

## Accepted Manuscript

Title: Efficacy of non-pharmacological interventions to treat malnutrition in older persons: A systematic review and meta-analysis. The SENATOR project ONTOP series and MaNuEL Knowledge Hub project



Authors: Andrea Correa-Pérez, Iosef Abraha, Antonio Cherubini, Avril Collinson, Dominique Dardevet, Lisette CPGM de Groot, Marian A.E. de van der Schueren, Antje Hebestreit, Mary Hickson, Javier Jaramillo-Hidalgo, Isabel Lozano-Montoya, Denis O'Mahony, Roy L. Soiza, Marjolein Visser, Dorothee Volkert, Maike Wolters, Alfonso J. Cruz Jentoft

PII: S1568-1637(18)30166-1  
DOI: <https://doi.org/10.1016/j.arr.2018.10.011>  
Reference: ARR 868

To appear in: *Ageing Research Reviews*

Received date: 6 August 2018  
Revised date: 20 October 2018  
Accepted date: 25 October 2018

Please cite this article as: Correa-Pérez A, Abraha I, Cherubini A, Collinson A, Dardevet D, de Groot LC, de van der Schueren MAE, Hebestreit A, Hickson M, Jaramillo-Hidalgo J, Lozano-Montoya I, O'Mahony D, Soiza RL, Visser M, Volkert D, Wolters M, Jentoft AJC, Efficacy of non-pharmacological interventions to treat malnutrition in older persons: A systematic review and meta-analysis. The SENATOR project ONTOP series and MaNuEL Knowledge Hub project, *Ageing Research Reviews* (2018), <https://doi.org/10.1016/j.arr.2018.10.011>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Efficacy of non-pharmacological interventions to treat malnutrition in older persons: A systematic review and meta-analysis. The SENATOR project ONTOP series and MaNuEL Knowledge Hub project.**

**Authors:**

Correa-Pérez, Andrea <sup>1\*</sup>  
Abraha, Iosef <sup>2</sup>  
Cherubini, Antonio <sup>2</sup>  
Collinson, Avril <sup>3</sup>  
Dardevet, Dominique <sup>4</sup>  
de Groot, Lisette CPGM <sup>5</sup>  
de van der Schueren, Marian A.E. <sup>6</sup>  
Hebestreit, Antje <sup>7</sup>  
Hickson, Mary <sup>3</sup>  
Jaramillo-Hidalgo, Javier <sup>8</sup>  
Lozano-Montoya, Isabel <sup>1,9</sup>  
O'Mahony, Denis <sup>10</sup>  
Soiza, Roy L. <sup>11</sup>  
Visser, Marjolein <sup>12</sup>  
Volkert, Dorothee <sup>13</sup>  
Wolters, Maïke <sup>7</sup>  
Cruz Jentoft, Alfonso J<sup>1</sup>

**Affiliations:**

<sup>1</sup> Servicio de Geriátría. Hospital Universitario Ramón y Cajal (IRYCIS). Madrid, Spain.

<sup>2</sup> Geriatria, Accettazione geriatrica e Centro di ricerca per l'invecchiamento, Italian National Research Center on Aging (IRCCS- INRCA), Ancona, Italy.

<sup>3</sup> Institute of Health and Community, University of Plymouth. United Kingdom.

<sup>4</sup> Université Clermont Auvergne, INRA, UNH, Centre de Recherche en Nutrition Humaine (CRNH). Clermont-Ferrand, France.

<sup>5</sup> Division of Human Nutrition and Health, Wageningen University. Wageningen, Netherlands.

<sup>6</sup> Department of nutrition and health, HAN University of Applied Sciences, Nijmegen. The Netherlands, and department of nutrition and dietetics, VU University Medical Center, Amsterdam, the Netherlands

<sup>7</sup> Leibniz Institute for Prevention Research and Epidemiology – BIPS. Bremen, Germany.

<sup>8</sup> Servicio de Geriátría. Hospital Central de la Cruz Roja San José y Santa Adela. Madrid, Spain.

<sup>9</sup> Servicio de Medicina Interna. Hospital El Escorial. Madrid, Spain (Present address).

<sup>10</sup> Department of Geriatric Medicine, Cork University Hospital. Cork, Ireland.

<sup>11</sup> Department of Medicine for the Elderly, NHS Grampian, Aberdeen, United Kingdom.

<sup>12</sup> Department of Health Sciences, Vrije Universiteit Amsterdam. The Netherlands.

<sup>13</sup> Institute for Biomedicine of Aging, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nuremberg, Germany.

**\*Corresponding author:**

[Andrea.correa@salud.madrid.org](mailto:Andrea.correa@salud.madrid.org)

Servicio de Geriátría. Hospital Universitario Ramón y Cajal. Crta. De Colmenar, Km 9.1, 28034. Madrid, Spain

## HIGHLIGHTS

- We made a systematic review of non-pharmacological interventions in malnourished older people
- Relevant nutritional and clinical outcomes were agreed by a wide panel of experts in nutrition and geriatrics
- We included 19 studies from 17 systematic reviews after reviewing 7984 references
- Our findings were negative: we did not find high quality evidence on interventions to treat malnutrition in older people
- High quality research studies are urgently needed in this area

## Abstract

### INTRODUCTION

We aimed to perform a review of SRs of non-pharmacological interventions in older patients with well-defined malnutrition using relevant outcomes agreed by a broad panel of experts.

### METHODS

PubMed, Cochrane, EMBASE, and CINHALL databases were searched for SRs. Primary studies from those SRs were included. Quality assessment was undertaken using Cochrane and GRADE criteria.

### RESULTS

Eighteen primary studies from seventeen SRs were included. Eleven RCTs compared oral nutritional supplementation (ONS) with usual care. No beneficial effects of ONS treatment, after performing two meta-analysis in body weight changes (six studies), mean difference: 0.59 (95%CI -0.08, 1.96) kg, and in body mass index changes (two studies), mean difference: 0.31 (95%CI -0.17, 0.79) kg/m<sup>2</sup> were found. Neither in MNA scores, muscle strength, activities of daily living, timed Up&Go, quality of life and mortality.

Results of other intervention studies (dietary counselling and ONS, ONS combined with exercise, nutrition delivery systems) were inconsistent. The overall quality of the evidence was very low due to risk of bias and small sample size.

## CONCLUSIONS

This review has highlighted the lack of high quality evidence to indicate which interventions are effective in treating malnutrition in older people. High quality research studies are urgently needed in this area.

## KEYWORDS

protein energy malnutrition; elderly, dietary supplementation; review, systematic

## 1. INTRODUCTION

Malnutrition has been defined as “a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue or body form (body shape, size and composition), function and clinical outcomes”(Borum, 2004). In this paper, we refer to malnutrition as a state of deficiency rather than excess, of macronutrients, specifically in older adults. It is due to inadequate protein and energy intake resulting in underweight and/or muscle mass and function loss.

Malnutrition is not only associated with the early development of dependency but also has been reported to be a significant clinical problem adversely affecting individuals' physical and cognitive functional status, general wellbeing and quality of life in the hospital, long-term care and community setting (Elia M, 2009). Malnutrition is associated with increased length of recovery, hospital stay, health deterioration, healthcare costs (Guest et al., 2011; Thomas et al., 2007) and the decrease in the number of Healthy Life Years (Beltrán-Sánchez et al., 2015).

It is often assumed that malnutrition is inevitably associated with aging and hence nutritional interventions may have only minimal positive impact. However, there is some evidence from cohort studies showing that appropriate or elevated protein intake is associated with a better body composition and lean mass during aging, and with a reduced risk of mobility limitations (Chan et al., 2014; Houston et al., 2017; Scott et al., 2010) although other intervention studies have opposite results (Beelen et al., 2017; Van Wymelbeke et al., 2016). A number of systematic reviews have investigated a range of non-pharmacological interventions (e.g. dietary counselling, oral nutritional supplements, food fortification, dietary advice) in the prevention or treatment of malnutrition in older people. These have suggested that energy and protein intake can be improved (Abbott et

al., 2013; Baldwin and Weekes, 2011; Collins and Porter, 2015; Milne et al., 2009a; Poscia et al., 2018) but have unfortunately not shown clear results for functional or clinical outcomes. Indeed, several reviews have commented on the weaknesses in methodological design of primary studies which result in inconclusive results (Beck et al., 2016). These include a lack of consistency in the assessment of function, meaning meta-analysis is not possible, lack of power due to small sample size leading to a risk of type-2 errors, differences in the amount and composition of nutrients included in the supplement, inclusion of well-nourished persons who are less likely to benefit from treatment, and high risk of bias and differences in baseline measures between groups (Beck et al., 2016). Other reviews have also only examined specific population groups (e.g. dementia, frailty and hip fracture) (Allen et al., 2013; Artaza-Artabe et al., 2016; Avenell et al., 2016; Droogsma et al., 2014) or intermediate outcomes (e.g. protein or energy intake) (Kimber et al., 2015; Trabal and Farran-Codina, 2015).

In order to develop evidence-based policy and to design effective clinical services it is appropriate to examine again the published literature for malnourished older people or those at high risk. It is important to summarise the evidence for all tested nutritional interventions and relevant clinical outcomes, and this is the aim of the present systematic review. Moreover, this review only included studies that used a definition of malnutrition and outcomes relevant and important to this age group as agreed by a broad panel of experts. This work is part of the ONTOP project (Abraha et al., 2015), a work package of the SENATOR study (see acknowledgments), in partnership with the MaNuEL Knowledge hub (Visser et al., 2017). The ONTOP aim is to undertake a literature search of systematic reviews concerning evidence-based non-pharmacological treatments of 15 prevalent medical conditions affecting older people, including malnutrition. One of the objectives of MaNuEL is to review the effectiveness of nutritional and other non-pharmacological interventions for the treatment of malnutrition in older persons. Here, we joined forces to achieve both aims. This paper will report non-pharmacological interventions for the treatment of malnutrition in older people.

The aims of this study were to identify all published systematic reviews (SRs) concerning non-pharmacological interventions used to treat malnutrition, to identify, extract and critically appraise the primary studies that were included in the SRs, to critically summarise the evidence extracted from the included primary studies, to discuss the limitations and suggest research priorities for future intervention studies in malnourished older persons.

## 2. METHODS

The methodology of the ONTOP and MaNuEI projects is detailed elsewhere (Abraha et al., 2015)(Visser et al., 2017). To define the clinical questions, the working group identified a list of potentially relevant interventions and outcomes used to prevent or treat malnutrition, independent from the available evidence for each outcome, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schünemann H, Brożek J, Guyatt G, Oxman A, 2013): To define which outcomes were relevant for inclusion in the clinical questions, we followed a procedure that has been described in detail elsewhere (Correa-Pérez et al., 2018). In brief, we manually searched some clinical trials, systematic reviews and clinical guidelines in the field of nutrition to identify the most frequently used outcomes reported in research of interventions for malnutrition. A list of 13 outcomes was prepared and a Delphi process with 41 experts in nutrition and geriatric medicine was started, asking them to rate the relevance of each outcome from 1 to 9 points. They were also asked to reword outcomes and to propose further outcomes not included in the initial list. Only those outcomes rated in the last round from 7 to 9 points (critical) were considered as critical and used in this systematic review. These outcomes were: nutritional status (e.g. changes in body weight, body mass index, muscle mass, fat free mass), morbidity (e.g. hospital complications, infections, pressure sores), functional status (e.g. changes in mobility, activities of daily living, physical performance, and muscle strength), mortality, and quality of life. Only studies using these outcomes were included in this systematic review.

### **2.1. Search strategy and inclusion criteria for systematic reviews**

To identify the systematic reviews of interest, search strategies in the following databases were launched on December 2016: Cochrane Database of Systematic Reviews, PubMed, EMBASE and CINHALL. The search strategy included the following terms: systematic review, meta-analysis, underweight, weight loss, underfed, protein energy malnutrition, undernourished, undernutrition (search strategies for each database are detailed in Appendix A). Montori's search strategy (Montori et al., 2005) was used in PubMed. After extracting the references from the literature databases and after eliminating duplicates, title and abstract screening was undertaken by two independent reviewers to include: a) systematic reviews or meta-analyses, that mentioned b) any non-pharmacological intervention to treat malnutrition in older persons (mean age of participants >65 years old), and c) risk of malnutrition or malnutrition defined by the objective measures agreed by the panel: Mini Nutritional Assessment (MNA) <24 points, Subjective Global Assessment (SGA) B-C, Malnutrition Universal Screening Tool (MUST) ≥1, Nutritional Risk Screening (NRS) 2002 ≥1, Body Mass Index (BMI) <22

kg/m<sup>2</sup>, and unintentional weight loss >5% over the last 3 months or >10% indefinite of time. Guidelines that did not include a systematic review were excluded.

Subsequently, full-texts of all relevant abstracts were obtained and screened to identify SRs of interest based on: a) the use of at least two medical literature databases; b) used a systematic search strategy; c) quality of primary studies reported; d) the inclusion of at least one comparative primary study; e) the use of at least one non-pharmacological intervention for malnutrition; and f) the inclusion of at least one study with older persons (mean age of participants >65 years old) at risk of malnutrition or malnourished (see definitions above). We considered papers written in English, German, Italian, Portuguese or Spanish, as all these languages are covered in the MaNuEL consortium and ONTOP working group. Pairs of reviewers independently screened titles, abstracts and full-texts of SRs.

## **2.2. Inclusion and exclusion criteria for primary studies**

Systematic reviews were examined to identify any experimental comparative primary study (based on the information provided by the review of which they came from) either randomised or non-randomised that investigated any non-pharmacological intervention to treat or prevent malnutrition in older persons. We included all primary studies enrolling individuals with a mean sample age above 65 years. Primary studies were excluded if they were observational studies or before-after studies with historical controls. Conference proceedings or programme abstracts were excluded. Primary studies were also excluded if malnutrition or risk of malnutrition were assessed by other measures or criteria not previously specified. Studies considering exclusively patients admitted to intensive care, palliative care, oncology patients, and HIV-infected patients were excluded, as in such conditions cachexia is more frequent than malnutrition, and this condition needs specific nutritional approaches. Other diseases (i.e. Alzheimer's disease) were not excluded, as the role of inflammation is less clear. Oral nutritional supplements using only individual specific vitamins (e.g. vitamin D) or other micronutrients were also omitted.

## **2.3. Data extraction and management**

All the primary studies identified according to the inclusion/exclusion criteria were reviewed, data were extracted directly from the studies, not from the systematic reviews. Characteristics of the included primary studies were described based on the study design (randomised controlled trial [RCT] or controlled clinical trial [CCT]), population, setting, intervention, outcomes, and funding (Table 1). Data extraction was also performed

by two independent reviewers. Disagreement was resolved by discussion and, when needed, by a third senior reviewer.

#### **2.4. Methodological quality assessment. Risk of bias**

Assessment of bias for the included primary studies was carried out using criteria from the Cochrane Collaboration (Higgins J, Higgins JPT, Altman DG, 2011). Domains considered were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential biases (e.g. similar baseline characteristics of the study sample). Risk of bias was graded by including each study in one of three categories: low risk, high risk and unclear risk. Two reviewers independently assessed the risk of bias of individual studies and any differences in quality assessment results were resolved through consensus.

#### **2.5. Data synthesis and analysis**

Following a PICO (Patient Intervention Comparator Outcome) process (O'Connor D, Green S, 2011), studies were pooled together for meta-analysis if they used the same intervention, outcome measure and study design. When a meta-analysis was feasible with at least two studies, data synthesis was carried out using Review Manager Software 5.3 according to the Cochrane Collaboration Statistical Guidelines. A random effects model was chosen to perform the meta-analysis due to the heterogeneity of the study designs. Unless otherwise stated, data are presented as mean  $\pm$  SD. Results are presented in a narrative way when no meta-analysis could be performed. Participants were treated as the unit of analysis in all primary studies included in this review.

#### **2.6. Certainty of the evidence**

We assessed the certainty of evidence following the GRADE methodology (Schünemann H, Brożek J, Guyatt G, Oxman A, 2013). GRADE assessment considers the risk of bias, consistency of results across the available studies (heterogeneity), directness (if the evidence answers directly the health care question), precision of the results (e.g., width of the CI, sample size), and other considerations (e.g., publication bias) that may have influence on the effect of the intervention. The quality of the evidence was categorised as high, moderate, low, or very low based on the authors' judgments for the critical outcomes. A GRADE evidence profile table was prepared for each critical outcome.

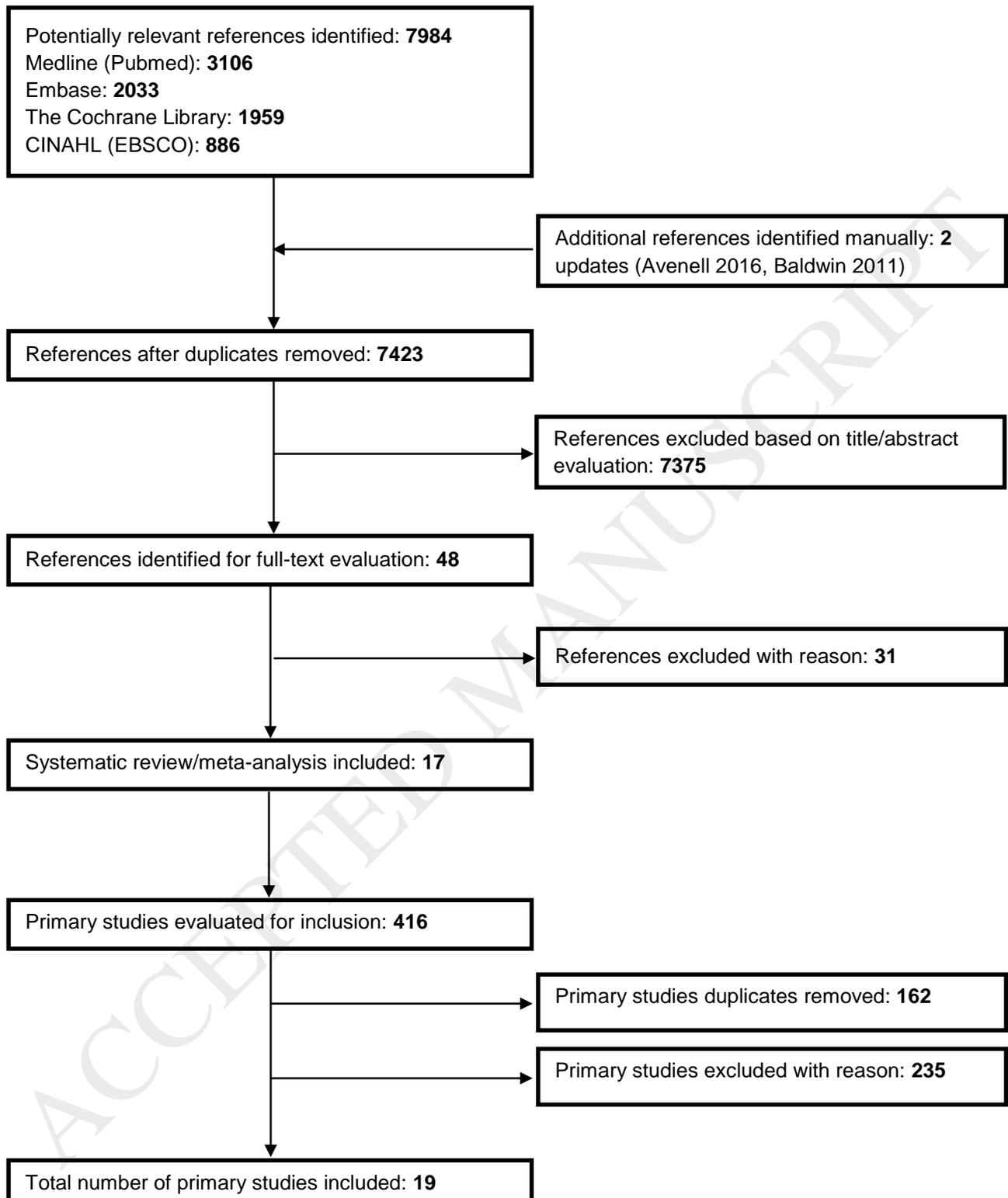
### 3. RESULTS

#### 3.1. Systematic reviews

Our search identified 7,423 references after removing duplicates, of which 7,375 references were excluded based on title/abstract. Among the 48 potentially relevant publications, 17 SRs were considered relevant for inclusion (31 were excluded for different reasons; see Appendix B) (see Figure 1 for the study screening process). The publication year ranged from 1996 to 2016, two updates were identified manually, when reviewers were looking at the full text (Avenell et al., 2016; Baldwin and Weekes, 2011).

ACCEPTED MANUSCRIPT

Figure 1. Study screening process



### 3.2. Primary studies

Overall, the 17 systematic reviews yielded 416 primary studies, of which 19 satisfied the inclusion criteria (Appendix C) and 235 studies were excluded due to different reasons. Two included journal articles were from the same study (Lammes et al., 2012; Rydwick et al., 2008), therefore we got eighteen original studies. The most frequent reasons for exclusion were the inclusion of participants who were not malnourished or at risk of malnutrition and a non-controlled study design (Appendix D). All the included studies were RCTs except for a single CCT (Campbell et al., 2013) (non-randomised study). The number of participants included in these trials ranged from 30 (de Luis et al., 2008) to 259 (Feldblum et al., 2011). The percentage of women was higher than 50% in all studies (in one study all participants were women (Volkert et al., 1996)). The studies were performed in different settings: hospitals (Campbell et al., 2013; Carver and Dobson, 1995; Feldblum et al., 2011; Gazzotti, 2003; Ha et al., 2010; Hickson et al., 2004; Lauque et al., 2004; Volkert et al., 1996), nursing homes (Lauque et al., 2000; Smoliner et al., 2008), and community-dwelling older people (de Luis et al., 2008; Edington et al., 2004; Feldblum et al., 2011; Gazzotti, 2003; Gray-Donald et al., 1995; Kim and Lee, 2013; Lammes et al., 2012; Lauque et al., 2004; Payette et al., 2002; Price et al., 2005; Rydwick et al., 2008; Sugawara et al., 2010; Volkert et al., 1996). Main participants' conditions from the studies varied from acutely ill (Campbell et al., 2013; Edington et al., 2004; Feldblum et al., 2011; Gazzotti, 2003; Hickson et al., 2004; Price et al., 2005; Volkert et al., 1996), acute stroke (Ha et al., 2010), frail (Gray-Donald et al., 1995; Kim and Lee, 2013; Lammes et al., 2012; Payette et al., 2002; Rydwick et al., 2008; Smoliner et al., 2008), and chronic diseases as dementia (Carver and Dobson, 1995; Lauque et al., 2004), chronic obstructive pulmonary disease (Sugawara et al., 2010) or type-2 diabetes mellitus (de Luis et al., 2008). In four studies (Feldblum et al., 2011; Gazzotti, 2003; Lauque et al., 2004; Volkert et al., 1996) participants were included during hospitalization and followed after discharge. To assess malnutrition, the criteria used were: MNA (Feldblum et al., 2011; Gazzotti, 2003; Kim and Lee, 2013; Lauque et al., 2004, 2000; Smoliner et al., 2008), BMI and unintentional weight loss (Edington et al., 2004; Gray-Donald et al., 1995; Lammes et al., 2012; Payette et al., 2002; Price et al., 2005; Rydwick et al., 2008), BMI alone (Carver and Dobson, 1995; Hickson et al., 2004; Sugawara et al., 2010; Volkert et al., 1996), unintentional weight loss (de Luis et al., 2008), MUST (Ha et al., 2010) and SGA (Campbell et al., 2013).

The non-pharmacological interventions studied were: oral nutritional supplementation (ONS) (Carver and Dobson, 1995; de Luis et al., 2008; Edington et al., 2004; Gazzotti, 2003; Gray-Donald et al., 1995; Kim and Lee, 2013; Lauque et al., 2004, 2000; Payette et al., 2002; Price et al., 2005; Smoliner et al., 2008; Volkert et

al., 1996), dietary counselling plus ONS (Feldblum et al., 2011; Ha et al., 2010; Hickson et al., 2004), and combination of ONS and physical exercise (Lammes et al., 2012; Rydwik et al., 2008; Sugawara et al., 2010). The duration of the intervention ranged from 2 weeks to 6 months. Follow-up after intervention ranged from 4 weeks to 6 months. All critical outcomes selected by the panel were found in at least one of the included studies and were considered for analysis.

### **3.3. Methodological quality assessment. Risk of Bias.**

Risk of bias of each included primary study is summarised in Table 2. In general, the included studies had high risk of bias mostly due to selection, performance and detection bias. Following the GRADE guidelines, the quality of the evidence was reduced if significant risk of bias was detected, as described below.

### **3.4. Evidence of the intervention effects**

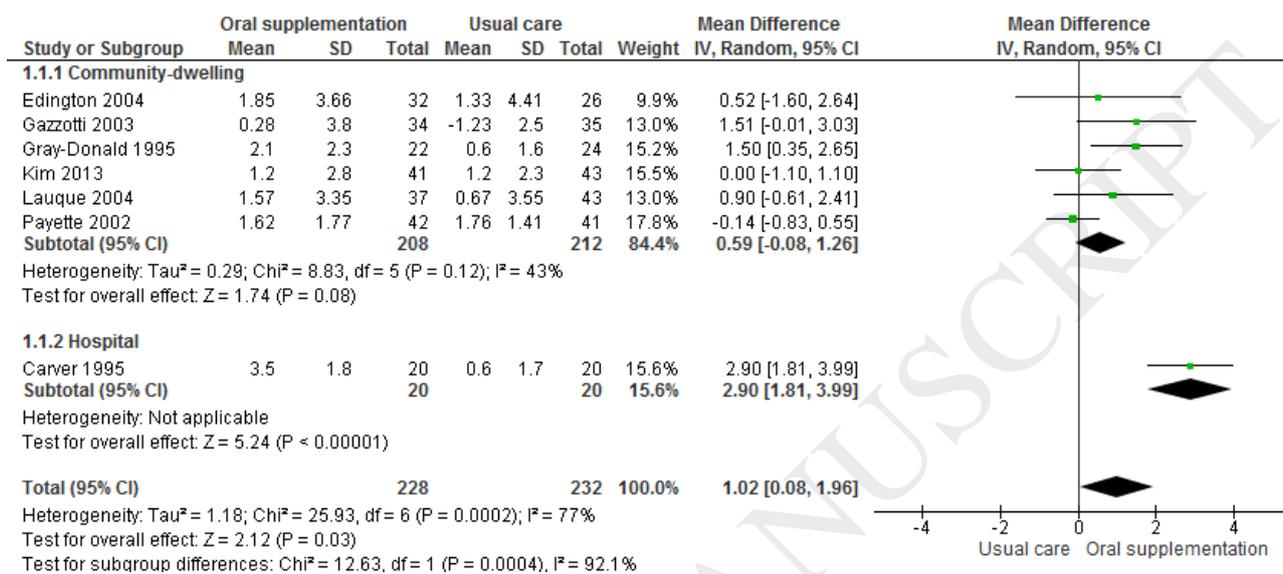
Due to the differences in study designs, meta-analysis was only feasible for some studies that compared oral nutritional supplementation vs usual care (the main comparator) and that used changes in body weight and BMI as outcome. We could not separate malnourished participants from participants at risk of malnutrition because both conditions are poorly defined and treated altogether in the included studies.

#### **3.4.1. Evidence on effect of oral nutritional supplementation (ONS) vs. usual care (UC) on body weight (BW, kg) in malnourished (or at risk of malnutrition) older people.**

Ten studies (Carver and Dobson, 1995; Edington et al., 2004; Gazzotti, 2003; Gray-Donald et al., 1995; Kim and Lee, 2013; Lauque et al., 2004, 2000; Payette et al., 2002; Smoliner et al., 2008; Volkert et al., 1996) including 713 participants evaluated the effect of ONS versus UC on BW changes before and after the intervention or the follow-up period in hospital and community-dwelling settings. The composition of the nutritional supplements that ranged from 300 to 1000 kcal per day, length of intervention and control group varied among the studies (see Table 1). Body weight measure was also different among studies: seven RCTs (Carver and Dobson, 1995; Edington et al., 2004; Gazzotti, 2003; Gray-Donald et al., 1995; Kim and Lee, 2013; Lauque et al., 2004; Payette et al., 2002) including 460 participants presented BW as the absolute difference in kg between baseline and the end of the intervention comparing both groups, irrespective of baseline BW. Meta-analysis was performed showing a significant BW gain in the intervention group (1.02 kg [0.08, 1.96]) (Figure 2). However, statistical heterogeneity was high ( $I^2 = 77%$ ,  $p=0.0002$ ). A sensitivity analysis

by subgroups was done according to setting, as only one study (Carver and Dobson, 1995) was done in a long-term hospital setting (residents in a psychiatric hospital), showing a non-significant BW increase in studies in community-dwelling older persons, with reduced heterogeneity ( $I^2=43%$   $p=0.12$ ).

**Figure 2: Oral nutritional supplementation versus usual care, outcome: changes in body weight (kg)**



The other three RCT studies (Lauque et al., 2000; Smoliner et al., 2008; Volkert et al., 1996) only showed the final value of BW (kg) at the end of follow-up, finding no significant differences between groups (we did not pool these studies because they do not report the changes in BW after the intervention).

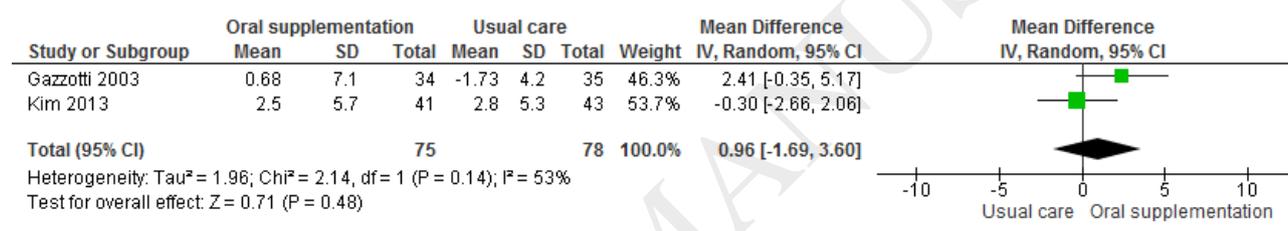
### Methodological issues

The quality of the evidence had to be downgraded by two levels due to serious concern regarding risk of bias (allocation concealment was unclear in three (Edington et al., 2004; Gazzotti, 2003; Payette et al., 2002) and biased in one (Gray-Donald et al., 1995) of 6 studies and sequence generation was unclear in four studies; all studies (Edington et al., 2004; Gazzotti, 2003; Gray-Donald et al., 1995; Kim and Lee, 2013; Lauque et al., 2004; Payette et al., 2002) suffered from performance bias due to the nature of the intervention and no placebo supplements were given to the control group, while detection bias was present in three studies (Gazzotti, 2003; Gray-Donald et al., 1995; Lauque et al., 2004), Table 2) and serious concern regarding imprecision (although the sample size is greater than 400, clinical significance of a 0.59 kg BW increment is unclear). The global certainty of the evidence was rated as low (Table 3a).

### 3.4.2. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to increase body weight (BW, percent change) in malnourished (or at risk of malnutrition) older people

Three studies reported the percentage of BW changes (Gazzotti, 2003; Kim and Lee, 2013; Price et al., 2005) in 279 participants. In these studies, the ONS provided between 400 and 600 kcal per day. Only two RCTs including 153 participants were pooled (Gazzotti, 2003; Kim and Lee, 2013) since the data results were reported. However, the meta-analysis showed a non-significant difference between groups (Figure 3) with no significant heterogeneity ( $p=0.14$ ,  $I^2=53\%$ ). In the other study (Price et al., 2005) the percentage differences in BW were reported as not significant (3.0% and 3.9% in the control and intervention groups, respectively;  $p=0.44$ ).

**Figure 3: Oral nutritional supplementation versus usual care, outcome: changes in body weight (percent)**



#### Methodological issues

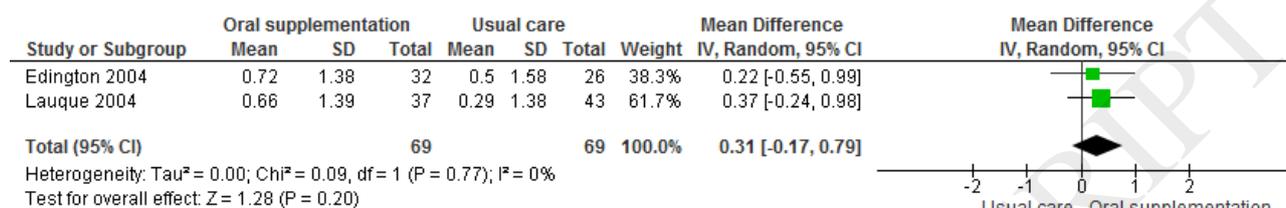
We downgraded the certainty of the evidence due to serious concern regarding risk of bias (performance bias was evident in the studies whereas allocation concealment was unclear and detection bias was evident for one study (Gazzotti, 2003), see Table 2) and very serious concern regarding imprecision. We rated the certainty of the evidence as very low (Table 3a).

### 3.4.3. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to increase body mass index (BMI) in malnourished (or at risk of malnutrition) older people

Five studies (Carver and Dobson, 1995; Edington et al., 2004; Lauque et al., 2004, 2000; Smoliner et al., 2008) including 289 participants evaluated the role of ONS vs UC by assessing changes in BMI (Table 1). Only in one study (Carver and Dobson, 1995) an oral placebo was given to the control group, and in another study home visits were performed by a dietitian (Edington et al., 2004). Two trials (Edington et al., 2004; Lauque et al., 2004) including 138 participants, and where ONS provided between 300 and 1000 kcal per day, assessed the differences in BMI before and after the intervention between groups. We pooled both studies, finding a

non-significant mean difference in BMI increment (0.31 kg/m<sup>2</sup>; CI: -0.17, 0.79 kg/m<sup>2</sup>). The heterogeneity was not significant ( $p=0.77$ ,  $I^2=0\%$ ) (Figure 4). The other three studies (Carver and Dobson, 1995; Lauque et al., 2000; Smoliner et al., 2008) where ONS provided between 300 and 600 kcal per day, only measured the final BMI after the intervention.

**Figure 4: Oral nutritional supplementation versus usual care, outcome: changes in BMI (kg/m<sup>2</sup>).**



#### Methodological issues

We downgraded the quality of the evidence due to serious concern regarding risk of bias (sequence generation and allocation concealment was unclear, whereas performance and attrition bias were evident in the studies, see Table 2) and very serious concern regarding imprecision due to the small sample size. We finally rated the certainty of the evidence as very low (Table 3a).

#### **3.4.4. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to increase mini-nutritional assessment (MNA) score in malnourished (or at risk of malnutrition) older people**

Four trials (Gazzotti, 2003; Lauque et al., 2004, 2000; Smoliner et al., 2008) including 301 participants evaluated ONS (providing between 300 and 600 kcal per day) vs. UC in malnutrition assessed by changes in the MNA. Only one study (Lauque et al., 2004) reported the difference of MNA between baseline and intervention and compared both groups. MNA score was higher in the intervention group only at three-months after starting the intervention. However, at 3 months of follow-up differences between groups were not reported.

The other RCTs (Gazzotti, 2003; Lauque et al., 2000; Smoliner et al., 2008) reported the absolute value of MNA score after the intervention. Of these, two studies (Gazzotti, 2003; Smoliner et al., 2008) compared MNA score between intervention and control groups; only in one study the MNA (Gazzotti, 2003) was higher in the intervention group than in control group ( $23.5 \pm 3.9$  vs  $20.8 \pm 3.6$ ,  $p < 0.01$ ). We did not pool these studies because they do not report the changes in MNA score after the intervention.

*Methodological issues*

We downgraded the quality of evidence to low evidence due to serious concern regarding risk of bias and very serious concern regarding imprecision (Table 3a). Risk of bias is reported in Table 2.

**3.4.5. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to increase fat-free mass (FFM) in malnourished (or at risk of malnutrition) older people**

Two RCTs (Lauque et al., 2004; Smoliner et al., 2008) including 143 participants assessed FFM in participants receiving ONS (providing between 300 and 600 kcal per day) vs UC. FFM was measured using dual-energy x-ray absorptiometry (DEXA) (Lauque et al., 2004) and bioelectrical impedance analysis (BIA) (Smoliner et al., 2008). Only in one of them (Lauque et al., 2004) FFM was assessed as the difference (kg) before and after intervention; this study did not find differences between groups. In the second study (Smoliner et al., 2008), FFM (kg) was measured as the final value after the intervention, and again there was no difference between groups.

*Methodological issues*

We downgraded the quality of evidence by two levels to very low due to serious concern regarding risk of bias (Table 2) and very serious concern regarding imprecision (Table 3a).

**3.4.6. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to improve the Timed-Up&Go (TUG) in malnourished (or at risk of malnutrition) older people**

Two studies (Kim and Lee, 2013; Payette et al., 2002) including 170 participants assessed the TUG test (measured in seconds) comparing both groups ONS (providing between 400 and 700 kcal per day) vs UC. In one study (Kim and Lee, 2013) TUG, reported as median percent change (interquartile range) decreased by 7.2% (-24.7, 9.9) in the intervention group (a shorter time means better physical performance) and increased by 3.4% (-14.9, 28.9) in the control group ( $p=0.038$ ). In the second study (Payette et al., 2002), TUG differences were reported graphically without differences between groups.

*Methodological issues*

GRADE assessment was only performed with one study (Kim and Lee, 2013) due to a better clarity in the presentation of the results. We rated the evidence as very low due to performance bias (Table 2) and the low sample size (Table 3a).

### **3.4.7. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to increase handgrip strength in malnourished (or at risk of malnutrition) older people**

Seven RCTs (Edington et al., 2004; Gray-Donald et al., 1995; Kim and Lee, 2013; Lauque et al., 2000; Payette et al., 2002; Price et al., 2005; Smoliner et al., 2008) including 584 participants assessed muscle strength (a measure of sarcopenia) by handgrip strength after ONS (providing between 300 and 700 kcal per day) compared to UC. The results were not pooled because the report of measures of handgrip were very different across the studies. Only three studies (Edington et al., 2004; Kim and Lee, 2013; Price et al., 2005) measured the changes showing the absolute difference (graphically) (Edington et al., 2004) or the percentage of change (Kim and Lee, 2013; Price et al., 2005) in handgrip strength after the intervention. No difference was found between intervention and control groups.

#### *Methodological issues*

GRADE assessment was performed with two studies (Kim and Lee, 2013; Price et al., 2005), where the results were given clearly. We downgraded the certainty of the evidence to very low due to serious concern regarding risk of bias (Table 2) and imprecision (Table 3a).

### **3.4.8. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to improve activities of daily living (ADL) in malnourished (or at risk of malnutrition) older people**

Three RCTs (Lauque et al., 2004; Smoliner et al., 2008; Volkert et al., 1996) including 189 participants assessed ADL using different scales (Barthel Index, Katz Index) after oral nutritional supplementation providing between 300 and 600 kcal per day. One RCT (Volkert et al., 1996) showed a higher proportion of independent participants (Barthel Index >65 points) after six months of follow-up in the adherent participants to the intervention compared with the control group (72% vs 28%,  $p < 0.05$ ). More treated participants (subgroup of adherents to the intervention) improved Barthel Index in  $\geq 15$  points between admission and discharge than those in the control group (64% vs 23%,  $p < 0.05$ ). However, no differences in the mean change of Barthel Index between groups were reported. Another study (Smoliner et al., 2008) only reported the final score of Barthel Index at the end of the intervention showing no significant differences between groups. Only one study (Lauque et al., 2004) reported changes in Katz index, showing significant differences in both groups between baseline and end of follow-up, but the intervention and control groups were not compared.

#### *Methodological issues*

GRADE assessment was performed for one study (Lauque et al., 2004) as changes in ADL (changes in Katz index score) were reported. We downgrade the quality of evidence due to serious concern regarding risk of bias (Table 3) and very serious concern regarding imprecision (Table 3a).

#### **3.4.9. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to improve quality of life (QoL) in malnourished (or at risk of malnutrition) older people**

Four studies (Edington et al., 2004; Gray-Donald et al., 1995; Payette et al., 2002; Smoliner et al., 2008) including 283 participants, where ONS provided between 400 and 1000 kcal per day, evaluated the QoL using different scales: the EuroQoL Questionnaire (EQ5D) (Edington et al., 2004), the general well-being score and self-perceived health status (Gray-Donald et al., 1995), the subscale of physical function from the 36-Item Short Form Health Survey (SF-36) (Smoliner et al., 2008), and different dimensions of the SF-36 form (physical function, emotional function and vitality) (Payette et al., 2002). All the results of these scales were given as the final values after intervention. Study groups were compared without finding significant differences between them.

##### *Methodological issues*

Risk of bias of these studies is reported in Table 2. GRADE assessment was not performed as the studies did not assess our outcome of interest which is the change in QoL scores after an intervention (Table 3a).

#### **3.4.10. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to decrease mortality in malnourished (or at risk of malnutrition) older people**

Only one RCT (Edington et al., 2004) including 100 participants, where ONS provided between 400 and 1000 kcal per day, assessed mortality in participants with malnutrition in terms of number of deaths (17 participants died in the intervention group whereas 15 died in the control group). There was no difference in mortality between groups.

##### *Methodological issues*

See Table 2 for risk of bias. The quality of the evidence for this outcome was rated as very low (Table 3a).

#### **3.4.11. Evidence of oral nutritional supplementation (ONS) vs. usual care (UC) to decrease morbidity in malnourished (or at risk of malnutrition) older people**

Only one RCT (Lauque et al., 2004) including 91 participants, where ONS provided between 300 and 500 kcal per day, assessed morbidity in terms of number of fractures, pressure ulcers, or hospitalization in participants with Alzheimer's disease. No differences were found between groups.

#### *Methodological issues*

This study (Lauque et al., 2004) suffered from high risk of performance, detection, attrition, and publication bias (Table 2). GRADE assessment was not performed as morbidity data were not reported (Table 3a).

#### **3.4.12. Evidence of individualised dietary counselling plus oral nutritional supplementation (ONS) vs. usual care (UC) in nutritional, functional, quality of life, and mortality outcomes in malnourished (or at risk of malnutrition) older people**

Three studies (Feldblum et al., 2011; Ha et al., 2010; Hickson et al., 2004) including 512 participants compared the effect on individualised dietary counselling plus ONS versus usual care in different nutritional outcomes (body weight, body mass index, and MNA score), muscle strength (handgrip strength), quality of life (EQ-5D), and mortality in a hospital setting. There were significant changes in MNA score: 1 RCT (Feldblum et al., 2011), 168 participants, mean difference of 1.2 points (95% CI 0.34-2.06); changes in handgrip strength: 1 RCT (Ha et al., 2010), 121 participants, mean difference of 2.6 kg (95% CI 1.6-4.4). See Table 3b for more details.

#### *Methodological issues*

The quality of the evidence was very low (Table 3b) mainly due to serious concern regarding risk of bias (high risk of performance and attrition bias, unclear risk of selection and detection bias (Table 2) and very serious concern of imprecision (the number of participants was less than 200 participants). Overall, single trials with very low quality do not allow for relevant conclusions.

#### **3.4.13. Evidence of oral nutritional supplementation (ONS) plus physical exercise vs. education to improve nutritional, functional, and quality of life outcomes in COPD malnourished (or at risk of malnutrition) older people**

One study (Sugawara et al., 2010) included 35 participants suffering from chronic obstructive pulmonary disease (COPD). It compared the intervention effects (ONS provided 400 kcal per day) on nutritional status (body weight, fat mass index, FMI, and fat free mass index, FFMI), functional status (quadriceps strength, 6-minuts walk distance) and quality of life (CRQ: Chronic Respiratory Disease Questionnaire) with educational sessions (control group). All these outcomes improved in the intervention group compared with the control group. See Table 3c for more details.

*Methodological issues*

The quality of the evidence was very low mainly (Table 3c) due to serious concern regarding risk of bias (see Table 2) and very serious concern to imprecision (only one RCT with 32 participants in the final analysis).

**3.4.14. Evidence of either physical exercise or dietary counselling interventions or both interventions combined vs. nutritional and physical advice to improve nutritional and functional outcomes in malnourished (or at risk of malnutrition) frail older people**

One RCT (Lammes et al., 2012; Rydwik et al., 2008) including 96 participants compared the effects of a physical training program (combining aerobic, muscle strength, balance plus dietary advice), a nutritional counselling intervention program (individually targeted dietary advice plus physical training advice), and a combination of both interventions with the control group (diet and physical training advice) during 12 week-intervention and 6-month follow-up (no frequency of the training sessions or advice giving was specified). Several nutritional and functional outcomes were assessed (see Table 1) without significant between-group differences at 6-month follow-up for any of these outcomes.

*Methodological issues*

This study suffered from high risk of bias in all domains (Table 2) and the quality of the evidence was rated as very low.

**3.4.15. Evidence of new vs. traditional oral nutritional supplementation delivery systems to improve nutritional status, quality of life, and morbidity in malnourished (or at risk of malnutrition) older people**

One non-randomised trial (Campbell et al., 2013) including 98 participants compared two new ONS delivery systems (MedPass and mid-meal trolley) vs a traditional ONS delivery system providing between 500 and 700 kcal daily in an acute and rehabilitation setting during two weeks (Table 1). They found a significant improvement in the EQ5D-index (0-1) with mid-meal trolley (vs. control group) and significantly better overall EQ5D ratings (1-100) with MedPass (vs. control group). There were no differences in weight change, and presence or degree of pressure sores across the three groups.

*Methodological issues*

The evidence was rated as very low: high risk of selection bias, imbalance of baseline characteristics (Table 2) and imprecision due to small sample size.

#### 4. DISCUSSION

Overall, the results show that evidence to support nutrition intervention in older people is limited, due to both the low number of trials and the low methodological quality of most of the trials (that have usually a high risk of bias). The choice and report of outcome measures in these trials is heterogeneous and, in many cases, quite poor, not allowing for relevant meta-analysis except for BW and BMI.

We were able to perform a meta-analysis on a few studies comparing the effect of ONS versus usual care on nutritional status (measured by changes in BW and BMI), showing small gains in body weight (in kg) after interventions, which was not confirmed by changes in BMI or percent change in body weight. Two RCT (Kim and Lee, 2013; Volkert et al., 1996) showed improvements in functional status assessed by TUG and ADL in the group treated with ONS. There were no significant differences in all other relevant outcomes, including morbidity, mortality or quality of life. Some isolated studies of other non-pharmacological interventions (dietary or exercise counselling, physical exercise together with nutrition intervention) showed some impact on different outcomes, but overall the evidence is inconsistent and of low quality. Although changes in BW and BMI are intermediate (surrogate), not final outcomes from a clinical perspective, the study of such changes may help to understand if potential impact on outcomes of nutrition intervention is mediated through changes in body composition. Interestingly, experts in nutrition seem to give more weight to such outcomes than geriatricians (Correa-Pérez et al., 2018). Also, it has to be reminded that changes in BW and BMI during acute hospitalization may also reflect changes in hydration.

A specific problem in many trials is the definition of the comparator for the control group as “usual care”, as this has been shown to be quite different in different countries and settings and is usually poorly described in trials.

Most of the systematic reviews that were the source of the included primary studies reached similar conclusions to ours. However, there are some relevant differences that can be explained by the difference in methodological approach. Many SRs were performed in specific subgroups of patients (hip fracture (Avenell et al., 2016), dementia (Allen et al., 2013; Droogsma et al., 2014; Jackson et al., 2011), frailty (Artaza-Artabe et al., 2016)) or in specific care settings (Collins and Porter, 2015; Koretz et al., 2007). In many of them baseline nutritional status (normal, at risk of malnutrition or malnourished) was not controlled or reported (Droogsma et al., 2014; Howson et al., 2017; Marshall et al., 2013; Munk et al., 2016) while different effects may be expected

in well-nourished and malnourished patients (Milne et al., 2009b). Many systematic reviews showed effects on total daily energy or protein intake (Hubbard et al., 2012; Tassone et al., 2015; Trabal and Farran-Codina, 2015), an outcome that our group did consider less relevant when it would not translate into a better nutritional status or improved clinical outcomes. In addition, most of the SR identified did not exclude non-controlled trials, which introduces a bias, and used less stringent criteria to grade the strength and quality evidence (we followed the Cochrane guidelines for this) (Abraha et al., 2015; O'Connor D, Green S, 2011). We opted to use a strict methodological approach, similar to that used for drugs or medical devices, as we understand that the efficacy of nutrition intervention should be based on strong evidence (randomized controlled trials with blinded assessment of outcomes) showing effect in clinical outcomes that are relevant for patients.

Our study has several limitations. Due to the long review process and the use of a methodology of overview of systematic reviews, recently published studies might not have been included. The large heterogeneity of the included trials precluded us from using meta-analytic techniques for more comparisons, and also from including length of interventions and settings in the effects of trials. The physio-pathology of malnutrition and its progression also is different depending on the setting. The study population included in the primary studies ranged from the hospital to the community-dwelling setting. Even though, in several RCTs the participants comprised two settings: hospital and community-dwelling people. In these participants a nutritional intervention was performed before and after hospital discharge.

This SR focuses on the treatment of malnutrition rather than prevention. However, the included studies have malnourished and at risk of malnutrition patients who receive the same intervention in spite of both conditions have different approaches. Also, the results of the intervention effects are not reported separately by subgroups of patients.

We consider that our approach has several strengths. Including only old persons with well-defined malnutrition or at risk of malnutrition and excluding those using alternative (or less validated) definitions identifies a group with special care needs, as this condition is linked to adverse outcomes. Using only controlled trials and a strict methodologic approach allowed to identify the limitations of current research. The input from a large international group of researchers with expertise in nutrition and geriatric medicine in defining critical outcomes is also important.

In conclusion, this overview of studies included in systematic reviews has showed there is little evidence on which non-pharmacological interventions can be used to effectively treat malnutrition in older people. There is a clear need for well-designed RCTs that follow standard criteria for reporting non-pharmacological

interventions on relevant outcomes for the treatment of malnutrition in older people. Such trials should include detailed reporting of baseline and final measures, larger numbers of participants to ensure sufficient statistical power to detect true treatment effects, careful definition and selection of target participants, some degree of blinding, focus on critical outcomes, standardisation of outcome measures, description of the type of proteins used, the amount given, the timing and the associated energy, appropriate comparator therapy, consideration of potential confounders, careful elucidation of compliance and any adverse effects and cost-utility of the therapy.

ACCEPTED MANUSCRIPT

**FUNDING**

The preparation of this paper was supported by the MalNutrition in the ELderly (MaNuEL) knowledge hub. MaNuEL is supported by the Joint Programming Initiative 'Healthy Diet for a Healthy Life'. The MaNuEL funding agencies supporting this paper are (in alphabetical order of participating Member State): France: Ecole Supérieure d'Agriculières (ESA); Germany: Federal Ministry of Food and Agriculture (BMEL) represented by Federal Office for Agriculture and Food (BLE); The Netherlands: The Netherlands Organisation for Health Research and Development (ZonMw). This work was also supported by the SENATOR trial (FP7-HEALTH-2012-305930).

ACCEPTED MANUSCRIPT

## REFERENCES

- Abbott, R.A., Whear, R., Thompson-Coon, J., Ukoumunne, O.C., Rogers, M., Bethel, A., Hemsley, A., Stein, K., 2013. Effectiveness of mealtime interventions on nutritional outcomes for the elderly living in residential care: a systematic review and meta-analysis. *Ageing Res. Rev.* 12, 967–81. <https://doi.org/10.1016/j.arr.2013.06.002>
- Abraha, I., Cruz-Jentoft, A., Soiza, R.L., O'Mahony, D., Cherubini, A., 2015. Evidence of and recommendations for non-pharmacological interventions for common geriatric conditions: the SENATOR-ONTOP systematic review protocol. *BMJ Open* 5, e007488. <https://doi.org/10.1136/bmjopen-2014-007488>
- Allen, V.J., Methven, L., Gosney, M.A., 2013. Use of nutritional complete supplements in older adults with dementia: systematic review and meta-analysis of clinical outcomes. *Clin. Nutr.* 32, 950–7. <https://doi.org/10.1016/j.clnu.2013.03.015>
- Artaza-Artabe, I., Sáez-López, P., Sánchez-Hernández, N., Fernández-Gutierrez, N., Malafarina, V., 2016. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. *Maturitas* 93, 89–99. <https://doi.org/10.1016/j.maturitas.2016.04.009>
- Avenell, A., Smith, T.O., Curtain, J.P., Mak, J.C., Myint, P.K., 2016. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane database Syst. Rev.* 11, CD001880. <https://doi.org/10.1002/14651858.CD001880.pub6>
- Baldwin, C., Weekes, C.E., 2011. Dietary advice with or without oral nutritional supplements for disease-related malnutrition in adults. *Cochrane Database Syst. Rev.* <https://doi.org/10.1002/14651858.CD002008.pub4>
- Beck, A.M., Dent, E., Baldwin, C., 2016. Nutritional intervention as part of functional rehabilitation in older people with reduced functional ability: a systematic review and meta-analysis of randomised controlled studies. *J. Hum. Nutr. Diet.* 29, 733–745. <https://doi.org/10.1111/jhn.12382>
- Beelen, J., de Roos, N.M., de Groot, L.C.P.G.M., 2017. A 12-week intervention with protein-enriched foods and drinks improved protein intake but not physical performance of older patients during the first 6 months after hospital release: a randomised controlled trial. *Br. J. Nutr.* 117, 1541–1549. <https://doi.org/10.1017/S0007114517001477>
- Beltrán-Sánchez, H., Soneji, S., Crimmins, E.M., 2015. Past, Present, and Future of Healthy Life Expectancy. *Cold Spring Harb. Perspect. Med.* 5. <https://doi.org/10.1101/cshperspect.a025957>
- Borum, P.R., 2004. Disease-Related Malnutrition: An Evidence-Based Approach To Treatment. *Am. J. Clin. Nutr.* 79, 1128–1129. <https://doi.org/10.1093/ajcn/79.6.1128>
- Campbell, K.L., Webb, L., Vivanti, A., Varghese, P., Ferguson, M., 2013. Comparison of three interventions in the treatment of malnutrition in hospitalised older adults: A clinical trial. *Nutr. Diet.* 70, 325–331. <https://doi.org/10.1111/1747-0080.12008>
- Carver, A.D., Dobson, A.M., 1995. Effects of dietary supplementation of elderly demented hospital residents. *J. Hum. Nutr. Diet.* 8, 389–394. <https://doi.org/10.1111/j.1365-277X.1995.tb00334.x>
- Chan, R., Leung, J., Woo, J., Kwok, T., 2014. Associations of dietary protein intake on subsequent decline in muscle mass and physical functions over four years in ambulant older Chinese people. *J. Nutr. Health Aging* 18, 171–7. <https://doi.org/10.1007/s12603-013-0379-y>

- Collins, J., Porter, J., 2015. The effect of interventions to prevent and treat malnutrition in patients admitted for rehabilitation: a systematic review with meta-analysis. *J. Hum. Nutr. Diet.* 28, 1–15. <https://doi.org/10.1111/jhn.12230>
- Correa-Pérez, A., Lozano-Montoya, I., Volkert, D., Visser, M., Cruz-Jentoft, A.J., 2018. Relevant outcomes for nutrition interventions to treat and prevent malnutrition in older people: a collaborative Delphi study. *Eur. Geriatr. Med.* 9, 243–248. <https://doi.org/10.1007/s41999-018-0024-8>
- de Luis, D. a, Izaola, O., Aller, R., Cuellar, L., Terroba, M.C., Martín, T., Cabezas, G., Rojo, S., Domingo, M., 2008. A randomized clinical trial with two enteral diabetes-specific supplements in patients with diabetes mellitus type 2: metabolic effects. *Eur. Rev. Med. Pharmacol. Sci.* 12, 261–266.
- Droogsma, E., van Asselt, D., van Steijn, J., Veeger, N., van Dusseldorp, I., De Deyn, P.P., 2014. Nutritional interventions in community-dwelling Alzheimer patients with (risk of) undernutrition: a systematic review. *Int. psychogeriatrics* 1–9. <https://doi.org/10.1017/S1041610214000817>
- Edington, J., Barnes, R., Bryan, F., Dupree, E., Frost, G., Hickson, M., Lancaster, J., Mongia, S., Smith, J., Torrance, A., West, R., Pang, F., Coles, S., 2004. A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. *Clin. Nutr.* 23, 195–204. [https://doi.org/10.1016/S0261-5614\(03\)00107-9](https://doi.org/10.1016/S0261-5614(03)00107-9)
- Elia M, R.C., 2009. Combating Malnutrition: Recommendations for Action. Report from the advisory group on malnutrition, led by The British Association for Parenteral and Enteral Nutrition (BAPEN), The British Association for Parenteral and Enteral Nutrition (BAPEN).
- Feldblum, I., German, L., Castel, H., Harman-Boehm, I., Shahar, D.R., 2011. Individualized nutritional intervention during and after hospitalization: The nutrition intervention study clinical trial. *J. Am. Geriatr. Soc.* 59, 10–17. <https://doi.org/10.1111/j.1532-5415.2010.03174.x>
- Gazzotti, C., 2003. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing* 32, 321–325. <https://doi.org/10.1093/ageing/32.3.321>
- Gray-Donald, K., Payette, H., Boutier, V., 1995. Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. *J. Nutr.* 125, 2965–71. <https://doi.org/10.1093/jn/125.12.2965>
- Guest, J.F., Panca, M., Baeyens, J.-P., de Man, F., Ljungqvist, O., Pichard, C., Wait, S., Wilson, L., 2011. Health economic impact of managing patients following a community-based diagnosis of malnutrition in the UK. *Clin. Nutr.* 30, 422–429. <https://doi.org/10.1016/j.clnu.2011.02.002>
- Ha, L., Hauge, T., Spennig, A.B., Iversen, P.O., 2010. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: A randomized, controlled trial. *Clin. Nutr.* 29, 567–573. <https://doi.org/10.1016/j.clnu.2010.01.011>
- Hickson, M., Bulpitt, C., Nunes, M., Peters, R., Cooke, J., Nicholl, C., Frost, G., 2004. Does additional feeding support provided by health care assistants improve nutritional status and outcome in acutely ill older in-patients? - A randomised control trial. *Clin. Nutr.* 23, 69–77. [https://doi.org/10.1016/S0261-5614\(03\)00090-6](https://doi.org/10.1016/S0261-5614(03)00090-6)
- Higgins JHiggins JPT, Altman DG, on behalf of the C.S.M.G. and the C.B.M.G. (editors), 2011. Chapter 8: Assessing risk of bias in included studies. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*, in: Higgins JPT, G.S. (Ed.), .

The Cochrane Collaboration.

- Houston, D.K., Tooze, J.A., Garcia, K., Visser, M., Rubin, S., Harris, T.B., Newman, A.B., Kritchevsky, S.B., 2017. Protein Intake and Mobility Limitation in Community-Dwelling Older Adults: the Health ABC Study. *J. Am. Geriatr. Soc.* 65, 1705–1711. <https://doi.org/10.1111/jgs.14856>
- Howson, F.F.A.A., Sayer, A.A., Roberts, H.C., 2017. The Impact of Trained Volunteer Mealtime Assistants on Dietary Intake and Satisfaction with Mealtime Care in Adult Hospital Inpatients: A Systematic Review. *J. Nutr. Health Aging* 21, 1038–1049. <https://doi.org/10.1007/s12603-016-0847-2>
- Hubbard, G.P., Elia, M., Holdoway, A., Stratton, R.J., 2012. A systematic review of compliance to oral nutritional supplements. *Clin. Nutr.* 31, 293–312. <https://doi.org/10.1016/j.clnu.2011.11.020>
- Jackson, J., Currie, K., Graham, C., Robb, Y., 2011. The effectiveness of interventions to reduce undernutrition and promote eating in older adults with dementia: A systematic review. *JB Libr. Syst. Rev.* 9, 1509–1550.
- Kim, C.-O., Lee, K.-R., 2013. Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. *J. Gerontol. A. Biol. Sci. Med. Sci.* 68, 309–16. <https://doi.org/10.1093/gerona/gls167>
- Kimber, K., Gibbs, M., Weekes, C.E., Baldwin, C., 2015. Supportive interventions for enhancing dietary intake in malnourished or nutritionally at-risk adults: a systematic review of nonrandomised studies. *J. Hum. Nutr. Diet.* 28, 517–545. <https://doi.org/10.1111/jhn.12329>
- Koretz, R.L., Avenell, A., Lipman, T.O., Braunschweig, C.L., Milne, A.C., 2007. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am. J. Gastroenterol.* 102, 412–29; quiz 468. <https://doi.org/10.1111/j.1572-0241.2006.01024.x>
- Lammes, E., Rydwik, E., Akner, G., 2012. Effects of nutritional intervention and physical training on energy intake, resting metabolic rate and body composition in frail elderly. A randomised, controlled pilot study. *J. Nutr. Heal. Aging* 16, 1–6.
- Lauque, S., Arnaud-Battandier, F., Gillette, S., Plaze, J.-M., Andrieu, S., Cantet, C., Vellas, B., 2004. Improvement of Weight and Fat-Free Mass with Oral Nutritional Supplementation in Patients with Alzheimer's Disease at Risk of Malnutrition: A Prospective Randomized Study. *J. Am. Geriatr. Soc.* 52, 1702–1707. <https://doi.org/10.1111/j.1532-5415.2004.52464.x>
- Lauque, S., Arnaud-Battandier, F., Mansourian, R., Guigoz, Y., Paintin, M., Nourhashemi, F., Vellas, B., 2000. Protein-energy oral supplementation in malnourished nursing-home residents. A controlled trial. *Age Ageing* 29, 51–56. <https://doi.org/10.1093/ageing/29.1.51>
- Marshall, S., Bauer, J., Capra, S., Isenring, E., 2013. Are informal carers and community care workers effective in managing malnutrition in the older adult community? A systematic review of current evidence. *J. Nutr. Health Aging* 17, 645–51. <https://doi.org/10.1007/s12603-013-0341-z>
- Milne, A.C., Potter, J., Vivanti, A., Avenell, A., 2009a. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane database Syst. Rev.* CD003288. <https://doi.org/10.1002/14651858.CD003288.pub3>
- Milne, A.C., Potter, J., Vivanti, A., Avenell, A., 2009b. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane database Syst. Rev.* CD003288. <https://doi.org/10.1002/14651858.CD003288.pub3>
- Montori, V.M., Wilczynski, N.L., Morgan, D., Haynes, R.B., 2005. Optimal search strategies for retrieving

systematic reviews from Medline: analytical survey. *BMJ* 330, 68.

<https://doi.org/10.1136/bmj.38336.804167.47>

Munk, T., Tolstrup, U., Beck, A.M., Holst, M., Rasmussen, H.H., Hovhannisyanyan, K., Thomsen, T., 2016.

Individualised dietary counselling for nutritionally at-risk older patients following discharge from acute hospital to home: a systematic review and meta-analysis. *J. Hum. Nutr. Diet.* 29, 196–208.

<https://doi.org/10.1111/jhn.12307>

O'Connor D, Green S, H.J. (editors), 2011. Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S (editors), *Cochrane Handbook of Systematic Reviews of Intervention*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Avail.

Payette, H., Boutier, V., Coulombe, C., Gray-Donald, K., 2002. Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: A prospective randomized community trial. *J. Am. Diet. Assoc.* [https://doi.org/10.1016/S0002-8223\(02\)90245-2](https://doi.org/10.1016/S0002-8223(02)90245-2)

Poscia, A., Milovanovic, S., La Milia, D.I., Duplaga, M., Grysztar, M., Landi, F., Moscato, U., Magnavita, N., Collamati, A., Ricciardi, W., 2018. Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis. *Eur. J. Public Health* 28, 275–283.

<https://doi.org/10.1093/eurpub/ckx199>

Price, R., Daly, F., Pennington, C.R., McMurdo, M.E.T., 2005. Nutritional supplementation of very old people at hospital discharge increases muscle strength: A randomised controlled trial. *Gerontology* 51, 179–185. <https://doi.org/10.1159/000083991>

Rydwik, E., Lammes, E., Frändin, K., Akner, G., 2008. Effects of a physical and nutritional intervention program for frail elderly people over age 75. A randomized controlled pilot treatment trial. *Aging Clin. Exp. Res.* 20, 159–70. <https://doi.org/10.1007/BF03324763>

Schünemann H, Brożek J, Guyatt G, Oxman A, editors., 2013. *GRADE handbook for grading quality of evidence and strength of recommendations*. Updated October 2013. The GRADE Working Group, 2013. Available at: [www.guidelinedevelopment.org/handbook](http://www.guidelinedevelopment.org/handbook). [WWW Document].

Scott, D., Blizzard, L., Fell, J., Giles, G., Jones, G., 2010. Associations Between Dietary Nutrient Intake and Muscle Mass and Strength in Community-Dwelling Older Adults: The Tasmanian Older Adult Cohort Study. *J. Am. Geriatr. Soc.* 58, 2129–2134. <https://doi.org/10.1111/j.1532-5415.2010.03147.x>

Smoliner, C., Norman, K., Scheufele, R., Hartig, W., Pirlich, M., Lochs, H., 2008. Effects of food fortification on nutritional and functional status in frail elderly nursing home residents at risk of malnutrition. *Nutrition* 24, 1139–1144. <https://doi.org/10.1016/j.nut.2008.06.024>

Sugawara, K., Takahashi, H., Kasai, C., Kiyokawa, N., Watanabe, T., Fujii, S., Kashiwagura, T., Honma, M., Satake, M., Shioya, T., 2010. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir. Med.* 104, 1883–1889. <https://doi.org/10.1016/j.rmed.2010.05.008>

Tassone, E.C., Tovey, J.A., Paciepnik, J.E., Keeton, I.M., Khoo, A.Y., Van Veenendaal, N.G., Porter, J., 2015. Should we implement mealtime assistance in the hospital setting? A systematic literature review with meta-analyses. *J. Clin. Nurs.* 24, 2710–21. <https://doi.org/10.1111/jocn.12913>

Thomas, J.M., Isenring, E., Kellett, E., 2007. Nutritional status and length of stay in patients admitted to an Acute Assessment Unit. *J. Hum. Nutr. Diet.* 20, 320–8. <https://doi.org/10.1111/j.1365-277X.2007.00765.x>

- Trabal, J., Farran-Codina, A., 2015. Effects of dietary enrichment with conventional foods on energy and protein intake in older adults: A systematic review. *Nutr. Rev.* 73, 624–633.  
<https://doi.org/10.1093/nutrit/nuv023>
- Van Wymelbeke, V., Brondel, L., Bon, F., Martin-Pfitzenmeyer, I., Manckoundia, P., 2016. An innovative brioche enriched in protein and energy improves the nutritional status of malnourished nursing home residents compared to oral nutritional supplement and usual breakfast: FARINE+ project. *Clin. Nutr. ESPEN* 15, 93–100. <https://doi.org/10.1016/j.clnesp.2016.06.012>
- Visser, M., Volkert, D., Corish, C., Geisler, C., de Groot, L.C., Cruz-Jentoft, A.J., Lohrmann, C., O'Connor, E.M., Schindler, K., de van der Schueren, M.A., 2017. Tackling the increasing problem of malnutrition in older persons: The Malnutrition in the Elderly (MaNuEL) Knowledge Hub. *Nutr. Bull.* 42, 178–186.  
<https://doi.org/10.1111/nbu.12268>
- Volkert, D., Hübsch, S., Oster, P., Schlierf, G., 1996. Nutritional support and functional status in undernourished geriatric patients during hospitalization and 6-month follow-up. *Aging - Clin. Exp. Res. Clin. Exp* 8, 386–395.

Table 1. Characteristics of included studies.

Author year	Setting, country	Population				Intervention	Comparator	Intervention period and follow-up	Outcomes	Funding
		N, (% female)	Age (years), mean $\pm$ SD	Patient's conditions	Malnutrition assessment					
Campbell 2013*	Hospital, Australia	Group 1 (traditional) 33 (54.5); Group 2 (MedPass) 32 (68.8); Group 3 (mid-meal trolley) 33 (48.5)	Group 1 (traditional) 80.6 $\pm$ 6.9; Group 2 (MedPass) 79.9 $\pm$ 2.3; Group 3 (mid-meal trolley) 75.8 $\pm$ 8.1	Acute ill and rehabilitation	SGA (B or C)	All patients received education on choosing a high-protein/high-energy diet from the food service provided and tailored nutritional advice (usual care). Group 2 (MedPass) = 60 mL of a 2 Kcal/mL supplement ordered on the medication chart and dispensed by nurses as part of the medication round four times a day (475 kcal and 20 g protein/day). Group 3 (mid-meal trolley) = self-selection from a mid-meal trolley of high-protein and/or high-energy snacks or commercial drinks (70–120 kcal and 0-6 g protein, per selection; up 4/day)	All patients received education on choosing a high-protein/high-energy diet from the food service provided and tailored nutritional advice (usual care).  Group 1 (traditional) = 1 or 1.5 Kcal/mL supplement in-between meals (500–750 kcal and 18–26 g protein/day).	2-week intervention	<b>Nutritional status:</b> body weight (% change, kg) <b>Quality of life:</b> EQ-5D (% change 0-1, overall 0-100) <b>Morbidity</b> pressure ulcers: Waterlow assessment	Princess Alexandra Hospital Foundation Grant

Carver 1995	Long-term hospital, UK	Intervention group: 23 (78,3); Control group: 23 (78,3)	Intervention group: men (69±9), women (80±10); Control group: men (68±7), women (79±10)	Residents in a psychiatric hospital (mean hospital stay 6.6 years) with some degree of dementia	BMI = 15.1- 19.9	ONS (in addition to normal meals): two 200 mL cans which provide 600 kcal of energy per day from protein 20.0 g, carbohydrate 79.6 g and fat 26 g in addition to a range of vitamins and minerals: Vitamin A 208 µg, Vitamin D 2.0 µg, Vitamin E 12.8 mg, Vitamin B1 0.28 mg, Vitamin B2 0.4mg, Niacin 4.0 mg, Vitamin B6 0.4 mg, Vitamin C 20.0 mg, Vitamin B12 0.8 mg, Folic acid 100 mg, Pantothenic acid 2.0 mg, Biotin 60 µg, Inositol 92 mg, Choline 180 mg.	Placebo oral supplementation: a 200 ml oral vitamin preparation twice daily providing the same vitamins as the intervention group but no macronutrients: 6.0 kcal, carbohydrate 1.5 g, Vitamin A 210 µg, Vitamin D 1.5 µg, Vitamin E 9.6 mg, Vitamin B1 0.22 mg, Vitamin B2 0.3 mg, Niacin 3.0 mg, Vitamin B6 0.3 mg, Vitamin C 15.0 mg, Vitamin B12 0.6 mg, Folic acid 75 mg, Pantothenic acid 1.5 mg, Biotin 45 µg, Inositol 79 mg, Choline 0 mg.	12-week intervention	<b>Nutritional status:</b> change in body weight (kg), and BMI (kg/m <sup>2</sup> )	Mental Health Unit of Lothian Health Board and Cow & Gate Ltd.
de Luis 2008	Community- dwelling, Spain	Group 1: 16 (56.25); Group 2: 14 (57.1)	Group 1: 74.6 ± 7.1; Group 2: 77.1 ± 8.7	Diabetes mellitus type 2	Involuntary weight loss of >5% in the last 3 months	Diabetes-specific oral supplementation (group 1): 49.95% Kcal from fats. Two 250-ml cans per day which provide 490 kcal of energy, 21 g protein, 27.2 g fat (37% MUFA), 40.6 g CHO, and 7.2 g fibre.	Diabetes-specific oral supplementation (group 2): 34% Kcal from fats. Two 230-ml cans per day which provide 410 kcal, 21.4 g protein, 15.6 g fat (24% MUFA), 52 g CHO, and 2 g fibre.	10-week intervention	<b>Nutritional status:</b> body weight (kg); BMI (kg/m <sup>2</sup> ); FFM (BIA, kg); fat mass (kg)	Not stated

Edington 2004	Community-dwelling, UK	Intervention group: 51 (56.86); Control group: 49 (53.06)	Intervention group: 76.8±5.3; Control group: 79.3±8.0	Patients discharged from hospital to community-dwelling	BMI <20; or BMI ≥20- ≤25 and 6-month ≥10% or 3-month ≥5% weight loss prior the study (malnourished)	ONS: Supplement intakes between 600 and 1000 kcal/day. The energy and protein requirements were estimated using the Schofield equation. First day of ONS was at home. Home visits by a dietitian at weeks 4, 8, 12 and 24. These subjects were given a choice of one or more nutritional supplements (Ensure Plus® tetrapak, Enlive® tetrapak, Formance® Pudding or Ensure Bar®, Abbott Laboratories). Although these supplements have different nutrient compositions, the objective was to increase subjects' energy and macronutrient intake overall and to help to improve compliance by minimising taste fatigue.	Standard care: not supplementation post discharge. Home visits by a dietitian at weeks 4, 8, 12 and 24.	8-week intervention + 16-week follow-up	<b>Nutritional status:</b> change in body weight (kg); change in BMI (kg/m <sup>2</sup> ) <b>Functional status:</b> changes in handgrip strength (kg) <b>Quality of life</b> (EQ5D) <b>Mortality</b>	Abbott Laboratories
Feldblum 2011	Hospital and community-dwelling, Israel	Group 1: 78 (56,4); Group 2: 73 (53,4); Group 3: 108 (58,3)	Group 1: 75.3 ± 5.8; Group 2: 75.2 ± 5.6; Group 3: 75.1 ± 5.8	Acute ill hospitalised patients and discharged patients	MNA-sf (<10 points) and >10% weight loss in the previous six months.	Group 1: In-hospital and community treatment. One visit by a dietician in the hospital and three home visits. Participants at risk (MNA 17–23): Increase calories to 35 kcal/kg per day, increase proteins to 1–1.5 g/kg per day during recovery period, behavioural strategies for specific eating problems, ONS available in liquid or pudding (237 ml cans	Group 2: only in-hospital treatment (one visit by a dietitian and ONS). Group 3: standard care. Groups 2 and 3 were combined into a single control group for the analysis.	Hospitalization period + 6-month follow-up	<b>Nutritional status:</b> changes in body weight (kg) and MNA <b>Functional status:</b> ADL (changes in Barthel Index) <b>Mortality</b>	Israel National Institute for Health Policy and Health Services Research

						<p>containing 360 kcal, 13 g protein, 47.3 g carbohydrates, 12.6 g of fat, 15% DRIs for vitamins and minerals), and modify medication if possible. The fat content is 29% of the total calories: 2.7% as saturated fatty acids, 9.8% polyunsaturated, and 16.1% as monounsaturated. Fat sources in the formula are 50% canola oil, 25% corn oil, and 25% high oleic safflower oil. In cases in which the specific intake of micronutrients was found to be lower than 75% of the DRI, appropriate vitamin and mineral supplements were given as indicated.</p> <p>Undernutrition (MNA&lt;17): Increase caloric and micronutrients intake using the appropriate ONS, implement behavioural strategies for specific eating problems.</p>				
Gazzotti 2003	Hospital, community-dwelling and nursing home, Belgium	Intervention group: 39 (71.8); Control group: 41 (80.5)	Intervention group: 81.5±7.6; Control group: 78.8±6.1	Patients discharged from hospital to community-dwelling or nursing home	MNA 17-23.5	ONS: two 200 mL cans twice a day which provided 500 kcal and 21 mg of protein/day (Clinutren soup (1 kcal/ ml) and one Clinutren 1.5 (1.5 kcal/ml) (Nestlé Clinical Nutrition) in addition to the regular meals. One follow-up visit	Standard care: not supplementation post discharge, One follow-up visit at the end of the intervention.	8.6-week intervention	<b>Nutritional status:</b> change in body weight (kg, %); MNA	Not stated. One author works in Nestlé Clinical Nutrition

						at the end of the intervention.				
Gray-Donald 1995	Community dwelling, Canada	Intervention group: 24 (74); Control group: 24 (67)	Intervention group: 76±7; Control group: 79±8	Frail (no objective measured)	1) Involuntary weight loss of >5% in the last month, >7.5% in the last 3 months or >10% in the last 6 months and BMI<27 kg/m <sup>2</sup> or 2) BMI<24 kg/m <sup>2</sup>	Oral supplementation: two 235 ml cans (Ensure <sup>®</sup> , Enrich <sup>®</sup> with fiber, Ensure Plus <sup>®</sup> , Abbot Laboratories) per day which provide between 1045, 1085/1480 kJ, 8.74, 9.4, 13.0 g of proteins, 8.7, 8.8, 12.5 g of fat, 34.08, 38.3, 47.2 g of carbohydrates, and fiber 0, 3.3, 0 g per can respectively. Home visits and a dietary interview weekly.	Weekly home visits to give suggestions and encouragement to improve the quality of diet.	12-week intervention	<b>Nutritional status:</b> change in body weight (kg) <b>Functional status:</b> handgrip strength (kg) <b>Quality of life</b> (General well-being score and self-perceived health status)	National Health Research and Development Program (NHRDP) Health Canada (grant n° 6605-3833-62)
Ha 2010	Hospital, Norway	Intervention group: 58 (57); Control group: 66 (47)	Intervention group 78.5±7.4; Control group 79.9±6.8	Acute stroke	MUST (undernourished and at nutritional risk)	Individualized nutritional treatment plan. Oral energy and protein rich feedings or enteral tube feeding were used according to individual intake and needs. Oral nutritional advice or written nutritional advice if the patient was tube fed were given before discharge. Participants were not more contacted before follow-up.	Usual ward care: use of oral sip feedings or tube feeding at the discretion of the attending physician.	12-week intervention + 12.6-week follow-up	<b>Nutritional status:</b> ≥5% body weight losses (% patients) <b>Functional status: changes in</b> handgrip strength (kg) <b>Quality of life</b> (EQ-5D)	South-Eastern Norway Regional Health Authority and Østfold Hospital Trust.

Hickson 2004	Hospital, UK	Intervention subgroup: (a) 31 (-) and (b) 39 (-); Control subgroup: (a) 31 (-) and (b) 28 (-). Female sex of the total study sample: Intervention group 68.5%; Control group 57.7%	Age of the study sample: Intervention group 82.0 [76–86]; Control group 82.0 [77–87]	Acute ill	BMI <22kg/m2 Two subgroups of patients: (a) BMI (kg/m2) 21,8-18.8; (b) BMI (kg/m2) 18.8-12,6	Feeding support by a trained health care assistance: identifying reduced food intake and other risk factors for malnutrition and planning care to resolve these problems, encouraging and enabling patients in feeding and supporting the ward staff in this role, and offering snacks and drinks throughout the day.	Usual ward care	2.3-week intervention (16 days)	<b>Nutritional status:</b> change in BMI (kg/m2, median)	NHS Executive
Kim 2013	Community-dwelling, Republic of Korea	Intervention group: 43 (79.1); Control group: 44 (79.6)	Intervention group: 78.9±5.5; Control group: 78.4±6.0	Frail (UGS <0,6m/s) and low socioeconomic status	MNA<24 (risk of malnutrition or malnourished)	ONS: two 200 mL cans per day which provide 400 kcal of energy, 25 g of protein, 9.4 g of essential amino acids (60.2% leucine), 56 g of carbohydrate, 9 g of lipid, 400 mL of water, and micronutrients (vitamin A, 0.3 mg; thiamin, 0.42 mg; riboflavin B2, 0.6 mg; pyridoxine, B6 0.6 mg; vitamin B12, 0.96 µg; vitamin C, 40 mg; vitamin D3, 2 µg; vitamin E, 4 mg; vitamin K1, 30 µg; folate, 0.16 mg; niacin, 6.4 mg; biotin 12 µg; pantothenic acid, 2 mg; choline, 146 mg; L-carnitine, 40 mg; taurine, 40 mg; calcium, 280 mg; phosphorus, 280 mg; magnesium, 88 mg;	Participants were visited by the same research dietitian and gave a small gift (not specified) every month. They did not receive any treatment or counselling during the study period.	12-week intervention	<b>Nutritional status:</b> change in body weight (kg, %) <b>Functional status:</b> changes in handgrip strength (kg, %), SPPB (0-12 points, %), PF score (0-30, %), UGS (m/s, %), and TUG (s, %)	Health Promotion Fund, Ministry of Health & Welfare, Republic of Korea (G11-16)

						zinc, 4 mg; iron, 4 mg; iodine, 60 µg; and copper, 0.32 mg). Dietitian home visits every two weeks.				
Lammes 2012, Rydwick 2008	Community-dwelling, Sweden	Group N: 25 (-) group T: 23 (-); group T+N: 25 (-); group C: 23 (-). Total study sample: 96 (60.4%)	Group N: 83.1 ± 4.5; group T: 83.5 ± 3.7; group T+N: 83.1 ± 4; group C: 82.9 ± 4	Frail (≤ 3 Mattiasson-Nilo physical activity)	Unintentional weight loss ≥ 5% during last year and/or BMI ≤ 20 kg/m <sup>2</sup>	1. Nutrition group (N): Specific individualized diet counselling based on baseline food record data. The dietician/nutritionist tested different options that would cover the estimated needs of each individual, and then gave advice on food intake at an individual session lasting about one hour, and five group session education covering such topics as the nutritional needs of elderly people, meal frequency and cooking methods. At each session, an example of a nutritionally well-balanced between-meal snack was served, plus general physical training advice. 2. Training group (T): Specific physical training one hour twice a week, with three sections: warm-up, including aerobic training; individually prescribed muscle-strength training (60-80% intensity); and balance exercises (Qigong exercises), including cool-down, performed in groups of 5-8	4. Control (C): General physical training advice and general diet advice.  The general physical training advice for the control group was to walk three times per week for at least 20 minutes, to use staircases instead of an elevator from time to time, and to follow WHO recommendation of a total amount of 30 minutes of physical activity/day.  The general diet advice was to eat three main courses and 2-3 between-meal snacks including meat, fish or egg, fruit and vegetables, dairy products and fibre, in combination with fluid every day.	12-week intervention + 6-month follow-up	<b>Nutritional status:</b> body weight (kg); BMI (kg/m <sup>2</sup> ); FFM (DEXA, kg) <b>Functional status:</b> TUG (s); UGS (m/s); 10-m walking speed (s) Knee and hip extension (kg); 30-s chair-stand test (n°); activities of daily living (FIM, IAM).	Åldreforskning NordVäst, (research centre for the elderly)

						<p>subjects, plus general diet advice.</p> <p>3. Training and nutrition group (T+N): Specific physical training, plus specific individualized diet counselling and group session education.</p>				
Lauque 2000	Nursing home, France	<p>Group A: 19 (78.9);</p> <p>Group B: 22 (90.9);</p> <p>Group C: 13 (78.6);</p> <p>Group D: 24 (91.3)</p>	<p>Group A: 83.7 (7.5);</p> <p>Group B: 84.7 (5.5);</p> <p>Group C: 84.6 (5.5);</p> <p>Group D: 88.4 (3.8)</p>	No specified	MNA $\leq$ 23.5	<p>Group C: MNA 17-23.5, ONS; Group D: MNA &lt;17, oral supplements. The nutritional supplements were 300-500 kcal and were given in addition to regular meals. Four oral supplementation products (Clinutren<sup>®</sup>, Nestle Clinical Nutrition) were offered, each in three different flavours: Clinutren<sup>®</sup> Soup (200 kcal and 10 g of protein per 200 ml), Clinutren<sup>®</sup> Fruit (120 kcal and 7.5 g of protein per 200 ml), Clinutren<sup>®</sup> Dessert (150 kcal and 12 g of protein per 150 ml) and Clinutren HP<sup>®</sup> (Hyper-Protein; 200 kcal and 15 g of protein per 200 ml). These products were either sweet or savoury, liquid or creamy, and were served hot, warm or cold. Patients were strongly encouraged to consume the entire</p>	<p>Group A: MNA <math>\geq</math>24, no oral supplementation;</p> <p>Group B: MNA 17-23.5, no oral supplements. Dietitian visits weekly or bi-weekly.</p>	8.6-week intervention	<p><b>Nutritional status:</b> changes in body weight (kg), BMI (kg/m<sup>2</sup>), MNA; <b>Functional status:</b> handgrip strength (kgW)</p>	Nestle <sup>™</sup> Clinical Nutrition

						amount offered. Dietitian visits weekly or bi-weekly.				
Lauque 2004	Hospital and community-dwelling, France	Intervention group: 46; Control group: 45. No reported female ratio	Intervention group: 79.52 (5.97); Control group: 78.11 (4.80)	Alzheimer's disease	MNA $\leq$ 23.5	ONS: 300-500 kcal/day enriched with proteins, vitamins and minerals in addition to the patients' spontaneous food intake. The ONS used was Clinutren <sup>®</sup> (Nestle' Clinical Nutrition). Three products were proposed, each in various flavors: Clinutren <sup>®</sup> Soup (200 kcal, 10 g protein per 200 mL), Clinutren <sup>®</sup> Dessert (150 kcal, 12 g protein per 150 mL), and Clinutren <sup>®</sup> 1.5 (300 kcal, 11 g protein per 200 mL). These products were savory or sweet and liquid or creamy and were served hot, warm, or cold. They A dietitian regularly visited the patients at home and controlled product distribution and intake.	Usual care (not specified).	12.8-week intervention + 12.8-week follow-up	<b>Nutritional status:</b> changes in body weight (kg); BMI (kg/m <sup>2</sup> ); FFM (DEXA, kg); MNA. <b>Functional status:</b> ADL (Barthel Index); <b>Morbidity:</b> fractures, pressure ulcers, hospitalization.	Nestle' Clinical Nutrition

Payette 2002	Community-dwelling, Canada	Intervention group: 41 (71); Control group: 42 (71)	Intervention group: 81.6±7.5; Control group: 78.6±6.1	Frail (no assessed by objective measures) ; older people with functional limitations in carrying out basic or instrumental ADL.	1) Involuntary weight loss of >5% in the last month, >7.5% in the last 3 months or >10% in the last 6 months and BMI<27 kg/m <sup>2</sup> ; or 2) BMI<24. (Risk of malnutrition or malnourished)	ONS: two 235 mL cans per day providing 440-700 kcal. The ONS offered was Ensure <sup>®</sup> , and Ensure Plus <sup>®</sup> (Abbot Laboratories) in different flavours to minimise flavour fatigue. Every month a home visit and phone call every 2 weeks were taken to give nutrition counselling and encourage to improve food and supplement intake.	Control group: They were visited at home each month and given a small gift (not specified)	16-week intervention	<b>Nutritional status:</b> change in body weight (kg) <b>Functional status:</b> handgrip strength (kPA), quadriceps strength (Knee extension, N), TUG (s) <b>Quality of life</b> (SF-36)	Abbott Laboratories Limited
Price 2005	Community-dwelling, UK	Intervention group: 66 (63.6); Control group: 70 (84.3)	Intervention group: 83.7±5.2; Control group: 85.4±5.4	Hospital discharged patients	BMI ≤ 24 and triceps skinfold or mid-arm muscle circumference < 10th percentile and/or a weight loss ≥ 5% during hospital stay	ONS: two 200 mL cans per day (Fortisip <sup>®</sup> or Fortifresh <sup>®</sup> , Nutricia, UK) providing 600 kcal and 24 g protein from the time of hospital discharge. The energy density was 1.5 kcal/ml (6.3 kJ/ml). A choice of flavours was offered.	Usual care and followed up at fortnightly intervals over 12 weeks.	8-week intervention + 4-week follow-up	<b>Nutritional status:</b> change in body weight (%), (kg) <b>Functional status:</b> change in handgrip strength (%), (kg)	Health Foundation grant 2006/594

Smoliner 2008	Nursing home, Germany	Intervention group: 22 (77.3); Control group: 30 (70)	Intervention group: 82.2 ± 9.5; Control group: 84.0 ± 9.5	Frail (no objective measured)	MNA ≤23.5	Food-fortification group: standard diet  + protein and energy-enriched soups and sauces: 5 g of protein powder (from hydrolysed milk) per 100 mL, and 5 g of rapeseed oil per 100 mL of sauce and 10 mL of heavy cream per 100 mL of soup.  + two protein and energy-enriched snacks between meals: 150 mL milk cups with 300 kcal, 20 g of protein (15 g from added protein powder), 20 g of fat, and 20 g of carbohydrates.	Standard diet: 2000 kcal of energy, 80 g of protein, 60 g of fat, and 260 g carbohydrates.	12-week intervention	<b>Nutritional status:</b> body weight (Kg); BMI (kg/m <sup>2</sup> ); MNA; FFM (BIA, kg) <b>Functional status:</b> handgrip strength (kg); ADL (Barthel Index); <b>Quality of life</b> (SF-36 PF)	Schubert Holding AG & Co. KG.
Sugawara 2010	Community-dwelling, Japan	Intervention group: 17; Control group: 15. No reported female ratio	Intervention group: 77.3±7.0; Control group: 78.2±6.7	COPD	BMI≤19	ONS combined with low-intensity home exercise. ONS: two 200 ml (400 kcal per day) packages containing 60% energy from carbohydrates, 25% from fat, and 15% from protein. This drink contains omega-3 PUFAs 0.6 g and vitamins A 248 mg in total ingredients. Home exercise training: upper and lower limb exercises, and respiratory muscle exercises. Exercise was performed daily at home and supervised every 2 weeks at hospital. Patients also underwent a monthly 45-min education program as the control group.	A monthly 45-min education program including lectures on respiratory disease, control of dyspnoea, medication and equipment use, nutrition, stress management, and relaxation techniques once every 4 weeks.	12-week intervention	<b>Nutritional status:</b> changes in body weight (%), kg, FM index FFM Index (%), kg/m <sup>2</sup> ) <b>Functional status:</b> changes in 6-min walk (%), m) and quadriceps strength (%), kg) <b>Quality of life</b> change in CRQ score (%)	Not stated
Volkert 1996	Hospital and community-dwelling, Germany	Intervention group: SG + (11) and SG- (9); Control group: 26.	Intervention group: SG+ 84.5±6.7 and SG- 88.7±6.6; Control	Acute ill	Clinical diagnosis: subcutaneous fatty tissue markedly reduced or	Standard hospital diet + two 200 ml of ONS portions daily providing, 1 portion, 250 kcal, 15 gr protein/portion during hospitalisation: 200 mL soup in the mid-morning (supplement A composition per 100 ml: Energy 122	Usual care (standard hospital diet)	Hospital intervention (mean 28 ± 13 days) + 6-month intervention	<b>Nutritional status:</b> body weight (kg) <b>Functional status:</b> ADL (Barthel Index,	Bundesministerium für Gesundheit. Bonn and from

		100 % women	group: 84.0±5.6		<p>prominent rib and shoulder bones observed or slack flabby skinfolds at backside and abdomen; BMI was used to confirm if available.</p> <p>kcal; Protein 7 g; Vitamin A 0.1 mg; Vitamin E 1.5 mg; Vitamin D 0.6 µg; Vitamin B 1 0.2 mg; Vitamin B2 0.2 mg; Vitamin B6 0.2 mg; Vitamin B12 0 µg; Vitamin C 10 mg; Folic acid 45 µg; Potassium 334 mg; Calcium 185 mg; Magnesium 60 mg; Zinc 0.7 mg; Iron 2.6 mg) and 200 mL sweet drink in the afternoon (supplement B composition per 100 ml: Energy 128 kcal; Protein 8 g; Vitamin A 0.23 mg; Vitamin E 3 mg; Vitamin D 1.88 µg; Vitamin B 1 0.3 mg; Vitamin B2 0.38 mg; Vitamin B6 0.38 mg; Vitamin B12 1.13 µg; Vitamin C 15 mg; Folic acid 50 µg; Potassium 250 mg; Calcium 150 mg; Magnesium 60 mg; Zinc 3 mg; Iron 3.13 mg; or supplement C composition per 100 ml: Energy 120 kcal; Protein 8 g; Vitamin A 0 mg; Vitamin E 1.5 mg; Vitamin D 0 µg; Vitamin B 1 0.2 mg; Vitamin B2 0.3 mg; Vitamin B6 0.3 mg; Vitamin B12 0.6 µg; Vitamin C 9 mg; Folic acid 50 µg; Potassium 350 mg; Calcium 250 mg; Magnesium 68 mg; Zinc 0.8 mg; Iron 2.5 mg). Different brands with similar composition but different flavours were used in order to increase variety and patient acceptance.</p> <p>One daily portion of supplement after discharge (at home) for 6 months.</p> <p>This group was divided into 2 subgroups: SG + (good acceptance: one or nearly one portion per day) and SG - (poor acceptance: one portion every 2 days or less).</p>		at home (187 ± 9 days)	>65 points % of independent patients)	Fa. B. Braun, Melsungen . Germany
--	--	----------------	--------------------	--	--	--	------------------------------	---	--

\*Non-randomized Controlled Trial.

ADL: Activities of daily living; BIA: Bioelectrical impedance analysis; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRQ: Chronic respiratory disease questionnaire; DRIs: Dietary reference intakes; DEXA: Dual energy x-ray absorptiometry; EQ5D; EuroQol questionnaire; FM: Fat mass; FFM: Fat-free mass; FIM: Functional independence measure; IAM: Instrumental activity measures; MNA: Mini nutritional assessment; MUFA: Monounsaturated fatty acids; MUST: Malnutrition universal screening tool; ONS: Oral nutritional supplementation; PF: Physical function; SGA: Subjective global assessment; SF-36: 36-Item short form health survey; SPPB: Short physical performance battery; TUG: Time up and go test; UGS: Usual gait speed.

Table 2: Risk of Bias of included studies.

Author year	Type of study	Sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding Participants and personnel (Performance bias)	Blinding outcome assessor (Detection bias)	Incomplete outcome data (Attrition bias)	Selective outcome reporting (Reporting bias)	ITT analysis	Similar baseline characteristics
Campbell 2013	CCT	X	X	X	X	X	✓	NO	NO
Carver 1995	RCT	?	?	?	?	✓	✓	NO	YES
De Luis 2008	RCT	?	?	X	X	X	✓	?	YES
Edington J 2004	RCT	?	?	X	?	X	✓	YES	YES
Feldblum 2011	RCT	?	?	?	✓	X	✓	NO	YES
Gazotti 2003	RCT	?	?	X	X	✓	✓	YES	YES
Gray-Donald 1995	RCT	X	X	X	X	✓	✓	YES	YES
Ha 2010	RCT	✓	✓	X	?	X	✓	NO	YES
Hickson 2004	RCT	✓	✓	?	?	X	✓	NO	YES
Kim 2013	RCT	✓	✓	X	✓	✓	✓	YES	YES

Lammes 2012, Rydwick 2008	RCT	X	X	X	X	X	X	NO	YES
Lauque 2000	RCT	X	X	X	X	X	✓	NO	NO
Lauque 2004	RCT	?	✓	X	?	X	✓	YES	YES
Payette 2002	RCT	?	?	X	✓	✓	✓	YES	YES
Price R 2005	RCT	✓	✓	X	X	X	✓	YES	YES
Smoliner 2008	RCT	X	X	X	?	?	✓	NO	YES
Sugawara 2010	RCT	?	?	X	?	✓	✓	YES	YES
Volkert 1996	RCT	?	?	X	X	X	✓	NO	YES

✓ Low risk, ? Unclear risk, X High risk; RCT: Randomized controlled trial, CCT: controlled clinical trial.

**Table 3a: GRADE assessment and summary of findings table.****Question:** Oral nutritional supplementation (ONS) compared to usual care (UC) for (risk of) malnutrition in older people.**Setting:** Any setting

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplementation (ONS)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
Changes in Body Weight (kg)												
6 1,2,3,4,5,6	randomised trials	serious <sup>a</sup>	not serious <sup>b</sup>	not serious	serious <sup>c</sup>	none	208	212	-	MD 0.59 higher (0.08 lower to 1.26 higher)	⊕⊕○○ LOW	CRITICAL
Changes in Body Weight (% , kg)												
2 <sup>3,5</sup>	randomised trials	serious <sup>d</sup>	not serious <sup>e</sup>	not serious	very serious <sup>f</sup>	none	75	78	-	MD 0.96 higher (1.69 lower to 3.6 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in BMI (kg/m <sup>2</sup> )												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplementation (ONS)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
2 <sup>2,6</sup>	randomised trials	very serious <sup>g</sup>	not serious <sup>h</sup>	not serious	very serious <sup>f</sup>	none	69	69	-	MD 0.31 higher (0.17 lower to 0.79 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in MNA score												
1 <sup>2</sup>	randomised trials	serious <sup>i</sup>	not serious	not serious	very serious <sup>f</sup>	none	37	43	-	MD 0.84 higher (1.06 lower to 2.74 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in FFM (kg)												
1 <sup>2</sup>	randomised trials	serious <sup>i</sup>	not serious	not serious	very serious <sup>f</sup>	none	37	43	-	MD 0.46 higher (0.4 lower to 1.32 higher)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplementation (ONS)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
Changes in TUG test (% , s)												
1 <sup>3</sup>	randomised trials	serious <sub>j</sub>	not serious	not serious	very serious <sub>k</sub>	none	Only one RCT including 84 participants reported TUG as the difference in % mean change (interquartile range). TUG decreased by 7.2% (-24.7, 9.9) seconds in the intervention group and increased by 3.4% (-14.9, 28.9) seconds in the control group (p=0.038).		⊕○○○ VERY LOW		CRITICAL	
Changes in handgrip strength (% , kg)												
2 <sup>3,7</sup>	randomised trials	serious <sub>l</sub>	not serious <sup>m</sup>	not serious	very serious <sub>m,n</sub>	none	There were no differences in hand grip strength between groups. In the study by Kim et al. participants from the intervention group increased the hand grip strength by 2.7% (-13.2, 13.9) kg, whereas it decreased in the control group by -5.1% (-12.5, 9.8) kg (p=0.561). In the study by Price et al. a 13.9% of increment occurred in the intervention group, compared to 7.2% in the control group (p = 0.055).		⊕○○○ VERY LOW		CRITICAL	
Changes in ADL (Katz Index)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplementation (ONS)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
1 <sup>2</sup>	randomised trials	serious <sub>i</sub>	not serious	not serious	very serious <sub>f</sub>	none	37	43	-	MD 0.1 higher (0.44 lower to 0.64 higher)	⊕○○○ VERY LOW	CRITICAL
Mortality (number of deaths)												
1 <sup>6</sup>	randomised trials	serious <sub>o</sub>	not serious	not serious	very serious <sub>k</sub>	none	Only one RCT including 100 patients assessed mortality: 17 participants died in the intervention group whereas 15 died in the control group. There were no differences in mortality between groups.			⊕○○○ VERY LOW	CRITICAL	

**ADL:** activities of daily living; **BW:** Body weight; **BMI:** Body Mass Index; **CI:** Confidence interval; **MD:** Mean difference; **MNA:** Mini Nutritional Assessment; **TUG:** time up and go test.

### Explanations

a. One out of six studies is at low risk of selection bias, all studies are at high risk of performance bias, 2/6 are at low risk of detection bias, 5/6 studies are at low risk of selective reporting outcome bias and attrition bias.

b. Statistical heterogeneity is high:  $I^2=77%$  ( $p=0.0002$ ) when the 7 RCTs were pooled. After a sensitivity analysis, we excluded Carver 1995 due to the different population (residents in a psychiatric hospital) from the meta-analysis and the heterogeneity decreased ( $I^2=43%$ ,  $p=0.12$ ).

- c. Although the sample size is greater than 400, the increment of 0.59 kg in BW was not significant. The 95% CI is wide (-0.08 to 1.26 kg).
- d. The two RCTs suffered from performance bias; one RCT suffered from detection bias and the selection bias was unclear.
- e. Heterogeneity was not significant:  $I^2= 53%$ ,  $p=0.14$ .
- f. The CI comprises the null effect. Small sample size.
- g. The two RCTs suffered from several risk of bias (see Table 3).
- h. There is no heterogeneity ( $p=0.77$ ,  $I^2= 0%$ )
- i. Performance, detection, attrition bias.
- j. Performance risk of bias.
- k. Only one RCT with small sample size.
- l. Both RCTs suffered from performance bias. One RCT suffered also from detection and attrition bias.
- m. The studies were not pooled due the lack of reported numeric data.
- n. Two RCTs with small sample size.
- o. Selection and detection risk of bias were unclear due to the lack of information. Performance and attrition risk of bias were high and publication risk of bias was low.

## References

1. Payette, H., Boutier, V., Coulombe, C., Gray-Donald, K., 2002. Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: A prospective randomized community trial. *J. Am. Diet. Assoc.* [https://doi.org/10.1016/S0002-8223\(02\)90245-2](https://doi.org/10.1016/S0002-8223(02)90245-2)
2. Lauque, S., Arnaud-Battandier, F., Gillette, S., Plaze, J.-M., Andrieu, S., Cantet, C., Vellas, B., 2004. Improvement of Weight and Fat-Free Mass with Oral Nutritional Supplementation in Patients with Alzheimer's Disease at Risk of Malnutrition: A Prospective Randomized Study. *J. Am. Geriatr. Soc.* 52, 1702–1707. <https://doi.org/10.1111/j.1532-5415.2004.52464.x>.
3. Kim, C.-O., Lee, K.-R., 2013. Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. *J. Gerontol. A. Biol. Sci. Med. Sci.* 68, 309–16. <https://doi.org/10.1093/gerona/gls167>
4. Gray-Donald, K., Payette, H., Boutier, V., 1995. Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. *J. Nutr.* 125, 2965–71. <https://doi.org/10.1093/jn/125.12.2965>

5. Gazzotti, C., 2003. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing* 32, 321–325. <https://doi.org/10.1093/ageing/32.3.321>
6. Edington, J., Barnes, R., Bryan, F., Dupree, E., Frost, G., Hickson, M., Lancaster, J., Mongia, S., Smith, J., Torrance, A., West, R., Pang, F., Coles, S., 2004. A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. *Clin. Nutr.* 23, 195–204. [https://doi.org/10.1016/S0261-5614\(03\)00107-9](https://doi.org/10.1016/S0261-5614(03)00107-9)
7. Price, R., Daly, F., Pennington, C.R., McMurdo, M.E.T., 2005. Nutritional supplementation of very old people at hospital discharge increases muscle strength: A randomised controlled trial. *Gerontology* 51, 179–185. <https://doi.org/10.1159/000083991>

**Table 3b. GRADE assessment and summary of findings table.****Question:** Individualised dietary counselling plus oral nutritional supplementation compared to usual care for (risk of) malnutrition in older people**Setting:** Hospital and community-dwelling

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutritional counselling (NC)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
Changes in Body Weight (kg)												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	66	102	-	MD 0.35 higher (0.51 lower to 1.21 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in BMI (kg/m <sup>2</sup> )												
1 <sup>2</sup>	randomised trials	serious <sup>c</sup>	not serious	not serious	very serious <sup>b</sup>	none	The RCT included 67 participants. The change in BMI were even higher in the control group than in the intervention group: 0.1 (-1.8, 1.7) vs -0.3 (-1.4, 2.3), p=0.04.			⊕○○○ VERY LOW	CRITICAL	
Changes in MNA score												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutritional counselling (NC)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	66	102	-	MD 1.2 higher (0.34 higher to 2.06 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in hand grip strength (kg)												
1 <sup>3</sup>	randomised trials	serious <sup>c</sup>	not serious	not serious	very serious <sup>b</sup>	none	56	65	-	MD 2.6 higher (1.6 higher to 4.4 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in QoL (EQ-5D score)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutritional counselling (NC)	Usual care (UC)	Relative (95% CI)	Absolute (95% CI)		
1 <sup>3</sup>	randomised trials	serious <sup>c</sup>	not serious	not serious	very serious <sup>b</sup>	none	The RCT included 124 patients hospitalized due to a stroke. There were no differences of changes in EQ-5D scores between the study groups. Only the change in EQ VAS score (1-100) was significantly different between the study groups with a higher increase in EQ VAS score in the intervention group: median 10 (-80 to 60) compared with the control group: median 0 (range -35 to 70), p=0.0009.		⊕○○○ VERY LOW	CRITICAL		
Mortality												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	The RCT included 168 participants. Mortality was significantly lower in the intervention group than in control group (3.8% vs 11.6%, p=0,046).		⊕○○○ VERY LOW	CRITICAL		

**BMI:** Body Mass Index; **CI:** Confidence interval; **MD:** Mean difference; **MNA:** Mini Nutritional Assessment; **QoL:** quality of life.

#### Explanations

- a. The RCT suffered from high risk of attrition bias. Risk of selection bias, risk of performance bias were unclear and risk of detection bias and publication bias were low.
- b. Single study. Small sample size.
- c. The RCT suffered from high risk of performance and attrition bias. Risk of selection bias and publication bias were low; and risk of detection bias was unclear.

**References**

1. Feldblum, I., German, L., Castel, H., Harman-Boehm, I., Shahar, D.R., 2011. Individualized nutritional intervention during and after hospitalization: The nutrition intervention study clinical trial. *J. Am. Geriatr. Soc.* 59, 10–17. <https://doi.org/10.1111/j.1532-5415.2010.03174.x>
2. Hickson, M., Bulpitt, C., Nunes, M., Peters, R., Cooke, J., Nicholl, C., Frost, G., 2004. Does additional feeding support provided by health care assistants improve nutritional status and outcome in acutely ill older in-patients? - A randomised control trial. *Clin. Nutr.* 23, 69–77. [https://doi.org/10.1016/S0261-5614\(03\)00090-6](https://doi.org/10.1016/S0261-5614(03)00090-6)
3. Ha, L., Hauge, T., Spenning, A.B., Iversen, P.O., 2010. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: A randomized, controlled trial. *Clin. Nutr.* 29, 567–573. <https://doi.org/10.1016/j.clnu.2010.01.011>

**Table 3c: GRADE assessment and summary of findings table.****Question:** Oral nutritional supplementation (ONS) plus low-intensity exercise compared to educational program for malnutrition in COPD patients**Setting:** Community-dwelling

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ONS plus low-intensity exercise	educational program	Relative (95% CI)	Absolute (95% CI)		
Changes in Body Weight (% , kg)												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	15	-	MD 4.2 higher (1.95 higher to 6.45 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in FFMI (% , kg/m <sup>2</sup> )												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	15	-	MD 2.7 higher (0.59 higher to 4.81 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in quadriceps strength (% , kg)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ONS plus low-intensity exercise	educational program	Relative (95% CI)	Absolute (95% CI)		
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	15	-	MD 24.7 higher (10.97 higher to 38.43 higher)	⊕○○○ VERY LOW	CRITICAL
6-minutes walk distance (% , m)												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	15	-	MD 17.5 higher (8.1 higher to 26.9 higher)	⊕○○○ VERY LOW	CRITICAL
Changes in QoL (% , CRDQ)												
1 <sup>1</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious <sup>b</sup>	none	17	15	-	MD 4.5 higher (0.78 higher to 8.22 higher)	⊕○○○ VERY LOW	CRITICAL

**CI:** Confidence interval; **CRDQ:** Chronic Respiratory Disease Questionnaire; **FFMI:** Fat free mass index; **MD:** Mean difference; **QoL:** Quality of life

### Explanations

- a. The RCT suffered from high risk of performance bias, and unclear risk of selection and detection bias.
- b. Only one RCT with small sample size (32 participants).

### References

1. Sugawara, K., Takahashi, H., Kasai, C., Kiyokawa, N., Watanabe, T., Fujii, S., Kashiwagura, T., Honma, M., Satake, M., Shioya, T., 2010. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir. Med.* 104, 1883–1889. <https://doi.org/10.1016/j.rmed.2010.05.008>.