven days[64]. The RCT[61] found no difference on mortality rate of early versus delayed feeding, while all three cohort studies[62-64] found a positive influence on mortality. A positive relationship between early feeding and reduced LOS in hospital and ICU was found in the case series that assessed LOS[65]. One cohort[39] explored the effect of timing on GOS demonstrating a positive influence on GOS at three, but not at six, months. The case series[65] found that timing had no effect on GCS at time of discharge.

Route of administration of feeding:

Three RCTs[66-68] explored the influence of feeding route on the defined outcome measures as shown in Table 1. One of these explored parenteral versus enteral feeding[66] and the other two examined transpyloric versus gastric feeding[67,68]. Two of the three RCTs explored the influence of route on mortality, one reporting no difference in mortality between parenteral and enteral[43,] and the other finding no difference between transpyloric and gastic[44]. All three RCTs concluded that the route of feeding had no impact on LOS in ICU[66-68], and two reported no impact on LOS in hospital[44, 45]. No original research study was found that used GOS as an outcome.

Type of nutrients provided:

As summarised in Table 1, five primary research studies (four RCTs[69-72], and one cohort study[64]) considered the effect of specific nutrient provision on TBI outcomes. Studies investigating the addition of glutamine and branched-chain amino acid (BCAA)[69], probiotics[71], or immunonutrient-rich enteral nutrition[72], found no impact on mortality. Hartl and colleagues demonstrated that every 10kcal/kg decrease in energy increased mortality by 30-40%[64]. A reduction in ICU LOS was shown with the provision of probiotics delivered nasogastrically[71], and a glutamine-probiotic combination[70], but not with a glutamine-BCAA combination[69].

Feeding environment:

No articles exploring the influence of feeding environment, such level of feeding assistance provided or ward versus dining room, on outcome measures were found. All studies focused on the acute care setting, in particular nutrition therapy in the intensive care unit, and no identified studies explored nutrition during the rehabilitation phase or until nutrition treatment is no longer required.

Review Articles:

Timing of feed provision:

Two systematic reviews[49,50], one meta-analysis[73], and three narrative reviews[74-76] examined the impact of timing of initiation of feeding on the defined outcome measures as summarised in Table 1. One systematic review[49] and the meta-analysis[73] concluded a positive influence of early versus delayed feeding on mortality, with the meta-analysis showing significant reduction of mortality rate with early feeding[73]. The meta-analysis concluded that timing of feed provision had no significant difference in ICU LOS[73] in contrast to that found in the case-series by Vitaz and colleagues[65]. Two of the reviews explored the effect of timing on GOS: the systematic review concluded that early feeding improves GOS at three but not six months[50]; and the meta-analysis concluded that early feeding resulted in a significantly lower risk of poor outcome however time points of GOS measurement were not stated[73]. The three narrative reviews each provided a recommendation for early initiation of feeding within 24-72 hours[74], 48 hours[76], and 72 hours[75], using other narrative reviews, articles using different modes of feeding as well as timing, or the practice guidelines to support these recommendations[50,77,78].

Route of administration of feeding:

One systematic review[49], one meta-analysis[73], and three narrative reviews[74-76] explored the influence of feeding route on the defined outcome measures as shown in Table 1. Both the systematic review and the meta-analysis explored parenteral versus enteral feeding on mortality[49,73]. The systematic review found that enteral feeding increased the relative risk for mortality above parenteral feeding[49], and the meta-analysis found a trend toward lower mortality rate with parenteral nutrition[73]. Only the meta-analysis reported on GOS, showing a trend towards a reduction in the relative risk of poor outcome with parenteral nutrition[73]. However, all three narrative reviews recommended enteral nutrition over parenteral feeding[74-76], unless in the case of prolonged gastrointestinal dysfunction[75] or when enteral is unable to meet nutritional goals[74]. While one of these narrative reviews referenced the Canadian Clinical Practice Guidelines[74], the other two narrative reviews provided no references to support these recommendations[75,76].

Type of nutrients provided:

As summarised in Table 1, one systematic review[50] and three narrative reviews[74,75,79] considered the effect of specific nutrient provision on TBI outcomes. The systematic review found a non-significant trend for zinc supplementation and reduced mortality[50] as supported by one narrative review[79]. Both Cope[79] and Vizzini[74] conclude that zinc supplementation can improve GCS scores, however the optimal dose is currently unknown. Only one narrative review[75] discussed the effect of immune-enhancing diets, concluding that a high-protein formula enriched with L-arginine, glutamine, and omega-3 fatty acids for the first 7-10 days post-injury can reduce hospital LOS.

Given no studies were found on the impact of feeding environment on TBI outcomes it is unsurprising that no reviews addressed this.

Guidelines:

Three practice guidelines for use in the critically ill or trauma patient were identified and included[50,77,78]. The Guidelines of the Brain Trauma Foundation in the USA focused specifically on nutrition in severe TBI[50]; The Eastern Association for the Surgery of Trauma in the USA focused on general trauma which included head injury and burns[78]; and the Canadian Critical Care Practice Guidelines in Canada focused on the critically ill population with some head injury specific recommendations[77]. All guidelines made recommendations on the common areas of timing of feed initiation (early versus delayed), administration of feeding (gastric versus jejunal versus parenteral), and nutrient provision (immune-enhancing, and macronutrient composition)[50,77,78]. There was a recommendation for early initiation of enteral feeding (within 24-48 hours of admission) over parenteral nutrition or delayed feeding[77,78] and a further recommendation for full energy requirements to be met by day seven post-injury[50]. Two sets of guidelines provided a recommendation on overcoming barriers of nutrition therapy in TBI; one set of guidelines recommended using post-pyloric feeds if gastric feeding is not tolerated within 48 hours of injury[77], and another set highlighted the importance of implementing strategies to optimise delivery of nutrients such as starting at target rate, jejunal feeding, and higher thresholds for gastric residual volumes[78]. Importantly, all guidelines stated that there was insufficient data to support recommendations regarding macronutrient intake, and immune-modulating or enhanced nutrition including omega-3 fatty acids, glutamine, arginine, nucleotides, antioxidants, and provision of additional nutrients such as zinc and selenium[50,77,78].

Discussion

This scoping review examined the evidence on nutrition therapy in TBI, identifying a range of research topics previously not captured by systematic reviews or meta-analyses, including provision of nutrients and immunonutrition. No published research about the feeding environment was found. Nutrition therapy appears to be an under-researched area and evidence that does exist is equivocal. Practitioners therefore lack evidence-based guidance on the optimal timing of initiation or administration of feeding, or nutrient provision, in terms of improving mortality or morbidity outcomes. The few relatively small trials that have been conducted may have been underpowered to show significant differences, and larger, high quality trials may be needed.

The two identified systematic reviews covered more than one aspect of nutrition therapy, such as timing and administration[49], and the ability of nutrition therapy to meet requirements[50]. The combination of numerous research questions into a single review may demonstrate the limited evidence available to complete a systematic review on a single aspect of nutrition care. Many of the conclusions in these reviews are based on the finding of only one or two studies. The meta-analysis published by Wang and colleagues in March 2013 provides a synthesis of RCTs and prospective cohort studies investigating timing, route, and nutrient provision in TBI however it inadequately reflects the breadth of research conducted[73].

Three sets of guidelines were identified that provide recommendations on nutrition therapy in TBI[50,77,78], however the recommendations were based on small numbers of studies of both questionable quality and relevance. Some of the practice recommendations were supported by one or two studies only, many of which were conducted in the 1980s under different medications and technological regimes, with inadequately defined outcome measures and small patient numbers. The guidelines were found to be limited in the scope of practice covered, or generalised to the critically ill or general trauma population despite the unique needs of the TBI patient being well documented.

A major finding from the current scoping review is the inconsistency of methods used in nutrition studies, particularly in relation to outcome definitions. This current review included studies that had mortality, morbidity (using GCS, GOS, or APACHE II), or ICU or hospital LOS as an outcome, however inconsistencies in the way these outcomes were measured is a limitation previously recognised to affect likely results[80]. Some reviews failed to define how outcomes, such as neurological outcome, were measured in the included studies[50]. Different studies used different protocols to measure the same outcome, for example the extent of disability was measured using GCS, GOS, and APACHE II. In addition, there was often not one clear primary outcome measure used. Time points of outcome measurements varied between studies; for example morbidity was measured between two weeks[64] and six months[62] post-injury depending on the trial, which is likely to have a significant impact on results, given the severity of injury and length of stay in ICU and hospital. Most studies did not explore mortality beyond three weeks post-injury. Many articles which were included did not use mortality or morbidity as an outcome measure, hence the safety of the intervention may be unknown. Anthropometric data were not routinely collected in the included studies and such intermediate outcomes could be useful in future studies. Further consensus of the ideal outcome measures, and the most appropriate method and timing of their measurement, is required to enable comparison between studies and synthesis of the evidence.

Clearer definitions of threshold values of continuous measures are also required for interventions since inconsistencies in classifications of hyperglycaemic and feeding intolerance were found between studies[67,68]. Methods to determine nutritional requirements varied greatly between studies. Many studies compared early versus delayed feeding but the definition of timeframe that constituted early or delayed was inconsistent, making comparisons difficult. The early feeding classification varied from 48 hours[61,63], day three[62], day four[65], or day five post-injury[64], whilst variations in delayed feeding included meeting requirements after day four[61,65], day seven[62,63], or day nine post-injury[49,50]. Many of the clinical studies explored similar nutrients, such as glutamine, probiotics, and branched chain amino acids, however comparisons between studies was difficult as these were included in different combinations and doses[70-72].

Follow-up assessment periods varied between studies, with nine studies[50,61,65-67,70-73] not stating when follow-up was conducted. All studies focused on the acute hospital admission, generally classified as the first two weeks post-injury, and only one of the systematic reviews[49] and one of the included studies[62] extended past this acute phase to examine outcome measures up to six months post-injury (rehabilitation phase). The provision of nutrition therapy in rehabilitation was therefore not able to be examined. This leads to a lack of evidence to support management guidelines in the later post-injury stage, where many of the complications of TBI persist. Given the changing nature of the brain injury on inflammation and nutritional requirements, further research to guide best practice guidelines through all phases of care including intensive care, acute ward, and rehabilitation, is required.

The current scoping review was limited to articles published in English and, as such, relevant studies in other languages may have been missed. Furthermore, systematic reviews were relied on for the results of studies published before 2003, which may have resulted in incomplete reporting of the literature. Nevertheless, these findings from the current scoping review demonstrate that the evidence base to support best practice guidelines for nutrition therapy in moderate to severe TBI patients is limited in scope and methodology. While early initiation of nutrition support can improve patient outcomes, the field is characterised by small study sizes, and inconsistencies between outcome measures and nutrition intervention methodologies which prevent meaningful data synthesis on which to base recommendations. Further high quality, adequately powered clinical trials specific to TBI, with enhanced consistency between definitions and protocols, are essential to improve the evidence-base necessary for safe and effective recommendations for nutritional management of patients with moderate to severe TBI. Internationally accepted definitions of outcomes of mortality, Glasgow Outcome Scale, and nutritional status (e.g. muscle mass and weight) need to be established and applied. Further research is particularly required on the influence of the feeding environment and macro- and micro-nutrient provision on TBI outcomes in the medium to long term. Until further high quality research is available, nutrition therapy should be initiated to meet full caloric requirements by day seven post-injury using strategies to optimise the delivery of nutrients and overcome physiological challenges as determined by experienced clinical judgment, taking into account the individual requirements of the patient.

Author Contribution

This scoping review formed part of LSC's postgraduate studies. LSC, LTW, FEL were responsible for design of the study, development of the search strategy, screening of the studies, performing data extractions, and interpretation of results, and contributed to all drafts of the manuscript. LSC conducted the search and retrieval, drafted the initial paper, and is responsible for the final content. RLG made critical revision of the manuscript for intellectual content and contributed to drafts of the manuscript. All authors read and approved the final manuscript. RLG is supported by a Practitioner Fellowship from the Australian National Health and Medical Research Council.

Figure 1: Overview of scoping review search and inclusions

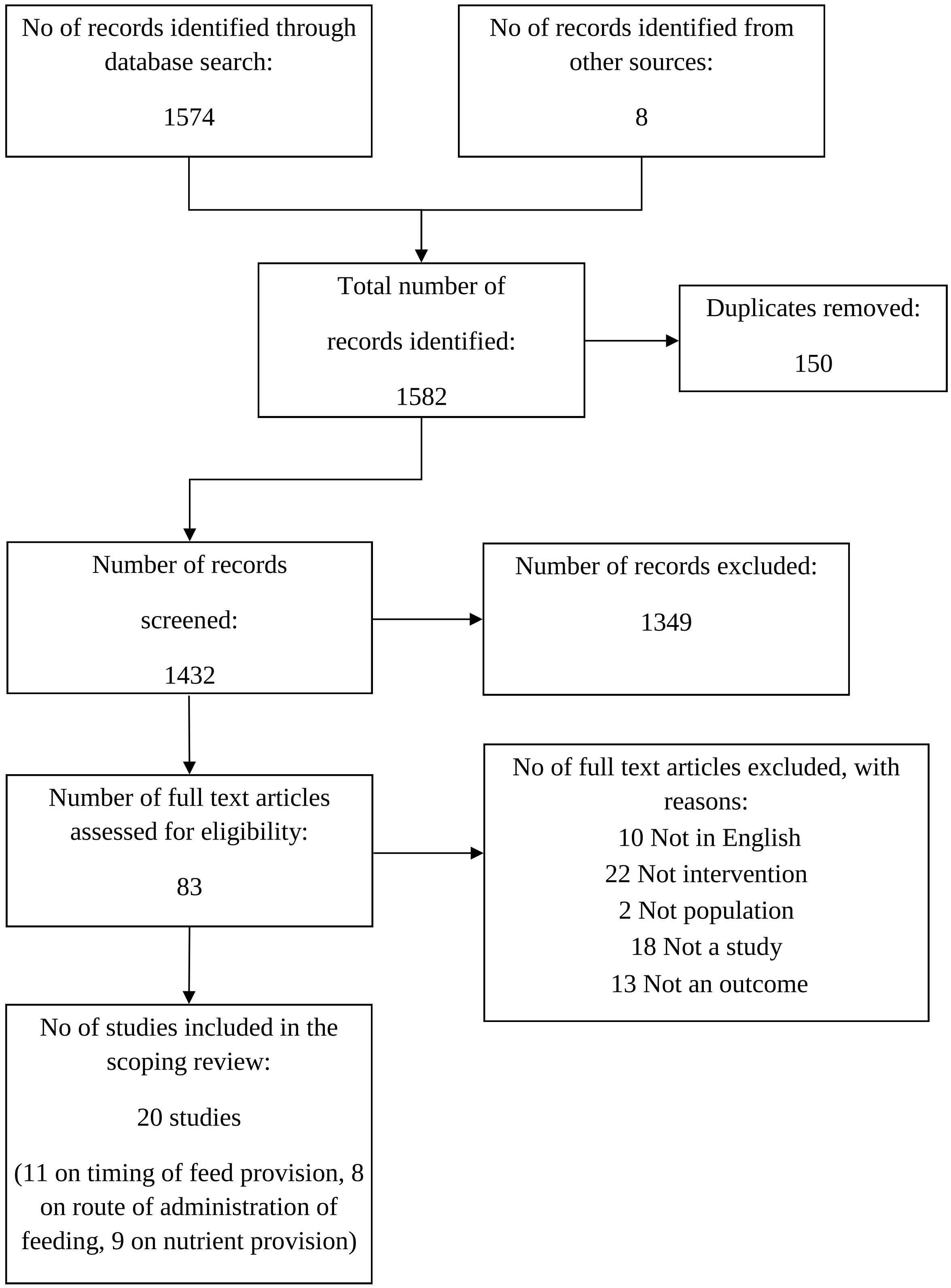

Figure 2: Number of included articles in each category

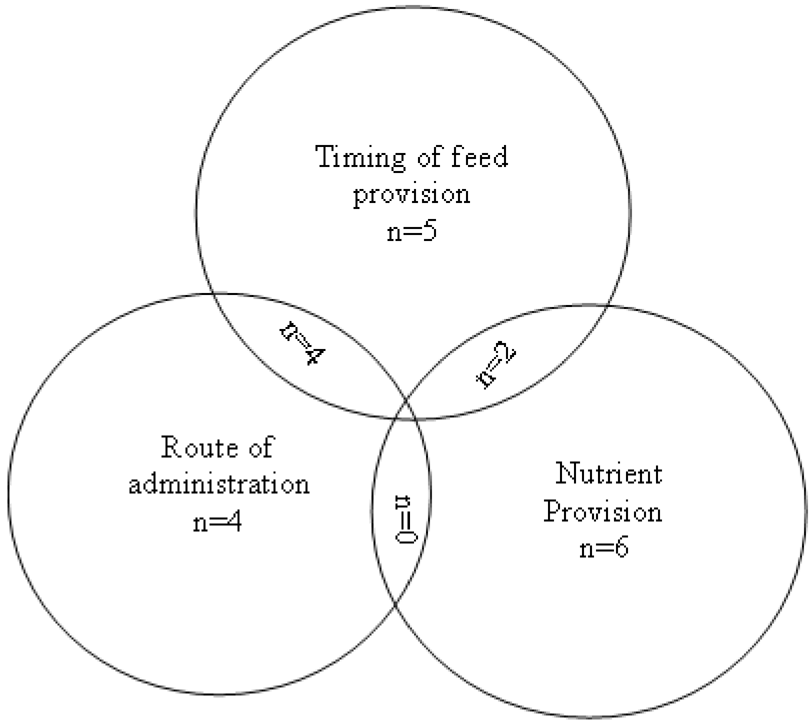

Table 1: Summary of outcomes for all papers

Author, Year	Study Type	Intervention/Aim	Follow-Up	Outcome	Change
Timing of feed provision					
Chourdakis[61], 2012	RCT	Delayed EN when gastroparesis resolved (>48h-5d) vs early (within 24-48h) EN	Not stated	ICU LOS Mortality	✓ ↔
Dhandapani[62], 2012	Cohort	Prescribed energy requirements met via EN at 3d, 4-7d & after 7d	6mo	Mortality GOS (3mo) GOS (6mo)	✓ ✓ ↔
Chiang[63], 2012	Cohort	EN commenced within 48h vs non-EN IV transfusion	1mo	Mortality	✓
Hartl[64], 2008	Cohort	EN initiation from day 1 to 7	2w	Mortality	✓
Vitaz[65], 2003	Case series	EN commenced by day 3, TPN by day 6 for pts not meeting 50% nutritional goal	Not stated	Hospital/ICU LOS GCS	✓ ↔
Wang[73], 2013	Meta-analysis	Early vs delayed nutrition	Not stated	Mortality & GOS ICU LOS	✓ ↔
Perel[49], 2006	Systematic review	Early vs delayed nutrition	2w-12mo	Mortality & GOS	✓
Bratton[50], 2007	Systematic review Practice Guideline	Early vs delayed nutrition	Not stated	GOS (3mo) GOS (6mo)	✓ ↔
Brody[81], 2008	Narrative review	Early (within 72h) vs delayed EN	-	Mortality	✓
Vizzini[74], 2011	Narrative review	Early (within 24-72h) vs delayed EN	-	GOS (3 mo)	✓
Cook[76], 2008	Narrative review	Early (within 48h) vs delayed EN	-	Mortality	✓
Heyland[77], 2003	Practice Guideline	Early EN (within 24-48h) vs delayed nutrition	-	Mortality	↔
Route of administration of feeding					
Justo Meirelles[66], 2011	RCT	EN vs TPN	Not stated	ICU LOS & mortality	↔
Grecu[67], 2008	RCT	Jejunal vs gastric	Not stated	ICU/hospital LOS & mortality	↔

Acosta-Escribano[68], 2010	RCT	Transpyloric vs gastric feeding	Discharge or 30d	ICU/hospital LOS	↔
Wang[73], 2013	Meta-analysis	EN vs TPN	Not stated	Mortality & GOS	✓
Perel[49], 2006	Systematic review	EN vs TPN	2w-12m	Mortality	✓
Brody[81], 2008	Narrative review	EN vs TPN	-	Mortality	↔
Vizzini[74], 2011	Narrative review	EN vs TPN	-	GCS Mortality	✓ ↔
Cook[76], 2008	Narrative review	EN vs TPN	-	Mortality	✓
Jacobs[78], 2004	Practice Guideline	EN vs TPN and gastric vs jejunal	-	Mortality	↔
Type of nutrients provided					
Ozgultekin[69], 2008	RCT	EN vs EN + IV branched chain amino acid vs EN + IV glutamine	Discharge or 30d	ICU LOS & mortality	↔
Falcao de Arrunda[70], 2004	RCT	EN vs EN + glutamine & probiotic	Not stated	ICU LOS	✓
Tan[42], 2011	RCT	EN vs EN + probiotic	Not stated	ICU LOS Mortality	✓ ↔
Khorana[72], 2009	RCT	EN vs EN + immunonutrient formula (arginine, glutamine, omega-3 fatty acid)	Not stated	Mortality	↔
Hartl[64], 2008	Cohort	Decreased EN (kcal/kg body weight)	2w	Mortality	✓
Bratton[50], 2007	Systematic review, Practice Guideline	Evidence of feed formulation and additional nutrients	Not stated	Mortality & GCS	↔
Genton[75], 2010	Narrative review	High protein formula with L-arginine, glutamine, omega-3 fatty acids	-	Hospital LOS	✓
Vizzini[74], 2011	Narrative review	Provision of zinc	-	Mortality GCS	↔ ✓
Cope[79], 2012	Narrative review	Role in zinc on TBI	-	Mortality & GCS	✓

EN-Enteral Nutrition, GCS-Glasgow Coma Scale, GOS-Glasgow Outcome Scale, ICU-Intensive Care Unit, kcal-Kilocalories, kg-Kilograms, IV-Intravenous, LOS-Length of Stay, RCT-Randomised Controlled Trial, TBI-Traumatic Brain Injury, TPN-Total Parenteral Nutrition.

✓-Positive improvement, ↔-No change

Manuscript 2:

Energy and protein deficits throughout hospitalisation in patients admitted with a traumatic brain injury

Authors:

Lee-anne S. Chapple[1, 2], Adam M. Deane[1, 2, 3], Daren K. Heyland[4], Kylie Lange[5], Amelia Kranz[1], Lauren T. Williams[6], Marianne J. Chapman[1, 2, 3]

[1]Discipline of Acute Care Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia

[2]National Health and Medical Research Council of Australia Centre for Clinical Research Excellence in Nutritional Physiology and Outcomes, Level 6, Eleanor Harrald Building, North Terrace, Adelaide, South Australia, Australia

[3]Intensive Care Unit, Level 4, Emergency Services Building, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia

[4]Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

[5]Discipline of Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia

[6]Menzies Health Institute of Queensland, Griffith University, Queensland, Australia.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Corresponding author responsible for study conception and design, acquisition of data, statistical analysis and drafting the manuscript		
Overall percentage (%)	70		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	7/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work, statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Professor Daren Heyland		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Ms Kylie Lange		
Contribution to the Paper	Statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Ms Amelia Kranz		
Contribution to the Paper	Acquisition of data and critical revision of the manuscript for important intellectual content		
Signature		Date	13/12/16

Name of Co-Author	Professor Lauren Williams		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Abstract

Background and Aims:

Patients with traumatic brain injury (TBI) experience considerable energy and protein deficits in the intensive care unit (ICU) and these are associated with adverse outcomes. However, nutrition delivery after ICU discharge during ward-based care, particularly from oral diet, has not been measured. This study aimed to quantify energy and protein delivery and deficits over the entire hospitalisation for critically ill TBI patients.

Methods:

Consecutively admitted adult patients with a moderate-severe TBI (Glasgow Coma Scale 3-12) over 12 months were eligible. Observational data on energy and protein delivered from all routes were collected until hospital discharge or day 90 and compared to dietician prescriptions. Oral intake was quantified using weighed food records on three pre-specified days each week. Data are mean (SD) unless indicated. Cumulative deficit is the mean absolute difference between intake and estimated requirements.

Results:

Thirty-seven patients [45.3 (15.8) years; 87% male; median APACHE II 18 (IQR: 14-22)] were studied for 1512 days. Median duration of ICU and ward-based stay was 13.4 (IQR: 6.4-17.9) and 19.9 (9.6-32.0) days, respectively. Over the entire hospitalisation patients had a cumulative deficit of 18242 (16642) kcal and 1315 (1028) g protein. Energy and protein intakes were less in ICU than the ward (1798 (800) vs 1980 (915) kcal/day, p=0.015; 79 (47) vs 89 (41) g/day protein, p=0.001). Energy deficits were almost two-fold greater in patients exclusively receiving nutrition orally than tube-fed (806 (616) vs 445 (567) kcal/day, p=0.016) while protein deficits were similar (40 (5) vs 37 (6) g/day, p=0.616). Primary reasons for interruptions to enteral and oral nutrition were fasting for surgery/procedures and patient-related reasons, respectively.

Conclusions:

Patients admitted to ICU with a TBI have energy and protein deficits that persist after ICU discharge, leading to considerable shortfalls over the entire hospitalisation. Patients ingesting nutrition orally are at particular risk of energy deficit.

Running title:

Nutrition after traumatic brain injury

Keywords:

Nutrition, oral intake, critical care, head injury, traumatic brain injury

Abbreviations and definitions: (for all used more than 3 times)

APACHE II: Acute Physiology and Chronic Health Evaluation II

DAI: Diffuse Axonal Injury

BMI: Body Mass Index

EN: Enteral Nutrition

GCS: Glasgow Coma Scale

ICU: Intensive Care Unit

SD: Standard Deviation

SOFA: Sequential Organ Failure Assessment

TBI: Traumatic Brain Injury

Introduction:

Traumatic brain injury (TBI) acutely increases metabolic rate and protein catabolism[19]. Observational data consistently show that during the initial phase after moderate or severe TBI, when patients are in the intensive care unit (ICU), they are substantially underfed, similar to critically ill patients admitted with other diagnoses[4,13,14]. Energy and protein deficits are associated with worse outcomes, both for ICU patients with TBI and other conditions[4,12,73].

Confusion, delirium, fasting for repeated procedures and swallowing difficulties are all prevalent in patients after a TBI and are risk factors for persistent energy and protein deficits[23,42,82,83]. Furthermore, in patients with TBI these energy and protein shortfalls can result in malnutrition which is associated with adverse outcomes such as longer duration of admission to rehabilitation facilities and unfavourable neurological outcome at six months[41,84]. Conversely, critically ill patients achieving energy requirements early during ICU admission have better self-reported physical function six months after ICU discharge[85]. Given patients recovering from a TBI typically have prolonged periods of recovery, nutritional strategies that facilitate rehabilitation are likely to be of benefit[86].

There is a paucity of research on the provision of nutrition support in survivors of critical illness[1]. Few studies have precisely quantified energy and protein deficits from oral intake in the critically ill[87]. Moreover, relatively little information is available as to the provision of energy and protein to patients throughout the entire hospitalisation including both ICU and ward-based care[88]. Finally, the few studies in hospitalised patients that do measure oral intake use methods that either rely on reporting capabilities of the patient, estimate consumed intake, or do not account for individual food items with varying nutritional compositions. The use of investigator-led weighed food records provides accurate and detailed data regarding energy and protein intake and is considered the gold-standard in free-living individuals[89], yet has not been previously reported in the literature for hospitalised patients.

The primary objective of this study was to precisely quantify the amount of energy and protein prescribed and delivered throughout hospitalisation to patients initially admitted to ICU with a moderate-severe TBI. The secondary objective was to describe barriers that exist to achieving nutrient targets in TBI patients.

Materials and Methods:

Study design and population

A prospective observational study was conducted at a single university-affiliated hospital that is the major acute neuro-trauma referral centre for the state of South Australia. All patients admitted throughout a 12-month period (June 2014 – May 2015) were eligible to participate in this study if they: had a moderate or severe TBI (Glasgow Coma Scale 9-12 or 3-8 respectively); were ≥18 years of age; and were in ICU for ≥48 hours. Patients were excluded if they were expected to die imminently. For patients who were deemed incompetent to provide consent, the patient's legally authorised representative was approached. The protocol was approved by the Royal Adelaide Hospital Human Research Ethics Committee (HREC/14/RAH/100).

Data collection

Demographic information was collected including cause of injury, brain injury classification using the International Classification of Disease-10, and post-hospital discharge location. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Trauma Injury Severity Scores (TRISS) were collected from the first day of ICU admission to assess the severity of illness. The Nutrition Risk in the Critically ill (NUTRIC) score[90] was calculated to determine those patients that were more likely to benefit from aggressive nutrition therapy. A score of 0-4 indicates a low malnutrition risk, while a score of 5-9 represents a high malnutrition risk associated with worse clinical outcomes. Data were collected up until hospital discharge or, for those remaining in hospital, censored at 90 days from hospital admission. Data collected on the day of transfer from ICU to the ward were categorised as ICU data.

Dietary assessment

Data on nutrition delivered from all routes were collected by two trained dietitians. Information regarding nutrition provided via the enteral and parenteral routes was collected from fluid balance and intravenous fluid charts completed as routine care by nursing staff, and the amount of total energy and protein delivered was calculated. To precisely quantify nutrient consumed orally, investigator-led weighed food records were conducted on three pre-determined days: two days between Monday and Friday and one day on the weekend. All food and fluids provided from breakfast to one hour post-dinner were included and data extrapolated to provide a weekly average. Individual meal components were weighed by the two dietetic investigators using Salter Brecknell Model 405 digital scales (Australia) both prior to delivery to the patient, and after consumption to measure waste and calculate the total proportion consumed. Items provided outside of observation times were estimated using collection of wrappers, nursing notes, and communication with patients, family, and nursing staff. Where actual amounts could not be weighed, estimates using standardised serving sizes were used. When meal trays were collected before plate waste could be weighed, it was assumed that half of the items provided were consumed. Recorded weights for each item were entered into FoodWorks 8 dietary analysis software (Australia) to calculate energy and protein intakes. The provision of therapeutic diets (e.g. smooth pureed diet) and dietitian prescriptions were assessed from review of meal tickets, catering software and case note documentation.

Data from weighed food records and nutritional requirements were extrapolated to represent daily intake data. Nutritional intake and estimated requirements from ICU admission and hospital discharge day were extrapolated to a 24 hour period to enable comparison with full data days.

Barriers to intake

Interruptions to nutrient provision were recorded from the patient's case notes and barriers to intake observed during weighed food records. The number of occasions that feeding tubes were removed was extracted from the medical notes. The length of time enteral nutrition was interrupted or number of meals interrupted was recorded. Provision of medications known to contribute additional calories, such as propofol, were documented and added to the total intake.

Estimated energy and protein requirements

Data on energy and protein requirements prescribed by the hospital dietitians as part of standard care and the methods used to calculate requirements were recorded. A small number of patients were not seen by a clinical dietitian during their admission and therefore did not have a nutrition prescription. As these patients had short length of stays in hospital they would contribute minimal data and would be less likely to benefit from nutrition support, so it was decided post-data collection but prior to data analysis that their data would be excluded from deficit analyses.

Statistical analysis

Statistical analyses were conducted using SPSS (v.22, IBM Inc). Categorical data are presented as counts and percentages, and continuous data are reported as mean (standard deviation) or median [range or interquartile range (IQR)] as appropriate. Energy and protein deficit was calculated as the mean daily absolute difference between intake and estimated requirements. Energy and protein intake, deficit, and the proportion of estimated nutritional requirements that were met were calculated from all nutrient sources over all days. Comparisons between energy and protein delivery, intake, and deficit in ICU versus the ward, and oral versus enteral nutrition (EN) were assessed using paired samples t-tests. Differences in duration of interruptions between ICU and the ward, and between oral and EN were assessed using independent samples t-tests. To explore variations in energy and protein intakes over time data were analysed on a per seven-day basis, both from ICU admission and from transfer to the acute ward. Post-hoc analyses comparing deficits for the initial three weeks of ICU admission and initial three weeks of ward-based care were conducted because only a few patients received > 3 weeks of both ICU and ward-based care leading to skewed data.

Results:

Of the 105 patients admitted with a TBI over the study period, 47 patients met eligibility criteria and 37 provided consent (**Figure 1**). There were 1512 study days in total, with 530 days in ICU and 982 days of ward-based care after ICU discharge. The mean age of patients at hospital admission was 45.3 (15.8) years and 87% were male. Patient demographics are shown in **Table 1**.

<u>Nutrition assessment and prescription</u>

Each patient was seen by the clinical dietitian a mean of 12.8 (8.0) times; 4.6 (3.1) in ICU and 8.3 (7.0) on the ward. This was equivalent to 2.2 (1.3) visits per week in ICU and 2.2 (1.0) visits per week on the ward. On average, the dietitian spent 34 (20) minutes on each individual occasion of service, and delivered care for 7.4 (5.3) hours per patient over their entire stay. Over the hospitalisation, 71.5% of the dietitian's time was spent managing EN, 20.4% was on oral nutrition support, and 8% of time was not stated.

The clinical dietitian calculated energy and protein requirements on average once every 12.2 (21.4) days; every 10.1 (4.8) days in ICU and 14.4 (30.5) days on the ward. Nutritional needs were prescribed a mean of 3.5 (range: 1-20) days after hospital admission. Three (8%) patients did not have their nutritional needs calculated by a clinical dietitian at any point during their hospital stay.

Energy requirements were estimated using one of two methods. A weight-based calculation, typically 25 kcal/kg body weight/day, was used in 72% of energy assessments, and was favoured during mechanical ventilation. The predictive equation Schofield was used in the remainder (28%) of calculations of energy requirements, generally after patients were no longer receiving mechanical ventilator support. Protein prescriptions were estimated using a weight-based factor which ranged from 1.2 to 2.2 g/kg body weight. The body weight used was the actual weight for patients with a healthy body mass index (BMI) and an ideal body weight (upper end of the healthy weight range for height) for patients with a BMI >25 kg/m^2.

Mean prescribed energy requirements were 2078 (358) kcal/day in ICU and 2457 (457) kcal/day on the ward. Mean prescribed protein requirements were 111 (20) g/day in ICU and 118 (27) g/day on the ward.

<u>Nutritional delivery</u>

Nutrition was received from various sources over the hospital admission and categorised as enteral, parenteral, or oral nutrition, propofol, or other sources such as intravenous dextrose. Thirty-four (92%) patients received EN at some point during their hospitalisation; in all cases this was commenced in ICU, with a mean time to initiate EN of 22.4 (21.7) hours from ICU admission. No patient received parenteral nutrition during the study period.

Of the 34 patients that received nutrition enterally, orogastric tubes were inserted initially on ICU admission in 25 cases, and nasogastric tubes (NGTs) were inserted in nine patients. On discharge to the acute ward, 18 patients were still receiving nutrition enterally. Feeding tubes were inadvertently removed a total of 139 times by 26 patients during the study period; 42 times in ICU by 56% of patients (19/34) and 83 times on the ward by 94% of patients (17/18). In those who removed feeding tubes this was equivalent to 5.3 (range: 1-17) tubes removed per patient per admission or 25 (19.3) times per 100 patient feeding days. After receiving EN via temporary tubes for 47.4 (28.3) days, five patients had a percutaneous endoscopic gastrostomy (PEG) inserted during their hospital admission. PEG placement occurred after 47.6 (28.0) days of admission, with all PEGs being placed after ICU discharge.

Thirty-two patients (86%) ingested nutrition orally at some stage during their hospitalisation. Of the 32 patients that ingested nutrients orally 63% (n=20) commenced oral intake during ICU admission and 37% (n=12) commenced oral intake on the ward. Of these, three commenced oral intake in ICU and did not receive any additional nutrition support. The mean time to commence oral intake was 17.5 (16.5) days after ICU admission. For those patients consuming nutrients orally a range of types of diets were prescribed. Twenty patients (63%) required a texture modified (smooth pureed or minced and moist) diet at some time during their admission, and an additional seven patients (22%) required a soft diet. Over the entire hospitalisation period 12 patients (32%) progressed to a standard, full diet. Over the study period energy and protein intakes for 909 individual meals were recorded. Of these 97.5% (n=886) were weighed, 1.1% (n=10) came from nursing food record charts, and for 1.4% (n=13) it was assumed that half of the meal was consumed.

Energy and protein intake

Over the entire hospitalisation, mean daily intakes from all sources were 1916 (880) kcal and 86 (43) g protein, with absolute energy and protein intakes less in ICU (1798 (800) kcal, 79 (47) g protein) than post-ICU ward-based care (1980 (915) kcal and 89 (41) g protein) (p=0.015 and 0.001, respectively).

Contributions from all sources of energy and protein per week in ICU and ward-based care are shown in **Figure 2**. Daily contributions to energy and protein were greater from EN than oral ingestion of nutrition (EN: 1778 (959) kcal/day and 88 (45) g/day protein; oral: 1259 (872) kcal/day and 57 (41) g/day protein; p=0.488 energy, 0.373 protein).

Energy and protein deficits and adequacy

Deficit data were available for 34 patients who had energy and protein requirements prescribed. Over the entire hospitalisation patients had a mean cumulative deficit of 18,242 (16,642) kcal energy and 1,315 (1,028) g protein. Deficits appeared to persist throughout hospitalisation (**Figure 3**) and overall the mean deficits were 411 (851) kcal/d of energy and 30 (42) g/d of protein. Compared with dietitian prescriptions, patients met an average of 83 (36) % energy and 75 (37) % protein requirements over the entire hospital admission.

Deficits in daily energy and protein were similar between ICU and ward-based care (283 (801) kcal/d and 32 (42) g/d protein vs 480 (870) kcal/d and 29 (41) g/d protein respectively: p=0.118 energy, 0.126 protein). Patients met 87 (39) % of energy and 70 (40) % of protein requirements in ICU, and 81 (35) % of energy and 77 (35) % of protein requirements on the ward.

When the first three weeks of ICU and ward-based admissions were analysed independently, patients had significantly higher energy deficits on the ward than in ICU (407 (557) vs 652 (514) kcal, p=0.039), but protein deficits were similar (37 (27) vs 30 (27) g, p=0.278) (Figure 3).

When comparing patients receiving nutrition exclusively via enteral tube feeding with those only ingesting nutrient orally, energy deficits were greater from oral only than EN only (806 (616) vs 445 (567) kcal/d, p=0.016), while the mean protein deficits were similar (40 (5) vs 37 (6) g/d, p=0.616). For the days that patients received exclusive EN 89 (34) % of energy requirements and 76 (34) % of protein requirements were met, while those solely ingesting nutrients orally met 75 (37) % energy and 74 (40) % protein requirements (p=0.046 energy, 0.378 protein).

Interruptions to nutrient intake

Over the hospital admission, patients had EN interrupted on 608 of 1008 days (60%); 309/491 days (63%) in ICU and 299/517 (58%) days on the ward. When EN was interrupted, the daily average length of interruptions was 8.8 (3.4) hours in ICU and 6.4 (2.6) hours per patient on the acute ward (p=0.020). The primary reason for interruption to the delivery of EN was fasting for surgery or procedures, accounting for 33% of hours of interruptions (38% of hours in ICU and 24% on the ward). For those patients consuming nutrients orally, intake was recorded as being interrupted on 234 of 639 days (37%). When oral intake was interrupted, the mean number of meals affected was 2.3 (0.9) per day. Over the hospital admission, the primary reason for interruption to oral intake was patient-related (e.g. agitation, refusal) accounting for 65% of interruptions to meals, followed by fasting for surgery or procedures accounting for 21% of interruptions to oral intake.

Outcomes

All patients were alive at day 90 with four (11%) remaining in hospital. Clinical outcomes are shown in **Table 2**.

Discussion:

This is the first study to measure the amount of energy and protein prescribed and delivered over the entire hospitalisation to adult patients with a TBI who were initially admitted to an ICU. The key finding is that not only did substantial energy and protein deficits occur during ICU admission for these patients but that these deficits persisted after discharge to the ward, contributing to considerable nutritional shortfalls over the entire hospitalisation. In addition, patients ingesting nutrition orally had greater energy and protein deficits than those exclusively tube-fed.

While it may be assumed that commencing oral intake is a progression towards the patient's recovery, this study revealed that energy deficits were significantly greater with exclusive oral intake when compared with exclusive tube feeding. A previous study that evaluated oral intake in patients recovering from critical illness reported that energy and protein intakes failed to exceed 55% of estimated requirements in the week following liberation from invasive mechanical ventilation[87]. Additionally, a one-day snapshot study of general hospital patients reported an association between reduced oral intake and increased mortality[91]. Given these findings, clinicians need to be aware that oral intake after critical illness is diminished, particularly during the transition phase to exclusive oral ingestion of nutrients. Strategies such as the provision of energy and protein-fortified foods and oral liquid supplementation to improve oral intake, or supplemental tube feedings until oral intake is sufficient should therefore be considered.

This study found that, according to dietetic prescriptions, energy and protein deficits were greater on the post-ICU acute ward. Deficits may be exacerbated after ICU discharge as the benefits of early nutrition support within ICU are generally well accepted: not only is there an emphasis on nutrition delivery in ICU but because there are more health care providers available per patient than on the ward, interventions may be more successful[92-94]. Conversely, additional challenges exist with an awake TBI patient that, particularly after discharge to the ward, may prevent adequate nutrition such as the frequent removal of feeding tubes, food refusal, and swallowing difficulties shown in this study. Fasting for surgical or diagnostic procedures was found to interrupt nutritional intake frequently and for extended periods of time both in ICU and on the ward, which has previously been reported in both general trauma and critically ill patients in the ICU[21]. Given the long length of stay of TBI patients in the hospital setting, prolonged nutritional deficits throughout the hospital admission may impact on functional recovery. Adequate nutrition in the critically ill has shown to improve self-reported physical function at six months and hence enhanced nutrient delivery throughout the hospital admission using strategies such as minimisation of interruptions may be of benefit[85].

A large portion of energy intake in ICU was received from propofol, which increased energy provision but when considered in the total caloric load by the clinician subsequently may have been detrimental to protein delivery. While it is recognised that propofol can contribute significant calories and hence needs to be considered in the energy prescription to prevent overfeeding[95], the impact on protein delivery has not previously been reported. As protein deficit may be important[96], the use of a high protein enteral formula, or the addition of a protein powder to the formula could be considered for patients receiving greater doses of propofol. Similarly, propofol administration will increase the lipid load, which may have negative effects on anabolic drive, and hence increase muscle protein degradation[97-99]. In this patient group, however, there is frequently a need for sedative drugs to modulate intracerebral pressures, with adverse events potentially occurring with all sedative drugs and/or their formulations[100]. Accordingly, strategies to reduce lipid administration via a reduction in propofol administration could be considered in the overall context of the complex management of these patients, but this would need to be rigorously evaluated including any potential adverse effects of alternative drugs to be given[101,102].

This is the first study of its kind to measure nutritional intake from all sources in a hospitalised patient group over the entire hospital admission. The primary strength of this study is the robust nature of the nutritional intake data. Nutrition studies in a critically ill population tend to include enteral or parenteral feeding data only and either exclude patients consuming nutrients orally, or disregard energy and protein consumed via this route. Studies that do report nutrients consumed orally tend to rely on less precise methods of measurement such as patient recall, subject to recall bias. The investigator-led weighed food record methodology utilised in this study has not previously been reported in hospitalised patients but enables accurate and detailed measures of energy and protein intakes[87,103,104]. The second major strength of this study is the longitudinal data collection period for each patient. Most nutrition studies in critical illness focus on the first few days or weeks of admission. No other identified observational study has collected daily data on nutrition prescription and delivery, and interruptions to nutrition support from ICU admission through to hospital discharge. Finally, because consecutive patients were eligible throughout a 12 month period and ~80% of patients consented with no loss to follow up, selection bias was limited.

There are however limitations to this study. The study was performed in a single hospital in Australia and due to different geographical practices these data may not be generalisable. Energy and protein intakes found in this study were greater than those reported in a recent multi-centre international observational study of TBI patients; in the first two weeks of ICU admission patients met 88% energy and 65% protein requirements compared to 58% energy and 53% protein requirements in the international study[4]. Strategies such as early initiation of feeding, dietetic intervention, management of feeding intolerance and use of bedside feeding protocols that are utilised at the study site and have been shown to be effective in a heterogeneous critically ill population may have assisted with nutrition provision[93]. While previous data suggests inadvertent tube removal is common in patients following TBI[105], certain centres may have specific techniques to reduce the frequency of this problem.

The relatively small sample size of this study precludes evaluating relationships between energy and protein intakes and patient-centred outcomes. This needs further evaluation given the potential for nutrition to improve outcomes, as there were associations reported between patients with TBI who had greater energy and protein deficits early in ICU and longer times until discharge alive[4]. It is recognised that interpreting energy and protein deficit data is reliant on dietetic prescriptions and this could be improved by comparing intake data to indirect measures of energy and protein needs rather than relying on predictive equations (which have inherent inaccuracies)[106], however the behavioral aspects associated with the recovery phase of TBI make meaningful measurement using indirect calorimetry or nitrogen balance challenging. Also, to better understand the reasons for inadequate oral intake it would be worthwhile to conduct a subjective questionnaire on aspects such as appetite, which was also not achievable in this population. Additionally, the priorities and roles that medical and nursing staff have in the delivery of nutrition over the hospitalisation of these patients may provide further insight into strategies to improve intake.

Future research should include measurement of oral intake in addition to enteral/parenteral nutrition, particularly in survivors of critical illness, and explore effective strategies to improve intake over the entire hospital admission such as use of supplemental EN and early PEG placement in appropriate patients.

In conclusion, patients admitted to ICU with a moderate-severe TBI have considerable energy and protein deficits during ICU admission which persist after discharge to the ward. Given that these patients remain in hospital for extended periods of time, these deficits lead to sizable shortfalls over the entire hospitalisation, which has the potential to impact on nutritional status and long-term functional outcomes. Patients consuming nutrients orally are particularly at risk of energy deficits.

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Statement of Authorship:

LSC was responsible for study design, recruitment, data collection, data entry, data analysis, statistical analysis, interpretation of the data and drafting the manuscript. She is guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the accuracy of the data analysis.

MJC, AMD, LTW and DKH contributed to the study design, interpretation of the data, and critical revision of the manuscript for important intellectual content.

KL was responsible for analysis and interpretation of the data, contributed to the study design, and critical revision of the manuscript for important intellectual content.

AK contributed to data collection, data entry, interpretation of the data, and critical revision of the manuscript for important intellectual content.

All authors read and approved the final manuscript.

Conflict of Interest Statement:

The authors declare that they have no competing interests; such as employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/ registrations, grants or other funding.

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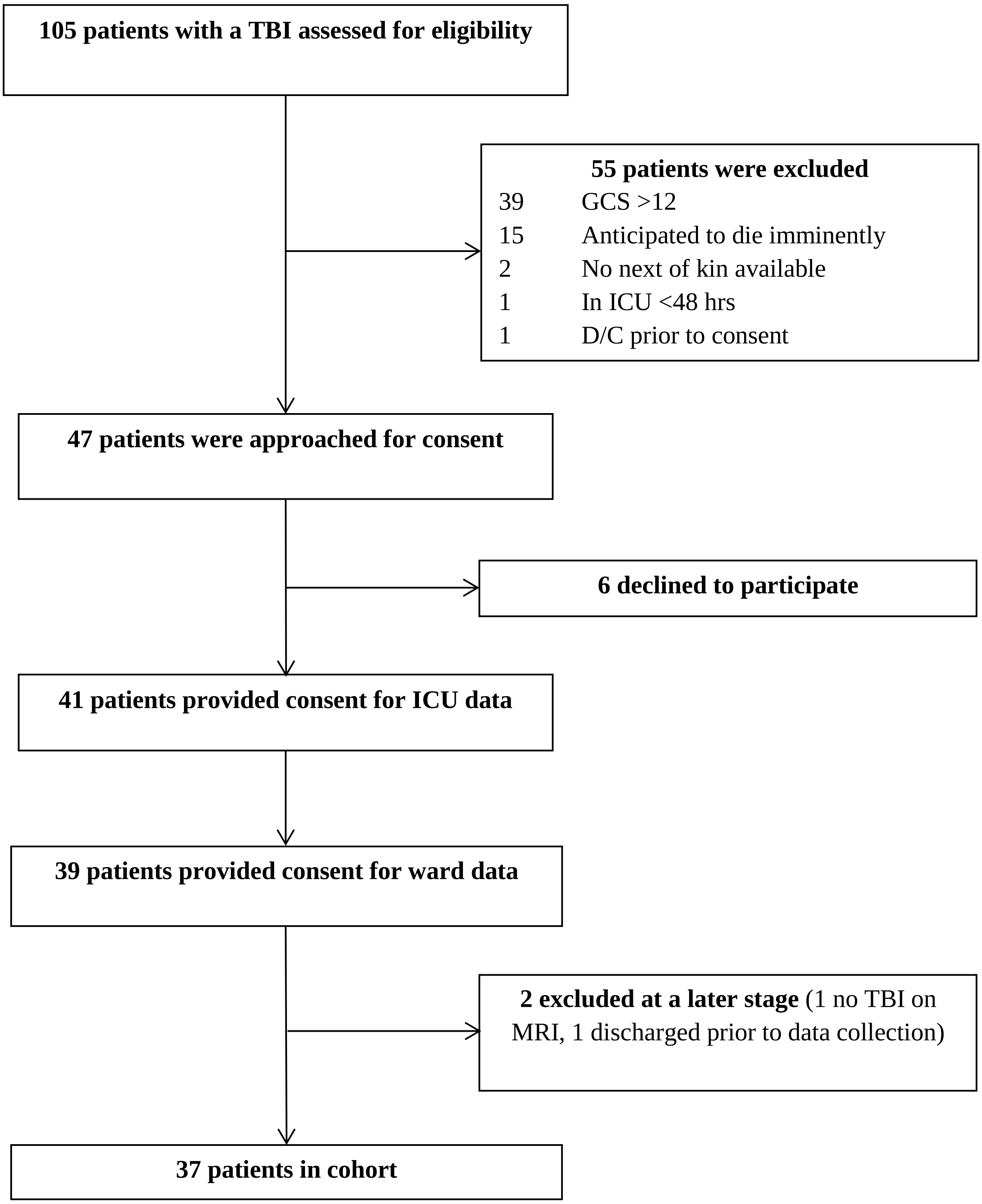
Figure 1: Consort diagram



D/C: Discharge, GCS: Glasgow Coma Scale, ICU: Intensive Care, MRI: Magnetic Resonance Imaging, TBI: Traumatic Brain Injury

Table 1: Patient demographics on admission to intensive care, n=37

	Total
Age (y), mean (SD)	45.3 (15.8)
Sex (male) n, (%)	32 (87)
Initial GCS: *(n=36)*	
GCS 3-8, n (%)	24 (67)
GCS 9-12, n (%)	12 (33)
APACHE II, median [IQR]	18 [14-22]
SOFA score, mean (SD) *(n=34)*	6.4 (2.8)
NUTRIC score*, n (%), *(n=34)*	
Low score, low malnutrition risk (0-4)	30 (88)
High score (5-9)	4 (12)
Body Mass Index (kg/m^2), mean (range)	26.7 (19.8-39.5)
Underweight (<18.5kg/m^2), n (%)	0 (0)
Healthy (18.5-24.9 kg/m^2), n (%)	18 (49)
Overweight (25-29.9 kg/m^2), n (%)	10 (27)
Obese (>30 kg/m^2), n (%)	9 (24)
Isolated TBI, n (%)	12 (32)
Multi-trauma with TBI, n (%)	25 (68)
TBI classification: n	
SAH	20
SDH	20
DAI	6
Epidural haemorrhage	5
Other	9
Cause of injury:	
Vehicular, n (%)	22 (60)
Fall, n (%)	8 (22)
Assault, n (%)	3 (8)
Sporting injury, n (%)	2 (5)
Other, n (%)	2 (5)

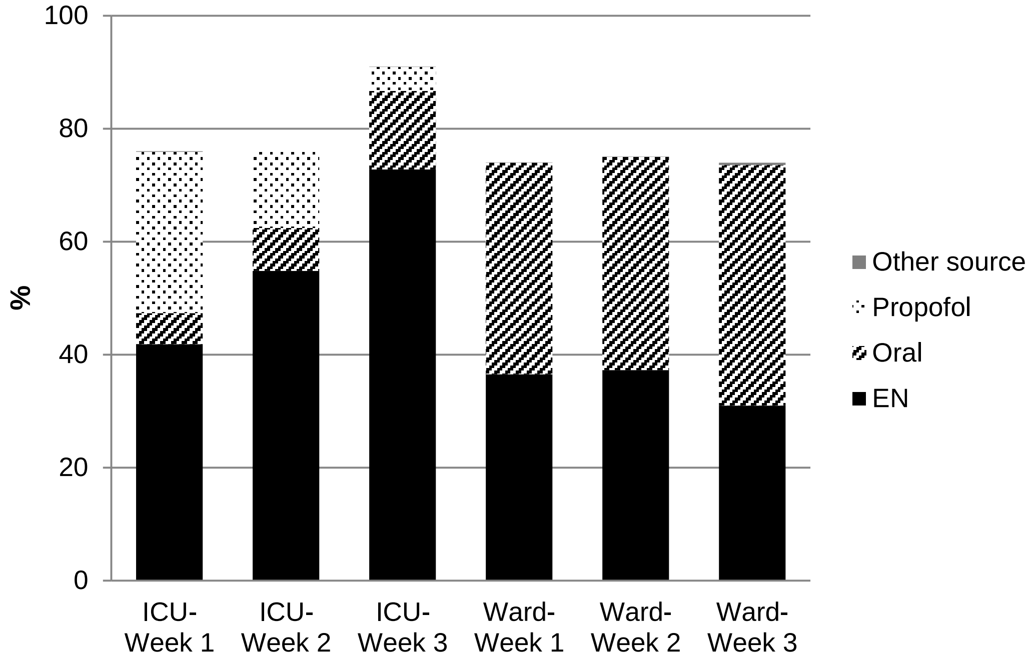
APACHE II: Acute Physiology and Chronic Health Evaluation II, DAI: Diffuse Axonal Injury, GCS: Glasgow Coma Scale, SAH: Subarachnoid Haemorrhage, SDH: Subdural Haemorrhage, SOFA: Sequential Organ Failure Assessment

*NUTRIC score: 0-4 = low malnutrition risk, 5-9 = high malnutrition risk

Note: Patients could have more than one TBI classification

Figure 2: Mean energy and protein contribution from enteral and oral nutrition support, 1% propofol and other sources per week in ICU and the ward as a % of estimated requirements

Panel A: Energy



Panel B: Protein

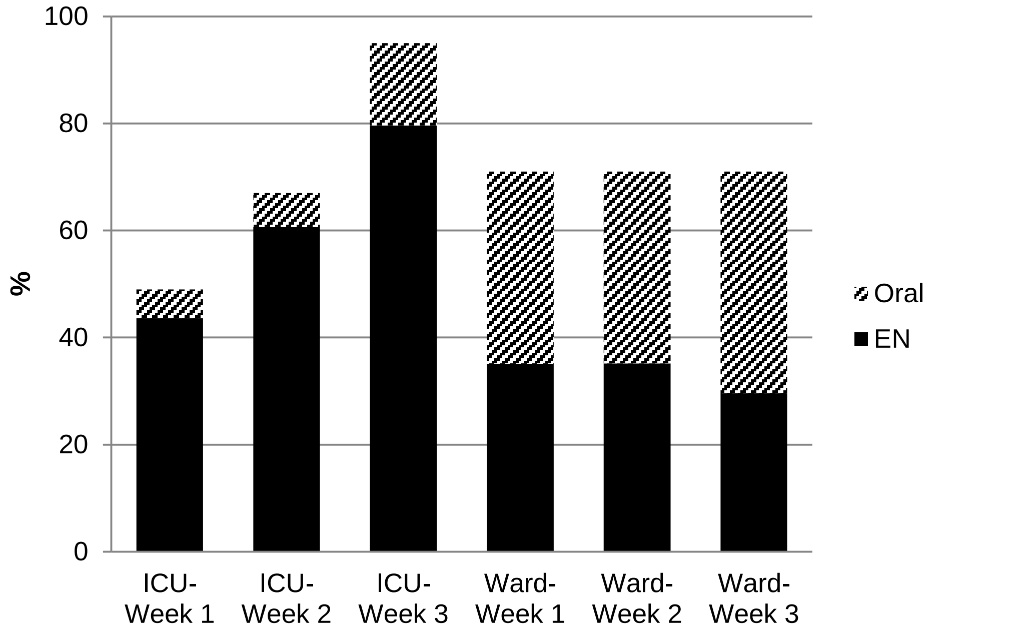
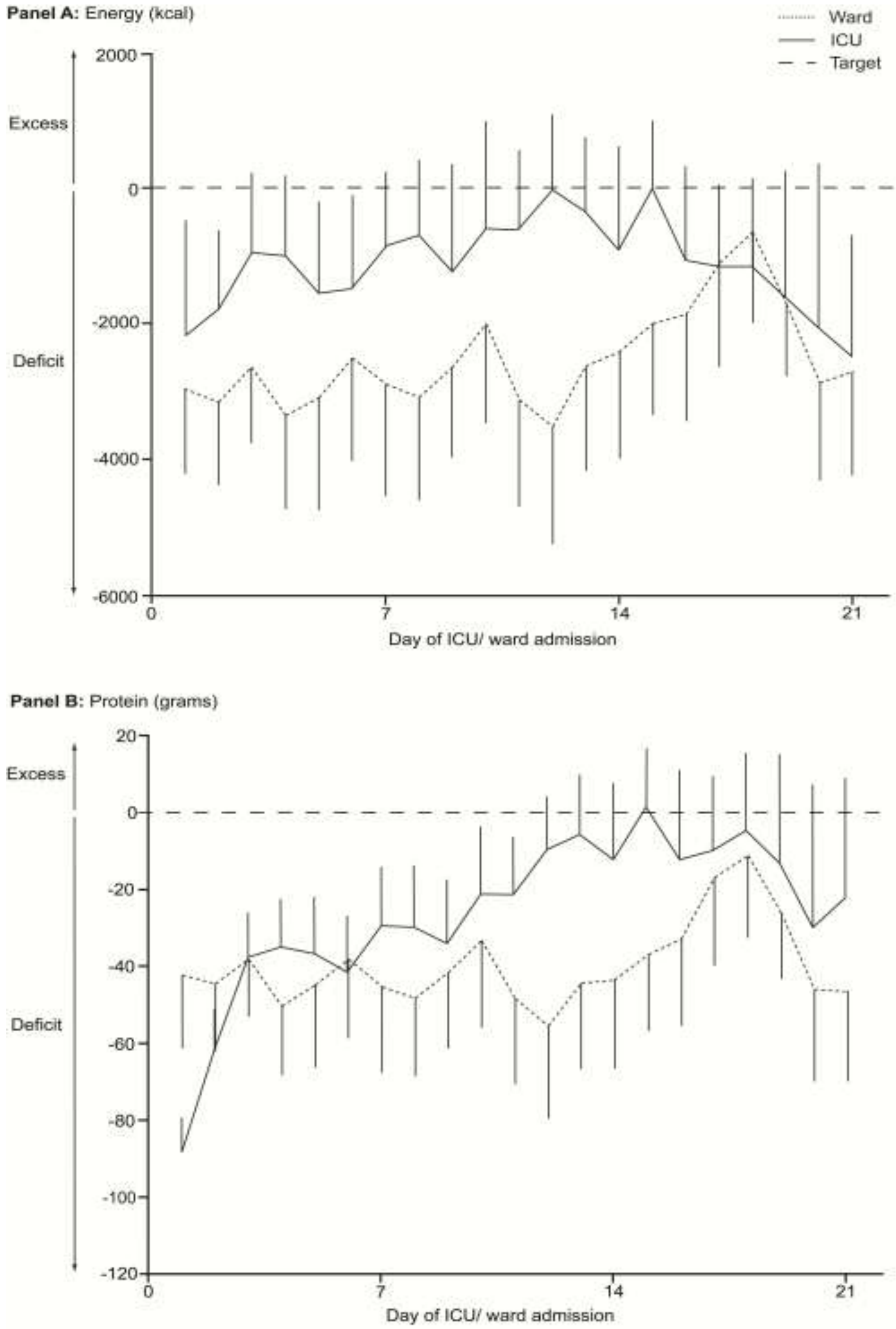


Figure 3: Mean daily energy and protein deficits, calculated as the mean daily absolute difference in intakes from all sources and estimated requirements for the first three weeks in ICU and the ward



Number remaining (n)

ICU	37	37	38	36	35	31	28	26	26	25	24	22	20	20	18	16	14	12	10	7	6
Ward	37	37	37	34	32	31	31	29	28	28	27	26	25	23	21	21	21	20	20	19	18

Table 2: Clinical outcomes in patients admitted with traumatic brain injury

Variable	**Total**
ICU LOS, median [IQR] (days)	13.4 [6.4-17.9]
Hospital LOS, median [IQR] (days)	37.8 [19.4-52.4]
LOS on ward, median [IQR] (days)	19.9 [9.6-32.0]
Patients requiring MV, n (%)	35 (94.6)
Length of MV, median [IQR] (days)	11.0 [5.0-24.3]
Tracheostomy inserted, n (%)	16 (43.2)
Hospital discharge location, n (%)	
Rehabilitation facility	24 (65)
Inter-hospital transfer	4 (11)
Home independently	4 (11)
Home with supports	3 (8)
Permanent care facility	2 (5)

IQR= Interquartile Range, LOS= Length of Stay, MV= Mechanical Ventilation

Manuscript 3:

Barriers to nutrition intervention for patients with a traumatic brain injury: Views and attitudes of medical and nursing practitioners in the acute care setting

Authors:

Lee-anne Chapple[1,2], MNutDiet, Marianne Chapman[1,2,3], PhD, Natalie Shalit[4], BNutDiet (Hons), Andrew Udy[5,6,7], PhD, Adam Deane[1,2,3,] PhD, Lauren Williams[8], PhD

[1]Discipline of Acute Care Medicine, University of Adelaide, Adelaide, Australia
[2]National Health and Medical Research Council Centre for Clinical Research Excellence in Nutritional Physiology and Outcomes, Adelaide, Australia
[3]Intensive Care Unit, Royal Adelaide Hospital, Adelaide, Australia
[4]Australian Centre for Health Innovation, Melbourne, Australia
[5]Department of Intensive Care and Hyperbaric Medicine, Alfred Health, Melbourne, Australia
[6]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[7]Australian and New Zealand Intensive Care Research Centre, Monash University. Melbourne, Australia
[8]Menzies Health Institute of Queensland, Griffith University, Australia

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Corresponding author responsible for study conception and design, acquisition of data, statistical analysis and drafting the manuscript		
Overall percentage (%)	80		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	4/1/17

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	5/1/17

Name of Co-Author	Ms Natalie Shalit		
Contribution to the Paper	Conceptualisation of work, assistance with study preparation, recruitment and critical revision of the manuscript for important intellectual content		
Signature		Date	10/1/17

Name of Co-Author	Associate Professor Andrew Udy		
Contribution to the Paper	Assistance with recruitment and critical revision of the manuscript for important intellectual content		
Signature		Date	10/1/17

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/1/17

Name of Co-Author	Professor Lauren Williams		
Contribution to the Paper	Conceptualisation of work, data analysis and critical revision of the manuscript for important intellectual content		
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Abstract

Background:

Nutrition delivered to patients with a traumatic brain injury (TBI) is typically below prescribed amounts. While the dietitian plays an important role in the assessment and provision of nutritional needs, they are part of a multi-disciplinary team. The views and attitudes of medical and nursing practitioners are likely to be crucial to implementation of nutrition to TBI patients, but there is limited information describing these.

Methods:

A qualitative exploratory approach was used to explore the views and attitudes of medical and nursing practitioners on nutrition for TBI patients. Participants at two major neurotrauma hospitals in Australia completed individual semi-structured interviews with a set of questions and a case-study. Interviews were transcribed and coded for themes.

Results:

Thirty-four health practitioners participated: 18 nurses and 16 physicians. Three major themes emerged: 1) nutrition practices over the hospital admission reflect the recovery course; 2) there are competing priorities when caring for TBI patients; and 3) the implementation of nutrition therapy is influenced by practitioner roles and expectations.

Conclusion:

Use of qualitative inquiry in the study of attitudes toward nutrition provision to TBI patients provided detailed insights into the challenges of operationalising nutritional therapy. These insights can be used to clarify communication between health practitioners working with TBI patients across the continuum of care.

Introduction:

Energy and protein usually provided to patients after a traumatic brain injury (TBI) is less than calculated requirements, both in the Intensive Care Unit (ICU) and following ICU discharge[2,4]. Delivery of nutrition is often hindered by dysphagia, gastric dysmotility and fasting[23,42].

While the dietitian plays an important role in the assessment of nutritional status and prescription of nutrition, they are part of a multi-disciplinary team. Clinical observations demonstrate that medical and nursing practitioners are responsible for making decisions around the commencement, route, and delivery of nutrition therapy and management of feeding complications in TBI patients, and hence have the potential to influence nutrition delivery, through factors such as extended fasting times and suboptimal management of delayed gastric emptying[107]. Our previous prospective cohort study demonstrated that interruptions to feeding were primarily due to reasons outside of the dietitian's control, such as fasting for surgery[2]. Nutrition TBI guidelines provide little advice on the delivery of nutrition beyond the ICU stay[1]. Therefore, bedside practices are more likely to be guided by the healthcare provider's previous experience.

A UK study reported that less than half of medical practitioners and only a quarter of nurses in intensive care had a sound knowledge of nutrition guidelines[108]. Insufficient knowledge of nutrition therapy has been shown to be associated with reduced nutrition delivery[109]. In other practice areas, including primary care and paediatrics, physician belief in the efficacy of nutrition is associated with greater nutrient delivery[110,111]. An understanding of the health practitioner's views and attitudes towards the provision of nutrition is therefore required to begin to identify and potentially address barriers to achieve optimal nutrition for patients.

The aims of this study were to: (1) explore the views and attitudes of health practitioners involved in decision-making processes around nutrition therapy throughout hospitalisation for TBI patients; (2) develop an understanding of how the experiences of health practitioners have informed their views of the role of nutrition; and (3) identify potential barriers and facilitators in providing adequate nutrition.

Methods:

A qualitative exploratory methodological approach with individual interviews was used. An understanding of perceived benefits and barriers to nutrition therapy in TBI patients was sought to inform the development of interventions that are relevant, effective, and likely to succeed.

Setting:

This study was conducted in one of the two designated adult major trauma services in each of the states of Victoria and South Australia. Ethical approval was obtained from the relevant hospital and university Human Research Ethics Committees.

Participants:

Eligible participants included those with significant experience in the care of TBI patients in an acute hospital environment: consultant and registrar physicians and nursing practitioners in the areas of intensive care, neurosurgery, and trauma. Participants included those with ≥12 months experience and ≥10% of their workload managing TBI patients.

Using a pragmatic approach the primary investigator contacted respective department administrators to identify and obtain contact details for potential participants who were then contacted through a personal approach. The primary investigator attended ward-based meetings to promote the study.

Protocol development:

The semi-structured interview questions were developed based on prior clinical experience and discussions with other health practitioners. A pilot protocol was trialed with health practitioners external to the research population to refine the protocol and estimate the time required. After the first three interviews, the protocol was revised based on the brevity of responses provided and through discussion with the senior experienced qualitative researcher.

In order to explore attitudes specific to each diverse role separate sets of interview questions were developed for medical and nursing practitioners, and for ICU and ward-based care. The interview questions for the medical profession were designed to reflect their role in overarching decision-making, whereas the interview questions for the nursing practitioners aimed to capture their opinions around the day-to-day management of TBI patients.

The interview protocol was divided into three sections. Section one included demographic and professional data. Section two included a semi-structured protocol with a set of seven questions to explore three distinct areas: nutritional needs, nutrition provision and management, and patient outcomes. Section three comprised a case-study based on real-life observations by the primary investigator divided into two parts followed by a set of questions to gain scenario-based responses to more closely reflect clinical decision-making in practice. A written copy of the case-study was provided to participants to aid the discussion about how the participant's nutritional management of the case changed over time.

Procedure:

One-on-one semi-structured interviews were completed in person by the primary investigator at a single time-point. An information sheet was provided to the participant and written consent obtained. Each participant was allocated a unique identification number to ensure confidentiality. Interviews were audio recorded and transcribed verbatim. Transcribed interviews were de-identified and audio recordings erased after transcription.

Transcription of interviews and coding of themes commenced early in the interview process and saturation was determined at the time where no new themes were emerging[112]. It was anticipated that if this point was not reached, data collection would continue until reasonable participant numbers were reached, considered as at least five participants per protocol.

Data analysis:

Simple descriptive statistics were used to report demographic and professional data. The transcripts were coded by a primary and secondary investigator into themes to increase confirmability of the results. As similar themes emerged they were consolidated into a primary theme, and from this over-arching themes were developed with associated sub-themes. Participant responses were coded using thematic analysis by a primary and secondary investigator to increase confirmability of the results.

Results:

Participant characteristics

Thirty-four interviews were conducted between August 2015 and May 2016 - 15 at site one and 19 at site two. Demographic data and professional data are shown in **Table 1**. The average interview length was 20 minutes and 49 seconds (SD: 4:45, range: 13:58 - 32:59).

Key Themes:

Key themes arising from the interviews are presented below as narrative text supported by verbatim quotes. Participants are designated by professional specialty and study ID number.

1. ***Nutrition therapy practices over the hospital admission reflect recovery course post-TBI:***

Participant's comments reflected that nutritional needs of a patient with a TBI change over time and recovery is both unpredictable and varies between individuals: *'they're all different, all head injuries are different'* (Ward nurse #4). The views and attitudes towards nutrition therapy thus varied with each stage of treatment and recovery. Three key sub-themes were identified: the first around tube-feeding; the second around taking responsibility for the nutrition of the patient while they are incapable of doing so; and the third around differences in nutritional care between ICU and the ward. For patients with a decreased level of consciousness artificial nutrition support is generally provided via a nasogastric tube (NGT) or nasoenteric tube (NET) for short-term, or a percutaneous endoscopic gastrostomy (PEG) for longer-term feeding.

1.1 To tube or not to tube

The first theme was around when, or if, to place or replace a feeding tube to deliver nutrition to patients incapable of eating to their requirements. Nursing practitioners, both in ICU and on the ward, expressed concerns about the balance between meeting nutritional needs and placing a NGT in a confused TBI patient. Ward nurses described the consequence of feeding tube insertion further aggravating the patient: *'it becomes a conflict of, you know, shove another tube down and agitate them versus, you know, not getting all their needs'* (Ward nurse #10), and the challenge of ensuring adequate nutrition therapy: *'you don't want to overly distress the patient, but then you want to make sure they're getting fed as well'* (Ward nurse #9). This was echoed by an ICU nurse who reported: *'if they just keep pulling out the NGT it's just causing trauma, and they're not getting what they need'* (ICU nurse #2).

The impact of this on staff, the patient, and their family was apparent, with negative statements reflecting the 'trauma' and 'forcefulness' of NGT insertions: *'Just the trauma of putting an NG in someone with a traumatic brain injury is quite traumatic in itself'* (Ward nurse #7) and *'it's so traumatic on the family,* *watching them removing these nasoenteric tubes all the time, it's just hard'* (Ward nurse #4).

Participants often saw progressing to oral intake as the priority: *'the ultimate aim would be to get the tube – the nasogastric tube out, and stop enteral feeding. You want to try and get them back to normality'* (ICU nurse #5). If the patient could physically eat, then provision of artificial feeding was seen as a negative: *'if we're going to place a tube, for how long are we going to do it, because we're moving back to square one again'* (Ward medical #1). One participant felt this attitude might compromise nutritional adequacy*:*

> *'I think people are less focused on feeds when patients are extubated, maybe because there may be some minimal oral intake happening. That might sort of falsely reassure that the patient is getting something in'* (ICU medical #1).

The decision to place a longer-term feeding tube was complex and responses varied between and within professional groups. Some participants felt PEG placement was too delayed: *'I think we should PEG them sooner rather than later [sic]'* (Ward nurse #1) and *'there's patients here who need PEGs but don't get them'* (Ward nurse #1), while others felt alternative routes should be exhausted first: *'when they're very keen on PEG feeding and we just want the patient just to wait a little bit longer because I think they're going to probably not require it'* (Ward medical #6) and *'we'd be more keen to give the patient a bit more time to recover as opposed to getting in there and just arranging a PEG'* (Ward medical #7). This shows that the decision to insert a PEG is seen as an impediment to recovery.

1.2 You have to be responsible for their nutrition

Participants noted that TBI patients were different from other patients in that their ability to participate in the decision-making process was frequently impaired: *'we are responsible for that person, because they can't be responsible for themselves'* (Ward nurse #5) and:

> *'You forget that they can't eat, forget they're not taking the initiative to do that, and they actually probably need a bit more support than the other groups'* (Ward medical #6).

One participant reflected that this was a phase that would resolve:

> *'It's something that passes. It's not something that's permanent. They do get over this and eventually their appetite does improve and it's usually weight loss until they start building it up'* (Ward nurse #4).

For this participant non-eating was seen as a stage in the recovery process, with weight loss tolerated as a characteristic of the condition rather than being seen as a cause for intervention.

1.3 ICU versus ward management

Participants discussed nutritional care in ICU as being different to the post-ICU ward. One ICU nurse agreed that nutritional needs increase after extubation but that *'it's easier for us because they're usually sedated, so it's easier to keep things like feeding tubes in'* (ICU nurse #4). Both ICU and ward-based medical practitioners commented that nutrition therapy takes a higher priority in ICU: *'I think, when they get on the ward, it's all very badly managed'* (Ward medical #2) and *'I think as patients get out of ICU, their nutritional support and sort of surveillance becomes less and less and less'* (ICU medical #3). While no participant described why nutritional management might decline after ICU discharge it seemed to be accepted, again as a stage of recovery rather than a need for more effective monitoring and intervention.

2. There are competing priorities when caring for patients with TBI:

While many participants expressed that nutrition was very important to patient recovery they expressed a number of key aspects that competed with the ability to provide nutrition. These included patient age at the time of injury, and a belief that while nutrition is important it is not the top priority.

2.1 Condition and age at injury

Patient's age and anthropometry seemed to have a marked influence on the views of health practitioners regarding nutrition therapy. Some participants regarded nutrition for younger patients to be a lesser priority than for older patients: *'they can go a bit longer (without nutrition intervention) being a bit younger'* (Ward nurse #1) and *'a cachectic old person is going to need certain different things than a young, fit, healthy person'* (ICU medical #9). Age was also a factor in deciding the route of feeding *'it's tricky because he's young, you don't want to put a PEG in'* (Ward medical #7). Participants mentioned baseline nutritional status as an indicator to determine the aggressiveness of nutrition therapy, but with different arguments. One participant felt that *'large muscle mass, we want to ensure that that's maintained'* (ICU nurse #8) with another feeling the opposite: *'he's young, fit, healthy, he had a high BMI to start with, um, he could probably afford to lose a little bit before he gets into strife'* (Ward medical #6).

2.2 Nutrition not the top priority

Participants felt there were a range of competing priorities that take precedence over nutrition: *'it's an important thing, but it's not an essential, you know, like the airway, breathing, circulation, those sort of – those things will always come first'* (ICU medical #7). Nutrition only became a priority once a problem arose: *'I think maybe we notice it more when – when you get the problems as opposed to as an initial step'* (Ward nurse #9). This approach to nutrition intervention clearly had limitations: *'I think by the time you can see that the patient is wasting away you've obviously missed the boat'* (Ward medical #3). Some medical practitioners felt that a greater focus on nutrition would be beneficial: *'if we looked at people's weight like we look at their intracranial pressure, then perhaps we might consider it a bit more'* (Ward medical #2).

One participant described the: *'lack of the awareness with nursing staff on how important it actually is'* (Ward nurse #6), and another acknowledged that *'nutrition goes under the radar in some respects'* (ICU nurse #3). One participant related this to how other aspects of patient care were managed:

> *'Once they get to the ward, I think, it's not something that, as I've seen on ward rounds, is at the forefront of every single discussion we have around our patients, we're talking about their wounds, we talk about their GCS (Glasgow Coma Scale), we don't talk about their nutrition'* (Ward medical #1).

3. Nutrition therapy is influenced by practitioner roles and expectations:

The actual delivery of nutrition to TBI patients was seen as complex. The sub-themes were: differing opinions regarding who is primarily responsible for managing nutrition; how to measure nutritional adequacy; and how decisions regarding nutrition therapy are made.

3.1 Whose responsibility is it?

Participants regarded the dietitian as the expert on nutrition for TBI patients: *'Dietitians, this is their bread and butter, they know what they're talking about'* (ICU nurse #6) and *'obviously if the dietitian has a specific recommendation, then there's a reason we're asking for that expert opinion'* (ICU medical #3). However, their role was seen as more advisory. Nursing practitioners reflected a strong ownership of nutrient delivery and felt they were best positioned to manage nutrition needs overall: *'the doctors don't necessarily understand what our patients need sometimes….whereas we're a bit more in tune with – we look after everything'* (Ward nurse #4). Medical practitioners agreed that nutrition was more the responsibility of nursing practitioners: *'it's normally overseen by the nurses'* (Ward medical #10) and *'the nurses will prompt you'* (ICU medical # 16).

Medical practitioners on the ward played less of a role in nutritional care, relying on the ICU team: *'It's the intensivists who will manage – we're more responsible on the, you know, surgical operation part'* (Ward medical #3) and *'the only time I play a role in nutrition is if there's going to be a delay in feeding them because of surgery'* (Ward medical #1). One participant reflected that this may not be ideal: *'I think we leave a lot to the nursing staff or allied health where we should be taking a bit more of a proactive role'* (Ward medical #6). The feeling in ICU was that all practitioners needed to play an active role in multidisciplinary team decisions rather than it being the sole responsibility of one practitioner: *'Obviously it needs to be a joint effort between the doctors and the nursing staff and the dietitian'* (ICU medical #3), and *'it's not just the nurses or doctors, it's both – it's all of us'* (ICU nurse #6).

3.2 Nutritional outcomes are unclear

While nutrition was described as being important, participants were not able to clearly articulate nutrition-related outcomes: *'I do understand the importance, but I don't know how to measure the outcome'* (Ward nurse #2). There was at best a somewhat vague understanding of the influence on longer-term outcomes, such as prevention of muscle atrophy: *'the most important consideration is sort of muscle wasting and weakness'* (ICU medical #3) and *'we're always thinking about how we're going to get their calories in and make sure they don't lose weight'* (Ward nurse #8).

Other participants felt that nutrition therapy may not affect clinical outcomes: *'I'm not too sure whether it has such an impact on their recovery'* (Ward medical #4). An ICU physician felt that while some nutrition is important, the amount mattered less so:

> *'I think if it's done poorly it could influence negatively someone's long-term outcome. However, I think if it's done moderately well or excellent it doesn't – it probably doesn't make much difference'* (ICU medical #6).

Two medical practitioners felt there were multiple aspects other than nutrition that would affect recovery *'it's not going to be the only thing that influences his outcomes in his course of stay'* (ICU medical #4) and *'as a single entity it's probably not going to make a huge difference'* (Ward medical #6).

3.3 Evidence-based or not

While the medical practitioners interviewed were experts on TBI, some admitted that they were unaware of the best available nutrition evidence: *'I'm sure there's* *research in that area, but I don't know anything about it'* (Ward medical #2) and *'I'm not even aware of any particular evidence in TBI populations specifically, but I haven't looked for a while'* (ICU medical #4). Other participants described the evidence for nutrition practices as insufficient: *'I don't think we've seen much, ah, stunning success of nutritional studies with clinical – gross clinical outcomes'* (Ward medical #5) and *'I'm not aware of any studies…which have actually made a difference to the outcome of these patients'* (ICU medical #7).

Instead participants indicated that nutrition practices were based on other factors. Participants felt that *'historical teaching'* (ICU medical #8) was largely responsible. One neurosurgeon described the way in which practices were modeled by senior to junior doctors:

> *'I think it's probably a training thing. And then also you watch your seniors and you learn from your seniors. And the more senior you get the more they, you know, forget about the simple stuff'* (Ward medical #6).

This observation of modeling was echoed by an ICU nurse: *'I think sometimes it's a consultant-driven thing, that they've been taught this way and this is the way they want to do it. It's a whole trying to get people adapted to change [sic]'* (ICU nurse #4). Other participants reported relying on intuition: *'that's all based on, I suppose, a gut feeling, not from hard evidence'* (Ward medical #6) and routine: '*it's what's routine or what they're comfortable with or what they've seen done before'* (ICU nurse #5).

The barriers and facilitators to optimal nutrition in TBI patients revealed in these conversations are outlined in **Table 2**.

Discussion:

This is the first qualitative exploration into the views and attitudes of medical and nursing practitioners involved in clinical decision-making regarding nutritional management of patients admitted to hospital with a TBI. Nutrition therapy for TBI patients is complex and there are a number of competing interests that can impede nutrient delivery. Results of this study raise a number of clinician-related reasons for inadequate nutrition delivery which provide an opportunity for the development of potential strategies to improve nutrition therapy in these patients.

Increased nutritional requirements in trauma have been well described[113], yet there was a lack of an evidence-based approach to nutrition intervention in the hospitals that participated in this study. While these sites were major teaching hospitals, there was no mention of procedures or evidence-based statements guiding nutrition practice specific to a TBI population. Both ICUs in this study had enteral feeding protocols in place, but these had no recommendations specific to TBI, and there were no protocols in place in the post-ICU wards. The presence of bedside nutrition protocols have been shown to improve the delivery of nutrition therapy both in an ICU and TBI population[4,114,115]. Additionally, there was no clear consensus between health practitioners of what role they played in the management of nutrition in TBI patients. Hence, there is a lack of ownership or perceived responsibility by health practitioners, particularly ward-based medical practitioners, in nutrition management. A number of studies in an ICU setting, mainly in the nursing domain, demonstrate the ability of nutrition practices by these health practitioners to affect nutritional adequacy[116,117]. Previous qualitative research has shown that the beliefs and attitudes of practitioners have the ability to influence the effectiveness of interventions in healthcare settings[111,118]. The instigation of nutrition teams has been shown to improve safety and outcomes in ICU with positive financial inferences[119,120] suggesting shared responsibility of a patient's nutrition may be of benefit.

Few participants in this study were able to report which outcomes may be influenced by nutrition or how to measure them. Perhaps one of the major challenges associated with the prioritisation of nutrition therapy is that clear benefits on recovery from a TBI are yet to be established[1]. Development of objective short-term outcome measures that are able to quantify the benefit of nutrition therapy may help improve prioritisation of nutrition and ensure that other health practitioners are aware of the influence nutrition can have.

The views and management of nutrition therapy differed between practitioners from ICU and the ward. These differences may have implications for nutritional adequacy of patients with an observational study reporting greater nutritional deficits on the post-ICU ward than in ICU[2]. Ward-based medical practitioners are often absent from the ward in the operating theatre and the nurse/patient ratio is much lower than in ICU[121]. This may be more important where roles and responsibilities around an intervention are not clearly defined[122]. Further, behavioural issues associated with recovery from a TBI may impact nutrition management on the ward more than in ICU. During this recovery period the nurse is integral to managing agitation to reduce the impact on providing care[123]. Ward-based nursing practitioners expressed frustration with maintaining NGTs *insitu* and the challenge of re-inserting NGTs removed during periods of patient confusion or agitation. Careful monitoring of this transition phase has been recommended[124], however, while practitioners in this study proposed approaches to maintain NGTs, evidence of effective strategies is scarce. Given the average time taken for TBI patients to be capable of consuming a full oral meal, let alone meet full nutritional needs, is 13 weeks[125], and that consideration of long-term feeding devices should occur when the need for enteral nutrition exceeds four weeks[126], prompt placement of a permanent feeding tube could be indicated for select patients. A concerning finding in this current study was that nutrition may only be prioritised when symptoms of under-nutrition occur, suggesting the need for proactive, rather than reactive, plans for nutrition therapy.

This is the first to provide insights into the views and attitudes of medical and nursing practitioners on nutrition therapy for hospitalised TBI patients and enables a greater understanding of some of the key barriers and facilitators to providing nutrition to this population. The use of one-on-one semi-qualitative interviews provided depth of knowledge, and the use of a case-study to replicate real-life decision-making strengthened the study methodology. This study also included participants across the continuum of care from ICU and the acute ward at two different clinical sites. However, as both participating sites are high performance nutrition units with dedicated ICU nutrition research programs, studies in less academic sites may have different findings. Further, the interviews were conducted by a dietitian which may have influenced participant responses.

This study highlights the challenges associated with providing nutrition therapy to TBI patients, with an emphasis on how nutrition provision and management varies with recovery. Practitioners working with TBI patients across the continuum of care have a key role to play in recovery through nutrition but current attitudes and beliefs drive practice more strongly than evidence-based guidelines. There is a need for education of the multi-disciplinary team and to provide higher quality evidence to guide decision-making and enhance nutrition intervention in order to improve outcomes for this patient group.

Statement of Authorship:

LSC contributed to the conception and design of the research, acquisition, analysis and interpretation of the data, and drafted the manuscript. LTW contributed to the conception and design of the research, and acquisition, analysis and interpretation of the data. MJC, AMD, NS, and AU contributed to the conception and design of the research. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Table 1: Participant characteristics

Patient ID	Profession	Age group (years)	Sex	Clinical experience (years)	Neurotrauma experience (years)
1	ICU nurse	26-35	Female	11-15	≤5
2	Ward nurse	36-45	Female	16-20	16-20
3	ICU nurse	46-55	Female	>25	>25
4	Ward nurse	36-45	Male	11-15	11-15
5	Ward nurse	26-35	Female	6-10	6-10
6	Ward nurse	56-65	Female	16-20	16-20
7	ICU nurse	36-45	Male	16-20	11-15
8	ICU nurse	26-35	Female	6-10	6-10
9	Ward medical	36-45	Male	6-10	11-15
10	Ward medical	36-45	Male	11-15	11-15
11	ICU nurse	26-35	Male	6-10	6-10
12	Ward nurse	46-55	Female	>25	11-15
13	Ward nurse	56-65	Female	>25	21-25
14	ICU nurse	36-45	Female	11-15	11-15
15	ICU medical	46-55	Female	21-25	11-15
16	ICU medical	36-45	Female	11-15	6-10
17	Ward nurse	26-35	Female	≤5	≤5
18	ICU medical	26-35	Male	6-10	≤5
19	Ward nurse	≤25	Female	≤5	≤5
20	Ward nurse	26-35	Male	6-10	6-10
21	Ward medical	46-55	Male	>25	16-20
22	ICU medical	36-45	Male	16-20	11-15
23	Ward medical	56-65	Male	>25	>25
24	Ward nurse	26-35	Male	6-10	6-10
25	ICU medical	36-45	Male	11-15	11-15
26	ICU medical	26-35	Male	6-10	≤5
27	ICU medical	36-45	Male	11-15	≤5
28	ICU medical	36-45	Male	16-20	11-15
29	ICU nurse	36-45	Male	6-10	6-10
30	ICU nurse	26-35	Female	6-10	6-10
31	ICU medical	26-35	Male	6-10	≤5
32	Ward medical	36-45	Male	11-15	6-10

Patient ID	Profession	Age group (years)	Sex	Clinical experience (years)	Neurotrauma experience (years)
33	Ward medical	26-35	Male	6-10	≤5
34	ICU medical	36-45	Male	11-15	6-10

Table 2: Reported barriers and facilitators to nutrition therapy in patients with a traumatic brain injury

Criterion	Facilitators	Barriers
Interruption to nutrition delivery	Feeding protocols: *'good feeding protocols'* (Ward medical #5) -*'a protocol driven on head injury severity and nutritional support and evidence-based medicine would be fantastic. Protocols tend to take the thinking out of it and makes it so much easier'* (Ward medical #6) Symptom management: -*'symptoms such as nausea can be brought up with the medical team and reviewed'* (Ward nurse #4)	Fasting: -*'philosophies regarding fasting are barriers'* (Ward medical #1) -*'a lot of our barriers are that we fast early'* (ICU nurse #6) Delayed surgery: -*'multiple teams involved, multiple surgeries, multiple potential chances to have feeds on and off'* (ICU nurse #3) Surgeries/procedures: *'interruptions for theatre is often an issue in a trauma TBI group'* (ICU medical #1) *'at this stage of injury any surgery that's planned tends to get bumped for other things so he may get into that cycle of fasting'* (ICU medical #2)
Patient behaviour	Minimise distractions -*'low stimulus, dark room, minimal visitors'* (ICU nurse #1) Family support: *'he may be less agitated around his family and so it may be that you can actually get some oral intake into him'* (ICU medical #2) -*'talk to her (mother), educate her and encourage her to persist'* (Ward nurse #2)	Agitation -*'agitation would be a barrier'* (ICU nurse #5) Inability to reason with patient -*'they can be quite difficult to manage and convince that feeding and other things are good for them'* (ICU medical #2) Reluctance to eat -*'patients after a head injury are very fatigued and so don't wake up or are reluctant to eat'* (ICU medical #2)

	-*'sometimes family can...insist on helping, and all it does is distract them'* (Ward nurse #5) -*'I think education of the family can be quite important'* (Ward nurse #9)	
Route of feeding	Restraints -*'you're probably going to be considering the restraints'* (ICU nurse #5)	Tube removal and delays in insertion -*'a barrier to meeting nutrition needs for many patients is actually pulling out their enteral tubes and then…waiting to get a new one reinserted'* (Ward nurse #3) -*'if you had more staff trained in being able to [insert a nasogastric] then instead of relying on one doctor to come and put in a nasogastric you could do it yourself'* (ICU nurse #4) Perceived prioritisation of feeding -*'I think people are less focused on feeds when patients are extubated'* (ICU medical #1)
Practitioner -related issues	Education and staff presence: *'firstly, surgeon education and then just having dietitian support on the ward round'* (Ward medical #1) Practitioner compliance: *'compliance from nursing staff'* (ICU nurse #5) Multidisciplinary team and nutrition care plan -*'I think getting onto the dietitian, and speech, early as well to get the plan, and that we actually try to be vigilant with that plan'* (Ward nurse #6)	Perceived importance -*'if nurses don't think that it's important then they won't do it'* (ICU nurse #8) -*'a big barrier is education, that people don't understand how important it is'* (ICU nurse #4) *'I think a lack of the awareness with nursing staff on how important it actually is'* (Ward nurse #6) *'to make sure that this is an important time, and actually make allowance for it, like physiotherapy'* (Ward nurse #6)

	Nutrition champion: -*'having clinical champions to motivate change would be a way to go…neurosurgeon or senior nurse or respected clinicians'* (Ward medical #3) Nutrition-focused unit: -*'a focus of feeding within the unit'* (Ward medical #5)	Staff time: -*'time for staff is probably the biggest barrier…some patients can take over an hour to have one meal'* (Ward nurse #3) -*'If you've got like eight people that you're looking after and all of them need to be fed, it's just – like, it's ridiculous'* (Ward nurse #8) Communication: -*'lack of communication'* (Ward nurse #4) Staff trial and error: -*'not thinking outside the square to get something done'* (Ward nurse #5) Monitoring: -*'we can't weigh them very easily'* (Ward nurse #10)
Nutrition provision	Improved meal provision: -*'trying to find out what foods the patients actually do enjoy'* (Ward nurse #3) -*'more frequent meals'* (Ward nurse #4) Feeding support: -*'I think that it's perseverance…a nurse needs to go in there, and actually offer him food regularly'* (Ward nurse #6) Prioritising meals: -*'making sure that other procedures aren't scheduled at meal times'* (Ward nurse #7)	Limitations to meal timing and options: -*'I think the kitchen is relatively inflexible'* (Ward nurse #5) -*'I think the barriers on our ward would be the time of meals. They come at handover'* (Ward nurse #7) Nutrition availability: -*'it's amazing the number of times we've gone to the cupboard to get the feed that we need and it's not there'* (ICU nurse #6)

	-*'making sure they're just focusing on eating'* (Ward nurse #8) Alternate feeding regimes: -*'the important thing would be to set a target intake but more – make it more of a 24-hour goal'* (ICU medical #3) -*'volume*-*based feeding rather than per hour based feeding would be a facilitator'* (ICU medical #5) -*'I wonder whether bolus feeds is better than continuous'* (ICU medical #3)	

NGT: Nasogastric tube

Chapter 2:

Methodology and measurement of nutritional intake

Manuscript 4:

Weekend days are not required to accurately measure oral intake in hospitalised patients

Authors:

Lee-anne S. Chapple[a,b], Adam M. Deane[a,b,c], Kylie Lange[b], Amelia J. Kranz[a], Lauren T. Williams[d], Marianne J. Chapman[a,b,c]

[a]Discipline of Acute Care Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia
[b]National Health and Medical Research Council of Australia Centre of Research Excellence in Translating Nutritional Science to Good Health, Level 6, Eleanor Harrald Building, North Terrace, Adelaide, South Australia, Australia
[c]Intensive Care Unit, Level 4, Emergency Services Building, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia
[d]Menzies Health Institute of Queensland, Griffith University, Queensland, Australia

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Corresponding author responsible for study conception and design, acquisition of data, statistical analysis and drafting the manuscript		
Overall percentage (%)	70		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work, statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Ms Kylie Lange		
Contribution to the Paper	Statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Ms Amelia Kranz		
Contribution to the Paper	Acquisition of data and critical revision of the manuscript for important intellectual content		
Signature		Date	13/12/16

Name of Co-Author	Professor Lauren Williams		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Abstract

Background:

Nutrition studies in patients admitted to hospital frequently disregard oral intake because measurement is time-intensive and logistically challenging. In free-living populations, weighed food records (WFR) are the gold-standard and are conducted on weekend and weekdays to capture variations in intake; yet this may not translate during hospitalisation. The present study aimed to determine whether oral intake differs between weekend and weekdays in hospitalised patients.

Methods:

For adult patients initially admitted to the intensive therapy unit with a moderate-severe head injury over a 12-month period, WFR were conducted each week on Tuesday, Thursday and Saturday throughout hospitalisation. Meal components were weighed before and after consumption, and energy and protein intakes calculated with specialised software. Data are reported as the mean (SD). Differences were assessed using paired t-tests and agreement using Bland-Altman.

Results:

Thirty-two patients had WFR collected on 220 days, 68% (n=149) on weekdays and 32% (n=71) on weekends. Overall, daily intakes were 1367 (877) kcal and 62 (40) g protein. There were no differences in intake across all days ($p=0.937$ energy, $p=0.797$ protein) or between weekdays and weekends in weeks one to three of oral intake (all $p>0.1$). Limits of agreement between mean intakes across days were wide for energy (range: -2680 to 2283 kcal) and protein (range: -125 to 110 g).

Conclusions:

Grouped energy and protein intakes from WFR in hospitalised patients are similar on weekdays and weekends, although large intra-patient variations occur.

Future quantification of oral intake during hospitalisation should include as many days as feasible, although not necessarily weekend days, to reflect true intake.

Running title:

Quantifying oral intake in hospitalised patients

Keywords:

Nutrition; oral intake; dietary intake methodology; weighed food record; head injured patients

Introduction:

Studies of nutrition practices in a hospitalised setting frequently disregard oral intake due to the time-intensive nature and logistic challenges associated with obtaining accurate intake measures. This may explain the absence of recommendations on oral intake in critical illness[24,78]. Excluding orally ingested nutrient may lead to considerable underestimation of energy and protein intakes over the entire hospitalisation. Of note inferences from nutrition interventions conducted within the intensive therapy unit (ITU) have not measured oral intake either in ITU or after ITU discharge[127-131]. The lack of detailed information regarding oral intake means that much of the nutritional intake throughout hospitalisation remains an unmeasured confounder, which could lead to incorrect inferences for both observational and interventional studies[132]. Accordingly, a precise but efficient and feasible method to measure oral intake in hospitalised patients is required.

Hitherto, hospital-based nutrition studies have used a range of methods to assess oral intake including recall, measures of waste, and estimates of intake[87,133,134]. These methods contain inherent inaccuracies, which may limit their use in high-quality research[135]. Methods that rely on patient memory are prone to recall bias and exclude patients with acute delirium and following certain presentations, such as head injury, reducing the generalisability of results. Similarly, methods that provide an indirect measure of intake lack precision[135].

Weighed food records (WFR) are considered the gold-standard technique for precise measurement of nutrient intakes in free-living populations[89]. It is recommended these be conducted at least three days per week, comprising two week days and one weekend day, to account for social variations and provide a reliable representation of actual intake[136]. The extent to which this is true in an institutionalised setting, such as a hospital, where variations in intake may differ from free-living individuals, has never been evaluated. If, similar to free-living individuals, intake varies between week days and weekends WFR will need to be conducted on both to accurately quantify intake in hospitalised patients. Such a requirement has considerable cost and feasibility implications for studies of nutritional therapies in critically ill and hospitalised patients, whereas if variations in intake do not occur across different days of the week, the need to conduct WFR on a range of days, or outside of usual work days, may be unnecessary. Finally, a rigorous evaluation of oral intake over time as patients recover from ITU has not been done.

It was therefore hypothesised that, because of fewer fasting periods for procedures and greater periods when family were present to assist with feeding, head-injured patients recovering from critical illness would consume more energy and protein on weekends. The primary aim of this study was to compare energy and protein intakes derived from investigator-led WFR conducted on weekdays and weekends in patients with a head injury. The secondary aim was to determine if energy and protein intakes increased over time as patients recovered from their primary illness.

Materials and Methods:

Adult patients consecutively admitted to ITU with a moderate-severe head injury (Glasgow Coma Scale score 3-12) to the major neuro-trauma referral centre in the state of South Australia over a 12-month period were screened for eligibility. Data on energy and protein consumed orally throughout the hospital stay were collected prospectively and censored at 90 days.

To precisely quantify oral intake WFR were conducted once tube feeding was ceased and on three pre-determined days per week, including two weekdays (Tuesday and Thursday) and one weekend (Saturday), by trained research dietitians. Patients received hospital meals as per usual practices, based on individual meal selection or standard menu choices. Individual meal components (e.g. meat portion, mashed potato, gravy) provided from breakfast to one hour post-dinner were weighed prior to delivery to the patient. Meal components were weighed separately as they were plated on the plating line using Salter Brecknell Model 405 digital scales (Australia) to the nearest 0.1 gram. After consumption individual components of waste were weighed and deducted from the pre-weights to calculate the total proportion consumed in grams. Items provided outside of observation times were estimated using collection of wrappers, nursing notes, and communication with patient, family, and nursing staff.

Recorded weights were entered into FoodWorks 8 Xyris dietary analysis software (Brisbane, Australia) using pre-entered hospital recipes to calculate energy and protein intakes. WFR were excluded if they were partial days (due to hospital discharge or day leave) or if patients also received artificial nutrition simultaneous (e.g. overnight enteral tube feeding). Energy and protein requirements prescribed by the hospital dietitians as part of standard care were recorded.

Ethical Approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the Royal Adelaide Hospital Human Research Ethics committee

(HREC/14/RAH/100). Written informed consent was obtained from all patients or their legal authorised guardian where appropriate.

Statistical Analysis

Data are presented as mean (SD). For weekend versus weekday analyses, mean intake data from the two weekdays per week were combined to be representative of a single weekday and this was compared to the corresponding weekend day for that week. Differences between energy and protein intakes on week versus weekend days were assessed using linear mixed models with a fixed effect for day of week and random effects to account for clustering of multiple days within subjects. Agreement between energy and protein intakes assessed on week versus weekend days were determined using Bland-Altman plots with the bias (mean difference) and limits of agreement calculated at two standard deviations from the derived mean and difference variables. Based on these results, all analyses were repeated for individual days. Poor agreement was defined *a.priori* to be approximately 25% of the patient's requirements[2] (>500 kcal/day and >25 g protein/day) given prior research suggests that weight loss occurs when less than 75% of daily requirements are delivered and therefore this is considered inadequate[133].

Results:

Consent to participate was obtained in 32 patients admitted to the ITU following a moderate-severe head injury and who were subsequently ingesting food orally while hospitalised. Baseline patient characteristics are shown in **Table 1**.

A total of 220 days of WFR were included, 68% (n=149) on a weekday and 32% (n=71) on a weekend. Patients contributed data from a mean of 6.9 (range 1-26) days; 5.0 (range 1-21) weekdays and 2.3 (range 1-7) weekends.

Overall, mean daily oral intake was 1367 (877) kcal/d and 62 (40) g protein/d, with similar amounts consumed on week and weekend days (1368 (894) vs 1364 (845) kcal/d, 61 (41) vs 63 (39) g protein/d). Days with interruptions were similar between groups (49.4% for weekdays and 50.6% for weekends).

There were no differences in energy or protein intakes received on any individual day (p=0.937 energy, p=0.797 protein) or between combined week versus weekend days (p=0.913 energy, p=0.567 protein). There were no differences in energy or protein intakes consumed across days in the first (p=0.665 energy, p=0.433 protein; n=83 WFR), second (p=0.529 energy, p=0.907 protein; n=56 WFR), or third (p=0.426 energy, p=0.110 protein; n=30 WFR) week of oral intake. In patients that remained in hospital for at least two full weeks, mean oral energy and protein intakes increased over time **(Table 2)**.

Bland Altman plots of mean difference in energy and protein intake across individual days are shown in **Figure 1**. There were wide limits of agreement for both energy and protein, but these were consistent across days. There were consistently wide limits of agreement across days and between combined weekdays and weekend days in both week one and week two (**Table 3**).

Discussion:

This is the first study to explore variations in oral intake in hospitalised patients measured on weekdays compared to weekends using the gold standard technique, investigator-led WFR. At the population level (e.g. mean intake for all patients) there were no differences in mean energy or protein intakes between weekday and weekends, or individual days per week. Hence, these results negate the hypothesis of this study, that head-injured patients recovering from critical illness would consume more energy and protein on weekends. This observation is important for future population-based research, such as observations of intake in specific patient groups, as representative intake could be collected on any day of the week.

Only one other study has previously attempted to quantify oral intake in a critically ill population. Peterson and colleagues reported that energy and protein intakes from oral intake were less than 50% of estimated requirements each day, however data were limited to the week following weaning from ventilatory support[87]. Given the lack of data the need to collect precise dietary intake information post-ITU has been identified by several authorities as an important objective[137,138]. Given the scarcity of research that includes the measurement of nutrition consumed orally in both critically ill and head-injured patients the finding that representative intake does not require measurement on weekend days provides an achievable, sufficiently accurate methodology to quantify energy and protein intakes, with positive inferences for funding.

However, on an individual patient-level, there was considerable day-to-day variation in energy and protein intakes, irrespective of the measurement day, and large intra-patient variation across days. Given this, in studies exploring the influence of oral intake in individual hospitalised patients (e.g. interventional or observational studies exploring associations between variables)[139,140], a single day is an imprecise measure of mean intake for that patient. Accordingly, WFR should be collected on as many days as possible to precisely reflect actual intake. This finding also has implications for clinical practice where estimates of oral intake made on a single day will need to be repeated as frequently as possible to improve accuracy. While in free-living populations a small selection of both week and weekend days are required to provide a true reflection of intake, in this patient group large intra-patient variation occurred across all days demonstrating the need to include measurements on as many days as possible. That there was no difference in oral intake between week and weekend days also has implications for staffing a clinical service as this information does not require measurement on the weekend.

In this study there was also an increase in mean energy and protein intakes over time. This requires consideration, both for research and clinical practice. Based on these results a longer duration of measurement is required when evaluating for nuanced relationships between oral intake and recovery[2,141].

While this study was conducted in a specific population, the measurement of energy and protein consumed via the oral route has been described in other patient groups. These studies have all used single day snapshots of oral intake, with data from self-reported intakes[91], visual reports of categorised food waste (e.g. nothing, <1/2, >1/2, all),[134,142] or measures of plate waste but not the portion provided[143]. While these studies have not been able to show changes in intake longitudinally, taken together they are consistent with the concept that patients consuming nutrients orally receive suboptimal nutrition[91,134,143,144], which is associated with adverse outcomes such as increased infection rates and mortality [91,142]. Therefore, assessment of ingested nutritional intake is important, and greater emphasis on accurate measurement of nutrients consumed via this route should take place both in clinical practice and nutrition research.

This study has a number of strengths. It is the first to investigate the variance and agreement between energy and protein intakes quantified using WFR on weekdays versus weekends in an institutional setting. Compared to WFR in free-living populations where the individual completes the measurements, these WFR were conducted by two independent study investigators not open to respondent bias. The main limitation was that two weekdays and one weekend were considered representative of weekly intake, as is common practice in dietary methodology. Additionally, any items consumed overnight were not included in the observation period. However, the latter was consistent for all days. Finally, these data were obtained from a small, defined group of patients admitted to a single-centre and so results may not be generalisable to all healthcare settings and patient groups.

Conclusions:

In hospitalised head-injured patients recovering from critical illness, mean energy and protein intakes were observed to be similar across days but with large intra-patient variations. This suggests that future quantification of oral intake in hospitalised populations, but not individuals, could be performed using investigator-led WFR on any day of the week. This has significant implications for resourcing nutrition research. Studies of individual treatment effects should include as many days as feasible, but not necessarily weekends, to adequately reflect true intake.

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Conflict of Interest and Funding Sources Statement:
The authors declare that they have no competing interests; such as employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/ registrations, grants or other funding.

AMD has received honoraria for participation on Clinical Advisory Board to treat nutritional insufficiency (Medtronic).

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Table 1: Patient demographics, n=32

	Total
Age (y), mean (SD)	44 (16)
Sex (male) n, (%)	28 (88)
Initial GCS:	
GCS 3-8, n (%)	20 (63)
GCS 9-12, n (%)	12 (37)
APACHE II score, median [IQR]	18 [13 - 21]
SOFA score, mean (SD)	6 (3)
Body Mass Index (kg/m^2), mean (SD)	26 (6)
ITU LOS (d), median [IQR]	12 [6 - 17]
Hospital LOS (d), median [IQR]	30 [19 - 50]
Days to commence oral intake, median [IQR]	13 [5 - 25]
Days received oral intake, median [IQR]	15 [9 - 23]

APACHE II: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Outcome Scale, IQR: Interquartile Range, ITU: Intensive Therapy Unit, LOS: Length Of Stay, SOFA: Sequential Organ Failure Assessment

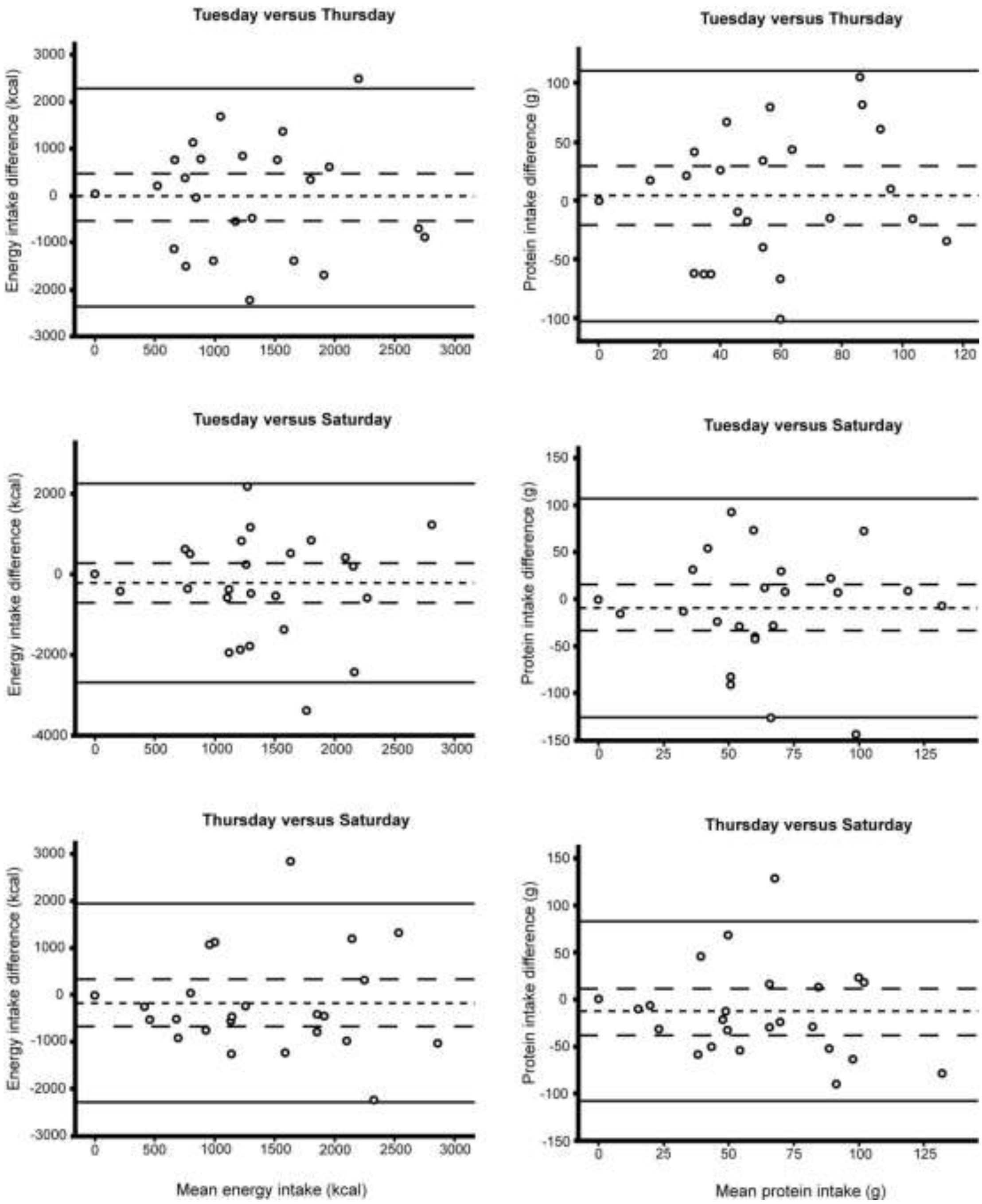
Table 2: Mean (SD) energy and protein intakes per day for week one and week two for patients with complete data, n=15

	Energy (kcal), mean (SD)			**Protein (g), mean (SD)**		
	Week 1	**Week 2**	**p-value**	**Week 1**	**Week 2**	**p-value**
Saturday	1073 (858)	1313 (729)	0.31	52 (44)	64 (36)	0.29
Thursday	935 (907)	1440 (914)	**0.035**	39 (35)	69 (45)	**0.005**
Tuesday	1140 (772)	1600 (945)	0.91	55 (41)	68 (44)	0.39
Mean for all days	1050 (833)	1451 (856)	**0.004**	49 (40)	67 (41)	**0.009**

SD= Standard deviation

Paired-samples t-test for means comparison

Figure 1: Bland Altman plots of difference versus mean of energy and protein intake measured across days



--------	Mean intake
— — –	Clinical agreement (500kcal and 25g protein from the mean)
———	Two standard deviations from the mean (Bland Altman limits of agreement)

Table 3: Mean energy and protein intakes and limits of agreement across days from Bland Altman plots

	Energy (kcal)		**Protein (g)**	
	Mean difference intake	**Limits of agreement (Mean+/-2SD)**	**Mean difference intake**	**Limits of agreement (Mean+/-2SD)**
Week one (n=25)				
Tues vs Thurs	-36	-2355, 2283	4	-103, 110
Thurs vs Sat	-175	-2281, 1931	-13	-108, 83
Tues vs Sat	-211	-2680, 2258	-9	-125, 107
Weekend vs weekday	-153	-2135, 1828	-11	-90, 67
Week two (n=15)				
Tues vs Thurs	161	-958, 1279	-2	-56, 53
Thurs vs Sat	126	-1779, 2031	5	-88, 98
Tues vs Sat	287	-1055, 1629	3	-59, 66
Weekend vs weekday	155	-1398, 1708	-2	-97, 94

SD= Standard deviation

Chapter 3:

Measurement of anthropometric changes over time in ICU survivors

Nutritional status in TBI:

The preceding chapters strongly support the concept that at a population level, and at specific centres, nutrition delivery to patients admitted to the ICU with a TBI is below prescribed targets. While the patients in this cohort were well-nourished on admission to the ICU, energy and protein deficits persisted throughout the hospital admission. However, it is also important to gain an understanding of the longitudinal changes that occur throughout the entire hospitalisation, particularly in regards to nutritional status and body composition.

Few studies have reported on nutritional status or body composition in a cohort of critically ill patients with a TBI. Crenn and colleagues[145] reported longitudinal changes in bodyweight in patients with a TBI on ICU admission, on admission and discharge from rehabilitation, and at least six months after ICU discharge, with weight in ICU reported retrospectively. In this study of 107 patients, mean weight decreased from a mean of 71 (SD: 13.5) kg at ICU admission to 60 (SD: 12.7) kg on admission to rehabilitation, with a mean increase in weight at subsequent time points[145]. While other studies have similarly reported patients with a TBI are malnourished on admission to rehabilitation[40,84] the trajectory of weight changes during hospitalisation is unknown. Further, valid and reliable measures of body composition that enable distinction between muscle and fat components have not been reported in survivors of ICU with a TBI. I conducted a prospective observational study in patients admitted to ICU with a TBI to document changes in body composition that occur over time using a series of techniques.

Manuscript 5:

Longitudinal changes in anthropometry and impact on self-reported physical function following traumatic brain injury

Authors:

Chapple LS[1, 2], Deane AM[1, 2, 3], Williams LT[4], Strickland R[3], Schultz C[5], Lange K[2], Heyland DK[6], Chapman MJ[1, 2, 3]

[1]Discipline of Acute Care Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia

[2]National Health and Medical Research Council of Australia Centre for Clinical Research Excellence in Nutritional Physiology and Outcomes, Adelaide, South Australia, Australia

[3]Intensive Care Unit, Level 4, Emergency Services Building, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia

[4]Menzies Health Institute of Queensland, Griffith University, Queensland, Australia

[5]Department Nuclear Medicine & Bone Densitometry, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[6]Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Corresponding author responsible for study conception and design, acquisition of data, statistical analysis and drafting the manuscript		
Overall percentage (%)	70		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work, statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Professor Lauren Williams		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Dr Richard Strickland		
Contribution to the Paper	Provision of training and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Chris Schultz		
Contribution to the Paper	Data acquisition and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Ms Kylie Lange		
Contribution to the Paper	Statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Professor Daren Heyland		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

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Critical Care and Resuscitation, 19(1), 29-36.

NOTE:
This publication is included on pages 122 - 141 in the print copy of the thesis held in the University of Adelaide Library.

Section One

Conclusions and future directions:

The scoping review (Chapter 1) identified a lack of rigorous data relevant to nutrition support practices in patients with a traumatic brain injury. Specifically, there were few studies that explored the influence of nutritional intake on recovery from a traumatic brain injury and the majority of studies did not report on anthropometric changes in response to nutrition support.

The second manuscript (Chapter 1) provides a detailed assessment of nutritional intake over the entire hospitalisation of a cohort of patients initially admitted to intensive care with a TBI. This study builds on previous literature and, using a precise technique to quantify nutrient delivery consumed orally, establishes that nutrition delivery to these patients is inadequate over the entire hospitalisation. What was somewhat unexpected was the greater protein deficits that occurred early in the ICU admission, which may have arisen because enteral formula delivery at the study centre was adjusted to account for the energy provided from the sedative drug propofol, as this is presented in a lipid formulation containing 1.1 kcal/ml. This protein deficit highlights an important issue that needs to be recognised and studied in further detail. Of perhaps greater significance, this was the first study to describe nutritional intake after ICU discharge, and energy and protein consumed orally. Energy and protein deficits were found to be greater after ICU discharge on the general hospital ward and two-fold greater when nutrients were consumed orally as opposed to delivered via a feeding tube. These novel data highlight potential key time-points for which strategies to reduce nutritional deficits in this patient population could be targeted.

The measurement of energy expenditure and nitrogen balance in the observational study was planned but proved unfeasible in this patient population. Patients recovering from a TBI frequently experienced post-traumatic amnesia, which exacerbated agitation when the indirect calorimetry hood was positioned, preventing safe and accurate measures of energy expenditure. Additionally, these patients were frequently incontinent and, because they had catheters removed on the post-ICU ward, 24-hour urine samples were not able to be collected to determine nitrogen balance. Therefore, a limitation of this study was that estimations for energy and protein requirements were determined using predictive equations. Given the known flaws associated with the use of predictive equations, further research should determine the relationship between nutritional intake and actual energy expenditure, quantified using indirect calorimetry, as well as the influence of energy and protein intake on clinical outcomes. This will be discussed further in section two of this thesis.

One of the challenges of conducting nutrition research in this population is the ability to accurately, yet simply, measure oral intake, particularly in patients with a TBI in which standard methodologies are not feasible. In Chapter 2 I have highlighted the methodological issues of using weighed food records to measure oral intake of hospitalised individuals. Further research is required to develop and validate appropriate methodologies to measure nutritional intake via this route, potentially through embracing new technologies.

Multiple barriers exist to achieving adequate nutrition support in TBI patients. These are both logistical and attitudinal in nature, and many may be preventable. Practitioners need to be made aware of the significant nutritional deficits that occur over the hospital stay after TBI, and perhaps take a more proactive approach in managing the nutritional status of these patients. Development of strategies to reduce cumulative nutritional deficits in these patients is required. This may include reduced fasting times, improved identification of both patients that have transferred from intensive care and long-stay patients, and exploration of early gastrostomy placement or delayed removal of nasogastric feeding tubes until the ability of the patient to maintain a consistent, adequate intake orally has been demonstrated. Whether these data are generalisable for ICU patients with different diagnoses should be explored in order to better target staffing and resources.

TBI patients appear to have marked changes in body composition during hospital admission and these changes in muscle size occurred irrespective of changes in weight. Therefore, clinicians should be aware of the limitations of relying on relatively gross techniques, such as subjective assessments of nutritional status or weight. This study also provides incremental evidence that bedside ultrasonography shows promise as a feasible, non-invasive, and cost-effective methodology to measure changes in muscle thickness, which may be representative of total lean body muscle mass and predict longitudinal physical function. Further development of objective and accurate bedside anthropometric measures, including ultrasonography, should be a priority. As part of this, the ability for ultrasonography to detect changes in muscle size in response to a nutritional intervention, and determination of what is a clinically relevant change in muscle size that will ultimately improve functional outcomes, needs to be determined.

Section Two:

Influence of nutritional intake on outcomes in critical illness and TBI

Section Two

Introduction:

Providing fewer calories or protein than expended results in weight loss and muscle wasting and, eventually, malnutrition. The prevalence of malnutrition in the critically ill patient on ICU admission has been reported to be approximately 50% of patients[174-176]. In critical illness, malnutrition on admission is associated with longer length of hospital stay[174], increased risk of infection, greater duration of ventilatory support, and an increased risk of complications[174]. Compromised nutritional status is further exacerbated over the course of an ICU stay where significant weight loss and increased rates of malnutrition occur[8,12].

As reported in section one of this thesis, despite there being three sets of international guidelines that provide recommendations for feeding of the ICU patient[24-26], there is a paucity of evidence from well conducted RCTs as to the benefit of specific energy and protein prescriptions on clinical outcomes in the critically ill. In a group of patients with a TBI I reported that energy and protein intakes are below prescribed targets (Chapter 1), and that muscle atrophy occurs during the intensive care admission (Chapter 3). Whilst observational studies of nutrition interventions have demonstrated benefits from increased intake[12,177,178], this has not been confirmed with definitive evidence from randomised controlled trials. Section two will focus on the influence that energy and protein provision can have on clinical outcomes, including mortality, and recovery in both a critically ill and head-injured population, and to explore strategies to improve the delivery of nutrition towards prescribed targets. This section will conclude by questioning the appropriateness of current outcome measures utilised in studies of nutrition interventions in these populations and suggesting potential alternative outcome measures.

In the previous section (Chapter 1) I provided a detailed description of current nutrition support practices in a small group of head-injured patients admitted to a single hospital. While this study provides insights into factors that impede nutritional adequacy, and an understanding of key time-points at which to target nutritional interventions, the small sample size precludes exploration of relationships between nutrition support and clinical outcomes. The first manuscript presented in section two is therefore complementary as it provides a global perspective on the influence that nutrition support during the intensive care admission has on clinical outcomes, including mortality, in a critically ill, head-injured population. While observational in nature, this is the largest cohort of TBI patients and nutritional interventions studied, which allowed the assessment of the relationship between nutrition and clinical outcomes.

The second manuscript in section two adds to the literature and understanding about the effect of protein intake on clinical outcomes. As highlighted in section one, there is an inadequate evidence-base to support clear recommendations to guide delivery of protein to critically ill patients. A number of observational studies suggest protein delivery closer to prescribed targets is associated with increased survival[12,96,179,180], shorter time to discharge alive from hospital[96], and more ventilator-free days[12]. However, the observational design of these studies precludes establishment of a causal relationship. Therefore, I conducted a systematic review and meta-analysis of RCTs of nutritional interventions in an ICU population that reported a significant difference in the protein dose received by the different study arms. This innovative meta-analysis design enabled preliminary conclusions to be drawn regarding protein delivery to support future research.

While research needs to continue to define the optimal energy and protein targets for critically ill patients, it is also necessary to work on the development of achievable strategies to meet these targets. Cahill and colleagues provided an international perspective of achievement of best practice relative to evidence-based guidelines and demonstrated that there is a disconnect between recommendations and current practice[181]. Therefore, strategies need to be developed and implemented that can feasibly improve practice and hence nutritional delivery to critically ill patients.

To date, only a few studies have explored interventions to improve energy delivery. In 2010 Heyland and colleagues[93] conducted a prospective cohort feasibility trial on the use of a protocol (PEPuP) incorporating volume-based nutritional goals, early initiation of motility agents and protein supplementation, and a liberalised gastric residual volume threshold to improve nutrient delivery. The adoption of this protocol improved delivery of enteral nutrition however the effect of the higher nutrition intake on clinical outcomes was not explored. In 2012 Soguel and colleagues[182] conducted a three-stage prospective interventional study to measure energy intake during (A) a control period, (B) implementation of a feeding guideline and (C) increased dietetic presence. It was found that the mean energy deficit was significantly lower between periods A and C, however no effect was seen on mortality or hospital length of stay. Further, in 2015 Jarden and colleagues[183] conducted a prospective cohort study to show that introduction of an evidence-based enteral nutrition delivery algorithm improved the volume of enteral nutrition received, however the influence on clinical outcomes was not explored.

In order to improve practice a simple, yet effective, method to deliver more calories to critically ill patients is required. The Augmented versus Routine approach to Giving Energy Trial (TARGET)[92] is a randomised, double-blind, feasibility study that proposes a unique strategy to overcome energy deficits in a critically ill population. The TARGET feasibility RCT was designed to determine whether substitution of a standard enteral formula (1 kcal/ml) with an energy-dense formula (1.5 kcal/ml) could result in greater energy delivery in a blinded fashion. However, it is important not only to determine the influence of an intervention on the ability to enhance nutrient delivery or to improve short-term clinical outcomes, but also the impact on long-term survival and patient-centred post-hospital outcomes such as functional recovery and quality of life. The third manuscript in this section aims to explore this with a longitudinal follow-up of patients recruited into the TARGET feasibility trial.

Up to this time there has been a focus in the critical care nutrition literature on survival. However, with declining mortality rates in ICU, it appears intuitive that it will become increasingly difficult for any intervention to further improve survival in a substantial number of patients. Consequently, as was the case in my study of patients initially enrolled in the TARGET feasibility trial, there is a growing movement to focus less on survival, and more on outcomes likely to be influenced by nutrition support. Wei and colleagues[85] in 2015 conducted a retrospective analysis of prospectively collected data to determine associations between short-term nutritional adequacy and long-term outcomes, including not only survival but also self-reported quality of life using the Short Form-36 questionnaire completed six months after ICU admission. They reported that an energy intake closer to target was associated with improved survival and improved health-related quality of life at six-months. The final manuscript of this thesis proposes an alternate view to the current orthodoxy of using mortality as the primary outcome in nutrition studies of the critically ill.

Chapter 4:

Influence of nutrition intake on mortality and clinical outcomes in intensive care and traumatic brain injury

Manuscript 6:

Nutrition support practices in critically ill head-injured patients: A global perspective

Authors:

Lee-anne S. Chapple[1], Marianne J. Chapman[1, 2], Kylie Lange[3], Adam M. Deane[1, 2], Daren K. Heyland[4]

[1]Discipline of Acute Care Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia 5000

[2]Intensive Care Unit, Level 4, Emergency Services Building, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia 5000

[3]Discipline of Medicine, University of Adelaide, North Terrace, Adelaide, South Australia, Australia 5000

[4]Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Conceptualisation of work, statistical analysis and wrote manuscript		
Overall percentage (%)	70		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Kylie Lange		
Contribution to the Paper	Statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Professor Daren Heyland		
Contribution to the Paper	Conceptualisation of work, provision of data and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Abstract

Introduction: Critical illness following head injury is associated with a hypermetabolic state but there are insufficient epidemiological data describing acute nutrition delivery to this group of patients. Furthermore, there is little information describing relationships between nutrition and clinical outcomes in this population.

Methods: We undertook an analysis of observational data, collected prospectively as part of International Nutrition Surveys 2007-2013, and extracted data obtained from critically ill patients with head trauma. Our objective was to describe global nutrition support practices in the first 12 days of hospital admission after head trauma, and to explore relationships between energy and protein intake and clinical outcomes. Data are presented as mean (SD), median [IQR], or percentages.

Results: Data for 1045 patients from 341 ICUs were analysed. The age of patients was 44.5 (19.7) years, 78% were male, and median ICU length of stay was 13.1 [7.9-21.6] days. Most patients (94%) were enterally fed but received only 58% of estimated energy and 53% of estimated protein requirements. Patients from an ICU with a feeding protocol had greater energy and protein intakes ($p<0.001$, 0.002 respectively) and were more likely to survive (OR 0.65; 95% CI 0.42-0.99; $p=0.043$) than those without. Energy or protein intakes were not associated with mortality. However, a greater energy and protein deficit was associated with longer times until discharge alive from both ICU and hospital (all $p<0.001$).

Conclusion: Nutritional deficits are commonplace in critically ill head-injured patients and these deficits are associated with a delay to discharge alive.

Key words: Nutrition support, nutritional status, head injury, head trauma, traumatic brain injury, critical illness

Introduction:

Head-injured patients frequently have increases in metabolic rate and protein catabolism that could lead to elevated nutritional needs[19,38]. Energy expenditure may increase to 200% of usual values but factors such as delayed gastric emptying, interruptions to feeding due to fasting for medical interventions, and inadvertent removal of feeding tubes hinder the provision of adequate nutrition in these patients[19,23,36,37,42]. This is associated with up to 30% loss of body weight and signs of malnutrition in about two thirds of patients two months after hospital admission[40]. It is plausible that such physical signs are associated with clinical outcomes such as length of hospitalisation[184].

Despite this, there is a paucity of epidemiological data that describe actual nutrition practices for critically ill patients' post-head injury and previous studies have generally included cohorts of relatively small numbers, with the majority of observations being retrospective and/or from single centres. Additionally, while patients may have poor nutritional status after head injury, the associations between nutrition delivery and clinical outcomes have rarely been explored.

Hitherto, the literature on nutrition after head injury focuses on the mode or timing of nutrient delivery, rather than energy or protein delivery[1,73]. Only one study has evaluated for relationships between nutrient intake and clinical outcomes: Hartl and colleagues reported after severe head injury there appeared to be an early survival benefit associated with maximum daily energy intake[64]. However, the relationships between mean energy, or protein, intake and overall survival or morbidity outcomes such as length of stay have not been explored. Hence it is understandable that guidelines on nutritional management of head-injured patients conclude that there are insufficient data to support specific recommendations on macronutrient intake[50,77,78]. Therefore, without evidence to support clinician decision-making it is likely that practice with regards to feeding of head-injured patients will vary greatly between institutions and countries.

A greater understanding of current feeding practices, including the use of feeding protocols, and the influence of nutrition support on recovery would be of benefit, particularly as head-injured patients are likely to stay in hospital for significant periods of time allowing nutrition to influence outcomes. Therefore, we aimed to: (1) describe global nutrition practices after head injury in the first 12 days of ICU admission; (2) evaluate factors that influence nutrition delivery; and (3) explore the relationships between energy and protein intake and clinical outcomes in this cohort.

Methods:

We undertook a post-hoc subgroup analysis of observational data collected prospectively as part of the International Nutrition Survey (INS) from 592 participating ICUs conducted from study years 2007, 2008, 2009, 2010, 2011, and 2013 (no survey took place in 2012). From this combined dataset we extracted data from all patients with a primary diagnosis of head trauma. Critically ill adult (≥18 years of age) patients that were mechanically ventilated within the first 48 hours of admission to the ICU and who remained in ICU for more than 72 hours were eligible. The full methodological details of the INS have been previously reported[12]. In brief, data were collected for the following variables: patient demographics; primary admission diagnosis; nutrition practices including energy and protein provision, estimated nutritional requirements, reasons for interruptions to feeding, and use of feeding protocols; dietetic involvement; and clinical outcomes including mortality, length of mechanical ventilation, and ICU/hospital length of stay. Nutrition data were collected from ICU admission for 12 days or until ICU discharge, with mortality assessed at hospital discharge or censored at day 60. Ethics approval for the INS was obtained from the Research Ethics Committee of the Queens University, Kingston, Ontario, in addition to local ethical approval from each participating site. Informed consent for data collected as part of the INS was waived.

Updates to the survey design that occurred over the six study years restricted the total population for some data variables. The presence of a baseline nutrition assessment and time to initiation of enteral nutrition from admission were collected from 2010 onwards only and the number of interruptions to enteral nutrition and lowest and highest daily blood glucose levels were recorded from 2009 onwards. Glasgow Coma Scale (GCS) and Sequential Organ Failure Assessment (SOFA) score were first collected in 2013.

For the purposes of data collection hypoglycemic events were defined as a blood glucose concentration <3.5 mmol/l. Energy and protein intake data included that provided through enteral and parenteral routes on a daily basis. Administration of lipid as a proportion of propofol was also collected. However, nutrient from dextrose or oral intake was not collected.

Statistical Analysis

Statistical analyses were conducted using SPSS (v.22, IBM Inc). Categorical data are presented as counts and percentages, and continuous data are reported as mean (standard deviation) or median [range or interquartile range (IQR)] as appropriate. Energy and protein deficit was calculated as the mean daily absolute difference between intake and prescribed requirements. No adjustment was conducted for the amount of nutrition received on admission or discharge days shorter than 24 hours as in previous analyses of INS data[12]. Energy and protein intake, deficit, and the percentage of prescribed nutritional requirements that was met were calculated from all sources over all days before permanent progression to exclusive oral intake.

Pearson correlation was used to assess linear relationships between continuous variables. Associations with mortality and nutrition intake were determined via logistic regression and linear mixed effects models, respectively, adjusted for age, sex, region, APACHE II score, body mass index (BMI) category, admission category, and clustering of patients within ICUs. Regions were categorised into Canada, USA, Australia and New Zealand, Europe and South Africa, Latin

America and Asia. Admission category was defined as medical or surgical. Associations with mortality and nutrition intake were also adjusted for evaluable nutrition days. Evaluable nutrition days are defined as any day on which artificial nutrition was received or should have been provided, and excludes days when patients are transitioning to oral intake[185]. Time until discharge alive from ICU/hospital and length of mechanical ventilation were analysed using Cox proportional hazards regression, adjusted for age, sex, region, APACHE II score, BMI category, admission category, and clustering of patients within ICUs, with death in ICU/hospital defined as a competing event in the time until discharge analyses. A sensitivity analysis was conducted on associations between time to discharge alive data and length of mechanical ventilation, and energy and protein deficit to include only those patients that stayed in ICU for a full eight days: this analysis was undertaken in order to account for those patients that had a short stay in ICU and therefore a better outcome, but for whom nutrition support might not be indicated.

Statistical significance was considered as a p value of <0.05.

Results:

Demographics

From 17,689 patients from 592 ICUs for whom data were available, data were extracted for all patients with a primary diagnosis of head trauma (with and without other traumatic injuries). 1045 patients had a diagnosis of head trauma recorded and were included for analysis. These patients were admitted to one of 341 ICUs from 31 countries with each ICU contributing an average of 3.1 (2.4) patients. The majority of patients admitted to ICUs in the United States (30%), Australia (14%), and Canada (12%). Most patients had data collected for the entire 12 study days (60%), with a total of 10,558 study days recorded. Patient demographics are shown in Table 1.

Feeding Protocols

Most patients (863/1045; 83%) were from an ICU where a bedside feeding protocol was used to allow the nurse to advance or withhold enteral feeds. Protocols contained algorithms for: motility agents (n=667, 64%); small bowel feeding (n=506, 48%); withholding nutrition for procedures (n=480, 46%); head of bed elevation (n=698, 67%); and gastric residual volume (GRV) thresholds (n=823, 79%). In those ICUs with a GRV algorithm, the median GRV threshold was 250 [range 50-500] ml and the mode threshold was 200ml (n=331, 40%).

Nutritional Assessment and Prescription

The majority of patients (n=871, 83%) were admitted to an ICU that employed a dietician, of which 40% had at least one full-time dietician. During the years that data relating to baseline nutrition assessments were recorded (2010-2013), 85% (n=443/519) of patients had a baseline nutrition assessment completed. This assessment included documentation of an actual body weight in half (n=260) and height for 46% (n=237) of patients.

A variety of methods were used to estimate energy requirements. The most frequently utilised method was a weight-based approach, for example 25 kcal/kg, which was used in 49% (n=508) of patients. Equations were used in 432 cases (42%), the most popular of these being Harris Benedict and Schofield. Eleven patients (1%) had their energy expenditure estimated through indirect calorimetry.

The mean amount of energy and protein prescribed daily was 1958 (376) kilocalories and 98.7 (26.6) grams respectively, equivalent to 25.9 (4.9) kcal/kg/day and 1.29 (0.3) g/kg/day.

Nutritional Delivery

At some point during the study period the majority of patients (94%, n=983) received enteral nutrition (EN), 13% (n=138) received parenteral nutrition (PN), and 20% (n=207) ingested nutrient orally. Sixteen patients (2%) received no nutrition during the study period. Twenty-four percent (n=239) of patients had EN commenced on day one of ICU admission, 41% (n=404) on day two, and 20% (n=195) on day three. The mean time from ICU admission to initiation of EN was 35.5 (32.7) hours.

Patients often received more than one concentration of EN formula; however, a 1 kcal/ml formula was the most common and delivered for 53% of all EN prescriptions. Twenty-five percent of prescriptions were of a concentrated enteral formula that provided 1.5 kcal/ml or greater.

One-hundred and twenty-two (12%) patients received glutamine during their ICU admission with a mean daily dose of 22 (11) grams. Glutamine was usually delivered via the enteral route (66% of cases).

Of those patients receiving EN the location of the feeding tube was reported for 926 (94%) patients. Gastric feeding was the most common route of EN, and used exclusively in 67% (n=620) of patients; 11% (n=101) of patients were exclusively fed via post-pyloric tubes, and 22% (n=205) received EN through a combination of gastric and post-pyloric routes. Gastrokinetic drugs were frequently prescribed; 70% (n=713) of patients received a gastrokinetic drug at some stage. The prevalence of gastrokinetic drug use varied according to day of admission, with 29% (n=185) of patients receiving gastrokinetics on day one, 50% (n=415) on day two, and a peak of 61% (n=556) by day five. Even at nutritional data censor (i.e. day 12) 56% (n=320) of patients were receiving gastrokinetics. Metoclopramide was the most commonly prescribed gastrokinetic drug and administered to 38% (n=400) of patients.

<u>Interruptions</u>

Of the patients who received EN, 66% (n=644) had interruptions to feeds at least once during the study period. Thirty percent (n=191) had interruptions to feeding on just one day, 21% (n=133) had interruptions on two days, 16% (n=103) had interruptions on three days, and 34% (n=217) had four or more days where feeding was interrupted. There were various reasons for interruptions to enteral feeds (Figure 1). From 2009 to 2013, the number of hours of interruptions to EN were collected, with a mean duration of 25.3 [range 0.2-120] hours per patient, equivalent to 2.6 [range 0.1-18.8] hours per day.

Energy and Protein Intake and Deficit

Energy and protein were received from various sources (Figure 2). Over half of the patients received propofol (59%, n=618), which provided a mean of 161 (165) kilocalories of additional energy per day. The mean amount of energy received from EN was 974 (524) kcal/day, and 86 (269) kcal/day from PN. The mean delivery of energy and protein to patients from all sources was 1154 (525) kcal/day and 52 (26) g/day, respectively; equivalent to 15.3 (7.2) kcal/kg/day and 0.69 (0.4) g/kg/day. The daily mean energy and protein deficit was 803 (527) kilocalories and 46 (30) grams, respectively. Nutrition from all sources met an average of 58 [range 0-166] % of estimated energy requirements and 53 [range 0-390] % of protein requirements. Daily intake data is shown in Figure 3.

Glucose Control

Eighty-nine percent (n=926) of patients were from an ICU that contained a protocol to monitor blood glucose and administer insulin. In those protocols that contained a blood glucose target, the median lower blood glucose target was 4.5 [range 3.0-8.3] mmol/l and the upper blood glucose target was 8.3 [range 5.3-15.0] mmol/l. For 700 patients from 2009-2013 the mean highest blood glucose recorded in the first 24 hours of ICU admission was 9.8 (3.3) mmol/l and the lowest 6.5 (1.9) mmol/l. The mean morning blood glucose during the study period was 7.5 (1.3) mmol/l. An episode of hypoglycemia occurred in 9% (n=90) of patients. Insulin was provided in 59% of cases (n=611), of which the average daily insulin dose provided was 36.5 (36.2) units.

Outcomes

Of the 1045 patients, 135 (13%) died in ICU, 38 (4%) died after ICU discharge in hospital, and 872 (83%) survived to hospital discharge or were alive in hospital at day 60. Male patients were more likely to survive a head trauma than females (OR 0.66; 95% CI 0.46, 0.96; p=0.026). The median ICU length of stay in survivors was 13.1 [IQR: 7.9-21.6] days, and the median hospital length of stay was 29.7 [IQR: 17.9-57.1] days. The median time patients required mechanical ventilation was 9.2 [IQR: 4.8-15.4] days.

Patients from an ICU that utilised a feeding protocol had greater energy and protein intakes per body weight than those without (p<0.001, 0.002 respectively) and were more likely to survive (OR 0.65; 95% CI 0.42, 0.99; p=0.043; Table 3). When the feeding protocol contained guidance on motility agents and small bowel feeding there was a smaller energy and protein deficit (Table 2). Patients from an ICU with a feeding protocol that contained details on GRVs had less protein deficit, but no difference in energy delivery.

Earlier initiation of EN was significantly associated with a reduction in energy and protein deficit (r=0.32 and 0.27 respectively, p<0.001). While the point estimate indicated reduced mortality when EN was commenced on day 1 when compared to days 2-4 or day 5 or later, this was not significant (Table 3). Greater duration of EN interruptions increased both energy and protein deficit (r=0.219 and 0.218 respectively, p<0.001). Energy and protein deficits were reduced when EN and PN were used in combination, compared with EN alone (p=0.023 and <0.001 respectively, Table 3).

There was a non-significant association between at least one recorded episode of hypoglycaemia and higher risk of mortality (OR=1.6; 95% CI: 0.96, 2.7; p=0.073). Any hypoglycaemic event was associated with a reduced probability of being discharged alive from ICU (HR=0.78; 95% CI 0.60, 0.99; p=0.043) and hospital: (HR=0.78; 95% CI: 0.58, 1.03; p=0.082).

A greater energy and protein deficit (OR per 100kcal/day) was associated with longer times until discharge alive from ICU (energy: p<0.001, protein: p=0.001) and hospital (energy: p=0.002, protein: p=0.024) (Table 4). A greater energy and protein deficit was also associated with longer time receiving mechanical ventilation (OR per 100kcal/day, p<0.001; Table 4). However, when a sensitivity analysis was performed to include only those patients that stayed in ICU for a full eight days a statistically significant relationship only remained for energy deficit on time to discharge alive from hospital and length of mechanical ventilation (p=0.001 n=816, and p=0.004 n=732 respectively; Table 4). In an unadjusted analysis there was a significant protective effect of energy (per 10kcal/kg/day), but not protein, delivery on mortality (energy: OR 0.79; 95% CI 0.63, 0.998; p=0.048). However, in the adjusted analysis both energy and protein delivery did not affect mortality (energy: OR 0.76; 95% CI 0.48, 1.22; p=0.256, protein: OR 1.01; 95% CI 0.92, 1.118; p=0.868) (Table 5).

Discussion:

The purpose of our study was to describe international nutrition support practices and factors that influence nutrient delivery, and evaluate relationships between nutrient delivery and clinical outcomes in critically ill head-injured patients. Our dataset of >10,000 patient days from 1045 patients provided a unique opportunity to evaluate these variables.

The most significant finding was the observation that head-injured patients were significantly underfed; receiving just 58% of their estimated energy and 53% of their estimated protein requirements. These data are consistent with studies in cohorts of mixed medical-surgical ICU patients[13,14,186], but are less than in other cohorts of patients that are considered to be hypermetabolic; trauma, neurosurgical and burns patients have been reported to meet between 67 and 76% of their nutritional requirements[21,22,187]. This observation is of interest given that gastrointestinal dysmotility and delayed gastric emptying occurs frequently in all these conditions[27]. It may be that in other hypermetabolic conditions, such as burns, the provision of nutritional support is of greater priority and is a focus of treatment. Additionally, many of the barriers associated with feeding after head injury, such as inadvertent removal of feeding tubes, may be more prevalent after the time when the patient is no longer sedated, and hence adequacy of nutrition over the longer term, after ICU discharge, may be more important[169]. Additionally, ICU admission and discharge days were counted as complete days and therefore achievement of 100% of nutritional requirements on these days is unlikely to be desirable.

Greater energy and protein deficits were significantly associated with longer times to discharge alive from ICU and hospital. However, when we undertook a sensitivity analysis to include only those patients with an ICU stay of ≥ eight days, only energy deficit was associated with a delayed time to discharge alive from hospital and length of mechanical ventilation. A recent meta-analysis on the delivery of enteral nutrition to critically ill patients reported no significant interaction between energy and protein intake on ICU or hospital length of stay[188]. However, interpretation of the latter study is limited as group data does not enable investigators to analyse death and length of stay as dependent variables. A strength of our study is that competing variables (death in ICU and ICU length of stay) were adjusted for appropriately[189]. We hypothesised that nutritional therapy could be of particular benefit to patients with head injury as the injury itself generally results in longer length of stay when compared to critically ill counterparts, which means that energy and protein intake may have a greater capacity to influence clinical outcomes. Correspondingly, research specific to head injury has shown that nutritional interventions, such as early when compared to delayed nutrition support, can reduce hospital and ICU length of stay[61,63,65]. Greater energy deficit, even after sensitivity analysis, was also associated with a longer time requiring mechanical ventilation. Whether these relationships are true, or are a result of underlying unadjusted factors such as severity of injury, requires further investigation.

When adjusted for evaluable nutrition days and clinical characteristics we did not observe relationships between energy and protein intakes and mortality. Our findings are contradictory to analyses by Hartl and colleagues who reported in

797 severely head-injured patients improved survival between seven and 14 days of admission with each 10 kcal/kg body weight/day increase in the maximum amount of energy received in the first five to seven days of ICU admission[64]. We believe variations between inclusion criteria and statistical analyses may account for the different results from our study. Severity of head injury, which may increase energy expenditure and be independently associated with outcome[190], was not collected in earlier INSs and hence not adjusted for in our analysis; whereas Hartl and colleagues adjusted for potentially important factors such as hypotension, pupil status, and CT scan findings, that were not collected as part of the INS. However Hartl and colleagues did not account for other confounders such as evaluable nutrition days or BMI, the study was conducted in a single region, and only reported deaths between day seven and day 14 – and the latter factor has the capacity to bias the results. The reasons for these contradictory results require further exploration. Nonetheless, because our analyses are based on those deemed to be the most appropriate at present[185], we believe it adds incrementally to the body of evidence on nutrition support for head-injured patients.

We recognise however that optimal energy and protein targets after head injury are unknown. The extent of hypermetabolism and catabolism are dependent on ventilation status, sedation, severity of head injury, and posturing, which makes it challenging to accurately estimate energy expenditure and protein needs for an individual patient[50]. Particularly after head injury, generalised predictive equations, as were used for the majority of patients in this dataset, have been shown to be somewhat inaccurate in determining nutritional needs when compared to more direct yet invasive methodology such as indirect calorimetry and nitrogen balance studies[106]. Additionally, these predictive equations and a weight-based approach incorporate patient’s body weight, yet obtaining a weight can be challenging and inaccurate in the intensive care setting; a weight was only documented in half of those patients with a nutritional assessment. While these equations are imprecise, and there are no definitive recommendations for energy and protein requirements, energy and protein delivery to meet predicted needs of

100-140% resting energy expenditure and 2-2.5 g protein/kg/day are suggested[50,191]. The energy and protein intakes we observed - 15.3 (7.2) kcal/kg/day and 0.69 (0.4) g/kg/day - are substantially less than these suggestions. Furthermore, because only 2% of patients received >1.5 g protein/kg/day, and no patient received more than 2 g/kg/day, we cannot exclude the possibility that a greater protein intake is associated with benefit (or harm) to attenuate the catabolic response and hence influence survival. An analysis from the same international dataset including all medical-surgical ICU patients reported that achieving ≥80% of prescribed protein intake was associated with reduced mortality[96]. Hence, further research with higher energy and protein intakes are required. Similarly, the interplay between energy and protein intakes could be important but we were not able to adequately assess these interactions with this dataset.

We did observe substantial energy and protein deficits, even early after head injury. A number of clinical barriers hinder adequate feeding, so strategies that assist to improve nutritional deficits in this population may be of importance. As reported previously and reiterated in this analysis, ICUs with a feeding protocol in place are able to significantly improve energy and protein delivery and should be commonplace[93,114]. We observed that patients from an ICU where the feeding protocol contained the use of gastric residual volumes had lower protein intakes. It is plausible that these ICUs also have differences in other practices, such as greater use of concentrated formulas, or higher propofol intakes that may have accounted for this relative lower protein intake in comparison to caloric intake. It is also plausible that this is a spurious finding that requires investigation through well-designed randomised trials. In our study, patients from ICUs where the feeding protocol contained guidance on motility agents had higher energy intakes. It is well documented that gastric dysmotility occurs frequently after head injury[42,45]; 70% of patients in this study received gastrokinetic agents, suggesting that the majority of patients experienced enteral feed intolerance or clinicians were sufficiently concerned to prescribe these drugs. In addition to the use of gastrokinetic drugs another strategy that has been shown to increase nutrition delivery is the use of a concentrated enteral formula[92,192]. In our cohort, only 20% of patients received a 1.5 kcal/ml enteral formula, and only 5% received a 2 kcal/ml formula at any time-point. While energy dense feeds ≥2 kcal/ml may have the capacity to slow gastric emptying and worsen feed intolerance[193], the utilisation of a concentrated enteral formula to improve energy intakes after head injury should be investigated. However, we also observed that use energy-dense formulas were associated with a greater protein deficit, likely due to the addition of fat to these formulas rather than protein to increase the calorie content and this requires consideration by clinicians when prescribing particular feeds. Additionally, protocols, such as the PEP uP protocol, that have been shown to improve energy and protein delivery in a critically ill population, could be utilised[93].

Current guidelines recommend early initiation of nutritional therapy, with achievement of goal requirements by day seven[50]. However, in our study nutritional intake remained suboptimal by day seven, and longer time to initiation of feeds was associated with greater energy and protein deficits. Additionally, multiple interruptions to enteral nutrition occurred which reduced intake[13]. Nutrition delivery was primarily interrupted due to fasting for procedures and intubation/extubation of trachea. While these interruptions may be largely unavoidable, exploration and minimisation of fasting times could be considered[21]. Additionally, the presence of a dietitian had conflicting results on energy and protein delivery, with the time spent in the ICU influencing nutrient intake. These results need to be cautiously interpreted, as there are several confounding variables that were not measured. Previous studies have suggested that a full-time dietitian is required to improve energy delivery[182]. Men were more likely to survive than women. This outcome has been reported in other traumatic conditions, and the mechanism/s behind this result requires further exploration[187].

A strength of our study is that it is the largest prospective observational study to evaluate nutrient delivery in critically ill head-injured patients from an international perspective. A multi-centre study enables greater generalisability of data, and larger numbers of patients minimises the effect of between-patient variation. Previous studies have been conducted retrospectively, in single-centres, or included small patient numbers. However, in our study patients were significantly underfed compared to prescribed requirements, and few patients met their estimated nutritional needs over the 12-day period, so it may be difficult to fully assess the influence of 'adequate' energy and protein intakes on outcomes. This is particularly true for protein, as in our study the greatest intake was 1.83 g/kg/day, which is less than the current recommendations of 2-2.5 g/kg/day[50,191]. Another limitation of our study is that we did not have access to data describing the severity of the head injury and presence of other injuries. These parameters have the capacity to alter metabolic demands and may influence outcomes. Unfortunately, these details were not collected in this prospective survey. In addition, the sample size we studied may have been insufficient to detect any mortality difference. Given most ICUs contributed just three patients to this dataset recommendations for individual site level processes cannot be deduced. Additionally, all ICUs participated in the INS on a voluntary basis which may have attracted those ICUs with an interest in nutrition and hence influence the generalisability of the results. Lastly, nutrition may be able to influence other important outcomes, such as repeat hospitalisation, functional status, and quality of life, which were not explored in this dataset. Therefore, future studies should consider the influence of nutrition over the longer-term on morbidity outcomes in addition to mortality to enable a greater understanding of the role nutrition plays in recovery from a head injury.

Conclusions:

We observed that delivery of energy and protein to critically ill head-injured patients is considerably less than recommended. Greater energy and protein deficits were associated with delays to discharge alive from ICU and hospital. However, we did not observe a relationship between these deficits and increased mortality. Further research into the optimal dose of energy and protein to enhance the long-term recovery of patients after head injury is warranted. In the meantime, our study suggests that efforts to increase nutritional intake and prevent energy and protein debt in these patients appear justified.

Key Messages:

- This is the largest international study on energy and protein delivery in critically ill head-injured patients
- Patients were significantly underfed receiving just 58% estimated energy and 53% protein requirements
- Greater energy and protein deficits were associated with a delay to discharge alive from ICU and hospital
- Efforts to increase intake to prevent energy and protein debt such as feeding protocols and minimisation of interruptions should be considered
- Future research should explore the effect of 'adequate' energy and protein intakes, including longer-term delivery, on morbidity outcomes in addition to mortality

Abbreviations:

APACHE II: Acute Physiology and Chronic Health Evaluation II
BMI: Body Mass Index
EN: Enteral Nutrition
GCS: Glasgow Coma Scale
GRV: Gastric Residual Volume
HR: Hazards Ratio
ICU: Intensive Care Unit
IQR: Inter Quartile Range
INS: International Nutrition Survey
OR: Odds Ratio
PN: Parenteral Nutrition
SD: Standard Deviation
SOFA: Sequential Organ Failure Assessment

Competing Interests:

DKH has received honorarium and research grant money from Nestle, Abbott Nutritional Inc, GlaxoSmithKline, and Baxter. AMD and MJC have received unrestricted grants from GSK and Theravance for investigator led studies and have also received research support in kind from Fresenius Kabi. The authors declare that while the results of this analysis may support the use of particular strategies to improve nutrition support practices, they do not promote specific products or drugs.

Authors' Contributions:

LSC was responsible for study design, data analysis, statistical analysis, interpretation and drafting the manuscript. She is guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the accuracy of the data analysis.

MJC and AMD contributed to the study design, data analysis, and critical revision of the manuscript for important intellectual content.

KL was responsible for analysis and interpretation of the data, contributed to the study design, and critical revision of the manuscript for important intellectual content.

DKH was responsible for study design, coordination of data acquisition, interpretation of the data, and critical revision of the manuscript for important intellectual content.

All authors read and approved the final manuscript.

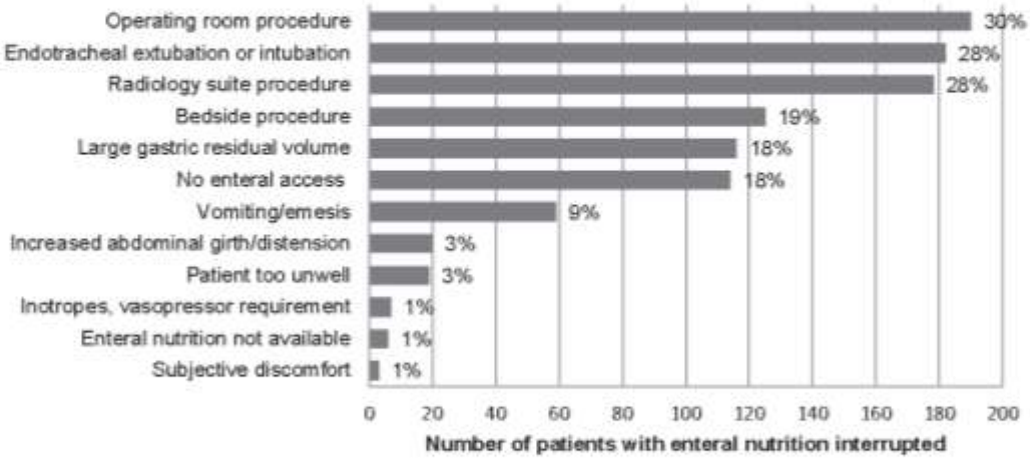
Table 1: Patient Demographics

	Total	**Patient sample**
Age (y), mean (SD)	44.5 (19.7)	1045
Sex (male) n, (%)	815 (78)	1045
Initial GCS:		251
GCS 13-15, n (%)	18 (7)	
GCS 10-12, n (%)	23 (9)	
GCS 6-9, n (%)	96 (38)	
GCS <6, n (%)	114 (45)	
APACHE II, mean (SD)	19.5 (6.9)	1038
SOFA score, mean (SD)	7.6 (3.1)	257
Weight (kg), mean (SD)	77.4 (17.3)	1045
Height (m), mean (SD)	1.73 (0.09)	1040
Body Mass Index (kg/m^2), mean (SD)	25.7 (5.2)	1040
Underweight (<18.5kg/m^2), n (%)	30 (3)	
Healthy (18.5-24.9 kg/m^2), n (%)	519 (50)	
Overweight (25-29.9 kg/m^2), n (%)	348 (34)	
Obese (>30 kg/m^2), n (%)	143 (14)	

GCS: Glasgow Coma Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment

GCS and SOFA data was collected in 2013 only

Figure 1: Reasons for interruptions to enteral nutrition support (n=644)



Patients could be assigned to more than one reason for enteral nutrition interruptions

Figure 2: Mean daily energy and protein contribution from enteral and parenteral nutrition and propofol

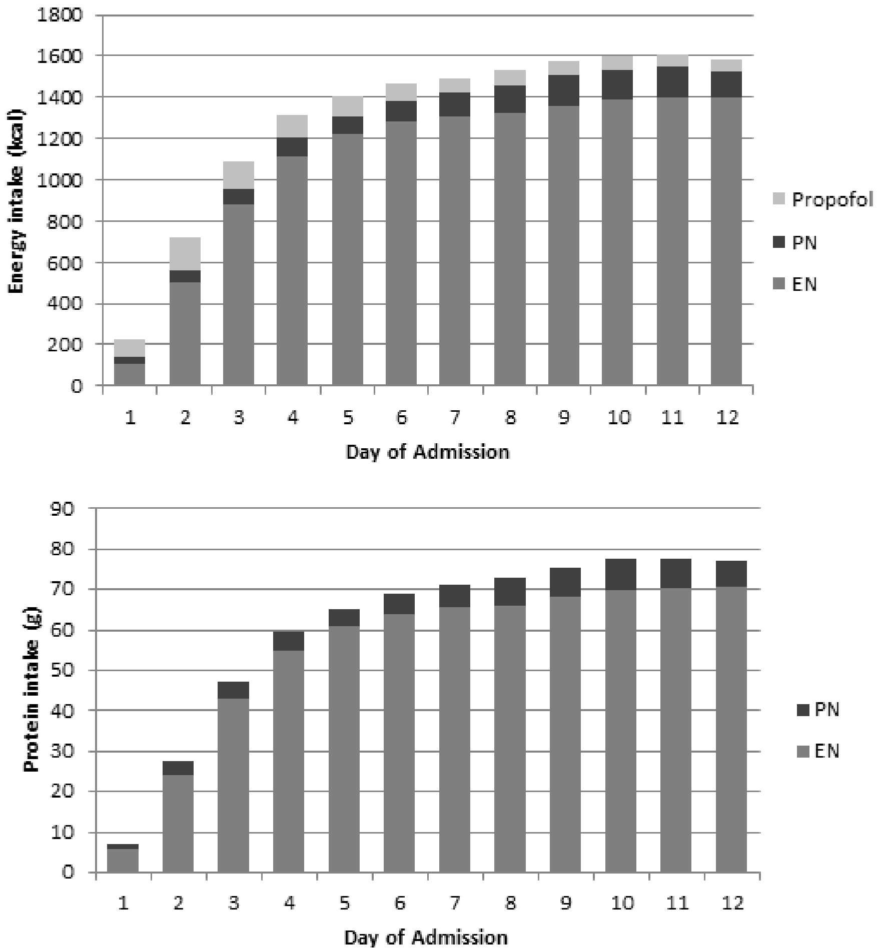
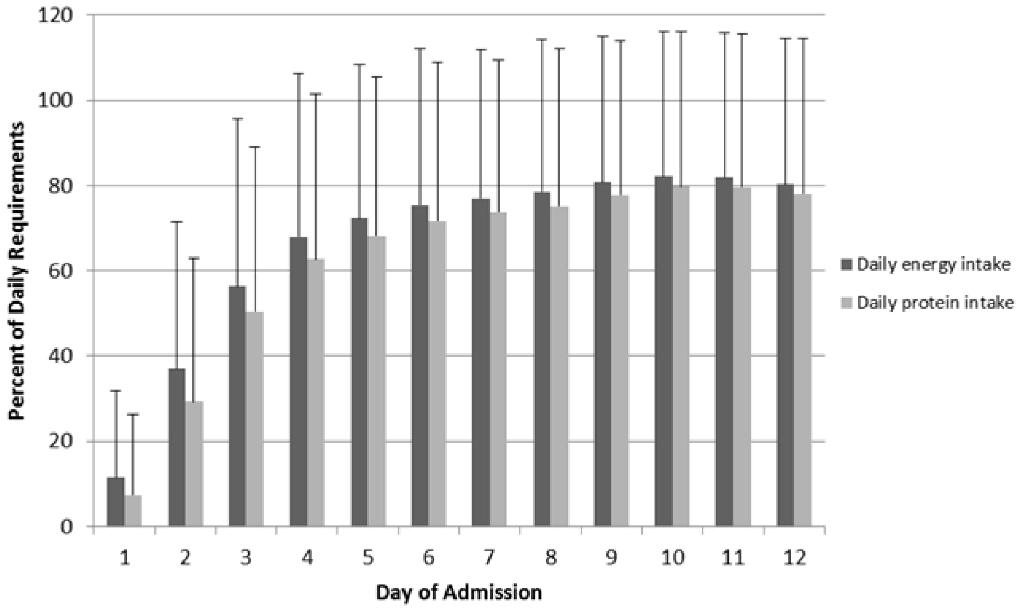


Figure 3: Mean daily energy and protein intake as a percent of requirements per study day



Energy data n=	1039	1029	1020	990	932	885	816	757	687	642	600	556
Protein data n=	1038	1028	1019	987	931	883	814	757	687	642	601	556

Table 2: Relationship between ICU and patient nutritional variables and energy and protein deficit

		Energy deficit (kcal/d)			Protein deficit (g/d)		
		Mean	**Standard deviation**	***p***	**Mean**	**Standard deviation**	***p***
Bedside feeding protocol	Yes	788	528	0.223	45.2	30.2	0.129
	No	877	518		52.0	30.0	
Bedside feeding protocol includes gastric residual volumes	Yes	783	532	0.094	44.7	30.0	**0.038**
	No	878	505		52.6	30.4	
Bedside feeding protocol includes motility agents	Yes	732	507	**<.001**	42.1	29.3	**<.001**
	No	930	539		54.1	30.5	
Bedside feeding protocol includes small bowel feeding	Yes	720	507	**<.001**	41.0	29.0	**0.001**
	No	883	535		51.6	30.5	
Bedside feeding protocol includes withholding for procedures	Yes	755	543	0.076	42.1	29.9	**0.008**
	No	844	511		50.1	30.1	
Bedside feeding protocol includes head of bed elevation	Yes	791	529	0.547	46.1	31.5	0.969
	No	827	524		47.1	27.6	
Dietician working in the ICU	None	658	524	**0.027***	29.9	26.1	**<.001**^
	< 1 FTE	844	539		48.6	29.5	
	≥ 1 FTE	820	505		51.3	30.6	
Timing of initiation of EN	By day 1	512	431	**<.001**$^{\#}$	31.3	23.6	**<.001**$^{\#}$
	Day 2-4	811	465		47.8	29.0	
	After day 4	1167	551		62.5	31.3	
Nutritional support route	EN only	734	468	**0.023**$^{+}$	44.4	28.2	**<.001**$^{+}$
	PN only	624	215		26.7	25.6	
	EN+PN	602	524		31.6	30.3	
Formula density (patients with >75% of days at one density)	≤1 kcal/ml	728	453	**0.011**$^{\pi}$	41.9	27.7	**0.006**$^{\pi}$
	>1 - <2 kcal/ml	816	540		48.7	30.6	
	≥2 kcal/ml	586	491		47.0	34.9	

** 'None' significantly different from '<1 FTE'*

^ 'None' significantly different from both '<1 FTE' and '1 or more FTE'

$^{\#}$*All groups significantly different to all others*

$^{+}$*'EN+PN' significantly different from 'EN only'*

$^{\pi}$*≤1 kcal/ml' significantly different from '>1-<2 kcal/ml'*

Table 3: Relationship between unadjusted ICU and patient nutritional variables and mortality

		Survivors		Non-survivors		OR	95% CI	p
		n	**%**	**n**	**%**			
Sex	Male	691	84.8	124	15.2	0.66	0.46, 0.96	**0.029**
	Female	181	78.7	49	21.3	ref	-	
EN interrupted	Yes	548	85.1	96	14.9	0.89	0.62, 1.27	0.506
	No	283	83.5	56	16.5	ref	-	
Bedside feeding protocol	Yes	730	84.6	133	15.4	0.65	0.42, 0.99	**0.043**
	No	142	78.0	40	22.0	ref	-	
Bedside feeding protocol includes gastric residual volumes	Yes	699	84.9	124	15.1	0.63	0.43, 0.92	**0.016**
	No	173	77.9	49	22.1	ref	-	
Bedside feeding protocol includes motility agents	Yes	562	84.3	105	15.7	0.85	0.60, 1.20	0.360
	No	442	82.0	97	18.0	ref	-	
Bedside feeding protocol includes small bowel feeding	Yes	430	85.0	76	15.0	0.81	0.58, 1.12	0.201
	No	442	82.0	97	18.0	ref	-	
Bedside feeding protocol includes withholding for procedures	Yes	399	83.1	81	16.9	1.04	0.75, 1.46	0.800
	No	473	83.7	92	16.3	ref	-	
Bedside feeding protocol includes head of bed elevation	Yes	586	84.0	112	16.0	0.90	0.63, 1.27	0.540
	No	286	82.4	61	17.6	ref	-	
Dietitian working in the ICU	None	139	79.9	35	20.1	ref	-	-
	< 1 FTE	427	86.1	69	13.9	0.64	0.41, 0.99	**0.047**
	≥ 1 FTE	302	81.4	69	18.6	0.91	0.58, 1.41	0.667
Formula density (patients with >75% of days at one density)	≤1 kcal/ml	391	85.2	68	14.8	ref	-	-
	>1 - <2 kcal/ml	275	83.6	54	16.4	1.13	0.77, 1.67	0.541
	≥2 kcal/ml	16	69.6	7	30.4	2.52	0.998, 6.34	0.051
Timing of initiation of EN	Day 1 or prior to ICU adm	210	87.9	29	12.1	ref	-	-
	Day 2-4	569	83.7	111	16.3	1.41	0.91, 2.19	0.122
	Day 5 or later	52	81.3	12	18.8	1.67	0.80, 2.50	0.173

FTE: Full time equivalent

Table 4: Relationship between energy and protein deficit and length of mechanical ventilation and time to discharge alive

Variable		Time until discharged alive from ICU (days)		Time until discharged alive from hospital (days)		Length of mechanical ventilation (days)	
		Hazard ratio (95% CI)	***p***	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
All patients		n=1027 energy, 1026 protein		n=1027 energy, 1026 protein		n=896	
	Energy deficit (kcal/day) OR is per 100 kcal/day	1.04 (1.02, 1.05)	<0.001	1.03 (1.01, 1.04)	0.002	1.07 (1.05, 1.08)	<0.001
	Protein deficit (g/day) OR is per 5 g/day	1.02 (1.01, 1.04)	0.001	1.02 (1.002, 1.03)	0.024	1.05 (1.03, 1.06)	<0.001
Patients that stayed at least 8 days		n=816		n=816		n=732	
	Energy deficit (kcal/day) OR is per 100 kcal/day	1.01 (0.99, 1.02)	0.948	1.02 (1.01, 1.04)	0.001	1.02 (1.01, 1.04)	0.004
	Protein deficit (g/day) OR is per 5 g/day	0.99 (0.98, 1.01)	0.275	1.01 (0.99, 1.03)	0.316	1.01 (0.996, 1.03)	0.161

Adjusted for age, sex, region, APACHE II score, BMI category, admission category, and clustering of patients within ICUs

Manuscript 7:

Protein delivery and clinical outcomes in the critically ill: A systematic review and meta-analysis

Authors:

Michael L Davies[1], **Lee-anne S Chapple[2]**, Marianne J Chapman[1,2], John L Moran[2,3], Sandra L Peake[2,3]

[1]Critical Care Services, Royal Adelaide Hospital, Adelaide, SA, Australia
[2]Discipline of Acute Care Medicine, University of Adelaide, Adelaide, SA, Australia
[3]Department of Intensive Care Medicine, Queen Elizabeth Hospital, Adelaide, SA, Australia

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Acquisition of data and critical revision of the manuscript for important intellectual content		
Overall percentage (%)	35		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Michael Davies		
Contribution to the Paper	Conceptualisation of work, acquisition of data, statistical analysis and wrote the manuscript		
Signature		Date	8/12/16

Name of Co-Author	Professor Sandra Peake		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Associate Professor John Moran		
Contribution to the Paper	Conceptualisation of work, statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	15/12/16

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

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Manuscript 8:

The effect of augmenting early nutritional energy delivery on quality of life and employment status one year after ICU admission

Authors:

Reid DB[1], **Chapple LS**[2], O'Connor SN[1,2], Bellomo R[3], Buhr H[4], Chapman MJ[1,2], Davies AR[5], Eastwood GM[3], Ferrie S[4], Lange K[9], McIntyre J[6], Needham DM[7], Peake SL[2,6], Rai S[8], Ridley EJ[5], Rodgers H[8], and Deane AM[1,2]

[1]Department of Intensive Care Medicine, Royal Adelaide Hospital, Adelaide, Australia

[2]Discipline of Acute Care Medicine, University of Adelaide, Adelaide Australia

[3]Department of Intensive Care, Austin Hospital, Melbourne, Australia

[4]Intensive Care Service, Royal Prince Alfred Hospital, Missenden Road, Camperdown, Australia

[5]Department of Epidemiology and Preventative Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia

[6]Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, Australia

[7]Outcomes After Critical Illness and Surgery Group John Hopkins University, Baltimore, USA

[8]The Canberra Hospital, Canberra, Australia

[9]Discipline of Medicine, University of Adelaide, Adelaide, Australia

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Acquisition of data, statistical analysis and drafting of the manuscript		
Overall percentage (%)	30		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr David Reid		
Contribution to the Paper	Corresponding author, acquisition of data, statistical analysis and wrote the manuscript		
Signature		Date	5/12/16

Name of Co-Author	Ms Stephanie O'Connor		
Contribution to the Paper	Conceptualisation of work, acquisition of data and critical revision of the manuscript for important intellectual content		
Signature		Date	13/12/16

Name of Co-Author	Professor Ricardo Bellomo		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Heidi Buhr		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Professor Marianne Chapman		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Associate Professor Andrew Davies		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	16/12/16

Name of Co-Author	Glenn Eastwood		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Susie Ferrie		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	14/12/16

Name of Co-Author	Kylie Lange		
Contribution to the Paper	Statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	5/12/16

Name of Co-Author	Joanne McIntyre		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	14/12/16

Name of Co-Author	Dale Needham		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	13/12/16

Name of Co-Author	Associate Professor Sandra Peake		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

Name of Co-Author	Sumeet Rai		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Emma Ridley		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Helen Rodgers		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

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Anaesthesia and Intensive Care, 44(3), 406-412.

NOTE:
This publication is included on pages 212 - 226 in the print copy of the thesis held in the University of Adelaide Library.

Chapter 5:

Alternative outcome measures for nutritional studies in intensive care

Manuscript 9:

Event-rate and delta inflation when evaluating mortality as a primary outcome from randomised controlled trials of nutritional interventions during critical illness: A systematic review

Authors:

*Matthew J Summers[1], ***Lee-anne S Chapple**[2], Stephen A McClave[3], Adam M Deane[1,2,4]

*These authors contributed equally to the manuscript.

[1]Department of Critical Care Services, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[2]Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia

[3]Department of Medicine, University of Louisville, Louisville, KY, USA

[4]National Health and Medical Research Council of Australia, Centre for Research Excellence in Translating Nutritional Science to Good Health, Adelaide, Australia

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Lee-anne Chapple		
Contribution to the Paper	Data acquisition, statistical analysis and wrote manuscript		
Overall percentage (%)	40		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	6/12/16

Co-Author Contributions

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ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mr Matthew Summers		
Contribution to the Paper	Data acquisition, statistical analysis and wrote manuscript		
Signature		Date	7/12/16

Name of Co-Author	Professor Stephen McClave		
Contribution to the Paper	Critical revision of the manuscript for important intellectual content		
Signature		Date	6/12/16

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Conceptualisation of work, statistical analysis and critical revision of the manuscript for important intellectual content		
Signature		Date	7/12/16

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American Journal of Clinical Nutrition, 103(4), 1083-1090.

Section Two

Conclusions and future directions:

Section two of this thesis provides a commentary of the influence of nutrition support, with a focus on energy and protein intakes, on outcomes of critically ill patients, in particular those with a TBI. Chapter three incorporates three papers, each using a distinct methodology, to provide greater insight into the role of energy and/or protein intake on clinical outcomes, including survival.

Whilst observational in nature, the first paper in section two is the largest of its kind to describe the influence of energy and protein intake in critically ill head-injured patients on clinical outcomes. These data suggest that greater energy and protein intakes, while not associated with survival, were associated with reduced length of stay both in ICU and hospital, and reduced duration of mechanical ventilation. In interpreting this observation, we acknowledge that all of the patients in this cohort were fed well below prescribed targets – although this is a reflection of current clinical practice[13,14] – and, hence it remains unknown whether delivery of 100 % of nutritional goals could in fact influence survival in this population. In addition, the study design was limited in being a retrospective, post-hoc analysis. The dataset included nutrition intake data from the first 12 days of ICU admission only and did not provide any measure of nutritional status or functional outcome. Future research is required to determine the influence of 'adequate' energy and protein delivered over a longer period of time on survival and measures of recovery.

The second manuscript in section two is a meta-analysis of nutrition studies in critically ill adult populations that report the delivery of statistically significant higher and lower protein doses in the individual papers. This meta-analysis found no association between higher or lower protein doses and mortality. However, as in the above paper, the mean higher protein dose in this meta-analysis – at 1.02 ± 0.42 g/kg – was significantly below the current recommended range for critically ill patients of 1.2 - 2.0 g/kg. There is a clear need for prospective intervention studies to provide an adequate level of energy and protein, with a distinct separation in dose between groups, in order to allow conclusions on the effect of nutrition support on clinical outcomes.

In the hope of addressing at least part of this conundrum, the third manuscript in this section details a unique intervention to deliver more calories to critically ill patients and explores the impact of this on outcomes. The outcomes include not only mortality, but also longitudinal patient-centred outcomes of quality of life and measures of self-reported functional recovery. As reported in the original TARGET feasibility trial, the replacement of a 1.0 kcal/ml enteral formula with a 1.5 kcal/ml formula was able to deliver more calories to critically ill patients. The follow-up study, presented in this thesis, indicated that there was a signal that, one year after ICU admission, patients who received the augmented calorie enteral formula were more likely to have returned to work when compared to patients that received the lower calorie formula. This provides a promising direction for future nutrition intervention studies, where a greater emphasis should be placed on objective measures of functional recovery from critical illness, rather than survival or self-reported/ subjective outcomes. While this was a feasibility trial, an adequately powered randomised controlled trial of the same intervention incorporating both structural measures of body composition and physical function, is underway. The methodology for this large RCT has been refined from the TARGET feasibility trial, particularly regarding timing of the outcome measures to improve follow-up responses. This follow-up component will provide a more nuanced understanding of the influence of caloric delivery on body composition, in particular changes in muscle size, and physical function.

The final chapter of section two presents an explanation as to why published and well-conducted RCTs evaluating nutritional therapy to critically ill patients have not yet succeeded in demonstrating a statistically significant effect on mortality. This systematic review and statistical analysis demonstrated that every randomised controlled trial in the critical care nutrition literature in the last 10 years with a primary outcome supposedly powered for mortality was actually underpowered due to an overestimation in the predicted effect size of the intervention. This is an important finding in the future development of clinical trials of nutrition interventions and suggests there needs to be a shift in focus by study methodologists to include more realistic outcome measures for the intensive care environments of today.

Overall conclusions

The aims of my thesis were to explore practices surrounding nutrition therapy to critically ill patients, with a focus on patients admitted with a TBI, and to explore the influence of energy and protein delivery on patient-centred outcomes in these populations.

Prior to commencing this thesis program there was controversy surrounding the role that delivery of energy and protein at a prescribed target has on outcomes such as mortality, clinical outcomes, nutritional status and functional recovery in both critically ill patients and those admitted with a TBI. Observational studies consistently reported that current clinical practice in intensive care provides patients with energy and protein intakes that are well below prescribed targets. However, it was unknown whether this persists after ICU discharge, particularly in patients consuming nutrients orally. Additionally, while it was reported that patients with a TBI are frequently malnourished on admission to a rehabilitation facility, there were no data to describe the changes in nutritional status of these patients throughout the entire hospitalisation.

The key findings reported in my thesis are:

1. Energy and protein delivery to critically ill patients admitted with a TBI is below prescribed targets and this is associated with longer time to discharge alive from ICU and hospital, and greater duration of mechanical ventilation (but is not associated with mortality) (Manuscripts 2 and 6).

2. Energy and protein delivery to TBI patients after ICU discharge is below prescribed targets and multiple barriers exist to adequate nutrition. These barriers are both logistical (e.g. fasting for procedures) and attitudinal (e.g. low prioritisation of nutrition), and largely preventable. (Manuscripts 2 and 3)

3. Patients admitted to intensive care with a TBI have marked changes in ultrasound-derived quadriceps muscle layer thickness from early in intensive care to hospital discharge. (Manuscript 5)

4. Bedside measurement of the quadriceps muscle layer thickness using ultrasonography is feasible, non-invasive, and correlates with total lean body muscle mass from the validated dual energy x-ray absorptiometry. (Manuscript 5)

5. Greater loss of muscle thickness is related to poorer longitudinal self-reported physical function three-months after ICU admission. (Manuscript 5)

6. The optimal energy and protein dose to optimise outcomes in critically ill patients need to be established. (Manuscripts 7 and 8)

7. Alternative outcome measures aside from mortality are needed to determine the benefit, or harm, of energy and protein delivery to critically ill patients. (Manuscript 8 and 9)

8. Recent nutrition interventional studies in critical care with a primary outcome of mortality have been powered inappropriately. (Manuscript 9)

Future directions:

Research design:

This thesis highlights a number of areas that investigators should consider in the design of nutrition studies involving critically ill patients. Given the number of 'negative' randomised controlled trials of nutritional interventions in ICU when mortality is used as the primary outcome, investigators need to consider a shift towards the inclusion of more realistic, physiologically-plausible, clinically-relevant outcome measures. Ideally, this should include a measurement of body composition, objective measures of physical function or strength and both short-term and longitudinal patient-centred outcomes such as quality of life and self-reported functional recovery. As has been done in other research fields, it is also worth considering the development of a set of core outcome measures for nutrition studies in critical illness to allow comparisons between studies.

Clinical practice improvements:

The findings from this thesis support the implementation of a number of clinical practice improvements to enhance the delivery of energy and protein to critically ill and TBI patients.

For critically ill patients with a TBI, incidental energy is frequently provided during the ICU admission from the sedative drug propofol (Chapter 1). When this is taken into account in energy provision it may be important to adjust the proportion of protein in the enteral formulation to account for the energy provided. The use of a higher protein formula, or the addition of a protein supplement to meet estimated requirements, should be considered and the effect of protein dose on clinical outcomes needs to be evaluated.

Given the likelihood of cumulative nutritional deficits and poor recovery in both survivors of intensive care admission and long-stay patients, such as those with a TBI, it is important that patients with ongoing nutritional deficits on the post-ICU hospital ward are identified. This will allow the evaluation of targeted intervention strategies, such as focused staffing and resources. Nutritional intake needs to be considered across the entire hospital stay as opposed to shorter, more immediate periods of intake, and this should be reflected in policy as well as in practice.

The results of manuscript 2 demonstrate that the transition period from artificial to adequate oral intake should be carefully monitored. This may incorporate: the exploration of early gastrostomy placement; delayed removal of nasogastric feeding tubes until the ability to maintain a consistent, adequate intake orally has been demonstrated; or a clearer pathway for re-instating artificial nutrition support in patients failing to meet nutritional needs orally.

Further, manuscript 3 shows that education of practitioners involved in the nutritional care of the critically ill and patients with a TBI should occur, both at University and in the practice setting. Practitioners working with TBI patients should have a greater awareness of the significant nutritional deficits that occur over the duration of hospital admission. This may enable them to take a more proactive approach in managing the nutritional deficits in these patients. Improved communication between members of the healthcare team with clearly defined clinical pathways regarding nutrition support should occur, particularly between transitional periods such as ICU and the ward, and enteral nutrition to oral nutrition. This should incorporate a holistic view of the patients' nutritional status over the entire hospital admission. In regards to monitoring the adequacy of nutrition support clinicians should be aware of the limitations of relying on relatively gross techniques, such as subjective assessments of nutritional status or weight.

Further research:

The results from this thesis open up future research avenues. In both intensive care and on the post-ICU ward, effective intervention strategies need to be developed and tested in order to reduce the cumulative energy and protein deficits in clinical practice. Potential strategies may be to reduce fasting times, maintain feeding tubes *in situ*, improve prioritisation of nutrition provision, and instigate nutrition teams.

There is a clear need for future research evaluating energy and protein delivery to critically ill patients and those with a TBI, to determine a level of nutrient delivery associated with best clinical outcomes. There is a distinct paucity of evidence on the influence of 'adequate' energy and protein delivered after ICU discharge. These data would provide important information to support evidence-based guidelines for the post-ICU ward setting.

Perhaps an alternate approach when conducting clinical trials of nutritional therapies would be to target therapies to individual patients rather than targeting to populations groups. Nutritional therapies may prove more effective if the relationship between nutritional intake and actual energy and protein expenditure could be evaluated. Further, in trying to answer the question of how much to feed critically ill patients, we need to gain a more sophisticated understanding as to how the body utilises nutrients at this time, in order to delineate how much is actually absorbed and anabolised.

To extend the understanding of the influence of nutrition on outcomes further development of objective and accurate bedside anthropometric measures, including ultrasonography, should be a priority. The ability for ultrasonography to detect changes in muscle size in response to an intervention, and the assessment of what is a clinically relevant change in muscle size that will ultimately improve functional outcomes, needs to be determined. Finally, further research is required to develop and validate specific methodologies within the appropriate patient population to measure oral nutritional intake, for use in both clinical practice and research, potentially through embracing new technologies.

Appendices

Appendix A:

Presentations during candidature

Accepted invitations to present at scientific meetings

Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Florida, USA. Title of presentation: 'Mortality: Are we using the wrong endpoint?' February 2017

Dietitians Association of Australia South Australian Branch, Extended Scope of Practice, Adelaide, Title of presentation: 'Use of ultrasonography to measure muscle size.' October 2016

Invited presenter and problem-based learning tutor, Advanced Clinical Nutrition course, Australasian Society of Parenteral and Enteral Nutrition (AuSPEN), Sydney. Title of presentation: 'Research in the nutrition support setting'. June 2016

Oral presentation: Muscle Matters Research Development Protocol Day, Toronto, Canada. October 2015

Presentations at meetings based on abstract submission

(*denotes oral, §denotes oral-poster presentation)

International:

§**Chapple L**, Deane A, Williams L, Strickland R, Schultz C, Lange K, Heyland D, Chapman M. 2016, *Changes in muscle thickness throughout hospitalisation after traumatic brain injury*. European Society of Intensive Care Medicine Congress, Milan, Italy.

Chapple L, Deane A, Heyland D, Lange K, Kranz A, Williams L, Chapman M. 2016, *Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury*. European Society of Parenteral and Enteral Nutrition, Copenhagen, Denmark.

Summers MJ, **Chapple LS**, McClave SA, Deane AM. 2016, *Event-rate and delta inflation when evaluating mortality as a primary outcome from randomised controlled trials of nutritional interventions during critical illness: A systematic review*. Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

Chapple L, Deane A, Heyland D, Lange K, Kranz A, Williams L, Chapman M. 2016, *Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury*. Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

Chapple L, Deane A, Heyland D, Lange K, Kranz A, Williams L, Chapman M. 2016, *Are weekends different? Comparisons of oral intake in hospitalized patients recovering from critical* illness. Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

Reid D, **Chapple L**, O'Connor S, Bellomo R, Buhr H, Chapman M, Davies A, Eastwood G, Ferrie S, Lange K, McIntyre J, Needham D, Peake S, Rai S, Ridley E, Rodgers H, Deane A. 2016, *The effect of early energy delivery on quality of life and employment status one year after ICU admission: A randomised controlled clinical trial.* Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

[§]**Costello L,** Chapman M, Lange K, Deane A, Heyland D. 2015, *Nutrition support practices in critically ill head injured patients: A global perspective.* European Intensive Care Society Meeting. Berlin, Germany.

National:

***Chapple L**, Deane A, Williams L, Strickland R, Schultz C, Lange K, Heyland D, Chapman M. 2016, *Longitudinal changes in body composition and impact on self-reported physical function following traumatic brain injury*. Australian and New Zealand Intensive Care Society Intensive Care Annual Scientific Meeting. Perth, Australia.

***Chapple L**, Deane A, Williams L, Strickland R, Schultz C, Lange K, Heyland D, Chapman M. 2016, *Longitudinal changes in body composition and impact on self-reported physical function following traumatic brain injury*. Australasian Society of Parenteral and Enteral Nutrition Annual Scientific Meeting (AuSPEN). Melbourne, Australia.

Costello L, Chapman M, Lange K, Deane A, Heyland D. 2015, *Nutrition support practices in critically ill head injured patients: A global perspective.* Australian and New Zealand Intensive Care Society, Annual Scientific Meeting, Auckland, New Zealand.

Costello L, Chapman M, Lange K, Deane A, Heyland D. 2015, *Nutrition support practices in critically ill head injured patients: A global perspective.* University of Adelaide Faculty of Health Sciences Postgraduate Research Conference, Adelaide, Australia.

***Costello L**, Lithander F, Gruen R, Williams L. 2014, *Nutrition therapy in the optimisation of health outcomes in patients with moderate to severe traumatic brain injury: Findings from a scoping review.* Australasian Trauma Society conference. Sydney, Australia.

Costello L, Lithander F, Gruen R, Williams L. 2014, *Nutrition therapy in the optimisation of health outcomes in patients with moderate to severe traumatic brain injury: Findings from a scoping review.* Australia and New Zealand Intensive Care Society Annual Scientific Meeting 2014, Melbourne, Australia.

*Reid D, **Costello L**, O'Connor S, Bellomo R, Buhr H, Chapman M, Davies A, Eastwood G, Ferrie S, Lange K, McIntyre J, Needham D, Peake S, Rai S, Ridley E, Rodgers H, Deane A. 2014, *Early Energy Delivery on Long-Term Survival and Functional Outcomes Following Critical Illness: A Randomised Controlled Clinical Trial.* Australasian Society of Parenteral and Enteral Nutrition Annual Scientific Meeting. Auckland, New Zealand.

Costello L, Lithander F, Gruen R, Williams L. 2014, *Nutrition therapy in the optimisation of health outcomes in patients with moderate to severe traumatic brain injury: Findings from a scoping review.* University of Adelaide Faculty of Health Sciences Postgraduate Research Conference, Adelaide, Australia.

Appendix B:

Prizes awarded during candidature

American Society of Parenteral and Enteral Nutrition 2017 Research Sector New Practitioner Award

Nominated for Future Health Leaders Award, 2016

Australian and New Zealand Intensive Care Society Annual Scientific Meeting, Perth 2016: Best Allied Health Paper. $2500

Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) Conference Travel Grant, Melbourne, 2016. $500

Dietitians Association of Australia Young Achievers Award 2016: Honourable Mention

University of Adelaide, School of Medicine Research Travel Award 2016: Round 1. $3000

Dietitians Association of Australia ICD LEAP 2016 Travel Award. $1000

International Abstract of Distinction. Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

International Abstract Award, International Chapter. Clinical Nutrition Week, American Society of Parenteral and Enteral Nutrition, Austin, Texas.

Appendix C:
Grants awarded during candidature

Australasian Society of Parenteral and Enteral Nutrition Substantive Project Grant

Chapple L, Summers M, Deane A, Chapman M. 2016

Title: Long-term effects of critical illness on energy intake, appetite, gastric emptying and appetite-regulating hormones in adult survivors of intensive care unit admission

Value: $20,000

Royal Adelaide Hospital Clinical Project Grant Award

Costello L, Chapman M, Deane A. 2015

Title: Quantification of muscle size and function in response to a randomised nutritional intervention in critically ill patients

Value: $46,198

Royal Adelaide Hospital Clinical Project Grant Award

Chapman M, Deane A, Soenen S, Van Loon L, **Costello L**. 2015

Title: The effect of protein hydrolysis on the rate and extent of protein absorption and muscle uptake in critically ill patients

Value: $49,560

Australasian Society of Parenteral and Enteral Nutrition Small Project Grant

Costello L, Chapman M. 2014

Title: The provision of energy and protein in adults with moderate-severe traumatic brain injury (PEP-TBI)

Value: $10,000

Neurosurgical Research Foundation Grant

Chapman M, **Costello L**. 2014

Title: The provision of energy and protein after traumatic brain injury (PEP-TBI)

Value: $28,150

Australian Post-Graduate Award

Chapple L. 2014-2016

Total value: $88,872

Royal Adelaide Hospital Dawes Top-up Scholarship

Chapple L. 2014-2016

Total value: $15,000

University of Adelaide, School of Medicine Supplementary Scholarship

Chapple L. 2015-2016

Total value: $43,653

Appendix D:
Supplementary publications completed during candidature

Gluck S, **Chapple L**, Chapman M, Iwashyna T, Deane A. *A scoping review to determine the use of wearable devices to evaluate outcomes in survivors of critical illness.* Critical Care and Resuscitation (accepted 17 March 2017).

Nguyen T, Ali Abdelhamid Y, Phillips LK, **Chapple L**, Horowitz M, Jones K, Deane A. *Nutrient stimulation of mesenteric blood flow - implications for older critically ill patients.* World Journal of Critical Care 2017;6(1):28-36.

Miller A, Deane A, Plummer M, Cousins C, **Chapple L**, Horowitz M, Chapman M. *Exogenous glucagon-like peptide-1 attenuates glucose absorption and glycaemia after small intestinal glucose delivery during critical illness*. Critical Care and Resuscitation 2017;19(1):37-42.

Liew V, Chapman M, Nguyen N, Cousins C, Plummer M, **Chapple L**, Manton N, Swalling A, Sutton-Smith P, Burt A, Deane A. *A prospective observational study of the effect of critical illness on ultrastructural and microscopic morphology of duodenal mucosa.* Critical Care and Resuscitation, 2016;18(2):102-8.

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4. Chapple LS, Chapman MJ, Lange K, Deane AM, Heyland DK. Nutrition support practices in critically ill head-injured patients: A global perspective. *Crit Care.* 2016;20:6.
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