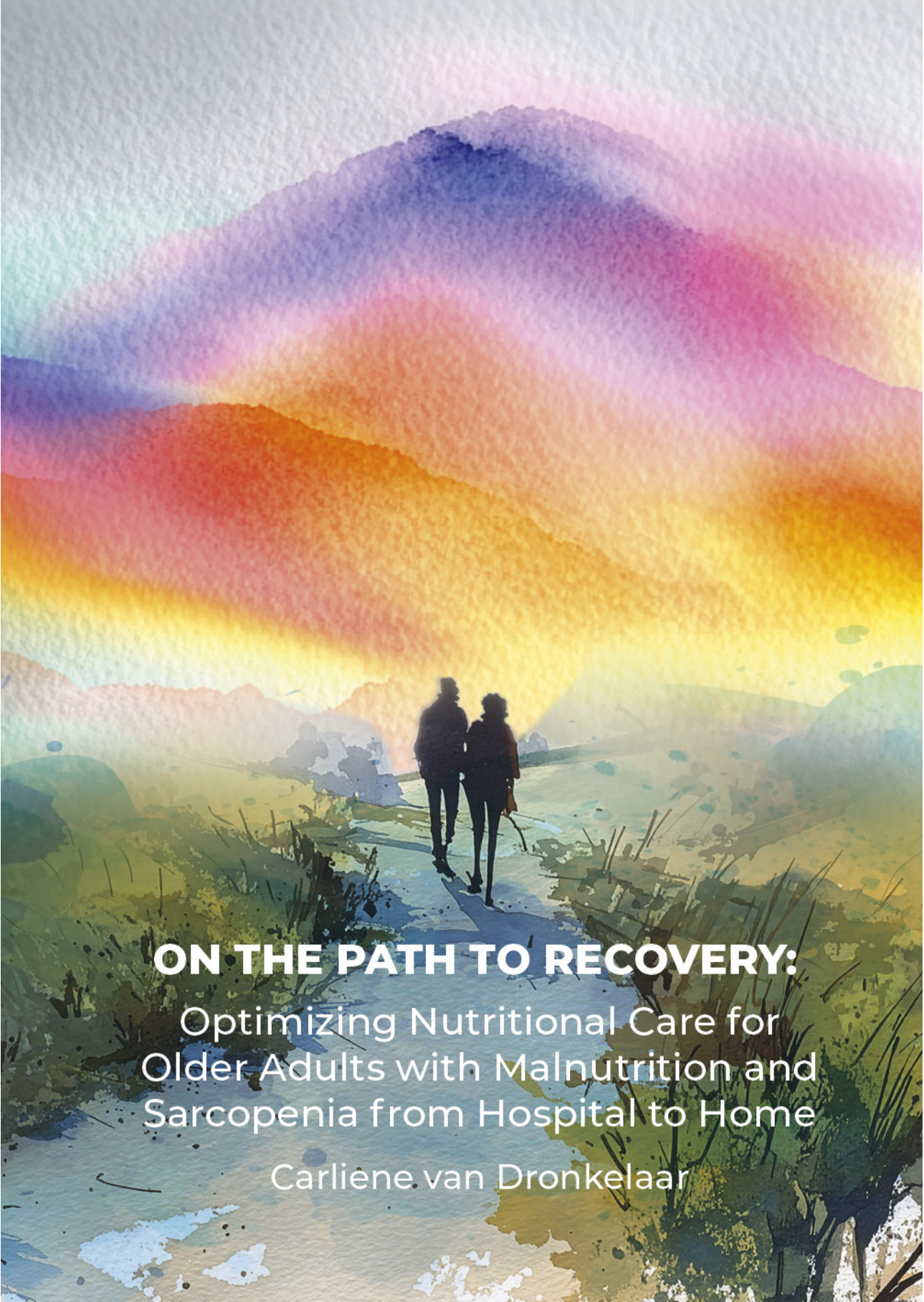

ON THE PATH TO RECOVERY:

Optimizing Nutritional Care for Older Adults with Malnutrition and Sarcopenia from Hospital to Home

Carliene van Dronkelaar

ON THE PATH TO RECOVERY:

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VRIJE UNIVERSITEIT

ON THE PATH TO RECOVERY

Optimizing Nutritional Care for Older Adults with Malnutrition and Sarcopenia from Hospital to Home

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
volgens besluit van de decaan
van de Faculteit der Geneeskunde
in het openbaar te verdedigen
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in de universiteit

door

Dirke Carliene van Dronkelaar

geboren te Apeldoorn

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copromotoren:	dr. M. Tieland dr.ir. H.M. Kruizenga
promotiecommissie:	prof.dr.ir. M. Visser prof.dr. B.M. Buurman-Es dr. M. van der Schaaf prof.dr. M.A.E. de van der Schueren prof.dr. C.G.M. Meskers

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CHAPTER 1

General introduction

THE AGING POPULATION

The world's population is aging at an exceptional rate, with the number of people age 65 years or older predicted to more than double by 2050.(1) As life expectancy increases, the incidence of age-related health conditions such as frailty, chronic diseases and mobility limitations become more prevalent. Among these geriatric health concerns, malnutrition and sarcopenia arose as conditions that can severely impact the quality of life of older adults. Malnutrition and sarcopenia are not only a challenge for the older adults themselves but also place an increasing burden on healthcare systems, making their effective management a priority in current health care for older adults.

MALNUTRITION

Malnutrition is a complex and multifactorial health problem that arises when there is a lack of intake or uptake of nutrients or a growing demand of nutrients due to for example illness. The shortage of nutrients leads to altered body composition and reduced biological functions which can have major consequences for older adults in particular. (2)

The underlying mechanisms of malnutrition can directly be affected or triggered by various factors such as chewing difficulties, poor appetite, malabsorption and inflammation. These factors in turn can indirectly be influenced by factors including pain, mobility limitations, gastro-intestinal disease and cancer among others. This complex interaction of factors are summarized in the Development of Malnutrition in Aged Persons (DoMAP) by Volkert et al. (3)

Based on the cause of malnutrition a distinction between different types of malnutrition can be made. The European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines distinguish between the existence of disease-relate malnutrition (DRM) with or without inflammation, and malnutrition without disease. (4) DRM with inflammation shows stronger metabolic effects then DRM without inflammation, such as in muscle protein breakdown and insulin resistance. The treatment strategies and effects might differ between the types of malnutrition, however all patients suffering from malnutrition benefit from early recognition and

treatment. Even though we know the impact malnutrition can have on older adults, it still remains underdiagnosed. (5)

Up until 2019, there was no global consensus on which parameters are able to define malnutrition. To fulfil the need for standardizing the diagnosis of malnutrition in clinical practice of malnutrition diagnosis, the Global Leadership Initiative on Malnutrition (GLIM) was established. (6) The GLIM framework suggests a three step approach (see Figure 1): first, patients are screened for the potential presence of malnutrition, after which the possibility of malnutrition is confirmed in the second step, followed by a determination of severity in the third step. The five diagnostic criteria of malnutrition in the second step, consists of three phenotypic criteria, i.e. unintended weight loss, low BMI and low muscle mass, and two etiologic criteria, i.e. reduced food intake or assimilation and disease burden, often verified by levels of inflammation. The diagnosis of malnutrition is set when at least on phenotypic and one etiologic criterion is present in a patient.

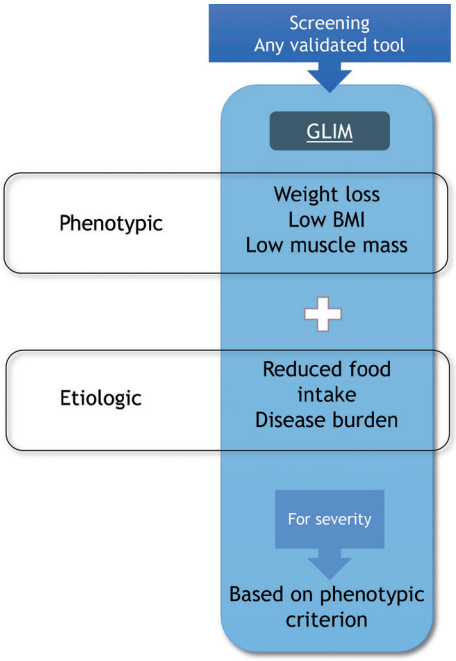

Figure 1. Steps of the GLIM framework for diagnosing malnutrition

SARCOPENIA

Another common health challenge among older adults is sarcopenia, a condition characterized by age-related loss of muscle mass, muscle strength, and physical performance (Figure 2). The first attempt to set a standardized definition for sarcopenia was done by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010.(7) With sarcopenia becoming part of the ICD-10-MC Diagnosis Code system, it is officially recognized as a muscle disorder which opens possibilities for health insurances to reimburse costs for its treatment. Advances were made by several international initiatives like the Asian Working Group for Sarcopenia (AWGS)(8) and Sarcopenia Definition and Outcomes Consortium (SDOC)(9) calling for an updated global consensus. In the 2018 update, the EWGSOP2 defines low muscle strength as the primary indicator for suspected sarcopenia, with the diagnosis confirmed by the additional presence of low muscle mass.(10) Severity of sarcopenia is determined by physical performance. In 2019, the AWGS consensus update maintained their original definition of sarcopenia to be determined by

low muscle mass and reduced muscle strength or physical performance. (11) The presence of all three parameters defines severe sarcopenia. The SDOC stated in their 2020 position paper that low muscle strength and a low gait speed are enough to determine sarcopenia.(12)

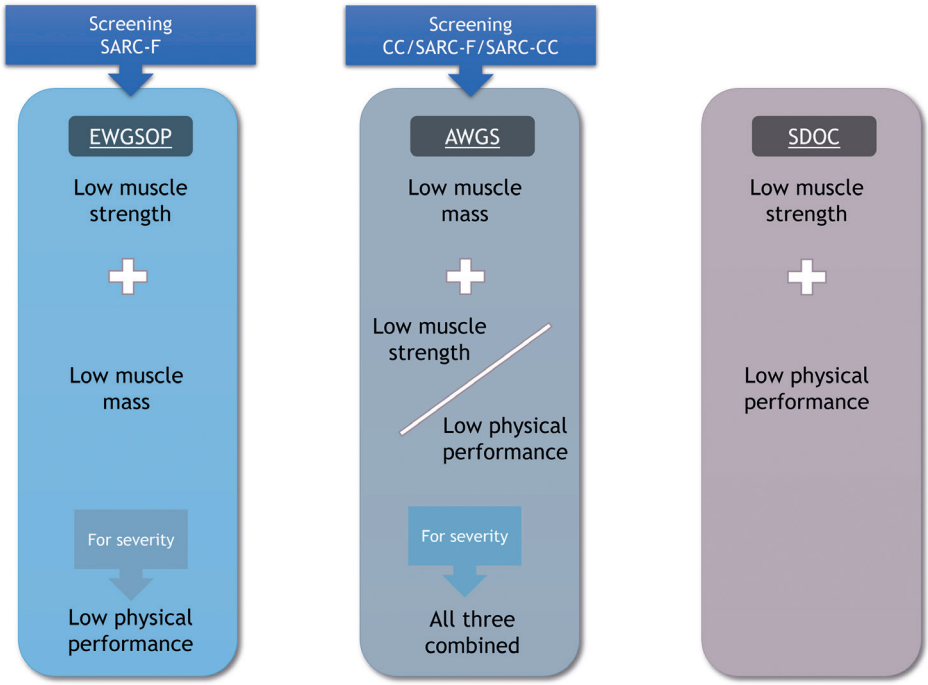

Figure 2. Steps of the different sarcopenia diagnoses according EWGSOP2, AWGS, SDOC.

In 2019-2021, the Global Leadership Initiative in Sarcopenia (GLIS) was formed with representatives from all relevant global scientific societies (AWGS, ANZSSFR, EWGSOP, FNIH, IWGS, and SDOC) in attempts to further harmonize the definition of sarcopenia. This Delphi consensus based conceptual definition of sarcopenia was presented in 2024.(13) The new definition was formulated as follows: sarcopenia comprises the concurrent combination of reduced muscle mass and muscle strength; is a skeletal muscle disease of which the prevalence increases with age but is potentially reversable; no different definitions per setting, age or condition should be used (see Figure 3). Additionally, muscle strength relative to muscle size is argued to be part of the definition. The GLIS

committee also determined that the effects of sarcopenia on health outcomes include limitations in mobility and physical performance, difficulties in performing (instrumental) activities of daily living ((i)ADL), increases in risk of falls, admissions to hospital or nursing homes and reduction in quality of life. The next step of the GLIS committee lies with implementing an operational definition of sarcopenia in both clinical and research settings.

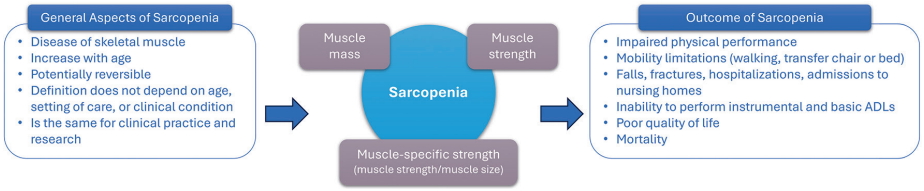

Figure 3. A graphical representation of the conceptual definition of sarcopenia according GLIS. Adapted from Kirk et al. (2024).(13)

In addition to defining sarcopenia, it is important to clarify the distinction between 'physical performance' and 'physical functioning'. Both terms are used interchangeably despite referring to different aspect of muscle-related capacity.(14) Physical functioning describes to the ability to perform everyday activities, such as Activities of Daily Living (ADL), typically assessed through self- or proxy reported measures. Physical performance, by contrast, refers to the ability to execute specific physical tasks, such as rising form a chair, and is assessed objectively using timed or standardized tests. Physical performance can therefore be viewed as an objective indicator of physical functioning.

CO-EXISTENCE OF MALNUTRITION AND SARCOPENIA

Malnutrition and sarcopenia are strongly correlated and may frequently co-exist in one person.(15) This can be even as high as 42% in a patient population.(16) Moreover, they may even exacerbate each other. As can be seen from figure 4, there is an overlap between the diagnostic criteria of malnutrition and sarcopenia, but also clear differences. The common ground in diagnostic criteria of malnutrition and sarcopenia lies with a reduced muscle mass. Unintended weight loss, which might happen with malnutrition, is inevitably accompanied with the loss of muscle mass, increasing the risk of sarcopenia. Pourhassan and colleagues (2020) showed that malnutrition was an independent risk factor for a

decrease of muscle mass.(17) Sarcopenia on the other hand may worsen the nutritional status. Ligthart-Melis et al (2020) revealed that when seven studies (n=2427 patients) were pooled together, 41% of the patients suffered from both (risk of) malnutrition and sarcopenia.(16)

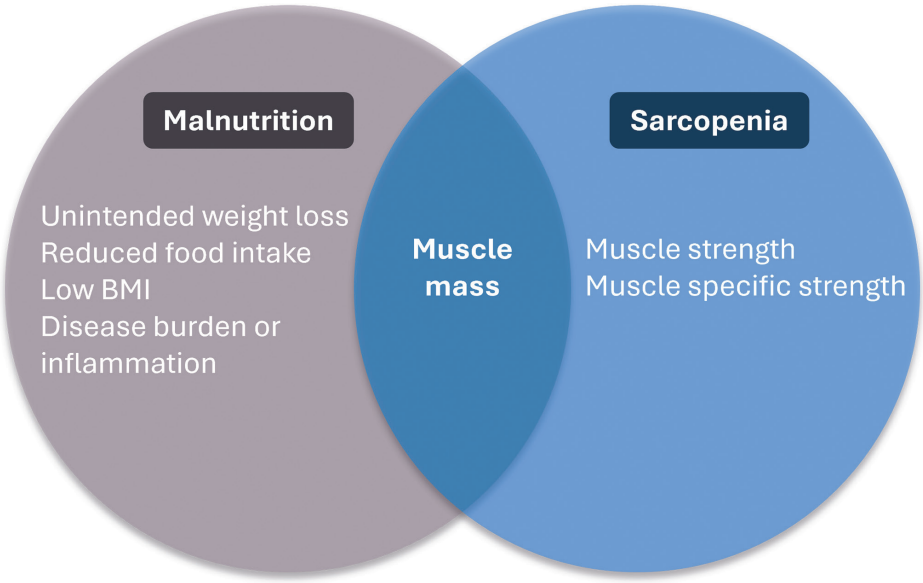

Figure 4. Overlap sarcopenia and malnutrition

IMPACT OF MALNUTRITION AND SARCOPENIA IN OLDER PATIENTS

The impact of malnutrition and sarcopenia appears to be more pronounced in older adults. Not only do older adults lose muscle mass at a faster rate compared to younger adults, but it is also more difficult to regain this lost muscle mass.(18) A rapid loss of muscle mass in older adults is especially the case during longer periods of physical inactivity. During hospitalization, prolonged bedrests are not uncommon, putting older adults who are admitted to hospital at an increased risks of malnutrition and sarcopenia.(19)

When malnutrition is left untreated, it has a negative impact on the course of disease and on health outcomes like wound healing, complications, length of hospital stay and quality of life.(20) Wound healing might be impaired due to malnutrition, mainly through micronutrient deficiencies. (21) Kruizenga et al. (2016) showed that patients who are

at risk of malnutrition stayed 1.4 days longer in hospital.(22) Furthermore, malnutrition is associated with an increased risk of mortality, regardless of the cause of death.(23) Sanchez-Rodriguez et al. (2020) showed that community dwelling older adults already have a 4.4-fold higher risk of mortality during a four-year follow-up period.(24)

This increased risk of mortality is also found in patients suffering from sarcopenia.(25) Sobestiansky et al. (2021) showed a Hazard Ratio of 4.06 and 4.8 for a one-year mortality in sarcopenic and malnourished geriatric inpatients respectively.(26)

Both malnutrition and sarcopenia have effect on muscle mass and physical functioning. It was found that malnutrition was an independent risk factor for an acute decrease in muscle mass during a two-week hospital stay. (17) The further acceleration of the loss of muscle mass due to prolonged bedrest can lead to increased dependency in activities of daily living (ADL) which can even persists after hospitalization.(27) Patients with sarcopenia-related muscle weakness additionally have an increased risk of falls, immobility and further functional decline.(28) For older adults on haemodialysis it was found that if they experienced both malnutrition and sarcopenia, they had a higher hazard ratio of 2.99 for mortality, compared to those who did not have malnutrition and sarcopenia.(29)

Taking this together, early identification of malnutrition and sarcopenia is important.

ECONOMIC EFFECTS OF MALNUTRITION AND SARCOPENIA

Not only can malnutrition and sarcopenia have major impacts on health of older adults, but it can also come with increased economic burden. Due to the increased morbidity and length of hospital stay, the presence of malnutrition and sarcopenia result in higher health care costs.(30, 31) This may even be as high as 10% and 4% of the national health expenditures for malnutrition and sarcopenia respectively for hospitalized patients. Several studies were able to show that investment in early screening, diagnosing and treatment of malnutrition and sarcopenia reduces costs by reducing length of hospital stay, prevention of readmissions and improvement of physical functioning and quality of life. (32-35)

CURRENT EVIDENCE AND CHALLENGES

Both malnutrition and sarcopenia are (partly) reversible when identified and treated in their early stages. Early identification and start of treatment support the overall recovery potential of older patients. Several strategies to combat malnutrition and sarcopenia have been developed in the recent years.(2, 36-39) One of these strategies is to increase protein intake. Existing guidelines suggest a protein intake of 1.2-1.5g/kg bodyweight per day to fully support muscle mass and physical functioning.(37) However, older adults admitted to hospital struggle to reach this target.(40) This might be partly due to the decreased appetite older patients report during but also after hospitalization.(41, 42) The use of protein-enriched familiar foods or Oral Nutritional Supplements (ONS) with dietary advice, might be strategies to help older patients to increase their protein intake. (36, 43) The large EFFORT-trial was able to show that with dietetic support in combination with ONS and enriched hospital nutrition, more than 75% of the older patients were able to reach their protein goals within 4 days of hospitalization.(38) Next to protein intake, emerging evidence suggest that other nutrients like minerals might play a role in managing malnutrition and sarcopenia.(44) For example, calcium and magnesium are involved in muscle contraction and relaxation, whereas zinc is involved with delaying muscle atrophy.(45-47)

Next to nutritional intake, physical activity is an important strategy in preserving physical functioning and combatting malnutrition and sarcopenia.(37) Especially in older patients, prolonged sedentary behavior during hospitalization may even cover up to 80% of the daytime.(48) In recent recommendations for physical activity during hospitalization, Baldwin and colleagues state that next to minimizing sedentary periods, it is important that older patients also perform muscle strengthening and balance exercises.(49) However, in practice patients face many barriers to physical activity during hospitalization.(50)

Even though evidence is present for intensive treatment of patients at risk of malnutrition and/or sarcopenia, there is still a gap between evidence-based knowledge and the current clinical practice. Due to the complexity of malnutrition and sarcopenia, their treatment asks for interdisciplinary and multifactorial interventions which continue post hospital stay.(51, 52) Dietitians play a crucial role in optimizing the dietary intake through

individualized nutritional care plans that align with their dietary needs. (36) On the other hand, physical therapists can support older patients in performing (bedside) exercises with an individualized training plan. However, these health care professionals often face barriers such as limited time, uncertainty in responsibilities, lack of interprofessional collaborations and challenges in maintaining continuity of care after discharge.(50, 53, 54)

AIM AND OUTLINE OF THE THESIS

This thesis aims to improve care for older adults facing malnutrition, sarcopenia, and the challenges of recovery following hospitalization, recognizing that addressing these conditions together is essential for enhancing recovery, maintaining independence, and reducing healthcare costs. The first part of this thesis focuses on understanding the problem—examining how malnutrition and sarcopenia manifest, how accurately they are detected, and what mechanisms underlie inadequate nutritional intake and functional decline. The second part builds on these insights by developing and evaluating an intensified, transmural dietetic care pathway designed to optimize protein intake and physical functioning in older patients during and after hospitalization. Finally, the third part broadens the perspective by exploring the role of micronutrients in muscle health, and methodological directions for advancing nutritional research in ageing populations.

PART I - NUTRITIONAL CHALLENGES DURING HOSPITALIZATION

As suggested by the GLIM framework for diagnosing malnutrition, identifying patients at risk begins with screening with any validated screening. However, the current available screening tools for older patients were developed and validated with older diagnostic criteria. Their ability to identify malnutrition as defined by the GLIM criteria remains uncertain. Moreover, in the Netherlands, the outcomes of these screening tools guide referrals to dietitians, making their accuracy crucial for timely and effective care. **Chapter 2** therefore evaluates the diagnostic performance of the five most commonly used screening tools against the GLIM-based diagnosis of malnutrition.

To gain insight into the nutritional adequacy of hospitalized patients, **Chapter 3** presents national data covering more than a decade from 339,720 hospital admissions. This analysis reveals trends in dietary intake and protein adequacy among patients at risk of malnutrition during hospital stay. **Chapter 4** extends this focus by examining the relationship between appetite and physical functioning. Using data from the Hospital-ADL study, this chapter explores how decreased appetite during and after hospitalization may contribute to sarcopenia and functional decline in older adults.(55) Together, these three chapters define the scope and underlying mechanisms of malnutrition and sarcopenia across the continuum of hospital care.

PART II - WORKING TOWARDS SOLUTIONS: FROM EVIDENCE TO CLINICAL PRACTICE

Building on these insights, Part II introduces and evaluates a practical solution to improve nutritional and functional recovery in older adults. **Chapter 5** presents the rationale and design of the ProIntens trial, which aimed to test an intensified, transmural dietetic care pathway to optimize protein intake and physical functioning during and after hospitalization. The main results of this intervention are discussed in **Chapter 6**, highlighting both its effects and the implementation challenges encountered in real-world practice. These findings provide valuable lessons for integrating dietetic and physical rehabilitation strategies into standard clinical care for older adults.

PART III – BROADENING THE PERSPECTIVE: EXPANDING NUTRITIONAL CARE IN AGING POPULATIONS

The final part of this thesis broadens the perspective on nutritional care and muscle health in ageing populations. **Chapter 7** systematically reviews the evidence on the role of minerals—such as magnesium, selenium, and zinc—in muscle metabolism and their potential contribution to preventing or mitigating sarcopenia. **Chapter 8** revisits this topic five years later to assess scientific progress and evolving insights in this emerging field. **Chapter 9** reflects on methodological and practical challenges encountered in nutrition research involving older

adults and proposes a guiding framework for designing more flexible, patient-centered, and pragmatic clinical studies.

Chapters 10 and 11 conclude this thesis with a general discussion and summary of the main findings, integrating insights across all studies and highlighting implications for improving nutritional care for older adults.

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PART I

NUTRITIONAL CHALLENGES DURING HOSPITALIZATION

CHAPTER 2

Malnutrition Screening Tools Are Not Sensitive Enough to Identify Older Hospital Patients with Malnutrition

Carliene van Dronkelaar,
Michael Tieland,
Tommy Cederholm,
Esmee M. Reijnierse,
Peter J. M. Weijs
and Hinke Kruizenga

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ABSTRACT

This study evaluates the concurrent validity of five malnutrition screening tools to identify older hospitalized patients against the Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria as limited evidence is available. The screening tools Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Universal Screening Tool (MUST), Malnutrition Screening Tool (MST), Mini Nutritional Assessment—Short Form (MNA-SF), and the Patient-Generated Subjective Global Assessment—Short Form (PG-SGA-SF) with cut-offs for both malnutrition (conservative) and moderate malnutrition or risk of malnutrition (liberal) were used. The concurrent validity was determined by the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the level of agreement by Cohen's kappa. In total, 356 patients were included in the analyses (median age 70 y (IQR 63–77); 54% male). The prevalence of malnutrition according to the GLIM criteria without prior screening was 42%. The conservative cut-offs showed a low-to-moderate sensitivity (32–68%) and moderate-to-high specificity (61–98%). The PPV and NPV ranged from 59 to 94% and 67–86%, respectively. The Cohen's kappa showed poor agreement (k = 0.21–0.59). The liberal cut-offs displayed a moderate-to-high sensitivity (66–89%) and a low-to-high specificity (46–95%). The agreement was fair to good (k = 0.33–0.75). The currently used screening tools vary in their capacity to identify hospitalized older patients with malnutrition. The screening process in the GLIM framework requires further consideration.

INTRODUCTION

Malnutrition has a major impact on health outcomes and quality of life for hospitalized older patients (1,2). Malnutrition is associated with a higher risk of complications, adverse functional outcomes, and increased mortality, independent of the underlying illness (3,4). Hospitalization carries a high risk for the loss of muscle mass and function, which can be accelerated by malnutrition (5). Early detection of malnutrition is therefore important in order to start nutritional treatment early during hospital admission and to continue it after discharge (1,6). Currently, malnutrition is identified with various validated malnutrition screening tools (7). Until recently, these screening tools have mainly been used to identify patients as either not at risk, at risk, or malnourished. In the Dutch context, the Short Nutritional Assessment Questionnaire (SNAQ) is established for identifying patients with malnutrition for dietetic assessment and treatment (8,9). In 2019, a new framework for diagnosing malnutrition was established by the Global Leadership Initiative on Malnutrition (GLIM), using a two-step approach (10). In the first step, the use of a screening tool is suggested to screen for any patient potentially at risk of malnutrition. The second step is a confirmation of malnutrition based on a set of five criteria: three phenotypic criteria, i.e., unintentional weight loss, low BMI, and low muscle mass, and two etiologic criteria, i.e., reduced food intake or assimilation and disease burden determined by inflammation. Malnutrition is then diagnosed if at least one phenotypic and one etiologic criterion is met. The GLIM criteria have been shown to have a high diagnostic accuracy for identifying patients with malnutrition, with a sensitivity of 81% and a specificity of 80% (4,11). Despite the high predictive ability of the GLIM malnutrition diagnosis for complications, length of hospital stay, and mortality in older adults, the feasibility of applying the criteria in different clinical care settings remains challenging (12,13).

A recent scoping review, analyzing mainly retrospective cohort studies, showed that only a third of the studies applied the full two-step approach; only 52% of the studies applied all five criteria, and up to 42% of the studies did not clearly describe the methods used to apply the GLIM criteria (14). Within the first step of the GLIM framework, no specific recommendations are made on which screening tool should be used in which population or setting (10). In the scoping review, it was highlighted

that there is a need to evaluate the screening tools used in the first step of the criteria as these tools were developed and validated against various previous sets of criteria for malnutrition (14).

This study aimed to evaluate the concurrent validity of five screening tools for malnutrition: the Short Nutritional Assessment Questionnaire (SNAQ), the Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), the Mini Nutritional Assessment—Short Form (MNA-SF), and the Patient-Generated Subjective Global Assessment—Short Form (PG-SGA-SF) with respect to identifying older hospitalized patients with potential malnutrition according to the GLIM criteria.

MATERIALS AND METHODS

Study Design and Participants

Data were collected from January 2021 to December 2022 in five hospitals in Amsterdam, the Netherlands: the university hospital Amsterdam University Medical Center (Amsterdam UMC) at the Academic Medical Center (AMC) (~1000 beds) and VU University Medical Center (VUmc) (~730 beds) locations; the teaching hospital Onze Lieve Vrouwen Gasthuis (OLVG), at the East (555 beds) and West (365 beds) locations; and the regional hospital BovenIJ (315 beds). Patients from several wards were assessed for eligibility: the acute admission ward, internal medicine, cardiology, gastroenterology, neurology, and the geriatric ward. With the BovenIJ hospital being a smaller regional hospital, several specialties there were grouped in one ward. In that case, all eligible patients regardless of specialized medical need were included. Patients were eligible when aged 55 or over, admitted to the hospital in the last 48 h, and having a reasonable understanding of the Dutch language. Patients were excluded if they were being nursed in contact isolation due to COVID-19 or other infectious diseases, suffered from severe cognitive impairment or delirium, or had end-of-life palliative care based on the judgment of the attending nurse. From all included patients, written informed consent was obtained. All questionnaires and measurements were performed by trained research staff. The medical ethical committee of the Amsterdam UMC, VUmc (2019.680) location, approved the study, and the study followed the Declaration of Helsinki.

Screening Tools

Five screening tools were used to screen for malnutrition, namely, the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF, to conduct a comprehensive evaluation of the most often used screening tools for older patients in a hospital setting within the Netherlands, based on the outcomes of a meta-analysis by Power et al. (7). The SNAQ consists of questions on unintentional weight loss in the past month, decreased appetite, and the use of oral nutritional support that had the best ability to predict malnutrition (8). The questionnaire was developed for hospitalized patients above 18 years of age. The MUST considers low BMI and unintentional weight loss over the past three to six months and asks if a patient has been ill and unable to eat for more than five days (15). The MST evaluates adults in various settings and consists of questions on unintentional weight loss over the last six months and decreased appetite; it was developed for hospitalized patients 18 years or older (16). The MNA-SF is the longest questionnaire of the five screening tools and is designed for older adults. The MNA-SF takes more risk factors into account and consists of questions on weight loss over the last three months, decreased intake, mobility, psychological stress or acute illness in the past three months, neuropsychological problems, and BMI (17). The PG-SGA was developed for adult cancer patients and considers multiple risk factors. The PG-SGA-SF (box 1 to 4) classifies weight loss over the last month if available, otherwise, weight loss over the past six months. Questions on food intake and physical activity over the past month and problems leading to decreased food intake over the past two weeks are part of the PG-SGA-SF (18). The PG-SGA-SF was added as the fifth screening tool in August 2022 and from that time point onwards applied to every patient included in this study.

The screening tools use different cut-offs to identify patients as well-nourished, malnourished, moderately malnourished, or at risk of malnutrition. In this study, patients were classified as malnourished based on the screening tools, without confirmation based on the GLIM criteria, if they scored ≥3 points on the SNAQ (max. 7 points), ≥2 on the MUST (max. 6 points) or MST (max. 5 points), ≤7 points on the MNA-SF (max. 14 points), and ≥9 points on the PG-SGA-SF (max. 35 points) (8,15–18). These cut-offs are considered as conservative cut-offs. The SNAQ, MUST, MNA-SF, and PG-SGA-SF also have more liberal cut-offs available to identify moderate malnutrition or risk of malnutrition. Additional analyses were conducted

with these more liberal cut-offs (≥2 points on SNAQ, ≥1 point on MUST, ≤11 points on MNA-SF, and ≥4 points on the PG-SGA-SF). Finally, as the MNA-SF is specially developed for older patients, additional analyses were conducted comparing patients aged < 70 years with those aged ≥ 70 years.

GLIM Criteria

The GLIM definition was used to identify malnutrition. Questions to assess unintentional weight loss, weight at admission, and weight from 1 month, 3 months, 6 months, and 12 months before admission were asked of the patient. In case the patient did not remember their weight, the electronic medical record was checked for available information on weight; if unavailable, weight was considered missing and excluded from analyses. Height and weight at admission were used to calculate the BMI. Bioelectrical impedance analysis (BIA) measurements were performed to assess muscle mass. The BIA was performed with a hand-to-foot device (BodyStat 500 or Quadscan 4000; BodyStat Body Composition Technology, Cronkbourne, UK), with the patient in a supine position with four electrodes connected to one side of the body and arms not touching the trunk and legs slightly separated. BIA measurements were performed between 9 a.m. and 1 p.m. Patients were not in a fasted state before the measurement (19,20). BIA measurements were not performed if the patient had severe edema or a pacemaker, was wearing a heart monitor, or had an IV drip in both hands or arms, according to hospital protocols (21). The impedance, reactance, and resistance at 50 kHz of the BIA were used to apply the Rutten (22), Sergi (23), and Janssen (24) equations to determine the fat-free mass index (FFMI), the appendicular skeletal muscle mass index (ASMI), and the skeletal muscle mass index (SMI), respectively. Within the second step of the GLIM framework, cut-offs for low muscle mass are recommended for FFMI as well as ASMI and SMI. For the main analysis, the cut-off for FFMI was used to determine low muscle mass, as the BIA was performed on the whole body and is used in that manner within the Dutch guidelines for identifying malnutrition (25). The other recommended measures of muscle mass (i.e., ASMI and SMI) were used to compare the impact of the selected measure on the prevalence of malnutrition. To assess the criterion of reduced intake and/or malabsorption, the question of the MNA-SF on reduced intake over the past three months and a question on malabsorption, stating ‘Did you suffer from dysphagia, nausea, vomiting, diarrhea, constipation, or

abdominal pain?', were used. Inflammation was defined using CRP or (pre-) albumin levels from three days before inclusion, and data were obtained from patients' medical files when available.

Patients were classified as malnourished based on the GLIM criteria, without prior screening, when at least one phenotypic and one etiologic criterion were fulfilled.

The phenotypic criteria were applied as follows:

- Weight loss: >5% within the past 6 months or >10% within the past 12 months (10);
- Low BMI: <20 kg/m2 for patients under 70 years old; <22 kg/m2 when aged 70 years or older (10);
- Reduced muscle mass: males with an FFMI of <17 kg/m2 and females with an FFMI of <15 kg/m2 (10);

The etiologic criteria were applied as follows:

- Reduced food intake or assimilation: having a severely decreased appetite or having answered 'yes' on the malabsorption question, 'Did you suffer from dysphagia, nausea, vomiting, diarrhea, constipation, or abdominal pain?' (10);
- Inflammation or disease burden: having CRP levels of ≥3 mg/L or pre-albumin levels of <30 mg/dl or albumin levels of <3.8 g/L (26,27).

Statistical Analysis

Patient characteristics were analyzed with descriptive statistics and presented as means and standard deviations, medians, and interquartile ranges or as frequencies and percentages. Sensitivity (the capacity to identify true positive cases), specificity (the capacity to identify true negative cases), positive predictive value (PPV), and negative predictive value (NPV) were calculated, and the Cohen's kappa coefficient (indicating agreement) was determined for each screening tool against the GLIM criteria. Sensitivity and specificity were considered low if <50%, moderate if 50–80%, and high if >80% (7,28). Cohen's kappa measures the agreement between the two tools and was classified as follows: <0.20 poor, 0.20–0.40 fair, 0.40–0.60 moderate, 0.60–0.80 good, and >0.80 very good (29,30). The McNemar test was performed to evaluate if the screening tools identified the same patients as the GLIM criteria. A non-statistically significant McNemar test would indicate that the

same patients are being identified. Univariate logistic regression was performed to identify the contribution of different criteria and cut-offs of the screening tools on the GLIM criteria. Subjects with incomplete basic data (i.e., missing data on either age, sex, weight, or height), or those who were included in the study within 30 days from the previous inclusion, were omitted from the analyses. In addition, subjects for whom one of the five GLIM criteria could not be assessed due to missing data were excluded from the analyses. Statistical significance was set at $\alpha < 0.05$. All analyses were performed in SPSS for Windows version 28.0.

RESULTS

Patient Characteristics

A total of 2623 patients gave informed consent and were screened for malnutrition. Of these, 55 patients (2%) had incomplete basic data (i.e., age, sex, height, or weight) and ten (0.4%) were included within 30 days since their prior inclusion and therefore excluded from the analyses. In addition, we were only able to perform a BIA measurement on 430 patients. The final analyses were performed on patients with complete data on all five criteria of the GLIM, leading to a sample size of 356 patients (Figure 1).

The included patients had a median age of 70 years (interquartile range 63–77 years) (range 55–98 years), and 54% were male (Table 1). The study population was a heterogenous group of older patients as 72% of them were screened at the acute admission ward, which has a large variety of medical specialties.

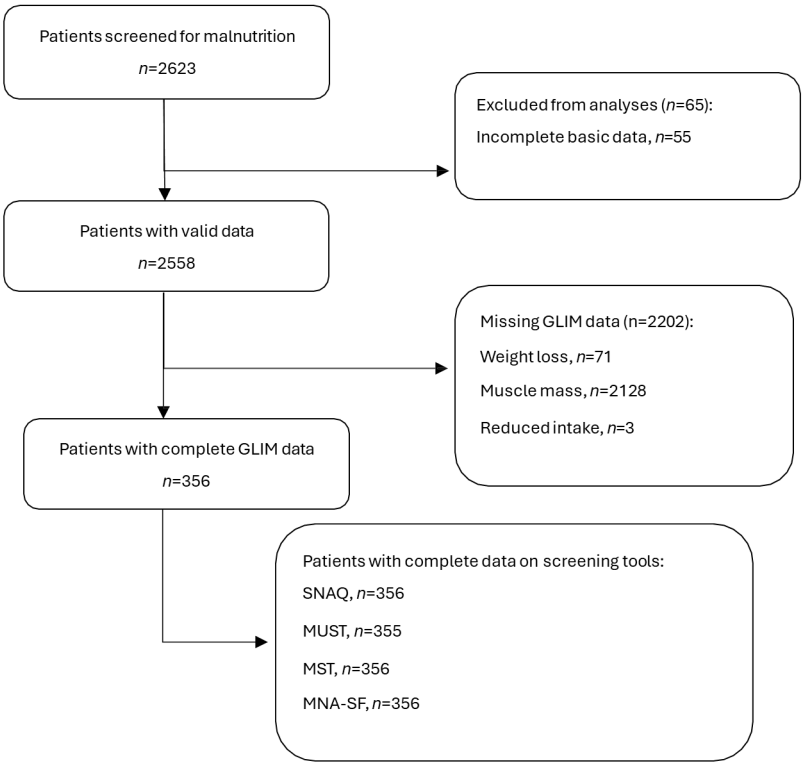

Figure 1. Flowchart of selection of final analysis sample. Several patients had more than one missing data point in their GLIM data.

Table 1. Study subject characteristics.

Patients	***n* = 356**
Sex, males, *n* (%)	192 (54)
Age in years, median (IQR)	70 (63–77)
BMI in kg/m2, median (IQR)	24.8 (22.6–28.1)
Hospital, *n* (%)	
Amsterdam UMC, location AMC	22 (6)
Amsterdam UMC, location VUmc	152 (43)
OLVG, location East	110 (31)
OLVG, location West	43 (12)
BovenIJ Hospital	29 (8)
Ward, *n* (%)	
Acute admission	257 (72)
Internal medicine	18 (5)
Cardiology	27 (8)
Neurology	18 (5)
Pulmonary	13 (4)
Gastroenterology	10 (3)
Geriatric	3 (<1)
Other	14 (4)

Prevalence of Malnutrition

Of the patients screened after August 2022, 126 patients had complete GLIM data and had therefore data on the PG-SGA-SF. The prevalence of malnutrition according to the different screening tools, without confirmation by the GLIM, ranged from 18 to 52% (Table 2). The prevalence according to the GLIM criteria was 42% when no screening tool was used a priori (Table 3). When the GLIM criteria were analyzed separately, the criteria with the highest proportions were unintended weight loss (32%), reduced intake (71%), and inflammation (83%). When the SMI measure (22%) was used, the prevalence of low muscle mass was similar to the FFMI measure, but the prevalence was higher when the ASMI measure was used (45%). Using these measures resulted in a prevalence of malnutrition based on the GLIM criteria of 44% and 54% for the SMI and ASMI measures, respectively.

Table 2. Prevalence of malnutrition and moderate malnutrition or risk of malnutrition according to the screening tools, without the confirmation diagnostic step of GLIM.

	n	**Prevalence, *n* (%)**
SNAQ	356	
Malnutrition (≥3)		88 (25)
Moderate malnutrition (≥2)		115 (32)
MUST	355	
Malnutrition (≥2)		65 (18)
Risk of malnutrition (≥1)		126 (36)
MST	356	
Malnutrition (≥2)		111 (31)
MNA-SF	356	
Malnutrition (≤7)		52 (15)
Risk of malnutrition (≤11)		206 (60)
PGSGA-SF	126	
Malnutrition (≥9)		65 (52)
Risk of malnutrition (≥4)		88 (70)

SNAQ: Short Nutritional Assessment Questionnaire; MUST: Malnutrition Universal Screening Tool; MST: Malnutrition Screening Tool; MNA-SF: Mini Nutritional Assessment—Short Form; PG-SGA-SF: Patient-Generated Subjective Global Assessment—Short Form.

Table 3. Prevalence of malnutrition according to the GLIM criteria, without prior screening, and the occurrence of each criterion.

	n	**Prevalence, *n* (%)**
GLIM	356	148 (42)
Phenotypic criteria	356	156 (44)
Weight loss	356	113 (32)
Low BMI	356	59 (17)
Low muscle mass	356	83 (23)
Etiologic criteria	356	330 (93)
Reduced intake	356	251 (71)
Inflammation	356	294 (83)

GLIM: Global Leadership Initiative on Malnutrition.

Concurrent Validity

When the conservative cut-offs of the screening tools were used to identify malnutrition, they performed with low-to-moderate sensitivity (32–68%) and moderate-to-high (61–98%) specificity (Table 4) in relation to the GLIM. Cohen's kappa showed that the agreement between each screening tool and the GLIM criteria was poor to moderate (0.21–0.59). The McNemar test showed that the screening tools identified different patients as malnourished in comparison to the GLIM criteria ($p < 0.001$). Only for the PG-SGA-SF was this was not the case ($p = 0.233$). When the liberal cut-off points, i.e., for identification of moderate malnutrition or risk of malnutrition, were used, the corresponding sensitivity was moderate to high (66–89%) and the specificity low to high (46–95%). The agreement based on Cohen's kappa was fair to good (0.33–0.75). The highest sensitivity was observed for PG-SGA-SF and MNA-SF, 89% and 86%, respectively.

Table 4. Concurrent validity of the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF on malnutrition (A) and moderate malnutrition or risk of malnutrition (B) against the GLIM criteria.

	SNAQ		**MUST**		**MST**	**MNA-SF**		**PG-SGA-SF**	
	(*n* = 356)		(*n* = 356)		(*n*=356)	(*n* = 356)		(*n* = 126)	
	A (≥3)	B (≥2)	A (≥2)	B (≥1)	A (≥2)	A (≤7)	B (≤11)	A (≥9)	B (≥4)
False positive, *n*	5	17	7	11	16	5	79	27	38
False negative, *n*	65	50	89	32	53	203	21	18	6
Sensitivity, %	56	66	40	78	64	32	86	68	89
Specificity, %	98	92	97	95	92	98	62	61	46
PPV, %	94	85	90	91	86	90	62	59	57
NPV, %	76	79	70	86	78	67	86	71	84
Cohen's kappa	0.57	0.60	0.39	0.75	0.59	0.21	0.45	0.29	0.33
McNemar	*p*<0.001	*p*<0.001	*p*<0.001	*p*=0.002	*p*<0.001	*p*<0.001	*p*<0.001	*p*=0.233	*p*<0.001

A: malnutrition (cut-off point); B: risk of/moderate malnutrition (cut-off point); PPV: Positive Predictive Value; NPV: Negative Predictive value; SNAQ: Short Nutritional Assessment Questionnaire; MUST: Malnutrition Universal Screening Tool; MST: Malnutrition Screening Tool; MNA-SF: Mini Nutritional Assessment—Short Form; PG-SGA-SF: Patient-Generated Subjective Global Assessment—Short Form; GLIM: Global Leadership Initiative on Malnutrition.

Comparing patients aged < 70 years to those aged ≥ 70 years, only the MNA-SF showed a slightly higher sensitivity when the liberal cut-off was used (82% and 89%, respectively). For the other screening tools and cut-off points, the sensitivity was higher with an average of 15% for those aged < 70 years (Tables S1 and S2).

The effect of applying different measures of low muscle mass within the GLIM criteria on the sensitivity and specificity of the screening tools can be found in Tables S3–S6. The SMI measure for low muscle mass showed similar results as when the FFMI measure for low muscle mass was used within the GLIM criteria. However, if the ASMI measure for low muscle mass was used within the GLIM criteria, the sensitivity of the screening tools dropped by ~10%, with the SNAQ screening tool shifting from moderate to low. Only in the PG-SGA did the concurrent validity remain similar to the FFMI measure.

DISCUSSION

The GLIM framework advises the use of any validated screening tool in the first step to identify patients at risk of malnutrition before applying the phenotypic and etiologic criteria to diagnose malnutrition. This observational study showed that the currently frequently used screening tools in hospital settings (SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF) were unable to identify 32–68% of the hospitalized older adults with malnutrition according to the GLIM criteria when applying the conservative cut-offs for malnutrition. When the more liberal cut-offs, i.e., for moderate malnutrition or risk of malnutrition, were used, the sensitivity was higher, especially for PG-SGA-SF and MNA-SF. The concurrent validity of the screening tools varied greatly depending on the measure for low muscle mass used and whether applied to those aged < 70 years compared to those ≥70 years.

Similar to our findings, a Brazilian study in older hospitalized patients showed that when the MNA-SF (liberal cut-off) was used in the first step of the GLIM framework, 83% of the older patients in the emergency ward were identified as at risk of malnutrition, of which 50% were confirmed as malnourished with the GLIM criteria (31). Another Brazilian study compared the liberal cut-offs of the MST, NRE-2017, NSR-2002, and SNAQ to the GLIM criteria in a general hospital population (32). Although their

population was younger (mean age 56 y), they found similar concurrent validity outcomes for the MST and the SNAQ as we found in our study. In a study with an older patient population (mean age 78 y), when the liberal cut-off was used, the MUST had lower concurrent validity than in our study, confirming that the MUST screening tool might be less appropriate for older hospital patients (33). In line with our findings, two studies showed a low-to-fair agreement between the screening tools PG-SGA-SF and MST against the GLIM criteria, where the GLIM criteria had a better predictive ability for mortality (28,34).

Our study therefore adds to the body of work that suggests that the first step of the GLIM framework needs to be further analyzed and more thoroughly considered. Although the PPVs of the screening tools were high, meaning that of those identified as malnourished by the screening tool most were also identified as malnourished by the GLIM criteria, the low sensitivity indicated that half of the patients with malnutrition were not identified by the screening tools. In a clinical setting, a screening tool needs to have a high sensitivity, to be able to start treatment for those at risk. Furthermore, we showed that the choice of screening tool and cut-off points has major implications for those who will be subject to further nutritional assessment and potential nutrition treatment. For example, currently, over 80% of Dutch hospitals use the SNAQ screening tool with the conservative cut-off to identify potential patients with malnutrition (9). Only for patients with a SNAQ malnutrition score (3 or higher) is a dietitian consulted to further assess nutritional status. Based on the findings of our study, this would mean that 34–54% of patients with malnutrition, based on GLIM criteria, are not assessed by a dietitian and do not receive nutritional treatment. Thus, for the implementation of the GLIM framework, a more sensitive screening procedure is warranted since specificity is provided by the GLIM confirmatory diagnostic step.

The prevalence of malnutrition based on the GLIM criteria was higher than expected in our study population (32–35). Despite the high prevalence of malnutrition in older hospitalized patients, nurses and medical staff experience difficulties in diagnosing malnutrition due to a lack of knowledge and skills (36). Early diagnosis and treatment are essential to prevent negative health outcomes (1). Hence, identifying malnutrition in the hospital setting should be quick and easy. A decade ago, medical records were only paper based. In the meantime, technology within the

hospital has developed tremendously, and electronic medical records have become available in most hospitals. This creates the opportunity for systems and algorithms in electronic patient files, allowing a more automated screening for malnutrition and the risk of malnutrition. The GLIM criteria of unintended weight loss, low BMI, reduced intake, and inflammation could be built into these electronic patient records. For example, when current height and weight and weight from six and twelve months ago are added to the record, unintended weight loss and low BMI can be calculated automatically. Taking this approach could improve the screening process. By adding setting-specific malnutrition risk factors, e.g., cognition, mobility, and marital status, the sensitivity of the screening procedure could be further ameliorated as the first step of the GLIM framework. In addition, this automated process could potentially ease the workload for nurses. The diagnosis of malnutrition could then be completed by the measurement of muscle mass, as a complete assessment of all five criteria is essential to be certain that malnutrition is not present. Further studies are needed to validate this approach and assess its applicability. When electronic medical records are not present, MNA-SF with a cut-off of ≤11 points could be used in the first step of the GLIM framework, especially for older patients. The second step of the GLIM framework, i.e., assessment and diagnostics, could then be completed by a dietitian.

Another important finding is the variability in malnutrition prevalence rates depending on the chosen measure for low muscle mass, a factor that is recommended by the GLIM consensus. Although BIA has been validated for the assessment of muscle mass, it has its limitations. BIA estimates muscle mass by relying on measurements of total body water and equations for estimating fat-free mass (FFM) or skeletal muscle mass (SMM). Changes in FFM tend to reflect changes in muscle mass over a longer period (37). Another approach is to assess appendicular skeletal mass (ASM), which is the sum of the lean soft tissue in the arms and legs. ASM is more sensitive to muscle mass changes and could be a more appropriate measure for evaluating nutritional status. However, when using BIA on a whole-body level, a segmental approach (ASM) relies on more assumptions than a whole-body approach (FFM). To use the ASM measure for the GLIM criteria, a more valid measure like DXA or CT would be preferable. A recent guidance paper for the assessment of low muscle mass within the GLIM still recommends both FFMI and ASMI measures

for low muscle mass, but our study showed that these measures have an impact on the prevalence of malnutrition in older hospitalized patients (38). This indicates that the recommended measures of low muscle mass require evaluation in the GLIM criteria.

One of the strengths of this study is that we had access to the data of 2623 patients, of which we could filter a complete dataset on the GLIM criteria of over 300 patients. Because of this, we were able to include a heterogenous patient population from several hospitals and admission wards, which makes our results not disease or hospital-specific but more generalizable to other older patient populations. However, in this heterogenous patient population, it was more difficult to assess low muscle mass with the BIA due to the presence of heart monitors, pacemakers, ICDs, or IV drips in both hands/arms. The missing data on low muscle mass could have led to underreporting of the prevalence of malnutrition. Still, this also reflects the 'real' clinical setting and shows the feasibility of applying the GLIM criteria, including the muscle mass measurement with a BIA, in a clinical setting. A major methodological strength of our study is the simultaneous screening and assessment of the GLIM criteria. This avoids any day-to-day variance within patients concerning the measurements. Although we were able to collect data on the admission ward, we did not have access to data on the reason for admission. With this information, subgroup analyses could have been performed to assess if the prevalence of malnutrition and the concurrent validity of the screening tools were different among different reasons for admission.

CONCLUSIONS

The results of this study indicate that the currently used screening tools for malnutrition in hospital settings are not sensitive enough to identify older patients who are malnourished according to the GLIM criteria. The first step of the GLIM framework therefore requires further consideration. Using electronic medical records to screen for malnutrition might be an option for improvement, where information on the GLIM criteria of unintended weight loss, low BMI, reduced intake, and inflammation can be easily assessed. Further studies are needed to validate this approach and assess its feasibility. When electronic medical records are absent,

the MNA-SF with the liberal cut-off (≤11 points) could be used for the screening step of the GLIM diagnostic procedure.

Supplementary Materials
The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu15245126/s1, Table S1: Concurrent validity of the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF on malnutrition (A) and moderate or risk of malnutrition (B) against the GLIM criteria in patients aged < 70 years. Table S2: Concurrent validity of the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF on malnutrition (A) and moderate or risk of malnutrition (B) against the GLIM criteria in patients aged ≥ 70 years. Table S3: Prevalence of confirmed malnutrition based on the appendicular skeletal mass index (ASMI) threshold. Table S4: Concurrent validity of the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF against the GLIM criteria based on the appendicular skeletal mass index (ASMI) threshold. Table S5: Prevalence of malnutrition based on the skeletal mass index (SMI) threshold. Table S6: Concurrent validity of the SNAQ, MUST, MST, MNA-SF, and PG-SGA-SF against the GLIM criteria based on the skeletal mass index (SMI) threshold.

Author Contributions
Conceptualization and methodology, C.v.D., H.K. and M.T.; formal analysis, C.v.D.; Investigation, C.v.D.; writing—original draft preparation, C.v.D.; writing—review and editing, H.K., M.T., E.M.R., T.C. and P.J.M.W.; supervision, M.T., P.J.M.W. and H.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement
This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Amsterdam UMC, VUmc location (protocol code 2019.680; date of approval 6 December 2019).

Informed Consent Statement
Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflicts of Interest

The authors declare no conflict of interest.

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CHAPTER 3

Protein intake during hospital admission; Dutch national data on protein intake in 339,720 malnourished patients from 2009-2019

Hinke M. Kruizenga,
Mireille Schager,
Carliene van Dronkelaar,
Elke Naumann

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ABSTRACT

Introduction: To stimulate early recognition and treatment of malnutrition, the Dutch Healthcare Inspectorate obliged all hospitals from 2008-2019 to report the number of malnourished patients with an adequate protein intake on the fourth day of hospital admission. In this article we present results over the past 11 years and discuss success factors and barriers for adequate treatment of malnourished patients in hospitals.

Methods: The annual reports of hospitals on the numbers of patients with a screening result 'malnourished' and an adequate protein intake on the fourth day of admission were analysed. Hospitals were categorized based on the percentage of malnourished patients with an adequate protein intake on the fourth day of admission as 'poor' (<40% of patients in a hospital achieve an adequate protein intake), 'moderate' 40-60% of patients in a hospital achieve an adequate protein intake), and 'good' (>60% of patients in a hospital achieve an adequate protein intake). To identify success factors and barriers for adequate treatment and registration of malnourished patients in hospitals, three focus groups were held in June and July 2020. Participants were dietitians and quality employees or nurses who were involved in data collection for malnutrition indicators in their hospitals.

Results: Between 2008-2019, data were reported of 339,720 malnourished patients. The relative number of patients with adequate intake of protein on the fourth day in hospital ranges from 44%-53% between 2011 and 2019. Before 2013, the number of hospitals that reported data was too small to draw conclusions about results of treatment of malnutrition. Data from 2013 to 2019, show a decline in the number of hospitals with a 'poor' score. The number of hospitals with a moderate score increased between 2015 and 2019 and the number of hospitals with a good score remained more or less stable, except for 2018 where more hospitals reached a 'good' score. Sixteen professionals from ten different hospitals participated in the focus groups and revealed several determinants of adequate treatment of malnourished patients in hospitals such as awareness, feeling responsible and the need of clear instructions and good collaboration.

Conclusion: This inventory of the protein intake of 339,720 hospital malnourished patients over 11 years shows that in one out of five

Dutch hospitals >60% of malnourished patients had an adequate protein intake on the fourth day of admission. This shows that meeting protein requirements remains a difficult challenge. Early recognition of malnutrition, optimal multidisciplinary treatment and continuous evaluation is necessary to provide optimal nutritional care in the hospital and beyond.

INTRODUCTION

In the Netherlands 14-15% of patients are screened as malnourished when admitted to the hospital. Prevalence highly differs between medical departments, with most patients with malnutrition at the departments of geriatrics, oncology, gastroenterology, and internal medicine (27-38%) (1). Malnutrition is associated with more complications, increased mortality, length of hospital stay and costs. Providing nutritional support during hospital stay improved clinical outcomes of malnourished patients, including survival. This emphasizes the importance of screening patients to identify patients at risk and start treatment early on (2-4).

Since its founding in 2006, the Dutch Malnutrition Steering Group (DMSG) aims to increase attention for malnutrition among health care professionals. This started in 2000 with a measurement of the prevalence of malnutrition in hospitals (5). As screening by a nurse proved necessary for early recognition and treatment, the Short Nutritional Assessment Questionnaire (SNAQ) was developed, validated and tested for cost-effectiveness (6,7). Screening on admission to hospital (with SNAQ or MUST) was implemented in all Dutch hospitals from 2006 to 2008 and is still common practice.

For this implementation of early screening and treatment of malnourished hospital patients, the DMSG worked closely together with the Dutch Inspectorate of Health Care. The Dutch Inspectorate of Health Care introduced quality indicators on screening for malnutrition on admission to the hospital in 2007 (1). In addition, from 2008-2020 Dutch hospitals were required to collect data on screening for and treatment of malnutrition at all hospital wards, and on screening for malnutrition at the outpatient clinics for preoperative geriatric care. The Dutch Inspectorate of Health Care annually collects and publishes data from hospitals regarding all quality indicators. The DMSG publishes fact sheets, also annually, about the quality indicators for malnutrition screening on its website. These fact sheets show mean scores on quality indicators and scores for each hospital. These scores are used by hospitals to mirror their own results against those of other hospitals and to share experiences and learn from each other.

The indicator on adequate protein intake on the fourth day of admission reflects the early recognition and treatment of malnutrition in the hospital. It is assumed that patients who are recognized and treated as malnourished early in the admission process, are also more likely to achieve adequate protein intake.

It is a big challenge for malnourished patients, who often have complex problems and feel sick, to achieve an adequate protein intake. Expert opinion revealed that it is not realistic to achieve adequate protein intakes in all malnourished patients on the fourth day of admission. Hence, the standard of this indicator was set at 60% and not 100%. Throughout the years, it turned out to be very difficult for hospitals to meet this standard. Moreover, there were large differences between hospitals in their achievements of reaching adequate protein intakes. For example, in 2019, the relative number of malnourished patients with adequate protein intakes on day 4 of admission, ranged from 15% to 84% between hospitals. Reasons for these differences between hospitals were unclear.

This article will present results of Dutch hospitals on early recognition and treatment of malnutrition, based on data retrieved from the Dutch Inspectorate of Health Care over the past 11 years. In addition, we will discuss success factors and barriers for adequate treatment of malnourished patients in hospitals.

METHODS

Indicator of adequate protein intake

From 2008 to 2019, Dutch hospitals annually submitted data to the Dutch Inspectorate of Health on the protein intake of malnourished patients on the fourth day of admission. Data were retrieved from electronic patient records by the hospitals and are available on the website of the Dutch Ministry of Health. In early years, 2008e2011, hospitals without electronic patient records, reported data from random sampling. Data from random sampling and data from hospitals that reported data from <250 patients were excluded in our analyses.

The quality indicator states that protein intake should be assessed in all adults with positive screening results for malnutrition. All hospitals screened all patients for malnutrition on admission to the hospital. Over 80% of the hospitals screened with the Short Nutritional Assessment Questionnaire (SNAQ) (6) and about 20% of the hospitals used the Malnutrition Universal Screening Tool (MUST) (8). A score of 3 or higher for the SNAQ and a score of 2 or higher for the MUST indicates malnutrition. According to these screening tools, patients who scored positive should be referred to a dietitian to start dietetic treatment to improve nutritional status. On the fifth day of admission, protein intake of the previous day was measured by a dietitian in an unstructured way, mostly with a 24-hour recall method.

The hospitals had to answer the following questions for the quality indicator:

- How many patients, hospitalized for more than 4 days, were at risk of malnutrition on admission as indicated by a screening tool?
- How many patients who had a screening result 'malnourished' at admission and hospitalized for more day than 4 days, had an adequate protein intake on the fourth day of admission?

Adequate protein intake was defined as a protein intake of 1.2 g/kg bodyweight for patients with BMI ≤27g/m^2. For patients with BMI >27g/m^2, body weight at BMI 27 was used to calculate adequate protein intake (9). For the quality indicator, hospitals are categorized based on the percentage of malnourished patients with an adequate protein intake on the fourth day of admission and categorized as follows: if <40% of patients in a hospital achieve an adequate protein intake, this is indicated as 'poor'; if 40-60% of patients in a hospital achieve an adequate protein intake, this is indicated as 'moderate', and if >60% of patients in a hospital achieve an adequate protein intake, this is indicated as 'good'. The average score per year of all hospitals was calculated by dividing the total number of malnourished patients with adequate protein intake by the total number of malnourished patients. In the Netherlands, ethical approval is not required for registry-based research with anonymous data.

Descriptive statistics were performed using IBM SPSS statistics for Windows (version 27). Data are presented as mean ± SD or as numbers (%).

Success factors and barriers for adequate treatment of malnourished patients in hospitals

In June and July 2020, three focus groups were held to identify success factors and barriers for adequate treatment and registration of malnourished patients in hospitals. Inclusion of hospitals was based on previous scores on the quality indicators and included three categories of hospitals: hospitals with high scores, hospitals low scores and hospitals that showed improvements over time. We asked dietitians involved in data collection for malnutrition indicators in their hospital to participate. We also asked the dietitian to invite a quality employee or nurse who was involved in data collection for malnutrition indicators in their hospital. In addition, hospitals were selected based on their location, making sure that the different Dutch regions were represented. All hospitals that were invited to participate, agreed to do so.

Focus groups were held online, due to covid-19 measures, through Microsoft Teams and video recorded with permission of all participants. Participants received a report of their discussion afterwards and were asked to correct misinterpretations. The final reports were read by two researchers. Of each report, text fragments that illustrated success factors and barriers for adequate treatment and registration of malnourished patients in hospitals were selected. Selected fragments of the three reports were combined to identify success factors and barriers for adequate treatment and registration of malnourished patients in hospitals.

RESULTS

Indicator of adequate protein intake

In 2020, there were 81 general hospitals and eight university hospitals in the Netherlands. This number has changed frequently in recent years for example through mergers. In addition, some of the hospitals did not deliver data, because they are highly specialized hospitals, for example for eye surgery. The number of hospitals that reported to the health inspectorate ranged from one to 68 in the period of 2008-2019 (Table 1). Since only one hospital met our inclusion criteria in 2008, we excluded data collected in 2008 from our analyses.

The number of recorded malnourished patients increased over the years (Table 2). The mean relative number of patients with adequate intake of protein on the fourth day in hospital ranges from 44%-53% between 2011 and 2019, with no clear increase over time. In 2019, an adequate protein intake was achieved in almost 29000 (50%) patients who were malnourished on admission.

When looking at the achievements on the quality indicator in different hospitals, the number of participating hospitals before 2013 was too low to draw conclusions. Data from 2013 to 2019 show a decline in the number of hospitals with a 'poor' score (<40% of patients reaches adequate protein intake on the fourth day in hospital) (Table 2). The number of hospitals where adequate protein intakes was reached in 40-60% of the patients increased between 2015 and 2019. The number of hospitals where over 60% of patients reached adequate protein intakes remained more or less stable, except for 2018 when more hospitals, for unknown reasons, reached a 'good' score (Fig. 1).

Success factors and barriers for adequate treatment of malnourished patients in hospitals

Sixteen professionals from ten different hospitals participated in the focus groups; nine dietitians, three quality employees, three team managers (e.g. of dietetic departments), one nurse. Participating hospitals had diverse scores on the quality indicator on treatment of malnutrition: in three hospitals ≤40%, in 4 hospitals 40-70%, and in 3 hospitals ≥70% of patients who were screened as malnourished had an adequate protein intake on day four of hospitalization.

Table 1. Hospitals included in analyses, based on continuous data collection and number of patients

Year of data collection	Number of hospitals that indicated to collect continuous data	Number of excluded hospitals with samples of < 250 patients	Number of hospitals included in the analysis
2008	25	24	1
2009	54	49	5
2010	68	60	8
2011	11	1	10
2012	73	71	2
2013	33	6	27
2014	44	10	34
2015	80	17	63
2016	80	14	66
2017	79	14	65
2018	74	8	66
2019	74	6	68

Focus group discussions revealed that several determinants may contribute to successes or barriers for adequate treatment of malnourished patients in hospitals. The electronic patient files can and should be constructed in a way that it facilitates easy registration of data on malnutrition and protein intakes. For example, real-time information facilitates early adjustment to treatment and policies. A reason for differences in achievements between hospitals may be differences in inclusion or exclusion of data from patients from specific departments, like the obstetrics or palliative department. Also, some hospitals excluded information from patients with missing data on protein intake on the fourth day of admission, while other hospitals included all patients, even if data on protein intake on the fourth day of admission were not available. The latter will result in lower scores on the quality indicator. Awareness among health professionals about the importance of treatment of malnutrition and the feeling of being responsible, as well as the way health professionals are instructed to register data on the quality indicator, are all considered important to make registration of treatment of malnutrition a success. This also requires good collaboration between health professionals and sufficient knowledge and time of all

professionals and patients involved. The way the food system in a hospital is organized may also affect the outcomes of malnutrition treatment. An important barrier for reaching adequate protein intakes in the fourth day of hospitalization, may be the short length of stay in hospitals. The mean length of hospital stay in the Netherlands is 5.2 days (10). The short time of being able to treat malnutrition, in combination with illness of patients that lead to increased requirements and/or reduced intakes, may be a reason for not reaching adequate intakes in hospitals.

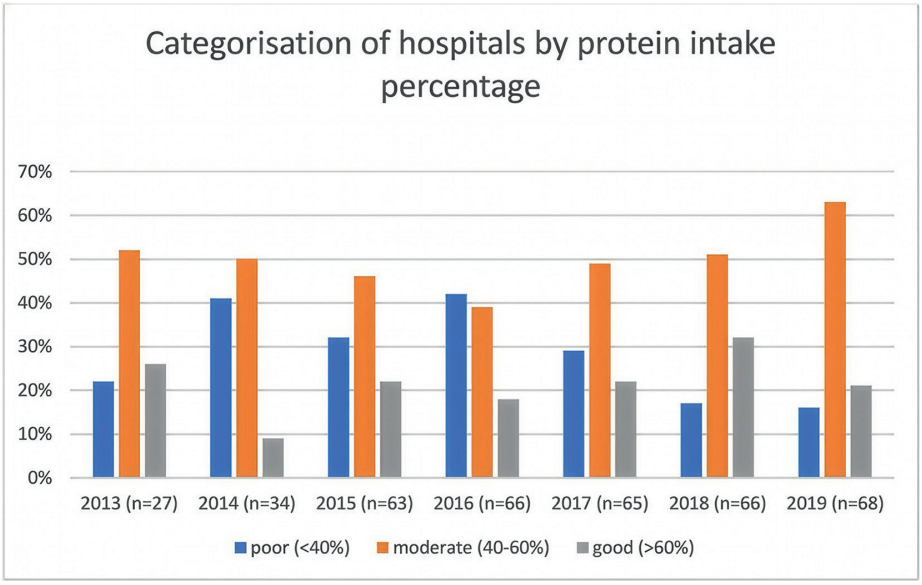

Fig. 1. Percentage of hospitals reaching adequate protein intakes on day 4 of hospital admission (poor: <40% of patients achieves adequate protein intake; moderate: 40-60% of patients achieves adequate protein intake; good: >60% of patients achieves adequate protein intake).

Table 2. Results from the quality indicator on protein intake of malnourished patients Dutch hospitals from 2009-2019

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Number of hospitals	5	8	10	2	27	34	63	66	65	66	68
Number of malnourished patients on the fourth day in hospital(denominator)											
	2.965	4.497	6.784	2.967	17.677	24.692	49.218	54.365	59.433	59.429	57.693
Number of malnourished patients with adequate protein intake on the fourth day in hospital (numerator)											
	1.427	1.264	3.209	1.451	8.957	10.734	21.919	24.744	28.570	30.446	28.908
Percentage of patients with adequate protein intake											
	48.1%	28.1%	47.3%	48.9%	50.7%	43.5%	44.5%	45.5%	48.1%	51.2%	50.1%
Categorization of hospitals by protein intake percentage											
<40% poor	3 (60%)	6 (75%)	4 (40%)	-	6 (22%)	14 (41%)	20 (32%)	28 (42%)	19 (29%)	11 (17%)	11 (16%)
40%-60% - moderate	0	1 (12%)	2 (20%)	-	14 (52%)	17 (50%)	29 (46%)	26 (39%)	32 (49%)	34 (51%)	43 (63%)
>60% good	2 (40%)	1 (12%)	4 (40%)	2 (100%)	7 (26%)	3 (9%)	14 (22%)	12 (18%)	14 (22%)	21 (32%)	14 (21%)

DISCUSSION

This inventory of the protein intake of 339,720 hospital malnourished patients over 11 years shows that meeting protein requirements remains a difficult challenge. In 2019, only in 14 out of 68 hospitals over 60% of their malnourished patients had an adequate protein intake on the fourth day of admission. Moreover, in 11 hospitals, less than 40% of patients had adequate protein intakes. On the other hand, in 2019, almost 29000 patients (50%) had an adequate protein intake on the fourth day of admission. It should be taken into account that reaching adequate food intake in hospital patients usually is a challenge, because of presence of complex diseases that affect food intake. It should also be realized that these conclusions are based on registration of food intake and on registration of data in patient records. Errors in these registrations could not be ruled out and may have affected the results. Moreover, since the performance indicator was limited to protein intake, we do not have results on energy intakes. Protein intake was chosen as a performance, because research showed that if protein requirements are achieved, patients usually also have sufficient energy intakes.

In this study, information on the reasons that requirements were not met, were not available. Previous studies, however, identified nausea, cancer, acute infections, BMI, age, chronic lung disease and tube feeding as predictors for not achieving protein and energy requirements. (11) In recent years, a lot of hospitals changed their nutrition concept: protein-rich main meals, protein-rich snacks, and more flexibility in supply improved food intake. (12-14)

Over more than 10 years, the DMSG worked on optimal recognition and treatment of malnutrition in Dutch hospitals. Therefore, the results presented here may be somewhat disappointing. However, due to the introduction of a quality indicator by the Dutch Inspectorate of Health, malnutrition became a recognized health problem. In addition, the quality indicator contributed to implementation of screening and early treatment of malnutrition in all sectors of healthcare. Continuous attention is necessary to keep malnutrition on the agenda. Recommendations to do this are:

- Provide a well-established electronic patient record that supports the process of screening and treatment of malnutrition.
- Monitor the number of patients screened and the number of patients with a sufficient nutritional intake to be able to adjust interventions when necessary. Integrate this into the hospital's quality system.
- Ensure that staff involved is sufficiently trained to carry out their tasks properly. Record everyone's role and required knowledge.
- Share the quality information on screening and treatment of malnutrition with all concerned, including management staff and all disciplines involved in the nursing department.
- Provide a nutritional concept in the hospital that facilitates to meet the nutritional needs of the malnourished patient.
- Involve patients in treatment. Provide good information and encourage self-management.
- Work together in a multidisciplinary manner; discuss the process in order to come to joint improvements.
- Provide training on the importance of good nutrition during illness to all healthcare professionals.
- Share knowledge and expertise between hospitals.
- Appoint a nurse per department as nutrition contact person.

It should also be realized that length of stay in hospital is short. Optimal nutritional care therefore should also include optimal transfer regarding nutritional care on hospital discharge. Early recognition of (the risk of) malnutrition, optimal intensive multidisciplinary treatment and continuous evaluation is necessary to provide optimal nutritional care in the hospital and beyond. Malnutrition is also prevalent at discharge. A recent study showed that 30% patients who were admitted well-nourished, became malnourished during stay and 82% of patients remained malnourished during stay. (15) Optimal nutritional care therefore should also include optimal transfer regarding nutritional care on hospital discharge.

CONCLUSION

This inventory of the protein intake of 339,720 hospital malnourished patients over 11 years shows that in one out of five Dutch hospitals >60% of malnourished patients had an adequate protein intake on the fourth day of admission. This shows that meeting protein requirements remains a difficult challenge. Early recognition of malnutrition, optimal multidisciplinary treatment and continuous evaluation is necessary to provide optimal nutritional care in the hospital and beyond to support the patients' recovery.

Contribution to authorship
HK, MS and EN designed the research; HK and CD analysed data; all authors wrote the article.

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Conflicts of interest
All authors report no conflict of interests. ICMJE disclosure of interest forms are submitted as supporting information

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CHAPTER 4

Decreased Appetite is Associated with Sarcopenia-Related Outcomes in Acute Hospitalized Older Adults

Carliene van Dronkelaar,
Michael Tieland,
Jesse J. Aarden,
Lucienne A. Reichardt,
Rosanne van Seben,
Marike van der Schaaf,
Martin van der Esch,
Raoul H. H. Engelbert,
Jos W. R. Twisk,
Jos A. Bosch,
Bianca M. Buurman
and on behalf of the Hospital-ADL Study Group

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ABSTRACT

Decreased appetite is one of the main risk factors of malnutrition. Little is known on how appetite changes during hospitalization and after discharge and how it relates with sarcopenia-related outcomes. We analyzed data of the Hospital-ADL study, a multicenter prospective cohort study that followed 400 acutely hospitalized older adults (≥70 year). Appetite (SNAQ), handgrip strength (Jamar), muscle mass (BIA), mobility (DEMMI), and physical performance (SPPB) were assessed within 48 h of admission, at discharge, and at one- and three-months post-discharge. The course of decreased appetite was analysed by Generalized Estimating Equations. Linear Mixed Model was used to analyze the associations between decreased appetite and the sarcopenia-related outcomes. Decreased appetite was reported by 51% at hospital admission, 34% at discharge, 28% one-month post-discharge, and 17% three months post-discharge. Overall, decreased appetite was associated with lower muscle strength (β = −1.089, $p = 0.001$), lower mobility skills (β = −3.893, $p < 0.001$), and lower physical performance (β = −0.706, $p < 0.001$) but not with muscle mass (β = −0.023, $p = 0.920$). In conclusion, decreased appetite was highly prevalent among acute hospitalized older adults and remained prevalent, although less, after discharge. Decreased appetite was significantly associated with negative sarcopenia-related outcomes, which underlines the need for assessment and monitoring of decreased appetite during and post hospitalization.

INTRODUCTION

As society ages, the number of people with limitations in physical function will increase (1–4). A major cause of these physical limitations is the age-related low muscle mass, strength, and physical function, also known as sarcopenia (5,6). These sarcopenia-related outcomes decline 1–4% per year, which may be accelerated during hospitalization (7,8). Notably, sarcopenic hospitalized older adults have a high risk for adverse health outcomes, such as increased hospital stay, readmissions, and mortality (9–11). Therefore, screening, treatment, and prevention of sarcopenia is of great importance for improving patients' quality of life and reducing health care costs (9,12).

A major risk factor for hospital related sarcopenia is malnutrition of which prevalence rates among hospitalized older adults can be as high as 38% (5,8,13–16). In these patients, a decreased appetite is the primary cause of malnutrition. (17–19). The prevalence of a decreased appetite is reported by 64% during hospitalization and by 28% after discharge (15,20–22). Yet, very limited data is available on the course of changes in decreased appetite during and post hospitalization. Pilgrim et al. showed that 52% of the older women that reported a decreased appetite at hospital admission still had a decreased appetite six months after discharge (15). However, although the first three months after discharge are critical for recovery, little is known on how appetite changes during hospitalization and three months after discharge (23,24). In addition, very little information is available on how a decreased appetite relates to sarcopenia-related outcomes such as muscle strength, muscle mass, mobility, and physical performance during and after hospitalization (5,22). Therefore, the aim of this study is to assess (1) the course of decreased appetite during acute hospitalization as well as one to three months post hospital discharge and (2) the association between decreased appetite and muscle mass, muscle strength, mobility, and physical performance during and post hospitalization in older adults.

MATERIALS AND METHODS

Subjects and Design

Data from the Hospital-Associated Disability and impact on daily Life study (Hospital-ADL study), a multicenter, observational, prospective cohort study, was used. The study protocol is described elsewhere (25). In short, 401 acutely hospitalized older adults admitted for at least 48 h, aged ≥70, Mini-Mental State Examination score ≥15, were recruited from departments of Internal Medicine, Cardiology or Geriatrics from six Dutch teaching and community hospitals. The aim was to investigate cognitive, behavioral, psychosocial, physical, and biological factors that may be associated with hospitalization-associated disability from hospital admission to three months post-discharge. The Hospital-ADL study was approved by the Institutional Review board of the Academic Medical Center (AMC) in the Netherlands (Protocol ID: AMC2015_150). Written informed consent was obtained from all subjects before inclusion.

Data Collection

All variables were measured at the following time points: within 48 h of hospital admission, at hospital discharge, at one month and three months post-discharge.

Decreased Appetite

The Short Nutritional Assessment Questionnaire was used to identify malnourished hospital patients (17). One of the questions of this questionnaire was on self-reported appetite, namely “Have you experienced a decreased appetite over the last month?” and was answered with “yes” or “no”. This question was adjusted for discharge measurement to “Have you experienced a decreased appetite since hospital admission?”.

Muscle Strength

Muscle strength was measured by handgrip strength (HGS; Jamar grip strength dynamometer; Lafayette Instrument Company, USA) (26). Subjects were measured in supine or sitting position and encouraged to show maximal isometric handgrip strength. The scores were noted in kilograms after HGS was performed three times for each hand. The maximum score for either hand was used for analyses.

Muscle Mass

Skeletal Muscle Mass (SMM) was assessed by bio-impedance analysis (BIA; Bodystat Quascan 4000) (27). Subjects were asked to assume a supine position with arms not touching the trunk and legs or feet not touching each other. Injection electrodes were placed wrist-to-ankle and sensing electrodes placed hand-to-foot on the ipsilateral side of the body. A small electrical signal circulated which measured the resistance of this electrical signal from which the SMM was estimated based on the equation of Janssen et al. (28). Patients' SMM in kilograms was used for analysis.

Mobility

In this paper, mobility was defined as a measure of how well one can move (4,29). The Dutch version of de Morton Mobility Index (DEMMI), a 15-item unidimensional measure based on Rasch analysis, was used to assess mobility (29). Subjects were asked to perform the following tasks: perform a bridge, roll onto side, lie to sit, sit unsupported in chair, sit to stand from chair, sit to stand without using arms, stand unsupported, stand feet together, stand on toes, tandem stand, walking distance, walking assistance, pick up pen from floor, walk 4 steps backwards, and jump. The tasks were scored according to the standardized protocol. The raw score was converted into an interval-level score out of 100. A higher score means a better mobility performance and a change of 10 points is reported as the minimally clinically important difference (30).

Physical Performance

In this paper, physical performance was defined as a measure of endurance of specific movements (4). Physical performance was measured by the Short Physical Performance Battery (SPPB) (31). The SPPB measures balance, strength, and gait speed. Subjects were asked to stand with their feet in a side-by-side position, a semi-tandem position, a full-tandem position, walk a distance of four meters, and to rise from a chair and return to the seated position five times as quickly as possible. The total score ranges from 0 to 12 points. A meaningful change in SPPB score ranges from 0.5 to 1.0 point (32,33).

Other Variables

Data on age, gender, education, ethnicity, living situation, marital status, cognitive impairment (Mini Mental State Examination (MMSE), score

≤23) (34), depression (Geriatric Depression Scale-15 (GDS-15) score ≥6) (35), activities of daily living (Modified Katz Index Scale-6 (ADL-KATZ6)) (36), fatigue (NRS fatigue) (37), fear of falling (NRS fear of falling), reason for initial admission, comorbidity (Charlson Comorbidity Index(CCI)) (38), length of hospital stay (LOS), malnutrition (Short Nutritional Assessment Questionnaire (SNAQ), score ≥3) (17) and readmission were collected.

Statistical Analysis

Data was analyzed using Statistical Package for Social Science (SPSS) version 24 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the patient demographic and medical characteristics. To assess the course of appetite, Generalized Estimating Equations (GEE) analyses were performed. The obtained odds ratios (ORs) represent the odds for finding a similar prevalence rate for a decreased appetite at discharge, one- or three-months post-discharge as compared to the prevalence rate at admission and indicates whether prevalence rates significantly increase or decrease. To test the association between decreased appetite (independent variable) and muscle strength, muscle mass, mobility, and physical performance (dependent variables) over time, Linear Mixed Model (LMM) analyses were performed (39). Data was checked on normality by plotting histograms of the residuals. All data was normally distributed. Both GEE and LMM take into account the correlation between the repeated observations. GEE is more suitable to analyze dichotomous outcomes, while LMM is more suitable to analyze continuous outcomes (39,40). To identify effect modification of gender, age, fatigue, and depression, interaction terms between decreased appetite and these variables were added to the crude model. For the LMM analyses, first an overall analysis was performed, taking the average of all timepoints. Second, the hospitalization period was compared with the post discharge period. Hospitalization was the average of the time points at admission and at discharge. For the post-discharge period the average of the timepoints one month post-discharge and three months post-discharge was used. Third, every timepoint was analyzed separately. Besides a crude analysis, also adjusted analyses were performed. The potential confounders were based on literature (41–44). All parameter estimates were expressed with a 95% confidence interval (95% CI). Statistical significance was set at $p < 0.05$.

RESULTS

Study Sample Characteristics

Between October 2015 and February 2017, 1024 acutely hospitalized patients were approached, of which 519 met the inclusion criteria and 401 agreed to participate. One patient did not have data available on decreased appetite at baseline. Therefore, data of 400 patients were included in the analytical sample. During the study, 84 patients were lost to follow up, four patients became terminally ill, and 40 patients died. Patients' baseline characteristics are provided in Table 1. Overall, 51.5% of the participants were men and the mean (SD) age was 80.1 (6.68) years.

Table 1. Baseline characteristics of study sample.

	All (*n* = 400)	**No decreased appetite at admission (*n* = 198)**	**Decreased appetite at admission (*n* = 202)**
Age, median (IQR)	79.5 (74.6–85.1)	78.7 (74.5–85.0)	80.0 (75.1–85.5)
Gender, male, *n* (%)	206 (51.5)	115 (58.1)	91 (45.0) *
BMI, kg/m2, median (IQR)	24.5 (21.9–28.6)	24.8 (22.9–28.7)	24.3 (21.2–28.1)
Reason for admission, *n* (%)			
Infection	58 (14.5)	32 (16.2)	26 (12.9)
Gastrointestinal	45 (11.3)	19 (9.6)	26 (12.9)
Cardiac	121 (30.3)	64 (32.3)	57 (28.2)
Respiratory	75 (18.8)	36 (18.2)	39 (19.3)
Cancer (including haematology)	13 (3.3)	5 (2.5)	8 (4.0)
Electrolyte disturbance	11 (2.8)	4 (2.0)	7 (3.5)
Renal	15 (3.8)	9 (4.5)	6 (3.0)
Other	62 (15.5)	29 (14.6)	33 (16.3)
Living arrangement before admission, *n* (%)			
Independent	337 (84.3)	170 (85.8)	167 (82.7)
Nursing home	8 (2.1)	3 (1.5)	5 (2.5)
Senior residence/Assisted living	55 (13.8)	25 (3.5)	30 (14.9)
Length of stay, days, median (IQR)	5.8 (3.9–8.9)	5.2 (3.4–7.9)	6.6 (3.9–11.5) *

Table 1. Baseline characteristics of study sample. (continued)

	All (*n* = 400)	**No decreased appetite at admission (*n* = 198)**	**Decreased appetite at admission (*n* = 202)**
Level of education, *n* (%)			
Primary school	101 (25.3)	48 (24.2)	53 (26.2)
Elementary technical/ domestic science school	88 (22.0)	43 (21.7)	45 (22.3)
Secondary vocational education	120 (30.0)	72 (36.4)	79 (39.1)
Higher level high school/ third-level education	91 (22.8)	35 (17.7)	25 (12.4)
CCI, median (IRQ)	2 (1–3)	1 (1–3)	2 (1–4) *
Polypharmacy, n (%)	259 (64.8)	118 (59.6)	141 (69.8) *
GDS-15, median (IQR)	3 (2–5)	3 (1–4)	4 (2–6) *
MMSE, median (IQR)	27 (24–28)	27 (25–28)	27 (24–28)
ADL-KATZ6, median (IQR)	1 (0–3)	1.0 (0.0–2.0)	1.5 (0.0–3.0) *
Fatigue, median (IQR)	6 (4–8)	6 (3–7)	7 (5–8) *
Malnourished, n (%)	132 (33.0)	17 (8.6)	115 (56.9) *
Handgrip strength, kg, median (IQR)	26 (20–34)	28 (21–36)	24 (18–32) *
Skeletal muscle mass, kg, median (IQR)	22.7 (17.5–28.1)	24.8 (18.7–29.5)	21.8 (17.3–26.9) *
DEMMI, median (IQR)	57 (41–74)	62 (44–74)	53 (39–67) *
SPPB, median (IQR)	5.0 (2.0–8.0)	6.5 (3.0–9.0)	4.0 (2.0–7.0) *

SD = Standard Deviation; IQR = Inter Quartile Range; BMI = Body Mass Index; CCI = Charlson Comorbidity Index (higher score indicating a greater risk of mortality); Polypharmacy = use of 5 different medications or more; GDS-15 = Geriatric Depression Scale 15 (depression with score ≥6); MMSE = Mini Mental State Examination (cognitive impairment with score ≤23); ADL-KATZ6 = Activities of Daily Living-Modified Katz Index Scale-6 (lower scores means less independency); Fatigue = NRS Fatigue, range 0–10 (higher score means worst possible fatigue); Malnourished = Short Nutritional Assessment Questionnaire (SNAQ, score ≥3); DEMMI = de Morton Mobility Index (range 0–100, higher score means better mobility skills); SPPB = Short Physical Performance Battery (range 0–12). * p-value < 0.05; Mann-Whitney U test was used for continuous variables; $\chi 2$ or Fisher's exact test were used for categorical variables; Median Test was used Length of Stay and MSSE variable.

The Course of Decreased Appetite

At admission, 51% of the subjects reported a decreased appetite. The subjects who reported to have a decreased appetite were more often women, had a longer length of stay, more comorbidities, more often polypharmacy, scored higher on fatigue and the geriatric depression scale, had more trouble to perform activities of daily living, were more often malnourished, had lower handgrip strength, lower skeletal muscle mass, and scored lower on mobility and physical performance (Table 1).

Of those who had a decreased appetite at admission, 21% still had decreased appetite three months after discharge. The prevalence rates of decreased appetite were significantly lower at discharge, one- and three-months post-discharge compared to admission. The odds ratios hardly changed when analyses were repeated using only complete cases on decreased appetite (Table 2).

Table 2. Prevalence of decreased appetite at admission, discharge, and one- and three-months post-discharge.

				Complete Cases		
Time Point	**Prevalence Rates, % (n)**	**OR (95% CI)**	***p*-Value***	**Prevalence Rates, % (*n*)**	**OR (95% CI)**	***p*-Value ***
Admission	50.5 (202)	-	-	50.0 (99)	-	-
At discharge	34.0 (136)	0.757 (0.600–0.956)	0.019	43.4 (56)	0.768 (0.569–1.036)	0.084
One month	27.8 (111)	0.579 (0.454–0.739)	<0.001	37.4 (74)	0.597 (0.435–0.819)	0.001
Three months	17.0 (68)	0.359 (0.267–0.482)	<0.001	26.3 (52)	0.356 (0.245–0.519)	<0.001

* *p*-value for finding similar prevalence rates as compared to the prevalence rate at admission.

Decreased Appetite and Muscle Strength

An inverse association was found between decreased appetite and muscle strength (crude model; β = −0.73, $p = 0.005$). This association became stronger, when the crude model was adjusted for age, gender, cognitive impairment, fatigue, depression, comorbidity, and lean body mass (β = −1.09, $p = 0.001$). This means that subjects who reported to have a decreased appetite performed lower on hand grip strength by 1.09 kg compared to the subjects who reported to not have a decreased appetite. No effect modification with age, gender, fatigue or depression was

found. Considering the specific time periods during hospitalization and post-discharge, a significant association was found between decreased appetite and muscle strength in both periods (adjusted model; β = −0.84, p = 0.030 and β = −1.71, p < 0.001 respectively). Analyses at every time point showed that these associations were most pronounced at three months post-discharge (adjusted model; β = −2.97, p < 0.001) (Table 3).

Decreased Appetite and Skeletal Muscle Mass

There was no significant association between decreased appetite and skeletal muscle mass in both the crude and adjusted model (β = −0.09; p = 0.712 and β = −0.02; p = 0.920 respectively). Also, no effect modification with age, gender, fatigue, or depression was found. Analyses at the different time points showed similar results (Table 3).

Decreased Appetite and Mobility

There was a significant inverse association between decreased appetite and mobility (crude model; β = −6.45; p < 0.001). After adjustment, this association became less strong (β = −3.89; p < 0.001). This association means that subjects who reported to have a decreased appetite scored 3.89 points lower on the DEMMI compared to the subjects who reported to not have a decreased appetite. No effect modification with age, gender, fatigue or depression was found. Decreased appetite was significantly associated with lower mobility skills during hospitalization (adjusted model; β = −3.98, p = 0.003). In addition, further analyses at every time point showed that this association was most pronounced (adjusted model; β = −4.15, p = 0.012) (Table 3).

Decreased Appetite and Physical Performance

There was a significant inverse association between decreased appetite and physical performance (crude model; β = −1.08, p < 0.001). This association remained significant after adjustment, but became less strong (β = −0.71, p < 0.001). This association means that subjects who reported to have a decreased appetite scored 0.71 points lower on the SPPB compared to the subjects who reported to not have a decreased appetite. No effect modification of age, gender, fatigue, or depression was found. The association was found to be present during hospitalization (adjusted model; β = −0.56, p = 0.017). Analyses at every time point showed that the significant association was most pronounced at one-month post-discharge (adjusted model; β = −0.79, p = 0.019) (Table 3).

Table 3. Longitudinal associations of decreased appetite and muscle strength, skeletal muscle mass, mobility, and physical performance, crude and adjusted for confounders.

	Crude Model β (95% CI) *p*-Value	Adjusted Model β (95% CI) *p*-Value
Muscle Strength [1]		
Overall analysis	−0.732 (−1.240; −0.224) **0.005**	−1.089 (−1.715; −0.463) **0.001**
Hospitalization	−0.367 (−0.994; 0.259) 0.250	−0.840 (−1.599; −0.081) **0.030**
Post-discharge	−1.692 (−2.375; −1.009) <**0.001**	−1.707 (−2.559; −0.854) <**0.001**
Admission	−0.497 (−1.275; 0.280) 0.210	−0.934 (−1.861; −0.006) **0.049**
At discharge	−0.025 (−0.876; 0.827) 0.955	−0.623 (−1.675; 0.430) 0.246
One month post-discharge	−0.899 (−1.754; −0.045) **0.039**	−0.976 (−2.010; 0.059) 0.064
Three months post-discharge	−2.712 (−3.746; −1.677) <**0.001**	−2.968 (−4.351; −1.584) <**0.001**
Skeletal Muscle Mass [2]		
Overall analysis	−0.086 (−0.545; 0.372) 0.712	−0.023 (−0.463; 0.417) 0.920
Hospitalization	−0.430 (−0.989; 0.129) 0.132	−0.191 (−0.724; 0.343) 0.483
Post-discharge	0.009 (−0.618; 0.636) 0.977	−0.006 (−0.615; 0.603) 0.984
Admission	−0.633 (−1.322; 0.055) 0.071	−0.382 (−1.034; 0.269) 0.250
At discharge	−0.209 (−0.983; 0.566) 0.597	0.056 (−0.699; 0.811) 0.884
One month post-discharge	0.042 (−0.726; 0.811) 0.914	0.022 (−0.722; 0.765) 0.954
Three months post-discharge	0.216 (−0.808; 1.239) 0.679	0.186 (−0.806; 1.177) 0.713
Mobility [3]		
Overall analysis	−6.452 (−8.568; −4.336) <**0.001**	−3.893 (−6.061; −1.725) <**0.001**
Hospitalization	−5.294 (−7.847; −2.742) <**0.001**	−3.983 (-6.602; −1.364) **0.003**
Post-discharge	−3.061 (−5.906; −0.215) **0.035**	−1.252 (-4.262; 1.757) 0.414
Admission	−5.260 (−8.392; −2.129) **0.001**	−4.148 (−7.367; −0.929) **0.012**
At discharge	−3.787 (−7.301; −0.272) **0.035**	−3.024 (−6.678; 0.629) 0.105
One month post-discharge	-3.299 (-6.814; 0.215) 0.066	−2.340 (−6.060; 1.379) 0.217
Three months post-discharge	−1.406 (−5.740; 2.928) 0.524	1.176 (−3.635; 5.986) 0.632
Physical performance [3]		
Overall analysis	−1.080 (−1.469; −0.692) <**0.001**	−0.706 (−1.083; −0.329) <**0.001**
Hospitalization	−0.770 (−1.259; −0.281) **0.002**	−0.561 (−1.021; −0.101) **0.017**
Post-discharge	−0.942 (−1.485; −0.399) **0.001**	−0.530 (−1.063; 0.004) 0.052
Admission	−0.595 (−1.199; 0.008) 0.053	−0.456 (−1.022; 0.111) 0.115

Table 3. Longitudinal associations of decreased appetite and muscle strength, skeletal muscle mass, mobility, and physical performance, crude and adjusted for confounders. (continued)

	Crude Model β (95% CI) *p*-Value	**Adjusted Model β (95% CI) *p*-Value**
At discharge	−0.741 (−1.424; −0.058) **0.033**	−0.578 (−1.226; 0.071) 0.081
One month post-discharge	−0.873 (−1.560; −0.186) **0.013**	−0.794 (−1.459; −0.130) **0.019**
Three months post-discharge	−1.160 (−1.938; −0.382) **0.004**	−0.099 (−0.932; 0.734) 0.815

[1] confounders for adjusted model: Age, gender, cognitive impairment, fatigue, depression, comorbidity and skeletal muscle mass, [2] confounders for adjusted model: Age, gender, cognitive impairment, fatigue, depression, comorbidity, [3] confounders for adjusted model: Age, gender, cognitive impairment, fatigue, depression, comorbidity and fear of falling. Bold *p*-values indicate a statistically significant difference.

DISCUSSION

This multicenter prospective cohort study showed that decreased appetite is highly prevalent among acute hospitalized older adults and remained prevalent, although less, three months post-discharge. Overall, decreased appetite was associated with lower muscle strength, mobility, and physical performance but not with muscle mass. In more detail, at admission, an association between decreased appetite and lower muscle strength and mobility was found. At one-month post-discharge there was an association between decreased appetite and lower physical performance. At three months after discharge, an association between decreased appetite and lower muscle strength was found.

At admission, a prevalence rate of a decreased appetite was reported by 51% of the subjects. Although our prevalence rates are in line with some studies, Pilgrim et al. did show a somewhat higher prevalence rate (38%) six months post-discharge (15,22,45). This difference might be due to the fact that our study had subjects who had a shorter length of stay and decreased appetite was reported in a shorter time after discharge. In another population, Tsaousi et al. showed that impaired appetite was an important determinant for predicting length of hospital stay (46). A longer length of hospital stay in malnourished patients is reported by several studies (14,47,48). Decreased appetite is one of the main risk factors for malnutrition (17–19). In line with these studies, our study showed that subjects with a decreased appetite at admission had a significantly longer length of hospital stay.

Subjects who reported decreased appetite at admission scored higher on depression and fatigue. Depression is often associated with changes in appetite, whereas this has not been shown for fatigue yet (42,49). In our study, we checked for effect modification of depression and fatigue, however this was not the case.

To our knowledge, this study is the first to assess the longitudinal association between decreased appetite and sarcopenia-related outcomes over the time span from hospital admission to three months post-discharge. The study of Pilgrim et al. reported an association of decreased appetite with lower handgrip strength at hospital admission in older female patients, which is in line with our findings (15). Furthermore,

Reijnierse et al. reported an association of decreased appetite with diagnostic measures of sarcopenia in geriatric outpatients, showing similar results for handgrip strength, but not for muscle mass (22). This discrepancy can be explained by the differences in the study populations. A meta-analysis of Van Ancum et al. reported that acutely hospitalized patients do not show a decline in skeletal muscle mass, whereas in elective hospitalized patients there was a decline in muscle mass (50). It is possible that in acutely hospitalized patients there was already a decline in muscle mass before hospitalization and therefore no decline showed post-discharge. Furthermore, length of stay was relatively short in our study in comparison with bed rest studies, which may explain the lack of change in skeletal muscle mass that was observed during hospitalization (7). Also, skeletal muscle mass was assessed with a non-segmental BIA. A BIA measurement can be influenced by hydration status (51). The use of BIA to measure skeletal muscle mass can give an underestimation of the change in muscle mass as patients may be dehydrated at admission and the increase in fluid may mask the change in muscle mass (51,52). No information on hydration status was available in this study. However, BIA is still the most feasible and non-invasive method in use for this older and frail patient group as dual-energy X-ray absorptiometry (DXA), which would be the preferred instrument, is not yet a portable device (5,53).

In our study, decreased appetite is associated with lower mobility skills and lower physical performance during hospitalization. Terminology of mobility and physical performance are used interchangeable or even taken all together with muscle strength in physical function (53). In addition, different tests are used to assess mobility and/or physical performance which makes it difficult to compare studies on a detailed level. In our study, we defined mobility as a measure of how well one can move, whereas physical performance was defined as a measure of endurance of specific movements (4,29). At admission, Pilgrim et al. reported an association between poor appetite and a lower Barthel Index score, which is a questionnaire on activities of daily living (15,54). The study of Reijnierse et al. found no association between decreased appetite and lower physical performance, measured with walking speed, in geriatric outpatients (22). Our longitudinal associations showed comparable results.

Decreased appetite is part of the SNAQ screening tool to assess patients at risk of malnutrition (17). Following the newest Global Leadership Initiative on Malnutrition (GLIM) criteria, screening for patients at risk for malnutrition is the key first step in evaluation of nutrition status (55). This study underlines the need for assessment of decreased appetite in the screening tool as it is associated with lower muscle strength, lower mobility skills, and lower physical performance in acutely hospitalized older patients. Furthermore, decreased appetite should be monitored during the course of hospitalization up to at least three months after discharge as it is still prevalent. In addition, interventions targeting sarcopenia in acutely hospitalized older adults should consider addressing decreased appetite and should be performed both during and after hospitalization.

To our best knowledge, this study is one of the first to show the course of decreased appetite from acute hospitalization to three months after discharge. A strength of this study is its multicenter longitudinal design with repeated measures in both teaching and community hospitals. The measurements were performed in a structural and protocolled manner (25). In addition, we were able to include 400 acutely hospitalized older adults in the study. However, some limitations need to be addressed. Firstly, due to the observational setting of the study, no causality could be studied. Secondly, 31% of the patients were lost to follow up or passed away within three months post-discharge. It is plausible that patients who were lost to follow-up may have had a decreased appetite. Therefore, we performed a sensitivity analysis on the prevalence of decreased appetite, which yielded similar results. In addition, the analyses on the associations were performed with linear mixed models, which accounts for missing data (39). Thirdly, no information was available on food intake. A decreased appetite could lead up to a reduced food intake (45). However, reduced food intake did not seem to be a predictor of the development of malnutrition within the development of the SNAQ tool (17). Also, when reduced food intake is associated with poor appetite it is unlikely that food intake will increase by simple provision of oral supplements (45). Therefore, it seems reasonable to assess decreased appetite in the context of malnutrition.

CONCLUSIONS

Decreased appetite was highly prevalent among acute hospitalized older adults and remained prevalent, although less, after discharge. Decreased appetite was associated with handgrip strength and physical function but not with skeletal muscle mass. Further research should focus on how to improve appetite and how to reduce malnutrition in hospitalized older adults and study its effects on muscle strength, mobility, and physical performance.

Author Contributions

Conceptualization, C.v.D. and M.T.; methodology, J.J.A., R.v.S., M.v.d.S., R.H.H.E., J.A.B., and B.M.B.; validation J.J.A. and B.M.B.; formal analysis, C.v.D. and J.W.R.T.; investigation, J.J.A., R.v.S., and L.A.R.; writing—original draft preparation, C.v.D.; writing—review and editing, all.; supervision, M.T. and B.M.B.; funding acquisition, B.M.B., R.H.H.E.

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Conflicts of Interest

The authors declare no conflict of interest.

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PART II

WORKING TOWARDS SOLUTIONS: FROM EVIDENCE TO CLINICAL PRACTICE

CHAPTER 5

A transmural intensive dietetic care-pathway for optimal protein intake and physical functioning in malnourished older patients: A protocol for the randomised *ProIntens* trial

Carliene van Dronkelaar,
Michael Tieland,
Hinke Kruizenga,
Juul J. J. Verstappen
Moritz Eggelbusch,
Rob C.I. Wüst,
Gerben ter Riet,
Judith E. Bosmans,
Peter J.M. Weijs

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ABSTRACT

Background Disease-related malnutrition is common among hospitalized and recently discharged older adults. Consequences of malnutrition are physical limitations, negative health outcomes, decreased quality of life and increased healthcare costs. Dietetic care can counteract the effects of malnutrition by increasing protein and energy intake. The ProIntens study aims to evaluate the impact of an intensive dietetic care pathway on dietary protein intake and physical functioning in older adults during hospitalization and after discharge. Process and economic evaluations will be performed.

Methods The ProIntens study is a multicenter two-armed parallel individually randomised trial in five hospitals in the Amsterdam region. In total, 250 hospitalized older adults, aged ≥55 years and at risk of malnutrition will be randomised to receive regular care (control) or intensive dietetic care (intervention). The intervention consists of intensive personalized care which involves transmural guidance by trained dietitians, supportive materials on protein intake in a social context and a mobilization program during hospitalization until three months after discharge. Controls will receive regular care. The primary outcome will be the between-groups difference in the mean change on the Short Physical Performance Battery three months after discharge. Secondary outcomes include dietary protein intake, body composition, physical activity, activities of daily living, quality of life and healthcare costs.

Discussion The ProIntens trial will study the effects and costs of an intensive dietetic treatment on recovery outcomes in hospitalized older adults at risk of malnutrition. The intervention will result in practical tools for care professionals which aim to improve malnutrition treatment for older patients.

Trial registration: Landelijk Trial Register (NL8041; NL72069.029.19); registered 2019-09-23; covering all WHO Trial Registration Data Set items.

BACKGROUND

For older adults, hospitalization in itself can have major side effects, regardless of the reason for their hospital admission (1). Malnutrition during hospitalization is associated with prolonged hospital stay, more complications and readmissions and increased health care costs (2, 3). This combination of a poor nutritional status and loss of physical functioning leads to decreased quality of life and increased mortality (2, 4).

Major factors in malnutrition and physical functional decline is an inadequate protein intake. Current guidelines suggest an intake of 1.2-1.5 g protein/kg bodyweight/day to support recovery during hospitalization and after discharge (5-7). To meet the nutritional guidelines, patients at risk of malnutrition should be provided with a nutritional care plan with guidance of a dietitian. Dietetic treatment focusing on protein and energy intake can improve patients' physical function, quality of life, and lower all-cause mortality (8, 9). However, older patients have difficulties meeting these guidelines. In 2019, Weijzen et al. observed an average protein intake of 0.6 g/kg/d in older patients (10). Also, dietitians stated in recently-held focus groups they perceive barriers (time, money, inter-disciplinary collaboration) in treating older patients according the guidelines. In addition, these issues are not only faced during hospitalization but also after discharge. The first three months after discharge are critical for health recovery for older patients (11). Improvement in the transmural care-pathway for older malnourished patients is therefore called for.

This protocol present the ProIntens study, which aims to develop and test a new intensive dietetic care intervention for older patients at risk of malnutrition, admitted to hospital, focusing on protein intake and mobility. The treatment will start at hospital admission and will continue until three months after hospital discharge. The primary objective of the ProIntens study is to study whether physical functioning of older patients at risk of malnutrition during hospitalization and after discharge is improved by this transmural intensive dietetic intervention. Secondary objectives of the ProIntens study are to investigate whether personal protein goals, improved mobility and Activities of Daily Living (ADL), increased muscle mass and strength, improved quality of life are achieved, and study reductions of length of hospital stay, readmission rates, mortality and societal costs.

METHODS

Study design

The ProIntens study is a two-armed multicenter parallel individually randomised trial. After determining eligibility and obtaining informed consent, participants are randomised 1:1 to either the control group or intervention group. Participants in the control group will receive regular care (RC), while participants in the intervention group will receive intensive dietetic care (IDC). Measurements will be performed at hospital admission (t_0), discharge (t_2), and at one (t_3)and three-months after discharge (t_4).

Setting, Participants and Recruitment

The study population will consist of hospitalized older adults (≥55y), who are at risk of malnutrition. Five hospitals in the region of Amsterdam will participate: Amsterdam University Medical Centers, location AMC (1000 beds) and VUmc (733 beds), teaching hospital OLVG, location Oost (555 beds) and West (366 beds) and regional hospital BovenIJ (313 beds). Participants will be recruited from the following medical wards: geriatrics, internal medicine, cardiology, gastroenterology, pulmonology and the acute admission unit (a non-emergency triage ward where patients undergo further tests and stabilization before being transferred to a suitable ward). To identify participants at risk of malnutrition, four validated screening tools specifically designed for older adults and the hospital setting will be performed within 48 hours after hospital admission, namely: Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment Short Form (MNA-SF), and the Malnutrition Screening Tool (MST) (12). The cut-off value for the risk of malnutrition for SNAQ is ≥3 points, for MUST is ≥2 points, for MST is ≥2 points and for MNA-SF is ≤11 points. Participants at risk of malnutrition are eligible for inclusion if one or more of the four screening tools indicates such risk as by their respective cut-offs. The patient will be approached for participation after consultation with the clinical team. After obtaining written informed consent, the participant is further screened for eligibility. Other in and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria for the ProIntens study.

Inclusion criteria	Aged 55 or older At risk of malnutrition Written informed consent Ability to comply with the study protocol Willingness to comply with the study protocol Agrees that his/her general practitioner will be notified about study participation Consent of the participants' in-hospital clinical team
Exclusion criteria	Inability to understand the Dutch language Cognitive impairment (MMSE <15) Current/admission diagnosis of cancer or active cancer treatment (systemic and/or immune therapy) COPD GOLD >3 Heart failure NYHA >3 Initially admitted to intensive care unit Use of total parenteral nutrition Palliative treatment or a life expectancy of ≤3 months

Note: MMSE=Mini Mental State Examination; COPD=Chronic Obstructive Pulmonary Disease; GOLD=Global Initiative for Chronic Obstructive Lung Disease; NYHA=New York Heart Association;

Sample size calculation

The sample size is based on the difference in changes of the Short Physical Performance Battery (SPPB) in the study of Tieland et al (13) and observational data from older patients, aged 70 and older, who were at risk of malnutrition (14). The following estimates were used: effect size of 1-point difference in mean change from admission to 3 months post-discharge between the intervention and control group and a standard deviation (SD) of 2.5. With a significance level (α) of 0.05 and a power of 80%, a sample size of 99 participants per group was estimated. Assuming a drop-out of approximately 25%, a total number of 125 participants per group was needed, leading to a total of 250 participants to be included in the study.

Procedures and Randomization

Eligible participants will be contacted by a member of the research team and after receiving written and oral explanation of the study procedures, the participants will have at least 3 hours to consider participation. When all questions are answered and the participant expresses his/her willingness to participate, the informed consent form will be signed, after which the participants will be screened on eligibility (see Table 1). Eligible patients will be randomized using data management program

Castor EDC block randomization algorithm (Castor EDC©, Amsterdam, The Netherlands). Variable block sizes (2, 4, 6) are used in random order, stratified by hospital. When a participant's case report form is entered in Castor EDC and fulfils all inclusion criteria and none of the exclusion criteria, a researcher with randomization rights (only CD and DS) clicks the 'Randomize' button within 1 hour after informed consent was obtained. Randomization cannot be undone and is logged in the audit trail. The group allocation of patients is not visible for data-entry personnel. Due to the nature of the intervention, the study coordinators (CD, JV, DS, ME), dietitians and participants are not blinded to allocation.

Data will be collected at five time points; within 48 hours after admission (t_0), at the 4th day of admission (t_1), at discharge (t_2), one month after discharge to home (t_3) and three months after discharge (t_4). Table 2 provides an overview of the time, location, content of assessment and duration of data collection per time point. The measurements will be performed by a team of trained professionals according to the Dutch Medical Research Involving Subjects Act, ICH-GCP guidelines and Standard Operating Procedures. The team is supervised by the study coordinators (CD, JV, DS). Data will be collected on paper using Case Report Forms, which are stored at participating centers. Research team members enter the data in the online data management system Castor EDC (Castor EDC©, Amsterdam, The Netherlands). Personal information will be stored in password protected files, only accessible by the research team, according to the European General Data Protection Regulation.

Table 2. Time, location, content of assessment and duration of the ProIntens study.

Time	Location	Content of assessment	Duration (minutes)
H0 *within 48 hours of admission*	Hospital	Informing patient Obtain written informed consent Socio-demographics Medical history Cognitive performance	20
Inclusion and randomization	Hospital	Inform patient about inclusion and group allocation	5
Control group continues in regular care; intervention group starts Intensive Dietetic Care-pathway			
H1 *withing 48 hours of admission*	Hospital	Physical functioning and performance Nutrition intake registration Body composition Medical and demographic data Behavioral and psychosocial functioning Health cost questionnaire Quality of life Blood parameters	90
H2 *4th day of admission*	Hospital	Body composition Nutrition intake registration	20
H3 *around hospital discharge*	Hospital or home visit	Physical functioning and performance Nutrition intake registration Body composition Behavioral and psychosocial functioning Health cost questionnaire Quality of life Blood parameters (medical record) Length of hospital stay	90
P1 *one-month post-discharge*	Home visit	Physical functioning and performance Nutrition intake registration Body composition Behavioral and psychosocial functioning Health cost questionnaire Quality of life Readmissions (timing, reason, duration)	90
P3 *three-months post discharge*	Home visit	Physical functioning and performance Nutrition intake registration Body composition Behavioral and psychosocial functioning Health cost questionnaire Quality of life Blood parameters Readmissions (timing, reason, duration) Mortality	90

Intervention Mapping

In the development of the intensive dietetic care pathway, an Intervention Mapping (IM) approach was used (15, 16). The framework consists of six steps and helped to process effective health behavioral theories and behavioral change techniques into the intervention. In step 1 of IM, we defined the problem (17) and performed an additional needs assessment with different disciplines involved in the treatment of older patients, to identify potential strategies (*publication in press)*. In step 2 and 3 of IM, a logical model of change was created to show which behavioral change techniques underlie parts of the intervention and their proposed change in the behavioral and health outcomes. Step 4 of IM consisted of the production of the intervention materials. For an extensive overview of the applications and their underlying behavioral changes techniques, see table S1 and S2 in Supplementary file 1. In step 5 of IM, the implementation of the intervention will be performed. Actions needed for implementation are providing training to dietitians, physiotherapists, nurses, treating physicians, nutrition assistants and care givers around the patient. Online and offline training sessions will be created for this purpose. Step 6 of IM consists of the evaluation. Next to the evaluation of the effect of the intervention, also process and economic evaluation will be performed. To evaluate the implementation process, information on five process indicators will be assessed, being Recruitment/Reach, Dose received, Acceptability, Applicability, Implementation integrity (18-21). For the economic evaluation, information on quality of life, and the use and costs of healthcare will be assessed using validated questionnaires(22, 23).

INTERVENTION

Control group

Participants in the control group will receive regular care and for the study only additional measurements will be performed (see Figure 1). Within current regular care, screening for risk of malnutrition is done with the SNAQ screening tool only (24). When the patient is found to be at risk, a dietitian is consulted by the nurse. When consulted, the dietitian specifies the nutritional status of the patient and develops a personalized protein and energy-enriched diet. The treatment goal is to reach the recommended protein and energy intake on the 4th day of admission based on the Dutch guideline for malnutrition (25). Oral nutritional supplements or enteral nutrition via tube feeding can be used to achieve this goal. Follow-up of treatment differs in practice. Some patients are lost to follow-up, some in-hospital dietitians perform a few telephone follow-ups, others hand over the patient to a primary care dietitian. If a patient has trouble with Activities of Daily Living (ADL) during hospitalization, an in-hospital physiotherapist may be consulted. The focus of physiotherapy is usually 'what must the patient be able to do, to be dischargeable'. A hand-over file is given to the patient at discharge, after which patients can decide for themselves if they want a follow-up treatment from a primary care physiotherapist.

	Instrument	t_{-1}	t_0	t_1	t_2	t_3	t_4
Enrolment							
Eligibility screening		x					
Informed consent		x					
Randomisation		x					
Interventions							
Control							
Intensive dietetic care-pathway							
Assessments							
1) Physical functioning and performance							
Physical performance	SPPB		x		x	x	x
Handgrip strength	Jamar handheld dynamometer		x		x	x	x
Knee extension	MicroFET2 handheld dynamometer		x		x	x	x
Physical activity	PAM		x	x	x	x	x
ADL	Barthel Index		x		x	x	x
Pain	NRS		x		x	x	x
Fatigue	NRS		x		x	x	x
Sleep Quality	PSQI		x		x	x	x
2) Nutrition							
Dietary food intake	24h recall		x	x			
	3-day dietary record				x	x	x
Appetite	NRS		x		x	x	x
3) Body composition							
Body weight	Scale		x	x	x	x	x
Height	Measure tape		x				
BMI	-		x	x	x	x	x
Body composition	BIA		x		x	x	x
Muscle morphology	Ultrasound		x		x	x	x
4) Medical and demographical data							
Socio-demographic characteristics	Age, gender, date and time of admission, education level, living arrangement	x	x				
Admission diagnosis	Medical record		x				
Medical comorbidity	CCI		x				
Medical history	Medical record		x				

	Instrument	t_{-1}	t_0	t_1	t_2	t_3	t_4
Polypharmacy	Medical record		x				
5) Behavioural and psychosocial functioning							
Fear of falling	NRS		x		x	x	x
Depression	GDS-15		x		x	x	x
Quality of life	EQ-5D & ASCOT		x		x	x	x
6) Other							
Cost	Questionnaire	x		-	x	x	
Blood parameters	Medical Record		x*		x*	x*	x*
Cognitive performance	MMSE	x					
Length of hospital stay	Medical record				x		
Number of readmissions	Cost questionnaire					x	x
Mortality	Date of death						x

Time points: screening (t-1), hospital admission (t0), 4th day after admission (t1), around discharge (t2), one-month after discharge (t3) and three months after discharge (t4)
*When available from medical records;
BIA= Bio-electrical Impedance Analyses; FFM= Fat Free Mass; NRS= Numeric Rating Scale; ONS= Oral Nutritional Support; SPPB=Short Physical Performance Battery; PAM= Physical Activity Monitor;

Figure 1. SPIRIT table: Summary of enrolment, intervention and outcomes assessed at the different time points.

Intervention group

For participants at risk of malnutrition in the intervention group, nutritional support will be initiated as soon as possible. Participants in this group will receive personalized intensive dietetic care (IDC) based on the scientific literature (see Table 3) (5, 25-29). The nurses and nutritional assistant will be informed by the research team to start patients on a protein and energy-rich diet within 24 hours after admission. In addition, the dietitian will be informed by the study coordinators immediately so treatment can start within 48 hours. The treatment goal is to reach the recommended protein and energy intake on the 4th day of admission and continuously after discharge. There is a set of smaller and larger adjustments that align consultation, interprofessional collaboration and communication. Determining the nutritional status, which is done at admission by a dietitian, are more specific than currently done in regular care (see Table 3). Oral nutritional support (ONS) or enteral nutrition via

tube feeding can be used to achieve the protein and energy goal. The monitoring by the dietitian is intensified and supported by nutritional assistants, nurses, physiotherapists and informal caregivers. For all strategies applied within the intensive dietetic care, see table 3. These strategies are based on the needs assessment and behavioral change theories and techniques (see Supplementary file 1, Table S1 and Table s2).

Table 3. Overview of different strategies applied within the intensive dietetic care intervention, compared with regular care.

Strategy	Regular care (control)	Intensive Dietetic Care (intervention)
Assessment of bodyweight	· Patient is asked his/her current weight; rarely is it measured	· Measured at admission and monitored every other day during hospital stay
Protein goal per day	· 1.2g/kg self-reported bodyweight	· 1.5g/kg fat free mass derived from BIA · If FFM not available à 1.2g/kg (adjusted) measured bodyweight (30)
Monitoring of energy and protein intake	· Diet history by dietitian, a few times during treatment	· Daily record with Rate-a-plate or EiFit application by patient with support of nurse, nutritional assistant and/or dietitian (31)
Evaluation of treatment plan	· Hospital: varying · After discharge: max 3 hours consultation per year	· Hospital: every other day · After discharge: 6 hours consultation in 3 months
Meals	· Served to bed · Energy/Protein-rich options available upon request of dietitian	· If possible, at a desk and in 'social context' (32, 33) · Energy/Protein-rich options always available · 25-30 g protein per main meal (26) · Late-night snack containing ≥10 g protein
ONS (when needed)	· Hospital available ONS	· Hospital available ONS · Protein powder supplement containing 10/15 g of whey-protein

Table 3. Overview of different strategies applied within the intensive dietetic care intervention, compared with regular care. (continued)

Strategy	Regular care (control)	Intensive Dietetic Care (intervention)
Information	· Hospital-specific leaflet	· Information folder containing: · Infographic "Protein&Exercise" · Summary of treatment plan of each involved discipline · Contact information of all involved disciplines · Instructions on how to register dietary intake · Exercise program based on SPPB outcome · Poster with simple exercises (34) · Example of a daily menu rich in protein and energy · Recipes of protein-rich meals · Protein-rich product list · Information on home delivery services · Knowledge clip "Protein&Exercise" · "Protein&Exercise" board (adapted from Elizabeth-Twee Steden Hospital)(35-37)
Physical activity	· Physiotherapist may be involved	· Active referral to a physiotherapist (38-40) · PAM to stimulate mobilization
Collaboration	· Minimal collaboration between involved disciplines	· Intensive collaboration between involved disciplines, initiated by the dietitian
Discharge follow up	· Dietitian: varying between no follow-up, follow-up by hospital dietitian, follow-up by primary care dietitian	· Dietitian: high frequency follow-up by primary care dietitian (41, 42)

BIA= Bio-electrical Impedance Analyses; FFM= Fat Free Mass; ONS= Oral Nutritional Support; SPPB=Short Physical Performance Battery; PAM= Physical Activity Monitor;

SPECIFIC TASKS FOR EACH PROFESSION IN THE INTERVENTION

During hospitalization

Hospital dietitian

The dietitian will have additional treatment time (90 minutes) for each patient to help achieve a tailored protein and energy rich diet. The extra time can be used to elaborate more on the importance of protein and mobility with the help of the knowledge-clip "Protein&Exercise" and infographic "Protein&Exercise". During an interactive moment, the dietitian informs the family and their caregivers on the importance of protein intake and physical activity of the patient (43). Extra information on how they can support the patient in reaching their goals will be given. The dietitian encourages the patient to not lay in the hospital bed (with assistance of a nurse or physiotherapist if needed) during the day to stimulate physical activity. Other tools the dietitian may use during treatment are motivational interviewing, ONS or enteral tube feeding, focus on timing of protein around exercise and the "Protein&Exercise board" to create an overview of the daily goals. The extra treatment time can be used to collaborate the hospital physiotherapist to align the treatment goals; collaborating and communicating with the nurse and Nutrition Assistant (NA) about the participants' food intake and treatment directly after first consult and every other day during hospitalization can improve the participants' adherence to the treatment plan. When the patient is discharged, the dietitian fills in the ProIntens medical file transfer and sends it to the dietitian in the primary care via secured e-mail. The dietitians will call each other to discuss details on the treatment of the patient within the first week post-discharge.

Hospital physiotherapist

During hospitalization, the physiotherapist will be consulted at least once to assess which physical activity is safe and feasible for the patient, and to inform the patient on the results of the assessment. The physiotherapist will collaborate with the dietitian and aligns the treatment plans on timing of mobilization and protein intake. When the patient will be discharged, the physiotherapist sends a medical file transfer to the primary care physiotherapist and/or dietitian.

Nutrition assistant (NA)
The nutrition assistant supports the patient in reaching the treatment goals by referring to the knowledge-clip and infographic "Protein&Exercise". The NA encourages the patient to consume protein rich meals and products and provides protein rich snacks with a minimum of 5g and optimally 10g of protein immediately when requested by a patient. The NA knows the potential barriers to food intake and how to tackle them. During hospitalization, the NA helps the patient monitoring their food intake with the Rate-a-Plate list or EiFit app (e-version of Rate-a-Plate). The NA provides feedback on nutritional status to the patient and the nurse daily and has direct contact with the dietitian every other day. If needed, the NA helps the patient with adjusting the "Protein&Exercise" board.

After discharge

Primary care dietitian
The dietitian in primary care receives the medical file from the hospital dietitian via secured e-mail and will contact the hospital dietitian to receive additional information on the patient within the first week after discharge. Within the same first few days, the dietitian will contact the patient to schedule the first home visit within the first week after discharge. In addition, the dietitian actively refers the patient to a physiotherapist to continue the support on mobilization (38-40). During the first visit, the follow-up consultations will be planned (weekly contact for four weeks, thereafter biweekly until three months after discharge; see table 4). During the first home visit, the dietitian may adjust the treatment plan to suit the participant's home setting. When needed, they can refer to knowledge-clip and infographic "Protein&Exercise" to repeat the importance to continue the treatment plan. During the three months of treatment, the dietitian aids patient learning to monitor food intake based on Rate-a-Plate list or EiFit app and evaluate on intake during every visit. At every visit, the dietitian mentions the importance of physical activity to the participants, family and informal caregivers and encourages the participant to be physically active. The dietitian may refer to the exercise program in the folder. When needed, the dietitian can inform the participant about home delivery and other social services, which are available in the discharge folder.

Table 4. Time and activity overview for primary care dietitian and physiotherapist.

Weeks post-discharge	Activity	Approximate Time (min)
0 (±3 days)	Telephone call	15
1	Home visit	45
	Contact with dietitian in hospital for hand-over	10
	Contact with primary care physiotherapist	15
2	Telephone call	20
3	Telephone call	20
4	Home visit	30
5		
6	Telephone call	20
7		
8	Home visit	30
9		
10	Telephone call	15
11		
12	Telephone call (closing)	15

Primary care physiotherapist (if consulted)

The consultation of the physiotherapist is dependent on insurance of the patient. When consulted, the physiotherapist receives information on the participant's participation in the study, and receives the patient files via secured e-mail. During the follow-up the dietitian and physiotherapist collaborate to align the interprofessional treatment plans on timing of mobilization and protein intake.

Community nurse (if consulted)

When a community nurse is consulted in support of recovery of the patient at home, they will receive information on the presence of malnutrition and the treatment plans, which are available in the discharge folder of the patient. The dietitian and physiotherapist will be notified of the involvement of the community nurse. The community nurse has knowledge on protein rich products and encourages the patient to consume protein rich products. Also, the community nurse can encourage the patient to be active. When the community nurse suspects

a low intake, based on the Rate-a-Plate list or the EiFit application, they will notify the dietitian.

OUTCOMES

Figure 1 provides a detailed overview of the primary and secondary outcomes measured at each time point.

Primary outcome

The primary outcome is the between-groups difference in the mean change on the Short Physical Performance Battery from admission (t_1) to three months post-discharge (t_4) (44). This battery consists of the following tasks: balance stance in three different positions: a side-by-side, semi tandem, and full tandem, walking three or four meters to measure gait speed, and rising from a chair and return, five times as quickly as possible. The total scores can range from 0 to 12 (best performance). If a patient is unable to perform a test, 0 points will be noted. A change of 1 point on the total score has been demonstrated to be clinically meaningful (45, 46).

Secondary outcomes

1) Physical functioning and performance

Handgrip strength Handgrip strength is an objective measure of muscle strength in the upper body. Three consecutive measures of handgrip strength (kg) of both hands will be recorded to the nearest 0.5 kg using a hand dynamometer (Jamar). Standardized vocal stimulation will be given, according to the Standard Operating Procedure (SOP) of the Nutritional Assessment Platform (NAP) (47). The highest score will be used as a parameter for muscle strength.

Knee extension strength The knee extension strength is measured with a hand-held dynamometer (MicroFET2). The strength is measured in kilograms (kg). Participants will be asked to be seated on an elevated chair with their knees at a 90° angle, feet off the floor and hands on their thighs. The dynamometer will be placed proximal to the talus and malleolus (ankle). The participants will be asked to slowly increase their muscle force to a maximum effort which will need to be sustained for

three seconds. The procedure will be repeated two times for each leg. The highest score will be used as a parameter for lower leg strength (48).

Physical activity Daily physical activity will be registered using a three-dimensional Physical Activity Monitor (PAM). The PAM is a compact, battery-operated electronic accelerometer. Participants are requested to wear the accelerometer around their ankle during hospital stay and a period of three days before t_3 and t_4. The PAM registers the amount of movement of the user, converted into number of steps and the Pam Score. The Pam Score is the ratio between activity induced energy expenditure and resting metabolic rate.

Activities of Daily Living (ADL) To assess ADL, the Barthel Index will be used. The questionnaire consists of 10 items on an ordinal scale that relate to the preceding 24-48 hours. A high score on the Barthel Index corresponds to a high degree of independence (49).

Pain and fatigue A Numeric Rating Scale (NRS) will be used to assess pain and fatigue. The NRS for pain is a validated continuous scale with a score range between zero and ten, where zero represents no pain and ten the worst pain possible (50, 51). The NRS for fatigue is a continuous scale with a score range between zero and ten, where zero represents no fatigue and ten the worst fatigue possible (52).

Sleep quality To assess sleep quality two questions of the Pittsburgh Sleep Quality Index (PSQI), a self-reported questionnaire, are used, being '*During the past month, how would you rate your sleep quality overall?*' and '*During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?*'. Both questions have a range of 0 (better) to 4 (worse) (53).

2) Nutrition
Dietary food intake Dietary food intake will initially be registered using the Rate-a-Plate list or the EiFit application (e-version of Rate-a-Plate) (31). Rate-a-Plate list and EiFit application are simple but comprehensive tools to make a global estimation of the participants' nutritional intake. This list will be used as a basis to perform a 24h recall at admission and on the 4th day of admission, and to complement a more detailed 3-day dietary record at discharge, one-month after discharge and three months after

discharge. All records will be coded using the Dutch Food Consumption Database (NEVO) (54).

Appetite is measured on a numeric rating scale from zero to ten, where zero represents no appetite and ten best appetite possible.

3) Body composition
Body weight Body weight (kg) will be measured to the nearest 0.1kg using a calibrated weighing scale without shoes and heavy clothing.

Height Height (m) will be measured to the nearest 0.01 meter using a stadiometer. If the subject is unable to stand straight, knee height will be measured as it is closely related to stature. Knee height will be measured in a supine position with the knee and ankle in a 90° angle. With a measuring tape, the lower leg is measured from heel to the upper side of the patella on the lateral side of the body. The formula of Chumlea (1998) will be used to assess stature height (55).

Body composition To estimate fat-free mass (FFM) and fat mass (FM) Bioelectrical Impedance Analyses (BIA; Bodystat500 and Quadscan 4000) will be used. Within 30 minutes prior the measurement, the patient is asked to empty their bladder. The patient will be asked to lie in a supine position with the arms not touching the trunk and legs and feet not touching each other. Regular 3M-electrodes will be arranged in the tetrapolar configuration, with the injection electrodes to be placed wrist-to-ankle and the sensing electrodes to be placed hand-to-foot, preferable on the right side of the body.

Muscle morphology Ultrasound imaging will be used to assess anatomical cross-sectional area (ACSA) of the rectus femoris and vastus lateralis muscle (56). B-mode ultrasound images will be taken with a broadband linear array probe (Phillips Lumify L12-4) at 50% muscle length of the vastus lateralis, and measurements will be performed with the patient in a seated position, with the right leg fully extended. Individual ultrasound images are combined into a single image representing the rectus femoris and vastus lateralis. ACSA and homogeneity (as a sign of fibrosis and/or fat infiltration) will be quantified using ImageJ (National Institutes of Health, USA) (57).

4) Medical and demographical data
Socio-demographics Participants' age, gender, living arrangement, highest level of education, date and time of admission and discharge and medical history will be noted.

Chronic conditions The Charlson comorbidity Index will be used to score the number and severity of comorbidities. To each condition, a score of 1, 2, 3, or 6 is given, where a higher score corresponds with a greater risk of mortality (58).

Polypharmacy Current medication use will be noted. Polypharmacy will be defined as the use of five medications or more (59).

5) Behavioral and psychosocial functioning
Fear of falling The Numeric rating scale (NRS) for fear of falling is a scale ranging from zero to ten. Zero represents no fear of falling and ten the worst possible fear of falling.

Depression The Geriatric Depression Scale-15 (GDS-15) will be used to assess symptoms of depression. The GDS-15 is a self-report questionnaire of 15 items on a binary (yes/no) scale and assess symptoms on the preceding week. The total score is the sum of the 15 items and ranges from 0-15, with a higher score indicating more depression symptoms. A score of 0-4 will be considered 'no depression', a score of 5-8 as 'mild depression', a score of 9-11 as 'moderate depression and a score of 12 or higher as 'severe depression' (60, 61).

Quality of life The EuroQol-5D (EQ-5D) and Adult Social Care Outcomes Toolkit (ASCOT) are used to assess quality of life. The EQ-5D is a quality-of-life instrument consisting of five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with five response levels (no problems to unable to perform). The resulting health states on the EQ-5D-5L will be converted to a utility score using the Dutch EQ-5D-5L tariff (22). The utility scores will be used to calculate Quality-Adjusted Life-Years. The ASCOT is a quality-of-life instrument that measures quality of life from a broader perspective than health alone (23). The ASCOT consists of eight domains (control over daily life, personal cleanliness and comfort, food and drink, personal safety, social participation and involvement, occupation, accommodation cleanliness and comfort, dignity) with four

response levels (ideal level to high needs). The ASCOT health states will be valued using the Dutch ASCOT tariff (62).

6) Others
Cost-effectiveness Costs will be assessed from a societal perspective using a retrospective questionnaire. Information on the following cost items will be collected: primary care (e.g., visits to the general practitioner, physical therapy sessions), secondary care (e.g., outpatient visits, AED visits), primary care, medication, informal care (i.e., help from family and friends), and lost productivity (i.e., absenteeism and presenteeism).

Blood parameters When available, blood parameters (C-Reactive Protein (CRP) and (pre-)albumin) from the medical records will be noted during hospital stay.

Cognitive performance The Mini Mental State Examination (MMSE) will be used to assess cognitive performance (63). The MMSE is a test that is used in the event of a suspicion of memory problems or dementia. The 23-item questionnaire gives an impression of a person's memory, language ability and concentration. The total score ranges from 0 to 30 points. Cognitive impairment is defined as a total score below 15 points.

Readmissions Information on any readmission to the hospital will be retrieved from the medical record and by asking the patient '*Have you been hospitalized in the last month?'*. Data on date of admission and discharge for any readmission, as well as whether the admission was planned or unplanned, will be retrieved from the medical record.

Process evaluation
To assess whether the implementation of the intervention was successful, a process evaluation will be conducted. A total of five process indicators are identified, being Recruitment/Reach, Dose received, Acceptability, Applicability, Implementation integrity (18-21). Recruitment/reach describes the procedures used to approach and attract participants and the proportion of intended target audience that participated in the intervention. This latter information will be obtained from the inand exclusion flowchart. Dose received describes to which extent the participants received the intervention, i.e. number of consultations by dietitian and physiotherapist, discussed items during consultation, times

intervention items are used. This information will be obtained from the cost questionnaire and surveys send to dietitian. Acceptability describes the degree of satisfaction of participants and healthcare professionals with the intervention. This information will be obtained through semi-structured interviews in a random subsample of participants who completed the study and healthcare professionals who carried out the intervention. Applicability describes the feasibility of implementing the intervention from the healthcare professional's point of view. This information will be obtained through semi-structured interviews. Implementation integrity describes the degree to which the intervention was implemented as intended. This information will be obtained through semi-structured interviews with healthcare professionals. In addition, structured observations will be conducted by the research staff and registration forms of the health care professionals will be checked.

Statistical analysis

Summary statistics (mean, median, standard deviation, interquartile range and frequency distribution) will be generated for baseline characteristics. Descriptive data will be used to assess time trends.

SPPB total scores will be visualized over time using mean and standard error of the mean per treatment group and period or with median and interquartile range if needed. Differences between treatment groups in the primary outcome parameter will be analysed using generalized linear mixed models. A dummy variable for time will be created. Important prognostic baseline values will be used as covariates. Secondary outcome measures will be visualized over time using mean and standard error of the mean per treatment group or with median and interquartile range if needed. Changes within and between groups will be modelled with linear mixed models. All data will be analysed according to the intention-to-treat principle. Missing data will be handled with linear mixed models. An α-level of 0.05 will determine statistical significance. Data validation is performed by blinded project leaders (HK, MT). Further analyses will be stated in the Statistical Analysis Plan which will be finalized and put in the public domain via Figshare repository before unblinding of the dataset.

Economic evaluation

The economic evaluation will be done from a societal perspective according to the intention-to-treat principle. Following the guidelines

for economic evaluations, provided by the Dutch Healthcare Institute, standard prices are used to calculate costs (64). Both a cost-effectiveness analysis with SPPB as the outcome measure and a cost-utility analysis with the EQ-5D5L and ASCOT as outcome measures will be performed. Missing cost and effect data will be imputed using multiple imputation with predictive mean matching. Cost and effect differences will be estimated using linear mixed models in combination with bootstrapping. Statistical uncertainty surrounding the incremental cost-effectiveness ratio will be estimated using bootstrapping. Cost-effectiveness acceptability curves will be estimated to show the probability that the intervention is cost-effective in comparison with usual care for different willingness-to-pay thresholds (i.e., the maximum amount of money society is willing to pay per unit of effect extra).

DISCUSSION

Disease related malnutrition is a prevalent problem in hospitalized and discharged older adults. Consequences of malnutrition are physical limitations, lower quality of life and higher healthcare costs. Dietetic care counteract the effects of malnutrition by increasing protein and energy intake. However, older adults have difficulties consuming adequate dietary protein and many are physically inactive. Important factors for improving dietetic care are patient self-management, early mobilization, multidisciplinary collaboration between professionals. Here we present a multi-component intensive dietetic care-pathway based on the pertinent literature. Using the intervention mapping framework to develop the intervention helped to incorporate behavioral change techniques and match the components of the intervention to the needs of the end-users. Our study builds on the needs of involved disciplines, expert opinions and previous studies conducted in the hospital setting or the post-discharge setting (8, 9, 65-68). The ProIntens intervention tries to provide evidence about the question to which extent an intensive treatment with guidance of a dietitian and a physiotherapist, compared to currently regular care in five hospitals in the Netherlands is able to improve a patients recovery by continuing care after discharge. Also, by basing the components of the intervention on behavioral change theories we hope to provide a constant awareness of the importance of protein intake and physical activity, with various tools within the direct surroundings of the patient, with the support of caregiver. Initially the study was designed as a stepped-wedge design, with 15 hospital wards as clusters. However, due to the outbreak of COVID-19, the hospital wards changed drastically, which made it impossible to conduct the study in that fashion. The study was redesigned to a parallel-RCT although this increases the chances of contamination during the hospital phase as hospital care professionals could guide control group patients similar to intervention group patients. We tried to overcome this by carefully instructing the care professionals to make sure intervention components are not used in regular care. An advantage of the parallel-RCT design is that within each hospital there are patients either receiving regular care or the intervention. Also, due to the use of block randomization, control and intervention patients will be spread evenly over time. In addition, the intervention is implemented in every participating hospital. The ProIntens study will provide valuable evidence and insights that may have a major impact on level and timing

of patients' recovery, both in a hospital and primary care setting. The latter might be a major step in improving dietetic care and implementing the ProIntens intervention.

List of abbreviations

ADL: Activities of Daily Living; ASCOT: Adult Social Care Outcomes Toolkit; BMR: Basic Metabolic Rate; CMST: Combined Malnutrition Screening Tool; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; EQ-5D: EuroQol-5D; FFM: fat-free mass; FM: fat mass; GDS-15: Geriatric Depression Scale-15; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICH-GCP: International Conference on Harmonisation's (ICH) Guideline for Good Clinical Practice (GCP); IDC: Intensive Dietetic Care-pathway; IGF-1: Insulin-like Growth Factor-1; IL-6: Interleukin-6; IM: Intervention Mapping; MMSE: Mini Mental State Examination; MNA-SF: Mini Nutritional Assessment – Short From; MST: Malnutrition Screening Tool; MUST: Malnutrition Universal Screening Tool; NA: Nutrition Assistant; NAP: Nutritional Assessment Platform; NYHA: New York Heart Association; NRS: Numeric Rating Scale; ONS: Oral Nutritional Supplement; PAM: Physical Activity Monitor; PSQI: Pittsburgh Sleep Quality Index; RC: Regular Care; SD: Standard Deviation; SNAQ: Short Nutritional Assessment Questionnaire; SOP: Standard Operating Procedure; SPPB: Short Physical Performance Battery; TEE: Total daily Energy Expenditure;

DECLARATIONS

Ethics approval and consent to participate

This study is approved by the Medical Ethics Committee (METc) of the Amsterdam University Medical Center (AUMC), location VUmc in The Netherlands (Protocol ID: 2019.689 and Amendment ID: A2020.361). Written informed consent is obtained from all participants before any data is collected. Insurance has been taken out for compensation to those who suffer harm form the trial participation. The research is performed according to the Dutch Medical Research Involving Human Subjects Act (WMO) and the principles of the Declaration of Helsinki (64th W MA General Assembly, Fortaleza, Brazil, October 2013).

Consent for publication

Not applicable.

Availability of data and materials
Recruitment of participants will continue until 31-12-2022. After completion of the trial, data will be stored and shared through Figshare. Supplementary files can be downloaded at: https://f1000research.com/articles/14-81

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
PW acts as the study Principal Investigator. PW, MT and HK wrote the research proposal that was sent to the funding organization. All authors designed the RCT. CD and JV drafted the manuscript and CD, JV, ME and JB wrote the protocol for the Medical Ethics Committee. JB provided expertise on cost-effectiveness. GT provided methodological and statistical expertise. ME and RW provided expertise on ultrasound measurements. CD, MT and HK are responsible for study management. CD, DS and ME are responsible for data collection. All authors critically revised and approved the final version of the manuscript.

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CHAPTER 6

Intensified dietetic care during and up to three months after hospital admission in older patients at risk of malnutrition, a randomised controlled trial

Carliene van Dronkelaar,
Hinke Kruizenga,
Moritz Eggelbusch,
Peter J.M. Weijs,
Michael Tieland

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ABSTRACT

Background Inadequate protein intake is associated with poor physical functioning and suboptimal recovery in hospitalized older adults. Despite standard dietetic care, dietary protein intakes falls well below the recommended levels. To address this problem, we developed an intensified trans-sectorial dietetic intervention that targets hospitalized older adults. This study aims to evaluate its impact on physical functioning and dietary protein intake during and post hospitalization.

Methods This multicenter individually randomised controlled trial was conducted in five hospitals from January 2021 until December 2022. Hospitalized older adults, aged ≥55 years and at risk of malnutrition were randomised to receive regular care (CON) or intensive dietetic intervention (INT). The intervention consisted of personalized, intensive care, including trans-sectorial guidance by trained dietitians, increased consultations, and supportive materials focused on protein intake. Additionally, the intervention emphasized engagement in dietary behavior and physical activity during hospitalization and continued for three months post-discharge. The primary outcome was change in physical functioning measured by the Short Physical Performance Battery (SPPB) from admission to three months post-discharge, analysed with linear mixed models for repeated measures. Secondary outcomes included protein intake, body composition, muscle strength, physical activity, activities of daily living , fear of falling, pain, fatigue, appetite and quality of life.

Results A total of 76 hospitalized older adults were included in the study of which 38 were in CON and 38 received INT. The overall drop-out was 30% (CON 26%; INT 34%). The participants had a median age 73y (Inter Quartile Range: 62-78y) with 50% females. Overall, Physical functioning improved from 6 points (IQR: 1-9 points) at baseline to 9 points (IQR: 7-11) at three months post-discharge ($p<0.0001$). Likewise, protein intake increased from 0.8g/kg bodyweight (IQR: 0.6-1.0) to 1.0 g/kg bodyweight (IQR: 0.8-1.2) ($p<0.0001$). There were no significant differences between intervention and control group. All secondary outcomes improved over time, except for fear of falling, leg extension strength, and body composition, with no significant differences between intervention and control group.

Conclusions Hospitalized older patients improved their physical functioning and protein intake after three months post-discharge, although the majority not to recommended levels. No effects of the intensive dietetic treatment could be detected due to low intervention adherence and a small sample size. Future research should be conducted with an intervention consisting of a strong combination of nutritional support and exercise with a successful implementation and a flexible study design catered to the needs of the older patient.

Trial registration: Landelijk Trial Register (NL8041; NL72069.029.19) www.onderzoekmetmensen.nl; registered 2019-09-23; covering all WHO Trial Registration Data Set items.

INTRODUCTION

Adequate dietary protein intake is essential for optimal recovery following hospitalization (1, 2). Data from the large EFFORT trial demonstrated that patients receiving optimal nutritional care showed improvements in clinical outcomes, such as readmissions, major cardiovascular events, respiratory failure among others (2). However, older patients at risk of malnutrition often struggle to meet protein and physical activity targets necessary for optimal recovery (3-5). This difficulty can be attributed not only to the severity of their illness but also to a lack of knowledge about the importance of adequate protein intake to support recovery (5).

Dietetic care has the potential to address these challenges (6). According to a Cochrane review by Baldwin et al., dietary advice, with or without oral nutritional supplements, can improve nutritional intake and quality of life in patients at risk of malnutrition (7). However, larger intervention studies are needed to confirm these findings. Despite the potential benefits of dietetic care, dietitians in the Netherlands have reported barriers in treating older patients at risk of malnutrition within hospital and primary care settings. These barriers, identified through focus groups, include limited treatment time, insufficient interdisciplinary collaboration, and inadequate continuation of care post-hospitalization (van Dronkelaar et al., unpublished).

To overcome these barriers, we developed a trans-sectorial intervention that includes intensive dietetic treatment for older patients at risk of malnutrition, with a focus on protein intake, reinforced by the behavioral change model (7). This intensive dietetic treatment allows dietitians more time to treat older patients, have better communication tools and encourages interdisciplinary collaboration, aiming to improve both protein intake and physical functioning.

MATERIALS & METHODS

This paper was reported following the CONSORT reporting guidelines (8).

Study design, participants and randomization

The study design, recruitment, randomization, sample size calculation, intervention and outcomes have been described in detail elsewhere (protocol article).

In short, the study followed a parallel individual randomised controlled design. Patients were recruited in five hospitals in the Amsterdam metropolitan area in the Netherlands, namely Amsterdam UMC, location AMC and VUMC (academic hospital), OLVG, location east and west (teaching hospital) and BovenIJ hospital (regional hospital) from January 2021 until December 2022. Eligible patients were aged 55 years or older, admitted to hospital no longer than 48 hours ago, and at risk of malnutrition according to the malnutrition screening tools SNAQ (≥3 points), MUST (≥2 points), MST (≥2 points), MNA-SF (≤11points) or PG-SGA-SF (≥9 points) (9). Exclusion criteria were: when patients suffered from cognitive impairment (MMSE <15), delirium or received palliative care, were treated in isolation due to COVID-19 or other infectious diseases, had COPD GOLD >3, heart failure NYHA >3, current diagnosis of cancer or cancer treatment, (acute) kidney insufficiency (eGRF <60 ml/min/1,73m2 when aged <70y and eGRF <30 ml/min/1,73m2 when aged >70y), were not discharged to home or were in a palliative phase with a life expectancy of less than three months, in which cases they were excluded from the study.

Eligible patients were randomised to either control (CON) or intervention (INT) by block randomization with variable block sizes (2, 3 or 6) in random order, stratified by hospital. Due to the nature of the intervention, blinding was not possible. However, the research staff responsible for performing the measurements were blinded for the allocation of the patient.

Intervention

Patients allocated to the control arm received standard care and no additional intervention. Patients allocated to the intervention received intensive personalized dietetic treatment starting within 24 hrs after inclusion which continued until three months post-discharge. The

intensive dietetic treatment, which was co-designed with dietitians, physical therapists and nurses, consisted of guidance by a trained dietitian, both in hospital as well as in primary care, who could spend double amount of time compared to regular care (intervention: 90 minutes consult time during hospital stay and 360 minutes consult time in three months post-discharge). In addition, supporting materials like a knowledge clip on the importance of protein intake and physical activity during hospitalization, a physical information folder for the patients, containing personalized nutritional information, tailored mobility program on paper and recipes for protein rich meals were available. All intervention materials are available on the VoedingenBeweging.nu website (10).

Outcomes

Measurements were performed within hospital after inclusion (H1), at hospital-discharge when at least 3 days had passed since H1 (H3), and at the patients' home at one-month post-discharge (P1) and at three months post-discharge (P3). At baseline, characteristic information was collected; socio-demographics, medical history, admission diagnosis and medical comorbidities (Charlson Comorbidity Index) were reported. Adherence to the intervention was assessed by total treatment time by the dietitian, use of supporting materials, total protein intake and physical activity.

Primary outcome

The primary outcome was improvement in physical functioning from baseline to three months post-discharge measured with the Short Physical Performance Battery (SPPB). The SPPB consists of three elements (balance, gait speed, chair rise) for which each 4 points can be scored (total score scale 0-12). Clinical meaningful change in SPPB is found to be at 0.5-1 point (11, 12).

Secondary outcomes

Secondary outcomes consisted of protein intake, assessed from a 24hr recall at admission and three-day dietary records at the follow-up measurements, coded with the NEVO-coding system, version 2021. Average protein intake in g/day and g/kg bodyweight were noted. Muscle mass corrected for height (fat-free mass index; FFMI), was derived from a Bio-electrical Impedance Analysis (BIA; Bodystat 500, BodyStat Body Composition Technology, UK) from which the reactance and resistance

were used in the equation of Rutten et al. (13). Muscle size (anatomical cross-sectional area; ACSA), of the rectus femoris and vastus lateralis muscles were measured mid-thigh using B-modus ultrasound (Lumify, Phillips, NL). Handgrip and knee extension muscle strength were measured with a handheld dynamometer (JAMAR, USA and MicroFET2, USA respectively). Maximum force was noted in kilograms. Physical activity (measured in steps) was recorded with a Physical Activity Monitor (PAM Atris, Peercode, NL). The 10-item Barthel Index (0-20 points) was used to assess Activities of Daily Living (ADL) functionality, with a higher score indicating a better ADL functionality. Quality of life was assessed using the EQ-5D-5L questionnaire and applying the Dutch tariff (14). The EQ-5D index ranges from 0 to 1, where one means a better quality of life. The EQ-5D also contains a measure of perceived health on a Visual Analog Scale (VAS) ranging from 0 to 100, where 100 means the best health one can imagine. Potential depression was assessed with the Geriatric Depression Scale-15, with a total score of 4 or higher indicating the presence of depressive symptoms. The amount of pain, fatigue, fear of falling and appetite were monitored with a Numeric Rating Scale (0-100).

Malnutrition was assessed according to the GLIM criteria (15). Unintended weight loss in the past 12 months was asked of the patient and low muscle mass was assessed as Fat Free Mass Index (FFMI) with BIA. Reduced nutritional intake was taken from the screening for malnutrition with the questions from MNA-SF and PG-SGA on reduced food intake, being: *'Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?'* and *'I have had the following problems that have kept me from eating enough during the past two weeks'*. When the first question was answered with '*moderate or severe decreased food intake*' or if any of the symptoms of the second question was checked, the etiologic criteria of the GLIM 'reduced food intake or assimilation' was fulfilled (9). The other etiologic GLIM criteria disease burden was assessed by elevated c-reactive protein (CRP) levels from the previous three days, taken from the medical files. Probable malnutrition was defined when one phenotypic or one etiologic criterium was present. Sarcopenia was assessed according to the EWGSOP2 definition (16). The handgrip strength was used to assess muscle strength, with muscle mass measurements employed to confirm the diagnosis. Severity of sarcopenia was determined using the SPPB total score.

Sample size calculation and statistical analysis

Based on 1-point difference in the mean change of the SPPB from admission to three months post-discharge between the intervention and control group, with a standard deviation of 2.5, a significance level of 0.05 and power of 80%, a sample size of 99 participants per group was estimated (17, 18). Assuming a drop-out of approximately 25%, a total number of 125 participants per group was indicated, leading to a total of 250 participants.

For statistical analyses we used an intention-to-treat strategy. The primary and secondary outcomes were analysed with linear mixed models (LMM) for repeated measures with intervention as fixed effect and random effects at patient level. All models were checked for improvement by a random intercept and/or random slope on hospital level, next to a random intercept for patient. The baseline value of the dependent variable was added to the model as a covariate. Intervention effect was assessed as average over time first, before assessing its effect at each of the follow-up moments and reported as difference between the intervention and control group with 95% confidence interval. Changes in the primary and secondary outcomes were visualized using estimated marginal means. Analyses were performed using STATA/SE v17.0 (StataCorp LLC). An α of 0.05 was used to assess statistical significance.

RESULTS

From January 2021 until December 2022, 2641 patients were screened for eligibility in the five Dutch hospitals. Due to COVID-19 limitations during the study period, the BovenIJ hospital started a year after the first four hospitals. Flow of inclusion is depicted in Figure 1. Of the 2641 patients screened for eligibility, 1460 patients (55%) were at risk of malnutrition according to one of the five screening tools used. From those 1460 patients, 76 patients were included in the study. As we were only able to include 5% of the eligible patients after two years of screening, the study was terminated before the intended inclusion of 250 patients was reached. In the intervention group and control group respectively, the patients were recruited from the AmsterdamUMC location AMC(n=2 and n=2), AmsterdamUMC location VuMC (n=7 and n=8), OLVG location east (n=14 and n=14), OLVG location west (n=5 and n=5) and BovenIJ hospital (n=10 and n=9). Most patients had to be excluded due to active cancer treatment (13%), (acute) kidney insufficiency (15%), were discharged before inclusion (14%) or did not live in the Amsterdam area (12%). After inclusion, there was a drop-out of 30%, as two patients passed away, nine patients met the exclusion criteria (discharge not to home, start cancer treatment, palliative phase), nine patients withdrew their informed consent and three patients had protocol violations. Due to early discharge from hospital, only 17 patients were remeasured at discharge (H3: CON n=12; INT n=9). Because of patients' refusal to be measured due to illness severity, COVID-19 limitations and because of drop-out, 54 patients were measured at one-month post-discharge and 53 patients were measured at three months post-discharge.

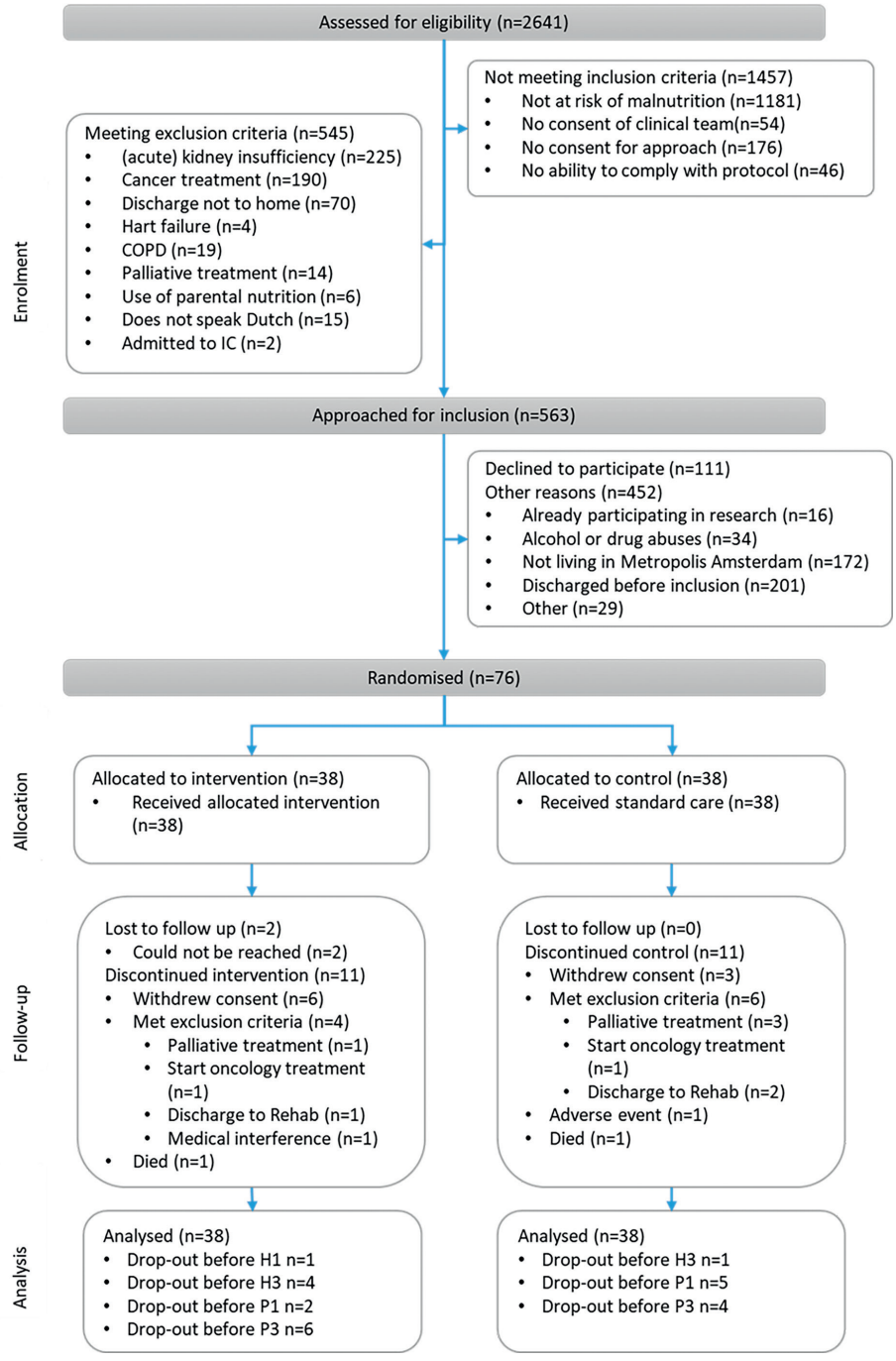

Figure 1. CONSORT flow diagram of the ProIntens study patients. H1: at admission, H3: at discharge, P1: at one month post discharge, P3: at three months post discharge.

The 76 included patients had a median (IQR) age of 73 years (63-78), and 50% was female. At admission, most patients had a poor physical functioning with an SPPB median (IQR) score of 6 (1-9) and a protein intake below recommendations (median (IQR) 0.73 (0.53-0.84) g/kg body weight). There was no major difference in baseline characteristics between the intervention and control group, except for CRP levels (CON: 97mg/L; INT: 29mg/L), and fear of falling (CON: 10 points; INT: 60 points) (see Table 1). Those who dropped out of the study after the first measurement (n=6) had a median (IQR) of 6 points (1-10) on the SPPB and a median (IQR) protein intake of 0.68 (0.16-1.2) g/kg body weight. No significant differences in age, sex, baseline SPPB score or baseline protein intake were found between patients that were able to complete the study (n=53) with those who drop-out during the study (n=23), data not shown.

Table 1. Baseline characteristic of the included patients (median (IQR) for continuous variables and *n* (%) for categorical variables).

	n	**Control**	***n***	**Intervention**	***n***	**Total**	**p-value***
Age (years)	38	74 (63-78)	38	70 (61-78)	76	73 (63-78)	0.331
Sex	38		38		76		
Female		21 (55%)		17 (45%)		38 (50%)	0.359
BMI (kg/m2)	38	24 (23-27)	38	25 (22-30)	76	24 (23-28)	0.685
Admission ward	38		38		76		0.740
Cardiology		10 (26%)		7 (18%)		17 (22%)	
Pulmonary		8 (21%)		4 (11%)		12 (16%)	
Gastro-Enterology		7 (18%)		7 (18%)		14 (18%)	
Internal Medicine		8 (21%)		12 (32%)		20 (26%)	
Neurology		1 (2.6%)		3 (8%)		4 (5%)	
Geriatrics		1 (2.6%)		1 (2.6%)		1 (1.3%)	
Orthopedics		1 (2.6%)		2 (5%)		2 (2.6%)	
Urology		1 (2.6%)		1 (2.6%)		3 (4%)	
Oncology		1 (2.6%)		1 (2.6%)		2 (2.6%)	
Mini Mental State Examination	38	27 (25-29)	38	27 (24-28)	76	27 (25-29)	0.575
GDS-15	32	3 (2-5)	30	5 (3-7)	62	4 (2-6)	0.097
EQ-5D index	35	0.65 (0.43-0.91)	33	0.77 (0.45-0.88)	68	0.72 (0.44-0.89)	0.690

	n	Control	*n*	Intervention	*n*	Total	p-value*
EQ-5D Health Score	35	65 (45-80)	33	60 (50-75)	68	65 (50-75)	0.929
CCI score	37	4 (3-5)	38	4 (3-5)	75	4 (3-5)	0.536
CCI 10y survival	37	53 (21-77)	38	53 (21-77)	75	53 (21-77)	0.529
CRP (mg/L)	34	97 (36-150)	34	29 (3-109)	68	58 (10-142)	**0.019**
Pain	33	20 (0-40)	30	43 (0-60)	63	25 (0-50)	0.196
Fatigue	33	70 (40-80)	30	78 (50-80)	63	70 (40-80)	0.178
Fear of Falling	33	10 (0-55)	30	60 (20-75)	63	40 (0-70)	**0.015**
Appetite	33	60 (50-75)	30	70 (60-85)	63	60 (50-80)	0.075
Physical Functioning							
SPPB	38	6 (1-9)	37	6 (2-9)	76	6 (1-9)	0.651
Repeated chair rise (sec)	20	18 (14-21)	23	16 (14-24)	43	17 (14-22)	0.903
Handgrip strength (kg)	34	27 (20-33)	29	28 (24-34)	63	28 (21-34)	0.576
Leg extension strength (kg)	32	17 (13-22)	28	18 (14-22)	60	17 (14-22)	0.589
FFM (kg)	34	52 (40-60	26	53 (45-60)	60	52 (42-60)	0.800
FFMI (kg/m2)	34	17 (15-19)	26	17 (16-19)	60	17 (15-19)	0.521
Rectus Femoris ACSA (cm^2)	11	2.7 (2.2-5.6)	18	3 .0 (2.5-3.6)	29	3.0 (2.5-4.0)	0.928
Vastus Lateralis ACSA (cm^2)	11	12 (8-18)	18	12 (11-15)	29	12 (10-15)	0.928

	n	Control	*n*	Intervention	*n*	Total	p-value*
Barthel Index	36	19 (18-20)	30	19 (17-19)	66	19 (18-20)	0.112
Activity (steps/ day)	25	1375 (875-2500)	22	1282 (531-1750)	47	1313 (656-2156)	0.462
Sarcopenia	20		23		43		0.640
no sarcopenia		9 (45%)		9 (40%)		18 (42%)	
probable sarcopenia		7 (35%)		11(48%)		18 (42%)	
confirmed sarcopenia		1 (5%)		0		1 (2%)	
severe sarcopenia		3 (15%)		3 (13%)		6 (14%)	
Nutrition							
Energy intake (kcal)	34	1206 (870-1409)	31	1321 (1038-1798)	65	1231 (1013-1572)	0.189
>75% Energy needs met	34	5 (15%)	31	12 (39%)	65	17 (26%)	0.028
Protein intake (g)	34	51 (38-66)	31	60 (48-85)	65	54 (46-70)	0.118
Protein intake (g/kg/day)	34	0.73 (0.53-0.84)	31	0.77 (0.66-1.12)	65	0.75 (0.59-0.97)	0.194
Protein needs met[a]	34	2 (6%)	31	4 (13%)	65	6 (9%)	0.329
Malnutrition (GLIM)	38		37		75		0.571

	n	Control	*n*	Intervention	*n*	Total	p-value*
no malnutrition		1 (3%)		1 (3%)		2 (3%)	
malnutrition		20 (53%)		15 (41%)		35 (47%)	
probable malnutrition		17 (45%)		21 (57%)		38 (50%)	
Hospital stay							
Length of stay (days)	38	4 (3-10)	38	4 (3-8)	76	4 (3-9)	0.285
Readmission within 1 month post-discharge	30		26		56		
Yes		3 (10%)		2 (8%)		5 (9%)	0.763
Days		10 (0-25)		3 (2-4)		4 (2-10)	0.564
Readmission between 1 and 3 months post-discharge	28		26		54		
Yes		3 (11%)		7 (27%)		10 (19%)	0.125
Days		14 (1-40)		2 (2-9)		3 (2-9)	0.409

*continuous variable were analysed with Mann-Whitney U test and categorical data with chi-square test. [a] Protein need set to 1,2g/kg bodyweight/day. GDS-15: Geriatric Depression Scale 15; CCI: Charslon Comorbidity Index; SPPB: Short Physical Performance Battery; FFM: Fat-Free Mass; FFMI: Fat-Free Mass Index; ACSA: Anatomical Cross Sectional Area; GLIM: Global Leadership Initiative on Malnutrition;

Main outcome

Average over time, all patients improved their physical functioning (SPPB +0.93, 95%CI 0.70; 1.17, p<0.0001). Specifically, from admission to three months post-discharge the SPPB improved with 2.7 points (SPPB +2.70, 95%CI 1.97; 3.42, p<0.0001), with the biggest improvement in the first month post discharge (SPPB +2.2, 95%CI 1.46; 2.90, p<0.0001) (see Figure 2). An unadjusted analysis showed a steady clinically relevant but non-significant treatment effect over time (INT SPPB +0.47, 95%CI -0.8; 1.7, p=0.466). In addition, no significant difference between the groups was found at the separate time points at discharge (H3), one month (P1) or three months (P3) post discharge (INT SPPB H3: -0.1, 95%CI, p=0.919; P1: +0.6, 95%CI -0.8; 2.0, p=0.393; P3: +0.3, 95%CI -1.0; 1.7, p=0.623) (see Table 2).

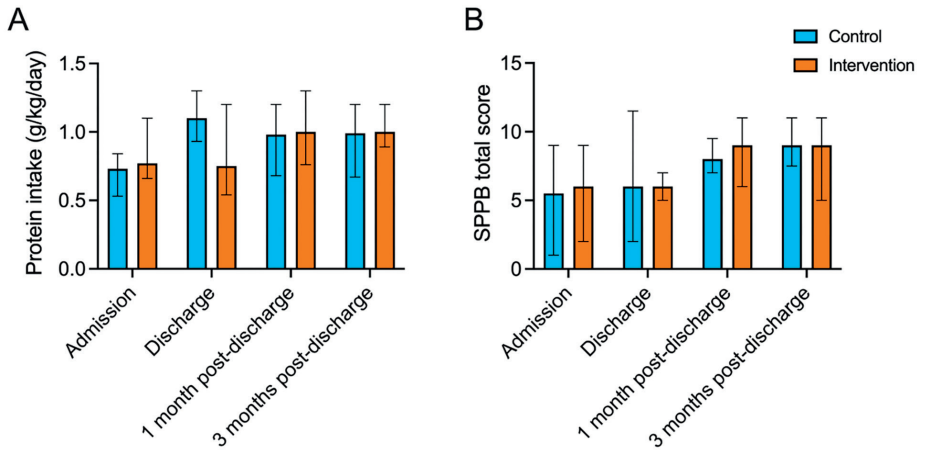

Figure 2. Median and the interquartile range of protein intake (g/kg/day) (A) and Short Physical Performance Battery (SPPB) total score (B) at every time point.

Secondary outcomes

Table 2 shows the effect of the intervention on the secondary outcomes. The average intake of protein increased overtime: 0.7g/kg/d at admission (n=65), 1.0g/kg/d before discharge (n=16), 1.0g/kg/d at one month (n=49) and 1.0g/kg/d at three months post discharge (n=52). Only a few patients in the intervention group were able to increase their protein intake to the recommended 1.2g/kg body weight (n=1, n=8 and n=6 for H3, P1 and P3 respectively). The increase of protein intake over time was not significantly different in the intervention group to the control group (INT P1: +0.04,

95%CI -0.15;0.23, p=0.693; P3: -0.003, 95%CI -0.19;0.18, p=0.975). Handgrip strength, knee extension strength, fat-free mass index, rectus femoris and vastus lateralis ACSA, physical activity, ADL or the EQ-5D health scores yielded no significant differences after intervention compared to the control group (see Table 1 and Table 2).

Table 2. Effects of intensive dietetic treatment on recovery of older patients. The beta reflects the difference between the intervention group and the control group, averaged over time and at each time point.

Outcome	Timepoint	*n*	β	95% CI	p-value
SPPB total score (0-12)	Average over time	128	0.5	-0.8 ; 1.7	0.466
	H3	21	-0.1	-1.9 ; 1.7	0.919
	P1	54	0.6	-0.8 ; 2.0	0.393
	P3	53	0.3	-1.0 ; 1.7	0.623
Repeated chair rise (s)	Average over time	103	-1.0	-3.7 ; 1.7	0.458
	H3	10	3.1	-1.7 ; 7.9	0.204
	P1	47	-1.1	-4.0 ; 1.8	0.462
	P3	46	-2.4	-5.3 ; 0.6	0.115
Handgrip strength (kg)	Average over time	122	-1.1	-3.6 ; 1.5	0.424
	H3	17	-4.6	-8.6 ; -0.6	0.026
	P1	53	-0.3	-3.1 ; 2.4	0.829
	P3	52	-1.1	-3.9 ; 1.7	0.427
Leg extension strength (kg)	Average over time	111	1.5	-1.6 ; 4.6	0.329
	H3	15	3.7	-2.6 ; 10.1	0.249
	P1	49	-0.4	-4.0 ; 3.3	0.845
	P3	47	3.4	-0.4 ; 7.1	0.082
FFMI (kg/m^2)	Average over time	99	0.1	-0.5 ; 0.6	0.757
	H3	13	0.1	-0.8 ; 1.0	0.858
	P1	42	0.3	-0.3 ; 0.9	0.387
	P3	44	-0.1	-0.7 ; 0.6	0.870
FMI (kg/m^2)	Average over time	96	0.2	-0.5 ; 0.8	0.553
	H3	13	1.2	-0.1 ; 2.4	0.065
	P1	39	0.0	-0.8 ; 0.7	0.925

Outcome	Timepoint	*n*	β	95% CI	p-value
	P3	44	0.2	-0.6 ; 0.9	0.639
Protein intake (g/day)	Average over time	118	-2	-12 ; 8	0.706
	H3	17	-18	-38 ; 2	0.071
	P1	49	2	-11 ; 14	0.794
	P3	52	-1	-14 ; 11	0.822
Protein intake (g/kg/day)	Average over time	117	-0.02	-0.17 ; 0.14	0.848
	H3	16	-0.28	-0.58 ; 0.01	0.061
	P1	49	0.04	-0.15 ; 0.23	0.693
	P3	52	0.00	-0.19 ; 0.18	0.975
Protein needs achieved (%)	Average over time	117	-1	-14 ; 12	0.179
	H3	16	-24	-48 ; 1	0.017
	P1	49	3	-12 ; 19	0.376
	P3	52	0	-16 ; 15	0.455
Energy needs achieved (%)	Average over time	117	-8	-20 ; 4	0.848
	H3	16	-27	-49 ; -5	0.061
	P1	49	-6	-20 ; 8	0.693
	P3	52	-5	-19 ; 9	0.975
Barthel Index (0-20)	Average over time	124	-0.2	-0.9 ; 0.4	0.475
	H3	17	-1.0	-2.4 ; 0.4	0.159
	P1	54	-0.3	-1.1 ; 0.5	0.460
	P3	53	0.0	-0.8 ; 0.9	0.959
EQ-5D Index	Average over time	124	-0.1	-0.1 ; 0.0	0.150
	H3	17	0.0	-0.2 ; 0.2	0.962
	P1	54	-0.1	-0.2 ; 0.0	0.088
	P3	53	0.0	-0.1 ; 0.0	0.348
EQ-5D health score (0-100)	Average over time	122	-3	-10 ; 4	0.447
	H3	16	-10	-26 ; 5	0.193
	P1	53	3	-6 ; 12	0.509
	P3	53	-8	-17 ; 1	0.091

Outcome	Timepoint	*n*	β	95% CI	p-value
GDS total score (0-15)	Average over time	115	-1	-2 ; 0	0.109
	H3	17	-1	-3 ; 1	0.227
	P1	50	-1	-2 ; 1	0.363
	P3	48	-1	-3 ; 0	0.081
Appetite (NRS, 0-100)	Average over time	121	1.4	-7.8 ; 10.6	0.767
	H3	16	-16.3	-33.1 ; 0.6	0.058
	P1	54	6.1	-4.4 ; 16.6	0.257
	P3	51	1.5	-9.1 ; 12.2	0.779
Pain (NRS, 0-100)	Average over time	121	3.3	-7.4 ; 13.9	0.547
	H3	16	11.4	-13.7 ; 36.5	0.375
	P1	54	3.9	-9.7 ; 17.4	0.575
	P3	51	-1.7	-15.7 ; 12.4	0.815
Fatigue (NRS, 0-100)	Average over time	121	-4.0	-16.2 ; 8.2	0.523
	H3	16	-5.0	-31.5 ; 21.5	0.710
	P1	54	1.4	-13.2 ; 16.0	0.854
	P3	51	-9.3	-24.4 ; 5.8	0.227
Fear of falling (NRS, 0-100)	Average over time	121	4.9	-9.5 ; 19.3	0.506
	H3	16	-2.7	-26.0 ; 20.5	0.819
	P1	54	7.2	-8.4 ; 22.8	0.368
	P3	51	3.0	-13.0 ; 19.0	0.716
Activity (steps/ day)	Average over time	68	-1871	-4907 ; 1164	0.227
	H3	10	-709	-4896 ; 3477	0.740
	P1	32	-2938	-5796 ; -80	0.044
	P3	26	-2499	-5672 ; 673	0.123

*H3: at discharge; P1: one month post-discharge; P3: three months post-discharge; CI: Confidence Interval; SPPB: Short Physical Performance Battery; FFMI: Fat-Free Mass Index; FMI: Fat Mass Index; GDS: Geriatric Depression Scale; NRS: Numeric Rating Scale

Delivery of intervention

During hospital stay 51% (n=19) of patients in the control group received a consultation of a dietitian as part of regular care. Of these 19 patients, 32% (n=6) also received dietetic treatment in the three months post discharge. In the intervention group, 55% (n=18) of the patients stayed in hospital long enough to receive dietetic treatment during their stay (median 6.9 days (IQR 4.0-9.4)). A total of 27 patients were handed over to the primary care dietitians, whom 24 completed the study. In the intervention group, 41% (n=11) of the patients started their dietetic treatment at home due to short hospital stay.

Within the intervention, dietitians spend a median of 90 minutes (IQR 60-150) over two (IQR 1-3) consultations within the hospital setting. In the three months post-discharge, dietitians spend a median of 263 minutes (IQR 195-345) over 8 (IQR 7-11) consultations. The distribution of treatment time during the three months post-discharge was as follows: 105 minutes (IQR 83-135) over three (IQR 2-4) consultations within the first month post discharge and 150 minutes (IQR 120-210) over six (IQR 4-7) consultations during the second- and third-month post discharge. Every patient within the intervention group received the folder with all supporting materials. Table 3 shows which subjects were discussed and which of the supporting materials were used by dietitian during the consultations with the patient within the intensive dietetic treatment. In Supplementary File 1, the treatment goals are shown.

Table 3. Discussed subjects and used materials by the dietitian during the intensive dietetic treatment as indicated by the dietitians themselves.

	During hospital stay (n=16)	During first month post discharge (n=24)	During second and third month post discharge (n=25)
Discussed subjects			
General nutrition	16 (100%)	22 (92%)	22 (88%)
Importance protein intake	16 (100%)	23 (96%)	23 (92%)
Importance exercise	8 (50%)	20 (83%)	22 (88%)
Alignment nutrition and exercise	11 (69%)	20 (83%)	18 (72%)
Product choices	14 (88%)	22 (92%)	21 (84%)
Appetite	14 (88%)	10 (42%)	15 (60%)
Others	3 (19%)	5 (21%)	6 (24%)
Used materials			
Knowledge clip 'Protein & Exercise'	3 (19%)	3 (13%)	4 (16%)
Infographic 'Protein & Exercise'	1 (7%)	4 (17%)	5 (20%)
Hospital or practice' own material	12 (75%)	10 (42%)	16 (64%)
'EiFIT' application	2 (13%)	5 (21%)	2 (8%)
'Rate-a-plate' dietary registration	0	1 (4%)	3 (12%)
Outcomes of measurements	2 (13%)	5 (21%)	9 (36%)
Study Information folder	13 (82%)	20 (83%)	21 (84%)
Activity based on PAM	0	2 (8%)	3 (12%)
Positive health	0	0	2 (8%)
Other	0	1 (4%)	2 (8%)
Actions taken			
Advised changes in intake	15 (94%)	22 (92%)	23 (92%)
Start or changes in ONS	3 (19%)	9 (38%)	13 (52%)
Start tube feeding	0	0	0
Consult other disciplines already involved	1 (6%)	0	0
Start involvement of other discipline	0	0	1 (4%)
Protein rich snack	2 (13%)	1 (4%)	1 (4%)

DISCUSSION

We hypothesized that intensive dietetic treatment in hospitalized older adults at risk of malnutrition would improve their physical functioning and protein intake. Despite the improvement by all patients after hospital admission and discharge, the physical functioning and protein intake did not reach recommended levels. All secondary outcomes improved over time for all patients, except for fear of falling, leg extensor size and strength, and body composition.

The improvement in physical functioning is in line with the observational Hospital-ADL study in acutely hospitalized older adults (19). Thus, within current regular care, our study showed that improvement of physical functioning and protein intake is possible. However, 58% of the patients did not reach the recommended levels. A low physical functioning is associated with a higher risk of disabilities in activities of daily living, hospital readmission and institutionalization, and mortality (20, 21). This shows that there still is need for interventions that can further improve the physical functioning and protein intake. The intensive dietetic treatment of our study was based on the success of previous studies like the exercise study of Martinez-Velilla and colleagues and the EFFORT trial with individualized nutritional support (2, 22). In addition, the intervention co-designed with care professionals involved with the treatment of malnutrition in the older patient. We expected therefore, that the intensive dietetic treatment would be able to further improve the physical functioning and protein intake of the older patients, compared to the patients within regular care. The differences between our study and those of Martinez-Velilla and Schuetz was the shorter length of hospital stay (median of 4 days), which made it difficult to perform the intervention during hospital stay.

The intervention was constructed in such a manner that the dietitians treating the patients within the intervention were still in control of the content of the treatment sessions. The dietitians performing the intervention were trained on how a different approach towards patients at risk of malnutrition could look like (i.e. interdisciplinary collaboration, use outcomes of measurements to adjust treatment, make use of ONS to increase protein intake, among others). However, we were unable to have a distinct difference in the treatment of the intervention group

compared to the control group post discharge, due to low adherence to the intervention by the trained dietitians. For example, despite the intensive dietetic treatment, only 33% of the patients in our intervention group were able to increase their protein intake to the recommended 1.2 g per kg bodyweight or higher at one-month post-discharge, whereas 24% of the control group was able to reach this level. At three-months post-discharge, this hardly changed (24% in intervention group and 30% in control group). Surveys conducted with the dietitians delivering the intervention revealed that oral nutritional supplements (ONS) or protein supplements were not subscribed often, even when whey isolate powders or ONS were freely available from the research team or through regular prescription reimbursed by health insurance. While studies by Elia and colleagues showed the importance of continuous use of ONS for recovery and readmissions (23, 24). More (qualitative) research is needed on why dietitians might feel hesitant in prescribing ONS or protein supplements in older adults with an acute risk of malnutrition and low protein intake.

The surveys with the dietitians delivering the intervention additionally revealed that in 70-80% of consultations the importance of physical activity and protein intake was discussed with the patient. However, none of the dietitians did consult other disciplines to help the patient to increase their physical activity or referred to the exercise program available in the intervention folder. During focus groups in the designing-phase of the intervention, dietitians indicated that they would like to collaborate more with physical therapists, for example. However, despite the extra treatment time that was spend within the intervention, it did not lead to more collaborations with other care professionals. Possibly there is a hesitancy to act. Further (implementation) research is needed to see how interdisciplinary collaboration can be promoted sustainably. Another point worth mentioning is that the dietitians performing the intervention needed to change work methods and way of treating the patients. This calls for a behavioral change and therefore a strong implementation phase to increase the self-efficacy and skills of dietitians to perform the intensive dietetic treatment. A stepped-wedge design would cater an implementation of such a practical intervention better than a two-arm parallel RCT. With a stepped-wedge, an intervention is implemented gradually and measurements of its effect are only started when full implementation of the intervention is ensured. Although a stepped-wedge design was initially planned for our study, due to the

COVID-19 pandemic, performing this design was not possible as wards within the participating hospitals (clusters within the design) were constantly changing (grouped together or put in complete isolation) (protocol article). In addition, the implementation of our intervention was not optimal due to practical limitations during the COVID-19 pandemic. For example, the training period of involved dietitians was shorter than planned and happened through instruction clips and online meetings. This catered mainly towards increasing their knowledge on how to perform the intervention and not towards increasing their self-efficacy and skills.

Study strength and limitations

A strong aspect of the current study was its multicenter design. By including not only academic, but also teaching and regional hospitals, allowed for possible effects from different hospital settings to be corrected for during the analyses. In addition, to match the current practice of the dietitians, the intervention was co-designed with the care professionals that are involved in the treatment of older patients at risk of malnutrition or sarcopenia. Furthermore, no specific patient groups were selected beforehand, making potential findings from the study to be generalized more easily.

However, several limitations of the current study should be mentioned. Only ~10% of the eligible patients approached by the research staff agreed to participate in the study. Patients who declined participation indicated that they felt too tired or were overwhelmed by the event of hospitalization itself. A commonly heard phrase was *"I have a lot on my mind right now, can you come back when I am back at home and have rested for a few days?"*. The current study design was not flexible enough to cater to these patients, as per protocol the intervention should have started within 48 hours of hospital admission. Future research should allow a more flexible design towards these kind of unforeseen events, which increases the chances for more frail older patients to be able to participate in clinical trials (25). Other important reasons to decline participation was due to the COVID-19 pandemic. Patients were hesitant to participate as they did not want the research team to come to their home for the follow-up measurements, in fear of contamination. Due to the setbacks with the inclusions and high drop-out rate, we were not able to reach the intended sample size. It is therefore difficult to say if

the lack of findings are due to low power or due to absence of effects. Next to the small sample size, the variation in the changes in the SPPB score was larger than expected. The mean differences and standard deviations in SPPB score for the intervention and control group of our study (Δ 3.16±3.62 and 2.25±3.18 respectively), gave us a post-hoc power of 16%. The results should hence be treated with caution. Further, the length of stay of the older adults in hospital was shorter than expected (median of 4 days) leaving only limited time for dietitians within hospital to provide the intervention. This shows that trans-sectorial and interprofessional care is important.

CONCLUSION

In both regular care and intensive dietetic care, older patients improved their physical functioning an protein intake from hospital admission up to three months post discharge, but not to recommended levels. We could not detect any additional effects of the intervention due to non-adherence to the intervention, COVID-19 pandemic limitations and a small sample size. Future research on improving physical functioning and protein intake to recommended levels should focus on an intervention consisting of a strong combination of nutritional support and exercise in an interprofessional setting with a confirmed successful implementation phase and a flexible study design catered to the needs of the older patient.

Supplementary Materials
The following supporting information can be downloaded at: https://www.sciencedirect.com/science/article/pii/S2405457724015523 . Table SF1. Treatment goals, discussed subjects and used materials during the intensive dietetic treatment.

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Conflict of interest
All authors report no conflicts of interest.

Author contribution
CD conceptualization, data curation, formal analyses, investigation, methodology, project administration, visualization, writing original draft; **HK** conceptualization, investigation, methodology, project administration, supervision, writing – review & editing; **ME** methodology, investigation, formal analyses, writing – review & editing; **PW** conceptualization, project administration, methodology, supervision, writing – review & editing; **MT** conceptualization, funding acquisition, investigation, methodology, project administration, writing – review & editing.

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CHAPTER 7

A holistic perspective on malnutrition in older adults: towards an integrated clinical nutrition research guiding framework

Carliene van Dronkelaar,
Maarten R. Soeters,
Philipp Schuetz,
Carla M. Prado,
Nicole Kiss,
Michael Tieland,
Hinke Kruizenga

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ABSTRACT

Malnutrition is a multifactorial and complex condition with significant consequences for recovery, functional outcomes, and healthcare systems. Research in malnutrition is often limited by single-component interventions, heterogeneous study designs, and variable outcome measures. This perspective paper introduces a practical guiding framework for clinical nutrition research, emphasizing interdisciplinary, multifactorial approaches, co-designed interventions, and pragmatic, adaptive study designs. Evidence from several trials demonstrates that individualized nutritional support delivered by multidisciplinary teams improves clinical outcomes, yet challenges remain in recruitment, adherence, and balancing intervention intensity with patient burden. The framework provides a structured approach to intervention development, outcome selection, and implementation, while remaining flexible to accommodate innovation, context-specific adaptation, and emerging outcome measures. By integrating lessons from prior trials, globally, and promoting systematic reporting and feasibility assessment, this framework aims to enhance the design, comparability, and translational impact of future research in clinical nutrition in older and other clinically vulnerable populations. Adoption of such a framework can guide research prioritization, optimize intervention delivery, and ultimately improve patient recovery and quality of life.

Keywords: undernutrition, guiding framework, co-design, interventions, core set outcomes, study design

INTRODUCTION

Malnutrition is common in adults and its prevalence increases with age, affecting more than half of hospitalized, mainly, older patients(1-3). Recently, the World Health Organization recognized malnutrition (also worded as undernutrition) as part of the International Classification of Diseases (ICD)-11 and will become active in 2027(4). If left untreated, it negatively impacts disease progression and health outcomes, including poor physical functioning, increasing dependency, decreased quality of life, and higher mortality(5).

Malnutrition develops from a complex interplay of reduced dietary intake, reduced nutritional assimilation or an increased nutritional demand, each of which may be influenced by medical, psychological, and functional factors. Direct contributors include chewing problems, poor appetite, dysphagia, malabsorption, diarrhea or inflammation. Indirect influences include social isolation, pain, dry mouth, dementia, physical inactivity. Volkert *et al*. synthesized these influences into the *Determinants of Malnutrition in Aged Persons* (DoMAP) model, which illustrates not only the multifactorial origins of malnutrition but also the challenges of designing effective interventions(6).

Research in this field is equally complex. Randomized controlled trials (RCTs) are considered the gold standard in clinical research, but are difficult to apply in nutrition research due to several interrelated challenges(7). First, nutrition is inherently multifaceted, involving food combinations, eating patterns, and nutrient interactions that are difficult to standardize and isolate. Second, strict trial protocols may have limited relevance for routine clinical practice, raising concerns about generalizability. Third, ethical and practical issues arise when restricting nutrition intake or altering patients' eating behaviors, particularly in frail or ill populations. Fourth, meaningful nutritional related outcomes often require long follow-up periods, increasing cost and complexity. Finally, delivering interventions in real-world healthcare is complicated by time limitations, competing priorities, resource constraints, and variability in professional involvement. Together, these factors make traditional RCTs inflexible, resource-intensive, and sometimes unrepresentative of real-world clinical care(7-9).

As shown in a Cochrane review by Baldwin *et al.*, most malnutrition studies are small, heterogeneous in design and inconsistent in outcome reporting, hampering the ability to draw robust conclusions(10). This lack of clear evidence continues to impede effective treatment, raising concerns about the right to adequate nutrition and hydration in clinically vulnerable patients(11).

Considering the DoMAP model and these methodological barriers, it is evident that nutritional interventions cannot rely on single component interventions or rigid designs. Instead, comprehensive, interdisciplinary strategies are needed strategies that address the multiple drivers of malnutrition while also being feasible in diverse healthcare settings. To support this, the present paper proposes a guiding framework for developing, evaluating, and implementing multifactorial malnutrition interventions in older adults. Its development was informed by insights from several studies, each contributing to specific aspects of the framework. Although the primary focus of this framework is developed from malnutrition research in older adults, several of the informing studies involved patient groups such as individuals with lung cancer or chronic disease who, due to high disease burden and functional vulnerability, share similar challenges in nutritional research. Therefore, we use the term 'vulnerable populations' to refer to both older adults and other clinically vulnerable groups. We recommend that future nutrition research adopt this framework when developing new interventions, enabling more robust assessments of both effectiveness and costs. This approach can support the identification and implementation of integrated nutritional care strategies that deliver meaningful outcomes.

THE GUIDING FRAMEWORK FOR OPTIMIZING CLINICAL NUTRITION RESEARCH

Building on the evidence and challenges of malnutrition research and other clinical nutrition research in other vulnerable patient groups, we developed a practical guiding framework to support actions and discissions in the design, delivery, and evaluation of interventions. The framework outlines a sequence of key steps—from stakeholder engagement and study design to intervention delivery and outcome selection—that together promote more integrated and patient-centered approaches. **Figure 1** provides a visual overview of the framework. In the sections below, each step of the framework is described in more detail.

The presented guiding framework aligns with the updated Medical Research Council framework for developing and evaluating complex interventions(12). The MRC framework emphasizes the articulation of a program theory, explicit consideration of context and key uncertainties, robust stakeholder engagement, iterative refinement and economic and sustainability considerations. Applying these principles to clinical nutrition research ensures that interventions are not only scientifically sound but also feasible, scalable and relevant in real-world clinical practice.

Start – Begin with Participatory Action Research and co-design
Before planning and designing a new intervention for clinical nutrition, issues specific to certain healthcare systems, local resources and cultural practices should be identified(12). This could be done with participatory action research (PAR). This approach brings relevant stakeholders such as patients, caregivers, healthcare professionals and policy makers together to co-develop the intervention. Which ensures that this new intervention is both evidence-based and contextually applicable, and is in line with the MRC framework(12). Stakeholder involvement may take the form of co-creation, co-design, or co-production(13). The alignment of treatment components and their delivery methods with the specific needs and traits of various subgroups is important. For example, intervention delivery may differ between acutely ill patients, chronically ill patients, and those in the perioperative phase. PAR therefore helps to implement the new intervention in the real-world setting from the starting stages which supports sustainability(8, 14, 15). Adequate evaluation and reporting of the co-design process are essential to inform and guide future studies(13).

Step 1 – Selection of the optimal research design

Given the complexity of clinical nutrition research in older adults, traditional RCTs are often too rigid to capture the multifactorial nature of malnutrition and its treatment(16). Alternative study designs such as stepped-wedge, pragmatic, and adaptive designs are better suited to real-world contexts(7).

Stepped wedge design: This design sequentially implements the intervention across different groups over time, ensuring that all study sites ultimately receive it. It provides both control and intervention conditions within the same study, which is particularly advantageous in clinical settings where permanently withholding an intervention may be unethical or impractical. In addition, stepped wedge trials allow evaluation of a new model of care where the intervention is embedded within the systems of the health care facility, which is challenging in traditional RCTs.

Pragmatic design: Pragmatic trials are designed to test interventions in real-world conditions rather than under strict experimental controls. This approach allows researchers to assess the effectiveness of a nutrition intervention in a broader, more diverse patient population, reflecting routine clinical practice and increasing adherence, and generalizability of results.

A complementary approach is Target Trial Emulation (TTE), as described by Hernán and Robins(17). The TTE framework applies the principles of randomised trial design to the analysis of observational data, explicitly specifying the target population, intervention, comparison, outcomes and follow-up as if a randomized trial had been conducted(18). This method enables researchers to estimate causal effects using real-world data while maintaining methodological rigor and transparency. The TTE framework can complement pragmatic designs through high-quality analyses of routinely collected data.

Adaptive design: Adaptive trials enable modifications to the study protocol based on interim data, allowing researchers to adjust elements such as dosage, intervention groups, or sample size. In clinical nutrition, this flexibility is valuable for addressing variations in patient responses

to dietary interventions and adapting the study as new information emerges.

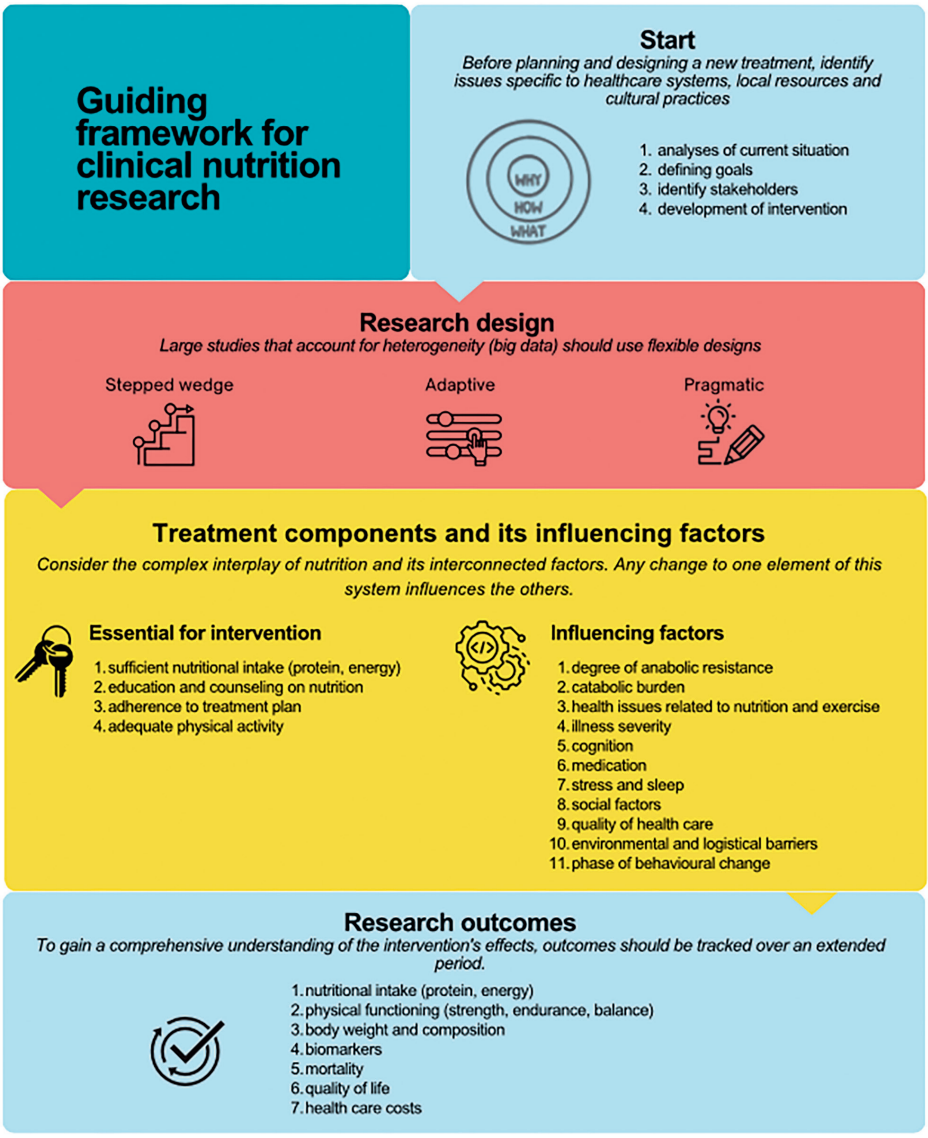

Figure 1. The guiding framework for optimizing clinical nutrition research and treatment.

Selecting the optimal design also requires assessing each site's readiness for implementation, ensuring that infrastructure, staffing, and resources are sufficient to deliver the intervention. When aligned with participatory action research and co-design, these designs allow studies to balance scientific accuracy with feasibility and patient-centeredness.

Step 2 – Treatment components and its influencing factors

While selecting an appropriate study design is critical, the success of any intervention ultimately depends on what is delivered, and which factors shape its effectiveness. Malnutrition in older adults is driven by a complex interplay of biological, psychosocial, and system-level determinants, meaning interventions must address both core treatment components and contextual influencing factors(6). Here it is important to address potential sources of bias and differentiate between exposure (direct targets) and mediators (indirect). Working from a clear logic model that outlines mechanisms of actions, moderators and mediators, as also mentioned by the MRC framework (12). Drawing up directed acyclic graphs (DAGs) can support in visualizing and distinguishing between confounding and mediating and key uncertainties to clarify the assumed causal structure(19).

Core treatment components (direct targets):

- Adequate nutritional intake (energy and protein)
- Nutrition education and counselling
- Adherence to treatment plan
- Adequate physical activity

Influencing factors (indirect, but critical to consider):

- Physiological: anabolic resistance, catabolic burden, illness severity, comorbidities, medication, cognition
- Psychosocial: stress, sleep quality, loneliness, financial status, caregiver support
- System-level: quality of care, reimbursement structures, food access, facility resources
- Behavioral: stage of change in both patients and healthcare professionals

By clearly addressing both treatment components and influencing factors, interventions can be better tailored to the heterogeneity of malnourished older adults, improving feasibility and effectiveness.

Step 3 – Research outcomes

Equally important as the intervention itself is *how its impact is measured*. Because malnutrition affects multiple domains, outcome selection should go beyond narrow nutritional endpoints and capture a broad picture of patient recovery, while also minimizing the burden of participation(6, 7, 20).

Essential outcome domains:

- Nutritional intake (protein, energy)
- Body weight and composition
- Physical functioning (strength, endurance, balance)
- Clinical outcomes (mortality, complications, biomarkers)
- Patient-centered outcomes (quality of life, independence)
- Health system outcomes (hospitalization, length of stay, costs)

Outcome considerations:

- Use composite outcomes in multifactorial interventions to reflect benefits across domains.
- Ensure follow-up is sufficiently long to detect sustainable effects on muscle mass, functional recovery, and behavior change.
- Integrate outcome assessment into routine care to reduce patient burden and improve adherence.
- Where possible, leverage digital health tools for real-time monitoring of diet, activity, and adherence.

Similar critical outcomes were identified for research in older adults in particular, in a large Delphi study by Mendonça and colleagues(21). The outcomes compassed malnutrition status, dietary intake, appetite, body weight or BMI, muscle strength, muscle mass, functional performance, functional limitations, quality of life and the acceptability of the intervention, and can be seen as a Core Outcome Set (COS) but are not limited to these outcomes. This COS can help in selecting outcomes for future malnutrition research and supports and enables comparing across studies. The ongoing project will further reveal appropriate measurements for these outcomes(22).

INSPIRATION FOR THE GUIDING FRAMEWORK

The development of this guiding framework was based on several studies and the research experience of the authors of these studies. **Table 1** summarizes their main characteristics and contributions. A detailed elaboration of the contribution of each study can be found in the **Appendix A**. Together, these studies illustrate the opportunities and challenges of nutrition research in primarily clinically vulnerable patients and older adults and highlight why a structured, yet flexible approach is needed.

The 2021 Cochrane review by Baldwin *et al.* (10) synthesized 94 RCTs with over 10,000 patients. It revealed that most studies were small, heterogeneous, and inconsistent in design and outcome measures. The authors called for adequately powered trials, core outcome sets, stratification by disease severity and care setting, and the use of digital tools to improve adherence and long-term follow-up.

The ProIntens trial (23) evaluated an intensified dietetic intervention targeting adequate protein intake and aiming to improve physical performance in hospitalized older adults at risk of malnutrition. Recruitment was hindered by patient fatigue at admission, and rigid RCT procedures limited flexibility. Although the intervention was grounded in behavioral theory, it primarily targeted patients rather than their environment or the dietitians delivering care, and limited funding reduced multidisciplinary engagement.

The EFFORT trial (24), a large pragmatic multicenter RCT with more than 2,000 participants, demonstrated that individualized nutritional support significantly reduced mortality and complications. Its strengths included a multidisciplinary approach and large sample size, while limitations included a relatively short follow-up period and uncertainty over which intervention components were most effective.

Table 1. Key studies informing the guiding framework.

Study	Population	Design	Key contribution	Link to framework
Cochrane review (Baldwin *et al.* 2021)(10)	94 RCTs (10,284 patients)	Systematic Review	Showed that most trials were small, heterogeneous, with diverse interventions and outcomes; advocated for stratification, core outcome sets, longer follow-up, and digital tools for adherence	Step 1 (design) Step 3 (outcomes)
ProIntens trial (van Dronkelaar *et al.* 2025)(23)	Hospitalized older patients at risk of malnutrition	Multicenter RCT	Experienced recruitment difficulties and attrition; rigid RCT design limited flexibility; behavioral change targeted patients more than environment or staff; limited multidisciplinary involvement due to funding constraints	Step 1 (design) Step 2 (treatment delivery) Step 3 (outcomes)
EFFORT trial (Schuetz *et al.* 2019)(24)	2088 hospitalized patients	Pragmatic RCT	Demonstrated possibilities of pragmatic trials with a treatment algorithm, large sample size and composite outcome	Step 1 (design) Step 2 (treatment delivery) Step 3 (outcomes)
NOURISH trial (Deutz *et al.* 2016)(25)	652 older patients with malnutrition	Double-blind, placebo-controlled RCT	Clear delivery but high exclusion (≈60%) due to comorbidities, limiting generalizability and flexibility to patient needs	Step 1 (design) Step 2 (delivery)
PRIMe trial (Ford *et al.* 2024)(26)	Colorectal patients undergoing chemotherapy	Open-label pilot RCT	Recruitment challenges and high attrition; rigid RCT design and high patient burden limited feasibility; late involvement of stakeholders	Start (co-design) Step 1 (design) Step 2 (treatment delivery)
Lung cancer trial (Kiss *et al.* 2016)(27)	Lung cancer patients undergoing (chemo) radiotherapy	Pilot RCT	Individualised counselling feasible and valued by patients but recruitment difficult (timing at diagnosis, high palliative proportion, 37% attrition)	Start (co-design) Step 1 (design) Step 3 (outcomes)
PREDICT trial (Kiss *et al.* 2024)(28)	Lung cancer patients undergoing (chemo) radiotherapy	Observational	Recruitment <50% of planned sample due to COVID; high burden of measurements led to non-adherence; highlighted feasibility challenges in real-world data collection	Step 1 (design) Step 3 (outcomes)

The NOURISH trial (25) was a double-blind, placebo-controlled multicenter RCT of 652 older inpatients with malnutrition. Specialized high-protein oral nutritional supplements reduced post-discharge mortality, but nearly 60% of screened patients were excluded due to comorbidities. This high exclusion rate limits generalizability and underscores the need for broader eligibility criteria and more flexible trial designs. Moreover, the placebo had a low energy density, making it uncertain whether the observed clinical benefit was due to the specific leucine metabolite (β-hydroxy-β-methyl butyrate, HMB) or simply to the additional energy or protein provided.

The PRIMe pilot trial (26, 29) aimed to test high- versus moderate-protein diets in patients with colorectal cancer during chemotherapy. Recruitment was difficult (<5%) and attrition high, especially in the higher-protein group. Rigid RCT design, COVID-19 restrictions, and burdensome data collection limited feasibility despite intensive dietitian counselling.

The 2016 lung cancer trial (27) tested intensive individualized nutrition counselling during (chemo)radiotherapy. Although adherence and satisfaction were high, recruitment was challenging due to timing at diagnosis, a high proportion of palliative patients, and 37% attrition. These findings highlight the need for pragmatic or adaptive designs and early co-design to reduce participation barriers.

Finally, the PREDICT study (28), an observational study of lung cancer patients undergoing (chemo)radiotherapy, recruited less than half of the planned sample due to the COVID-19 pandemic. The use of 3-day food diaries imposed a high burden, resulting in non-adherence and demonstrating the need for simpler, routine-care–based assessments.

Taken together, these insights informed the guiding framework by demonstrating the value of robust trial design, real-world applicability, interdisciplinary approaches, and patient-centered outcome selection. They also stress the need for pragmatic adaptations in clinical nutrition research to balance methodological rigor with feasibility and generalizability.

CONCLUSION AND FUTURE DIRECTIONS

Drawing together the evidence and insights reviewed above, several key challenges and opportunities emerge for future clinical nutrition research. For example, malnutrition in older adults is a complex, multifactorial health problem and single-component interventions are unlikely to address its diverse causes or support recovery from disease-related malnutrition. Future studies require adopting interdisciplinary and multifactorial approaches with extended follow-up periods in large, heterogeneous study groups.

Stepped-wedge, adaptive and pragmatic trial designs appear most suited to these settings, though they also need larger sample sizes to maintain statistical power(30, 31). Such large-scale trials demand stronger infrastructure and resources for nutrition research. Nevertheless, smaller studies remain valuable, especially for co-design, feasibility testing and the implementation of individual intervention components. To complement pragmatic and adaptive trial designs, researchers should also draw on causal inference frameworks, such as the concept of the 'target trial' and target trial emulation (TTE). The TTE approach can be applied when the optimal design is constrained by ethical or logistical barriers(18). By explicitly defining the population, intervention, comparator, outcomes, timing (PICOT), and then emulating this ideal trial using observational or routine-care data, researchers can better clarify causal effects and identify confounding. However, it is important to be aware of potential sources of bias. To improve validity and interpretability of findings other causal inference frameworks, such as Structural Causal Model (SCM) or Directed Acyclic Graphs (DAG) can be used(19, 32). Open science practices, such as adherence to FAIR (Findable, Accessible, Interoperable and Reusable) data principles and Decentralized Science (DeSci) approaches, can further improve transparency, data sharing and the integration of findings across studies(33, 34).

A model for how a framework could be operationalized is provided by the Canadian REaCT program, which established infrastructure to identify research challenges, harmonize questions and outcomes, and facilitate efficient trials in oncology(35). A similar program in malnutrition could use the framework presented here as a foundation for coordinated, scalable

research, helping to overcome current fragmentation while still allowing flexibility for innovation and context-specific adaptation.

Embracing this practical guiding framework can transform malnutrition research from isolated efforts into a coordinated, innovative field that accelerates discovery and improves outcomes for patients.

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Author contributions
Carliene van Dronkelaar: conceptualization, writing – original draft, visualization, project administration; **Maarten Soeters:** conceptualization, writing – review & editing, supervision; **Philip Schuetz:** conceptualization, writing – original draft; **Carla Prado:** conceptualization, writing – original draft; **Nicole Kiss**: conceptualization, writing – original draft; **Michael Tieland:** writing – review & editing; **Hinke Kruizenga:** conceptualization, writing – review & editing, visualization, supervision, project administration. All authors approve of the final version to be published and agree to be accountable for all aspects of the presented work. No one eligible for authorship has been excluded from the list of authors.

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We have the following interests to declare: The Institution of P. Schuetz has previously received unrestricted grant money unrelated to this project from Neste Health Science and Abbott Nutrition.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve structure and clarity of the manuscript. AI was not used to generate content. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Figure caption

Figure 1. The guiding framework for optimizing clinical nutrition research and treatment.

Figure 1 shows a guiding framework to support the design, delivery, and evaluation of interventions. The framework outlines a sequence of key steps—from stakeholder engagement and study design to intervention delivery and outcome selection—that together promote more integrated and patient-centered approaches.

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APPENDIX A.

Cochrane review (2021)

Study aim: In the Cochrane review of Baldwin et al (2021), a total of 94 RCTs with 10,284 patients were included.(7) These studies addressed disease-related malnutrition across various healthcare settings and compared dietary advice, with or without oral nutritional supplements (ONS), to no advice, ONS alone or dietary advice alone.

Recruitment and design: The review highlighted that malnutrition occurs across several health care settings, introducing heterogeneity into the study populations. The authors suggested that populations should be stratified based on disease types, severity of malnutrition and care settings to identify subgroup-specific effects of interventions. Achieving this level of stratification, however, requires more adequately powered trials (framework step 1). In addition, they recommended conducting nutrition research in diverse geographic and socioeconomic contexts to understand the impact of cultural, dietary and health care differences on malnutrition interventions. To achieve this, these contextual factors should be integrated into study design and considered in the analysis of intervention effects (framework step 3).

Outcome selection and duration: There was a large diversity in outcome measures among the 94 RCTs. These inconsistencies hinders the ability to draw definitive conclusions about intervention effectiveness. The authors advocated for the establishment of a core outcome set for nutrition-related trials, focusing on clinically relevant and patient-centered outcomes (framework step 3).

The duration of included studies varied, with some lasting as short as one month. Short-term studies may not capture the long-term effects of nutritional interventions, such as changes in body composition. Therefore, longer-term studies should be designed to evaluate sustained benefits or potential risks (framework step 3).

Furthermore, the authors of the Cochrane review advise utilizing promising technologies such as digital health tools for dietary and physical activity monitoring and adherence. Advanced methodologies can address limitations in data accuracy and participant adherence.

These digital tools can also support in capturing the long-term effects through consistent, real-time monitoring and follow-up.

ProIntens trial (2025)

Study aim: The ProIntens trial aimed to evaluate the impact of an intensified transmural dietetic intervention on physical functioning and dietary protein intake of hospitalized older patients at risk of malnutrition. (14) The study was designed as a parallel 2-arm randomized controlled trial. The intervention started within 48 hours of hospitalization to target the acute nutritional status of the patients and followed the participants up to three months post-discharge.

Recruitment and design: The study experienced difficulties in recruiting enough older patients to assess intervention effectiveness. Potentially eligible patients declined participation due fatigue at the time of inclusion. Due to the RCT design, there was no flexibility to include these patients later during their recovery or to offer them an adjusted intervention. Although originally designed as a stepped-wedge design, the COVID-19 pandemic made this design infeasible, as the clusters (hospital wards within the Netherlands) were constantly changing. These changes posed a threat to the statistical power of the study. A pragmatic design might have been better suited to account for such unforeseen events during the pandemic and to allow older patients to participate at their own pace (framework step 1).

Intervention delivery: The ProIntens intervention attempted to target several factors associated with malnutrition in older patients, with a main focus on protein intake. To match as closely to the real world as possible, the intervention was set up to be delivered by trained dietitians in both hospital and primary care settings. Although the intervention was based on behavioral change theories, these primarily targeted the patients themselves, with less emphasis on the surrounding environment or the dietitians delivering the intervention. Limited funding to support dietitians in modifying their routine practices also contributed to low adherence to the intervention. This shows that, in a real-world settings, greater time and budget are needed to support those responsible for implementing the intervention. A more pragmatic approach to determining when to begin measuring the intervention's effects could further enhance its feasibility (framework step 1).

Although the ProIntens intervention was designed to address several components of malnutrition (framework step 2), the RCT structure and budget constraints allowed only for the active involvement of dietitians. However, to be able to really support older adults in several components of malnutrition, a multidisciplinary approach is needed. Short meetings between all involved care professionals could facilitate this. Yet due to differences in reimbursement between hospital and primary care and between discipline within primary care, this is difficult to achieve.(26)

Outcome selection and duration: In addition to targeting several components of malnutrition, the ProIntens trial included numerous measurements and questionnaires to evaluate the intervention's effects. Some measurements assessed overlapping outcomes. For example, muscle mass was measured with both the Bioelectrical Impedance Analyses (BIA) and with 2D Ultrasound, and muscle strength was measured with handgrip and knee extension strength. While comparing these methods in the study population was scientifically valuable, the additional assessments may have been too demanding for older patients. Outcome measures should therefore be carefully selected to capture the effects of the intervention while considering the physical and cognitive limitations of older patients (framework step 3).

A careful selection of outcomes is essential, not only to assess relevant effect of the intervention, but also to ensure they are manageable for older patients. In addition, the ProIntens trial used only one primary outcome. For multifactorial intervention studies, a composite outcome may be more appropriate, as it captures a range of potential benefits across different patients. However, the use of composite outcomes often requires larger sample sizes to ensure adequate statistical power and to detect meaningful effects across multiple domains. In addition, the follow-up period should be long enough to detect meaningful changes in all relevant outcomes (framework step 3). The ProIntens trial had a follow-up period of 3 months post-discharge, which made it possible to assess the transition from hospital to the home setting. However, this duration could have been insufficient to detect changes in all outcomes such as muscle mass, sustainable dietary changes or behavioral changes.

EFFORT (2019) and NOURISH (2016)

Study aim: There are two important large-scale trials focusing on the inpatient medical ward, with important differences in study design: EFFORT (15) and NOURISH (16). EFFORT (*Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial*), was a pragmatic, non-blinded, randomised controlled multicenter trial in Switzerland. The EFFORT trial evaluated the impact of individualized nutritional support designed to meet patients' energy, protein, and micronutrient needs, compared to standard hospital meals.(27) The primary endpoint was a composite measure of severe complications, including mortality, ICU admission, cardiovascular and gastrointestinal events, functional decline, and hospital readmission. The results demonstrated that the nutritional intervention significantly reduced the risk of mortality, with a number needed to treat (NNT) of 37. The NOURISH trial was a multicenter, double-blinded, placebo-controlled trial. The trial assessed the impact of specialized, protein-rich oral nutritional supplements versus placebo on clinical outcomes in hospitalized older patients with malnutrition, across multiple centers in the United States.(16) Their primary outcome was a composite of 90-day post discharge incidence of death or nonelective readmission. They found a comparable beneficial effect on mortality risk as the EFFORT trial (NNT = 20).

Recruitment and design: The EFFORT trial was able to include over 2,000 medical patients at risk of malnutrition, while the NOURISH was able to enroll 652 patients. Both trials initiated recruitment through systematic screening for malnutrition risk, followed by a multidisciplinary assessment involving dietitians, nurses, and physicians to confirm malnutrition. Both studies used regular screening for malnutrition to identify patients eligible for inclusion, allowing for broad range of patients to be included. In addition, both studies used dedicated research staff for screening, assessment and intervention delivery. A major challenge illustrated by the NOURISH trial was the exclusion of nearly 60% of screened patients due to comorbidities, which limits generalizability to real-world populations of older, multimorbid patients. High exclusion rates could be reduced by using broader eligibility criteria and pragmatic or adaptive study designs (framework par 1). Pragmatic designs allow researchers to evaluate effectiveness in routine care, reducing exclusions that arise from tightly controlled RCTs. Adaptive study designs could allow interim assessments

of safety and feasibility, enabling broader inclusion at later stages. In addition, these designs allow for adjustment of the intervention for patients with conditions such as renal impairment or diabetes mellitus. By shifting from carefully defined "ideal" trial populations to those more reflective of routine care, nutrition research can generate findings that are both clinically relevant and broadly applicable.

Intervention delivery: In the EFFORT-trial, the intervention was based on patient specific targets within a pragmatic treatment algorithm. Nutrition strategies were escalated from fortified meals and oral nutritional supplements to enteral or parenteral feeding when necessary, under dietitian-guided monitoring (see **Figure A1**). The patient specific targets allowed for adjustment of the protocol towards patients with kidney failure. This approach ensured that the intervention remained manageable for patients and increased adherence but does asks for dedicated and well trained (research) staff for continuous monitoring and to adjust the nutritional plan to ongoing changes on patients levels.

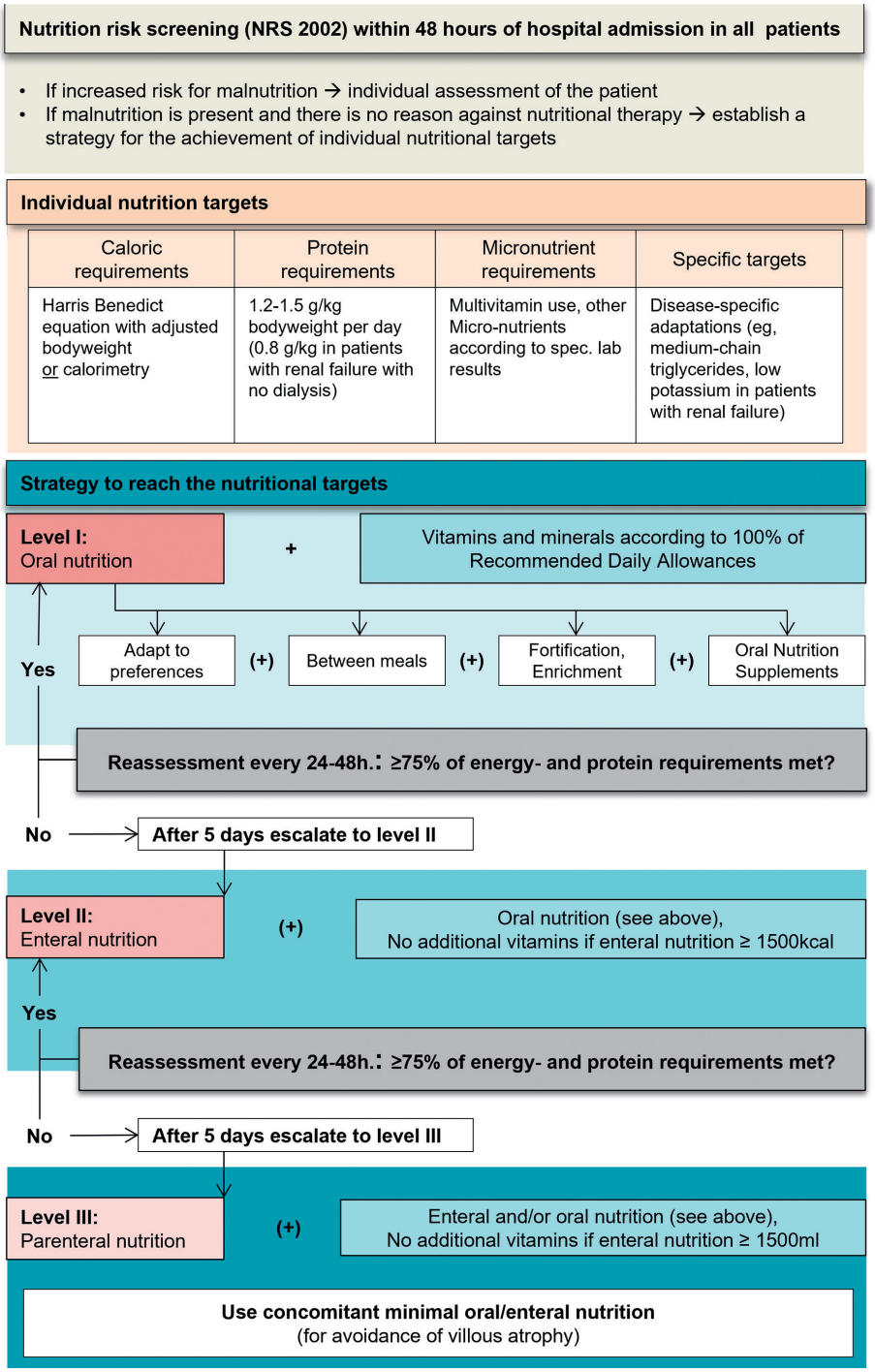
The clear set-up of the intervention in the NOURISH-trial (standard care plus study product or placebo) made it straightforward for patients and easy to deliver for healthcare professionals. But it is harder to adjust towards the needs for the patient and it only targets one of the treatment components being adequate nutritional intake (framework part 2).

Outcome selection and duration: The primary endpoint of EFFORT trial was a composite outcome including all-cause mortality, ICU admission, major complications, hospital readmission and functional decline in the 30 days after hospital admission. The large sample size allowed for enough statistical power for further analyses on different aspects of this composite outcome. Another strong point is that these outcomes are mainly assessed within regular care and are therefore not an additional burden for patients. The composite endpoint did not cover the complete picture of potential effects the intervention could have on the patients and the follow-up duration of 30 days post hospitalization could be considered mid-term. A longer follow-up could capture a more complete understanding of functional recovery and quality of life, which was done in secondary analyses.(28) Still, the composite endpoint and follow-period did allow for additional analyses on cost-effectiveness.(29) The endpoint of the NOURISH trial was 90-day all-cause mortality or nonelective

readmission, which covers a longer period. There were some additional secondary outcome measurements such as length of stay, readmission and activities of daily living (ADL), however they do not fully capture the effects on the trajectory of recover (framework part 3).

The main strength of EFFORT were its large sample size, adequately powered for a clinical endpoint, the multidisciplinary approach and the extensive data collection, which enabled post-trial analyses of costs, protein and biomarker subgroups, and the long-term effects of nutrition.(28-30) However, limitations included a relatively short follow-up period and it remains uncertain which specific component of the intervention contributed most to the observed effects. For NOURISH, the main strength was its placebo-controlled multicenter design, and the relatively large sample size. A limitation of the trial was the limited generalizability (hospitalized older adults with pulmonary or cardiovascular conditions) raising concerns about selection bias, and the notable rate of early discontinuations. However, regarding the latter, because most participants who discontinued still contributed outcome data (through post-exit follow-up), the risk of bias was minimized. Similar to the EFFORT trial, the combined components of the intervention made it difficult to determine what contributed most to the found effects.

Figure A1. A pragmatic treatment algorithm for managing malnutrition in hospitalized patients from Schuetz et al. 2019(15)



Protein Recommendations to Increase Muscle – PRIMe Study (2021)

Study aim: The Protein Recommendations to Increase Muscle (PRIMe) trial was a single-center, two-arm, open-label, randomized controlled pilot trial.(17, 20) It aimed to assess the feasibility of prescribing either 1.0 or 2.0 g/kg/day protein diets over 12 weeks in patients with stage II–IV colorectal cancer (non-cachectic) undergoing chemotherapy. The primary endpoint was to evaluate the feasibility of achieving these protein targets and their preliminary effects on muscle mass (via appendicular lean soft tissue as surrogate for muscle mass) and physical function.

Recruitment and design: PRIMe experienced a very low recruitment rate (<5%). Many patients declined participation due to being overwhelmed by a recent cancer diagnosis or the perceived burden of the study protocol. Moreover, attrition disproportionately affected the higher-protein group (2.0 g/kg/day), with 8 out of 10 dropouts occurring in this arm. The study's rigid design and intensive requirements likely contributed to these difficulties. Importantly, recruitment was also substantially impacted by the COVID-19 pandemic. Canada implemented strict public health restrictions during the study period, and institutional policies at the University prohibited unvaccinated individuals from entering campus facilities, further narrowing the eligible participant pool and limiting flexibility in data collection. These challenges highlight the need for more adaptive and pragmatic research designs, particularly in vulnerable patient populations and under restrictive external conditions (framework part 1).

Intervention delivery: Although the intervention included individualized dietitian-led counselling, weekly phone check-ins, and protein powder or pre-cooked meat when needed, adherence was variable. Only 35.3% of patients in the 2.0 g/kg/day group achieved their target by week 12, and there was contamination across groups, with some participants in the 1.0 g/kg/day group reaching higher intakes. The practical burden of weighing food, recording intake, and adjusting diets in real-time was high, and side effects (e.g., nausea, fatigue, ostomies) often interfered with food intake.

Patients were required to complete multiple weighed 3-day food records, attend in-person assessments, and respond to weekly 24-hour dietary recalls. Many found this burdensome, especially when dealing with cancer treatment side effects like fatigue or appetite loss. These demands may

have contributed to dropouts and limited generalizability (framework Start).

Outcome selection and duration: The primary outcome was feasibility of dietary adherence and maintenance of muscle mass, while secondary outcomes included physical function and protein intake changes. Although improvements were noted in protein intake and trends toward muscle maintenance, statistical significance was not achieved for group differences in muscle mass or physical function. This may be attributed to the limited sample size, as the study was designed as a pilot and not powered for these comparisons. Moreover, the 12-week duration may have been insufficient to detect more robust changes, particularly given the variability in treatment response and disease trajectory. Nonetheless, the maintenance of muscle mass itself represents a positive and promising finding, reinforcing the potential value of targeted nutritional interventions during cancer treatment.

The PRIMe trial illustrates both the strengths and limitations outlined in the proposed guiding framework for optimizing malnutrition research. It effectively incorporated key elements such as individualized nutritional counselling, protein-targeted interventions, behavioral support, and advanced outcome assessments, including qualitative evaluation.(31, 32) These features align with the framework's emphasis on patient-centered and comprehensive strategies. However, the trial also faced several challenges—particularly low recruitment, high burden, rigid RCT design, lack of early stakeholder engagement, and no long-term follow-up. These barriers, compounded by the context of cancer treatment, underscore the need for more pragmatic, flexible, and scalable nutrition interventions, as advocated in the framework.

Lung Cancer Trials (2016, 2024)

Study aim: A 2016 trial in patients receiving curative intent (chemo) radiotherapy for lung cancer aimed to evaluate the effect of intensive nutrition counselling on nutritional status, functional outcomes and quality of life.(18) The study was designed as a randomized controlled trial comparing the intervention to usual care within a radiotherapy outpatient setting of a metropolitan cancer center. The intervention involved individualized dietary counselling starting a week prior to treatment and continuing through to six weeks following treatment completion. The

intervention was designed to be pragmatic, delivered by dietitians, in person and via telephone, and guided by a care pathway, which outlined the timing and frequency of individualized counselling. The challenges of conducting such studies in patients with lung cancer is well established.(33) The more recent PREDICT study (Predicting Muscle Loss During Lung Cancer Treatment) study(19) was an observational study examining factors associated with muscle loss in patients with lung cancer receiving (chemo)radiotherapy.

Recruitment and design: This study experienced challenges in participant recruitment, having originally planned to recruit a larger sample to evaluate the effectiveness of the intervention and then pivoting to a feasibility study due to recruitment issues. The timing of the start of the intervention meant potential participants were approached about participation at a time they were relatively newly diagnosed with lung cancer and amid decisions regarding optimal treatment options. Although many patients recognized the importance of nutrition as part of their care, the overwhelming nature of this time period proved to be a burden for participation in the trial. Furthermore, a high proportion (68%) of patients who were screened for eligibility were planned for palliative treatment, rendering them ineligible for inclusion. In addition, attrition was 37% over the duration of the 12-week intervention for reasons including disease progression, treatment discontinuation and loss to follow up. A pragmatic and adaptive study design may have enabled inclusion of patients planned for palliative treatment as well as those planned for curative intent treatment (framework part 1).(4) Alternatively, a stepped wedge design in which the care pathway was embedded as a new model of care within the clinical setting may have improved recruitment and allowed patients to benefit from the new model of care and lessened the perception of being asked to do more than usual care.

Intervention delivery: Notably, adherence and patient reported satisfaction with the intervention were high, indicating once patients were involved in the study, they perceived a benefit and overcoming barriers to participation is critical. For this patient group who are known to experience a high burden of disease, co-design of nutrition interventions is likely to be particularly important (framework Start and part 3).

Similar challenges were faced in the more recent PREDICT study in the same patient group. Although not an interventional study, challenges with recruitment amid the COVID pandemic led to recruitment of less than 50% of the planned sample despite recruiting across three cancer services.

Outcome selection and duration: A further factor contributing to the burden of participation in the 2016 trial, was the time required for collection of study outcomes in addition to the dietary counselling delivered for the intervention and the already high number of appointments for treatment and medical care. Utilizing data collected within routine care would further minimize the burden of participation, however this makes the collection of robust dietary intake data unlikely (framework part 3). In the PREDICT trial, dietary intake was assessed with 3-day food diaries, however due to the burden of this method, non-adherence was high.

PART III

BROADENING THE PERSPECTIVE: EXPANDING NUTRITIONAL CARE IN AGING POPULATIONS

CHAPTER 8

Minerals and Sarcopenia; The Role of Calcium, Iron, Magnesium, Phosphorus, Potassium, Selenium, Sodium, and Zinc on Muscle Mass, Muscle Strength, and Physical Performance in Older Adults: A Systematic Review

Carliene van Dronkelaar,
Aafke van Velzen,
Maya Abdelrazek,
Anouk van der Steen,
Peter J.M. Weijs,
Michael Tieland

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ABSTRACT

Introduction: Minerals may contribute to prevent and treat sarcopenia, the age-related loss of muscle mass, muscle strength, and physical performance. So far, there is no comprehensive review on the impact of minerals on sarcopenia outcomes. The aim of this systematic review is to evaluate the role of calcium, iron, magnesium, phosphorus, potassium, selenium, sodium, and zinc on muscle mass, muscle strength, and physical performance in older adults.

Methods: A systematic search was conducted between March 2016 and July 2016, in the PubMed database using predefined search terms. Articles on the role of dietary mineral intake or mineral serum concentrations on muscle mass, muscle strength, physical performance, and/or the prevalence of sarcopenia in healthy or frail older adults (average age ≥65 years) were selected. Only original research publications were included. The search and data extraction were conducted in duplicate by 2 independent researchers. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was followed in constructing this systematic review. The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies was used to evaluate the quality of the selected articles.

Results: From the 3346 articles found, a total of 10 studies met the inclusion criteria. Observational studies showed that serum selenium (n = 1) and calcium intake (n = 1) were significantly associated with muscle mass, and magnesium (n = 1), selenium (n = 1), iron (n = 1), and zinc (n = 1) intake were significantly and positively associated with physical performance in older adults. Furthermore, magnesium (n = 2), selenium (n = 2), calcium (n = 2), and phosphorus (n = 1) intake were associated with the prevalence of sarcopenia. Magnesium supplementation improved physical performance based on one randomized controlled trial. No studies on the role of sodium or potassium on muscle mass, muscle strength, or physical performance were found.

Conclusion: Minerals may be important nutrients to prevent and/or treat sarcopenia. Particularly, magnesium, selenium, and calcium seem to be most promising. Most of the included studies, however, were observational studies. Therefore, more randomized controlled trials are

needed to elucidate the potential benefits of mineral intake to prevent and/or treat sarcopenia and support healthy aging.

INTRODUCTION

Aging is associated with sarcopenia, the age-related loss of muscle mass, muscle strength, and physical performance.[1] This loss is associated with dependence, poor quality of life, hospital admission, and premature death.[2] The cause of sarcopenia is multifactorial and includes poor nutritional intake.[3,4] The role of dietary protein and the development of sarcopenia has obtained most attention. Minerals, however, may be important nutrients that can contribute to the prevention and treatment of sarcopenia, but are poorly studied.[5]

It is known that several minerals play a role in muscle metabolism and muscle function. For example, calcium, potassium, and sodium are necessary for healthy muscle and nerve activity, and magnesium is thought to have a positive effect on muscle relaxation and could improve muscle function.[6-9] Low iron blood serum concentrations are thought to be associated with poor physical performance.[10] A lack of phosphorus can lead to muscle weakness,[11,12] whereas selenium deficiency is associated with several muscular diseases.[11-15] Zinc is able to delay oxidative processes, which are known to contribute to disuse muscle atrophy.[16-18]

Although it is clear that these minerals play an important role in muscle functioning, a comprehensive overview of their possible effects on sarcopenia outcomes in older adults is lacking. Therefore, the aim of this systematic review is to evaluate the role of calcium, magnesium, iron, sodium, potassium, phosphorus, selenium, and zinc on muscle mass, muscle strength, and physical performance.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was followed in constructing this systematic review.[19] The PRISMA checklist can be found in Supplemental Material 1.

Search Strategy and Selection

A systematic search in PubMed has been performed between March and July 2016, using predefined search terms deducted from the eligibility criteria. The complete search has been performed in duplicate by 2 independent researchers. Title and abstract were screened for eligibility according to predefined inclusion and exclusion criteria. If eligible, the full-text articles were screened for final inclusion. In addition, a manual search of reference lists of included and other relevant articles has been performed to increase the number of potentially usable articles. In case of discrepancy between inclusion of an article, the 2 investigators discussed the selection until agreement was reached. A standardized data extraction form has been used to summarize the information from the selected articles. A complete overview of the search can be found in Appendix 1.

Eligibility Criteria

The following inclusion criteria were used:

- Publishing date between 2006 and 2016
- Published in the English language
- Studying a human population with an average age of ≥65 years
- Studies on dietary intake or blood serum concentrations of calcium, iron, magnesium phosphorus, potassium, selenium, sodium, and zinc on muscle mass, muscle strength, physical performance, and sarcopenia of any definition
- Muscle mass measured with computed tomography, dual energy X-ray absorptiometry, magnetic resonance imaging, whole-body air plethysmography, bio impedance analysis (BIA), or dual photon absorptiometry
- Muscle strength measured with either hand grip strength, knee/leg extension, leg pressure strength, or elastic bands
- Physical performance measured with Short Physical Performance Battery (SPPB), chair stand, balance test, gait speed test, 400-m walk test, 6-minute walk test (6MWT), or Timed-Up-and-Go test

No criteria were established for study design, the length of follow-up, or the minimal number of participants. Intervention studies that included other macro- and micronutrients than the minerals of interest, exercise, or studies that included subjects with a disease that influences protein synthesis, muscle strength, muscle mass, or physical

performance such as muscle disorders, neoplasms, heart failure, cirrhosis, HIV, renal insufficiency, chronic obstructive pulmonary disease, and hyperparathyroidism were excluded.[20-27] Studies evaluating hyponatremia were excluded, because hyponatremia can be achieved independent of sodium intake, for example, because of vomiting. Studies evaluating regular or high blood concentrations of sodium were still of interest. Studies published as letters, commentaries, editorials, case reports, systematic reviews, or duplicate publications from the same studies were also excluded.

Quality Assessment

The Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies was used to evaluate the quality of the selected articles.[28,29] Articles were reviewed for risk of bias, study design, confounders, method of blinding, data collection methods, and withdrawals. No additional action was taken upon evaluation outcome.

RESULTS

A total of 3346 articles were identified. After removing duplicates, 2775 articles remained, of which 2727 were excluded after title and abstract screening. The remaining 48 articles were screened on full text, of which 10 studies met the eligibility criteria. A full overview of the selection of articles is summarized in Figure 1.

Study Characteristics

Details of the 10 studies are provided in Table 1. The average age ranged from 66.5 to 76.5 years and 55% of the subjects was female. All studies included community-dwelling older adults. In total, 1 randomized controlled trial,[30] 1 longitudinal study,[31] 1 case-control,[39] 1 cohort,[32] and 6 cross-sectional studies[33-38] were included.

Dietary calcium was evaluated by 5 studies,[33,36-39] dietary iron by 1,[33] serum iron by 1,[31] dietary magnesium by 3,[30,38,39] dietary phosphorus by 1,[32] dietary selenium by 4,[32,34,38,39] serum selenium by 1,[35] and dietary zinc by 3.[33,38,39] No studies on the role of potassium or sodium that met the inclusion criteria were found.

Muscle mass was measured by dual energy x-ray absorptiometry[34,36] or BIA.[35] Muscle strength was measured by isokinetic flexion and extension strength, isometric knee extension torque, and handgrip strength.[30] Physical performance was measured by Short Physical Performance Battery,[30,31] gait speed,[30,32,33] and chair stand.[30,32] In addition, 4 studies evaluated the association between minerals and the prevalence of sarcopenia.[36-39]

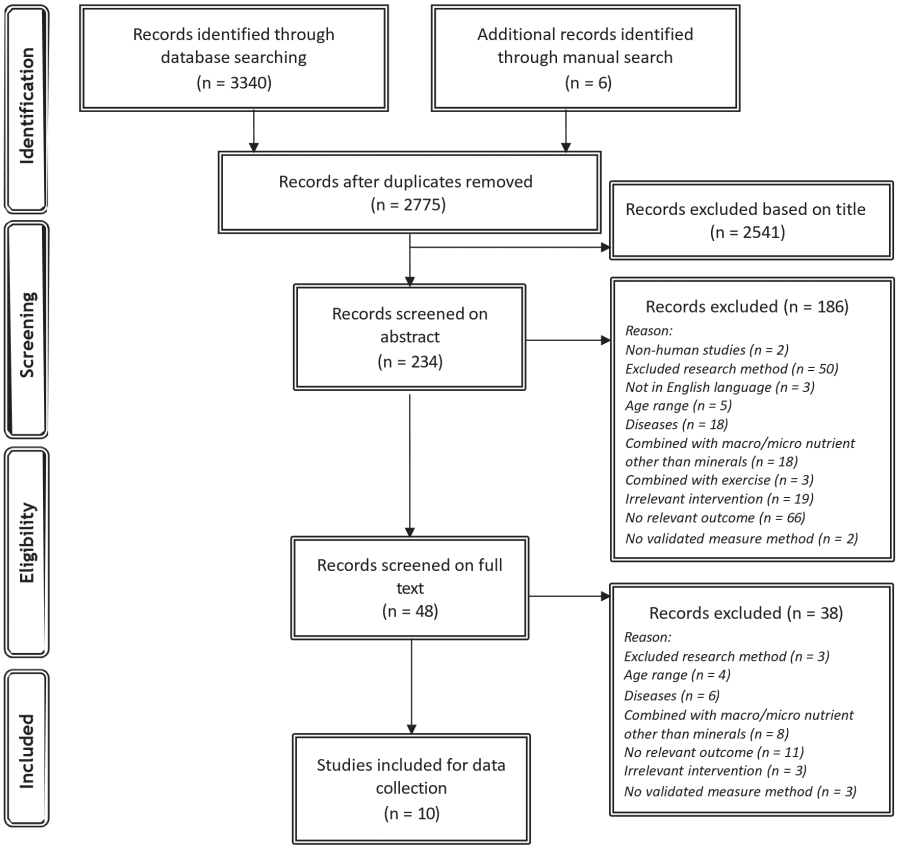

Figure 1. Flow-chart of search strategy and study selection.

Study Quality

Using the Quality Assessment Tool for Quantitative Studies,[28] 6 studies were rated as 1, 3 studies were rated as 2, and 1 study was rated as 3, with rating 1 being weak and 3 being strong (Table 1). The overall quality was rated as 1.5. The quality assessment per article is presented in Appendix 2.

Minerals

Table 2 provides details on the impact of calcium, iron, magnesium, phosphorus, selenium, and zinc on muscle mass, muscle strength, physical performance, and sarcopenia prevalence in older adults. Observational studies showed that serum selenium[35] and calcium intake[36] were significantly associated with muscle mass. Magnesium,[30] selenium,[32] iron,[33] and zinc[33] intake were significantly and positively associated with physical performance in older adults. Furthermore, magnesium,[38,39]

selenium,[38,39] calcium,[36,37] and phosphorus[39] intake were associated with the prevalence of sarcopenia. Magnesium supplementation improved physical performance based on one randomized controlled trial.[30] No studies on the role of sodium or potassium on muscle mass, muscle strength, physical performance, or the prevalence of sarcopenia were found.

Table 1 Study Details and Participant Characteristics of the 10 Included Studies

Author (y)	Mineral Studied	Study Design (Quality)*	Sample Size (% Female)	Mean Age (y)
Veronese et al (2014)[30]	Magnesium	Randomized controlled trial (2)	124 (100)	71.5
Bartali et al (2008)[31]	Serum iron	Longitudinal (3)	698 (54)	73.7
Martin et al (2011)[32]	Selenium	Cohort (2)	628 (45)	67.9
Waters et al (2014)[33]	Calcium	Cross-sectional (1)	315 (62)	76.5
	Iron			
Chaput et al (2007)[34]	Zinc Selenium	Cross-sectional (1)	50 (68)	66.5
Chen et al (2014)[35]	Serum selenium	Cross-sectional (1)	327 (68)	71.5
Seo et al (2013)[36]	Calcium	Cross-sectional (1)	1339 (53)	70.1
Oh et al (2015)[37]	Calcium	Cross-sectional (1)	1433 (54)	68.6
Ter Borg et al (2016)[38]	Calcium	Cross-sectional (1)	227 (52)	74.0
	Magnesium			
	Serum magnesium			
	Selenium			
Verlaan et al (2017)[39]	Zinc Calcium	Case-control (2)	132 (59)	71.0
	Magnesium			
	Phosphorus			
	Selenium			
	Zinc			

*Based on the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies.

Table 2 Outcomes of the 10 Included Studies

Author (year)	Mineral studied*	Outcome	Outcome measurement	Effect size†	p-value †
Veronese et al (2014)	**Magnesium**	Muscle strength	PT isokinetic flex	Δ 2.57 nm	p>0.05
			PT isokinetic extension	Δ 0.76 nm	p>0.05
		Physical performance	PT isometric	Δ 13.33 nm	p>0.05
			Handgrip	Δ 0.51 kg	p>0.05
			SPPB	**Δ 0.41 points**	**p=0.03**
			Chair stand	**Δ-1.31 seconds**	**p=0.0001**
			Gait speed	**Δ 0.14 meter/second**	**p=0.006**
Bartali et al (2008)	Serum iron	Physical performance	SPPB	OR=1.10 (95% CI 0.77;1.59)	p>0.05
Martin et al (2011)	**Selenium**	Physical performance	Gait speed	Male: β=−0.012 (95% CI -0.065;0.041)	p>0.05
				Female: β=−0.091 (95% CI-0.165;-0.018)	**p=0.015**
			Chair stand	Male: β=0.983 (95% CI 0.961;1.006)	p>0.05
				Female: β=0.983 (95% CI 0.955;1.012)	p>0.05
Waters et al (2014)	Calcium	Physical performance	Gait speed	Male: OR=2.18 (95% CI 0.67;7.09)	
				Female: OR=1.15 (95% CI 0.55;2.41)	
	Iron			**Male: OR=4.81 (95% CI 1.51 ;15.31)**	
				Female: OR=0.94 (95% CI 0.44 ;2.01)	
	Zinc			**Male: OR=3.57 (95% CI=1.14-11.18)**	
				Female: OR=2.33 (95% CI=1.12-4.85)	
Chaput et al (2007)	Selenium	Muscle mass	DXA	ρ_s=0.08	p>0.05

Author (year)	Mineral studied*	Outcome	Outcome measurement	Effect size†	p-value †
Chen et al (2014)	**Serum selenium**	Muscle mass	BIA	**OR=4.62 (95% CI 2.11;10.1)**	**p=0.001**
Seo et al (2013)	**Calcium**	Muscle mass	DXA	**ρ=0.276**	**P<0.001**
		Sarcopenia by definition of Lim (2010)		**OR=0.259 (95% CI 0.087;0.768)**	**p for trend=0.014**
Oh et al (2015)	**Calcium**	Sarcopenia by definition of Muscaritoli (2010)			**Male: p=0.002** Female: p>0.05
Ter Borg et al (2016)	Calcium	Sarcopenia by definition of Cruz-Jentoft (2010)			p>0.05‡ p>0.05·
	Magnesium				**p=0.009‡** **p=0.024·**
	Serum magnesium				p>0.05 **p=0.02‡**
	Selenium				p>0.05· p>0.05‡
	Zinc				p>0.05·
Verlaan et al (2015)	Calcium	Sarcopenia by definition of Cruz-Jentoft (2010)			p>0.05
	Magnesium				**p=0.015**
	Phosphorus				**p=0.014**
	Selenium				**p=0.039**
	Zinc				p>0.05

SPPB, short physical performance battery; DXA, dual energy X-ray absorptiometry; BIA, bio impedance analysis; PT, highest-peak torque; ρ_s, Spearmans' rho; OR, odds ratio;

* Statistically significant minerals are shown in bold;

† Statistically significance are shown in bold;

‡ dietary intake without supplement intake;

· dietary intake with supplement intake;

DISCUSSION

This review is the first systematic review that provides a comprehensive overview of the role of minerals on muscles mass, muscle strength, and physical performance in relation to sarcopenia in older adults. Magnesium, selenium, and calcium seem to be the most promising minerals to prevent and/or treat sarcopenia.

In this review, magnesium intake was significantly associated with sarcopenia, and one randomized controlled trial showed that magnesium supplementation improved performance in older adults. These findings are supported by studies of Scott et al[40] and Dominguez et al.[41] Magnesium intake was significantly and positively associated with appendicular lean mass, based on a prospective cohort study.[40] Serum magnesium correlated independently with muscle strength.[41] Dietary magnesium intake did significantly differ between sarcopenic subjects and nonsarcopenic subjects.[38,39] Mechanistically, magnesium plays an important role in muscle function and metabolism, along with its involvement in more than 600 enzymic reactions. For example, magnesium is involved in protein synthesis and ATP synthesis, and is responsible for muscle relaxation.[7,8]

Serum magnesium concentrations did not differ between sarcopenic subjects and nonsarcopenic subjects in the study of Ter Borg et al.[38] This might be explained by the strict regulation of serum magnesium by urinary excretion, bone stores, and gastrointestinal tract.[42] This means that serum magnesium concentrations may not be sensitive to small differences in magnesium intake, but is to larger differences in magnesium intake.[42] This finding has been confirmed by the randomized controlled trial of Veronese et al,[30] where a significant increase of serum magnesium concentrations was found after supplementation with 300 mg/d magnesium oxide for 12 weeks. In the same study, the effect of magnesium on physical performance was more evident in subjects with a dietary magnesium intake below the recommended dietary allowance (RDA)[43] at baseline.[30] This finding is in agreement with previous research.[8,44] In addition, the dietary intake of magnesium was below the RDA[43] in sarcopenic older adults in the studies of Ter Borg et al[38] and Verlaan et al.[39] Collectively, magnesium may be an important nutrient to prevent and treat sarcopenia in older adults.

Another potential nutrient that may positively affect sarcopenia outcomes is selenium. In our review, we included 4 studies that showed a positive association of selenium and muscle mass, physical performance, and sarcopenia.[32,35,38,39] These findings are in agreement with the studies of Beck et al[45] and Lauretani et al.[46] However, in the study of Chaput et al,[34] no association was found between selenium and muscle mass. This could be explained by the high intake of selenium, which was twice the RDA.[43] This is in agreement with the review of Rayman.[14] In the studies that found an association between selenium and muscle mass or physical performance, selenium intakes were below the RDA.[43] Moreover, all subjects had low serum selenium concentrations. In addition, selenium intakes were significantly lower in sarcopenic older adults in comparison with nonsarcopenic older adults.[38,39] These associations may be explained by the potential action of selenium on muscle tissue. Through selenoproteins, selenium is thought to have an effect on muscle synthesis and function, although the exact underlying mechanisms still remain unclear.[47] A selenium deficiency is thought to cause myopathy.[48] All this together indicates that selenium has the potential to prevent and treat sarcopenia.

In this review, the findings on the relation between calcium and sarcopenia were contradictory.[33,36-39] This could be due to the difference in calcium intake of the study populations. The intake was higher in the studies that did not find an association[38,39] than in the studies that did find an association[36,37] between calcium and sarcopenia. In addition, calcium intake was high in the study of Waters et al,[33] who also did not find an association between calcium and physical performance. The calcium intake was low (<415 mg/d) in the study of Seo et al,[36] who did find an association between calcium and muscle mass. This suggests that the role of calcium in the prevention and treatment of sarcopenia seems to be more promising in older adults with a low calcium intake. A hypothesis of the underlying mechanism could be a decreased calcium absorption and an altered calcium homeostasis, which is linked with muscle weakness in the aged muscle, according to recent studies.[49,50] Calcium is highly dependent on the presence of vitamin D for its absorption from the diet. Nevertheless, recent animal research suggests that calcium uptake is also possible through passive absorption.[51] Serum 25hydroxyvitamin D levels were significantly lower in sarcopenic older adults in the studies that did find an association[36,37] than in the studies that did not find an

association[38,39] between calcium and sarcopenia. However, the study of Seo et al[36] showed that after adjusting for serum 25-hydroxyvitamin D, calcium intake was still associated with sarcopenia. The study of Waters et al[33] found a significantly lower vitamin D intake in sarcopenic older adults, but serum 25-hydroxyvitamin D levels were not provided. Clearly, more research is warranted to elucidate the potential role of calcium in the development of sarcopenia.

Zinc and iron may be important in the prevention and treatment of sarcopenia, as they can be linked with oxidative stress.[17,52] Oxidative stress, through accumulation of reactive oxygen species, might cause muscle degeneration and a reduction of muscle strength.[53,54] Studies of Waters et al[33] and Scott et al[40] showed an association between iron and zinc, and physical performance and appendicular lean mass. However, Bartali et al,[31] Ter Borg et al,[38] and Verlaan et al[39] were unable to find an association with sarcopenic outcomes. This inconsistency may be explained by the differences in study design and outcome measures. At this stage, the role of iron and zinc on sarcopenia remains unclear.

The possible effect of phosphorus, potassium, or sodium on sarcopenia remains unclear because of an insufficient amount of articles that met the eligibility criteria.

This present review is, to our knowledge, the first systematic review studying the potential role of minerals on sarcopenia outcomes, giving a clear overview. An additional strength of this review is that we aimed to only include studies that investigated the role of a single mineral. By doing so, the role of the studied minerals on sarcopenia exclusively becomes clear. In addition, the search and selection of the articles were done by 2 independent researchers to limit selection bias. However, there were also some limitations. The studies of Scott et al,[40] Dominguez et al,[41] Beck et al,[45] and Lauretani et al[46] were excluded from this review because of strict criteria on age and underlying disease. However, these studies supported our findings. Most of the studies included in this review scored low on the quality assessment. This is because the design of most of the studies was cross-sectional. Only 1 study was a randomized controlled trial, which produces more sound evidence than cross-sectional studies. This limits the power of the findings. More studies with a strong study design, preferably randomized controlled trials, are warranted to gain

insight in the direction of the observed relations and the possible different effects of magnesium, selenium, and calcium on muscle mass, muscle strength, and physical performance.

CONCLUSION

Based on the current available literature, minerals may be important nutrients to prevent and/or treat sarcopenia. In particular, magnesium, selenium, and calcium are most promising. Most of the included studies, however, were observational studies. Therefore, more randomized controlled trials are needed to elucidate the potential benefits of mineral intake to prevent and/or treat sarcopenia and support healthy aging.

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CHAPTER 9

Minerals and Sarcopenia in Older Adults: An Updated Systematic Review

Carliene van Dronkelaar,
Maaike Fultinga,
Mitchell Hummel,
Hinke Kruizenga,
Peter J. M. Weijs,
Michael Tieland

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ABSTRACT

Objective This systematic review aims to re-evaluate the role of minerals on muscle mass, muscle strength, physical performance and the prevalence of sarcopenia in community-dwelling and institutionalized older adults.

Design Systematic review.

Setting and participants In March 2022, a systematic search was performed in PubMed, Scopus and Web of Sciences using predefined search terms. Original studies on dietary mineral intake or mineral serum blood concentrations on muscle mass, muscle strength and physical performance or the prevalence of sarcopenia in older adults (average age ≥65 years) were included.

Methods Eligibility screening and data extraction was performed by two independent reviewers. Quality assessment was performed with the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies. Risk of Bias was evaluated using the Risk Of Bias In Non-randomized Studies-of Exposure (ROBINS-E) tool.

Results From the 15622 identified articles, a total of 45 studies were included in the review, mainly being cross-sectional and observational studies. Moderate quality of evidence showed that selenium (n=8) and magnesium (n=7) were significant associated with muscle mass, strength and physical performance as well as the prevalence of sarcopenia. For calcium and zinc no association could be found. For potassium, iron, sodium and phosphorus the association with sarcopenic outcomes remains unclear as not enough studies could be included or were non-conclusive (low quality of evidence).

Conclusions and Implications This systematic review shows a potential role for selenium and magnesium on the prevention and treatment of sarcopenia in older adults. More randomized controlled trials are warranted to determine the impact of minerals on sarcopenia in older adults.

INTRODUCTION

Ageing is associated with various geriatric syndromes, such as sarcopenia. Sarcopenia is defined by age-related loss of muscle mass, muscle strength and physical performance and is associated with hospitalization, care dependency and poor quality of life.[1, 2] To prevent or treat sarcopenia, exercise and nutrition interventions have been developed and implemented in clinical practice.[3] These nutritional interventions focused predominantly on energy intake, dietary protein and vitamin D, but much less on minerals.[4, 5] Minerals, however, may have a major impact on muscle mass, strength and physical performance. For example, calcium is involved in muscle contraction and is essential to create muscular force.[6, 7] Magnesium is involved in energy metabolism, crucial for muscular performance and iron has a major impact in the transport of oxygen and therefore may impact muscle functioning.[6] Selenium and zinc both have an anti-oxidative function.[8, 9] Antioxidants counter Reactive Oxygen Species (ROS) released with exercise, which in excess can cause muscle fatigue and contractile dysfunction.[10]

Van Dronkelaar et al. previously investigated the role of minerals on muscle mass, muscle strength and physical performance in older adults.[11] They found that particularly magnesium, selenium and calcium seemed promising, but were only able to include ten studies. This review was published in 2018 and as many articles were published on the matter since, an update is warranted. This systematic review will re-evaluate the role of minerals on muscle mass, muscle strength, physical performance and the prevalence of sarcopenia in community-dwelling and institutionalized older adults.

METHODS

Search strategy and selection

The systematic search has been performed in PubMed, Scopus and Web of Science in March 2021, using predefined search terms. The full search strategy for each database can be found **Appendix 1**. After removing duplicates, two independent reviewers (MF, MH) screened the title and abstract of all found articles for eligibility. An article was eligible if it was published between January 2006 and March 2022. Further inclusion and exclusion criteria can be found in **Table 1.**

Of the eligible articles, full texts were screened for final inclusion. An additional manual search of the reference lists of included articles has been performed to check for more potential useful articles. In case of any discrepancies between the two independent reviewers, a third reviewer (CD) was consulted and discrepancies were discussed until consensus was reached. To construct this systematic review the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was followed.[12]

Data extraction

The following data was extracted: author and year of publication, study design, population characteristics (sample size, mean age (SD) in years, gender ratio), type of mineral(s) studied and note outcomes (outcome category, outcome measurement, effect size and p-value). A meta-analysis was considered when study outcomes were comparable.

Table 1. inclusion and exclusion criteria for eligible studies.

Inclusion criteria	Subjects	Average age ≥65 years, Community-dwelling, Hospitalized, Institutional
	Exposure	Dietary intake or blood serum concentrations of: Calcium, Iron, Magnesium, Phosphorus, Potassium, Selenium, Sodium, Zinc
	Outcome	Muscle mass Computed tomography (CT), Magnetic resonance imaging (MRI), Dual energy x-ray absorptiometry (DXA), whole-body air plethysmography, bioelectrical impedance analysis (BIA), dual photon absorptiometry Muscle strength Handgrip, knee-, legand ankle extension, knee-, ankleand hip flexor, hip abductor, leg press, elastic bands Physical performance Short Physical Performance Battery (SPPB), Chair stand, Balance test, Gait speed test, 400-m walk test, 6 minute walk test (6MWT), Timed-Up-and-Go (TUG) test Sarcopenia of any definition
Exclusion criteria	Subjects	Participants with muscle disorder or disease Heart failure, Cirrhosis, HIV, Neoplasms, Renal insufficiency, Hyperparathyroidism, Chronic obstructive pulmonary disease
	Exposure	Intervention mixed with exercise or other macroor micronutrients, hyponatremia
	Design	conference abstract, letters, comments, editorials, case reports, systematic reviews

Quality assessment

The quality of included articles was assessed by two independent reviewers (MF, CD) with the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies.[13] The tool assesses risk of bias, study design, confounders, method of blinding, data collection methods and withdrawals. The total score ranges from one to three, with one being low quality and three being high quality. The quality assessment per included article can be found in **Appendix 2**. No articles were excluded based on the outcome of the quality assessment. Risk of Bias was evaluated using the Risk Of Bias In Non-randomized Studies – of Exposure (ROBINS-E) tool and visualized with *robvis*.[14, 15] The GRADE approach was used to assess the quality of evidence. The protocol of this review is registered in PROSPERO register under the number 243666 and can be assessed at *https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=243666* .

RESULTS

Our search identified a total of 15622 articles. After removing duplicates, 10481 articles were screened on title and abstract, from which 171 articles were screened on full text. Finally, a total of 45 articles were eligible.[16-60] A full overview of the selection of articles can be found in **Figure 1.** The overall quality of the included studies was moderate (**Appendix 2**). The overall risk of bias evaluation indicated that most of the studies showed some concerns, mainly within selection of the reported results or selection of participants into the study/analysis (**Figure 2**). Evaluation per study can be found in **Appendix 3**.

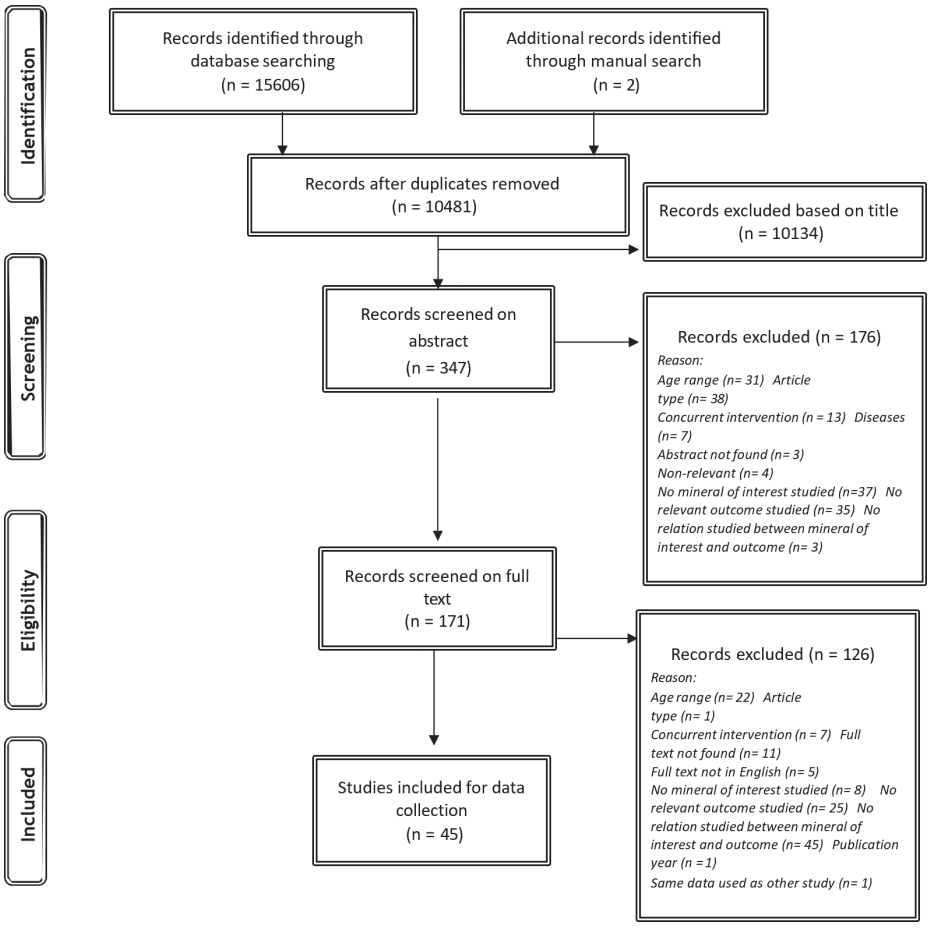

Figure 1 Flowchart of selection

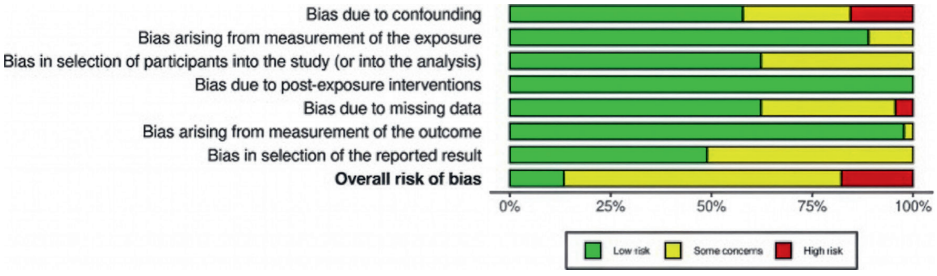

Figure 2 Overall risk of bias of included studies

Study characteristics

Characteristics of the included articles can be found in **Table 2.** Of the 32982 studied subjects, 58% was female and the average age ranged from 65 to 86. Most of the participants were community dwelling[16-29, 32, 34-41, 44-47, 49, 50, 52-60], in three studies participants were hospitalized[33, 43, 48], in two studies participants were institutionalized[31, 42] and in one study participants were outpatients[28]. In total, three randomized controlled trial (RCT)[39, 46, 57], two longitudinal studies[19, 41], one case-control[56], 12 cohort[16-18, 29, 30, 35, 38, 40, 44, 47, 49, 54], three prospective observational studies[27, 32, 36], one observational[43] and 23 cross-sectional studies[20-26, 28, 31, 33, 34, 37, 42, 45, 48, 50-53, 55, 58-60] were included.

The included studies evaluated calcium (n=18)[18, 20, 21, 23, 26, 28, 31, 34, 38, 39, 42, 45, 49, 52, 55, 56, 58, 60], iron (n=13)[18, 19, 21, 26, 34, 35, 38, 42, 43, 46, 58-60], magnesium (n=15)[17, 18, 21, 26, 27, 32, 34, 38, 42, 51-53, 56, 57, 60], phosphorus(n=7)[20, 21, 34, 38, 42, 55, 56], potassium (n=11)[18, 21, 26, 34, 36, 38, 42, 48, 50, 56, 60], selenium (n=14)[16, 22, 24, 25, 29, 30, 34, 37, 40, 42, 47, 52, 56, 60], sodium (n=10)[18, 21, 28, 34, 36, 38, 42, 44, 50, 60] and zinc (n=15)[18, 26, 30, 31, 33, 34, 38, 41, 42, 52, 54, 56, 58-60].

Most articles used muscle strength as outcome (n=21)[20, 22, 27, 29, 31, 32, 37, 38, 41, 43, 44, 46-48, 50, 51, 53, 55, 57, 59, 60], measured by handgrip, knee-, leg- and ankle extension, ankle-, knee- and hip-flexor or hip abductor strength. Physical performance was measured in 17 studies[16-19, 29, 31, 36, 38, 40-42, 47, 53, 54, 57, 58, 60] by Short Physical Performance Battery (SPPB), gait speed, Timed Up and Go test (TUG) or the repeated chair-rise test. Studies that assessed muscle mass (n=7)[24, 25, 34, 39, 49, 53, 60] used either dual energy x-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA). A total of 13 studies[21, 23, 26, 28, 30, 33, 35, 45, 49, 51-53, 56] evaluated the relationship between a mineral and any definition of sarcopenia.

Minerals

The relationship between minerals and muscle mass, muscle strength and physical performance and sarcopenia prevalence is provided in **Table 3**. Out of the seven studies which assessed muscle mass, only two studies showed a positive significant association with selenium and calcium.[25, 49] Twelve of the 21 studies on muscle strength found a positive significant association with calcium, iron, magnesium, potassium, selenium and sodium intakes, and with serum/plasma phosphorus levels.[20, 22, 27, 29, 37, 38, 43, 44, 46, 50, 55, 59] Iron and magnesium supplementation each improved muscle strength in a randomized controlled trial.[46, 57] In nine out of 18 studies,

a higher physical performance was associated with higher intakes of calcium, iron, magnesium, potassium, selenium, sodium and zinc, and with serum levels of selenium and zinc.[16, 17, 29, 31, 36, 40, 54, 57, 58] Of the 13 studies that looked at the prevalence of sarcopenia, ten found an association with lower intakes of magnesium, phosphorus, calcium, iron, zinc, selenium or potassium, or with low serum levels of calcium, ferritin and zinc.[21, 23, 26, 28, 30, 35, 45, 49, 52, 56]

Table 2. Characteristics of included studies.

Author(y)	Mineral studied*	Study design	Sample size (% female)	Mean age (y)
Alipanah et al. (2009)	**Serum selenium**	Cohort	687 (100)	>65
Arias-Fernandez et al. (2022)	**Magnesium**	Cohort (*Seniors-ENRICA)*	863 (51)	70.5
Asamane et al. (2020)	Potassium, magnesium, calcium, iron, zinc, sodium	Cohort	100 (41)	70.8
Bartali et al. (2008)	Serum iron	Longitudinal	643 (100)	
Bates et al. (2012)	Plasma calcium **Plasma phosphorus**	Cross-sectional	1054 (49)	75.8
Beaudart et al. (2019)	Sodium, **potassium, magnesium, phosphorus, iron,** calcium	Cross-sectional	331 (59)	74.8
Beck et al. (2007)	**Serum selenium**	Cross-sectional	676 (100)	77.4
Can et al. (2017)	**Serum calcium**	Cross-sectional	72 (63)	80.2
Chaput et al. (2007)	Selenium	Cross-sectional	50 (68)	66.5
Chen et al. (2014)	**Serum selenium**	Cross-sectional	327 (68)	72.1
Das et al. (2021)	**Magnesium, calcium, potassium, iron, zinc**	Cross-sectional	794 (0)	81.1
Dominguez et al. (2006)	**Serum magnesium**	Prospective (*InCHIANTI)*	1138 (54)	66.7
Fukuoka et al. (2019)	Serum sodium Serum potassium **Serum calcium**	Cross-sectional	267 (40)	73.7
Garcia-Esquinas et al. (2021)	**Serum selenium**	Cohort (*NHANES;* *Seniors-ENRICA-2)*	1733 (56) 2548 (53)	≥ 65
Gariballa et al. (2018)	Serum selenium **Serum zinc**	Cohort	432 (49)	≥ 65
Grieger et al. (2007)	**Serum zinc,** calcium	Cross-sectional	115 (68)	80.2

Table 2. Characteristics of included studies. (continued)

Author(y)	Mineral studied*	Study design	Sample size (% female)	Mean age (y)
Henderson et al. (2010)	Serum magnesium Serum phosphate	Prospective	43 (58)	83.8
Heo et al. (2015)	Serum zinc	Cross-sectional	86 (63)	79
Khanal et al. (2021)	Calcium, zinc, iron, selenium, potassium, phosphorus, sodium, magnesium	Cross-sectional	281 (100)	70
Kim et al. (2014)	**Serum ferritin**	Cohort (*KHANES-IV*)	2332 (59)	M: 69.06 F: 69.36
Lana et al. (2020)	**Sodium, potassium**	Prospective	868 (51)	70.5
Lauretani et al. (2007)	**Plasma selenium**	Cross-sectional	891 (56)	74.7
Lengelé et al. (2020)	Iron, calcium, sodium, **potassium,** magnesium, phosphorus, zinc	Cohort (*Baseline data)*	238 (61)	Median: 72
Lewis et al. (2019)	Calcium supplement	RCT	1368 (100)	75.2
Martin et al. (2011)	**Selenium**	Cohort	628 (45)	M: 67.8 F: 68.1
Mocchegiani et al. (2012)	Plasma zinc	Longitudinal (*iiSIRENTE*)	346 (67)	M: 86.1 F: 85.7
Moradell et al. (2021)	Calcium, iron, sodium, magnesium, potassium, iodine, selenium, zinc, phosphorus	Cross-sectional	101 (77)	80.4
Neidlein et al. (2021)	**Iron supplement**	Observational	224 (67)	81.4
Noh et al . (2019)	**Sodium density** (mg/1000kcal)	Cohort (*KHANES IV)*	2982 (52)	>65
Oh et al. (2015)	**Calcium**	Cross-sectional	1433 (54)	68.6
Oztorun et al. (2018)	**Iron supplement**	RCT	81 (69)	76.8

Table 2. Characteristics of included studies. (continued)

Author(y)	Mineral studied*	Study design	Sample size (% female)	Mean age (y)
Perri et al. (2020)	Selenium	Cohort (*Baseline data)*	791 (62)	>85
Schiara et al. (2020)	Serum potassium	Cross-sectional	2166 (54)	>65
Seo et al. (2013)	**Calcium**	Cohort (*KHANES IV)*	1339 (53)	70.1
Shimizu et al. (2021)	**Serum sodium** Serum potassium	Cross-sectional	246 (0)	65.4
Suranto et al. (2020)	Serum magnesium	Cross-sectional	28 (100)	>65
Ter Borg et al. (2016)	Calcium, **magnesium,** serum magnesium, **selenium,** zinc	Cross-sectional	227 (52)	Median: 74
Ter Borg et al. (2019)	Serum magnesium	Cross-sectional	227 (52)	Median: 74
Vega-Cabello et al. (2022)	**Zinc**	Cohort (*Seniors-ENRICA)*	2963 (53)	69
Verde et al. (2019)	**Serum calcium** **Serum phosphorus**	Cross-sectional	273 (53)	75.7
Verlaan et al. (2017)	Calcium, **magnesium, phosphorus, selenium,** zinc	Case-control	132 (59)	71.0
Veronese et al. (2014)	**Magnesium supplement**	RCT	139 (100)	71.5
Waters et al. (2014)	Calcium, **iron, zinc**	Cross-sectional	315 (62)	≥60
Yamada et al. (2015)	**Serum iron** Serum zinc	Cross-sectional	202 (100)	76.3
Yeung et al. (2021)	Sodium, calcium, iron, zinc, potassium, magnesium, selenium	Cross-sectional	58 (66)	77.2

F: Female; M: Male; RCT: Randomized controlled trial.

*All minerals listed are dietary intake, unless otherwise indicated; minerals in bold showed a significant association with sarcopenic outcomes.

Table 3. Overview of outcome of included studies.

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Alipanah et al. (2009)	Serum selenium	Physical performance	Mean walking speed (m/s)	Multivariate (age, BMI, chronic diseases) β=0.002 ± 0.00005	0.0003	Some concerns
Arias-Fernandez et al. (2022) *Seniors-ENRICA*	Magnesium	Physical performance	SPPB (points)	β=1.01 (95% CI 0.49, 1.52) β=-0.09 (95% CI -0.59, 0.41)	F: 0.001 M: >0.05	Some concerns
Asamane et al. (2020)	Potassium, magnesium, calcium, iron, zinc, sodium	Muscle strength Physical performance	Hand grip strength (kg) SPPB (points)	r=0.101; r=0.106; r=-0.011; r=-0.083; r=-0.187; r=0.012; r=0.179; r=0.139; r=-0.009; r=-0.001; r=-0.122; r=-0.162;	>0.05 >0.05	Some concerns
Bartali et al. (2008)	Serum iron	Physical performance	SPPB (points)	OR=1.10 (95% CI 0.77, 1.59)	>0.05	Some concerns
Bates et al. (2012)	Plasma calcium Plasma phosphorus	Muscle strength	Hand grip strength (kg)	NR M: *t*=-0.4; F: *t*=-0.8 M: *t*=-2.2; F: *t*-=-0.9	>0.05 0.03 >0.05	Some concerns
Beaudart et al. (2019)	Sodium Potassium Magnesium Phosphorus Iron Calcium	Sarcopenia	EWGSOP 1	NA	>0.050.04 0.03 0.04 0.005 >0.05	Some concerns
Beck et al. (2007)	Serum selenium	Muscle strength	Hand grip strength (kg)	β=2.280 ± 0.799	0.005	High

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Can et al. (2017)	Serum calcium	Sarcopenia	EWGSOP 1	NA	0.008	Some concerns
Chaput et al. (2007)	Selenium	Muscle mass	DEXA (MMI)	r=0.08	>0.05	Low
Chen et al. (2014)	Serum selenium	Muscle mass	BIA (LMM)	OR 4.62 (95% CI 2.11, 10.1)	<0.001	Some concerns
Das et al. (2021)	Magnesium Calcium Potassium Iron Zinc	Sarcopenia	FNIH EWGSOP 1 EWGSOP 2	NA	<0.0001 0.03 <0.0001 0.03 0.02 All > 0.05 >0.05 >0.05 >0.05 >0.05 0.02	Some concerns
Dominguez et al. (2006) *InCHIANTI*	Serum magnesium	Muscle strength	Ankle extension isometric (kg) Hand grip strength (kg) Knee extension torque (N/dm) Lower-leg muscle power (W)	β=3.8±0.5 β=2.0±0.5 β=31.2±7.9 β=8.8±2.7	<0.0001 0.0002 <0.0001 0.001	Low
Fukuoka et al. (2019)	Serum sodium Serum potassium Serum calcium	Sarcopenia	AWGS	NA	>0.05 >0.05 <0.05	Some concerns

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Garcia-Esquinas et al. (2021) **NHANES; Seniors-ENRICA-2*	Whole blood selenium (per log2)	Muscle strength Physical performance	Low hand grip strength (study specific cut-off; kg) Low SPPB (≤9 points)	OR 0.54 (95% CI 0.32; 0.76) OR 0.59 (95% CI 0.34; 0.82)	NR	Some concerns
Gariballa et al. (2018)	Serum selenium Plasma zinc	Sarcopenia	EWGSOP 1	NA	>0.05 <0.05	High
Grieger et al. (2007)	Calcium Serum zinc	Muscle strength Physical performance	Hand grip strength (kg) TUG (s)	NR NR NR r=0.449	>0.05 >0.05 >0.05 0.001	High
Henderson et al. (2010)	Serum magnesium, serum phosphate	Muscle strength	Hand grip strength (kg) Leg strength (kg)	r=-0.03; r=0.13 r=-0.01; r=0.10	All >0.05	High
Heo et al. (2015) 20	Serum zinc	Sarcopenia	AWGS	NA	>0.05	High
Khanal et al. (2021)	Calcium, Zinc, Iron, Selenium, Potassium, Phosphorus, Sodium, Magnesium	Muscle mass	BIA (relative SMM)	NR	All >0.05	Low

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Kim et al. (2014) **KNHANES-IV*	Serum ferritin	Sarcopenia	KNHANES cut-off (ASM %)	M: OR 1.40 (95% CI 0.75; 2.65) F: OR 1.74 (95% CI 1.02; 2.97)	NR	Low
Lana et al. (2020)	Sodium Potassium	Physical performance	SPPB (points)	−0.13 (95% CI−0.26; −0.01) per 1 SD increase 0.19 (95% CI 0.05; 0.34) per 1 SD increase	NR	Some concerns
Lauretani et al. (2007)	Plasma selenium	Muscle strength	Low hand grip strength (kg) Low hip strength (kg) Low knee strength (kg)	OR 1.94 (95% CI 1.19; 3.16) OR 1.69 (95% CI 1.02; 2.83) OR 1.94 (95% CI 1.18; 3.19)	0.008 0.040 0.009	Some concerns
Lengelé et al. (2020) *(Baseline)*	Iron, Calcium, Sodium, Potassium, Magnesium, Phosphorus, Zinc	Physical performance Muscle strength	Gait speed (m/s) Hand grip strength (kg)	β=-0.005; β=-9.261 x 10^{-5}; β=6.525 x 10^{-5}; β=5.335 x 10^{-5}; β=-3.843 x 10^{-5}; β=-5.244 x 10^{-5}; β=0.006; β=-0.179 β=0.004 β=0.002 β=0.003 β=0.005 β=0.005 β=0.119	All >0.05 >0.05 >0.05 >0.05 0.035 >0.05 >0.05 >0.05	Some concerns
Lewis et al. (2019)	Calcium supplement	Muscle mass	DEXA (LM)	Placebo: -0.01; calcium: -0.07	>0.05	Some concerns

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Martin et al. (2011)	Selenium	Physical performance	Chair rise(s) 3-m walk (s)	M: β=0.983 (95% CI 0.961; 1.006) F: β=0.983 (95% CI 0.955; 1.012) M: β=-0.012 (95% CI 0.065; 0.041) F: β=-0.091 (95% CI 0.165; 0.018)	>0.05 >0.05 >0.05 0.015	Some concerns
Mocchegiani et al. (2012) **iiSIRENTE*	Plasma zinc	Physical performance Muscle strength	4-m walk (s) SPPB (points) Hand grip strength (kg)	$\beta=0.013 \times 10^{-2}$ $\beta=0.167 \times 10^{-2}$ $\beta=0.167 \times 10^{-2}$	All >0.05	Some concerns
Moradell et al. (2021)	Calcium, Iron, Sodium, Magnesium, Potassium, Selenium, Zinc, Phosphorus	Physical performance	SPPB (groups: dependent, frail, pre-frail, robust)	NR	All >0.05	Some concerns
Neidlein et al. (2021) *iron deficient patients*	Iron supplement	Muscle strength	Hand grip strength (kg) Knee extension (kg)	Control: 21.0±9.4; supplement: 23.0±9.4 Control:14.3±6.4; supplement: 19.1±7.8	>0.05 0.005	High
Noh et al . (2019) **KNHANES IV*	Sodium density (mg/1000kcal)	Muscle strength	Low hand grip strength (kg)	M: Q1: OR 1.08 (95% CI 0.68; 1.72); Q2: OR 1 Q3: OR 0.99 (95% CI 0.68; 1.43) Q4: OR 1.15 (95% CI 0.71; 1.86) F: Q1: OR 1.01 (95% CI 0.74; 1.38); Q2: OR 1 Q3: OR 1.18 (95% CI 0.89; 1.58); Q4: OR 1.51 (95% CI 1.10; 2.07)	NA	Low

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Oh et al. (2015)	Calcium	Sarcopenia	KHANES cut-off (ASM/Wt)	NA	0.002 (M) >0.05 (F)	Some concerns
Oztorun et al. (2018)	Iron supplement	Muscle strength	Hand grip strength (kg)	M: *Z*= -2.772 F: *Z*= -3.345	0.006 0.001	High
Perri et al. (2020) *(Baseline)*	Selenium	Muscle strength Physical Performance	Hand grip strength (kg) TUG (log10-s)	β=-0.69 SE:0.65 β=-0.002 SE:0.024	>0.05 >0.05	Some concerns
Schiara et al. (2020)	Serum potassium	Muscle strength	Hand grip strength (kg)	normokalemic: 20.4±8.9 hypokalemic: 21.3±8.9	>0.05	Some concerns
Seo et al. (2013) **KNHANES IV*	Calcium	Muscle mass Sarcopenia	DEXA KHANES cut-off (ASM/Wt)	r=0.276 OR 0.259 (95% CI 0.087; 0.768)	<0.001 0.014	Some concerns
Shimizu et al. (2021)	Serum sodium Serum potassium Serum calcium Serum phosphorus	Muscle strength	Hand grip strength (kg)	Without hypertension r=0.32 r=0.08; r=0.13; r=0.13 With hypertension r=0.03; r=0.07; r=0.08; r=0.14	<0.001 All >0.05 All >0.05	Some concerns
Suranto et al. (2020)	Serum magnesium	Sarcopenia	AWGS	NA	>0.05	Some concerns

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Ter Borg et al. (2016)	Calcium Magnesium Serum magnesium Selenium Zinc	Sarcopenia	EWGSOP 1	NA	>0.05 0.009 >0.05 0.020 >0.05	Low
Ter Borg et al. (2019)	Serum magnesium	Muscle mass Muscle strength Physical performance Sarcopenia	BIA (SMI) Hand grip strength (kg) Gait speed (m/s) Chair stand (s) EWGSOP 1	NR NR NR NR OR 2.663 (95% CI 0.025; 228.118)	All >0.05	Some concerns
Vega-Cabello et al. (2022) *Seniors-ENRICA*	Zinc	Physical performance	SPPB (≤6 points)	HR 0.64 (95% CI 0.43; 0.94)	NR	Some concerns
Verde et al. (2019)	Serum calcium Serum phosphorus	Muscle strength	Hand grip strength (kg)	OR 1.087 (95% CI 1.028; 1.150) OR 1.263 (95% CI 1.078; 1.480)	0.003 0.004	High
Verlaan et al. (2017)	Calcium Magnesium Phosphorus Selenium Zinc	Sarcopenia	EWGSOP 1	NA	>0.05 0.015 0.014 0.039 >0.05	Some concerns

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Veronese et al. (2014)	Magnesium supplement	Physical performance	Chair stand (s)	Δ -1.31	0.0001	Some concerns
			Gait speed (m/s)	Δ 0.14	0.006	
			SPPB (points)	Δ 0.41	0.03	
		Muscle strength	Hand grip strength (kg)	Δ 0.51 kg	>0.05	
			Peak torque isokinetic knee flexion (nm)	Δ 2.57 nm	>0.05	
			Peak torque isokinetic knee extension (nm)	Δ 0.76 nm	>0.05	
			PT isometric knee extension (nm)	Δ 13.33 nm	>0.05	
Waters et al. (2014)	Calcium Iron Zinc	Physical performance	Gait speed (m/s)	M: OR 2.18 (95% CI 0.67; 7.09) F: OR 1.15 (95% CI 0.55; 2.41) M: OR 4.81 (95% CI 1.51; 15.31) F: OR 0.94 (95% CI 0.44; 2.01) M: OR 3.57 (95% CI 1.14; 11.18) F: OR 2.33 (95% CI 1.12 4.85)	NA	Some concerns
Yamada et al. (2015)	Serum iron Serum zinc	Muscle strength	Hand grip strength (kg)	r=0.20 r=0.12	<0.05 >0.05	Some concerns

Author (y)	Mineral studied†	Outcome	Outcome measurement	Effect size	P-value	Risk of Bias
Yeung et al. (2021) *SHAPE	Sodium, Calcium, Iron, Zinc, Calcium, Magnesium, Selenium	Muscle mass	DEXA (SMMI)	β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=0.03 (SE 0.06); β=-0.03 (SE 0.04);	All > 0.05	Some concerns
		Muscle strength	Hand grip strength (kg)	β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=0.00 (SE 0.01)	All >0.05	
		Physical performance	Chair stand (s)	β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=-0.04 (SE 0.06); β=-0.08 (SE 0.05); β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=0.00 (SE 0.01) β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=-0.05 (SE ; 0.06); β=-0.09 (SE 0.05); β=0.00 (SE 0.00); β=0.00 (SE 0.00); β=-0.01 (SE 0.01)	All >0.05	

†All minerals listed are dietary intake, unless otherwise indicated.

ASM: appendicular skeletal muscle mass; AWGS: Asian Working Group for Sarcopenia; BIA: Bio-electrical Impedance Analysis; DEXA: Dual-Energy X-ray Absorptiometry; EWGSOP: European Working Group on Sarcopenia in Older People; F: Female; LMM: low muscle mass; M: Male; MMI: muscle mass index; NA: not applicable; NR: not reported; PT Peak torque; SE standard error; SMM: skeletal muscle mass; SMMI: skeletal muscle mass index; SPPB: Short Physical Performance Battery; TUG: Timed-up and go test; Wt: weight.

DISCUSSION

This update on the systematic review by van Dronkelaar et al. 2018, provides a comprehensive overview of the current literature on the potential role of minerals on muscle mass, muscle strength and physical performance and prevalence of sarcopenia in older adults. Selenium and magnesium were associated with muscle mass, strength, performance and sarcopenia prevalence. The associations between calcium and zinc and the sarcopenic outcomes were equivocal. For the other minerals, the potential role remains unclear as not enough studies could be included or were non-conclusive.

Magnesium

Most of included studies on magnesium intake showed a significant positive relation with muscle mass, muscle strength, physical performance and/or sarcopenia prevalence. In these studies, the magnesium intake was below Recommend Dietary Allowance (RDA), suggesting a potential role for supplementing or increasing magnesium. Indeed, the only RCT on magnesium supplementation included in this review showed a significant improvement of physical performance in older adults. This was also concluded by a study of Wang et al (2017), who performed a systematic review and meta-analysis of 14 randomized clinical trials on the relation of magnesium supplementation on muscle fitness in younger and older adults. They concluded that magnesium supplementation may benefit individuals with magnesium deficiency, such as in older adults, but may not be of added value for individuals with a relative high magnesium status.[61]

Studies on serum magnesium on the other hand were not able to support these findings. This might be explained by a tight regulatory control of serum magnesium levels in the body. As thoroughly described by de Baaij et al. 2012, magnesium homeostasis is regulated by the intestine, bone and kidneys.[62] Magnesium is stored mainly in bone tissue, but also in muscle tissue where it antagonizes calcium in muscle contraction. When dietary magnesium intake is inadequate, absorption of magnesium in the intestine can rise from 30-50% up to 80-90%. Also, about 90-95% of daily filtered magnesium in the kidney is resorbed. These three systems maintain plasma magnesium homeostasis between 0.65 and 1.05 mmol/L. In the case of older adults, however, osteoporosis, malabsorption

and (chronic) renal failure are prevalent issues.[63, 64] A higher dietary magnesium intake might therefore compensate a disrupted absorption, storage and resorption system, and maintain stable serum magnesium levels.

As only one RCT was identified in this review, more experimental research is needed to clarify the extent to which a higher magnesium intake potentially affects sarcopenic outcomes, especially in older adults with an inadequate magnesium status.

Selenium

Studies included in this review on selenium showed that there is an association between low serum levels and worse sarcopenic outcomes. However, this association was not found for dietary intake of selenium. A possible explanation has not been determined. Although, studies on selenium intake included in this review which did not show a significant association with sarcopenic outcomes, all had intakes above RDA levels. This could imply that there might be an association between selenium and sarcopenic outcomes in older adults with selenium intake below RDA levels. Patients with selenium deficiency, often develop skeletal muscle disorders such as muscle pain, proximal weakness and fatigue, emphasizing a possible positive relation selenium might have on muscle function.[65] The exact underlying mechanisms, however, remain unclear.

Calcium

The absence of a significant association between calcium and sarcopenia related outcomes was not expected as calcium has a vital role in muscle function, such as in the activation of the muscle-contraction process, as described by Kuo et al. 2015.[66] Without sufficient calcium available, the activation of the contractile apparatus cannot occur, inhibiting muscle contraction and therefore possibly normal muscle function. However, based on studies included in this review it seems that there is no clear role for calcium independently. Calcium homeostasis is regulated by vitamin D, parathyroid hormone (PTH) and calcitonin with bone as the main storage. Due to interaction between calcium and vitamin D it could be that they only can play a role in counteracting sarcopenia when both calcium and vitamin D are sufficient.[67] This is also seen in the study of Petermann et al. (2020) where 396,283 UK biobank participants with the highest tertial of vitamin D and calcium intake had the lowest odds of

sarcopenia.[68] Kim et al. (2020) were able to show a significant association between low serum calcium levels and ≥5% muscle loss among 3342 participants, aged 50 and over, who were followed for 10 years.[69] However, they did not take vitamin D levels or PTH in consideration as they mention in the limitations of the study. As the underlying mechanisms are complicated, further studies are warranted to explore the role of calcium and vitamin D in the prevention and/or treatment of sarcopenia.[70]

Zinc

Five studies found a significant association between zinc and sarcopenic outcomes, yet a majority of 11 studies did not report any significant association. This is different from the conclusion on zinc of the systematic review performed in 2018, as inconclusive results were reported then. We expected to find association between low zinc levels or intakes and sarcopenic outcome due to zinc's anti-oxidative function. As set out by Hernandez-Camacho et al. 2020 , zinc upregulates the antioxidant system, preventing production of reactive oxygen species.[9] In excess, ROS can have a negative impact on muscle function.[10] Studies that were able to find a significant association reported low levels of serum zinc. Studies that did not find a significant association all had zinc intakes above RDA or serum levels above the norm. Hence, it seems that if zinc status is sufficient, it is able to prevent negative impacts on muscle, however, more RCTs are warranted to determine the exact relation of zinc with sarcopenia related outcomes.

Potassium, iron, sodium, phosphorus

The results of included studies on potassium, iron, sodium and phosphorus were either non-conclusive due to or indecisive results or an insufficient number of articles. The possible relation of these minerals on muscle mass, muscle strength, physical performance and/or sarcopenia therefore remains unclear.

The 2018 van Dronkelaar et al. study on the role of minerals on muscle mass, muscle strength, physical performance and/or sarcopenia that this update was based on, reported to be the first systematic review presenting a clear overview on this topic. The updated search was performed in three databases, whereas the 2018 review only performed the search in one database. This update included a total of 45 studies, as opposed to ten in the original review. Due to the significantly larger

number of studies being included, this update presents stronger evidence on the potential role minerals have in the prevention/treatment of sarcopenia. Additionally, the search and selection of articles was performed by two independent researchers and discussed with a third researcher, thereby limiting selection bias.

However, there were some limitations to this review. No meta-analysis of the data has been performed due to lack of usable studies per mineral. Furthermore, three of the articles included in this study used data from the Korea National Health and Nutrition Examination Study or KHANES IV. Although the included studies using this data focused on different minerals (sodium, iron and calcium, respectively), this data is derived from the same participants and could therefore be more related to each other. Other minerals such as iodine and manganese were included in the study by Khanal et al. 2021, yet these minerals have not been included in this review due to not being defined in advance formulated search strings.[34]

Although we were able to include more articles than in the previous review, the quality of evidence is moderate, due to most data being from observational studies and cross-sectional analyses. This is also reflected by the Quality Assessment scoring of included studies (**Appendix 2**) and the Risk of Bias evaluation (**Appendix 3**). In addition, some of the included studies had a small sample size which could have affected the findings due to lack of power. More studies with a stronger study design, preferably randomized controlled trials, with larger study populations are warranted to gain insight in the direction, size and strength of the observed relations of calcium, magnesium, selenium and zinc on muscle mass, strength, physical performance and the prevalence of sarcopenia.

CONCLUSION AND IMPLICATIONS

This review shows a potential role for selenium and magnesium on the prevention/treatment of sarcopenia in older adults. For example, by increasing mineral intake to recommend daily levels. If more experimental research is performed, this could potentially lead to better interventions for sarcopenia and contribute to healthy ageing and a better quality of life in an increasing older population.

Conflict of interest
The authors have no conflicts of interest to declare.

Supplementary Materials
The following supporting information can be downloaded at: *https://www.jamda.com/article/S1525-8610(23)00481-4/fulltext*
Appendix A1. Search strings. Appendix A2. Quality Assement. Appendix A3. Risk of Bias.

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CHAPTER 10

Discussion and future perspectives

This thesis focused on optimizing nutritional care for older adults at risk of malnutrition and sarcopenia, aiming to identify strategies that enhance recovery, quality of life, and healthcare efficiency.(1, 2) Malnutrition and sarcopenia are a growing burden as the risk for both conditions increases for the aging population. In addition, both conditions reinforce each other.(3) Older adults are especially vulnerable during hospitalization due to age-related physiological changes and multiple health conditions, which increase their risk of sarcopenia, functional decline, and hospital readmission. In addition, malnutrition often develops or worsens during hospital stay and continues after discharge, impacting recovery and long-term health outcomes. Providing consistent nutritional care beyond the hospital setting is therefore essential to promote sustained recovery and improve overall quality of life.

SUMMARY OF FINDINGS

Chapter 2 showed that widely used malnutrition screening tools lack sufficient sensitivity to identify all older hospitalized patients at risk, underscoring the need for improved screening methods.

In **Chapter 3** Dutch national data from 339,720 malnourished patients (2009-2019) were analysed and revealed that protein intake during hospital stay remains far below recommended levels, despite the availability of nutritional support.

Chapter 4 demonstrated that decreased appetite during and after hospitalization is common and strongly associated with sarcopenia-related outcomes, including reduced muscle mass, strength, and physical performance.

Chapter 5 presented the protocol for the ProIntens trial, designed to evaluate a transmural, intensive dietetic care pathway aimed at optimizing protein intake and physical functioning in older patients with malnutrition during and after hospitalization.

Chapter 6 reported on the main effects of the ProIntens randomized controlled trial. It identified practical barriers in implementing an intensive

dietetic care pathway in the real-world setting, such as fragmented care, resource limitations and variability in patient needs. Due to low inclusion rates and attrition, power was too low to report on effects.

In **Chapter 7** a holistic guiding framework for malnutrition research is introduced. It emphasized the integration of nutritional, functional and medical factors, and the adoption of more flexible designs to better capture real-world effects.

Chapter 8 and 9 showed results of systematically reviewed evidence on minerals and sarcopenia. The studies revealed that micronutrients such as magnesium and selenium may play an interactive role alongside protein in maintaining muscle mass, strength, and physical performance in older adults.

DETECTION OF MALNUTRITION

The detection of malnutrition follows a two step approach.(4) It starts with screening patients for the risk of malnutrition which is followed by assessment of criteria for the diagnoses of malnutrition. For screening, any validated screening tool is recommended. Yet, it differs greatly how these screening tools are developed, against which malnutrition definition and in what kind of patient group. In addition, the purpose of screening also differs(5). Some tools refer to the risk of malnutrition in a sense that a person is at risk of developing malnutrition in the near future, while other screening tools are developed to assess if there might be malnutrition present, after which it could be confirmed by assessing diagnostic criteria. (6) The term 'risk of malnutrition' might therefore compass different aspects. In Dutch hospitals, all admitted patients are screened for potential existing malnutrition. For the last decade this process has been part of a set of quality indicators, which has triggered the implementation of screening tools as part of regular care.(7) Upon a positive screening outcome, a patient is referred to an in-hospital dietitian. However, the findings presented in this thesis underscore the limitations of existing malnutrition screening tools in accurately identifying older patients with malnutrition according to the most recent diagnostic criteria (**Chapter 2**). Current available screening tools often lack sensitivity and may fail to

detect patients at risk of malnutrition. The misclassification of older patients can be as high as 68%. This stresses the need for improvement in screening methods that are both sensitive and practical for use. We argued that due to the high prevalence of malnutrition (i.e. 42%) that for this specific patient group, one could directly assess the diagnostic criteria for malnutrition, without prior screening. This is very recently also advocated by the working group on malnutrition screening of the Global Leadership Initiative for Malnutrition (GLIM).(8) For patient groups that are known to be at risk of malnutrition, such as older adults and cancer patients, quick and easy identification of malnutrition is essential for an early start of treatment to prevent negative health outcomes. Integrating the diagnostic criteria of GLIM without prior screening should therefore be easily accessible, for example through electronic health records, where most of needed information is readily available. This could allow for a more automated identification without increasing the workload for health care professionals. The use of digital systems to support in screening seems underutilized.

INCREASING PROTEIN INTAKE AND PHYSICAL FUNCTIONING IN CLINICAL PRACTICE

Once patients are identified as being malnourished, the current guidelines recommend optimizing protein intake and the encouragement of physical activity.(9) However, Dutch national data over a decade, revealed that protein intake remains insufficient among hospitalized patients at risk of malnutrition, with many failing to meet even the minimum recommended levels (**Chapter 3**). Poor appetite might be one of the underlying factors for this insufficient intake. As seen in the Hospital-ADL study (**Chapter 4**), poor appetite is frequently reported during hospitalization, often persists after discharge, and is related with sarcopenic related outcomes such as poor physical functioning. Similarly, physical activity levels often decline sharply during hospitalization, further contributing to rapid muscle loss and functional decline.(10) While dietetic counselling and physiotherapy can support recovery, the ProIntens trial (**Chapter 5 and 6**) revealed the difficulties of embedding such multidisciplinary approaches into daily practice, reflecting both patient- and system-level barriers, as elaborated in the following sections..

Personalization and behavioral changes in clinical practice

One key challenge is the need for more personalized treatment approaches. Current malnutrition guidelines and many interventions apply a "one-size-fits-all" model, which risks overlooking the heterogeneity of older patients. Malnutrition and sarcopenia can happen to any patient during hospitalization, regardless of their reason for hospitalization. Therefore, their needs and recovery goals can also differ greatly. Although the ProIntens intervention allowed dietitians some flexibility to adjust the intervention towards the patients' needs, the number of contacts and intervention materials were standardized across participants. A more personalized approach, tailored to diagnosis, recovery goals and expected trajectory, may be more effective, yet complicated in traditional research design as it increases heterogeneity. Demonstrating measurable effects on patient levels directly requires nutritional interventions to be intensive and clearly distinct from usual care. This intensity, however, can be too demanding for older patients. Finding this balance between clear distinction for research effects and adjusting treatment towards patients needs might be a difficult task for dietitians to take on.

Optimizing care might therefore rely more on system-level improvement than solely on patient-level changes. Profiling patients upon admission to match them with the appropriate professionals, e.g. dietitians, physiotherapist, nurse, or other health professional, could strengthen outcomes. However, traditional RCTs limit such flexibility in the intervention. Alternative designs such as pragmatic, adaptive, or stepped wedge design may be more suitable for real-world setting research. The ProIntens intervention was initially designed as a stepped wedge trial to allow sufficient time for implementation and training of professionals, but the COVID-19 pandemic disrupted care organization and cluster stability, which is needed for the statistical power of a stepped wedge design. This made it unfeasible to conduct the trial as intended. Consequently, the parallel RCT design was used as an alternative, and left insufficient time to train and support healthcare professionals in adopting the new practices of the intervention.

In addition to these methodological obstacles, the trial revealed implementation barriers that were not fully anticipated. Although ProIntens was designed as an effect study, in hindsight it would have benefitted from being approached as an implementation study. The

evidence supporting increased protein intake and physical activity for treating malnutrition was already there. The remaining bottleneck lay in how to operationalize these principles in daily practice and across the hospital–home continuum. Earlier adoption of an implementation perspective could have helped identify the underlying reasons why increasing protein intake and promoting physical activity remain so challenging, as well as the stakeholder groups—patients, nurses, dietitians, physiotherapists, and primary care providers—whose engagement is essential for success. This experience underscores that advancing nutritional care requires not only effective interventions, but also a structured understanding of how to embed them within complex clinical environments. To optimize interdisciplinary collaboration and enhance patients' self-management, a future implementation study could adopt a structured co-design approach. Such a study would begin with joint development sessions involving patients and health care professionals to create a roadmap that spans the full care trajectory from hospital admission to return home. This road map could incorporate profile-based triage at admission, coordinated care pathways with decision trees, goal-setting cards and referral overviews, ensuring that all disciplines work from a shared framework. In parallel, a patient-centered decision support tool could be developed with patients and informal caregivers to help them understand which types of care are most relevant to achieving their recovery goals. Dietitians, physical therapists or nurses could guide patients in setting realistic and meaningful goals within this tool. Both the roadmap and decision support tool would benefit from iterative cycles of development, testing and refinement to ensure alignment with real-world practice and to facilitate sustainable integration into routine care.

Patient Engagement and co-creation

There is a need for personalized and interdisciplinary health care. However, this approach also depends on patient engagement and self-management.(11) Within the ProIntens intervention, next to support from the dietitian, self-management was integrated through an information folder based on behavior change principles. However, the folder was rarely used by participants, revealing a gap between intervention design and patient needs. The absence of patient co-creation during the development phase of the intervention likely limited its relevance. Intensively engaging end-users of intervention materials is essential. A more thorough needs assessment with potential end-users would likely

have improved the alignment of the intervention materials and delivery methods with patients' capabilities, preferences, and recovery needs. However, identifying and recruiting potential end-users prior to the trial proved challenging. To comply with privacy regulations, we asked participating dietitians whether we could contact the patients they were currently treating, but many were hesitant to approach their patients out of concern for adding burden during an already vulnerable period. Attempts to recruit community-dwelling older adults through flyers in neighborhood centers also yielded no responses. These challenges highlight the practical barriers in involving frail older adults in early intervention design, even when their input is essential for creating truly patient-centered materials.

Integrating physical activity

Because the information folder was underused, the physical activity component of the intervention was less pronounced then intended. While the treatment of malnutrition calls for (an increase in) physical activity. A physiotherapy-led mobilization program had been planned, but reimbursement differences between dietetic care and physiotherapy care hindered implementation. Not every patient has insurance for physiotherapy or is able to afford it.(12) As a result, patients received paper-based exercise programs to perform independently after discharge – requiring high intrinsic motivation despite ongoing fatigue and poor appetite.

As the dietary guideline for malnutrition mention, a treating dietitian can also stimulate a patient to increase their physical activity.(9) Although dietitians were informed about patients' physical performance levels, post-study evaluations revealed limited integration of this information into counselling. Similarly, warm handovers and transmural collaboration were found difficult due to time and reimbursement constraints. It needs to be studied what is needed to change this treatment reluctance. However, it does highlight that behavioral change is required not only from patients but also from healthcare professionals, and that successful implementation demands system-level support. Ensuring aligned responsibilities of health care professionals, dedicated time for interprofessional collaboration and adequate funding are prerequisites for sustainable, effective nutritional care.

SARCOPENIA IN COEXISTENCE

Together, the presented findings show that improving nutritional care in clinical practice requires more than the implementation of guidelines, it demands alignment between patient capacity, professional collaboration, and system structures. Yet, even when these elements are optimized, maintaining muscle mass and function in older adults remains a major challenge. This reflects not only gaps in care delivery but also the biological complexity of aging, where malnutrition, inflammation, and inactivity interact to accelerate muscle loss and undermine recovery. Understanding this interplay between nutrition and muscle health is therefore crucial for developing interventions that support long-term functional outcomes.

Sarcopenia, defined by the progressive loss of muscle mass, strength, and function, emerges in this thesis as a multifactorial condition affected by nutritional status, disease burden, appetite, and physical activity level. While adequate protein intake remains central to muscle maintenance, our findings also highlight the importance of micronutrients such as magnesium and selenium in supporting muscle metabolism, oxidative balance, and neuromuscular function (**Chapters 8 and 9**). Poor appetite, frequently observed during and after hospitalization, further compromises nutritional intake and thereby muscle preservation (**Chapters 3**).

Importantly, an increasing number of older adults experience low muscle mass and muscle strength in combination with excess adipose tissue, a condition known as sarcopenic obesity. This paradoxical phenotype illustrates that undernutrition and overnutrition may coexist, and that body composition, rather than body weight alone, determines functional risk. To support clinical clarity, international collaborations such as GLIM, GLIS, and SOGLI are working towards harmonizing definitions and cut-off values for low muscle mass in malnutrition, sarcopenia, and sarcopenic obesity, reflecting shared underlying mechanisms.

Together, these insights demonstrate that addressing sarcopenia requires a holistic, integrated approach that combines dietary optimization, appetite support, and targeted physical activity within coordinated multidisciplinary care.

FUTURE DIRECTIONS

The coexistence of malnutrition, sarcopenia, and sarcopenic obesity underscores the complexity of nutritional care in older adults. Body weight alone is insufficient to guide assessment or intervention; careful evaluation of muscle mass, function, and dietary intake is essential. Future strategies must therefore combine sensitive screening, timely detection, and integrated, interprofessional interventions that address both nutrition and functional outcomes.

Scalable and pragmatic approaches are needed to overcome persistent research and implementation challenges. Adaptive, pragmatic, or hybrid trial designs can allow flexible, patient-centered interventions while generating robust evidence, and embedding evaluation within routine care can capture real-world effectiveness. Transmural interdisciplinary collaboration, between dietitians, physiotherapists, nurses, and physicians, is crucial, particularly for complex phenotypes like malnutrition and sarcopenia, where individualized strategies may be required to prevent further muscle loss and optimize recovery.

Finally, systemic support is essential: adequate funding, clear role allocation, and alignment of responsibilities across healthcare settings can ensure sustainable implementation. By addressing these challenges, nutritional care can be fully integrated into treatment pathways for older adults, improving recovery, functional independence, and long-term health outcomes. The guiding framework in **Chapter 7** represents a first step toward this vision, highlighting opportunities for research, clinical practice, and policy innovation.

CONCLUSION

This thesis demonstrates that malnutrition and sarcopenia are highly prevalent and interrelated conditions in older adults, particularly during and after hospitalization. Together, these conditions significantly compromise physical function, recovery, and quality of life, while increasing healthcare use and costs. Through a combination of national data, clinical trials, and review studies, this work highlights critical gaps in detection, intervention, and continuity of care, while providing evidence-based strategies to address them.

First, current malnutrition screening tools often fail to identify at-risk older adults, particularly those with subtle declines in nutritional status or with overlapping conditions such as sarcopenic obesity. Second, achieving recommended protein intake and promoting physical activity remain major challenges in hospital and post-discharge care. Factors such as poor appetite, heterogeneous patient needs, and system-level barriers limit adherence and effectiveness of nutritional interventions. Third, integrating interprofessional dietetic and physiotherapy-led care into routine practice requires interprofessional collaboration, patient engagement, and structural support to be sustainable and impactful. Finally, methodological constraints in traditional randomized controlled trials limit the ability to study interventions in frail, complex patients, emphasizing the need for pragmatic, adaptive, and real-world study designs.

Taken together, these findings advocate for a shift from isolated interventions to integrated, patient-centered, and system-supported strategies. Future research should combine sensitive screening, personalized interventions, and multidisciplinary care pathways, while leveraging digital systems and learning health frameworks to improve implementation and evidence generation. For policymakers and clinicians, this work underscores the urgency of embedding nutritional care as a core component of treatment pathways for older adults, thereby promoting recovery, functional independence, and quality of life.

Ultimately, optimizing nutritional care for older adults is not just a clinical imperative – it is a strategic investment in preserving independence, improving recovery, and enhancing quality of life across an aging population.

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CHAPTER 11

Summary

ENGLISH SUMMARY

Malnutrition and sarcopenia are two closely related conditions that frequently affect older adults, especially those who are acutely ill or hospitalized. Both conditions are associated with reduced physical function, impaired recovery, and increased morbidity and mortality. Their coexistence creates a downward spiral of declining nutritional intake, muscle loss, and functional dependency, often extending beyond hospital discharge and into long-term care. Despite growing recognition of their impact, nutritional care for older adults remains suboptimal, fragmented, and inconsistently embedded within clinical practice.

The overarching aim of this thesis was to optimize nutritional care for older adults at risk of malnutrition and sarcopenia, both during and after hospitalization. This was done by examining gaps in screening and treatment, evaluating strategies to improve nutritional intake and recovery, and proposing directions for future research and clinical practice.

This thesis is structured in three parts:

- **Part I** explores the identification, mechanisms, and prevalence of malnutrition and sarcopenia in older adults.
- **Part II** focuses on developing and evaluating solutions to optimize protein intake and physical functioning in clinical practice and discussing future research directions.
- **Part III** broadens the perspective by exploring the role of micronutrients

Part I – Identifying malnutrition and sarcopenia in older adults
Early and accurate identification of malnutrition is essential to ensure timely and targeted nutritional care. However, screening practices in hospitals vary widely, and the diagnostic criteria have evolved over time. **Chapter 2** examined the performance of five widely used malnutrition screening tools in hospitalized older patients, comparing their results against the Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria. The findings showed that most tools lacked sufficient sensitivity, leading to 32–68% of malnourished patients remaining unidentified, respectively to the used screening tool. This underlines the need to refine

current screening approaches to better align with GLIM, ensuring early recognition and appropriate referral to dietitians.

To stimulate early recognition and treatment of malnutrition, the Dutch Healthcare Inspectorate obliged all hospitals from 2008-2019 to report the number of malnourished patients with an adequate protein intake on the fourth day of hospital admission. **Chapter 3** analysed the collected data the collected, covering over 339,000 malnourished hospital patients across an 11-year period (2008–2019). The results revealed that protein intake remained consistently below recommended levels throughout the decade, despite increased awareness and efforts to address hospital malnutrition. These findings highlight persistent challenges in translating nutritional guidelines into daily practice.

Chapter 4 investigated the role of appetite as a key driver of poor nutritional intake and sarcopenia-related outcomes. Using data from the Hospital-ADL study, it was shown that decreased appetite is highly prevalent during hospitalization and often persists after discharge. Poor appetite was associated with reduced muscle strength, lower physical functioning, and indicators of sarcopenia. These findings emphasize that interventions should not only address nutrient intake but also consider stimulation of appetite to support physical functioning.

Together, the first part of this thesis demonstrates that malnutrition and sarcopenia remain underdiagnosed and undertreated in older hospitalized adults. Addressing these issues requires a combination of improved diagnostic sensitivity, targeted nutritional strategies, and greater attention to patient-specific factors such as appetite and disease burden.

Part II – Working Towards Solutions: From Evidence to Clinical Practice

Building on these findings, the second part of this thesis focuses on the development, implementation, and evaluation of an intensified dietetic intervention to optimize protein intake and recovery in older adults with malnutrition.

Chapters 5 and 6 describe the design and main outcomes of the ProIntens trial, a multicenter randomised controlled trial testing a transmural

dietetic care pathway that provided intensive dietary counselling during hospitalization and in primary care up to three months post-discharge. The intervention aimed to bridge the gap between hospital and home, supporting continuity of care and early recovery. Although the intervention proved feasible and was positively received by patients and professionals, inclusion rates were lower than anticipated due to illness severity, fatigue, and patient burden. Moreover, implementation in real-world hospital settings was challenged by limited time, staffing, and strict research design that left little room for personalization.

Despite these challenges, the ProIntens trial provided valuable insights into the barriers and facilitators of intensive nutritional care. It demonstrated that older adults potentially benefit most when dietetic support is coordinated with physical activity, appetite management, and patients' readiness for change. The trial also highlighted the need for adaptive study designs that allow for more flexibility, such as stepped-wedge or pragmatic trials, especially in vulnerable populations.

Chapter 7 builds on these insights by presenting a guiding framework for future nutritional research. This framework emphasizes the need for realistic, patient-centered methodologies that integrate research into clinical care (a "learning health system" approach). It also advocates for more holistic, multicomponent interventions that combine nutritional care, physical activity, and behavioral strategies, supported by multidisciplinary teams. The framework outlines how future studies can balance methodological challenges with feasibility, ensuring that research outcomes are both scientifically strong and clinically meaningful.

Part III – Expanding nutritional care in aging populations

While Part II focused on malnutrition and sarcopenia in the context of protein intake, physical activity, and post-hospital recovery, it is also important to consider additional nutritional determinants that may influence muscle health. Minerals are among these key factors, potentially affecting muscle metabolism, strength, and physical performance in older adults.

Chapters 8 and 9 present systematic reviews evaluating the role of minerals in sarcopenia. The first review highlighted associations between deficiencies in minerals such as magnesium, selenium, and calcium, and

poorer muscle mass, strength, and function. These minerals may support muscle metabolism and antioxidative processes, which are critical for preserving muscle health in older adults.

The updated review **(Chapter 9)** confirmed the relevance of these minerals and identified emerging evidence on interactions between multiple minerals and muscle health. However, studies remain heterogeneous, and high-quality interventional trials are limited. These findings suggest that optimizing mineral intake could complement protein and exercise interventions to prevent or attenuate sarcopenia.

Together, these reviews emphasize that muscle health in older adults is influenced by multiple nutritional factors. Addressing mineral status, alongside established strategies such as adequate protein intake and physical activity, can support a comprehensive approach to maintaining functional independence and quality of life.

Conclusions and Implications

This thesis demonstrates that improving nutritional care for older adults requires a comprehensive approach that spans early detection, effective intervention, and sustainable implementation. Malnutrition and sarcopenia are often underdiagnosed and insufficiently treated, largely due to insensitive screening tools, fragmented care systems, and limited interdisciplinary collaboration.

The findings call for:

1. **Enhanced detection** – aligning screening tools with GLIM criteria and integrating them into electronic health records.
2. **Personalized and integrated care** – embedding dietetic and physical activity support as core components of recovery pathways.
3. **Innovative research designs** – adopting adaptive, pragmatic, and implementation-focused methodologies that reflect real-world care.
4. **System-level change** – ensuring interdisciplinary training, adequate resources, and policy support to make nutritional care routine practice.

By bridging the gap between research and clinical care, this work contributes to a more holistic, patient-centered approach to nutrition

and functional recovery in ageing populations. Ultimately, embedding nutrition as a core element of treatment can support healthy ageing, enhance independence, and improve quality of life for older adults across care settings.

NEDERLANDSE SAMENVATTING (SUMMARY IN DUTCH)

Ondervoeding en sarcopenie (een conditie die wordt gekenmerkt door leeftijdsgebonden verlies van spierkracht, spiermassa en fysieke functie) zijn twee nauwverwante aandoeningen die vaak voorkomen bij ouderen, vooral bij mensen die acuut ziek zijn of in het ziekenhuis liggen. Beide aandoeningen gaan gepaard met een vertraagd herstel, functionele achteruitgang en een verhoogd risico morbiditeit en mortaliteit. Het gelijktijdig voorkomen van ondervoeding en sarcopenie kan leiden tot een neerwaartse spiraal, waarbij een verminderde voedingsinname, verder spierverlies en toenemende afhankelijkheid in het fysiek functioneren elkaar versterken. Deze vicieuze cirkel reikt vaak verder dan de ziekenhuisopname en kan uitmonden in een langdurige zorgbehoefte. Ondanks de toenemende bewustwording van de impact van ondervoeding en sarcopenie, blijft de diëtistische zorg voor ouderen suboptimaal, gefragmenteerd en inconsistent geïntegreerd in de klinische zorg.

Het overkoepelende doel van dit proefschrift was het optimaliseren van de diëtistische zorg voor ouderen die risico op ondervoeding en sarcopenie hebben, zowel tijdens als na een ziekenhuisopname. Dit werd gedaan door tekortkomingen in het screenen en behandelen van ondervoeding te onderzoeken, verschillende strategieën voor het optimaliseren van de voedingsinname en ziekteherstel te evalueren en suggesties te geven voor toekomstig onderzoek en de klinische praktijk.

Dit proefschrift bestaat uit drie delen:

- **Deel I** kijkt naar de identificatie en prevalentie van ondervoeding en de onderliggende mechanismes van sarcopenie bij ouderen.
- **Deel II** richt zich op het ontwikkelen en evalueren van een interventie om de eiwitinname en het fysieke functioneren bij ouderen met ondervoeding in de klinische praktijk te optimaliseren. Tevens worden aanbevelingen voor toekomstig onderzoek gedaan.
- **Deel III** kijkt vanuit een breder perspectief naar sarcopenie door de rol van micronutriënten te evalueren.

Deel I – Het identificeren van ondervoeding en sarcopenie bij ouderen

Vroegtijdige en nauwkeurige identificatie van ondervoeding is essentieel om tijdige en passende voedingszorg te bieden. Echter lopen de methoden voor het screenen op ondervoeding sterk uiteen en zijn de diagnostische criteria voor ondervoeding in de loop van de tijd veranderd. In **hoofdstuk 2** werd de prestatie en nauwkeurigheid van vijf veel gebruikte screeningsinstrumenten voor ondervoeding onderzocht bij oudere ziekenhuispatiënten, waarbij de resultaten werden vergeleken met de huidige wereldwijd geldende diagnostische criteria van het Global Leadership Initiative on Malnutrition (GLIM). Uit het onderzoek bleek dat de meeste instrumenten onvoldoende in staat zijn om mogelijke ondervoeding in kaart te brengen. Hierdoor werd 32–68% van de ondervoede patiënten niet geïdentificeerd, afhankelijk van welk screeningsinstrument gebruik werd. Dit laat zien dat het nodig is om de huidige screeningmethoden te verfijnen, zodat ze beter aansluiten bij de GLIM criteria en vroegtijdige herkenning en correcte doorverwijzing naar diëtistische zorg kan worden gewaarborgd.

Om vroegtijdige herkenning en behandeling van ondervoeding te stimuleren heeft de Nederlandse Inspectie voor de Gezondheidszorg alle ziekenhuizen verplicht om van 2008 tot 2019 het aantal ondervoede patiënten met een adequate eiwitinname op de vierde dag van ziekenhuisopname te rapporteren. In **hoofdstuk 3** hebben we deze gegevens geanalyseerd, die betrekking hebben op meer dan 339.000 ondervoede ziekenhuispatiënten. Uit de resultaten bleek dat de eiwitinname gedurende het hele decennium consistent onder de aanbevolen hoeveelheid bleef, ondanks het toegenomen bewustzijn en inspanningen om ondervoeding in ziekenhuizen aan te pakken. Deze bevindingen wijzen op de aanhoudende uitdagingen bij het vertalen en toepassen van voedingsrichtlijnen in de dagelijkse praktijk..

Hoofdstuk 4 beschrijft het onderzoek naar de rol van verminderde eetlust als belangrijke oorzaak van een verslechterde voedingsinname en sarcopenie-gerelateerde uitkomsten. Met behulp van data uit de Hospital-ADL studie werd aangetoond dat verminderde eetlust veel voorkomt tijdens ziekenhuisopname en vaak ook na ontslag aanwezig blijft. Een verminderde eetlust werd geassocieerd met verminderde spierkracht, verminderd fysiek functioneren en andere indicatoren van

sarcopenie. Deze bevindingen benadrukken dat interventies niet alleen gericht moeten zijn op de voedingsinname maar ook rekening dienen te houden met het stimuleren van de eetlust ter bevordering van het fysiek functioneren.

Gezamenlijk laat het eerste deel van dit proefschrift zien dat ondervoeding en sarcopenie bij oudere volwassenen in het ziekenhuis nog steeds te weinig wordt (h)erkent en behandeld. Om dit aan te pakken, moet de sensitiviteit van diagnosticeren worden verbeterd, moeten er gerichte voedingsstrategieën komen en moet er meer aandacht besteed worden aan patiëntspecifieke factoren, zoals een verminderde eetlust en vermoeidheid bij ziekte..

Deel II – Werken naar oplossingen: van bewijs naar de klinische praktijk

Voortbouwend op de bevindingen uit deel I, richt het tweede deel van dit proefschrift zich op de ontwikkeling, implementatie en evaluatie van een intensieve diëtistische interventie om de eiwitinname en het herstel bij oudere met ondervoeding te optimaliseren.

Hoofdstuk 5 en 6 beschrijven het ontwerp en de belangrijkste resultaten van de ProIntens-studie, een multicenter gerandomiseerd gecontroleerd onderzoek naar een transmuraal diëtistisch zorgpad dat intensieve diëtistische begeleiding bood aan oudere patiënten met ondervoeding tijdens ziekenhuisopname en in de eerstelijnszorg tot drie maanden na ontslag. De interventie was bedoeld om de kloof tussen het ziekenhuis en thuis te overbruggen en zo de continuïteit van de zorg en een snel herstel te ondersteunen. Hoewel de interventie haalbaar bleek en positief werd ontvangen door patiënten en professionals, waren de inclusiepercentages lager dan verwacht. Dit kwam onder andere door de ernst van ziekte, vermoeidheid en de verminderde belastbaarheid van patiënten. Bovendien werd de implementatie van de interventie in de dagelijkse praktijk van het ziekenhuis bemoeilijkt door beperkte tijd voor patiënt en zorgprofessionals en het strikte onderzoeksdesign dat weinig ruimte liet voor het personaliseren van de interventie.

Ondanks deze uitdagingen leverde het ProIntens onderzoek waardevolle inzichten op in wat belemmerende en bevorderende factoren zijn voor intensieve voedings- en beweegzorg. Het toonde aan dat ouderen

mogelijk het meest baat hebben bij ondersteuning in de voeding die wordt afgestemd op fysieke activiteit, eventuele verminderde eetlust en de bereidheid van de patiënt om aan herstel te werken. Het onderzoek benadrukte ook de noodzaak van alternatieve, flexibelere onderzoeksopzetten, die beter aansluiten bij de behoeften van kwetsbare patiëntgroepen, zoals een stepped wedge of pragmatisch design.

In **Hoofdstuk 7** wordt er voort gebouwd op deze inzichten door een richtinggevend kader te presenteren voor toekomstig onderzoek naar voeding en beweging bij kwetsbare patiëntgroepen in de klinische praktijk. Dit kader benadrukt de noodzaak van een realistische, patiëntgerichte onderzoeksmethodes die het onderzoek integreren in klinische zorg (een 'zelf lerend zorgsysteem'- benadering). Het pleit voor een meer holistische, multifactoriële interventies die voedings- en beweegzorg combineren met gedragsveranderingsstrategieën, ondersteund door interprofessionele samenwerkende zorgteams. Het kader schetst hoe toekomstige studies een balans kunnen vinden tussen methodologische uitdagingen en haalbaarheid. Op die manier kunnen onderzoeksresultaten zowel wetenschappelijk robuust als klinisch relevant zijn.

Deel III – Uitbreiding van de voedingszorg voor de ouder wordende populatie

Hoewel Deel II zich richtte op ondervoeding en sarcopenie in de context van eiwitinname, fysieke activiteit en herstel na ziekenhuisopname, spelen mogelijk ook andere voedingsdeterminanten een belangrijke rol in de spiergezondheid. Mineralen behoren tot deze mogelijke determinanten, gezien de invloed die ze hebben op het spiermetabolisme, spierkracht en het fysieke functioneren van oudere volwassen.

Hoofdstukken 8 en 9 beschrijven de resultaten van twee systematische reviews waarin de rol van mineralen bij sarcopenie wordt geëvalueerd. De eerste systematische review benadrukte het verband tussen tekorten aan mineralen zoals magnesium, selenium en calcium en een lage spiermassa, spierkracht en spierfunctie. Deze mineralen kunnen het spiermassametabolisme ondersteunen en hebben antioxidantatieve eigenschappen, die belangrijk zijn voor het behoud van spiergezondheid bij oudere volwassenen. Het geüpdatete systematische review **(Hoofdstuk 9)** bevestigde het belang van deze mineralen en bracht

nieuw bewijs naar voren. De studies blijven echter heterogeen en er zijn maar weinig studies van hoogwaardige kwaliteit, zoals gerandomiseerde gecontroleerde onderzoeken. Deze bevindingen suggereren dat het optimaliseren van de mineraleninname een aanvulling kan vormen op de eiwitinname- en beweeginterventies om sarcopenie te voorkomen of te verminderen.

Conclusies en implicaties

Dit proefschrift toont aan dat het verbeteren van de voedings- en beweegzorg voor oudere volwassenen een alomvattende aanpak vereist met aandacht voor vroegtijdige diagnostiek, effectieve interventies en duurzame implementatie. Ondervoeding en sarcopenie worden vaak ondergediagnosticeerd en daardoor onvoldoende behandeld, mede door niet-sensitieve screeningsinstrumenten, gefragmenteerde zorg en beperkte interdisciplinaire samenwerking.

Daarom vragen de bevindingen in dit proefschrift om:

1. **Verbetering in diagnostiek** – screeningsinstrumenten die afgestemd worden op de GLIM criteria en geïntegreerd worden in elektronische patiëntendossiers.
2. **Gepersonaliseerde en geïntegreerde voedings- en beweegzorg** – ondersteuning op het gebied van voeding en beweging integreren als kernonderdelen van de behandeling op weg naar herstel.
3. **Innovatieve onderzoekdesigns** – adaptieve, pragmatische en implementatiegerichte onderzoeksopzetten toepassen die een afspiegeling zijn van de klinische praktijk.
4. **Verandering op systeemniveau** – zorg voor interdisciplinaire training, voldoende middelen en tijd en ondersteuning vanuit beleid om voedings- en beweegzorg tot routine zorg te maken

Door de kloof tussen onderzoek en de klinische praktijk te overbruggen, draagt dit proefschrift bij aan een meer holistische, patiëntgerichte benadering van voedings- en beweegzorg en functioneel herstel bij oudere volwassenen. Het integreren van voeding en beweging als kernelementen van de behandeling kan uiteindelijk leiden tot het gezonder ouder worden, een grotere mate van onafhankelijkheid en een verbetering van de kwaliteit van leven van oudere volwassenen binnen het hele zorglandschap.

APPENDICES

PHD PORTFOLIO

Name PhD student: Carliene van Dronkelaar
PhD period: 2018-2026
Supervisior & co-supervisiors: prof.dr.ir Peter Weijs; dr. Micheal Tieland; dr. Hinke Kruizenga

PhD training	Year	ECs
External courses		
Intervention Mapping	2018	1.3
eBROK	2018	1.5
Exposure Assessment in Nutrition Research	2018	1.5
Gespreksleider Focusgroepen	2018	0.5
Vervolg Focusgroepen	2018	0.5
Writing a Scientific Article	2019	3
Research Integrity	2019	2
Muscle Histology	2020	0.5
Statistics in R	2022	2
Practical Biostatistics	2022	1.4
Multilevel and longitudinal data-analyses	2022	4
Research related		
Seminars/ Journal clubs	2018-2023	2
Presenting at (inter)national conferences (EUGMS 2019; ESPEN 2020, 202, 2022; NVZF 2021; NSD 2022; ONCA 2023;)	2018- 2023	3
Attending conferences and symposia (ESPEN 2018, 2023)	2018-2023	1
Other academic activities		
Conferences	2018	1
Clinical lectures (52x)	2019	1
Peer-review	2022	0.5
Teaching/Student supervision		
Supervising student thesis (42x)	2018-2023	4
Total EC		30.7

LIST OF PUBLICATIONS

Publications as part of this thesis

van Dronkelaar C, Tieland M, Cederholm T, Reijnierse EM, Weijs PJM, Kruizenga H. *Malnutrition Screening Tools Are Not Sensitive Enough to Identify Older Hospital Patients with Malnutrition*. Nutrients. 2023;15(24).

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ABOUT THE AUTHOR

Carliene van Dronkelaar was born on June 30, 1990, in Apeldoorn. After completing high school, she started her studies in Nutrition & Dietetics at the Hanze University of Applied Sciences in Groningen in 2008. During her bachelor's program, she developed a broad interest in applied nutrition through a minor in sports nutrition at Papendal, an internship at the top clinical hospital Isala in Zwolle, and a thesis project on nutritional education in primary schools at Aruba.

After obtaining her Bachelor's degree in 2012, Carliene continued with the Master's program Nutrition & Health at Wageningen University & Research. During this period, her interest broadened into clinical nutrition research. She completed an internship at Seoul National University in South Korea and conducted her master's thesis on seasonal variations in vitamin D status and its association with dietary intake and sun exposure in Dutch elite and sub-elite athletes. These experiences strengthened her ambition to contribute to research with direct relevance for clinical practice.

In 2015, Carliene started working as a research assistant at the lectureship Nutrition & Exercise at the Amsterdam University of Applied Sciences. Together with Jantine van den Helder, she worked on the VITAMIN study, investigating a blended home-based exercise and protein intervention in community-dwelling older adults. This project marked an important step in her development as a researcher and led to the start of her PhD trajectory with the ProIntens study in 2018, under the supervision of Prof. dr.ir. Peter Weijs, dr. Michael Tieland, and dr. Hinke Kruizenga. During her PhD, Carliene further developed her methodological expertise, project coordination skills, and ability to collaborate with a wide range of stakeholders, including healthcare professionals, patients, and students.

Currently, Carliene works as a postdoctoral researcher at the Netherlands Institute for Health Services Research (NIVEL) and at Amsterdam

University Medical Centers. In her future work, she aims to continue bridging the gap between research and clinical practice, with a focus on improving nutritional care and outcomes for older adults.

DANKWOORD

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