Sissel Urke Olsen

Refeeding syndrome among older multimorbid malnourished enteral-fed hospitalized patients by focusing on hand grip strength, incidence rates, and mortality

Thesis for the degree of Philosophiae Doctor (PhD)
PhD programme in Health Sciences
Faculty of Health Sciences
OsloMet – Oslo Metropolitan University

Table of content

List of papers

Paper I

Refeeding syndrome occurs among older adults regardless of refeeding rates: A systematic review.

S. U. Olsen, K. Hesseberg, A.-M. Aas, A. H. Ranhoff and A. Bye, Nutrition Research 2021 Vol. 91 Pages 1-12. DOI: https://doi.org/10.1016/j.nutres.2021.05.004

Paper II

A comparison of two different refeeding protocols and its effect on hand grip strength and refeeding syndrome: a randomized controlled clinical trial.

S. U. Olsen, K. Hesseberg, A. M. Aas, A. H. Pripp, A. H. Ranhoff and A. Bye, Eur Geriatr Med. 2021. DOI: 10.1007/s41999-021-00520-5

Paper III

The incidence and mortality of refeeding syndrome in older hospital patients based on three different diagnostic criteria.

S. U. Olsen, K. Tazmini, K. Hesseberg, A.-M. Aas, A. H. Ranhoff and A. Bye, Journal of Parenteral & Enteral Nutrition

List of figures

List of tables

List of abbreviation

ASPEN: American Society of Parenteral and Enteral Nutrition

BMI: Body mass index: (BMI = kg/m^2)

CI: Confidence4 interval

CRP: C-reactive protein

COPD: Chronic obstructive pulmonary disease

CONSORT: Consolidated Standards of Reporting Trials

EN: Enteral nutrition

ESPEN: European Society for Clinical Nutrition and Metabolism

GLIM: Global Leadership Initiative on Malnutrition

HGS: Hand grip strength

ICD-10: International Statistical Classification of Disease and Related Health Problems 10th edition

IV: Intravenous

ITT: Intention-to-treat

LOS: Length of stay

NICE: National Institute for Health and Clinical Excellence

OR: Odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomized controlled trial

RFS: Refeeding syndrome

SD: Standard deviation

SGA: Subjective global assessment

WHO: World Health Organization

1. Introduction

The current thesis is based on a systematic review, a randomized controlled trial (RCT), and a longitudinal study follow-up of the patients included in the RCT. The thesis has a particular emphasis on nutritional therapy when refeeding older malnourished hospitalized patients.

The overall aim is to contribute to evidence-based research regarding safe refeeding regimes by comparing two different enteral nutrition (EN) refeeding protocols in older hospital patients regarding the effect on nutritional status, which is measured as hand grip strength (HGS), incidence of refeeding syndrome (RFS), and mortality

We hypothesized that in older malnourished hospitalized patient at risk of developing RFS, a more assertive EN refeeding protocol will improve nutritional status (HGS), reduce mortality, but potentially aggravate RFS compared with a cautious refeeding protocol.

People are living longer, but advanced age comes with challenges, and individuals' health needs tend to be more chronic and complex. Aging is the major risk factor for developing chronic diseases and life-threatening conditions, including cardiovascular disease, cancer, neurodegenerative diseases, and general loss of function [1]. These conditions often impact a patient's appetite ability to eat and cause metabolic changes; some conditions also require dietary restrictions [2]. All these factors may contribute to the fact that malnutrition is highly prevalent among frail and sick elderly individuals in geriatric care facilities and in hospitals (between 25% and 65%, respectively) [1]. Even though malnutrition is prevalent, it is often overlooked in older adults. Malnutrition is known to cause a decline in functional status and an increase in recovery time, it is also associated with a longer hospital length of stay (LOS), higher readmission, and higher mortality rate [1, 3, 4]. In addition to affecting the individual, it also places a greater load on the health care system, and it is a major cost burden for society [5-8]. To reduce the burden of malnutrition, adequate nutritional treatment is an important piece in improving both function, nutritional status, and independency for malnourished individuals [9, 10].

When malnourished patients receive nutrition intervention, they are subjects to a potentially fatal side effect called the RFS [11]. Even in the year 1507, the physician A. Benivieni reported deaths in starved deserters fleeing a Roman camp when food again became available [12]. RFS was first reported on in articles in the late 1940s and early 1950s when starved prisoners and victims who went through severe famine developed cardiac, neuralgic symptoms, and/or peripheral edema or even death during the recommencement of feeding [13, 14].

Similar symptoms were noticed again during the 1970s and 1980s, when parenteral nutrition became more widely used, but the large amount of carbohydrates in parenteral nutrition at the time caused detrimental outcomes in many malnourished patients [15, 16]. The most well-known published case report article regarding death because of overzealous feeding was published by Weinsier in 1981 [16]; this article describes two severely malnourished female patients who died because of high load of carbohydrates were provided rapidly and intravenously. This caused cardiac arrest shortly after infusion. This article is often cited when describing the danger of RFS in malnourished individuals.

Since the 1980s report of fatal RFS cases, few clinical studies have been conducted, and those that have been have mostly focused on patients with anorexia nervosa [17] and on critically ill patients [18]. The three recent systematic reviews [17, 19, 20] conducted on RFS all conclude the lack of clinical studies for making recommendations regarding a definition, diagnostic criteria, and treatment algorithm. Over the past three years, two consensus reports regarding definitions, diagnostic criteria, and treatment algorithm have been conducted, one by an European group—Friedli et al. in 2018 [21]—and one by an American group—the American Society for Parenteral and Enteral Nutrition (ASPEN) in 2020 [11]. These consensus reports diverge from each other in both definition, diagnostic criteria, and treatment algorithm [11, 21]. Hence, more research is required, especially in older malnourished hospital patients.

The present thesis is based on three papers. First, a systematic review was performed to map the current knowledge regarding older adults and RFS (Paper I). Second, an RCT was conducted to compare a more assertive refeeding protocol with and more cautious refeeding protocol regarding HGS as a nutritional marker and mortality 3 months after hospital discharge and RFS during the hospital stay (Paper II). Finally, in the longitudinal study (Paper III), we investigated how different RFS diagnostic criteria would influence the incidence of RFS and mortality rates at 3 months and 1 year after hospitalization in patients with and without RFS.

2. Background

This chapter provides an overview of the relevant literature, paying close attention to RFS and older adults, before further branching out into the systematic literature review (Appendix). Both in-depth definitions and descriptions of the central themes are included to enable a more thorough understanding of the complexity of RFS in relation to older hospital patients. The literature search encompassed both publications before and after the start of the current thesis and the searches included examining databases as PubMed, MEDLINE, and Cochrane.

First, older and geriatric patients will be defined and presented to provide the framework for this clinical study. Second, the concept of malnutrition will be explored. Third, and which is the main topic of the thesis, EN and RFS are discussed.

The terms older adults are preferred terms to use according to the United Nations Committee on Economic Social and Cultural Rights 1995 and will be used in this thesis when discussing older patients [22].

2.1. Older and geriatric patients

Giacomo Leopardi (1798–1837) describes old age as “the supreme evil, because it deprives us of all pleasures, leaving us only the appetite for them, and it brings with it all sufferings. Nevertheless, we fear death, and we desire old age” [23]. This is in contrast to today’s description of older adults, with a life expectancy in the United States of 67.6 years, 69.9 years in Canada [7], and 82.3 years in Norway [24] compared with only 40 years in the 1800s [25]. Older adults today have opportunities to pursue new activities and even education, and they are able to keep contributing to their families and communities. Despite the fact that older adults are living an active life, one cannot get away from the fact that aging also comes with increased morbidity and mortality [7].

The present thesis concentrates mostly on older geriatric hospital patients. The European Union of Medical Specialists (UEMS) of Geriatric Medicine describes “geriatric patients” as patients who have a high degree of frailty and active multiple pathology requiring a holistic approach, preferably by a multidisciplinary team rather than just organ-oriented medicine [26]. This is part of the comprehensive geriatric assessment that is described as a multidimensional, multidisciplinary process, that identifies medical, social, and functional

needs, and that comes with the development of an integrated/coordinated care plan to meet those needs [27, 28].

2.2. The aging process

The aging process is not fully understood, but the physiological changes occurring during aging are a result of several complex biological mechanisms, all of which are interconnected and influencing each other [29-31]. The aging process is influenced by age-related diseases, and disabilities increase with age [32, 33]. The environment and people's lifestyle habits play an important role in the rate of the aging process. Healthy behaviors such as exercise, healthy food, avoidance of smoking and excess alcohol, in addition to a clean environment, will help reduce the speed of aging [34, 35]. Thus, functional decline becomes inevitable and accelerates along with the biological changes of aging. A decrease in lean mass, increase in fat mass, reduced cognitive function, and a chronic low-grade inflammation are all part of the aging process [31, 35, 36].

Inflammation can be defined as "a series of complex response events which are caused by the host system facing a pathogen infection or various types of tissue injury" [37]. The term inflammaging, which came into use around the year 2000, is described as a chronic, systemic, and low-grade inflammation during the aging process [38]. Inflammaging is an important factor in the speed of the development of certain diseases such as Alzheimer's disease, neurological diseases, atherosclerosis, type II diabetes, and cancer. Innflammaging has also been associated with increased morbidity and mortality [37]. Based on this, one may consider this low-grade inflammation the possible culprit or accelerator of the aging processes and age-related diseases [36, 39, 40].

2.2.1 Multimorbidity

Multimorbidity is a key factor of the aging process. Older hospital patients are often admitted with several underlying medical conditions, and this process of accumulating conditions starts decades before manifestation [39]. Multimorbidity is defined by several authors, the most common used definition, developed by WHO is "the coexistence of ≥ 2 long-term conditions in the same individual." (page 6) [41] Another definition commonly used is published by Le Reste et al., and defined; "as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk" (page 56) [41].

Because of a better health care system, patients can live longer with their medical conditions, resulting in prevalence rates of more than 45% when living with one long-term chronic disease or more [42]. Living with multimorbidity has its consequences and may cause poor quality of life, worse health outcomes, and a higher cost and burden on the health care system [43].

Comorbidity and multimorbidity are often used interchangeably. However, there is no consensus on how to define comorbidity or multimorbidity or what the distinction is between the two constructs [44]. The term comorbidity term was first defined by Feinstein in 1970, referring to "any additional co-existing ailment" [44, 45]. This can be interpreted as any co-occurrence of more than two diseases that are codependent and with an identified index disease [46] [44].

Measuring the burden of medical conditions does not have a gold standard. Some indices measure the total burden of predefined diseases or conditions by the numbers, while others weight them based on their seriousness [44, 47]. Despite these discrepancies, measuring medical conditions is important in both clinical and public health research and when planning for health resources [44]. In clinical research, the number of medical conditions may affect the evaluation of an intervention and often statistically controlled for. In public health research, recording the medical condition will enable an estimation of the incidence and prevalence of the number and type of conditions present in the community. This will be helpful when deciding on the allocation of resources and future health costs [44, 46].

2.2.2 Factors related to mortality in older adults

Mortality depends on age, sex, and underlying conditions. Having more than three medical conditions has been found to cause increased stress on the body and has been shown to have a strong association with mortality rates, as demonstrated in a meta-analysis [48]. The risk of death is also associated with the number of medications (polypharmacy), disability, = access to health care service, and weight loss [48, 49]. Low muscle strength is also strongly associated with increased mortality among adults 50 years or older [50]. This finding was confirmed in a review that summarized that low HGS is a predictor of mortality [51]. Weight loss is also able to predict mortality, which has been demonstrated in a recent meta-analysis in older adults, where a 59% increase in mortality risk with weight loss was found. This is in line with a study finding a significant increased risk of 30-day mortality with weight loss compared with weight-stable patients [49, 52]. Furthermore, the access to nutritious food,

health care options, and health information can all influence mortality [53]. A study with over 300,000 participants has shown people with a good social network and relationship have a 50% increased likelihood of surviving compared with people with a poorer social network [54].

2.2.3 Wasting syndromes in geriatric patients

A syndrome can be understood as a combination of clinical signs and symptoms, often with undefined or complex etiology and/or pathophysiology [55]. In older adults, frailty, sarcopenia, cachexia, and malnutrition are the four most frequent syndromes. The etiology behind these syndromes in older adults are complex and overlapping, but aging itself, lifestyle habits, medical conditions, and access to health services are contributing factors [56, 57]. These syndromes are associated with an increased risk of poor outcomes such as mobility limitation, falls and fractures, increased LOS, hospital readmission, morbidity, and mortality. Importantly, these syndromes have a burden on both the individual and social levels, as well as a large economic burden on society [56, 58].

All four syndromes come with a loss of body tissue, either body fat, muscle, or both. **Table 1** demonstrates the different diagnostic criteria of each syndrome, revealing that several of the criterion overlap between the syndromes. HGS is one of the diagnostic criteria in all four syndromes, and unintended weight loss in the previous six months to one year is a criterion for frailty, cachexia, and malnutrition [59-63]. All syndromes share related etiological features that are expressed in different ways: reduced energy intake, inflammation, reduced physical function, or reduced activity [56].

Several studies in geriatric patients have demonstrated that because of the similarity in etiology in the four syndromes, they often present concurrently [64-66]. This has been confirmed by one study [56] finding that 8% of older patients have all four syndromes present at once; another study indicates that 26% of patients who were malnourished also had sarcopenia and cachexia [65]. This makes it difficult to differentiate between the syndrome, which can become a challenge when it comes to interventions because energy requirements may be different between the syndromes [65]. A recent review confirms the overlap of the syndromes, suggesting a standardized screening tool and including the syndromes as part of the comprehensive geriatric assessment [66].

However, studies have shown that it is possible to reverse frailty, sarcopenia, and malnutrition by using adequation energy, especially protein, in addition to exercise [67, 68]. In patients with cachexia, who usually have severe underlying illnesses, nutrition intervention may not reverse the syndrome, but adequate protein and exercise have been proposed as being beneficial [69-71].

Table 1. Diagnostic criteria for the four wasting syndromes

Criteria	**Frailty** [61]	**Sarcopenia** [58]	**Cachexia** [56, 60, 63].	**Malnutrition** [d]**GLIM** [62]
Diagnosis based on	>3 of the 5 criteria needs be fulfilled to be considered frail	Low HGS When all criteria are met, sarcopenia is considered severe	Weight loss and three or more of the following criteria	At least one phenotypic criterion (weight loss, BMI, or low muscle mass) and one etiology criterion (food intake or inflammation)
Weight loss	<4.5 kg unintended in previous year	-	>5% weight loss in the previous year	>5% within the past 6 months or >10% beyond 6 months
BMI	-	-	<20 kg/m^2	<20 if <70 years, or <22 if >70 years
Low muscle quantity or quality Skeletal muscle index[a]	--	Women: kg/m^2 ≤6.75 Male: ≤10.75	Fat-free muscle index <15 for women <17 male	[c]Reduced by validated body composition measuring techniques
Energy intake	-	-	Poor appetite or low energy intake	Etiology criterion ≤50% of ER >1 week, any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption
HGS (kg)	Women ≤17–21 Men ≤29–32	Women <16kg Male <27kg	Women ≤17–21 Male ≤29–32	-
Gait Speed m/s[b]	Women <0.65 Male <0.76	< 0.8 m/s	-	-
Physical activity	Women <270 Kcal/week Male <383 Kcal/week	-	-	-
Fatigue and exhaustion	Yes on 1 of the 2 self-reported questions on exhaustions		Functional Assessment of Chronic Illness Therapy Fatigue <30 points	--
CRP/inflammation or Hb or albumin	-	-	CRP >5.0 mg/L or Hb <12 g/dL or Albumin <32	Acute disease/injury or chronic disease related

BMI; body mass index, CRP; C-reactive protein, ER; estimated requirements, Hb; Hemoglobin, GI; gastrointestinal condition.

[a]Skeletal muscle index: DXA scan as appendicular skeletal muscle mass (ASM) and defined as a skeletal muscle mass index (SMI) of ASM/height^2 (kg/m^2)
[b]m/s; meter per second,
[c]For example, fat-free mass index (FFMI, kg/m^2) by dual-energy absorptiometry (DXA) or CT or MRI or standard anthropometric measures such as mid-arm muscle or calf circumferences.
[d]GLIM, The Global Leadership Initiative on Malnutrition

Frailty

The term frailty was first described in the late 1990s [72]. Despite this, it was not until 2013 that a consensus regarding the definition of frailty was developed by six major international, European, and US societies: "A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" [68]. Different methods of evaluating frailty have been used, though; for example, Fried et al. [61] **(Table 1)** use specific phenotypes to summarize function and physiological variable. Another method is the Frailty Index, which summarizes the accumulated deficit, here related to aging, dysfunction, and disease [73]. Although the Clinical Frailty Scale uses a scale to describe frailty, here ranging from 1 (very fit) to 9 (terminally ill), the obtained score is based on a comprehensive assessment, including comorbidity, function, and cognition [74].

Patients with frailty have gradually lost their built-in body reserves. Events such as having the flu, pneumonia, or other diseases are stressors that, in an individual with reduced physiological reserves, can cause adverse outcomes and even death [75]. Treatment aspects such as sufficient calories and protein, micronutrients, exercise, and reduction in the number of medications has been proposed as having some effect on frailty [68]. Exercise intervention studies have found improved functional performance, improved walking speed, a reduction in falls, and reduced progression of frailty. Although weight loss is a part of the frailty phenotype syndrome, providing adequate nutrition, especially protein, may help stop weight loss, preventing further deterioration of the syndrome [68, 76, 77].

Sarcopenia

Sarcopenia is reduced muscle quality and function and increases the risk of falls and fractures, which impacts the individual's ability to perform the activities of daily living (ADL). Sarcopenia also affects muscle function the respiratory and cardiac system, causing reduced cardio-respiratory function [58].

The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as patients who present with a loss of muscle mass and function, either from low HGS or poor physical performance (slow gait speed) [58]. These validated criteria from the EWGSOP are often used to identify sarcopenia [58] (see **Table 1**).

Sarcopenia is identified if present with low HGS, but one more criterion is needed to confirm the diagnosis **(Table 1)**. If all three criteria are met, sarcopenia is considered severe [58]. The prevalence rates of sarcopenia depend on the definition used; studies have found rates ranging from 10% to 40% in community-dwelling older adults [78, 79].

In 2016, sarcopenia was recognized as a disease entity and was classified with a code in the International Classification of Disease–10th Revision (M62.84) [80]. Despite the criteria from the EWGSOP and that sarcopenia has been accepted as a disease in the ICD–10th revision, unified international agreement on a clinical definition or diagnostic criteria are still lacking [81]. As with frailty, sufficient protein in the diet, along with muscle strengthening exercises, can help improve muscle strength and mobility in older adults [67].

Cachexia

Cachexia is defined as follows: "Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" [60]. Cachexia is a Greek word meaning "bad thing" and "in a state of being," and it is a multifactorial syndrome known to have detrimental outcomes [63]. Involuntary progressive weight loss in adults is a prominent clinical feature of cachexia, along with anorexia, inflammation, and insulin resistance. Cachexia also increases muscle protein breakdown, which is known as catabolism (Table 1) [63]. Cachexia seldom appears abruptly but instead develops over time and is often associated in patients with chronic diseases such as chronic obstructive pulmonary disease, congestive heart failure, cancer, kidney disease, rheumatoid arthritis, and liver disease [60]. Few studies have reported on the prevalence of cachexia in older adults, but one study [56] indicates that 32% of older malnourished medical inpatients had cachexia [56]. To date, there are no proven nutrition interventions that will reverse cachexia, but exercise and high protein diets are recommended, and certain pharmacological intervention may help [63, 69-71].

2.2.4 Malnutrition

Malnutrition may be the most well-known syndrome. Recently, a consensus regarding its diagnostic criteria was developed into the GLIM criteria (Table 1) [62]. ESPEN guidelines define malnutrition as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" [82, 83].

Malnutrition shares similar criteria as frailty, sarcopenia, and cachexia **(Table 1)**, but in malnutrition, both fat-free mass and fat mass are reduced, which is either caused by reduced energy intake, an altered metabolism, or both [56].

Malnutrition has recently become better depicted, and definitions have been published [83]. In 2017, the ESPEN guidelines published an illustration of different types of origins of malnutrition, distinguishing between malnutrition with or without inflammation and malnutrition without disease. Disease-related malnutrition with inflammation could arise either because of acute or chronic disease or cachexia. Disease-related malnutrition without inflammation, could be because of, for example, dysphagia, stroke, dementia, or amyotrophic lateral sclerosis. The third origin could be related to the individual's socioeconomic status, psychological challenges, or hunger-related malnutrition (Table 2) [84].

Anorexia of aging

Anorexia of aging is related to malnutrition [85-87]. It was first described by Morley and Silver in 1988 as "age-related reduction in appetite and food intake, which occurs even in illness-free adults and in the presence of adequate food supply" [86, 88].

The word anorexia is more often seen in connection with anorexia nervosa in younger people, including in anorexia nervosa, where a self-induced restriction of food dominates, along with vigorous exercise with the aim of losing weight. Anorexia nervosa is rarely present with underlying metabolic disturbances and is considered malnutrition without inflammation, but it is still very complex to treat, and should include a multidisciplinary team [89, 90]. This is in contrast to anorexia of aging, where a deterioration of satiation and change in hunger and appetite is seen [85, 88, 91]. Older adults experience delayed gastric emptying, resulting in foods staying longer in the upper part of the stomach before moving to the lower part of the stomach, hence leading to longer satiety feeling [92]. Furthermore, the sensory system, such as olfactory (smell) and taste, changes with age. Both taste sensation and perception are affected, and there is a decline in the taste thresholds for sweet, bitter,

sour, and salty [85]. Decreased olfactory perception is found to be associated with lower BMI and may affect dietary intake [93]. Dietary intake might also be affected by oral and dental problems, including dysphagia, which is also found to increase with age [94]. A meta-analysis [95] indicates that older adults of around 73 years of age experienced less hunger than younger adults of around 26 years of age, causing a reduction of energy intake by 20%. The sum of these changes may lead to malnutrition. The etiology and consequences of weight loss and malnutrition in older patients has been described [85]. **Table 2** gives the causes and consequences of weight loss and malnutrition in older patients [85].

The groundbreaking study that was fundamental for the understanding of malnutrition, called the Minnesota starvation experiment, took place in the 1940s. This study informed the medical field of the effects, both physical and psychological, of starvation on a healthy body. The consequences of malnutrition reported were edema, anemia, polyuria, bradycardia, dizziness, fatigue, irritability, depression, and some issues of social isolation [96, 97].

The knowledge from this study, one that would not have been approved under today's ethical regulations, should be remembered when assessing older malnourished adults. Many of the symptoms can be related to other diseases but also to malnutrition [97].

Table 2. List of causes and consequences of weight loss in older adults [2, 85, 98, 99]

Medical	Social /environments	Psychological	Consequences of malnutrition
Medications	Poverty	Dementia	Loss of muscle function, mass and strength (sarcopenia)
Oral and swallowing problem	Functional impairment, maintain daily activities	Depression	Increased risk of fractures, bone mass loss, and increased risk of falling
Increased metabolism (hyperthyroidism)	Social isolation or lack of network	Bereavement	Reduced functional status
Other medical causes -Cancer, parkinsonism (neurological disorders), -Chronic obstructive pulmonary disease, cardiac cachexia	Difficulty with shopping, or preparing meals, Self-managing eating	Alcoholism	**Impacts the immunes system** Increased risk of infection (involves the T-cell, interleukin-2, cytolytic cell activity)
-Acute illness, endocrine disorders, infections	Elder abuse	Excessive burden of life	Poor wound healing Increased risk of pneumonia and pressure sores
Gastrointestinal disorders, rheumatic diseases, alcoholism	Poor nutritional knowledge		Fatigue, depression, irritability
Number of comorbidities	**Institutional factors** -Ethnic food preferences -Monotony of food in institution		Delayed convalescence
	Special diets or restricted diets		Increased hospital length of stay More readmissions
			Increased mortality

2.2.5 Diagnostic criteria, screening and assessing of malnutrition

To diagnose and treat malnutrition, early identification of the risk factors such as weight loss, low BMI, and reduced food intake is crucial; this is referred to as nutritional screening [100]. Screening is widely used in medicine as a strategy to look at the risk markers for malnutrition. Thus, nutritional screening is defined "as a rapid process performed to identify subjects at nutritional risk" [83]. Screening tools often include markers such as weight loss, low BMI, disease activity, and food intake [83].

According to guidelines all patients should be screened when admitted to the hospital or other health care institutions; it is recommended that nutritional screening should be performed using an appropriate validated screening tool in all patients who come in contact with the

healthcare services [2, 83, 101]. Patients found to be at nutritional risk are those who are at the highest risk of developing deficiencies, but they can also already be malnourished [2]. A person identified with nutrition risk factors should be further assessed; this encompasses a comprehensive approach using a combination of medical, nutrition, medication histories, and social and psychological history. It also includes anthropometric measurements, laboratory data, assessing energy, protein and fluid needs, and micronutrients needs [83, 100, 102]. This helps establish the cause of malnutrition and develops an appropriate nutrition care plan, confirming the malnutrition diagnosis [100].

Consensus criteria for diagnosing malnutrition

Even though the causes of malnutrition are known, a consensus regarding diagnostic criteria for malnutrition has been lacking. The Global Leadership Initiative on Malnutrition (GLIM) was developed in 2018 with the aim of unifying the diagnostic criteria for malnutrition around the globe. According to these criteria, diagnosing malnutrition is a two-step process. The first step involves screening to identify patients at risk for malnutrition, here by using any validated malnutrition screening tool. Second, those who are classified as at risk are then evaluated to confirm the diagnosis and grade the severity of the malnutrition [62].

A global diagnostic consensus will make it easier to compare the incidence rates of malnutrition. The GLIM criteria are planned to be incorporated into the International Classification of Disease and Related Health Problems 11 (ICD-11), presumably substituting the current diagnostic criteria in ICD-10, as well as seeking to be adopted by the World Health Organization (WHO) [84].

The diagnostic criteria for malnutrition in the current thesis were ICD-10, "E44, mild or moderate protein-caloric malnutrition" and "E43, unspecified severe protein-calorie malnutrition" [65] (Table 3).

The Norwegian diagnostic ICD-10 criteria for malnutrition take into account weight loss and BMI cut-offs, in addition to the percent of energy intake, here according to the estimated need when diagnosing malnutrition [101].

Table 3. ICD-10 criteria for diagnosing malnutrition in Norway

E46:00 Unspecified protein/energy malnutrition
At nutritional risk according to NRS 2002, MUST, MNA, or SGA

E44:00 Moderate malnutrition: needs to fulfill one of the following criteria

- Involuntarily weight loss >10% in the last 3–6 months or 5% last 2 months
- BMI <18.5 (>70 years BMI <20)
- BMI <20.5 (>65 years BMI <22) and nonvolitional weight loss >5% last 6 months
- Energy intake less the 50% of estimated needs

E43:00 Severe malnutrition: needs to fulfill one of the following criteria

- Involuntarily weight loss >15% in the last 3–6 months or 5% last 1 months
- BMI <16 (>70 years BMI <18.5)
- BMI <18.5 (>70 years BMI <20) and nonvolitional weight loss of > 5% last 3 months
- Energy intake less the 25% of estimated needs

NRS 2002: Nutritional Risk Screening-2002; MUST: Malnutrition Universal Screening Tool; SGA: Subjective Global Assessment; MNA: Mini Nutritional Assessment.

Hand grip strength as a surrogate marker for nutritional status and strength

HGS is a relevant marker of physical function but has also become a legitimate marker for nutritional status; yet it is not validated as such. HGS is a part of all four diagnostic syndrome criteria: sarcopenia, frailty, cachexia, and malnutrition [103] and is considered a noninvasive and easy-to-use method [104], one that is proven to be highly reliable in measuring muscle strength [105, 106]. It is well established that muscle strength and mass decreases—and fat mass increases—with age [107]. This is rooted in many underlying causes such as in the increasing immobility among older adults, reduced protein intake, and altered endocrinal function that can affect muscle mass and strength [108, 109]. A decrease in strength may also be because of the metabolic effect of disease, where inflammation plays a central role, as well as in electrolyte imbalance, comorbidity load, and disease severity, which are conditions that are often seen in many wasting syndromes [110-112]. Low HGS is related to increased risk of complications, longer recovery after disease, predicting hospital LOS and survival, and early onset of dependency [51, 103, 112-116]. It is also associated with higher 30-day readmission rate and mortality, which is why HGS is part of the diagnostic marker of the wasting syndromes [50, 51, 115, 116].

As a marker for nutritional status, HGS is utilized because nutrition deficit and restoration seem to influence HGS earlier than body weight and improved physical function is often the first sign of improvement when refeeding malnourished patients [112]. Despite the association between HGS as a predictor of nutrition status, it is still not recommended to be used as a sole indicator of malnutrition [117].

2.2.6 Prevalence of malnutrition in older adults

In 1974, Charles Butterworth wrote an article called "The Skeleton in the Hospital Closet," which referred to the lack of awareness among clinicians in relation to malnutrition; this was regarded as one of the most serious nutritional problems at the time [118]. Forty-seven years later, malnutrition is still highly prevalent in hospitals, but there has been growing attention given to malnutrition within the past decades.

In 2019, based on studies from European countries, a large systematic review and meta-analysis regarding the prevalence of the risk of malnutrition was published [119]. This systematic review shows a high prevalence of patients at risk of malnutrition but different rates according to the setting: 53% in hospital, 52% in residential care, and 33% in community settings [119]. The highest occurrence was found to be among older patients (>80 years) and in women in all settings [119]. A similar result is shown in an article by O`Shea et al. [120], with 45% of older patients (>70 years) being at risk of malnutrition according to the Mini Nutritional Assessment tool (MNA) and more so in women [120]. The difference in incidence rates is partly because of the different definitions and screening tools used [2].

As with the prevalence of risk of malnutrition, a malnutrition diagnosis also depends on the definition used [2]. In a multicenter study in Korea, 300 patients were screened using the Subjective Global Assessment (SGA) tool, with the results showing malnutrition diagnosis in 38% of patients 70 years and older compared with 17% in the younger population. Overall, the highest prevalence was seen in patients admitted for medical treatment (32%) compared with elective surgery (7%) [121]. Similar results have been found in a hospital sample of 583 patients using the SGA tool to diagnose malnutrition, which indicates 29% of the patients are either moderately or severely malnourished [99]. A systematic review and meta-analysis of 114,000 patients shows malnutrition diagnosis in 29.4% in rehabilitation/subacute care, 22.2% hospital, 17.5% in nursing homes, and 3.1% in community settings [6].

2.2.7 Treatment of malnutrition

Nutrition interventions aim to lessen the consequences of malnutrition. Multiple measures have been used to prevent further deterioration and to reverse the state of malnutrition, for instance, the fortification of food, nutritional supplements, nutrition counseling, or medical nutrition therapy such as EN or IV nutrition [2, 10, 122]. In 2018, the ESPEN guidelines on clinical nutrition and hydration in geriatric were published [2]. These guidelines aim to provide evidence-based nutrition and hydration recommendations for older adults regarding both the prevention and treatment of malnutrition and hydration. The ultimate goal is to improve a person's quality of life and maintain or improve functional status, thereby increasing autonomy [2]. Short overall recommendations for older persons with malnutrition regarding energy, protein, and fluid are as follows:

- Energy: 30 kcal/kg/day, but adjust according to disease state.
- Protein: 1 g/kg/day, but adjust according to disease state.
- Fluids: for women 1.6 liter a day and for men 2.0 liters a day.
    - These recommendations need to be adjusted according to disease state, nutritional status, physical activity, and tolerance.

Energy requirements vary greatly, and in those who are underweight, the needs may range from 32–38 kcal/kg/day, while in very sick old patients, needs may be between 27 and 30 kcal/kg/day. To ensure adequate energy provision, body weight should be closely monitored. Protein requirements vary greatly according to disease, and protein requirements of 1.2–1.5 g/kg/day in sick older have been suggested, with even as much as 2.0 g/kg/day being suggested [2]. Fluid recommendations are not very well founded, varying between 1.0 liter (L)/day in the Nordic countries to 3.0 L/day in other parts of the world. Provision should be adjusted according to temperature and body size and if there is excess loss through fever, vomiting, and diarrhea, as well as disease state [2].

Even though guidelines recommend nutrition support, the evidence of the effect of interventions (e.g., mortality, weight, adverse events, LOS, readmission rates) have varied in studies, and much of this is because of the number of low-quality studies [10, 123, 124]. A successful nutrition intervention does not only depend on the available energy, but also on if the environment surrounding the older individual can stimulate appetite; here, eating with others has also been found to increase nutrition intake [2]

A recent systematic review [3] explores the effect of nutrition support in hospitalized patients. Twenty-seven trials are included, and 11 of these include geriatric patients; the results show that nutrition support improved survival and reduce readmission rate among malnourished hospitalized patients [3]. In a large RCT [10], "The Effect of Early Nutritional Support on

Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT)," the effect of an individualized nutrition support protocol is compared with standard hospital food in 2,088 patients. The results show increased energy intake, reduced risk of adverse outcomes, and a reduction in 30-day mortality in patients receiving the individualized nutrition protocol. Based on these findings, the authors recommend systematic screening, assessment, and individualized nutrition protocols in patients at risk of malnutrition [10].

EN studies in older adults, either via a nasogastric tube or percutaneous endoscopic gastrostomy (PEG) tube [125], are few [2]. ESPEN guidelines on nutrition and hydration in geriatrics recommends the following regarding EN: "Older persons with reasonable prognosis shall be offered EN if oral intake is expected to be impossible for more than three days or expected to be below half of energy requirements for more than one week, despite interventions to ensure adequate oral intake, in order to meet nutritional requirements and maintain or improve nutritional status" [2]. On average, the available studies regarding the effect of EN in older patients are more than 10 years old (1990–2011), but some studies show improvements using EN when it comes to mortality, quality of life, and function [2].

EN in patients with dementia are often discussed, and in 2015, new ESPEN guidelines were published on nutrition in dementia [126]. These guidelines recommend that in patients with mild to moderate dementia, EN is only recommended for overcoming a crisis and when reducing oral food intake is the dominating reason. However, in advanced dementia, EN is not recommended because studies do not show improved survival or mental or physical function [126]. However, it is always important to evaluate the benefit of EN compared with the potential harm or discomfort of treatments in older adults [2, 126]. In relation to this issue, the ethical perspectives regarding nutrition interventions are discussed in the next section.

2.3 Ethical reflections regarding nutrition intervention in older multimorbid patients

Respecting the four ethical principles of autonomy, beneficence, nonmaleficence, and justice when treating vulnerable group is of the utmost importance. Autonomy, beneficence, nonmaleficence, and justice means that there is a respect of patients' wishes and preferences and that patients are involved in the decision making, not necessarily the type of treatment but whether they would like to abstain from the treatment or fully accept the treatment

(autonomy) [127]. It is important to ensure that treatment is in the best interest of the patients and clinical status, that the treatment will benefit the patient, and that the benefit will outweigh the harm (beneficence and nonmaleficence). The last ethical principle is justice, which means that the treatment is fair to all patients and in accordance to the healthcare costs [128, 129]. It seems easy in theory, but the decision on whether to provide artificial nutrition or withdraw nutrition is one of the more challenging dilemmas for health professionals [130]. This decision must balance all opinions of the involving parties, and all aspects must be considered and should follow all ethical principles [129]. Therefore, an EN intervention should only be initiated if it realistically can increase life expectancy, improve function and independency, and outweighs the discomfort and suffering of the nutrition support. Such assessments should be made by a multidisciplinary team, and the patient and next of kin needs to be well informed and understand the magnitude of the treatment [126].

An important aspect in the decision is that vulnerable populations, for example, older adults, are at risk of being harmed, manipulated, persuaded, coerced, or deceived by stakeholders who have their self-interests in mind [127, 131].

2.4 Refeeding syndrome

2.4.1 Pathophysiology and diagnostic criteria

RFS has been known about for decades, but there still exists little evidence-based knowledge regarding the risk factors, incidence rate, time course of occurrence, therapeutic strategies in preventing or treating this syndrome, or a unified definition [17, 19, 20]. Three recent systematic reviews have been conducted: one by Friedli et al. [20] in 2017 and one by Matthews-Rensch et al. [19] in 2020, which includes only children, and while the third systematic review by Rizzo et al. [17] includes only patients with anorexia nervosa.

The overall findings from these studies is that RFS is defined widely, but low serum phosphate is one of the most used clinical signs for RFS and is often considered the hallmark finding of RFS [19]. However, this has changed in the past few years toward including all electrolytes—phosphate, magnesium and potassium—as well as clinical symptoms such as tachycardia, tachypnea peripheral edema, lung failure, or heart failure [11, 20, 132, 133].

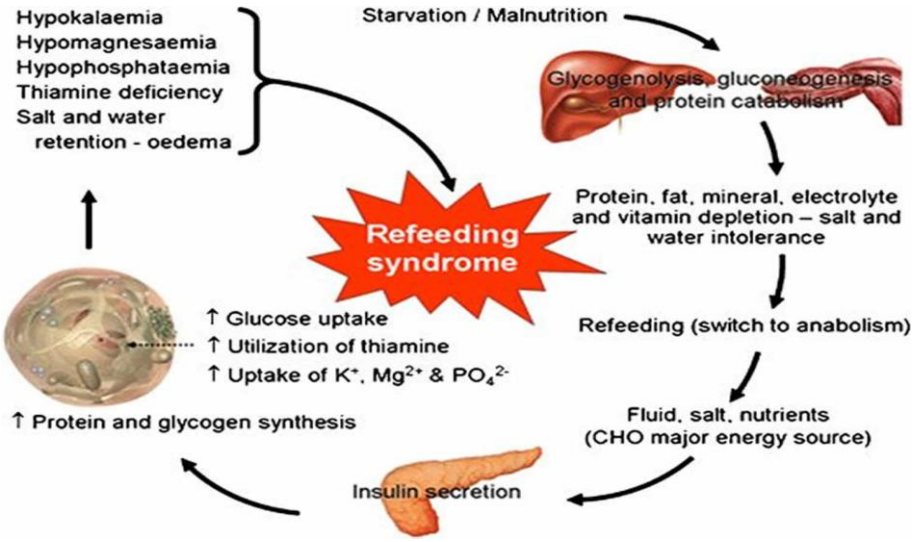
Pathophysiology

The pathophysiology behind the syndrome has been well described **(Figure 1)** [11, 134]. During starvation, the body's metabolism switches from using glucose as the primary energy source to catabolizing fat and protein as the main source of energy [97, 135]. When nutrition is deprived and the body is in a katabolic state, the preserved energy in glycogen stores is depleted, causing low insulin production. At the same time, vitamin, minerals, electrolytes (intracellular), and thiamin continue to be utilized, so the stores are further depleted. When nutrition is reintroduced, especially carbohydrates (whether enterally, parenterally, or orally), glucose becomes the main energy source again, and anabolism sets in instantaneously. Once food is available, insulin secretion rises in response to the increased plasma concentration of glucose [136]. Subsequently, insulin stimulates the sodium-potassium adenosine triphosphatase pump (ATPase), and intracellular shifts occur, leading to an influx of electrolytes (phosphate, magnesium, and potassium) from the extracellular room; this results in a low level of electrolytes in the blood [137]. This metabolic shift that results in low levels of electrolytes may lead to detrimental outcomes [134, 137].

Thiamin deficiency is most likely a part of the RFS because thiamin is an important cofactor in the glucose-dependent metabolic pathway. Thiamin demands increases during the switch from starvation to refeeding when carbohydrates become readily available again [11]. It is well known that thiamin deficiency may cause symptoms such as neuropathy, ataxia, nystagmus, and cause lactic acidosis; it may also lead to symptoms such as confabulation and loss of memory. This, in turn, may result in Wernicke's encephalopathy and/or Wernicke–Korsakoff syndrome [138]. Thiamin deficiency affects many of the body's organ systems: the nervous system, gastrointestinal tract, and heart [138]. Currently, there is a need to better understand thiamin's role in RFS regarding prevention, the amount needed during the refeeding phase, and what level of deficiency will cause the abovementioned symptoms [134, 138].

Notably, older (frail) patients in two recent studies [139, 140] did not demonstrate high incidence rate of thiamine deficiency. In the study by Pourhassan et al. [140], none of the 238 older hospitalized patients had thiamine deficiencies, while in Kurkcu et al.'s [139] study, only 5% had thiamine deficiency among the 475 studied geriatric outpatients.

Figure 1. Refeeding syndrome and its pathogenesis and features [141]



Reprinted with permission from Springer Nature. License nr. 5177590323097

Diagnostic criteria

After the NICE guidelines were published in 2006, two new diagnostic consensus criteria for RFS emerged: a European-based consensus by Friedli et al. [21] and an American-based consensus by ASPEN [11], which are shown in **Table 4.** The diagnostic criteria from Friedli et al. [21] are divided into two stages: imminent and manifest RFS. If electrolyte disturbances occur within 72 hours after recommencing food, it is considered an imminent RFS, and if clinical symptoms are present in combination with imminent RFS, it should be considered manifest [142].

Table 4. Diagnostic criteria for refeeding syndrome criteria.

	Friedli et al. criterion Imminent and manifest [21]	ASPEN criterion [11]
Time of occurrence after initiation of nutrition	Within 72 hours after recommencement of nutrition therapy	Within 5 days after recommencement of nutrition therapy
Defining RFS after initiating feeding	**Imminent**: A decrease in baseline values of serum phosphate >30% or <0.6 mmol/L or any two other electrolytes below normal range: Serum phosphate <0.80 mmol/L Serum magnesium <0.75 mmol/L Serum potassium < 3.5 mmol/L **Manifest:** RFS is considered manifest if it is imminent, in conjunction with clinical symptoms like tachycardia, tachypnea, peripheral edema, lung, or heart failure	A decrease in baseline values of phosphate magnesium and/or potassium of**:** Level of deficiency: 10–20% (mild RFS), 20–30% (moderate RFS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or because of thiamin deficiency (severe *RFS).

*RFS; Refeeding syndrome

Management of RFS in older adults is the focus in the current thesis. To prevent RFS in frail older patients, early detection and a multidisciplinary team are suggested. In an article by Aurbry et al. [142] (2018) explore prevention, diagnosis, and management of RFS in older adults, recommending the use of the same diagnostic criteria of RFS as in Friedli et al. [21].

2.4.2 Risk of refeeding syndrome

Older adults are at risk of developing RFS, this may because of several reasons, as follows: an increased number of chronic comorbidity diseases in older age (dementia, COPD, heart failure and kidney disease, and diabetes, among others) and being at a high risk of disease-related malnutrition [143]. However, because the clinical manifestation of RFS is similar to other symptoms in older adults, RFS might not be easily identified [142]. Several other patient groups are also at risk, such as those with uncontrolled diabetes, cancer, malabsorption syndromes, excessive use of alcohol, surgical patients, elderly, and patients who are fasting or have undergone bariatric surgery [132, 144].

It is challenging to accurately identify patients who will develop RFS. Two screening tools have been assessed for their ability to identify patients at risk: the NICE guideline screening tool (**Table 5**) [145] and the Short Nutritional Assessment Questionnaire (SNAQ) [146]. The NICE screening tool can assess patients on IV nutrition and EN but has shown poor sensitivity of 50% (actual RFS cases) in those on IV nutrition and moderate specificity (76%) (did not develop RFS) [147]. For those on EN, the sensitivity is 38%, and the specificity is 73% [148]. Whereas the NICE screening tool uses sensitivity and specificity, the SNAQ screening tool [146] evaluates the predicted values of RFS, finding poor positive predictive values of 13%, (percent tested positive who actually develop the disease) and a negative predicted value of 95% (percent of patients not at risk according to the SNAQ screening who did not develop RFS). In a retrospective validation analyses, both the NICE and SNAQ screening tool score poorly on sensitivity and specificity [11]. Two studies have found that older age and patients who score ≥3 on the Nutritional Risk Screening tool (NRS-2002) in conjunction with comorbidities, especially malignancy, cardiovascular disease, and diabetes, are risk factors for developing RFS [146, 149].

Table 5. Screening tool developed by the National Institute for Health and Care Excellence (NICE) [150] guidelines for detecting patients at risk of refeeding syndrome.

High risk of RFS

Patient has **one** or more of the following:

- [a]BMI <16 kg/m^2
- Unintentional weight loss >15% within the last 3–6 months
- Little or no nutritional intake for more than 10 days
- Low levels of phosphate, potassium or magnesium prior to feeding

Moderate risk of RFS

Patient has **two** or more of the following:

- [a]BMI <18.5 kg/m^2
- Unintentional weight loss >10% within the last 3–6 months
- Little or no nutritional intake for more than 5 days
- A history of alcohol abuse or drugs, including insulin, chemotherapy, antacids, or diuretics

[a]BMI: Body mass index

2.4.3 Phosphate, magnesium, potassium, sodium, and physiology in relation to refeeding syndrome

The compartmental shifts of electrolytes that occur during refeeding is what causes RFS. Electrolytes such as potassium and sodium are measured routinely, but magnesium and phosphate are not included in routine laboratory tests, so they are often overlooked [151, 152].

Phosphate occurs mainly at the intracellular level, and it plays an important role in cellular metabolism, helping to regulate the release of oxygen from the hemoglobin to tissues. It is also important in the energy transport and maintenance of the acid–base balance. Furthermore, it is also a component of all tissues, playing an important role in skeletal and muscle contraction [153]. The supply of phosphate depends on, among others, the availability of phosphate in the diet, vitamin D, magnesium intake, and alcohol, is reduced if using glucocorticoids and antacids, and is excreted if using diuretics [153]. Hypophosphatemia (HP) is mainly caused because of the shift of phosphate from the extracellular room into the intracellular room when stimulated by insulin, as in RFS. This shift also occurs during hyperventilation and respiratory alkalosis. The latter is often seen in patients with sepsis, liver disease, and mechanically ventilated patients [153]. Other causes of HP may be burns, diabetic ketoacidosis, alcoholism, and chronic obstructive pulmonary disease and the use of several drugs; these aspects must be considered when looking at phosphate levels. Deficiency may affect all large organs: the muscular and skeletal system, the nervous system, cardiac function, and the respiratory and renal system, and among others, it may cause anemia, weakness, rhabdomyolysis, bone pain, confusion, tremors [11, 16, 154].

Magnesium plays an important role as a cofactor in over 300 enzymes and in the movement of sodium and potassium across the membrane. Magnesium is also an essential component of the DNA structure and in ATP stabilization, which provides cellular energy in addition to maintaining neuromuscular functions [21]. It is mostly stored in the bones, muscle, and soft tissue, with a small amount also being found in red blood cells [155].

There are several reasons behind the low values of magnesium, including insufficient dietary intake, overconsumption of alcohol, diabetic ketoacidosis, pancreatitis, and RFS. The mechanism behind a low level of magnesium in RFS is not fully understood, but it is suspected that this relates to the movement of magnesium from the extracellular to the intracellular room during the refeeding of carbohydrates; this is also the case in hungry bone syndrome, diabetic ketoacidosis, and pancreatitis [11, 155]. Other reasons for low levels of magnesium might be some medication types, hypercalcemia, and loss through the gastrointestinal tract [155]. Clinical manifestations of low levels of magnesium are often hard to recognize but might be muscle weakness, tremors, seizures, and paresthesia, in

addition to cardiovascular and metabolic abnormalities (hypokalemia and hypocalcemia) [155].

Both *sodium and potassium* may have a detrimental effect when they are dysregulated. Both electrolytes are readily available in normal diets and as a part of the sodium/potassium pump. Sodium is a regulator for cell volume and is mostly an extracellular entity, while potassium is mostly found in the intracellular room (this is distorted during RFS). Hypo- or hypernatremia can causes fatal side effects and they present with similar clinical manifestations, such as seizures, brain injury, brain swelling, behavioral abnormality, movement disorders (hyponatremia) or headache, delirium, cramps, coma, and brain shrinking (hypernatremia) [156].

Hypokalemia is seen frequently and occurs when potassium is redistributed from the extracellular space into the intracellular room (RFS), when dietary intake is low, or when potassium is lost through the kidney or gastrointestinal track [157]. Potassium and magnesium intertwine with each other, and hypokalemia will not correct itself until magnesium levels are normal. This is because potassium depends on magnesium's role in the sodium/potassium pump which can be seen in how hypomagnesemia may inhibit the pump and exacerbating the hypokalemia [155, 157]. Clinical manifestations of hypokalemia are cardiac arrhythmias fatigue and muscle twitching [158].

2.4.4 Occurrence of refeeding syndrome

A clear and concise definition of RFS is lacking, and each study defines RFS differently. In a systematic review, 16 of the 24 included studies used low serum phosphate as their primary or secondary outcome measure, and six of these studies used phosphate as their only clinical sign for RFS, while the others used a combination of clinical signs and electrolyte deficiency [19]. In recent consensus, both electrolyte imbalance in addition to clinical symptoms are more widely incorporated in the definition of RFS [11, 20, 132]. Based on the wide variety of definitions, it is challenging to estimate RFS rates.

An occurrence of around 14% seems to be common in patients at risk, even when using different definitions. In an RCT study in 2020 [159], RFS was confirmed in 14.6%, with the diagnostic criteria of either more than one major criterion or two minor criteria. The major criterion here is phosphate <0.32 mmol/l, magnesium <0.5 mmol/l, potassium <2.5 mmol/l or two minor criteria of phosphate <0.81mmol/l, magnesium <0.74 mmol/l, or potassium <3.6 mmol/l and peripheral edema [159]. Further, in a study by Zeki et al, 33% of the patients at risk in the EN group developed RFS, while 13% in the IV nutrition group did. In this study, RFS is defined

as a drop in serum phosphate to <0.6 mmol/L [148]. Another study uses the same definition of RFS (fall in serum phosphate to <0.6 mmol/L), finding an overall incidence of 8%, while 14% of the patients screened were at risk of developing RFS [146]. In critically ill patients, prevalence rates of RFS have ranged from 34% to 40% using serum phosphate of <0.65 mmol/L, while 4–10% has been found RFS using phosphate < 0.32 mmol/L[152]. One can carefully conclude that the incidence rates are highly dependent upon the definition set for RFS in each study. The systematic review by Friedli et al. [20] is the most comprehensive one done on RFS in adults. This systematic review includes all articles published until 2015, here finding an average day of nadir on day three [20]. Studies published after 2015 have found the following day of nadir: mean (SD) day 5 (1.8) in internal medicine patients [146] within the first 2 days of EN in surgical intensive care [160], within the first 3 days after recommencing nutritional therapy in malnourished adults [159], mean (SD) day 4.6 (1.9) in anorexia nervosa in the rapid calorie protocol group, and mean (SD) day 5.8 (2.5) in a lower calorie group [161].

2.4.5 Nutrition protocols and treatments

In 2006, the NICE guidelines on RFS were developed. These guidelines recommend a cautious refeeding rate of 5 or 10 kcal/kg/day according to a BMI of <14 kg/m^2 or > 14 kg/m^2, respectively, reaching the estimated needs between days 4 and 7 [145]. Further, the guidelines provide clinical criteria for patients at "moderate" and "high risk" for RFS, aiming at early identification and prevention **(Table 5)**. Earlier guidelines indicate to wait with feeding until electrolyte levels have been corrected, but these guidelines recommended to start refeeding immediately to avoid a further decline of nutrition status [137]. The supporting literature underpinning the evidence that results in the NICE guidelines recommendation is weak and mostly based on cohort studies, case series, and consensus expert opinions [134, 137]. As a note, the group developing the NICE guidelines is multidisciplinary, including patient stakeholder [137].

Today's recommendations, for both initial calories and feeding advancement vary greatly [11]. A recent overview over previous refeeding recommendations from 1990 to 2018 demonstrates a variation of initial calories between 5 and 20 kcal/kg/day. In studies before the NICE guidelines were developed, the recommendations vary mostly between 10 and 20 kcal/kg/day, but after 2006, a trend toward a lower range, 5 kcal/kg/day (at high risk) and 10–

15 kcal/kg/day, became more common. Many of the guidelines are vague, suggesting a gradual increase to meet energy needs within 7–10 days.

Friedli et al.'s [21] group divide the risk of RFS into low, high, and very high risk, recommending an initial calorie level of 15–25 kcal/kg/day in the low risk, 10–15 kcal/kg/day in the high risk, and 5–10 kcal/kg/day in the very high risk. Further, they recommended advancement of feeding to meet the estimated goal rate at day 4 in the low risk group and days 7–9 and day 10 in the high and very high risk of RFS, respectively.

Although ASPEN consensus is much in line with previously published guidelines with initial calories between 10 and 20 kcal/kg/day the first 24 hours, their recommendation regarding titration rate is more assertive than earlier guidelines and compared with Friedli et al.'s consensus [21, 134, 142, 145], with an increase of 33% of energy goals every 1 to 2 days [11].

Table 6, provides a comparison and an overview of the recommendations between the two consensus recommendations [11, 21].

Table 6. Overview and a comparison of general recommendations in each consensus.

	Friedli et al [21]	ASPEN [11]
Thiamin before feeding	Yes	Yes (100mg) 5–7 days
Multivitamin daily	Yes	Yes
Fluid restriction	Yes	No
Sodium restriction	Yes (for 7 days)	No
Daily weight	Yes (symptoms of fluid overload)	Yes (monitory input and output)
Daily monitoring of electrolyte	3 days	Every 12 hours for 3 days
Prophylactic provision of electrolytes (with normal prefeeding values)	Yes	No
Vital signs	Yes (signs and symptoms of fluid overload, 72 hours)	Yes (every 4 hours, the first 24 hours)

There is little knowledge when it comes to recommendations for different disease groups or ages, and for years, a low-calorie approach has been recommended for refeeding patients with anorexia nervosa (AN) [162]. This approach has led to poor weight gain and prolonged hospital stay [163, 164], but in recent years, there has been an increasing recognition that the low-calorie approach might further aggravate malnutrition and that a higher initial calorie feeding could be safe and improve

outcomes in this group of patients [161]. Although patients with anorexia seem to benefit from a more assertive load and rapid advancement [163], this seems to the contrary for critical ill patients [165-168] A recent literature review and guidelines in 2020 [18] and another study[165] conclude that providing a more cautious refeeding approach seems to lead to better outcomes in critically ill patients.

2.4.6 Consequences of RFS

Low serum levels of electrolytes can cause detrimental consequences, but RFS may manifest as both mild and with fatal symptoms; thus, it is a preventable condition [16]. Most of these symptoms are related to electrolyte abnormalities. These disturbances, which affect the cardiac and lung organs, the gastrointestinal system, and the immune system, have mostly been demonstrated in articles presenting case series and case reports [11, 141, 144, 169, 170]. Mortality and RFS has been reported on for centuries, [171] being confirmed by a recent large RCT study called the EFFORT trial [159]; this study finds that patients with RFS (low electrolytes in conjunction with symptoms) had an increased rate of mortality of 29.8% compared with 17.5% within 180 days.

.

3. Aims

The overall aim of the current research project was to develop evidence-based knowledge regarding RFS among older malnourished hospitalized patients. A systematic review was essential for obtaining the current evidence available regarding RFS in older adults. Previous systematic reviews in the field were have been based on different populations and could not be generalized to our older multimorbid patient group [20, 162, 163, 169]. Further, we aimed to explore if providing a more assertive initial refeeding protocol would improve nutrition status as measured by HGS but if it would potentially aggravate RFS. We also explored the mortality in relation to the different diagnostic criteria of RFS.

3.1 Paper I

The aim of the systematic review was to explore the knowledge of RFS in patients aged 65 years and older. The following outcomes were a special focus: (1) incidence of HP in relation to refeeding, (2) refeeding rates (kcal/kg/day), (3) number of days until the lowest level of phosphate occurred (day of nadir), and (4) associations between refeeding rates, adverse events, and death.

3.2 Paper II

The primary aim of this study was to assess the effect of a refeeding protocol that initially provided 20 kcal/kg/day on muscle strength at 3 months follow-up as an indicator, comparing it with the current, cautious NICE protocol (5–10 kcal/kg/day) in a population of malnourished older hospital patients. The secondary outcomes were the occurrence of RFS during hospital stay and 3 months mortality. We hypothesized that the more assertive refeeding protocol would improve muscle strength and reduce mortality but potentially aggravate RFS.

3.3 Paper III

The aim of our study was to investigate the incidence rates of RFS using three different diagnostic criteria in older hospitalized patients and to study the mortality rates in patients with or without RFS according to these criteria.

We hypothesized that using different definitions of RFS will cause a wide range of incidence in RFS, and patients with RFS will have a higher mortality rate 3 months and 1 year measured by all three criteria.

4. Methods

4.1 Design

The purpose of this chapter is to outline the choice of methodology and the methods used. The first paper (Paper I) was a systematic review and was conducted to identify the evidence regarding RFS in older patients [172]. The main study was designed as a pragmatic randomized clinical trial (RCT) (Paper II) [173], while the last study (Paper II) was a longitudinal study using the data from the RCT. The rationale for the selected designs and description of the designs and sample population are further presented in this chapter. Further, a description of the participants, recruitment procedures, data collection, randomization and blinding, and ethical consideration are presented. The statistical analysis and rationale for the research project are also described in this chapter.

4.2 The systematic review (Paper I)

A systematic review was important to obtain an overview of the research of RFS in older adults. Former systematic reviews [17, 19, 20, 162, 169, 172] in this field have been based on patients with anorexia nervosa, cases and case series and a mixed population (both young and older patients); hence, these studies could not be generalized to our older multimorbid population.

The methodology of the systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [174]. A protocol was registered in the PROSPERO data base a priori [175] (registration number CRD 42019119282). The methodology of the systematic review will be described in more depth in the next section. A systematic review was important to obtain the evidence available regarding RFS in older adults.

4.2.1 Data sources and search strategy

Eligible studies were checked by an experienced health science librarian with expertise in systematic literature searches. The medical subject headings (MeSH) for appropriate terms in addition to the chosen keywords was used during the search strategy. We included all types of quantitative studies, prospective and retrospective studies, pre–post studies, case control studies, RCT and quasi-RCTs, and case series/case reports. The search was restricted to publications in English, Norwegian, Swedish, and Danish because of the limited resources for translation.

The following databases were searched: the Cochrane Central Library, Ovid, MEDLINE, Embase, CINAHL, SveMed+, BMJ Best Practice, National Guidelines Clearinghouse, NICE guidelines, Nursing References, and Center Plus. In addition, searches were conducted in the International Clinical Trials Registry Platform, ClinicalTrials.gov, and PROSPERO for ongoing or recently completed trials and systematic reviews.

4.2.2 Article Screening and selection

The comprehensive search conducted by the librarian was compiled in an EndNote file that was structured and shared with an assistant performing the first sorting, where duplicates and irrelevant titles were discarded. Two reviewers (Siri Nesse and Sissel Urke Olsen (SUO)) independently reviewed all the titles and abstracts from the EndNote file. Because automated databases may be incomplete, we hand-screened the reference lists of all the reviews A total of three rounds was performed to ensure all eligible articles were included; the coreviewers evaluated all full-text articles (SUO, Asta Bye, Karin Hesseberg (KH)). The population, intervention, comparison, and outcome (PICO) method for assessing eligibility—in accordance with the PRISMA guidelines—was used and published in Paper I [172]. The inclusion criteria were patients enrolled and admitted to a health care setting who were 65 years or older, information on the nutrition and phosphate levels needed to be included in the articles, and the incidence rates, adverse events, and death. In the case of uncertainty or disagreement, the coreviewers discussed the findings until an agreement has been reached. Ultimately, 15 papers were included in the systematic review.

The PhD candidate extracted the following data from the articles: authors, country, year, study design, population, including sample size and disease, the inclusion criteria, details of the interventions, outcomes, and the results of the study.

4.2.3 Quality assessment of the included trials

Because of the wide heterogeneity among the studies, it was not possible to perform a quantitative meta-analysis, so a narrative description was performed.

To assess the quality of the observational studies, we used the Critical Appraisal Skills Program (CASP) checklists [176], and these were assessed independently by SUO and KH. The CASP checklists apply three headlines to check for the quality of the research:

1. Is the study valid? Evaluates the methodology of the study.
2. What are the results? Based on statistical analysis and methods, are the results clinically important?
3. Are the results useful? Its generalizability—meaning; can the results be transferred to situations or people other than those originally studied?

The case series/case reports were assessed using the case report checklist from Garg et al. [177]. To date, there are no existing tools to assess the risk of bias (methodological quality) of case reports or case series. This checklist focuses on nine topics: 1) Is this novel, which asks if it is a novel occurrence, investigation, or treatment of a patient? 2) Did the article obtain patient consent to publish the patient case? 3) Was the case using ethical practice as per the standards of care? 4) Did the title describe the core message of the case? 5) Did the abstract contain a core message? 6) Were key words/MeSH included in the article? 7) Did the case contain a thorough description of the case? 8) Did the case discuss potential clinical implications and limitations related to the case study? 9) Did the case study contain a core key message in the conclusion? [177]

4.3 The randomized controlled trial (Paper II)

To investigate the effect of two different EN protocols on nutritional status 3 months after nutritional treatment of malnutrition, an RCT was conducted. Using an RCT design is seen as the gold standard for research because the design lends itself to robustness and prevents selection bias, which, in turn, ensures proper randomization [178]. A sufficient sample size is needed to ensure that all factors that might influence the study are equally distributed between the groups, hence enabling the researcher to reveal the causal interpretation of the treatment outcomes[147].

4.3.1 Design

The RCT was based on a semi-double-blinded parallel group RCT with a pragmatic design. The intervention lasted for 7 days in a hospital with two assessment points in addition to baseline, at day 4, at day 7, and a follow-up point at 3 months **(Figure 2).** The CONsolidated Standard of Reporting Trials—CONSORT 2010—was followed as a reporting protocol in our study [179].

4.3.2 Sample recruitment and eligibility criteria

The participants were recruited from both surgical and medical wards at Diakonhjemmet Hospital. This hospital serves approximately 135,000 inhabitants and is a local general acute care hospital in the capital of Norway: Oslo.

Inclusion and exclusion criteria

To be included in the RCT study, patients needed to be 65 years or older, admitted to the Department of Medicine or Surgery at Diakonhjemmet Hospital, and screened to be at risk for RFS, here by using the NICE screening tool criteria (Table 5)[145].

We excluded patients with end-stage dementia (according to ICD 10 code F00-03), those already on EN or intravenous nutrition (IV nutrition), not wanting to stay in the hospital for at least 7 days, admitted directly to the intensive care unit, previously participated in the study,

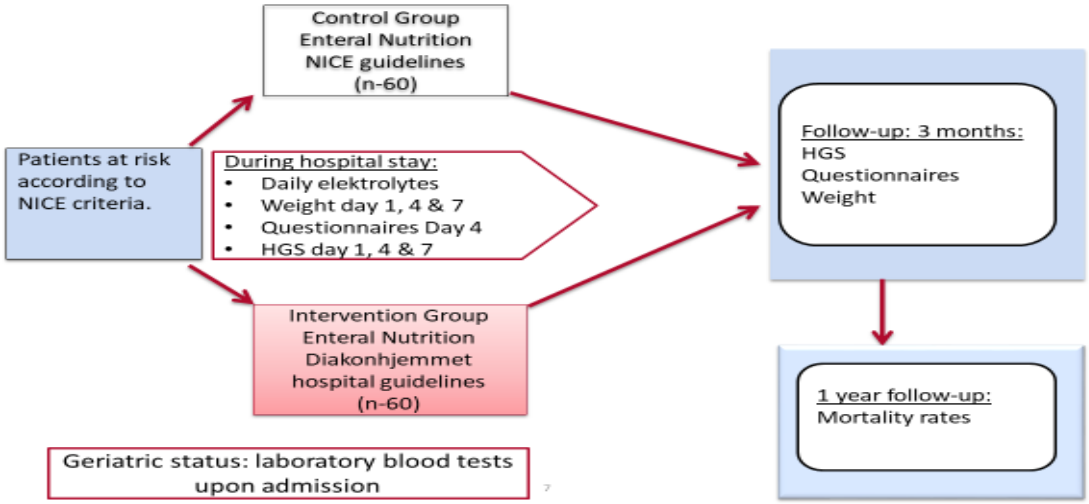
or terminally ill or a short life expectancy, as evaluated by the medical doctor. Further, patients with severe kidney disease with glomerular filtration rate <30 or congestive heart failure NYHA class III or IV needed to be cleared by a medical doctor to participate.

4.3.3 Procedure

The data collection project started in April 2017 and lasted until August 2019.
The recruitment process was carried out by the PhD candidate, and patients were either referred to by clinical dietitians or medical doctors; in addition, the PhD candidate obtained a patient list and checked patients for eligibility, when possible. The PhD candidate also participated in rounds and multidisciplinary team meetings to increase the recruitment of patients. Potential eligible patients were screened according to the NICE guideline tool for risk of RFS (**Table 5)**, which includes height and weight and questions regarding weight, weight loss, and energy intake. Information regarding weight loss was confirmed by earlier registered weight in the electronic medical record (EMR), from the next of kin, or from the care home the patients were residing at, if available.

Eligible patients were approved by medical doctors before they were asked to participate to ensure there were no medical contraindications for participating. Patients who fit the inclusion criteria were asked to join the study in a way that did not make them feel obligated to participate. It they agreed, the PhD candidate obtained written consent from the patients or through a proxy. A trained nurse inserted a feeding tube, and a radiograph confirmed correct placement.

Figure 2. Flow of inclusion, treatment allocation, and follow-up



HGS: Hand grip strength; questionnaire: Health-related Quality of Life (EQ5D5L) and Cognitive Screening Tool (4AT)

4.3.4 Randomization and blinding

A computer-generated block randomization schema designed by a statistician at the Faculty of Health Science at Oslo Metropolitan University was used to allocate the patients. Randomization blocks ranged from four to ten. The randomization list was not accessible to the main investigator, nor was the block size. An external assistant provided the treatment allocation by phone. The PhD student developed the EN refeeding protocol and copied it into the medical chart after obtaining signed consent.

4.3.5 Intervention and control group

Patients in the intervention group (the Diakonhjemmet Hospital group (DH group)) and control group (the NICE guidelines group (NICE group)) received EN through a nasogastric feeding tube.

A standardized refeeding protocol that was based on patient weight was developed for both groups. The energy requirement was estimated to 30 kcal/kg/day and protein requirements 1.2–1.5g /kg/day, as recommended for older adults with acute and chronic diseases. For patients with

renal failure (GFR <30), a lower target of protein (0.8 g/kg/day) was used. Fluid requirement was set at 30 ml/kg/day as standard, unless medical therapy required otherwise [2].

The DH group received a more assertive EN refeeding protocol, with an initial calorie level of 20 kcal/kg/day that was titrated up to estimated needs within 3 days, continuing to EN refeeding for a minimum of 7 days.

The NICE group received a more cautious EN refeeding protocol with initial 5 kcal/kg/day if BMI <14 m^2 or 10 kcal/kg/day with BMI >14 m^2 and were titrated up to meet the estimated calories needs within 7 days. Table 7 demonstrates a case of the refeeding protocol.

The DH group and NICE group had the same protocols regarding electrolyte replacement protocol, EN formula (adjusted if needed, according to disease state), oral nutrition registration, supplementations of vitamin and mineral, thiamine, and laboratory blood work.

- Electrolytes were monitored daily, and the PhD student ensured that laboratory tests were ordered. Diakonhjemmet Hospital electrolyte replacements protocol was used [158]. Electrolytes were supplemented when phosphate levels were < 0.65 mmol/, magnesium levels < 0.65 mmol/L, and potassium levels < 3.6 mmol/L [145]. (Appendices in Article III, the full Electrolyte replacement protocol is published).
- EN formula Nutrison Protein Pluss (produced by NUTRICIA Norge AS) contains 1250 kcal, 63 g (20%) protein, 49 g (35%) fat, 142 g (45%) carbohydrates and 84% water per 1000 ml. This formula is appropriate for older malnourished patients and is a standard formula in the hospital.
- Regarding oral nutrition intake, because of ethical reasons, it was not possible to deny patients oral intake during EN. Food intake was recorded by the nurses in the electronic medical journal and retrospectively analyzed by the PhD candidate. A premade standardized calorie and protein fact sheet of the food used in our hospital was used, in addition to obtaining recipes from the kitchen and using the food analyzer tool called “Matvaretabellen” [180].
- Thiamine: 100 mg intramuscular for a maximum of 10 days or until discharged.
- Multivitamin and mineral: 1 tablet a day during the stay, which contains all vitamins and minerals.
- B-complex: 3 tablets a day, which contain all B vitamins, (thiamin 1.4 mg, riboflavin 1.7 mg, vitamin B6 1.6 mg, vitamin B12 2 μg, folate, 400 μg, niacin 19 mg, pantothenic acid 5 mg, and biotin 30 μg), during the stay.

Table 7. Demonstration of a refeeding protocol for a patient; women 40 kg and BMI 16 kg/m^2 with an estimated energy need of 1200 kcal/day

NICE group 10 kcal/kg/day			DH group 20 kcal/kg/day		
Day		Titration rates Days 1–7	Day		Titration rates Days 1–7
Day 1 Full needs on day 7		320 ml/16 ml/t 428 ml/21 ml/t 535 ml/27 ml/t 644 ml/33 ml/t 752 ml/38 ml/t 860 ml/43 ml/t 960 ml/48 ml/t	Day 1 Full needs on day 3		640 ml/32 ml/t 800 ml/40 ml/t 960 ml/48 ml/t 960 ml/48 ml/t 960 ml/48 ml/t 960 ml/48 ml/t 960 ml/48 ml/t
IV fluids should be limited, if possible, to 30 ml/kg/day, and nonglucose-containing IV fluids should be used for rehydration Thiamine 100mg x 1/day for maximum 10 days, 1 vitamin and mineral, and 3 B-complex a day					

BMI: Body mass index; IV: intravenous; DH: Diakonhjemmet Hospital; NICE: National Institute for Health and Clinical Excellence

4.3.6 Compliance

Patients' ability to follow the refeeding protocol (compliance) can be defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider," as defined by the WHO [181]. The word compliance often carries a negative connotation in a healthcare setting [182]. However, the compliance of EN refeeding protocols are simply the ability to follow the set refeeding protocol. However, noncompliance with the refeeding protocol was not merely up to the patients but could have been because of concurrent events like medical testing, the EN formula not being available, accidental dislocation of the tube, or being too busy to insert new feeding tube. In addition, adverse events such as worsening of the disease, nausea, vomiting, constipation, or bloating and early discharge affected the compliance with the refeeding protocol. EN was recorded to estimate the energy received during the 7-day intervention period.

Table 8 demonstrates the potential adverse events and undesirable consequences of EN that may contribute to a lack of compliance.

Adverse events that often occur during EN were registered because these may have implications for patients' nutritional status. All six variables were retrospectively registered after the initiation of EN, and information was obtained from the patient's EMR.

Table 8. Registration of undesirable events during enteral nutrition during the study [183-185]

	Variables registered as undesirable events during enteral nutrition	Description and definition	Undesirable consequences
1.	Dislocation of tube	Accidently removing feeding tube	If tube is not identified as being mitigated, formula might be given in esophagus, increasing the risk of aspiration pneumonia
2.	Diarrhea [186]	Diarrhea is defined as reduced stool consistency with an increased water content and at least 3 evacuations a day	EN might cause diarrhea -Needs for stopping the feeding, reducing energy provision -Causing soar and multiple changes of bedding
3.	Constipation [187]	Evacuation /Defecation less than 3 times a week	Constipation might cause nausea, vomiting, pain, and discomfort Causing reduction in energy provision
4.	Vomiting/aspiration		Vomiting might cause aspiration pneumonia
5.	Nausea	During EN	Nausea might cause stop in EN, reducing energy provided
6.	Lung and breathing /respiratory distress	The presence of dyspnea, oxygen saturation fall, or pulmonary crepitations after the initiation of refeeding and indicated respiratory distress.	Side effect of refeeding/RFS
7.	Intensive care unit (ICU)	Transferred to ICU after initiation of refeeding protocol	Adverse effect of refeeding/RFS

EN: enteral nutrition; ICU: intensive care unit; RFS: refeeding syndrome.

4.3.7 Assessments

This section provides a detailed description of all the outcome measures used in Papers II and III. To quantify and describe the results in the RCT and the longitudinal study, we selected outcome measures based on both theoretical and practical reasons. The primary outcome in the RCT was nutritional status, here as measured by HGS, and the secondary outcomes were RFS and mortality. The outcomes in the longitudinal study were (**Table 9)** the incidence of

refeeding syndrome based on three different diagnostic RFS criteria and mortality in patients with and without RFS at 3 months and 1 year.

The CONSORT group recommends to ensure that both the validity and reliability of outcome measures and that essential quality property in all test tools and instruments are of a high quality, as well as ensuring that the instrument and measures have high sensitivity and responsiveness to change [179]. Validity is defined as the degree to which an instrument measured what was intended or rather measures what it is supposed to measure [147, 188]; this concept encompasses both internal and external validity. A high internal validity shows that there is a causal link between two variables and that alternative explanations of the results are unlikely. Whereas external validity relates to the results' ability to be generalizable to a broader setting [147]. Reliability or the internal consistency relates to the tests' stability and consistence and examines if the results are replicable in different settings [147].

Two other factors that are important when choosing a test instrument is the sensitivity of the instrument and the responsiveness. Sensitivity is the ability to accurately identify the true cases (true positive), that is, having no false positives [147, 188], and responsiveness is the ability to detect changes over time, when a change has occurred, and if it is clinically meaningful (minimal clinically important difference [189, 190]). Specificity is the ability to accurately identify patients who do not develop the case, that is, find the negative predicted value (true negatives) [147].

Baseline testing was conducted by the PhD candidate prior to the randomization by using the NICE screening tool (this tool contains many of the same questions used in various screening tools for malnutrition): BMI, weight loss and oral intake (NRS 2002 and MUST) to detect patients at risk of RFS **(Table 5)**.

Assessors were clinical dietitians working at the hospital and blinded to allocation, and we strived to use the same clinical dietitian to follow the patient throughout the study. In the current study, 85 were tested at baseline, 79 at day 4, 68 at day 7, and at 32 at the 3-month follow-up. Written procedures were developed to standardize the measurements.

Hand grip strength

Hand grips strength was measured using a JAMAR PLUS® Hand dynamometer (Patterson Medical, USA). It was adjusted to the appropriate grip width [191] and read to the nearest 100 grams. We tested both arms while the patients were seated with their shoulders adducted, their elbow flexed 90°, and their forearms in a neutral position [192]. If the patients were not able to sit in an upright position, testing in bed was done. When tested in bed, the head of the bed was raised as far up as possible into a sitting position. The shoulders were abducted, their elbows were moved to 90°, and their wrists were placed in a neutral position not touching the bed. The tester could help by holding the dynamometer underneath when needed. The same test method was used every time, with two trials on both hands and minimum of rest between trials. The highest recorded HGS score for each hand was recorded. Measurements of HGS have good test–retest reliability[193].

Furthermore, several studies have looked at using HGS as a surrogate indicator for nutritional status to validate it as a nutritional marker. Clinical studies proving HGS as a valid indicator are still lacking, but studies have demonstrated indirect associations with HGS and nutritional status [104, 112, 115, 117, 194-196]. A recent study in 2020 [104] shows higher sensitivity predicting malnutrition using HGS compared with using arm circumference, BMI, and calf circumference. Because of lack of validated nutritional status biomarkers [197], we decided to use HGS when investigating the effect of nutritional intervention (Paper II).

Mortality

Mortality is assessed from the day of inclusion in the study and at 3 months and 1 year. Mortality was obtained either from EMR or from the National Population Register [198]. The cause of death was not obtainable for patients after being discharged from the hospital.

Serum blood values and assessment for RFS

To provide information regarding patients' medical status, all patients had a blood analysis set called "*geriatric status*" taken upon admission, which includes the following: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBC), differential leukocyte count, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), thrombocyte, vitamin B12, folic acid, sodium, potassium, calcium, magnesium, phosphate, blood urea

nitrogen (BUN), creatinine, glomerus filtration rate (GFR), creatinin clearance, alanin amino transferase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase, albumin, glucose, thyroid-stimulating hormone (TSH), and thyroxine T4 free, 25-OH-vitamin D3.

The following values were measured daily during the intervention period: phosphate, magnesium, potassium, sodium, CRP, and glucose.

Laboratory tests were ordered either by the PhD student or a medical doctor. The tests were followed up on by the PhD student in addition to the medical doctor to ensure low values were corrected and were in line with the electrolyte replacement protocol [158]

The incidence of RFS was defined in Paper II as phosphate levels <0.65 mmol/L at any time during the 7-day hospital stay [158] (Diakonhjemmet Hospital Laboratory applies International System Units (SI units) [151]).

In Paper III, RFS was defined based on three different diagnostic criteria. The first criterion was the same as in Paper II, with phosphate levels <0.65 mmol/L at any time during the 7-day hospital stay [173]. The second criterion was based on the ASPEN consensus report [11] for RFS: "a decrease in any 1,2,3 of serum phosphorus, potassium, and/or magnesium levels by 10%-20% (mild RFS), 20-30% (moderate RFS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or because of thiamin deficiency (severe RFS)" "And occurring within 5 days of reinitiating or substantially increasing energy provision" (page 189). The third criterion for RFS was based on a consensus paper written by Friedli et al. [21] that defines a decrease of phosphate from baseline >30% or <0.6 mmol/L or any two other electrolyte shifts below normal range: phosphate <0.80 mmol/L, magnesium <0.70–0.75 mmol/L or potassium <3.5 mmol/L occurring within 72 hours after initiating nutrition therapy [21] (see **Table 4**).

Height and weight and body mass index

Height was measured on day 1 either by standing or using a laser gauge for patients not able to stand. For patients who could not stand, they were asked to lay stretched out on the bed, a tray was placed at the top of the head, and at the end of the foot, then the laser beam measured the length from tray to tray.

When measuring patients' weight, they wore light clothing; we used either an electronic chair scale (SECA Germany) or a standing electronic scale (Soehnle scale). Based on height and weight, BMI was calculated (weight in kilogram divided by the square of the height in meters) [199].

4.4 Paper III, longitudinal study

A longitudinal study can describe the OR and risk and relative risk while finding an association—but not a causal relationship—between variables. Here, the reasoning behind merging the two treatment groups was to increase the power of the results. The longitudinal design used data from the RCT (Paper II) [173]. The sample recruitment and eligible criteria and protocols are described in sections 4.3.2, 4.3.3, 4.3.4, 4.3.5 and 4.3.6.
The control and intervention groups were merged into one sample because there was no significant difference between the groups regarding baseline values, the primary or secondary outcomes, HGS, RFS, and mortality. As a note, there was a difference of energy provision between the groups at day 1 and day 2, and the DH group experienced significantly more respiratory distress than the NICE group. The three different diagnostic criteria are defined in **Table 4.**

4.5 Data analyses

4.5.1 Sample size and power calculations

The sample size estimation was calculated based on the primary endpoint HGS. A clinically important difference was defined as a mean difference in change in HGS of 1 kg from baseline to the 3-month follow-up between the two treatment groups. With an estimated SD of 1.8 kg, a tentative sample size of 104 patients had to be included to achieve 80% power at an alpha of 0.05. To account for dropouts, we increased the sample size by 20%, giving a total of 126 patients, with 63 patients in each group.

We anticipated to include 1.5 patients a week (63 patients in a year). This estimation was based on a point prevalence survey at Diakonhjemmet Hospital regarding malnutrition that was conducted in

2016. Out of the 72 screened patients who were 65 years or older, 12 (16.7%) had BMI <18.5, and if 10% agreed to participate with an accessibility of 4,000 new admissions a year, we anticipated reaching a sufficient number of patients in around 2 years.

4.5.2 Statistical analysis

Statistical analyses were performed with IBM SPSS v27. The level of significance was set at $p<0.05$ for all coefficients, and all tests were two sided. Skewness was examined by comparing mean and median values, and the normality of the distributions was looked at using the histograms and Q-Q plots. Descriptive data are presented as the means and standard deviation (SD), and categorical data are given as proportions and percentages.

Table 9. Outcome measures and statistical analysis used in Papers II and III

Variables	Paper II	Paper III
Sociodemographic variables		
Age and Sex	x	x
NICE screening tool	x	x
Outcome measurements		
Hand grip strength	x	
Refeeding syndrome	x	x
Incidence of s-phosphate	x	x
Incidence of s-magnesium		x
Incidence of s-potassium		x
Mortality at 3 m and 1 yr	X 3 months	x 3 months and 1 year
Statistical analysis		
Independent sample t-test	x	x
Chi-square test	x	x
Kaplan-Meier analysis		x

4.5.3 Statistical analysis Paper I

The systematic review was a narrative descriptive paper of RFS among older adults <65 years. Excel 2018 was used to create the figure in Paper I [172].

4.5.4 Statistical analysis Paper II

Data were analyzed using the intention-to-treat (ITT) principles on the between-group differences in change from baseline to follow-up on day 4, day 7. and 3 months using an independent samples t-test. The study included all patients in the analysis, regardless of incomplete intervention such as death or any other deviation from the protocol [200]. A common saying in ITT is “once randomized, always analyzed” [201]. This rule helps preserve the integrity of the randomization process and represents the real world, with missing, drop outs, or a lack of adherence to treatments [202].

To assess the difference in HGS and weight from baseline to day 4, day 7, and 3 months between the groups, a linear mixed models for repeated measurements with a subject-specific random intercept was used. The interaction between time and group were modeled as fixed effects. This model is considered a robust method for handling missing data in the ITT analysis; because of its ability to statistically adjust for missing data, there was no reason for the imputation of missing data [203]. The ITT principle will be discussed further in the discussion section.

4.5.5 Statistical analysis Paper III

In the longitudinal study, numbers and percentages were used to report electrolyte incidence rates in the different RFS criteria. An independent t-test and person’s chi-squared test were used to compare the difference between patients with and without RFS in each criterion. The Kaplan-Meier (KM) test can analyze time to event and is the best option to measure patients living for a certain amount of time after intervention [204]. The KM survival curve together with a log rank test was used to investigate if patients with RFS had a higher one-year mortality rate compared with patients without RFS. The survival estimate was recorded for the different RFS criterion [205].

4.6 Ethical perspectives

The research project was approved by the Regional Committee for Medical Research Ethics in South-eastern Norway (REC) (ref. no. 2015/676). The project was conducted according to the World Medical Associations' Declaration of Helsinki [206], and protocols for personal protections and information security were followed. Further ethical perspectives are discussed in section 6.2.1.

5. Summary of the Results

In this section the aims and methods are briefly presented, as well as a summary of the findings in Papers I, II, and III. A detailed presentation of the results is presented in Papers I, II, and III in the appendix. The implications and future directions based on these results will be discussed further in the discussion section.

5.1 Paper I

Title: *Refeeding syndrome occurs among older adults, regardless of refeeding rates. A systematic review.*

The overall aim of this systematic review was to explore the current knowledge of RFS in patients 65 years and older, with a special focus on (1) the incidence of RFS in relation to refeeding, (2) refeeding protocols (kcal/kg/day), (3) number of days until the lowest level of phosphate occurred (day of nadir), and (4) initial refeeding rates for adverse events and death.

Summary of findings

- Of the 936 titles examined, two cohort studies [207, 208], one case control study [209] (observational studies), and 12 case series/case report studies [210-220] with 19 individual cases met the inclusion criteria.
- The quality of evidence, according the CASP checklist, came with a moderate to high risk of bias, whereas the case series/case reports came with a high risk of bias.
- The incidence of hypophosphatemia <0.5 mmol/L was reported to be up to 25%.
- High mortality rates up to 48% was found after recommencing feeding.
- Day of phosphate nadir was found to be occurring between days 2 and 4, regardless of the energy levels.
- The most commonly reported adverse events in relation to low phosphate values in the case series/case reports were reduced muscle tonus, edema, and altered mental status.
- No meta-analysis was performed because of studies being too heterogeneous to be pooled and because many case series/case reports were used.

5.2. Paper II

Title*: A comparison of two different refeeding protocols and its effect on hand grip strength and refeeding syndrome: a randomized controlled clinical trial*

The overall aim of this study was to assess the effect of two different refeeding protocols on HGS at the 3-month follow-up. The secondary outcomes were the incidence of RFS when receiving two different EN refeeding protocol during a 7-day hospital stay and the 3-month mortality rate.

The study included 85 patients, 41 of which were randomized into the intervention group, which was the more assertive refeeding protocol, and 44 of which were placed in the cautious refeeding protocol, or the control group.

Summary of findings

- For the primary outcome HGS, the repeated measurements showed no statistical significance regarding the between-group difference at the 3-month follow-up (mean difference 0.78 kg, 95% CI -2.52 to 3.36, $p = 0.42$) (**Table 4** in Paper II). A total of 32 patients were included in the analysis.
- A more assertive refeeding protocol did not aggravate RFS, which was defined as phosphate <0.65 mmol/L, with incidence rates of 17.1% (n = 7) in the intervention group compared with 9.3% (n = 4) in the control group (p = 0.29).
- There was a high mortality rate, but no statistical significance between the groups, with 39% in the intervention group compared with 34.1% in the control group at 3 months ($p = 0.64$).
- There was a statistically significant difference between groups in favor of the intervention group in respiratory distress 53.6% vs. 30.2% ($p = 0.029$). Here, 19 of the 35 (54%) patients with respiratory distress died within 3 months (22 (62.8) patients within 1 year and significantly more in the more assertive refeeding protocol ($p = 001$) unpublished data).
- Patients not included in the study were similar in age and sex as the included patients. The reasons for not participating are published in the appendix of Paper II.

5.2. Paper III

Title: *The incidence and mortality of refeeding syndrome in older hospital patients based on three different diagnostic criteria*

The overall aim of our study was to investigate the incidence rates of RFS using three different diagnostic criteria in older hospitalized patients and to study mortality rates in patients with or without RFS according to these criteria.

Summary of findings

- The three different RFS diagnostic criteria showed a wide range of incidence rates, with 13.3% (n = 11), 31.7% (n = 27), and 64.7% (n = 55) for the TC, Friedli et al[21]., and ASPEN criteria, respectively.
- The incidence rate of hypophosphatemia was 13.5% (n = 11) for the TC, 7.3% (n = 6) for Friedli et al., and 45.9% (n = 39) for the ASPEN criteria [11].
- Day of nadir was on mean (SD) day 3 (1.8) for serum phosphate, for serum magnesium on mean (SD) day 2.7 (1.6), and for serum-potassium on mean (SD) day 2.6 (1.7).
- The initial mean (SD) energy intake (oral and EN) was 19 (11.0) kcal/kg/day, and the average energy intake during the 7-day intervention period was mean (SD) 23.7 (10.9) kcal/kg/day. The mean (SD) average 7-day protein intake was 1.2 (0.5) g/kg/day.
- The Kaplan-Mainer analysis showed no statistical difference in mortality in patients with and without RFS in the different criteria: TC, p = 0.38, Friedli et al., p = 0.75, ASPEN, and p = 0.83.

6. Discussion

The discussion is divided into two main sections: the methodological considerations and discussion of the main findings and the clinical implications and future perspectives.

6.1 Methodological considerations

First, ethical considerations regarding research on severely malnourished patients is discussed, and then, the methodological considerations, including the internal and external validity, are examined. This is followed by a discussion of the choice of intervention and outcome measures in the three papers. Finally, the statistical methods that are employed are elaborated on.

6.1.1 Research on severely malnourished older hospitalized patients and ethical considerations

Respecting autonomy, beneficence, nonmaleficence, and justice when recruiting a vulnerable group for research is crucial. This means that patients should be able to choose freely to participate. that their participation will be beneficial for the patient, and, importantly, that the benefit will outweigh the harm of participating. Here, justice means that the treatment is fair to all patients [128, 206]. The current study targeted a vulnerable group of patients, most in their 80s, severely malnourished, and with several comorbidity diseases. Vulnerable populations, as in older adults, are at risk of being harmed, manipulated, coerced, or deceived when being recruited for research because of diminished competence or incapacity [131]. Hence, in the present study, recruiting older multimorbid and severely malnourished patients, with and without dementia or cognitive decline, was challenging both ethically and methodologically. REC approved the inclusion of patients with dementia. REC emphasized that excluding patients with cognitive decline/dementia will be discriminatory and inhibit valuable information in a group with a high prevalence of malnutrition and that is potentially prone to developing RFS.

The user committee at Diakonhjemmet Hospital was informed about the research project and its ethical considerations regarding including patients with dementia. They voiced their concern regarding the need to balance the protection of the patients versus the need to ensure that high-risk patients, who are under-represented in medical research, have the opportunity to participate in clinical studies; this is also stated in the Helsinki Declaration [206]. One concern was to ensure patients with dementia had their integrity cared for throughout the study. It was also important to reflect critically and continually on the participative process and if this study benefited the patients. It was also of concern that they understand the nature of the research and their participation. Also important was the patients' ability to consider alternatives, including the option not to participate. The consent form went through extensive revisions by colleagues, professional users, the hospital's user committee, and REC.

The recruitment of patients held a fine balance between considering the patients' best interest and the need of recruiting patients. This was especially the case because participation in the study required initiating of EN in patients in their 80s and 90s. The need of EN was discussed with a medical doctor and nurses. When the PhD student asked patients to participate, the researcher clearly stated her biases. It was also emphasized that it was possible to withdraw from the study at any time with no consequences regarding the treatment; however, doing so might change the length of the hospital stay (shorter). Another ethical discussion was the high mortality rate and challenges because of the follow-up in this vulnerable group. We found an almost 40% mortality at 3 months, and here, there was a huge challenge with the follow-up because of worsening of illness, not wanting to, or not being able to be reached, leading to insufficient patients for a meaningful analysis. The present study illustrates the challenges in conducting studies on a multimorbid severely malnourished older population with a high mortality rate.

6.1.2 Methodological considerations in the systematic review, Paper I

We aimed to systematically summarize the literature on RFS among older patients with a focus on the incidence of RFS in relation to refeeding, refeeding rates (kcal/kg/day), number of days until the lowest level of phosphate occurred (day of nadir), and associations between refeeding rates, adverse events, and death. This decision was made because of the lack of existing systematic reviews on the specific topic in older adults. We included all types of studies, including case series and cases reports, which are considered the lowest on the

hierarchical pyramid when it comes to quality of evidence [221]. We knew there would be limited studies on the topic, but we anticipated more than three clinical studies. Thus, studies claiming to investigate older adults often had large standard deviations and included patients in their 40s and 50s. In the systematic review, it was key that all patients were 65 years or older, which ensured that the conclusion was based on the appropriate age group.

To have a systematic review with a high level of quality, there is an assumption that comprehensive, rigorous, and systematic methods are performed so that the results and conclusions are reliable [222]. The strength of our systematic review was that the protocol was registered in PROSPERO a priori and that the research question and inclusion criteria were established before the search was conducted. Registering the study a priori can help minimize the reporting bias and increase the transparency of the systematic review [223]. This study was also conducted in the accordance with PRISMA, hence enabling future reproduction or follow-ups [174]. Another strength was the comprehensive literature search, which was performed by a trained librarian, and that the search strategy was included in the appendix of the published paper.

The limitations of our study were the lack of studies and that the studies were too heterogenic, which prevented us from pooling the data into a meta-analysis. Pooling case reports and case series poses challenges because they are uncontrolled studies and increase the risk of bias; hence, we chose not to perform this in our systematic review [224, 225]. Because of a large number of excluded articles, a comprehensive list of excluded articles is not provided [222].

6.1.3 Methodological considerations in Paper II and Paper III

Internal and external validity and bias.

The validity of the study results is critical because it indicates to what degree the conclusion is credible, valuable, and generalizable [147]. The ultimate goal is to enhance the knowledge of the field and to apply the findings beyond the study setting [147].

If the study answers the research questions without bias in its design, the randomization process, blinding, sample size, outcome measures, dropouts, analysis, and interpretation, a study is considered internally valid [226]. If the sample population represents the target population, the study has high external validity [227]. When we designed the current study, we carefully considered the above factors to avoid bias or systematic errors [228].

Sampling bias.

This occurs when the study sample does not represent the study population it is intended to study (threat to external validity [227]) or if there are systematic differences between the selected samples and the results because of the difference between the groups rather than differences in the intervention (internal validity) [147, 227]. This may occur for several reasons, for example, when the recruiter enrolling is able to determine with some degree of accuracy the next treatment allocation [229]. This threat was reduced substantially in our study by keeping to the carefully developed randomization protocol and validated methods of randomization [173]. All patients were randomly allocated to an intervention group or control group after baseline testing, and the randomization of patients was based on a computer-generated permuted block randomization system, leading to different block sizes from four to ten [230]. The randomization list was not accessible to the recruiter, nor was the block size, and an external assistant provided the treatment allocation by phone.

Another threat to the internal validity is selection bias. A certain degree of selection bias will always be present in a study where the recruiter is the main investigator, even if it is unintentional [229]. In the current study, patients were recruited through several methods: by clinical dietitians, nurses, and MDs who contacted the PhD candidate for potential eligible patients. The PhD candidate also recruited from preround meetings, patient lists, and asking the nurses and MDs on the wards for eligible patients. However, some MDs, nurses, and wards were more accommodating for recruitment, and a higher number of patients were recruited from certain wards, leading to a certain degree of selection bias. Another possible selection bias was to what degree the patients would benefit from EN. This decision was made by the MDs and nurses. If they thought this treatment option would be too uncomfortable for the patients, they denied participation, potentially unrightfully speaking on the patients' behalf [231]. Some patients were excluded because of active delirium and difficulties with cooperation or because of not having a next of kin to sign the consent. Furthermore, patients who had a confirmed place at a nursing home would lose their place if joining the study, so they were not allowed to participate.

Diakonhjemmet Hospital serves mainly districts that include people with a high socioeconomic background, but in recent years, areas from Oslo known to be more disadvantaged have been added to Diakonhjemmets' sector; this has caused a mix of patients from both areas. However, the hospital includes only people living in urban areas in the

biggest city in Norway, so the participants in more rural districts were missing, causing less generalizability [227].

The exclusion and inclusion criteria will influence the external validity [227]. Thus, strict inclusion criteria ensure high internal validity but are a threat to external validity. The inclusion criteria in the current study were strict regarding nutrition status: patients needed to be severely malnourished and 65 years or older. Apart from being malnourished, the inclusion criteria were broad regarding diseases, and patients from both the surgical and medical wards were included. Moreover, the present study is a pragmatic study and represents real clinical practice [232]. Of the 167 patients screened, 82 patients declined, and of those, only two did not fulfill the inclusion criteria, with no differences in age and sex in those patients not included in the study.

The reasons for not participating are published in Paper II in the appendix [173]. The current study had a population with a high proportion of comorbidity, with an average age close to the mid-80s; hence, one should be very careful when generalizing these results to groups other than those similar to the study population [147].

Outcome measures.

HGS was the primary outcome and was used as a surrogate marker for nutritional status to measure the effect of two different refeeding regimes [104, 117, 196]. As an instrument, HGS has been used extensively in different populations, including older adults, [106, 112]. HGS has been used to measure the effect of nutritional intervention in older malnourished patients since the 1990s [104, 117, 195, 196, 233-240] but is still not fully validated as a marker for nutritional status or as a measure of the effect on nutrition interventions. This might pose a challenge to the reliability and internal consistency of the test. However, the aim was to demonstrate if HGS improved after the intervention of using two different refeeding protocols, which included more than simply the nutritional status.

Refeeding protocols.

The choice of the refeeding protocols used in the current study (in 2015/2016) was based on conflicting studies regarding the initial kcal/kg/day and titration rate, in addition to having

clinical experience that a higher initial kcal/kg/day and a faster titration rate than the recommended NICE guidelines with close monitoring of electrolytes would be safe [145]. Indeed, studies in patients with anorexia have shown better outcomes when the initial refeeding kcal/kg/day and titration rates were higher [162].

Deciding on the initial calorie level and titration rate was a difficult task. The decision behind 20 kcal/kg/day was a previous recommendation in some studies before the NICE guidelines were developed in 2006 [134, 136, 145]. This resulted in approximately 30% more calories and protein during the 7 days on EN in the intervention group compared with the control group.

The PhD candidate deciding the initial calorie levels and titration rates may pose bias because the candidate might think the intervention would be more favorable. However, this potential bias was reduced because of the randomization procedure and because of the PhD candidate not being involved in the testing of the patients.

Mortality.

Mortality is considered the gold standard for measuring the effect of treatment and poses few biases [241]. However, using mortality as an outcome usually requires a large sample size [241], but for our older multimorbid hospitalized malnourished patient group, we did expect a certain percentage of mortality, especially because RFS might cause detrimental outcomes.

Monitoring adverse events of EN.

Diarrhea, vomiting, aspiration, constipation, edema, nausea, respiratory distress, and admission to the ICU, in addition, to dislocation of the tube, are all common adverse events in EN [185, 242]. The adverse events were defined before the study began, except for respiratory distress, and there was a risk of bias of this symptom because it was done retrospectively and by the PhD candidate. Even when being conscious of potential bias, it cannot be eliminated.

Registration of oral dietary intake/calorie counting:

Patients receiving EN also had their oral dietary intake recorded in their EMR by the nurse (blinded). Registration of dietary intake is often ordered by the clinical dietitian, and it is a known procedure by the nurses. Having the nurses record patient intake instead of the patients themselves was a more reliable method because many older adults have difficulties remembering food intake [243]. The randomization helped even out the differences in the accuracy of the nurses, and the nurses were blinded and not privy to the results. The PhD candidate did all the analysis of the oral intake, including the oral nutrition supplement, here by using a premade standardized calorie and protein containing fact sheet of the food used in the hospital; this was done in addition to obtaining recipes from the kitchen and using the food analyzer tool called "Matvaretabellen" [180]. The internal validity of the analysis could be considered good because one person performed the analysis; however, it could have been further increased by using an external person not related to the study.

Assessment points on day 4, day 7, and 3 months.

The thoughts behind the assessment points was that the more assertive refeeding protocol would have reached estimated needs on day 3 or 4 and on day 7 for the cautious refeeding protocol. Assessing health-related quality of life using the questionnaire EQ-5D-5L [244] and patients cognitive function, using the questionnaire 4AT [245] (these data are not published) on day 1, may not have shown the correct answer, due to the trauma of being admitted into the hospital, and some acutely ill. Especially for the question on how the patient perceived their health that day. It would also have been overwhelming for the patient with both the insertion of a feeding tube and being given questionnaires. It was also important to measure weight to control for fluid overload in relation to refeeding on day 4 [142]. Day 7 was the end of the study intervention, and HGS and weight were important to measure at this point.

Blinding.

To improve the internal validity, blinding is an important measure. In the current study, both groups received EN but at a different initial rate and titration rate. The patients, nurses, and

MDs were all blinded to the treatment allocation. The nurses administrating the refeeding protocol did not have knowledge of the study details or aim of the study.

The assessors who tested patients at day 4, day 7, and 3 months were also blinded to the treatment allocation. However, the PhD student, who copied the treatment plan in the electronic journal and ordered laboratory tests, was aware of the allocation but was not involved in the testing of patients. Because of the blinding, the internal validity of this study is high.

Sample size.

Both the sample size and power calculation affect the internal and external validity [147]. To detect small differences between groups, larger sample sizes are needed. In the current PhD study, we wanted to demonstrate 1.8 kg difference in HGS between the two groups, and the power calculation showed that a total of 104 participants were required to reach a *p* level of <0.05 and a power of 80% [147]. The power calculation is further discussed in the statistic section.

This study (Paper II [173]) did not obtain the estimated sample size, and the high attrition rate at 3 months was detrimental to the sample size, with only 38% follow-ups; this significantly affected the internal validity.

Compliance.

Having compliance with the study protocols is an essential outcome in a pragmatic trial [246]; in this study, several obstacles were registered as the reason not to comply with the refeeding protocols.

- Dislocation of the tube by accident
- Pause in EN for medical reasons
- Patients simply deciding to discontinue the feeding because of discomfort, not understanding the importance of feeding, or feeling unwell
- Patients leaving the hospital against medical advice

The total provided energy is recorded and discussed in section 6.2.3.

Confounding variables.

The confounding variables are also called the third variable; that is, they are an extraneous factor that distorts the results. This may lead to a false association disguising the true results, affecting the internal validity [147]. In an RCT, there is no need to control for confounding variables because this is automatically controlled for during the randomization process. The CONSORT statement is clear, stating that as long as the randomizations have not been compromised, one should expect that the RCT design will naturally adjust for all baseline characteristics [230].

In the longitudinal study, we did not explore associations or try to find a causal relationship, but rather, we looked at the percent (and number) of patients with RFS, and if there was a difference in mortality if present with or without RFS. In addition, we used KM to look at the time until an event occurred.

6.1.4 Statistical considerations

In Paper II, we used the ITT principle, and patients were analyzed according to the group they were randomized to, regardless of adherence to the intervention. Hence, all randomized patients were analyzed, regardless of dropouts, death, nonadherence, or deviation from the protocols [147]. Using the ITT principle reduces bias, and it is the recommended analysis to use in RCTs, being considered the gold standard [230, 247]. In the current study, lost to follow-up is the largest challenge, with 36.5% deaths occurring before the 3-month follow-up. In addition, 24.7% of our patients were not included in the analyzes because they were not able to, did not want to, or could not be followed-up with (not possible to locate, moved too far), and they were considered as lost to follow-up. Active measures were taken to prevent lost to follow-up; for example, the assessors visited patients at their place of living, they called to ensure patients were at home, and they were flexible when to meet. Still, only 32 patients were assessed at 3 months. The insufficient sample size may have caused a type II error, failing to demonstrate a real difference when there actually was a difference [147].

The goal was to look at the difference in HGS from baseline to day 4, day 7, and 3 months. Because of the large amount of missing numbers, we have used a fairly new statistical model—the linear mixed model—for repeated measurements. This model is robust for missing data and considers the entire data set. In addition, it can be adjusted for baseline

values. This is a very flexible method for modeling continuous outcomes on data with a dependency structure between the observations: “Mixed methods, use different types of effects for describing relationships between study variables and the outcome of interest, and for accounting for correlation among related observations” (page 913) [248] [37].

In Paper III, which was the longitudinal study, we used the percentage as the primary analysis when comparing the incidence rates of RFS, and we used a chi-square and independent t-test when comparing the patients with RFS and patients without RFS for categorical and continuous variables, respectively.

The KM curve was used to measure the numbers of patients alive in each criterion at 1 year. The KM survival curve is described as “the probability of surviving in a given length of time after treatment” (page 274) [204].

KM also displays the censored data, showing patients who survived after the study period had ended, which was 1 year. To check for statistical difference in survival, the log rank test was used. KM is similar to a logistic regression analysis (univariable analysis) and is not designed for testing confounding variables [204, 249].

6.2 Discussion of the results

The overall aim of the present thesis was to contribute—and thereby substantiate—the knowledge of different EN refeeding protocols in older malnourished hospital patients. As part of this PhD project, we conducted the first systematic review on RFS in older patients (Paper I). We also conducted the first RCT in a malnourished multimorbid older hospitalized patient group using two different refeeding protocols, here by measuring the effect on HGS as a nutritional marker (Paper II). In addition, the present dissertation contains the first study to investigate RFS using three different diagnostic criteria, comparing if RFS was more prevalent than in patients with or without RFS (Paper III).

Our review demonstrated limited research regarding knowledge of RFS, with only three clinical studies and 12 case series/case reports. We found incidence rates between 15% and 25%, along with 4% in the case control study (phosphate <0.5 mmol/L), here with a rapid drop in phosphate both receiving 30 kcal/kg/day and 8–10 kcal/kg/day. The most common adverse events reported in the review article were altered mental status, reduced muscle tonus

and edema occurring in almost all case series/reports. The day of nadir occurred between day 2 and day 4 (Paper I). The results from Paper III supported the findings in the review article, showing a wide range of incidence rates when using the newly defined diagnostic criteria for RFS. Further, the results from the RCT (Paper II) showed that RFS was not more prominent in the intervention group, despite the initial refeeding rates being higher than recommended in the NICE guidelines. A more assertive refeeding also did not demonstrate higher mortality rates [178], but 36% of the patients in our study died within 3 months, regardless of refeeding rates (Paper II). In Paper III, we found that the mortality rate at 3 months and 1 year were not significantly different in patients with and without RFS in any of the three diagnostic RFS criteria. Regarding the results on the main outcome in our RCT study—HGS—we found that a more assertive refeeding protocol providing 20 kcal/kg/day did not result in improved HGS as measured 3 months after discharge when compared with a cautious refeeding (10 kcal/kg/day) protocol.

6.2.1 Refeeding protocols and effect on outcomes, including hand grip strength

The scarcity of clinical studies in older malnourished patients leads to a lack of evidence-based knowledge, underpinning the challenges faced by health care systems in creating appropriate clinical nutrition treatment protocols. This is despite the fact that this group is the largest consumer of health service who also pose an immense cost for society [48, 250]. The main aim in geriatric medicine is to ensure the greatest possible autonomy and a good quality of life, and adequate nutrition is an important piece in obtaining good health in older adults [2].

The NICE guidelines recommend the use of a cautious refeeding protocol when recommencing feeding in patients at risk of RFS, but the guidelines are inconsistent and lack empirical evidence for older malnourished patients, as we demonstrated in Paper I [145, 172]. Years before the present PhD project, studies started questioning the recommendation whether all patients should receive low feed intake during the first few days. There was a concern that these guidelines were an obstacle in providing adequate nutrition to malnourished patients, especially among patients with anorexia nervosa [251-253]. Several studies in this patients group confirm that there is no correlation between initial refeeding energy

levels (kcal/kg/day) and hypophosphatemia and that more aggressive feeding may lead to a shorter LOS [252, 254]. One shows that it is the severity of malnutrition in the patient with anorexia nervosa that causes RFS, not the energy load during refeeding [162].

In contrast to anorexia nervosa studies, studies in critically ill patients have found that a slower refeeding rate is a preferred approach [11, 152, 165-168]. This is demonstrated in the RCT study by Doig et al. (2016)[165], who use a calorie restricted protocol on patients with RFS (phosphate levels <0.65 mmol/L); they show an improved overall survival time, reduced 60-day mortality rates, and reduced incidence of major infection compared with the control group receiving the standard hospital feeding protocol of 69 kcal/hour. A retrospective study [168] shows a significant reduction in the 6-month mortality risk in patients with RFS (phosphate levels <0.65 mmol/L) when receiving <50% of goal calories compared with patients receiving >50% of goal calories. Arabi et al. [166] and Rice et al. [167] also find no difference in electrolyte disturbances using a more cautious compared with a more assertive refeeding protocol. However, a cautious refeeding protocol providing 40–60% of the caloric requirements has been found to require less renal replacement therapy than providing 70–100% of caloric requirements [166]. In addition, Rice et al. show that using a full feeding of 1300 kcal/day causes more gastrointestinal intolerance than providing a more cautious refeeding feed of 400 kcal/kg/day [167]. Thus, and as demonstrated in a systematic review [19], when including all types of patients, regardless of age, diagnosis, or disease state, no difference in adverse events are found in patients at risk of RFS when comparing an assertive refeeding protocol to a conservative refeeding protocol (>20 kcal/kg/day versus <20 kcal/kg/day), [19]. This indicates the need for differentiating refeeding protocols, and pooling data may cause potentially fatal recommendations for some groups.

Studies have begun confirm a higher initial refeeding (kcal/kg/day) and titration rate to reach the estimated goal in patients with anorexia nervosa and have moved toward a more cautious initial refeeding rate (kcal/kg/day) in the critically ill [18, 255]. The recommendations for older adults based on our results were not conclusive, but no difference in RFS among patients receiving cautious refeeding protocol 10 kcal/kg/day compared with those receiving a more assertive refeeding protocol 20 kcal/kg/day were found. There was neither a difference in LOS (14.5 (8.7) days vs. 13.6 (10.8) days) or mortality (39% (n = 16) vs. 34% (n =15)) in the more assertive protocol compared with cautious refeeding protocol, respectively. We found no difference in the side effects of EN between the groups: 22% of patients experienced some cases of diarrhea, vomiting, aspiration, constipation, edema, nausea, and admission to

the ICU, but this was evenly divided between the groups. However, the more assertive refeeding protocol received a higher total energy intake (oral and EN) only on day 1 and 2, and in light of this, the results should be interpreted with a degree of caution. A finding that may be a cause for concern is that the patients receiving the more assertive refeeding protocol seemed to experience more respiratory distress than the cautious group, which was the only clinical sign registered in the current study: 53.6% (n = 22) compared with 30.2% (n = 13). This may be because of a greater volume load and/or fluid overload, which is common in malnourished patients [256]. Another finding was that 16 out of the 35 patients with respiratory distress were admitted with pneumonia, with 11 being in the more assertive refeeding protocol. This may indicate that patients with pneumonia should be monitored closely [173]. However, there are other possible explanations: the group of patients receiving the more assertive refeeding protocol had a higher incidence of patients with a high risk of RFS, according to NICE guidelines (see **Table 5**) (46.3% (n = 19) of 36.4% (n = 16)) (p =0.029) when compared with the more cautious refeeding protocol [145].

Recently, ASPEN [11] and Friedli et al. [21] have published new consensus refeeding protocols that deviate from each other both in initial refeeding rate and time to reach estimated goal calories. Friedli et al. [21] recommend classifying patients according to their risk of RFS—low risk, high risk, and very high risk—with the initial refeeding protocols and titration rate according to the risk of RFS. Initial feeding is recommended as 15–25, 10–15, and 5–10 kcal/kg/day, with the titration rates to meet the estimated goal rate on day 5, day 7, or >10 days in low risk, high risk, and very high risk, respectively. Although ASPEN [11] does not classify patients according to risk, the guidelines suggest starting with10–20 kcal/kg/day for the first 24 hours, then to advance by 33% of the goal every 1 to 2 days. In the ASPEN regime, the estimated goal rate will be met approximately between day 2 and day 5, depending on initial rate and titration rate.

In our study, the cautious refeeding protocol was a duplicate of Friedli et al.'s [21] protocol for patients at a high risk of RFS, and the patients reached an estimated goal rate at day 7. The ASPEN [11] guidelines are more in line with our more assertive refeeding protocol, and it is an interesting finding that our two different refeeding protocols fit into the new guidelines.

In Paper II, we aimed at improving HGS, which can be used as a surrogate marker for nutrition status, by providing 30% more energy during the 7-day intervention period. Even though HGS has good reliability and validity and several studies have shown that nutrition

intervention improves HGS, it was not sensitive enough to detect a difference between the two groups [236, 237, 257]. This may be related to the short intervention time and the lack of difference in the energy intake (EN and oral intake) between the groups, with a significant difference in the refeeding protocol for 33% of the duration [173]. Comparing our study to a RCT by Ha et al., in a similar patient group, it has been found that HGS improved at 3 months (mean (SD) of 2.3 kg (3.7) compared with -0.3 kg (4.9), p = 0.001) with a nutrition intervention of a mean of 11 days; the study indicates a difference in calories, with a mean (SD) 19.1 (6.9) kcal/kg/day versus 15.3 (4.8) kcal/kg/day, (p = 0.005) between the two groups [237]. Most studies have longer nutrition intervention periods: 11 days in Ha et al. and between 8 and 12 weeks in other studies [233-237, 257]. Moreover, we can only speculate that if there would have been a statistically difference in energy between the groups on days 1 through day 6, then there would have been a difference in HGS between the groups.

The results from our study will hopefully help build further evidence for future recommendations. Following Friedli et al.'s [21] high-risk group recommendation regarding titration to reach the goal rate on day 5 or NICE guidelines between days 4 and 7 might be the recommendation. In addition to tight electrolyte control, monitoring the signs and symptoms that develop after recommencing feeding would be appropriate for this older patient group [11, 21, 83]. However, our findings call for more research, which draws attention to the need of differentiated recommendations according to disease state and age.

6.2.2 Refeeding syndrome

A more assertive refeeding protocol did not aggravate the development of RFS as expected. The question is whether developing RFS depends on the rate of refeeding or if it will occur regardless of rate, as demonstrated in the systematic review (Paper I) that shows that RFS occurred with both an initial calorie level of 10 and 20 kcal/kg/day (phosphate <0.5 mmol/L, 15% and 25%, respectively) [172]. Also, in Paper II, 17.1% in the more assertive refeeding group (20 kcal/kg/day) and 9% in the cautious group (10 kcal/kg/day) developed RFS using phosphate <0.65 mmol/L, but this difference was not significantly different (p = 0.29) [173].

The diagnostic criteria for RFS has evolved from using phosphate as a hallmark finding to including the clinical signs and symptoms, in addition to electrolyte disturbances, when diagnosing RFS [83]. Although the word syndrome indicates multiple abnormalities, there is

no consensus on which anomalies or the number required to confirm the diagnosis or if using just phosphate is sufficient enough to set the diagnosis [55, 169]. Even though RFS was not aggravated when using a more assertive refeeding protocol, in Paper II, we did find more respiratory distress. Here, 19 of the 35 patients died within 3 months [173] and 22 of 35 within 1 year, with a significantly higher mortality rate in the assertive refeeding protocol (p = 001). As mentioned earlier, this indicates that respiratory distress should be further investigated because it may be a diagnostic sign for RFS. The sign is considered measurable and present with a physical manifestation, while symptoms are subjective, not measurable, and perceived by patients only [258]. Both Friedli et al. and ASPEN lists the symptoms and signs in their guidelines, and a total of 34 and 62 symptoms and signs are listed as possible consequences for RFS by Friedli et al. and ASPEN, respectively [11, 21]. In our study, respiratory distress was considered a symptom because it was observed by the nurses and MDs by auscultation of their lungs, registering increased rattling in their chests and increased need for oxygen after recommencing feeding.

However, there is an urgent need to investigate which sign and symptoms are common in relation to RFS because it will be difficult to use the numbers listed in each consensus recommendation when diagnosing RFS [11, 21]. However, during clinical practice, it is important to become aware of new signs and symptoms in conjunction with electrolyte disturbances after recommencing nutrition because this may relate to RFS rather other causes of disturbances.

The longitudinal study (Paper III) demonstrated the consequences in incidence rates when lacking a unified diagnostic criterion. The incidence rates were 12.9% when using only phosphate as the cut-off, 31.8 % when using Friedli et al.'s consensus, and 65.9% when using the ASPEN consensus (**Table 4,** defining each criteria) [11, 21]. This shows the challenges that healthcare workers are having on how and when to provide treatment to patients with RFS. A standardized terminology is universal to the healthcare community and will help understand the conditions of the patients and which treatment they need to undergo. When the healthcare community operates with different definitions and diagnostic criteria, the patient may not get appropriate treatment [83, 259]. Which criteria to use in a clinical setting is yet to be determined. However, it seems more practical to use a clear cut-off value for RFS as in our study (phosphate <0.65 mmol/L) [158] than including a set of cut-off values for all electrolytes as in Friedli et al. [21] or to calculate a percent fall in electrolytes during a specific time frame as in ASPEN. However, there is not enough evidence to support using

either a clear cut-off or percent fall when diagnosing RFS, and further research is needed to investigate if either of the consensus guidelines would be a better diagnostic tool for RFS [11, 21].

To reach a global consensus on RFS, including its definition, a screening tool, and improved diagnostic criteria, developing safe refeeding protocols can enhance the medical community's ability to identify the syndrome and embed it into a classification system such as ICD [260]. Thus, coming to a consensus on RFS globally will take time and money, as demonstrated in the making of the GLIM criterion, a process that started in 2012 and published consensus in 2019 [83, 84].

6.2.3 Mortality

Even though mortality was not the overall aim of the RCT, the intention of the nutritional intervention was to mitigate malnutrition, that is, improving nutritional status by providing severely malnourished patients with adequate energy and protein through EN during the hospital stay, thereby hopefully also having an effect on mortality. Being diagnosed with malnutrition increases the risk of dying [99]. A BMI <23.6kg/m^2 is independently associated with increased mortality, while weight stability is associated with the lowest mortality, regardless of BMI [261]. Based on this, all our patients were expected to have an increased mortality risk because they were diagnosed with ICD-10 criteria for malnutrition, E43, and E44 (**Table 3**) [99, 262]. However, we did not detect any significant differences in the mortality rate between the two refeeding protocols, but 36.5% (n = 31) and 56.5% (n = 48) died within 3 months and 1 year, respectively [173]. These mortality rates were comparable with the mortality rates in our systematic review (Paper I), ranging from 26% up to 48% within 1 month [172]. The similarity may be explained by the fact that the energy intake in the two groups was significantly different only during the first 3 days of treatment, and it is dubious to assume that this would have any effect on the mortality rates [173]. Additionally, many of these patients were very old and multimorbid; in addition to malnutrition, frailty, sarcopenia, and cachexia were probably present in many of our patients. All of these wasting syndromes are associated with increased mortality [69, 75, 79]. A recent systematic review and meta-analysis summarizes the association between physical frailty, sarcopenia, and

malnutrition in older hospitalized adults, finding that almost 50% of the older adults had two and three of these wasting syndromes at the same time [66].

Sarcopenia was probably present in our patient population, as indicated by a mean (SD) HGS of 13.3 (7.2) kg in women and 17.2 (11.4) kg in men. This is well below the cut-off points for detecting sarcopenia (i.e., 16 kg in women and 27 kg in men) [58]. Sarcopenia, frailty, and malnutrition are somewhat reversible conditions with a nutrition intervention and exercise [263-265]; indeed, a nutrition intervention in malnourished patients has proven to increase survival and reduce mortality [122, 266]. As discussed in Paper II, many of our patients might have presented with cachexia (described as BMI <20 kg/m^2, low HGS, poor appetite, and elevated CRP [63, 267]), a multiorgan syndrome often associated with chronic diseases [69]. During cachexia, the body is in a negative protein and energy balance because of a hypermetabolic state in relation to the inflammation disorder. Hypermetabolism increases energy expenditure often in a combination with reduced appetite. Besides increasing energy expenditure, the metabolism also has an impaired protein synthesis [264, 267]. Cachexia is also called the wasting syndrome and comes with the highest risk of mortality; it is most often seen in cancer patients and has no proven treatment to reverse the syndrome [265]. Studies have indicated that nutrition intervention will not help if the main cause of weight loss is not related to inadequate nutrition intake or uptake but rather to the metabolic changes in relation to inflammation. This might be part of the explanation for the similarity in mortality and malnutrition as measured by HGS, even with adequate nutrition [264].

To differentiate between the four wasting syndromes in older adults, screening tools should include questions and measures to identify each syndrome. This will help individualize and optimize the intervention, both for physical and nutrition interventions [66] Nevertheless, RFS has been associated with increased mortality [16, 136, 169]. However, there has been conflicting evidence regarding RFS and its association with mortality [171]; this is demonstrated in a recent systematic review and meta-analysis aiming to investigate the differences in the risk of dying among patients developing RFS compared with patients who did not during refeeding in a malnourished patients group ranging from 50 to 74 years. The review finds a nonsignificant trend (odds ratio [OR] = 1.27, 95% CI: 0.93–1.72) toward an increased short-term (< 1 month) mortality and an significant increase in mortality at 6 months among patients developing RFS during refeeding (OR = 1.54, 95% CI 1.04–2.28) [268]. These results do not correspond with our results in Paper III, which found no increased mortality in patients with RFS compared with patients without RFS in any of the three

different diagnostic criteria. Importantly, the systematic review shows that when refeeding was supervised by a nutrition support team, no excess mortality occurred [268]. This was also the case in our study, where all patients had an individualized refeeding protocol and were followed up by close monitoring of electrolytes, signs of RFS, and adverse events of EN throughout the study period. It is possible that because of close monitoring and the supplementation of electrolytes throughout the refeeding period, the most severe cases of RFS, including death, were avoided. Few RCT studies have included older multimorbid patients. In fact, many studies have age and reduced cognitive function as their exclusion criteria. This is mostly because older age is associated with reduced cognitive function, which increases the work to obtain consent and higher mortality rates. The latter, combined with high attrition rates, will necessarily affect the quality of the results [250, 269]. Excluding these patients from studies is unfortunate because it will be difficult to develop evidence-based nutrition treatment protocols [250]. However, in the present study, we included this group. Almost all patients were acutely admitted, and they were multimorbid with several chronic diseases, including dementia, and were prone to increased mortality. To prevent patients with a short life expectancy affecting the drop out and power of the study, we ensured that those patients were excluded from the study.

6.3 Clinical implications

The area around RFS has a huge limitation because it lacks a global unified definition, diagnostic criteria, validated screening tool, and refeeding protocols, of which the latter was the focus in the current thesis.

For decades, studies have warned of the consequences of RFS, and guidelines have recommended calorie restrictions and careful titration rates. The slogan has been “start low-go slow” [270]. However, in recent years, studies have confirmed that patients with anorexia nervosa would benefit from a more aggressive refeeding rate. This is to the contrary for the critical ill, with studies verifying that the best method is a cautious refeeding approach. Based on our study, we suggest moving toward a higher initial refeeding rate of 20 kcal/kg/day rather than following the NICE guidelines [145] or Friedli et al.’s [21] guidelines. However, meeting the estimated goal rate at day 3 can be disputed because the more assertive refeeding protocol experienced more respiratory distress, which is indication that this time frame might

be too fast. This is a finding that needs to be further investigated. Also, the more assertive refeeding protocol seemed to not be able to follow the titration rates, with 3 out 6 intended days difference of energy provision between the groups. Based on our findings, a better treatment approach would be to follow Friedli et al.'s [21] or the NICE guidelines [145] regarding titration rates to reach the goal rate within 4 to 7 days. Although we did not find any difference in HGS between our groups, we experienced measuring HGS as an easy instrument for use in clinical practice. Whereas many studies have used HGS as a nutritional marker, it is still not validated as such, and future studies should aim to build evidence to use HGS as a surrogate marker for nutrition status.

Lacking a unified diagnostic criterion has been proposed by many studies as an obstacle in estimating the true incidence rates of RFS [132, 146, 169], which was demonstrated in Paper III, with incidence rates ranging from 12.9% up to 65.9%. Whether using set cut-off values for electrolytes or using a percent fall from baseline needs to be determined. However, neither of the criteria found a higher mortality rate in patients with RFS compared with patients without. It is not surprising that patients are dying with increasing age, but the mortality rate of 56.5% within 1 year raises ethical questions regarding the level of treatment these older severely malnourished multimorbid are receiving. It may imply that this patient group does not benefit from nutrition therapy to the same extent as younger patients or that nutrition treatment is coming in too late in the patient's disease trajectory. In addition, many patients may have an underlying wasting syndrome such as cachexia that, to some extent, is irreversible and nonresponsive to nutrition intervention.

6.4 Future research

With the current thesis, we have attempted to substantiate more knowledge about the syndrome; hopefully, this will be a part of the building block in understanding the complexity of the syndrome. This may help in building more evidence-based knowledge for future definitions, diagnostic criteria, and safe refeeding protocols for older malnourished patients.

Future clinical trials should try to gain more evidence regarding the following bullet points:

- A universal consensus on how to adequately define RFS
- The importance of the initial refeeding rate

- What the safest titration rate is to meet estimated goal rate
- Determining the optimal refeeding nutritional composition for patients at risk or with RFS
- Validating the electrolyte replacement protocols for patients with RFS, hypophosphatemia, hypomagnesemia, and hypokalemia
- Building further evidence on the time course of occurrence or day of electrolyte nadir
- Global diagnostic criteria
- Increasing the awareness of clinicians toward the earlier recognition and appropriate management of RFS
- Studying the different patient groups, for example, older patients, cancer patients, and other patients, at risk of malnutrition, hence adding to the current understanding
- Further investigating hand grip strength as a nutritional marker

7. Conclusion

The overall aim of the current thesis was to contribute to evidence-based research regarding a safe nutrition regime by investigating two different EN refeeding protocols in older hospital patients and their effect on nutritional status, as measured by HGS, RFS, and mortality.

We hypothesized that a more assertive enteral refeeding protocol will improve nutritional status, as measured by HGS, but potentially aggravate RFS in older malnourished hospitalized patients.

The conclusion from the three papers can be summarized as follows:

- The systematic review revealed a scarcity of studies on RFS in older patients. However, low phosphate values occurred in up to 25% of the patients, even when refeeding cautiously. The day of phosphate nadir occurred most frequently between days 2 and 4, which means that it is important to measure electrolytes daily during refeeding.
- When comparing a more assertive refeeding protocol with a cautious protocol, there was no improvement in HGS—when used as a nutritional marker—incidence of RFS, or mortality, but importantly, the nutrition intervention was only different on days 1 and 2. Day of phosphate nadir occurred on mean day 3, which is similar to the findings from the systematic review.
- When using different diagnostic criteria, the incidence of RFS occurred widely. Although with high mortality rates, patients with RFS did not have a higher probability of dying than patients without RFS.

8. References

[1]Fávaro-Moreira NC, Krausch-Hofmann S, Matthys C, Vereecken C, Vanhauwaert E, Declercq A, et al. Risk Factors for Malnutrition in Older Adults: A Systematic Review of the Literature Based on Longitudinal Data. Adv Nutr. 2016;7(3):507-22.
[2]Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr. 2019;38(1):10-47.
[3]Gomes F, Baumgartner A, Bounoure L, Bally M, Deutz NE, Greenwald JL, et al. Association of Nutritional Support With Clinical Outcomes Among Medical Inpatients Who Are Malnourished or at Nutritional Risk: An Updated Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(11):e1915138.
[4]Marshall S, Bauer J, Isenring E. The consequences of malnutrition following discharge from rehabilitation to the community: a systematic review of current evidence in older adults. J Hum Nutr Diet. 2014;27(2):133-41.
[5]Oliver D. 21st century health services for an ageing population: 10 challenges for general practice. Br J Gen Pract. 2012;62(601):396-7.
[6]Cereda E, Pedrolli C, Klersy C, Bonardi C, Quarleri L, Cappello S, et al. Nutritional status in older persons according to healthcare setting: A systematic review and meta-analysis of prevalence data using MNA(®). Clinical nutrition (Edinburgh, Scotland). 2016;35(6):1282-90.
[7]World Health Organization W. Global strategy and action plan on ageing and health. In: IGO. LCB-N-S, editor. 2017.
[8]Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. Am J Manag Care. 2013;19(2):121-8.
[9]Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, et al. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial. Clin Nutr. 2016;35(1):18-26.
[10]Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019;393(10188):2312-21.
[11]da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. Nutr Clin Pract. 2020;35(2):178-95.
[12]De Santo NG, Bisaccia C, Phillips ME, De Santo LS. Refeeding syndrome as described in 1507 by Antonio Benivieni in Florence. Nephrol Dial Transplant. 2020.
[13]Brozek J, Chapman CB, Keys A. Drastic food restriction; effect on cardiovascular dynamics in normotensive and hypertensive conditions. J Am Med Assoc. 1948;137(18):1569-74.
[14]Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med. 1951;35(1):69-96.
[15]Miller SJ. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Nutr Clin Pract. 2008;23(2):166-71.
[16]Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr. 1981;34(3):393-9.
[17]Rizzo SM, Douglas JW, Lawrence JC. Enteral Nutrition via Nasogastric Tube for Refeeding Patients With Anorexia Nervosa: A Systematic Review. Nutr Clin Pract. 2019;34(3):359-70.
[18]McKnight CL, Newberry C, Sarav M, Martindale R, Hurt R, Daley B. Refeeding Syndrome in the Critically Ill: a Literature Review and Clinician's Guide. Curr Gastroenterol Rep. 2019;21(11):58.
[19]Matthews-Rensch K, Capra S, Palmer M. Systematic Review of Energy Initiation Rates and Refeeding Syndrome Outcomes. Nutr Clin Pract. 2020;00.
[20]Friedli N, Stanga Z, Sobotka L, Culkin A, Kondrup J, Laviano A, et al. Revisiting the refeeding syndrome: Results of a systematic review. Nutrition. 2017;35:151-60.
[21]Friedli N, Stanga Z, Culkin A, Crook M, Laviano A, Sobotka L, et al. Management and prevention of refeeding syndrome in medical inpatients: An evidence-based and consensus-supported algorithm. Nutrition. 2018;47:13-20.

[22]Avers D, Brown M, Chui KK, Wong RA, Lusardi M. Editor's message: Use of the term "elderly". Journal of geriatric physical therapy (2001). 2011;34(4):153-4.
[23]da Costa JP, Vitorino R, Silva GM, Vogel C, Duarte AC, Rocha-Santos T. A synopsis on aging-Theories, mechanisms and future prospects. Ageing Res Rev. 2016;29:90-112.
[24]Health NIoP. Life expectancy in Norway https://www.fhi.no/en/op/hin/population/life-expectancy/2018 [
[25]Roser MO-O, E.; Ritchie H. Life Expectancy https://ourworldindata.org/life-expectancy2019 [First published in 2013; last revised in October 2019:[
[26]Medicine G. Geriatric Medicine, European Union of Medical Specialists https://uemsgeriatricmedicine.org/www/land/definition/english.asp [
[27]Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. J Am Geriatr Soc. 1991;39(9 Pt 2):8S-16S; discussion 7S-8S.
[28]Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. Age and ageing. 2018;47(1):149-55.
[29]Kirkwood TB, Melov S. On the programmed/non-programmed nature of ageing within the life history. Curr Biol. 2011;21(18):R701-7.
[30]He S, Sharpless NE. Senescence in Health and Disease. Cell. 2017;169(6):1000-11.
[31]Margolick JB, Ferrucci L. Accelerating aging research: how can we measure the rate of biologic aging? Exp Gerontol. 2015;64:78-80.
[32]Nations U. Department of Economic and Social Affairs

Disability https://www.un.org/development/desa/disabilities/disability-and-ageing.html [
[33]Szanton SL, Thorpe RJ, Boyd C, Tanner EK, Leff B, Agree E, et al. Community aging in place, advancing better living for elders: a bio-behavioral-environmental intervention to improve function and health-related quality of life in disabled older adults. J Am Geriatr Soc. 2011;59(12):2314-20.
[34]Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, et al. Measuring biological aging in humans: A quest. Aging Cell. 2020;19(2):e13080.
[35]Ferrucci L, Levine ME, Kuo PL, Simonsick EM. Time and the Metrics of Aging. Circ Res. 2018;123(7):740-4.
[36]Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576-90.
[37]Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, et al. An Update on Inflamm-Aging: Mechanisms, Prevention, and Treatment. J Immunol Res. 2016;2016:8426874.
[38]Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244-54.
[39]Fulop T, Witkowski JM, Olivieri F, Larbi A. The integration of inflammaging in age-related diseases. Semin Immunol. 2018;40:17-35.
[40]López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194-217.
[41]Xu X, Mishra GD, Jones M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. Ageing Res Rev. 2017;37:53-68.
[42]Zemedikun DT, Gray LJ, Khunti K, Davies MJ, Dhalwani NN. Patterns of Multimorbidity in Middle-Aged and Older Adults: An Analysis of the UK Biobank Data. Mayo Clin Proc. 2018;93(7):857-66.
[43]Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. Eur J Public Health. 2018;29(1):182-9.
[44]Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009;7(4):357-63.
[45]Feinstein AR. THE PRE-THERAPEUTIC CLASSIFICATION OF CO-MORBIDITY IN CHRONIC DISEASE. J Chronic Dis. 1970;23(7):455-68.

[46]Meghani SH, Buck HG, Dickson VV, Hammer MJ, Rabelo-Silva ER, Clark R, et al. The Conceptualization and Measurement of Comorbidity: A Review of the Interprofessional Discourse. Nurs Res Pract. 2013;2013:192782.
[47]Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. Ann Fam Med. 2012;10(2):134-41.
[48]Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr. 2016;67:130-8.
[49]Alharbi TA, Paudel S, Gasevic D, Ryan J, Freak-Poli R, Owen AJ. The association of weight change and all-cause mortality in older adults: a systematic review and meta-analysis. Age and ageing. 2021;50(3):697-704.
[50]Li R, Xia J, Zhang XI, Gathirua-Mwangi WG, Guo J, Li Y, et al. Associations of Muscle Mass and Strength with All-Cause Mortality among US Older Adults. Med Sci Sports Exerc. 2018;50(3):458-67.
[51]Bohannon RW. Grip Strength: An Indispensable Biomarker For Older Adults. Clin Interv Aging. 2019;14:1681-91.
[52]Barazzoni R, Sulz I, Schindler K, Bischoff SC, Gortan Cappellari G, Hiesmayr M. A negative impact of recent weight loss on in-hospital mortality is not modified by overweight and obesity. Clinical nutrition (Edinburgh, Scotland). 2020;39(8):2510-6.
[53]Gu D, Yang F, Sautter J. Socioeconomic status as a moderator between frailty and mortality at old ages. BMC Geriatr. 2016;16:151.
[54]Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.
[55]Olde Rikkert MG, Rigaud AS, van Hoeyweghen RJ, de Graaf J. Geriatric syndromes: medical misnomer or progress in geriatrics? Neth J Med. 2003;61(3):83-7.
[56]Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, et al. Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. BMC Geriatr. 2019;19(1):120.
[57]Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care. 2012;15(3):213-9.
[58]Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
[59]Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
[60]Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008;27(6):793-9.
[61]Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
[62]Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle. 2019;10(1):207-17.
[63]Dev R. Measuring cachexia-diagnostic criteria. Ann Palliat Med. 2019;8(1):24-32.
[64]Sánchez-Rodríguez D, Marco E, Ronquillo-Moreno N, Miralles R, Vázquez-Ibar O, Escalada F, et al. Prevalence of malnutrition and sarcopenia in a post-acute care geriatric unit: Applying the new ESPEN definition and EWGSOP criteria. Clin Nutr. 2017;36(5):1339-44.
[65]Yaxley A, Miller MD, Fraser RJ, Cobiac L, Crotty M. The complexity of treating wasting in ambulatory rehabilitation: Is it starvation, sarcopenia, cachexia or a combination of these conditions? Asia Pac J Clin Nutr. 2012;21(3):386-93.
[66]Ligthart-Melis GC, Luiking YC, Kakourou A, Cederholm T, Maier AB, de van der Schueren MAE. Frailty, Sarcopenia, and Malnutrition Frequently (Co-)occur in Hospitalized Older Adults: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2020;21(9):1216-28.

[67]Liao CD, Chen HC, Huang SW, Liou TH. The Role of Muscle Mass Gain Following Protein Supplementation Plus Exercise Therapy in Older Adults with Sarcopenia and Frailty Risks: A Systematic Review and Meta-Regression Analysis of Randomized Trials. Nutrients. 2019;11(8).
[68]Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7.
[69]Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: Diagnosis, assessment, and treatment. Crit Rev Oncol Hematol. 2018;127:91-104.
[70]Del Fabbro E. Combination therapy in cachexia. Ann Palliat Med. 2019;8(1):59-66.
[71]Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11-48.
[72]Sieber CC. Frailty – From concept to clinical practice. Exp Gerontol. 2017;87:160-7.
[73]Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323-36.
[74]Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. BMC geriatrics. 2020;20(1):393.
[75]Dodds R, Sayer AA. Sarcopenia and frailty: new challenges for clinical practice. Clin Med (Lond). 2016;16(5):455-8.
[76]Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. The Cochrane database of systematic reviews. 2009;2009(2):Cd003288.
[77]Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. J Aging Res. 2011;2011:569194.
[78]Mayhew AJ, Amog K, Phillips S, Parise G, McNicholas PD, de Souza RJ, et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. Age and ageing. 2019;48(1):48-56.
[79]Cerri AP, Bellelli G, Mazzone A, Pittella F, Landi F, Zambon A, et al. Sarcopenia and malnutrition in acutely ill hospitalized elderly: Prevalence and outcomes. Clinical nutrition (Edinburgh, Scotland). 2015;34(4):745-51.
[80]Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle. 2016;7(5):512-4.
[81]Kara M, Kaymak B, Frontera W, Ata AM, Ricci V, Ekiz T, et al. Diagnosing sarcopenia: Functional perspectives and a new algorithm from the ISarcoPRM. J Rehabil Med. 2021;53(6):jrm00209.
[82]Stratton RJG, Elia. Disease-related malnutrition: an evidence-based approach to treatment. MA,USA: CABI 2003.
[83]Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):49-64.
[84]Cederholm T, Jensen GL. To create a consensus on malnutrition diagnostic criteria: A report from the Global Leadership Initiative on Malnutrition (GLIM) meeting at the ESPEN Congress 2016. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):7-10.
[85]Morley JE. Anorexia of aging: physiologic and pathologic. Am J Clin Nutr. 1997;66(4):760-73.
[86]Dent E, Hoogendijk EO, Wright ORL. New insights into the anorexia of ageing: from prevention to treatment. Current opinion in clinical nutrition and metabolic care. 2019;22(1):44-51.
[87]Cox NJ, Morrison L, Ibrahim K, Robinson SM, Sayer AA, Roberts HC. New horizons in appetite and the anorexia of ageing. Age and ageing. 2020;49(4):526-34.
[88]Morley JE, Silver AJ. Anorexia in the elderly. Neurobiol Aging. 1988;9(1):9-16.
[89]Schorr M, Klibanski A. Anorexia Nervosa and Bone. Curr Opin Endocr Metab Res. 2018;3:74-82.
[90]Ozier AD, Henry BW. Position of the American Dietetic Association: nutrition intervention in the treatment of eating disorders. J Am Diet Assoc. 2011;111(8):1236-41.
[91]Morley JE. Anorexia of ageing: a key component in the pathogenesis of both sarcopenia and cachexia. J Cachexia Sarcopenia Muscle. 2017;8(4):523-6.

[92]Landi F, Picca A, Calvani R, Marzetti E. Anorexia of Aging: Assessment and Management. Clin Geriatr Med. 2017;33(3):315-23.
[93]Bathini P, Brai E, Auber LA. Olfactory dysfunction in the pathophysiological continuum of dementia. Ageing Res Rev. 2019;55:100956.
[94]Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, et al. Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients. 2016;8(2):69.
[95]Giezenaar C, Chapman I, Luscombe-Marsh N, Feinle-Bisset C, Horowitz M, Soenen S. Ageing Is Associated with Decreases in Appetite and Energy Intake--A Meta-Analysis in Healthy Adults. Nutrients. 2016;8(1).
[96]Kalm LM, Semba RD. They starved so that others be better fed: remembering Ancel Keys and the Minnesota experiment. J Nutr. 2005;135(6):1347-52.
[97]The biology of human starvation. [press release]. Minneapolis: University of Minnesota Press1950.
[98]Soenen S, Chapman IM. Body weight, anorexia, and undernutrition in older people. J Am Med Dir Assoc. 2013;14(9):642-8.
[99]Lim SL, Ong KC, Chan YH, Loke WC, Ferguson M, Daniels L. Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. Clin Nutr. 2012;31(3):345-50.
[100]Correia M. Nutrition Screening vs Nutrition Assessment: What's the Difference? Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2018;33(1):62-72.
[101]Guttormsen AB. Nasjonale faglige retningslinjer for forebygging og behandling

av underernæring. https://www.helsedirektoratet.no: Helsedirektoratet 2009.
[102]Abd Aziz NAS, Teng N, Abdul Hamid MR, Ismail NH. Assessing the nutritional status of hospitalized elderly. Clin Interv Aging. 2017;12:1615-25.
[103]Mendes J, Azevedo A, Amaral TF. Handgrip strength at admission and time to discharge in medical and surgical inpatients. JPEN Journal of parenteral and enteral nutrition. 2014;38(4):481-8.
[104]Mendes NP, Barros TA, Faria BS, Aguiar ES, Oliveira CA, Souza ECG, et al. Hand grip strength as predictor of undernutrition in hospitalized patients with cancer and a proposal of cut-off. Clin Nutr ESPEN. 2020;39:210-4.
[105]Hamilton GF, McDonald C, Chenier TC. Measurement of grip strength: validity and reliability of the sphygmomanometer and jamar grip dynamometer. J Orthop Sports Phys Ther. 1992;16(5):215-9.
[106]Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. Journal of hand therapy : official journal of the American Society of Hand Therapists. 2005;18(4):426-7, quiz 8.
[107]Short KR, Nair KS. The effect of age on protein metabolism. Curr Opin Clin Nutr Metab Care. 2000;3(1):39-44.
[108]Mundi MS, Patel J, McClave SA, Hurt RT. Current perspective for tube feeding in the elderly: from identifying malnutrition to providing of enteral nutrition. Clin Interv Aging. 2018;13:1353-64.
[109]van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. Lancet Diabetes Endocrinol. 2018;6(8):647-58.
[110]Bautmans I, Van Puyvelde K, Mets T. Sarcopenia and functional decline: pathophysiology, prevention and therapy. Acta Clin Belg. 2009;64(4):303-16.
[111]Van Ancum JM, Scheerman K, Jonkman NH, Smeenk HE, Kruizinga RC, Meskers CGM, et al. Change in muscle strength and muscle mass in older hospitalized patients: A systematic review and meta-analysis. Exp Gerontol. 2017;92:34-41.
[112]Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011;30(2):135-42.
[113]Wiener JM, Hanley RJ, Clark R, Van Nostrand JF. Measuring the activities of daily living: comparisons across national surveys. J Gerontol. 1990;45(6):S229-37.

[114]Allard JP, Keller H, Gramlich L, Jeejeebhoy KN, Laporte M, Duerksen DR. GLIM criteria has fair sensitivity and specificity for diagnosing malnutrition when using SGA as comparator. Clinical nutrition (Edinburgh, Scotland). 2020;39(9):2771-7.
[115]Allard JP, Keller H, Teterina A, Jeejeebhoy KN, Laporte M, Duerksen DR, et al. Lower handgrip strength at discharge from acute care hospitals is associated with 30-day readmission: A prospective cohort study. Clinical nutrition (Edinburgh, Scotland). 2016.
[116]Wang YC, Liang CK, Hsu YH, Peng LN, Chu CS, Liao MC, et al. Synergistic effect of low handgrip strength and malnutrition on 4-year all-cause mortality in older males: A prospective longitudinal cohort study. Arch Gerontol Geriatr. 2019;83:217-22.
[117]McNicholl T, Dubin JA, Curtis L, Mourtzakis M, Nasser R, Laporte M, et al. Handgrip Strength, but Not 5-Meter Walk, Adds Value to a Clinical Nutrition Assessment. Nutr Clin Pract. 2019;34(3):428-35.
[118]Butterworth CE. The skeleton in the hospital closet. 1974. Nutrition. 1994;10(5):435-41; discussion , 41.
[119]Leij-Halfwerk S, Verwijs MH, van Houdt S, Borkent JW, Guaitoli PR, Pelgrim T, et al. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition screening tools validated for use in adults ≥65 years: A systematic review and meta-analysis. Maturitas. 2019;126:80-9.
[120]O'Shea E, Trawley S, Manning E, Barrett A, Browne V, Timmons S. Malnutrition in Hospitalised Older Adults: A Multicentre Observational Study of Prevalence, Associations and Outcomes. J Nutr Health Aging. 2017;21(7):830-6.
[121]Kang MC, Kim JH, Ryu SW, Moon JY, Park JH, Park JK, et al. Prevalence of Malnutrition in Hospitalized Patients: a Multicenter Cross-sectional Study. J Korean Med Sci. 2018;33(2):e10.
[122]Schultz TJ, Roupas P, Wiechula R, Krause D, Gravier S, Tuckett A, et al. Nutritional interventions for optimizing healthy body composition in older adults in the community: an umbrella review of systematic reviews. JBI Database System Rev Implement Rep. 2016;14(8):257-308.
[123]Bally MR, Blaser Yildirim PZ, Bounoure L, Gloy VL, Mueller B, Briel M, et al. Nutritional Support and Outcomes in Malnourished Medical Inpatients: A Systematic Review and Meta-analysis. JAMA Intern Med. 2016;176(1):43-53.
[124]Feinberg J, Nielsen EE, Korang SK, Halberg Engell K, Nielsen MS, Zhang K, et al. Nutrition support in hospitalised adults at nutritional risk. Cochrane Database Syst Rev. 2017;5(5):Cd011598.
[125]Ojo O, Brooke J. Recent Advances in Enteral Nutrition. Nutrients. 2016;8(11).
[126]Volkert D, Chourdakis M, Faxen-Irving G, Frühwald T, Landi F, Suominen MH, et al. ESPEN guidelines on nutrition in dementia. Clin Nutr. 2015;34(6):1052-73.
[127]Report TB. Ethical principles and guidelines for the protection of human subjects of research. J Am Coll Dent. 2014;81(3):4-13.
[128]Seaman JB, Erlen JA. "Everyday ethics" in the care of hospitalized older adults. Orthop Nurs. 2013;32(5):286-9.
[129]Schwartz DB, Barrocas A, Annetta MG, Stratton K, McGinnis C, Hardy G, et al. Ethical Aspects of Artificially Administered Nutrition and Hydration: An ASPEN Position Paper. Nutr Clin Pract. 2021;36(2):254-67.
[130]Monod S, Chiolero R, Büla C, Benaroyo L. Ethical issues in nutrition support of severely disabled elderly persons: a guide for health professionals. JPEN Journal of parenteral and enteral nutrition. 2011;35(3):295-302.
[131]Bartlett R, Milne R, Croucher R. Strategies to improve recruitment of people with dementia to research studies. Dementia (London). 2019;18(7-8):2494-504.
[132]Walmsley RS. Refeeding syndrome: screening, incidence, and treatment during parenteral nutrition. J Gastroenterol Hepatol. 2013;28 Suppl 4:113-7.
[133]Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013;3(1).
[134]Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z. Management of Refeeding Syndrome in Medical Inpatients. J Clin Med. 2019;8(12).

[135]Crook MA. Refeeding syndrome: problems with definition and management. Nutrition. 2014;30(11-12):1448-55.
[136]Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr. 1990;14(1):90-7.
[137]Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008;336(7659):1495-8.
[138]Frank LL. Thiamin in Clinical Practice. JPEN J Parenter Enteral Nutr. 2015;39(5):503-20.
[139]Kurkcu M, Meijer RI, Lonterman S, Muller M, de van der Schueren MAE. The association between nutritional status and frailty characteristics among geriatric outpatients. Clin Nutr ESPEN. 2018;23:112-6.
[140]Pourhassan M, Biesalski HK, Angersbach B, Lueg G, Klimek C, Wirth R. Prevalence of thiamine deficiency in older hospitalized patients. Clin Interv Aging. 2018;13:2247-50.
[141]Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr. 2008;62(6):687-94.
[142]Aubry E, Friedli N, Schuetz P, Stanga Z. Refeeding syndrome in the frail elderly population: prevention, diagnosis and management. Clin Exp Gastroenterol. 2018;11:255-64.
[143]Correia MI, Hegazi RA, Higashiguchi T, Michel JP, Reddy BR, Tappenden KA, et al. Evidence-based recommendations for addressing malnutrition in health care: an updated strategy from the feedM.E. Global Study Group. J Am Med Dir Assoc. 2014;15(8):544-50.
[144]Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition. 2010;26(2):156-67.
[145]National Collaborating Centre for Acute C. National Institute for Health and Clinical Excellence: Guidance. Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. London: National Collaborating Centre for Acute Care (UK)

Copyright © 2006, National Collaborating Centre for Acute Care.; 2006.
[146]Kraaijenbrink BVC, Lambers WM, Mathus-Vliegen EMH, Siegert CEH. Incidence of refeeding syndrome in internal medicine patients. Neth J Med. 2016;74(3):116-21.
[147]Bowling A. Research Methods In Health: Investigating Health And Health Services. Fourth Edition ed. England: Mc Graw Hill Education, Open University Press; 2014. p. 176.
[148]Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr. 2011;30(3):365-8.
[149]Pourhassan M, Cuvelier I, Gehrke I, Marburger C, Modreker MK, Volkert D, et al. Risk factors of refeeding syndrome in malnourished older hospitalized patients. Clin Nutr. 2018;37(4):1354-9.
[150]National Institute for Health and Care Excellence: Clinical Guidelines. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. London: National Institute for Health and Care Excellence (UK)

Copyright © NICE 2019.; 2017.
[151]Tazmini K, Nymo SH, Louch WE, Ranhoff AH, Oie E. Electrolyte imbalances in an unselected population in an emergency department: A retrospective cohort study. PLoS One. 2019;14(4):e0215673.
[152]Reintam Blaser A, Hubert van Zanten AR. Electrolyte disorders during the initiation of nutrition therapy in the ICU. Curr opin Clin Nutr Metab Care. 2020;Publish Ahead of Print.
[153]Leung J, Crook M. Disorders of phosphate metabolism. J Clin Pathol. 2019;72(11):741-7.
[154]Manghat P, Sodi R, Swaminathan R. Phosphate homeostasis and disorders. Ann Clin Biochem. 2014;51(Pt 6):631-56.
[155]Ahmed F, Mohammed A. Magnesium: The Forgotten Electrolyte-A Review on Hypomagnesemia. Med Sci (Basel). 2019;7(4).
[156]Sterns RH. Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med. 2015;372(1):55-65.

[157]Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18(10):2649-52.
[158]Tazmini K. Elektrolyttveilederen

http://www.helsebiblioteket.no/nyhetsarkiv/ny-utvidet-utgave-av-elektrolyttveilederen2011 [
[159]Friedli N, Baumann J, Hummel R, Kloter M, Odermatt J, Fehr R, et al. Refeeding syndrome is associated with increased mortality in malnourished medical inpatients: Secondary analysis of a randomized trial. Medicine (Baltimore). 2020;99(1):e18506.
[160]Fuentes E, Yeh DD, Quraishi SA, Johnson EA, Kaafarani H, Lee J, et al. Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive Care Unit: Common but Unrelated to Timing of Initiation or Aggressiveness of Nutrition Delivery. Nutr Clin Pract. 2017;32(2):252-7.
[161]Garber AK, Cheng J, Accurso EC, Adams SH, Buckelew SM, Kapphahn CJ, et al. Short-term Outcomes of the Study of Refeeding to Optimize Inpatient Gains for Patients With Anorexia Nervosa: A Multicenter Randomized Clinical Trial. JAMA Pediatr. 2021;175(1):19-27.
[162]O'Connor G, Nicholls D. Refeeding Hypophosphatemia in Adolescents With Anorexia Nervosa: A Systematic Review. Nutr Clin Pract. 2013;28(3):358-64.
[163]Garber AK, Sawyer SM, Golden NH, Guarda AS, Katzman DK, Kohn MR, et al. A systematic review of approaches to refeeding in patients with anorexia nervosa. Int J Eat Disord. 2016;49(3):293-310.
[164]Garber AK, Mauldin K, Michihata N, Buckelew SM, Shafer MA, Moscicki AB. Higher calorie diets increase rate of weight gain and shorten hospital stay in hospitalized adolescents with anorexia nervosa. J Adolesc Health. 2013;53(5):579-84.
[165]Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3(12):943-52.
[166]Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med. 2015;372(25):2398-408.
[167]Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795-803.
[168]Olthof LE, Koekkoek W, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr. 2018;37(5):1609-17.
[169]Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012;27(1):34-40.
[170]Silvis SE, Paragas PD, Jr. Paresthesias, weakness, seizures, and hypophosphatemia in patients receiving hyperalimentation. Gastroenterology. 1972;62(4):513-20.
[171]Matthews KL, Capra SM, Palmer MA. Throw caution to the wind: is refeeding syndrome really a cause of death in acute care? European journal of clinical nutrition. 2018;72(1):93-8.
[172]Olsen SU, Hesseberg K, Aas A-M, Ranhoff AH, Bye A. Refeeding syndrome occurs among older adults regardless of refeeding rates: A systematic review. Nutr Res. 2021;91:1-12.
[173]Olsen SU, Hesseberg K, Aas AM, Pripp AH, Ranhoff AH, Bye A. A comparison of two different refeeding protocols and its effect on hand grip strength and refeeding syndrome: a randomized controlled clinical trial. Eur Geriatr Med. 2021.
[174]Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
[175]Ricon FJ, Sanchez P, Lajara F, Galan A, Lozano JA, Guerado E. Result of a pyrocarbon prosthesis after comminuted and unreconstructable radial head fractures. J Shoulder Elbow Surg. 2012;21(1):82-91.

[176]Programme CAS. Critical Appraisal Skills Programme CASP [webpage]. https://casp-uk.net/casp-tools-checklists/2019 [updated 2020 Juni22.06.20]. 2019:[Cohort and case-control checklist, for Systematic Review].
[177]Garg R, Lakhan SE, Dhanasekaran AK. How to review a case report. J Med Case Rep. 2016;10:88.
[178]Kendall JM. Designing a research project: randomised controlled trials and their principles. Emerg Med J. 2003;20(2):164-8.
[179]Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
[180]Mattilsynet. Matvaretabellen https://www.matvaretabellen.no/2003 [
[181]Organization WH. Adherence to long-term therapies: Evidence for action. http://www.who.int/chp/knowledge/publi2003 [
[182]Ingram TL. Compliance: a concept analysis. Nurs Forum. 2009;44(3):189-94.
[183]McCutcheon KP, Whittet WL, Kirsten JL, Fuchs JL. Feeding Tube Insertion and Placement Confirmation Using Electromagnetic Guidance: A Team Review. JPEN Journal of parenteral and enteral nutrition. 2018;42(1):247-54.
[184]Ni MZ, Huddy JR, Priest OH, Olsen S, Phillips LD, Bossuyt PMM, et al. Selecting pH cut-offs for the safe verification of nasogastric feeding tube placement: a decision analytical modelling approach. BMJ Open. 2017;7(11):e018128.
[185]Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. World J Gastroenterol. 2014;20(26):8505-24.
[186]Corinaldesi R, Stanghellini V, Barbara G, Tomassetti P, De Giorgio R. Clinical approach to diarrhea. Intern Emerg Med. 2012;7 Suppl 3:S255-62.
[187]De Giorgio R, Ruggeri E, Stanghellini V, Eusebi LH, Bazzoli F, Chiarioni G. Chronic constipation in the elderly: a primer for the gastroenterologist. BMC Gastroenterology. 2015;15(1):130.
[188]Pallant J. SPSS survival manual: a step by step guide to data analysis using IBM SPSS. McGraw Hill; 2016.
[189]Bohannon RW. Minimal clinically important difference for grip strength: a systematic review. J Phys Ther Sci. 2019;31(1):75-8.
[190]Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis. 1987;40(2):171-8.
[191]Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age and ageing. 2011;40(4):423-9.
[192]Sousa-Santos AR, Amaral TF. Differences in handgrip strength protocols to identify sarcopenia and frailty - a systematic review. BMC Geriatr. 2017;17(1):238.
[193]Rijk JM, Roos PR, Deckx L, van den Akker M, Buntinx F. Prognostic value of handgrip strength in people aged 60 years and older: A systematic review and meta-analysis. Geriatr Gerontol Int. 2016;16(1):5-20.
[194]Kizilarslanoglu MC, Kilic MK, Gokce D, Sakalar T, Ulger Z. Is It Possible Using Handgrip Strength Instead of Body Mass Index in MNA-SF Test to Assess the Nutritional Status of Geriatric Patients? J Nutr Health Aging. 2017;21(5):579-84.
[195]Zhang XS, Liu YH, Zhang Y, Xu Q, Yu XM, Yang XY, et al. Handgrip Strength as a Predictor of Nutritional Status in Chinese Elderly Inpatients at Hospital Admission. Biomed Environ Sci. 2017;30(11):802-10.
[196]Flood A, Chung A, Parker H, Kearns V, O'Sullivan TA. The use of hand grip strength as a predictor of nutrition status in hospital patients. Clin Nutr. 2014;33(1):106-14.
[197]Picó C, Serra F, Rodríguez AM, Keijer J, Palou A. Biomarkers of Nutrition and Health: New Tools for New Approaches. Nutrients. 2019;11(5).
[198]Skatteetaten. Registering a death https://www.skatteetaten.no/en/person/national-registry/registering-a-death/ [National Population Register].
[199]Burton RF. Why is the body mass index calculated as mass/height2, not as mass/height3? Ann Hum Biol. 2007;34(6):656-63.

[200]Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. JAMA. 2014;312(1):85-6.
[201]Del Re AC, Maisel NC, Blodgett JC, Finney JW. Intention-to-treat analyses and missing data approaches in pharmacotherapy trials for alcohol use disorders. BMJ Open. 2013;3(11):e003464.
[202]Lachin JM. Statistical Considerations in the Intent-to-Treat Principle. Control Clin Trials. 2000;21(3):167-89.
[203]Xi W, Pennell ML, Andridge RR, Paskett ED. Comparison of intent-to-treat analysis strategies for pre-post studies with loss to follow-up. Contemp Clin Trials Commun. 2018;11:20-9.
[204]Goel MK, Khanna P, Kishore J. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res. 2010;1(4):274-8.
[205]Dessu S, Habte A, Mesele M. The Kaplan Meier estimates of mortality and its predictors among newborns admitted with low birth weight at public hospitals in Ethiopia. PLoS One. 2020;15(9):e0238629.
[206]Helsinki WMADo. Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.
[207]Dror Y, Almashanu S, Lubart E, Sela BA, Shimoni L, Segal R. The impact of refeeding on blood fatty acids and amino acid profiles in elderly patients: a metabolomic analysis. JPEN J Parenter Enteral Nutr. 2013;37(1):109-16.
[208]Lubart E, Leibovitz A, Dror Y, Katz E, Segal R. Mortality after nasogastric tube feeding initiation in long-term care elderly with oropharyngeal dysphagia--the contribution of refeeding syndrome. Gerontol. 2009;55(4):393-7.
[209]Kagansky N, Levy S, Koren-Morag N, Berger D, Knobler H. Hypophosphataemia in old patients is associated with the refeeding syndrome and reduced survival. J Intern Med. 2005;257(5):461-8.
[210]Vaszar LT, Culpepper-Morgan JA, Winter SM. Refeeding syndrome induced by cautious enteral alimentation of a moderately malnourished patient. Gastroenterol. 1998;6(1):79-81.
[211]Crook MA, Collins D, Swaminathan R. Severe hypophosphatemia related to refeeding. Nutrition. 1996;12(7-8):538-39.
[212]Serin SO, Karaoren G, Okuturlar Y, Unal E, Ahci S, Karakoc E, et al. Thiamin and folic acid deficiency accompanied by resistant electrolyte imbalance in the re-feeding syndrome in an elderly patient. Asia Pac J Clin Nutr. 2017;26(2):379-82.
[213]Duerksen DR, Papineau N. Electrolyte abnormalities in patients with chronic renal failure receiving parenteral nutrition. JPEN J Parenter Enteral Nutr. 1998;22(2):102-4.
[214]Lamiell JJ, Ducey JP, Freese-Kepczyk BJ, Musio F, Hansberry KL. Essential amino acid-induced adult hyperammonemic encephalopathy and hypophosphatemia. Crit Care Med. 1990;18(4):451-2.
[215]Maier-Dobersberger T, Lochs H. Enteral supplementation of phosphate does not prevent hypophosphatemia during refeeding of cachectic patients. JPEN J Parenter Enteral Nutr. 1994;18(2):182-4.
[216]Marinella MA. The refeeding syndrome and hypophosphatemia. Nutr Rev. 2003;61(9):320-23.
[217]Gariballa S. Refeeding syndrome: a potentially fatal condition but remains underdiagnosed and undertreated. Nutrition. 2008;24(6):604-6.
[218]Tsiompanou E, Lucas C, Stroud M. Overfeeding and overhydration in elderly medical patients: lessons from the Liverpool Care Pathway. Clin Med (Lond). 2013;13(3):248-51.
[219]Windpessl M, Mayrbaeurl B, Baldinger C, Tiefenthaller G, Prischl FC, Wallner M, et al. Refeeding Syndrome in Oncology: Report of Four Cases. World J Oncol. 2017;8(1):25-9.
[220]Roldan CJ. A case of near-fatal hypophosphatemia. J Emerg Med. 2004;26(2):241-2.
[221]Järvinen TLN, Sievänen H, Kannus P, Jokihaara J, Khan KM. The true cost of pharmacological disease prevention. BMJ. 2011;342:d2175.
[222]Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
[223]Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Syst Rev. 2012;1:2.

[224]Sampayo-Cordero M, Miguel-Huguet B, Pardo-Mateos A, Moltó-Abad M, Muñoz-Delgado C, Pérez-López J. Agreement between the results of meta-analyses from case reports and from clinical studies regarding the efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age: An example of case reports meta-analyses as an useful tool for evidence-based medicine in rare diseases. Mol Genet Metab. 2018;123(2):69-75.
[225]Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23(2):60-3.
[226]Andrade C. Internal, External, and Ecological Validity in Research Design, Conduct, and Evaluation. Indian J Psychol Med. 2018;40(5):498-9.
[227]Dekkers OM, von Elm E, Algra A, Romijn JA, Vandenbroucke JP. How to assess the external validity of therapeutic trials: a conceptual approach. Int J Epidemiol. 2010;39(1):89-94.
[228]Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.
[229]Kahan BC, Rehal S, Cro S. Risk of selection bias in randomised trials. Trials. 2015;16:405.
[230]Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.
[231]Bond Sutton L, Erlen JA, Glad JM, Siminoff LA. Recruiting vulnerable populations for research: revisiting the ethical issues. J Prof Nurs. 2003;19(2):106-12.
[232]Dal-Ré R, Janiaud P, Ioannidis JPA. Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC Med. 2018;16(1):49.
[233]Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, Frost P, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. Clin Nutr. 1992;11(6):337-44.
[234]Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut. 2000;46(6):813-8.
[235]Edington J, Barnes R, Bryan F, Dupree E, Frost G, Hickson M, et al. A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. Clin Nutr. 2004;23(2):195-204.
[236]Price R, Daly F, Pennington CR, McMurdo ME. Nutritional supplementation of very old people at hospital discharge increases muscle strength: a randomised controlled trial. Gerontology. 2005;51(3):179-85.
[237]Ha L, Hauge T, Spenning AB, Iversen PO. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. Clin Nutr. 2010;29(5):567-73.
[238]Christie PM, Hill GL. Effect of intravenous nutrition on nutrition and function in acute attacks of inflammatory bowel disease. Gastroenterology. 1990;99(3):730-6.
[239]Hu CL, Yu M, Yuan KT, Yu HL, Shi YY, Yang JJ, et al. Determinants and nutritional assessment value of hand grip strength in patients hospitalized with cancer. Asia Pac J Clin Nutr. 2018;27(4):777-84.
[240]Mithal A, Bonjour JP, Boonen S, Burckhardt P, Degens H, El Hajj Fuleihan G, et al. Impact of nutrition on muscle mass, strength, and performance in older adults. Osteoporos Int. 2013;24(5):1555-66.
[241]Fetterplace K, Ridley EJ, Beach L, Abdelhamid YA, Presneill JJ, MacIsaac CM, et al. Quantifying Response to Nutrition Therapy During Critical Illness: Implications for Clinical Practice and Research? A Narrative Review. JPEN. 2021;45(2):251-66.
[242]Anziliero F, Beghetto MG. Incidents and adverse events in enteral feeding tube users: warnings based on a cohort study. Nutricion hospitalaria. 2018;35(2):259-64.
[243]Shumaker NL, Ball AL, Neils-Strunjas J, Smith R, Weiler E, Krikorian R. Using memory strategies to improve 24-hour dietary recalls among older adults. J Allied Health. 2003;32(3):196-201.
[244]Scalone L, Cortesi PA, Mantovani LG, Ciampichini R, Cesana G. Reference Eq-5d-3l and Eq-5d-5l Data From the Italian General Population. Value Health. 2014;17(7):A514-5.

[245]Evensen S, Saltvedt I, Ranhoff AH, Myrstad M, Myrstad C, Mellingsæter M, et al. Delirium and cognitive impairment among older patients in Norwegian emergency departments. Tidsskr Nor Laegeforen. 2019;139(6).
[246]Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol. 2003;3:28.
[247]Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. Phys Ther Rev. 2009;14(1):36-49.
[248]White NM, Barnett AG. Analysis of multisite intervention studies using generalized linear mixed models. Infect Control Hosp Epidemiol. 2019;40(8):910-7.
[249]Altman DG. Practical Statistics for Medical Research Chapman & Hall; 1999. 611 p.
[250]Briggs R, Robinson S, O'Neill D. Ageism and clinical research. Ir Med J. 2012;105(9):311-2.
[251]De Silva A, Smith T, Stroud M. Attitudes to NICE guidance on refeeding syndrome. BMJ. 2008;337(7661):a680.
[252]Madden S, Miskovic-Wheatley J, Clarke S, Touyz S, Hay P, Kohn MR. Outcomes of a rapid refeeding protocol in Adolescent Anorexia Nervosa. J Eat Disord. 2015;3:8.
[253]Redgrave GW, Coughlin JW, Schreyer CC, Martin LM, Leonpacher AK, Seide M, et al. Refeeding and weight restoration outcomes in anorexia nervosa: Challenging current guidelines. Int J Eat Disord. 2015;48(7):866-73.
[254]Agostino H, Erdstein J, Di Meglio G. Shifting paradigms: continuous nasogastric feeding with high caloric intakes in anorexia nervosa. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2013;53(5):590-4.
[255]Koerner T, Haas V, Heese J, Karacic M, Ngo E, Correll CU, et al. Outcomes of an Accelerated Inpatient Refeeding Protocol in 103 Extremely Underweight Adults with Anorexia Nervosa at a Specialized Clinic in Prien, Germany. J Clin Med. 2020;9(5).
[256]Dehesa-López E, Martínez-Felix JI, Inzunza-Soto MY, Sánchez-Ochoa J, Espinoza-Cuevas MLA, Valdez-Ortiz R. Clinical impact of disease-related malnutrition and fluid overload assessment via bioimpedance vector analysis in hospitalized patients. Clin Nutr ESPEN. 2020;39:131-6.
[257]Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease--a randomized controlled trial. Clin Nutr. 2008;27(1):48-56.
[258]Faiz KW. Symptomer er subjektive – tegn er objektive. Tidsskr Nor Legeforen. 2018.
[259]Process NC. Academy of Nutrition and Dietetics. Nutrition Terminology Reference Manual (eNCPT): Dietetics Language for Nutrition Care. http://ncpt.webauthor.com2021 [
[260]World Health Organization W. International Statistical Classification of Diseases and Related Health Problems https://www.who.int/standards/classifications/classification-of-diseases: World Health Organization; 2021 [
[261]Somes GW, Kritchevsky SB, Shorr RI, Pahor M, Applegate WB. Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program. Am J Epidemiol. 2002;156(2):132-8.
[262]Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: a prospective study. JAMA. 1999;281(21):2013-9.
[263]Sieber CC. Malnutrition and sarcopenia. Aging Clin Exp Res. 2019;31(6):793-8.
[264]Duerksen DR, Laporte M, Jeejeebhoy K. Evaluation of Nutrition Status Using the Subjective Global Assessment: Malnutrition, Cachexia, and Sarcopenia. Nutr Clin Pract. 2020.
[265]Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol. 2015;22:100-6.
[266]Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med. 2019;132:42-9.
[267]Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.

[268]Bioletto F, Pellegrini M, Ponzo V, Cioffi I, De Francesco A, Ghigo E, et al. Impact of Refeeding Syndrome on Short- and Medium-Term All-Cause Mortality: A Systematic Review and Meta-Analysis. Am J Med. 2021;134(8):1009-18.e1.
[269]Watts G. Why the exclusion of older people from clinical research must stop. BMJ. 2012;344:e3445.
[270]Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. Pharmacotherapy. 1995;15(6):713-26.