Oral nutrition interventions in hospitalised older people at nutritional risk

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[Intervention Protocol]

Oral nutrition interventions in hospitalised older people at nutritional risk: a network meta-analysis of individual participant data

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess in hospitalised older people with (risk of) malnutrition the effects of different nutrition interventions (e.g. supportive interventions, nutritional counselling, food modifications, oral nutritional supplements, comprehensive individualised nutritional interventions or combined approaches) compared to control groups (usual care, placebo or health education materials) on patient-relevant outcomes, and to rank the effects of the different treatments by using a network meta-analysis with individual participant data.

BACKGROUND

Description of the condition

Protein-energy malnutrition is a state of energy and protein deficiency leading to unfavourable changes in body composition and body functions associated with worse clinical outcomes (Allison 2000). The main etiologic mechanisms leading to malnutrition are insufficient dietary intake, increased energy or nutrient requirements or reduced nutrient bioavailability (Cederholm 2019).

Malnutrition is usually diagnosed by a two-step approach. First, screening is performed with a validated screening tool to identify persons at risk of malnutrition. The Nutritional Risk Screening 2002 (NRS) (Kondrup 2003a), the Malnutrition Universal Screening Tool (MUST) (Elia 2003), the Mini Nutritional Assessment (MNA) (Guigoz 1994; Kaiser 2009), and the Subjective Global Assessment (SGA) (Detsky 1987) are tools that are recommended by medical nutrition societies (Kondrup 2003b), hence are commonly used. As these tools are quick and easy to administer, their completion does not require specific educational training, and they can be performed by health care professionals (Kondrup 2003b; Reber 2019). In case of a positive screening result, a nutritional assessment for diagnosis, identification of causes and estimation of the nutritional deficit follows as the second step; this step is usually completed by registered dieticians or nutritionists (Reber 2019; Volkert 2019a). A commonly-used tool to facilitate assessment is the Patient-Generated Subjective Global Assessment (PG-SGA) (Ottery 1996; Soriano-Moreno 2022).

However, in research and clinical practice, different criteria and cut-off values are applied to define malnutrition (Cederholm 2017a; Heersink 2010; Leij-Halfwerk 2019; Soriano-Moreno 2022; Wolters 2019). To align the diagnostic procedure, the Global Leadership Initiative on Malnutrition (GLIM), a coalition of different international medical nutrition societies, has proposed consensus-based criteria (Cederholm 2019). If at least one phenotypic criterion ('unintentional weight loss', 'low BMI', or 'low muscle mass'), as well as at least one etiologic criterion ('reduced food intake or assimilation' or 'inflammation') are present, malnutrition can be assumed (Cederholm 2019).

Hospitalised older people (65 years and older) are at particular risk for malnutrition, as dietary intake is often diminished, metabolic demands are increased, and bioavailability of nutrients may be reduced in case of acute diseases including gastrointestinal problems (Pourhassan 2018; Tonkikh 2019). Furthermore, non-disease-related factors may be present (e.g. social isolation, functional impairment or psychological problems), making older people already vulnerable to the development of malnutrition before their admission to hospital (O'Keeffe 2019; Volkert 2019b). The German hospital malnutrition study (13 hospitals, 1886 people) reported age to be associated with malnutrition according to SGA on the day of admission (Pirlich 2006). Correspondingly, the prevalence of malnutrition was highest in geriatric departments (56%) compared to other specialties, e.g. oncology (38%), gastroenterology (33%) or surgery (14%) (Pirlich 2006). According to the MNA, about 30% of hospitalised older people suffer from malnutrition and a further 50% are at risk (Cereda 2016). Moreover, studies report distinct proportions of older people with malnutrition persisting until hospital discharge, as well as worsening nutritional status during hospital stay (Allard 2016; Zhu 2017).

An important attribute of malnutrition is the loss of body protein, leading to impaired immune and organ functions and a reduction of muscle mass (Deutz 2019; Landi 2019; Norman 2008). It is well known that malnutrition is associated with increased morbidity and mortality, as well as longer convalescence from diseases (Agarwal 2013; Norman 2008). In hospitalised older people, there is a distinct overlap between (risk of) malnutrition and the geriatric syndromes frailty and sarcopenia (Ligthart-Melis 2020); these also affect recovery from disease and are associated with poor clinical outcomes (Beaudart 2017; Cunha 2019; Veronese 2019). Compared to those unaffected, longer hospital stays, more complications, and increased readmission rates have frequently been reported in older people with (risk of) malnutrition (Mazzola 2017; O'Shea 2017; Rong 2022; Sharma 2017). Malnutrition in older people is associated with an increased risk of functional decline, e.g. after surgery and hospital discharge (Felder 2015; Zhang 2020), with reduced quality of life (Rasheed 2013), and higher health care costs (Abizanda 2016).

Description of the intervention

Nutritional interventions cover a wide range of different strategies to increase dietary intake and improve the nutritional status of persons with (risk of) malnutrition (Cederholm 2017b). In current guidelines on clinical nutrition and hydration in geriatrics, strategies are divided into (a) supportive interventions, (b) nutritional counselling, (c) food modification, (d) oral nutrition supplements, (e) enteral nutrition, and (f) parenteral nutrition (Volkert 2019c). Interventions to increase oral nutritional intake are generally favoured as they are less invasive and potentially safer (Druml 2016; Volkert 2019c). This Cochrane Review will, therefore, focus on oral nutritional interventions starting after admission to the hospital.

Supportive interventions mainly refer to the provision of meal-time assistance by nursing staff or volunteers, comprising comfortable positioning at the table, verbal prompting, cutting of foods as well as direct eating and drinking support (Tassone 2015; Volkert 2019c). Environmental aspects, including a pleasant home-like atmosphere during mealtimes, an appealing presentation of meals and nutritional education of patients and caregivers, are considered further supportive interventions (Volkert 2019c). Examples for supportive interventions applied in the hospital setting are the 'red tray system' attracting the attention of the nursing staff to patients at nutritional risk who need support with eating (Bradley 2003) or 'protected mealtimes' providing time to eat without any negative interruptions (e.g. ward rounds) but with adequate meal-time assistance (Porter 2017).

Nutritional counselling is usually provided by registered dieticians or nutritionists and consists of individual or group-based talks with advice to modify or increase dietary intake to prevent further weight loss and regain body weight (Baldwin 2021; Volkert 2019c). Personalised counselling can be supported by written materials and telephone or video follow-ups (Volkert 2019c).

Food modification focuses on adjustments of macro- and micro-nutrient intake (Cederholm 2017b), and comprises the provision of additional snacks, finger foods, fortified foods or meals (Volkert 2019c). Food fortification is defined as the enrichment of natural foods with energy or specific nutrients to increase

energy or nutrient density (Cederholm 2017b; Volkert 2019c). Food modification can also refer to texture-modification, e.g. puréed foods. However, randomised controlled trials solely focusing on texture modification are not within the scope of this review.

Oral nutritional supplements (ONS) are energy- and nutrient-dense products that can be offered in addition to the usual meals or can replace them entirely in the case that products are "nutritionally complete in a predefined volume" (Baldwin 2021). Oral nutritional supplements are available in different forms (liquid or solid), volumes, types (e.g. high protein) and flavours (Volkert 2019c).

In order to reach optimal benefits for patients, different oral nutritional strategies can be combined and individualised as comprehensive individualised nutritional interventions (Volkert 2019c).

Adverse effects of the intervention

As oral nutritional intervention strategies focus on eating support or changes in diet (e.g. fortification or supplementation), adverse effects of these interventions are assumed to be minimal. Nonetheless, some systematic reviews reported adverse effects of nutritional interventions, mainly related to gastrointestinal problems (e.g. bloating, nausea, vomiting or diarrhoea) due to intolerances towards fortified foods, snacks or ONS (Baldwin 2016; Milne 2009). However, in most studies, adverse effects were only reported for the intervention group, so no comparative data were available (Milne 2009).

Health care systems might be burdened by increased costs for intervention products and additional staff needed to provide the interventions, especially if interventions are ineffective. However, several investigations have shown nutritional interventions to be cost-effective for medical inpatients (Elia 2015; Schuetz 2021).

How the intervention might work

All oral nutritional intervention strategies aim to directly or indirectly increase energy, protein or other nutrient intake, and to meet individual energy and nutrient requirements to improve nutritional status (Baldwin 2021; Bally 2016; Mills 2018; Tassone 2015). Improving nutritional status goes in line with restoring body proteins and fat mass, and supports the recovery of body functions on cell and organ levels, which might have positive effects on health-related outcomes and quality of life for older people (Baldwin 2021; Feinberg 2017).

Why it is important to do this review

Malnutrition is highly prevalent but often unrecognised in hospitalised older people, and therefore poses a burden for the individual and the healthcare system (Abizanda 2016; Cereda 2016). In a paper published in 2010, annual healthcare costs attributed to malnutrition were estimated to be EUR 120 billion for the European Union (Ljungqvist 2010). To improve clinical outcomes in hospitalised older people with (risk of) malnutrition and to reduce related costs, knowledge about effective interventions is important for clinical practice. Even though evidence-based guidelines on clinical nutrition in geriatrics exist, the grades of recommendations are often rated down due to poor quality of available evidence, or recommendations are based on clinical experience ("good clinical practice points") due to insufficient evidence (Volkert 2019c).

Previously published systematic reviews on the effects of nutritional interventions reported inconsistent results. The Cochrane Review by Milne and colleagues focused on older people from different healthcare settings and found protein and energy supplementation effective in lowering mortality risk in the subgroup of older malnourished people (Milne 2009). A further Cochrane Review (Baldwin 2016) analysed supportive nutritional care interventions in adults at nutritional risk (mean age range 62 to 87 years) and showed effects on lowering all-cause mortality with moderate certainty of evidence, but not on reducing hospitalisation or increasing quality of life. The same group conducted a second Cochrane Review on the effects of dietary advice with or without oral nutritional supplements in adults with disease-related malnutrition (mean age range 49 to 87 years) and did not find evidence for lowering mortality risk, while for other outcomes, e.g. quality of life, some positive effects were described (Baldwin 2021). Two systematic reviews specifically focusing on nutritional support in hospitalised people showed no improvement in clinical outcomes (Bally 2016; Feinberg 2017). Another systematic review suggested that nutritional support was associated with improved survival and non-elective hospital readmission rates among medical inpatients who were malnourished, but did not show effects on infections, functional outcomes and length of hospital stay (Gomes 2019). Mills 2018 summarised evidence on energy- and protein-based food fortification in hospitalised older people, showing it to be an effective strategy to increase dietary intake, while results were inconclusive for nutritional and functional status.

For the specific population of hospitalised older people at nutritional risk, most of these previous systematic reviews have limited informative value as they either included younger age groups (Baldwin 2016; Baldwin 2021; Bally 2016; Feinberg 2017; Gomes 2019), or they did not focus exclusively on the hospital setting (Baldwin 2016; Baldwin 2021; Milne 2009). Furthermore, not all included studies used objective measures, e.g. screening tools or anthropometric parameters, to define the participants' nutritional risk (Baldwin 2021; Feinberg 2017; Mills 2018; Milne 2009). Some of the systematic reviews included studies with people in intensive care, recovering from cancer treatment, or with stroke, who may have specific nutritional needs due to their disease (Baldwin 2021; Bally 2016; Feinberg 2017; Gomes 2019; Mills 2018; Milne 2009). Importantly, all meta-analyses reported in these systematic reviews were pairwise meta-analyses, and therefore could not, or could only partially, compare the different types of nutritional interventions simultaneously (Schwingshackl 2019).

A large, multicentre randomised controlled trial published in 2019 was able to show the effectiveness of an individualised nutritional support intervention to lower adverse outcomes and all-cause mortality as well as to improve quality of life and functional status in medical inpatients at nutritional risk (mean age 73 years) (Baumgartner 2021; Schuetz 2019). This trial has not yet been integrated into a Cochrane Review, but it may help in answering the remaining question of which oral nutritional intervention approach offers the greatest health-related benefits in hospitalised older people who are at nutritional risk. To answer this question, the method of choice is a network meta-analysis (NMA), which is an extension of pairwise meta-analysis that enables a simultaneous comparison of multiple interventions (Chaimani 2022). The resulting estimates of the relative effects are usually considered more precise than a single direct or indirect estimate. In

addition, NMA allows an estimation of the ranking of interventions (Chaimani 2022). The collection of individual participant data (IPD) will help to reduce heterogeneity and improve data quality. An analysis of IPD will allow investigation of how participant-level covariates, such as age, gender or disease, might alter the impact of the intervention, providing in-depth explorations and robust meta-analysis results, which may differ from those based on aggregate data (Riley 2022; Tierney 2022). To the best of our knowledge, no systematic review has been conducted that used IPD to simultaneously compare different nutrition interventions on clinically relevant outcomes in hospitalised older people at nutritional risk.

OBJECTIVES

To assess in hospitalised older people with (risk of) malnutrition the effects of different nutrition interventions (e.g. supportive interventions, nutritional counselling, food modifications, oral nutritional supplements, comprehensive individualised nutritional interventions or combined approaches) compared to control groups (usual care, placebo or health education materials) on patient-relevant outcomes, and to rank the effects of the different treatments by using a network meta-analysis with individual participant data.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with individual or cluster randomisation. Cross-over studies are not suitable for our research questions due to expected carry-over effects (Higgins 2022a; Lichtenstein 2021).

Types of participants

The selection of eligibility criteria for participants considers the assumption of transitivity, implying that every included participant is equally eligible to be randomised to any of the interventions that will be compared in the NMA (Chaimani 2017).

We will include studies in older people (minimum age of 65 years) being hospitalised at the start of the intervention with (risk of) malnutrition.

Diagnostic criteria for (risk of) malnutrition

We will define (risk of) malnutrition according to internationally recognised criteria. We will include:

- older people characterised as malnourished or at risk of malnutrition according to validated screening tools, e.g. Nutritional Risk Screening 2002 (NRS) (Kondrup 2003a), Malnutrition Universal Screening Tool (MUST) (Elia 2003), Mini Nutritional Assessment (MNA) (Guigoz 1994; Kaiser 2009), Short Nutritional Assessment Questionnaire (SNAQ) (Kruizenga 2005), Subjective Global Assessment (SGA) (Detsky 1987), or based on the GLIM-criteria (Cederholm 2019);
- older people characterised as at least moderately at risk of malnutrition according to the screening tool NRS (Kondrup 2003a), i.e. body mass index (BMI) less than 20.5 kg/m^2, weight loss of at least 5% during the last three months, or insufficient food intake during the last week (50% of requirement or less); and
- older people characterised as at risk of malnutrition due to anthropometric markers (e.g. BMI < 20 or < 22 kg/m^2); triceps skinfold; arm muscle circumference; weight loss (e.g. at least 5% during the last three months or weight loss of at least 10% during the last six months)).

Summary of specific exclusion criteria

We will exclude studies exclusively focusing on participants who:

- are aged below 65 years;
- are not at nutritional risk according to our predefined criteria;
- are in intensive care;
- are receiving dialysis;
- have cancer or are recovering from cancer treatment; or
- have had a stroke.

We will exclude studies with the aforementioned participants because they may have specific nutritional needs relating to their condition (Feinberg 2017; Milne 2009). If we identify studies in which only a subset of participants are relevant to this review, we will include such studies if IPD are available separately for the relevant subset or if most of the participants meet the inclusion criteria.

Types of interventions

We will include oral nutritional interventions as defined in the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline on clinical nutrition and hydration in geriatrics (Volkert 2019c). Details of such interventions are given under the section Description of the intervention. We will focus on interventions that started shortly after admission to hospital, but they can continue after hospital discharge. There are no predefined restrictions regarding dose or mode of delivery.

Interventions

- Supportive interventions (e.g. meal-time assistance, pleasant meal environment)
- Nutritional counselling
- Food modification (e.g. fortified meals/foods, additional snacks/finger foods)
- Oral nutritional supplements
- Comprehensive individualised nutritional interventions
- Combinations of any of the aforementioned interventions

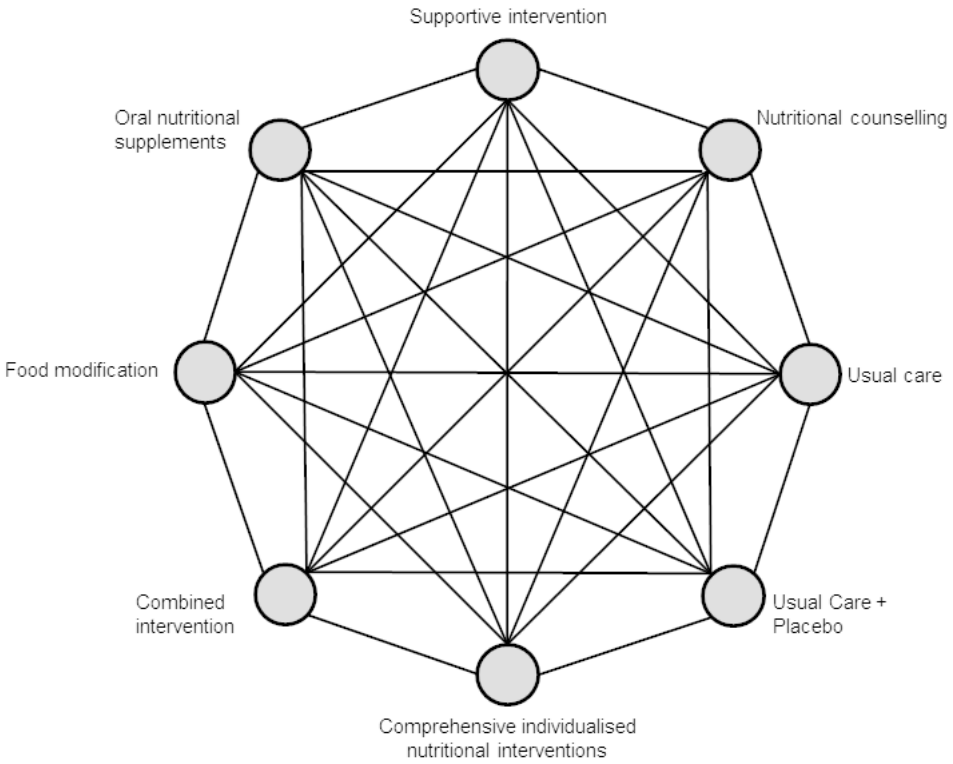
Comparisons

The following control groups are eligible.

- Inactive control (standard hospital care, usual hospital meals, standard hospital care or usual hospital meals plus placebo)
- Active control (e.g. health education materials)

Since we will conduct an NMA, we will compare all interventions against each other and the control groups (Figure 1).

Figure 1. Theoretical network plot of possible pairwise comparisons



We will define nodes by the type (supportive interventions, nutritional counselling, food modification, oral nutritional supplements, comprehensive individualised nutritional interventions and combined interventions) and the modality level (e.g. meal-time assistance, pleasant meal environment, fortified meals/foods, additional snacks/finger foods, etc.). If possible, we will further divide interventions based on their duration (until hospital discharge, postdischarge).

Concomitant interventions (e.g. exercise training) will have to be identical in both the intervention and comparator groups to establish fair comparisons. If a study includes multiple arms, we will include any arm that meets the inclusion criteria for this review.

Minimum duration of intervention

We will include studies that lasted at least until discharge from the hospital, but will not include experimental interventions lasting only one or two days.

Minimum duration of follow-up

We will include studies with any length of follow-up.

Summary of specific exclusion criteria

We will exclude studies of the following categories of interventions.

- Enteral or parenteral nutrition.
- Texture-modification, if it is not part of an individualised intervention strategy.
- Immune-nutrition or micronutrients such as vitamins, minerals, glutamine, arginine, fish oil, singly or in combination, and branched-chain amino acids.

We will exclude trials focusing on enteral and parenteral nutrition since oral nutrition interventions are less invasive and potentially safer, making them particularly suited for older people (Druml 2016; Volkert 2019c). Comprehensive individualised nutritional intervention studies using enteral or parenteral nutrition for participants not meeting nutritional goals by oral nutrition will be eligible if ≤ 10% of participants were affected (Schuetz 2019). In line with previous Cochrane Reviews, we will exclude interventions on immune nutrition or micronutrients (Feinberg 2017 Milne 2009).

Types of outcome measures

We will extract data on the following outcomes, chosen based on the Collaborative Senator-Ontop and MaNuEL Delphi study (Correa-Pérez 2018), using the methods and time points specified below.

Primary outcomes

- All-cause mortality

- Serious adverse events
- Functional status

Secondary outcomes

- Health-related quality of life
- Length of hospital stay
- Body weight and body composition
- Dietary intake

We will not exclude a study if it fails to report one or several of our primary or secondary outcome measures. We will only exclude studies if none of the outcomes relevant to this review were measured, provided that there is supporting evidence (e.g. contact with trial authors, access to the original protocol, etc.).

Method of outcome measurement

- All-cause mortality: defined as death from any cause.
- Serious adverse events: defined according to the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice, as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation or results in persistent or significant disability/incapacity (ICH-GCP 1997). Serious adverse events are not necessarily a consequence of the treatment.
- Functional status: assessed using validated measures of strength (e.g. handgrip strength, chair rise test (Beaudart 2019)), mobility (e.g. gait speed, timed up-and-go test, short physical performance battery (Beaudart 2019)) and performance of activities of daily living (ADL) (e.g. Barthel Index (Mahoney 1965)).
- Health-related quality of life: evaluated by validated instruments, such as the 36 items Short Form survey (SF-36) or EQ-5D (EuroQoL) and considering global health-related quality of life (mental, social, emotional, role and physical functioning (Garratt 2002)).
- Length of hospital stay: defined as the period (days) from admission to discharge from the hospital.
- Body weight and body composition: defined as body weight/BMI measured by calibrated scales as well as fat-free mass/lean body mass/muscle mass measured by bioelectric impedance analyses (BIA), dual x-ray absorptiometry (DXA), magnetic resonance imaging (MRI), ultrasound, computed tomography (CT) or air displacement plethysmography (Bod Pod).
- Dietary intake: defined as changes in intake of energy (kcal) and protein (g or g/kg bodyweight) based on usual diet as well as intervention 'products', e.g. supplements.

Timing of outcome measurement

All-cause mortality and serious adverse events:

- time to event, either until discharge or until one month after randomisation (the most relevant time point in this review);
- time to event until three months after randomisation;
- time to event until 12 months after randomisation.

Functional status, health-related quality of life, body weight and body composition:

- either at hospital discharge or until one month after randomisation (the most relevant time point in this review);
- more than one month until three months after randomisation;
- more than three months until 12 months after randomisation.

Length of hospital stay:

- number of days from first admission until first discharge.

Dietary intake:

- either at hospital discharge or until one month after randomisation.

Search methods for identification of studies

Electronic searches

An information specialist (KG) will search the following sources from the inception of each database to the date of search and will place no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (Wiley);
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost;
- Science Citation Index (Web of Science via Clarivate);
- Latin American and Caribbean Health Sciences Literature (LILACS) via bvsalud.org/en/;
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/).

We will not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (Cochrane 2020).

The search strategy combines search blocks on 'older people', 'malnutrition' and 'nutritional interventions'. For detailed search strategies, see Appendix 1. An email alert service for MEDLINE via OvidSP will be applied to continuously identify newly published studies using the search strategy detailed in Appendix 1. In addition, we will follow up on protocols of relevant RCTs identified by the systematic search.

Searching other resources

We will attempt to identify other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews and meta-analyses. We will also contact the authors of included studies to obtain additional information on the retrieved studies and establish whether we may have missed further studies. To retrieve grey literature, we will search BASE – (Bielefeld Academic Search Engine)and DART Europe (Appendix 1).

We will not use abstracts or conference proceedings for data extraction unless full data are available from study authors, because this information source does not fulfil the CONSORT requirements (CONSORT 2018; Scherer 2018). We will present information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table.

Data collection and analysis

Selection of studies

Two review authors (EK, JS) will independently screen the abstract, title, or both, of every record retrieved by the literature searches. We will obtain the full text of all potentially relevant records, and two review authors (EK, JS) will independently screen these. We will resolve disagreements through consensus or by recourse to a third review author (LS). If we cannot resolve a disagreement, we will categorise the study as 'awaiting classification' and will contact the study authors for clarification. We will present an adapted PRISMA flow diagram to show the process of study selection (Page 2021). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for exclusion (Page 2021).

Data extraction and management

For studies that fulfil our inclusion criteria, a review author (EK) will send a data request for the IPD-analysis to the first or corresponding author, or both, of all included trials, or to the trial sponsor where appropriate. In event of no response, we will send two follow-up emails with an interval of two weeks in between.

We will request information on the following items:

- trial methods (e.g. method of generation of random list, method concealment of randomisation, stratification factors, blinding factors);
- study characteristics (e.g. date of randomisation, dates of follow-up, duration);
- inclusion and exclusion criteria;
- individual participant characteristics (e.g. age, sex, type of condition/disease, functional status, mental status, nutritional status, definition of 'malnutrition' and 'risk of malnutrition');
- details and duration of intervention and the control/comparator;
- individual outcomes;
- related documents (case report forms, trial protocols, code books, clinical summaries);
- study funding sources;
- declarations of interest by primary investigators.

If IPD can be provided for statistical analyses, a data-use agreement between the review team and the data provider will be signed to regulate the terms and conditions of data usage. For the IPD approach, we will follow the guidance by Tierney and colleagues (Tierney 2015; Tierney 2021; Tierney 2022). We will ask data providers for de-identified data and will accept data files in any workable form (e.g. Excel, SPSS, delimited plain-text, etc.). Based on a data transfer guide, we will transfer all obtained IPD securely and afterwards store it on a dedicated network drive on a file server of the Institute of Medical Biometry and Statistics (IMBI), Freiburg. Access to the network drive will be restricted to researchers involved in the analyses. After receiving the data sets, we will conduct an initial check of the IPD to confirm de-identification as well as completeness of randomised participants, outcomes, covariates and other necessary variables. Based on a data dictionary developed by the review team, we will recode or redefine the IPD, as appropriate. We will document all changes and check the data for validity and plausibility, and discuss any inconsistencies with the data provider.

If a study cannot share its IPD, we will ask the trial authors to conduct the analyses in-house and to provide summary estimates for NMAs. We will also ask the authors of included studies whether they would be willing to answer questions regarding their studies. We will present the results of this survey in an appendix. We will, thereafter, seek relevant missing information on the study from the primary study author(s) if required.

If we do not receive an answer regarding our IPD-analysis request or the IPD cannot be provided, two review authors (EK, JS) will independently extract key information on participants, interventions and comparators from the studies. We will describe interventions according to the 'template for intervention description and replication' (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017).

We will report data on efficacy outcomes and adverse events using standardised data extraction sheets from the Cochrane Metabolic and Endocrine Disorders (CMED) Group. We will resolve disagreements by discussion or, if required, by consultation with a third review author (LS).

We will provide information, including the study identifier for potentially relevant ongoing trials in the 'Characteristics of ongoing trials' table and in a joint appendix entitled 'Matrix of study endpoint (publications and trial documents)'. We will attempt to find the protocol for each included study and will report in a joint appendix the primary, secondary, and other outcomes from these protocols, alongside the data from the study publications.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the information yield by collating all available data, and we will use the most complete data set aggregated across all known publications. If discrepancies in data across publications occur, we will contact the authors to resolve the issues. In case of no response, we will use the most up-to-date data. We will list duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study.

Data from clinical trials registers

If data from included studies are available as study results in clinical trial registers, such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the study, we will collate and critically appraise all available data. If an included study is marked as completed in a clinical trial register but no additional information (study results or publication, or both) is available, we will add this study to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

We will assess the risk of bias for all predefined primary and secondary outcomes. For all-cause mortality, serious adverse events, functional status, health-related quality of life, body weight and body composition, and dietary intake, we will only evaluate the risk of bias for the earliest timing of outcome measurement.

Two review authors (EK, JS) will independently assess the risk of bias. We will resolve disagreements by consensus or by consulting a third review author (LS). In the case of disagreement, we will consult the remainder of the review author team and make a judgement based on consensus. If adequate information is unavailable from the study publications, study protocols, or other sources, we will contact the study authors for more detail to request missing data on risk of bias items.

We will use RoB 2, the Cochrane risk of bias tool, to evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, according to the criteria and associated categorisations contained therein (Higgins 2022b).

The RoB 2 tool evaluates the following domains.

- Bias arising from the randomisation process.
- Bias due to deviations from the intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in the selection of the reported results.

For cluster-randomised trials, we will add an additional domain to address a potential identification/recruitment bias (Eldridge 2021). Within each domain, signalling questions provide information about features of the study that are relevant to the risk of bias. We are mainly interested in the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'). Possible answers to the signalling questions are 'yes', 'probably yes', 'probably no', 'no' and 'no information'. After answering the signalling questions and following the domain specific algorithms, we will make a judgement about the risk of bias, assigning one of three levels to each domain ('low risk of bias', 'some concerns', 'high risk of bias'). Based on these results, we will make summary assessments of the risk of bias for each predefined outcome (across domains), within and across studies (Higgins 2022b).

We will use the RoB 2 Excel tool to manage the data supporting the answers to the signalling questions and risk of bias judgements (available at www.riskofbias.info/). All these data will be publicly available as supplementary material in a public repository.

Summary assessment of risk of bias

We will present a risk of bias graph and a risk of bias summary figure. We will distinguish between participant-reported outcomes, performance-based outcomes, observer-reported outcomes not involving judgement, observer-reported outcomes involving some judgement, outcomes reflecting decisions made by intervention providers, and composite outcomes.

We will consider:

- health-related quality of life (participant-reported);
- dietary intake (participant-reported, observer-reported outcomes involving some judgement);
- serious adverse events (reflecting decisions made by interventions providers);
- functional status (performance-based (i.e. handgrip strength) or observer-reported outcomes involving some judgement (i.e. ADL));
- all-cause mortality (observer-reported outcomes not involving judgement);
- length of hospital stay (observer-reported outcomes not involving judgement);
- body weight and fat free mass (or proxy) (observer-reported outcomes not involving judgement).

Risk of bias for an outcome within a study and across domains

We will assess the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). For each specific outcome, we will establish an overall risk of bias judgement using the following criteria:

- low risk of bias: the study was judged to be at low risk of bias for all domains for this result;
- some concerns: the study was judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain;
- high risk of bias: the study was either judged to be at high risk of bias in at least one domain for this result, or the study was judged to raise some concerns for multiple domains in a way that substantially lowers confidence in the result.

Risk of bias for an outcome across studies and across domains

To facilitate our assessment of the certainty of evidence for key outcomes, we will assess risk of bias across studies and domains for the outcomes included in the summary of findings table. We will define the evidence as being at low risk of bias when most information comes from studies at low risk of bias, some concerns when most information comes from studies at low risk of bias or with some concerns, and high risk of bias when a sufficient proportion of information comes from studies at high risk of bias.

Measures of treatment effect

We will express dichotomous data as a risk ratio (RR) with 95% confidence intervals (CIs) and time-to-event data as a hazard ratio (HR) with 95% CIs. For continuous outcomes measured on the same scale (e.g. body weight in kg) we will estimate the intervention effect using the mean difference (MD) with corresponding standard deviation (SD) and 95% CIs. For continuous outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the standardised mean difference (SMD). The magnitude of the SMD will be interpreted according to Cohen (small/minor SMD: 0.2 or less, medium SMD: 0.2 to 0.8, large SMD: 0.8 or greater) (Cohen 1988).

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as individually-randomised or cluster-randomised trials, and multiple observations for the same outcome.

We will attempt to reanalyse cluster-RCTs that have not appropriately adjusted for potential clustering of participants within clusters in their analyses. We will inflate the variance of the intervention effects by a design effect; calculation of a design effect involves estimation of an intra-cluster correlation coefficient (ICC). We will obtain estimates of ICCs by contacting study authors, or by imputing ICC values using either estimates from other included

studies that report ICCs or external estimates from empirical research (e.g. Bell 2013).

For the two-stage IPD NMA, we will analyse all participants according to the group to which they were randomised.

If there are multi-arm studies with three or more treatment arms, we will include them as a series of two-arm comparisons and adjust the standard errors of these comparisons to account for the correlation between arms (Rücker 2014).

Dealing with missing data

If possible, we will obtain missing data from the authors of included studies. We will carefully evaluate important numerical data, such as the numbers of people screened and randomly assigned, as well as intention-to-treat, as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up and withdrawals) and we will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

For studies with aggregated data only, in which either the SD of the outcome is not available at follow-up or we cannot recalculate it, we will impute by the median of the pooled baseline SD from studies that reported this information. When included studies do not report means and SDs for outcomes, and we do not receive the requested information from study authors, we will impute these values by estimating the sample mean from the sample size, median, mid-range, and mid-quartile range (Luo 2018). We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we will report for every outcome which studies had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report pooled effect estimates in an NMA. We will assess the assumption of transitivity, implying that RCTs comparing different groups of interventions are sufficiently similar to allow valid indirect conclusions, by comparing the distribution of potential effect modifiers (e.g. age, disease condition, nutritional status) across the available direct comparisons. We will assess heterogeneity and inconsistency (the statistical manifestation of intransitivity) by decomposing the Q statistic into heterogeneity (within designs) and inconsistency (between designs) and visualise this using a net-heat plot (Krahn 2013). In addition, we will report and assess differences between direct and indirect effect estimates using the SIDE (Separating Indirect from Direct Evidence) method (Chaimani 2022; Schwarzer 2015). When we identify heterogeneity, we will attempt to determine possible reasons for this by examining individual characteristics of studies and subgroups.

Assessment of reporting biases

If we include 10 studies or more that investigate a particular outcome, we will evaluate the presence of small-study effects by drawing comparison-adjusted funnel plots that account for the fact that different studies compare different sets of interventions (Chaimani 2013).

Data synthesis

This review will use a two-stage approach, whereby we first analyse IPD within each study and then combine them in the second step as an NMA (Debray 2015). We will consider studies without IPD in meta-analyses if they provide the necessary aggregated data.

If the assumption of transitivity is met, we plan to undertake NMA for all predefined primary and secondary outcomes and time points. Otherwise, we will conduct NMA for a subset of interventions fulfilling transitivity or we will run pairwise meta-analyses.

We will present the available direct comparisons between different interventions and control groups using a network plot (Figure 1) for each outcome (Chaimani 2013). For each outcome of interest, we will perform a random effects NMA to determine the summary effect of each intervention relative to any other intervention/control arm. We will use data from intention-to-treat analyses when available. We will use the R packages “netmeta” (Rücker 2022) and “meta” (Balduzzi 2019) to conduct the NMA, based on a frequentist approach (Rücker 2012). For findings from the NMA, we will present summary effect estimates with 95% CI in a league table and as forest plots. For all outcomes, we will rank treatments by P-scores, a frequentist version of the Surface Under the Cumulative Ranking curve (SUCRA) (Rücker 2015). P-scores, like SUCRAs, are values between 0 and 1, where a value of 1 means that a treatment always ranks best and a value of 0 means that a treatment always ranks least best. P-scores answer the treatment hierarchy question of which treatment has the largest fraction of competitors that it beats (Salanti 2022).

We will perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chaimani 2022).

In case meta-analysis is not possible for certain outcomes, we will describe the results in tables ordered by study ID, using the guidance in the *Cochrane Handbook* (McKenzie 2022).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, for which we plan to carry out subgroup analyses.

- Baseline nutritional status (malnutrition versus risk of malnutrition)
- Health status (type of disease)
- Duration of the intervention (< 30 days versus ≥ 30 days)
- Age (< 75 versus ≥ 75 years)
- Sex

To have sufficient power, we will restrict subgroup analysis to those outcomes with at least 10 trials providing data for the NMA.

Sensitivity analysis

When applicable, we plan to explore the influence of important factors on effect sizes, by performing sensitivity analyses in which we restrict the analyses to the following.

- Studies that were published
- Studies with low risk of bias, as specified in the Assessment of risk of bias in included studies section
- Very long or large studies, to establish the extent to which they dominate the results
- Studies without imputed SDs

To have sufficient power, we will restrict sensitivity analysis to those outcomes with at least 10 trials providing data for the NMA.

Summary of findings and assessment of the certainty of the evidence

Certainty of the evidence

We will present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach for NMA (Brignardello-Petersen 2018). We will rate the certainty of evidence in each of the direct, indirect and network estimates. We will rate the direct evidence based on risk of bias, inconsistency, indirectness, and publication bias. If the certainty of direct evidence is high and its contribution is at least as much as that of the indirect evidence, we will not rate the indirect evidence (Brignardello-Petersen 2018). If rating of indirect evidence is necessary, we will use the certainty of direct estimates to inform indirect estimates, considering the lowest of the ratings of the two direct comparisons forming the most dominant first-order loop. In the presence of serious intransitivity, we will rate down the certainty of the indirect estimate. To address the certainty of network estimates, we will compare the ratings for direct and indirect estimates. We will choose the estimate with the higher contribution and rate it down in case of incoherence or imprecision (Brignardello-Petersen 2018). Two review authors (EK, JS) will independently rate the certainty of evidence for each outcome. We will resolve any differences in assessment by discussion or by consultation with a third review author (LS).

If NMA or pairwise meta-analyses are not possible, we will present the results in a narrative format in the summary of findings table. We will justify all decisions to downgrade the quality of studies by using informative footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review when necessary.

Summary of findings table

We will present a summary of the evidence in a summary of findings table. This will provide key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We will create the summary of findings table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021) and according to the GRADE summary of findings table format that displays the critical information from an NMA (Yepes-Nuñez 2019).

Interventions presented in the summary of findings table will be: supportive interventions, nutritional counselling, food modifications, oral nutritional supplements, comprehensive individualised nutritional interventions, or any combinations of these. The comparators will be usual care or placebo.

We will report the following outcomes, listed according to priority.

- All-cause mortality
- Serious adverse events
- Functional status (ADL, earliest timing of outcome measurement)
- Health-related quality of life (earliest timing of outcome measurement)
- Length of hospital stay.
- Body weight (earliest timing of outcome measurement)
- Fat free mass (or proxy) (earliest timing of outcome measurement)

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APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials via Wiley

#1 (Nutrition Therapy):MH

#2 (Diet Therapy):MH

#3 (Food, Formulated):MH

#4 (Food, fortified):MH

#5 Dietetics:MH

#6 (Dietary Supplements):MH

#7 (Nutritional Support):MH

#8 Enteral Nutrition:MH

#9 ONS:TI,AB,KY

#10 Alimentation?:TI,AB,KY

#11 (nutrition ADJ2 therap*):TI,AB;KY

#12 (nutrition* adj2 strateg*):TI,AB,KY

#13 (nutrition* ADJ1 supplement*):TI,AB,KY

#14 (nutrition* ADJ1 intervention*):TI,AB,KY

#15 (nutrition* ADJ2 counsel*):TI,AB,KY

#16 (diet* ADJ2 counsel*):TI,AB,KY

#17 (diet adj2 therap*):TI,AB,KY

#18 (diet* adj1 supplement*):TI,AB,KY

#19 (nutrition* ADJ2 support):TI,AB,KY

#20 (nutrition* ADJ2 enriched):TI,AB,KY

#21 ((meal* or eat*) adj2 (assist* or support*)):TI,AB,KY

#22 (food* ADJ1 modif*):TI,AB,KY

#23 (food* ADJ1 formulated):TI,AB,KY

#24 ((food* or meal*) adj2 fortif*):TI,AB,KY

#25 (food* ADJ1 enriched):TI,AB,KY

#26 (food* ADJ1 supplement*):TI,AB,KY

#27 ((enrich* or fortif*) adj2 drink?):TI,AB,KY

#28 ((oral energy or nutrient? or protein?) ADJ3 intake):TI,AB,KY

#29 (increase* adj2 ("dietary intake" or "nutritional intake" or "food intake")):TI,AB,KY

#30 (improve* adj2 (nutrition* or diet* or food*)):TI,AB;KY

#31 (clinic* adj2 nutrition*):TI,AB,KY

#32 (enteral adj1 nutrition):TI,AB,KY

(Continued)

#33 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10 OR #13 OR #14 OR #15 OR #16 OR #17 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32

#34 ((aged OR geriatrics OR "geriatric psychiatry" OR "geriatric nursing" OR "geriatric psychiatry" OR "dental care for aged" OR "health services for the aged")):MH

#35 elder* OR eldest OR frail* OR geriatri* OR ("old" NEXT age*) OR ("oldest" NEXT old*) OR senior* OR senium OR ("very" NEXT old*) OR septuagenarian* OR octagenarian* OR octogenarian* OR nonagenarian* OR centarian* OR centenarian* OR supercentenarian* OR "older people" OR ("older" NEXT subject*) OR ("older" NEXT patient*) OR ("older" NEXT age*) OR ("older" NEXT adult*) OR "older man" OR "older men" OR ("older" NEXT male*) OR "older woman" OR "older women" OR ("older" NEXT female*) OR ("older" NEXT population*) OR ("older" NEXT person*):TI,KW,KY

#36 #34 OR #35

#37 #33 AND #36

#38 Malnutrition:MH

#39 (protein energy malnutrition):MH

#40 MESH DESCRIPTOR Nutritional Requirements EXPLODE ALL TREES

#41 (Nutritional Status):MH

#42 (malnutrition or mal-nutrition or malnourish* or mal-nourish* or undernourish* or under-nourish* or underweight* or under-weight* or undernutr* or under-nutr* or (nutrition* adj1 risk) or nutrition* status or nutrition* requirement? or energy requirement?):TI,AB,KY

#43 #38 OR #39 OR #40 OR #41 OR #42

#44 #37 AND #43

MEDLINE(R) ALL via Ovid

1. Nutrition Therapy/

2. Diet Therapy/

3. Food, Formulated/

4. Food, fortified/

5. Dietetics/

6. Dietary Supplements/

7. Nutritional Support/

8. Enteral Nutrition/

9. ONS.ti,kf. or ONS.ab. /freq=3

10. Alimentation?.ti,ab,kf.

11. (nutrition adj2 therap*).ti,ab,kf.

12. (nutrition* adj2 strateg*).ti,ab,kf.

13. (nutrition* adj1 supplement*).ti,ab,kf.

14. (nutrition* adj1 intervention*).ti,ab,kf.

15. (nutrition* adj2 counsel*).ti,ab,kf.

16. (diet* adj2 counsel*).ti,ab,kf.

(Continued)

17. (diet adj2 therap*).ti,ab,kf.

18. (diet* adj1 supplement*).ti,ab,kf.

19. (nutrition* adj2 support).ti,ab,kf.

20. (nutrition* adj2 enriched).ti,ab,kf.

21. ((meal* or eat*) adj2 (assist* or support*)).ti,ab,kf.

22. (food? adj1 modif$).ti,ab,kf.

23. (food? adj1 formulated).ti,ab,kf.

24. ((food* or meal*) adj2 fortif*).ti,ab,kf.

25. (food? adj1 enriched).ti,ab,kf.

26. (food? adj1 supplement*).ti,ab,kf.

27. ((enrich* or fortif*) adj2 drink?).ti,ab,kf.

28. ((oral energy or nutrient? or protein?) adj3 intake).ti,ab,kf.

29. (increase* adj2 ("dietary intake" or "nutritional intake" or "food intake")).ti,ab,kf.

30. (improve* adj2 (nutrition* or diet* or food*)).ti,ab,kf.

31. (clinic* adj2 nutrition*).ti,ab,kf.

32. (enteral adj1 nutrition).ti,ab,kf.

33. or/1-32

34. exp aged/ or exp geriatrics/ or exp geriatric psychiatry/ or exp geriatric nursing/ or exp *geriatric psychiatry/ or exp *dental care for aged/ or exp *health services for the aged/ or (elder* or eldest or frail* or geriatri* or old age* or oldest old* or senior* or senium or very old* or septuagenarian* or octagenarian* or octogenarian* or nonagenarian* or centarian* or centenarian* or supercentenarian* or older people or older subject* or older patient* or older age* or older adult* or older man or older men or older male* or older woman or older women or older female* or older population* or older person*).ti,ab,kf.

35. 33 and 34

36. Malnutrition/

37. protein energy malnutrition/

38. exp Nutritional Requirements/

39. Nutritional Status/

40. (malnutrition or mal-nutrition or malnourish* or mal-nourish* or undernourish* or under-nourish* or underweight* or under-weight* or undernutr* or under-nutr* or (nutrition* adj1 risk) or nutrition* status or nutrition* requirement? or energy requirement?).ti,ab,kf.

41. (insufficient intake adj2 (nutri* or food* or diet*)).ti,ab,kf.

42. or/36-41

43. 35 and 42

44. randomized controlled trial.pt.

45. controlled clinical trial.pt.

46. randomi?ed.ab.

47. placebo.ab.

(Continued)

48. drug therapy.fs.

49. randomly.ab.

50. trial.ab.

51. groups.ab.

52. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53. exp animals/ not humans.sh.

54. 52 not 53

55. 43 and 54

CINHAL via EBSCOhost

S1 (MH "Nutrition Therapy (Iowa NIC)")

S2 (MH "Diet Therapy")

S3 (MH "Food, Formulated")

S4 (MH "Food, Fortified")

S5 (MH "Dietetics“)

S6 (MH "Dietary Supplements")

S7 (MH "Nutritional Support")

S8 (MH "Enteral Nutrition")

S9 (TI ONS OR AB ONS)

S10 (TI Alimentation? OR AB Alimentation?)

S11 (TI nutrition N2 therap* OR AB nutrition N2 therap*)

S12 (TI nutrition N2 strateg* OR AB nutrition N2 strateg *)

S13 (TI nutrition* N1 supplement* OR AB nutrition* N1 supplement*)

S14 (TI nutrition* N1 intervention? OR AB nutrition* N1 intervention?)

S15 (TI nutrition* N2 counsel* OR AB nutrition* N2 counsel*)

S16 (TI diet* N2 counsel* OR AB diet* N2 counsel*)

S17 TI (diet N1 therap* OR AB diet N1 therap*)

S18 (TI diet* N1 supplement* OR AB diet* N1 supplement*)

S19 (TI nutrition* N2 support OR AB nutrition* N2 support)

S20 (TI nutrition* N2 enriched OR AB nutrition* N2 enriched)

S21 ((TI meal* OR AB meal*) OR (TI eat* OR AB eat*)) N2 ((TI assist* OR AB assist*) OR (TI support* OR AB support*))

S22 ((TI food# N1 modif* OR AB food# N1 modif*))

S23 ((TI food# N1 formulated OR AB food# N1 formulated))

S24 ((TI food* OR AB food*) OR (TI meal* OR AB meal*)) N2 (TI fortif* OR AB fortif*))

S25 (TI food# N1 enriched OR AB food# N1 enriched)

(Continued)

S26 (TI food# N1 supplement* OR AB food# N1 supplement*)

S27 ((TI enrich* OR AB enrich*) OR (TI fortif* OR AB fortif*)) N2 (TI drink# OR AB drink#))

S28 (((TI "oral energy" OR AB "oral energy") OR (TI nutrient# OR AB nutrient#) OR (TI protein# OR AB protein#)) N3 (TI intake OR AB intake))

S29 ((TI increase* OR AB increase*) N2 ((TI "dietary intake" OR AB "dietary intake") OR (TI "nutritional intake" OR AB "nutritional intake") OR (TI "food intake" OR AB "food intake")))

S30 ((TI improve* OR AB improve*) N2 ((TI nutrition* OR AB nutrition*) OR (TI diet* OR AB diet*) OR (TI food* OR AB food*)))

S31 ((TI clinic* OR AB clinic*) N2 (TI nutrition* OR AB nutrition*))

S32 ((TI enteral OR AB enteral) N1 (TI nutrition OR AB nutrition))

S33 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32

S34 (MH aged+) OR (MH geriatrics+) OR (MH "geriatric psychiatry"+) OR (MH "geriatric nursing"+) OR (MM "geriatric psychiatry"+) OR (MM "dental care for aged"+) OR (MM "health services for the aged"+) OR ((TI elder* OR AB elder*) OR (TI eldest OR AB eldest) OR (TI frail* OR AB frail*) OR (TI geriatri* OR AB geriatri*) OR (TI "old age*" OR AB "old age*") OR (TI "oldest old*" OR AB "oldest old*") OR (TI senior* OR AB senior*) OR (TI senium OR AB senium) OR (TI "very old*" OR AB "very old*") OR (TI septuagenarian* OR AB septuagenarian*) OR (TI octagenarian* OR AB octagenarian*) OR (TI octogenarian* OR AB octogenarian*) OR (TI nonagenarian* OR AB nonagenarian*) OR (TI centarian* OR AB centarian*) OR (TI centenarian* OR AB centenarian*) OR (TI supercentenarian* OR AB supercentenarian*) OR (TI "older people" OR AB "older people") OR (TI "older subject*" OR AB "older subject*") OR (TI "older patient*" OR AB "older patient*") OR (TI "older age*" OR AB "older age*") OR (TI "older adult*" OR AB "older adult*") OR (TI "older man" OR AB "older man") OR (TI "older men" OR AB "older men") OR (TI "older male*" OR AB "older male*") OR (TI "older woman" OR AB "older woman") OR (TI "older women" OR AB "older women") OR (TI "older female*" OR AB "older female*") OR (TI "older population*" OR AB "older population*") OR (TI "older person*" OR AB "older person*"))

S35 S33 AND S34

S36 (MH Malnutrition)

S37 (MH "Protein-Energy Malnutrition")

S38 (MH "Nutritional Requirements+")

S39 (MH "Nutritional Status")

S40 ((TI malnutrition OR AB malnutrition) OR (TI mal-nutrition OR AB mal-nutrition) OR (TI malnourish* OR AB malnourish*) OR (TI mal-nourish* OR AB mal-nourish*) OR (TI undernourish* OR AB undernourish*) OR (TI under-nourish* OR AB under-nourish*) OR (TI underweight* OR AB underweight*) OR (TI under-weight* OR AB under-weight*) OR (TI undernutr* OR AB undernutr*) OR (TI under-nutr* OR AB under-nutr*) OR ((TI nutrition* OR AB nutrition*) N1 (TI risk OR AB risk)) OR (TI "nutrition* status" OR AB "nutrition* status") OR (TI "nutrition* requirement#" OR AB "nutrition* requirement#") OR (TI "energy requirement#" OR AB "energy requirement#"))

S41 S36 OR S37 OR S38 OR S39 OR S40

S42 MH randomized controlled trials

S43 MH double-blind studies

S44 MH single-blind studies

S45 MH random assignment

S46 MH pretest-posttest design

S47 MH cluster sample

S48 TI (randomised OR randomized)

S49 AB (random*)

(Continued)

S50 TI (trial)

S51 MH (sample size) AND AB (assigned OR allocated OR control)

S52 MH (placebos)

S53 PT (randomized controlled trial)

S54 AB (control W5 group)

S55 MH (crossover design) OR MH (comparative studies)

S56 AB (cluster W3 RCT)

S57 MH animals+

S58 MH (animal studies)

S59 TI (animal model*)

S60 S57 OR S58 OR S59

S61 MH (human)

S62 S61 NOT S60

S63 S37 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51

S64 S63 NOT S62

S65 S35 AND S41 AND S64

Web of Science (Advanced search) via Clarivate

SCI-EXPANDED 1945-present)/ ESCI 2017-present

#1 TI=(nutrition NEAR/2 therap*) OR AB=(nutrition NEAR/2 therap*)

#2 TI=(nutrition* NEAR/2 strateg*) OR AB =(nutrition* NEAR/2 strateg*)

#3 TI=(diet NEAR/2 therap*) OR AB=(diet NEAR/2 therap*)

#4 TI=(Dietetics) OR AB=(Dietetics)

#5 TI=(ONS) OR AB=(ONS)

#6 TI=(Alimentation?) OR AB=(Alimentation?)

#7 TI=(nutrition* NEAR/1 supplement*) OR AB=(nutrition* NEAR/1 supplement*)

#8 TI=(nutrition* NEAR/1 intervention*) OR AB=(nutrition* NEAR/1 intervention*)

#9 TI=(nutrition* NEAR/2 counsel*) OR AB=(nutrition* NEAR/2 counsel*)

#10 TI=(diet* NEAR/2 counsel*) OR AB=(diet* NEAR/2 counsel*)

#11 TI=(diet* NEAR/1 supplement*) OR AB=(diet* NEAR/1 supplement*)

#12 TI=(nutrition* NEAR/2 support) OR AB=(nutrition* NEAR/2 support)

#13 TI=(nutrition* NEAR/2 enriched) OR AB=(nutrition* NEAR/2 enriched)

#14 TI=(meal* NEAR/2 (assistance OR support)) OR AB=(meal* NEAR/2 (assistance OR support)) OR TI=(eat* NEAR/2 (assistance OR support)) OR AB=(eat* NEAR/2 (assistance OR support))

#15 TI=(food$ NEAR/1 modif*) OR AB=(food$ NEAR/1 modif*)

(Continued)

#16 TI=(food$ NEAR/1 formulated) OR AB=(food$ NEAR/1 formulated)

#17 TI=((food* OR meal*) NEAR/2 fortif*) OR AB=((food* OR meal*) NEAR/2 fortif*)

#18 TI=(food$ NEAR/1 enriched) OR AB=(food$ NEAR/1 enriched)

#19 TI=(food$ NEAR/1 supplement*) OR AB=(food$ NEAR/1 supplement*)

#20 TI=((enrich* OR fortif*) NEAR/2 drink$) OR AB=((enrich* OR fortif*) NEAR/2 drink$)

#21 TI=("oral energy" NEAR/3 intake OR nutrient$ NEAR/3 intake OR protein$ NEAR/3 intake) OR AB=("oral energy" NEAR/3 intake OR nutrient$ NEAR/3 intake OR protein$ NEAR/3 intake)

22 TI=(increase* NEAR/2 ("dietary intake" OR "nutritional intake" OR "food intake")) OR AB=(increase* NEAR/2 ("dietary intake" OR "nutritional intake" OR "food intake"))

#23 TI=(improve* NEAR/2 (nutrition* OR diet* OR food*)) OR AB=(improve* NEAR/2 (nutrition* OR diet* OR food*))

#24 TI=(clinic* NEAR/2 nutrition*) OR AB=(clinic* NEAR/2 nutrition*)

#25 TI=(enteral NEAR/1 nutrition) OR AB=(enteral NEAR/1 nutrition)

#26 #25 OR #24 OR #23 OR22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

#27 TI=(elder* OR eldest OR frail* OR geriatri* OR "old age*" OR "oldest old*" OR senior* OR senium OR "very old*" OR septuagenarian* OR octagenarian* OR octogenarian* OR nonagenarian* OR centarian* OR centenarian* OR supercentenarian* OR "older people" OR "older subject*" OR "older patient*" OR "older age*" OR "older adult*" OR "older man" OR "older men" OR "older male*" OR "older woman" OR "older women" OR "older female*" OR "older population*" OR "older person*") OR AB=(elder* OR eldest OR frail* OR geriatri* OR "old age*" OR "oldest old*" OR senior* OR senium OR "very old*" OR septuagenarian* OR octagenarian* OR octogenarian* OR nonagenarian* OR centarian* OR centenarian* OR supercentenarian* OR "older people" OR "older subject*" OR "older patient*" OR "older age*" OR "older adult*" OR "older man" OR "older men" OR "older male*" OR "older woman" OR "older women" OR "older female*" OR "older population*" OR "older person*")

#28 TI=((malnutrition OR mal-nutrition OR malnourish* OR mal-nourish* OR undernourish* OR under-nourish* OR underweight* OR under-weight* OR undernutr* OR under-nutr* OR (nutrition* NEAR/1 risk) OR "nutrition* status" OR "nutrition* requirement$" OR "energy requirement$")) OR
AB=(malnutrition OR mal-nutrition OR malnourish* OR mal-nourish* OR undernourish* OR under-nourish* OR underweight* OR under-weight* OR undernutr* OR under-nutr* OR (nutrition* NEAR/1 risk) OR "nutrition* status" OR "nutrition* requirement$" OR "energy requirement$")

#29 TI=("insufficient intake" NEAR/2 (nutri* OR food* OR diet*)) OR AB=("insufficient intake" NEAR/2 (nutri* OR food* OR diet*))

#30 #28 OR #29

#31 #26 AND #27 AND #30

#32 TI=(((random* or "randomi?ed controlled trial" or rct or controlled trial or controlled clinical trial))) OR AB=((random* or "randomi?ed controlled trial" or rct or controlled trial or controlled clinical trial))

#33 #31 AND #32

LILACS via bvsalud.org/en/

MH: Nutrition Therapy OR MH: Diet Therapy OR MH: Food, Formulated OR MH: Food, fortified OR MH: Dietetics OR MH: Dietary Supplements OR MH: Nutritional Support OR MH: Enteral Nutrition OR Alimentation$ OR "Nutrition Therapy" OR "Diet Therapy" OR "nutritional supplement" OR "nutritional supplements" OR "nutrition supplement" OR "nutrition supplements" OR "suplemento nutricional" OR "suplementos nutricionales" OR "suplemento nutricional" OR "suplementos nutricionais" OR "nutritional intervention" OR "nutritional interventions" OR "nutrition intervention" OR "nutrition interventions" OR "intervención nutricional" OR "intervenciones nutricionales" OR "intervenção nutricional" OR "intervenções nutricionais" OR "nutrition counselling" OR "nutritional counselling" OR "asesoramiento nutricional" OR "aconselhamento nutricional" OR "diet counselling" OR "dietary counselling" OR "asesoramiento dietético" OR "Aconselhamento dietético" OR "diet supplement" OR "diet supplements" OR "dietary supplement" OR "dietary supplements" OR "suplemento dietético" OR "suplementos dietéticos" OR "nutrition support" OR "nutritional support" OR "apoyo nutricional" OR "suporte nutricional" OR "enriched nutrition" OR "nutrición enriquecida" OR "nutrição enriquecida" OR

(Continued)

"meal time assistance" OR "mealtime assistance" OR "food modification" OR "food modifications" OR "modificación de alimentos" OR "modificaciones de alimentos" OR "Modificação de alimentos" OR "modificações alimentares" OR "formulated food" OR "formulated foods" OR "alimentos formulado" OR "alimento formulados" OR "fortified food" OR "fortified foods" OR "alimentos fortificado" OR "alimento fortificados" OR "enriched food" OR "enriched foods" OR "alimentos enriquecidos" OR "comida enriquecida" OR "alimentos enriquecidos" OR "supplemented food" OR "supplemented foods" OR "food supplementation" OR "food supplementations" OR "alimentos suplementados" OR "suplementos alimenticios" OR "alimentos suplementados" OR "suplementação alimentar" OR "suplementações alimentares" OR "enriched drink" OR "enriched drinks" OR "bebida enriquecida" OR "bebidas enriquecidas" OR "oral energy intake" OR "oral energy intakes" OR "nutrient intake" OR "nutrients intakes" OR "protein intake" OR "protein intakes" OR "ingesta de energía oral" OR "ingesta de nutrientes" OR "ingesta de proteínas" OR "ingestão de energia oral" OR "ingestão de nutrientes" OR "ingestão de proteínas"

AND

MH: aged OR MH: Aged, 80 and over OR MH: Frail Elderly OR MH: Geriatrics OR "old person" OR "old persons" OR "old people" OR "old population" OR "old populations" OR "old subject" OR "old subjects" OR "old patient" OR "old patients" OR "old participant" OR "old participants" OR "old adult" OR "old adults" OR "old age" OR geriatric$ OR elder$ OR senior$ OR "persona mayor" OR "personas mayores" OR "ancianos" OR "población anciana" OR "poblaciones antiguas" OR "sujeto viejo" OR "sujetos viejos" OR "pacientes viejos" OR "participantes antiguos" OR "participantes viejos" OR "adultos viejos" OR "vejez" OR geriátricos$ OR ancianos$ OR mayores$ OR "idoso" OR "idosos" OR "população idosa" OR "populações idosas" OR "pacientes velhos" OR "idosos participantes" OR "velhice" OR geriátrico$

AND

MH: Malnutrition OR MH: protein energy malnutrition OR MH: Nutritional Requirements OR MH: Recommended Dietary Allowances OR MH: Nutritional Status OR malnutrition OR mal-nutrition OR malnourish$ OR mal-nourish$ OR undernourish$ OR under-nourish$ OR underweight$ OR under-weight$ OR undernutr$ OR under-nutr$ OR "nutritional risk" OR "nutritional status" OR "nutritional requirement" OR "nutritional requirements" OR "energy requirement" OR "energy requirements" OR desnutrición$ OR "mala nutrición" OR "mal nutrición" OR "bajo peso" OR "bajo de nutricional" OR "bajo nutricional" OR "riesgo nutricional" OR "estado nutricional" OR "requerimiento nutricional" OR "requerimiento nutricional" OR "requerimiento energético" OR "requerimientos energéticos"

+ Controlled Clinical Trial

ClinicalTrials.gov **(Advanced Search)**

Condition or disease: Malnutrition OR malnourished OR undernourished OR underweight OR "nutritional risk" OR "nutritional requirement" OR "energy requirement"

Other terms: Elderly OR "frail elderly" OR geriatrics OR senior OR "old age"

OR

Other terms: ("nutrition therapy" OR "nutrition care" OR "fortified food" OR "enriched nutrition" OR "mealtime assistance" OR "nutrient intake" OR "protein intake") AND (Elderly OR "frail elderly" OR geriatrics OR senior OR "old age")

("nutrition therapy" OR "nutrition care" OR "fortified food" OR "enriched nutrition" OR "mealtime assistance" OR "nutrient intake" OR "protein intake") AND (Elderly OR "frail elderly" OR geriatrics OR senior OR "old age")

ICTRP Search Portal (who.int) **(Standard search)**

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elderly AND malnutrition

elderly AND malnourished

(Continued)

elderly AND undernourished

elderly AND underweight

elderly AND "nutritional risk"

elderly AND "nutritional requirements"

elderly AND "energy requirements"

elderly AND "nutrition therapy"

elderly AND "formulated food"

elderly AND ("fortified food" OR "fortified foods")

elderly AND "dietary supplement*"

elderly AND "nutrit* supplement*

elderly AND "enriched nutrition*"

elderly AND "mealtime assistance"

elderly AND "food* supplement*"

elderly AND "nutrient* intake*"

elderly AND ("protein intake" OR "protein intakes")

geriatric* AND malnutrition

geriatric* AND undernourished

geriatric* AND underweight

geriatric* AND "nutritional risk"

geriatric* AND "nutritional requirements"

geriatric* AND "energy requirements"

geriatric* AND ("fortified food" OR "fortified foods")

geriatric* AND "formulated food"

geriatric* AND "nutrition therapy"

geriatric* AND "nutrit* supplement*

geriatric* AND "enriched nutrition*"

geriatric* AND dietary supplement*"

geriatric* AND "mealtime assistance"

geriatric* AND "food* supplement*"

geriatric* AND "nutrient* intake*"

geriatric* AND ("protein intakes" OR "protein intake")

(old OR older) AND malnutrition

(Continued)

(old OR older) AND malnourished

(old OR older) AND undernourished

(old OR older) AND underweight

(old OR older) AND "nutritional risk"

(old OR older) AND "nutritional requirements"

(old OR older) AND "energy requirements"

(old OR older) AND "nutrition therapy"

(old OR older) AND "formulated food"

(old OR older) AND ("fortified food" OR "fortified foods")

(old OR older) AND "dietary supplement*"

(old OR older) AND "nutrit* supplement*

(old OR older) AND "enriched nutrition*"

(old OR older) AND "mealtime assistance"

(old OR older) AND "food* supplement*"

(old OR older) AND "nutrient* intake*"

(old OR older) AND ("protein intake" OR "protein intakes")

(senior OR seniors) AND malnutrition

(senior OR seniors) AND malnourished

(senior OR seniors) AND undernourished

(senior OR seniors) AND underweight

(senior OR seniors) AND "nutritional risk"

(senior OR seniors) AND "nutritional requirements"

(senior OR seniors) AND "energy requirements"

(senior OR seniors) AND "nutrition therapy"

(senior OR seniors) AND "formulated food"

(senior OR seniors) AND ("fortified food" OR "fortified foods")

(senior OR seniors) AND "dietary supplement*"

(senior OR seniors) AND "nutrit* supplement*

(senior OR seniors) AND "enriched nutrition*"

(senior OR seniors) AND "mealtime assistance"

(senior OR seniors) AND "food* supplement*"

(senior OR seniors) AND "nutrient* intake*"

(senior OR seniors) AND ("protein intake" OR "protein intakes")

(Continued)

Bielefeld Academic Search Engine**(Advanced Search)**
(Elderly OR frail elderly OR geriatrics OR senior) AND (Malnutrition OR malnourished OR undernourished OR "nutritional risk" OR underweight)
Document types: Conference Abstract, Report, Review, Dissertations
DART Europe
(Elderly OR frail elderly OR geriatrics OR senior) AND (Malnutrition OR malnourished OR undernourished OR "nutritional risk" OR underweight)

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

Eva Kiesswetter (EK): protocol draft.

Julia Stadelmaier (JS): protocol revision.

Kathrin Grummich (KG): search strategy development, protocol revision.

Guido Schwarzer (GS): protocol draft.

Brenda Bongaerts (BB): protocol revision.

Joerg J Meerpohl (JJP): protocol revision.

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Gabriel Torbahn (GT): protocol revision.

Marjolein Visser (MV): protocol revision.

Dorothee Volkert (DV): protocol revision.

Lukas Schwingshackl (LS): protocol draft.

DECLARATIONS OF INTEREST

EK: has declared that she has no conflict of interest.

JS: has declared that she has no conflict of interest.

KG: has declared that she has no conflict of interest.

GS: reports to be an external statistical consultant of Roche Pharma AG, Grenzach-Wyhlen, Germany; personal payment.

BB: has declared that she has no conflict of interest. She is the Co-ordinating Editor of the CMED Group. Nevertheless, she was excluded from the editorial processing of this protocol, and an independent editor (Dimitris Mavridis) acted as sign-off editor.

JJM: has declared that he has no conflict of interest.

KN: reports that she received honoraria for a lecture on an industry symposium from Fresenius Kabi USA, LLC; personal payment.

PS: reports that his institution has contracts with/receives grants from Abbott Fund, bioMerieux, Nestle HealthCare Nutrition Inc., and Thermo Fisher Scientific. PS was the investigator of a study which is eligible for the inclusion in the planned Cochrane Review (EFFORT Trial, NCT02517476). The study was initiated by the investigator and supported by grants from the Swiss National Science Foundation to PS and the Research Council of Kantonsspital Aarau, Switzerland.

GT: has declared that he has no conflict of interest.

MV: has declared that she has no conflict of interest.

DV: has declared that she has no conflict of interest.

LS: has declared that he has no conflict of interest.

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NOTES

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