NIHR | National Institute for Health and Care Research

Journals Library

Check for updates

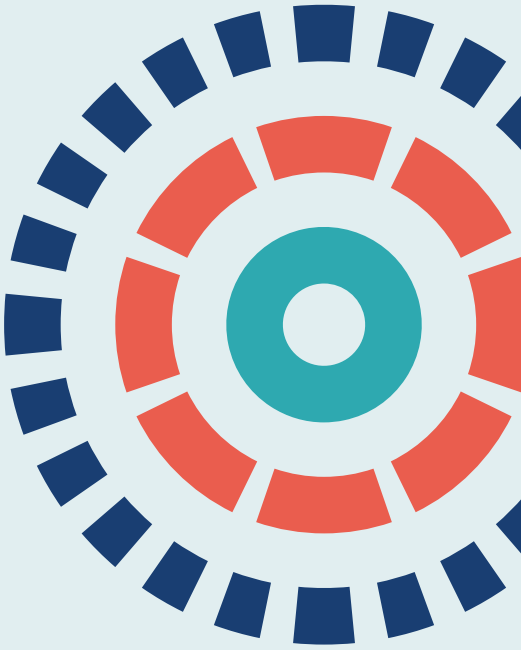
Health Technology Assessment

Volume 26 • Issue 51 • December 2022

ISSN 1366-5278

Oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition: a systematic review

Katie Thomson, Stephen Rice, Oluwatomi Arisa, Eugenie Johnson, Louise Tanner, Christopher Marshall, Tumi Sotire, Catherine Richmond, Hannah O'Keefe, Wael Mohammed, Margot Gosney, Anne Raffle, Barbara Hanratty, Claire T McEvoy, Dawn Craig and Sheena E Ramsay



DOI 10.3310/CCQF1608

Oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition: a systematic review

Katie Thomson,[1] Stephen Rice,[2] Oluwatomi Arisa,[1]
Eugenie Johnson,[2] Louise Tanner,[1]
Christopher Marshall,[1] Tumi Sotire,[2]
Catherine Richmond,[1] Hannah O'Keefe,[1]
Wael Mohammed,[2,3] Margot Gosney,[4]
Anne Raffle,[5] Barbara Hanratty,[2]
Claire T McEvoy,[6,7] Dawn Craig[1]
and Sheena E Ramsay[2*]

[1]Evidence Synthesis Group, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[3]School of Health and Related Research, University of Sheffield, Sheffield, UK
[4]Royal Berkshire NHS Foundation Trust, Reading, UK
[5]Elders Council of Newcastle upon Tyne, Newcastle upon Tyne, UK
[6]Centre for Public Health, Queen's University Belfast, Belfast, UK
[7]Institute for Global Food Security, Queen's University Belfast, Belfast, UK

*Corresponding author

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/CCQF1608.

Primary conflicts of interest: Margot Gosney was a member of the Health Technology Assessment (HTA) European Economic and Social Committee Panel and the National Institute for Health and Care Research (NIHR) HTA Prioritisation Committee (2013–19). Dawn Craig was a member of the NIHR Health and Social Care Delivery Research (HSDR) Researcher-Led Panel and is currently a member of the HSDR Funding Committee.

Published December 2022
DOI: 10.3310/CCQF1608

This report should be referenced as follows:

Thomson K, Rice S, Arisa O, Johnson E, Tanner L, Marshall C, *et al*. Oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition: a systematic review. *Health Technol Assess* 2022;**26**(51). https://doi.org/10.3310/CCQF1608

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 4.014 and is ranked 27th (out of 108 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2021 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), Embase (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number NIHR128729. The contractual start date was in December 2019. The draft report began editorial review in August 2021 and was accepted for publication in May 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition: a systematic review

Katie Thomson,[1] Stephen Rice,[2] Oluwatomi Arisa,[1] Eugenie Johnson,[2] Louise Tanner,[1] Christopher Marshall,[1] Tumi Sotire,[2] Catherine Richmond,[1] Hannah O'Keefe,[1] Wael Mohammed,[2,3] Margot Gosney,[4] Anne Raffle,[5] Barbara Hanratty,[2] Claire T McEvoy,[6,7] Dawn Craig[1] and Sheena E Ramsay[2*]

[1]Evidence Synthesis Group, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[2]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK
[3]School of Health and Related Research, University of Sheffield, Sheffield, UK
[4]Royal Berkshire NHS Foundation Trust, Reading, UK
[5]Elders Council of Newcastle upon Tyne, Newcastle upon Tyne, UK
[6]Centre for Public Health, Queen's University Belfast, Belfast, UK
[7]Institute for Global Food Security, Queen's University Belfast, Belfast, UK

*Corresponding author sheena.ramsay@newcastle.ac.uk

Background: Malnutrition worsens the health of frail older adults. Current treatments for malnutrition may include prescribed oral nutritional supplements, which are multinutrient products containing macronutrients and micronutrients.

Objective: To assess the effectiveness and cost-effectiveness of oral nutritional supplements (with or without other dietary interventions) in frail older people who are malnourished or at risk of malnutrition.

Data sources: MEDLINE, EMBASE, Cochrane Library, Scopus, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and grey literature were searched from inception to 13 September 2021.

Review methods: A systematic review and meta-analysis was conducted to evaluate the effectiveness and cost-effectiveness of oral nutritional supplements in frail older people (aged $\geq$ 65 years) who are malnourished or at risk of malnutrition (defined as undernutrition as per National Institute for Health and Care Excellence guidelines). Meta-analysis and network meta-analysis were undertaken, where feasible, along with a narrative synthesis. A cost-effectiveness review was reported narratively. A de novo model was developed using effectiveness evidence identified in the systematic review to estimate the cost-effectiveness of oral nutritional supplements.

Results: Eleven studies ($n = 822$ participants) were included in the effectiveness review, six of which were fully or partly funded by industry. Meta-analyses suggested positive effects of oral nutritional supplements compared with standard care for energy intake (kcal) (standardised mean difference 1.02, 95% confidence interval 0.15 to 1.88; very low quality evidence) and poor mobility (mean difference 0.03, $p < 0.00001$, 95% confidence interval 0.02 to 0.04; very low quality evidence) but no evidence of an effect for body weight (mean difference 1.31, 95% confidence interval −0.05 to 2.66; very low quality evidence) and body mass index (mean difference 0.54, 95% confidence interval −0.03 to 1.11; very low quality evidence). Pooled results for other outcomes were statistically non-significant.

There was mixed narrative evidence regarding the effect of oral nutritional supplements on quality of life. Network meta-analysis could be conducted only for body weight and grip strength; there was evidence of an effect for oral nutritional supplements compared with standard care for body weight only. Study quality was mixed; the randomisation method was typically poorly reported. One economic evaluation, in a care home setting, was included. This was a well-conducted study showing that oral nutritional supplements could be cost-effective. Cost-effectiveness analysis suggested that oral nutritional supplements may only be cost-effective for people with lower body mass index (< 21 kg/m^2) using cheaper oral nutritional supplements products that require minimal staff time to administer.

Limitations: The review scope was narrow in focus as few primary studies used frailty measures (or our proxy criteria). This resulted in only 11 included studies. The small evidence base and varied quality of evidence meant that it was not possible to determine accurate estimates of the effectiveness or cost-effectiveness of oral nutritional supplements. Furthermore, only English-language publications were considered.

Conclusions: Overall, the review found little evidence of oral nutritional supplements having significant effects on reducing malnutrition or its adverse outcomes in frail older adults.

Future work: Future research should focus on independent, high-quality, adequately powered studies to investigate oral nutritional supplements alongside other nutritional interventions, with longer-term follow-up and detailed analysis of determinants, intervention components and cost-effectiveness.

Study registration: This study is registered as PROSPERO CRD42020170906.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 51. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 List of excluded articles

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/CCQF1608).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

Glossary

Activities of daily living Essential and routine tasks that a healthy individual does on a daily basis without assistance.

Albumin A protein made in the liver. It maintains osmotic pressure of the blood compartment, providing nourishment to the tissues and transporting hormones, vitamins, drugs and other substances such as calcium throughout the body.

Cost-effectiveness analysis An economic analysis that describes the costs of additional health gain and adapts effects into health terms.

Dietary counselling A course by which a health professional with special training in nutrition helps people form healthy eating habits and make healthy food choices.

Fat-free muscle mass Encompasses tissues such as skeletal muscle, brain, heart, kidneys, liver and the gastrointestinal tract organs.

Meta-analysis A statistical technique used to combine the results of two or more studies to obtain a combined estimate of effect.

Oral nutritional supplements Liquid, semisolid or powder preparations, which provide a combination of macro- and micronutrients.

Publication bias The inclination of authors to publish studies with significant results while withholding negative results from publication.

Quality of life Encompasses an individual's emotional, physical and social well-being and their ability to perform the ordinary tasks of living.

Quality-adjusted life-year A measure of health gain used in economic evaluations, in which survival duration is adjusted or weighted by the patient's quality of life during the survival period.

List of abbreviations

ADL	activities of daily living
BMI	body mass index
CFB	change from baseline
CI	confidence interval
EQ-5D	EuroQol-5 Dimensions
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
MD	mean difference
MNA	Mini Nutritional Assessment
MUST	Malnutrition Universal Screening Tool
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ONS	oral nutritional supplements
PPIE	Patient and public involvement/ engagement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	risk ratio
SC	standard care
SD	standard deviation
SE	standard error
SF-12	12-Item Short Form Survey
SF-36	36-Item Short Form Survey
SMD	standardised mean difference
TIDieR	Template for Intervention Description and Replication
TTO	time trade-off
TUG	Timed Up and Go
VAS	visual analogue scale

Plain English summary

What was the question?

Malnutrition, in the form of undernutrition, is very common in frail older people. Dietary advice is recommended (e.g. adding nutrients to meals) for older adults who are malnourished, while powdered or liquid supplements (oral nutritional supplements) can be prescribed to those who are malnourished or at risk of becoming malnourished. In this study, we reviewed previous studies to see if oral nutritional supplements (as a form of dietary support) work at reducing malnutrition in frail older adults and whether or not they are value for money.

What did we do?

We searched for studies up to September 2021 on frail older people who were at risk of malnutrition or were malnourished in care homes, hospitals or the community in any country. We included studies that measured malnutrition and the consequences of malnutrition, quality of life, survival, costs and hospitalisations. We assessed the difference in malnutrition between those receiving oral nutritional supplements and those receiving usual care or other dietary (or nutritional) interventions. We also looked at the value for money of oral nutritional supplements.

What did we find?

We found 12 studies (11 studies looking at whether the supplements worked and one study looking at value for money). Most of which were of low quality, and many were funded by industry. Studies often did not report on longer-term effects, or how older people felt about the supplements. There was no clear or strong evidence that oral nutritional supplements worked or were value for money in reducing malnutrition or its consequences (such as the ability to perform everyday tasks).

What does this mean?

There is weak evidence for oral nutritional supplements in frail older adults. Future high-quality studies should be independent, assess longer-term effects, and have better reporting on factors that influence the impacts of oral nutritional supplements.

Scientific summary

The aim was to evaluate the effectiveness and cost-effectiveness of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition (defined as undernutrition as per National Institute for Health and Care Excellence guidelines). Oral nutritional interventions included prescribable oral nutritional supplements (ONS) with or without dietary advice, and food fortification (e.g. protein, carbohydrate and/or fat, vitamins).

Objectives

The key objectives were to:

- undertake a systematic review of the effectiveness and cost-effectiveness of oral nutritional interventions that include ONS in frail older people who are malnourished or at risk of malnutrition
- identify components of oral nutritional interventions associated with increased effectiveness or adherence, and to assess issues related to acceptability of ONS derived from the review
- undertake economic modelling to identify the cost-effectiveness of different models of oral nutritional interventions (including ONS) in frail older people who are malnourished or at risk of malnutrition
- develop a logic model for oral nutritional interventions (including determinants, components, outcomes) to reduce malnutrition in frail older people
- consult with stakeholders to identify (1) recommendations for interventions with potential for testing in future research and (2) implications for practice and policy.

Effectiveness and cost-effectiveness review

A systematic review and meta-analysis were conducted to evaluate the effectiveness and cost-effectiveness of ONS in frail older people (aged $\geq$ 65 years) who are malnourished or at risk of malnutrition. Effectiveness and cost-effectiveness studies were part of the same review; screening, data extraction and risk-of-bias/quality assessment were undertaken separately. The systematic review followed robust published methods, was registered on PROSPERO (CRD42020170906) and is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance.

Eligibility criteria

Population

Participants aged $\geq$ 65 years, able to swallow, malnourished (or at risk of malnutrition) and considered to be frail. All settings were considered (e.g. community, care homes and hospitals).

Intervention

Any form of prescribable ONS, with or without dietary advice or counselling. ONS were defined as multinutrient products containing macronutrients and micronutrients, designed to increase the energy and nutrient intake of individuals with or at risk of malnutrition.

Comparator

Studies that assessed an eligible intervention against any comparator intervention.

Outcomes

Malnutrition, outcomes associated with malnutrition (e.g. wound healing, hospitalisation, reduction in infections/falls), functional status, change in frailty status, quality of life (QoL), mortality, morbidity and adverse events. Outcomes also included acceptability of interventions, wastage, adherence, resource use and cost-effectiveness.

Study design

Parallel-arm, crossover and cluster-randomised controlled trials (RCTs), as well as prospective, comparative non-RCTs (e.g. cohort and case–control studies), were included. Mixed-methods and qualitative studies were also eligible for the review of acceptability and adherence. Cost-effectiveness studies needed to be full economic evaluations.

Search strategy

Population and intervention terms were combined to create a robust search strategy. Subject headings and free-text terms were used where appropriate in a range of bibliographic databases; Ovid MEDLINE, Ovid EMBASE, EBSCO*host* CINAHL, Scopus and Cochrane Library (CDSR and CENTRAL), searched from inception to 26 and 27 February 2020. Searches were updated on 13 September 2021. Relevant documents were also retrieved by searching grey literature databases, relevant professional bodies, charities and conference proceedings. No geographic filters were applied. The reference lists of included studies and relevant systematic reviews were hand-searched for additional papers.

Data selection and extraction

Two reviewers independently screened titles and abstracts, and full texts that were deemed relevant. Disagreements were resolved by discussion between the review team. Data were extracted by one reviewer and checked by a second.

Risk-of-bias assessment

Risk-of-bias assessment was conducted by two reviewers independently at a study level using Cochrane RoB 1.0 for RCTs. A tool for non-randomised studies was not needed because no studies of this type met the eligibility criteria. The BMJ checklist was used for the quality assessment of economic evaluations.

Data synthesis

Meta-analysis using a random-effects model to compare ONS against standard care (SC) was undertaken. Change from baseline and final values were computed, and forest plots detailing all studies and those adequately randomised are displayed. Heterogeneity between studies was assessed from chi-squared tests for heterogeneity and the I^2 statistic. Network meta-analyses were conducted to estimate the effect of ONS compared with alternative nutrition interventions as well as SC where there were evidence networks. Subgroup analyses were planned according to individual-level determinants and intervention characteristics. Where studies lacked appropriate data for the meta-analysis, narrative synthesis was used. A qualitative summary detailing the barriers to and facilitators of assessing acceptability was planned. Effectiveness estimates were considered for use in the economic model. Input from our public/patient involvement/engagement and stakeholder group of practitioners was sought to interpret findings and recommendations.

Economic modelling

Two approaches were considered for economic modelling: first, estimating the cost-effectiveness of ONS using evidence for the effectiveness of ONS on long-term health-care resource use, mortality and QoL outcomes; and, second, estimating cost-effectiveness using an appropriate proxy measure of malnutrition outcomes and then estimating the health-care resource and QoL outcomes associated with improvement in the proxy measure using evidence identified in a focused review of the literature. Body mass index (BMI) was selected as a proxy measure as it is commonly used as a marker of health status and was a frequently used outcome in the studies included in the review. The association of BMI with mortality, hospitalisation and QoL [measured using the EuroQol-5 Dimensions (EQ-5D)] was modelled, and the effect of ONS on these outcomes was estimated using the effectiveness estimate for ONS on BMI compared with SC (identified from the systematic review). This approach enabled the cost–utility of ONS to be evaluated for patient cohorts with different BMI values at baseline. EQ-5D outcomes over 1 year, outcomes per episode of hospitalisation occurring within 1 year, and lifetime QoL loss for mortality occurring within 1 year were calculated. Outcomes beyond 1 year were discounted at an annual rate of 3.5%. Sensitivity analyses using different model parameter estimates were conducted to investigate the sensitivity of the results to these alternative estimates. Threshold analyses were also conducted to identify the maximum cost of ONS per person for ONS to be cost-effective with high certainty.

Results

Eleven RCTs were identified in the effectiveness review and one (related paper) was included in the economics review, six of which were funded (at least in part) by industry. Most studies were based in nursing homes ($n = 5$), with four taking place in hospitals (or immediately post hospital discharge) and two taking place in the community. Too few studies were identified to undertake meta-analysis of key outcomes by population setting (e.g. community, long-term care, hospital). There was very limited information in studies related to active components, determinants or acceptability of interventions. The duration of follow-up for outcomes ranged from 28 days to 12 months.

Risk-of-bias assessment

Fewer than half of the RCTs were judged to be at low risk of bias for random sequence generation (45%), allocation concealment (45%), blinding the outcome assessor (45%) and selective reporting (45%). Forty-five per cent of studies were judged to be at high risk of bias for performance bias. Thirty-six per cent of RCTs were judged to be at high risk of attrition bias, with 27% of RCTs also judged at unclear risk of bias for this domain. Most of the included RCTs were rating as being at unclear risk of other bias (64%).

Nutritional intake outcomes

Energy intake

Four studies investigated the effect of ONS compared with SC on daily energy intake. Pooled results from the meta-analysis of change from baseline showed a positive effect of ONS on energy intake in comparison with SC [standardised mean difference (SMD) 1.02, 95% confidence interval (CI) 0.15 to 1.88; very low-quality evidence]. There was significant evidence of statistical heterogeneity ($p < 0.0001$, $I^2 = 87\%$).

Protein intake

Four studies reported the effect of ONS compared with SC on protein intake. Pooled results from change from baseline data demonstrated no evidence of an effect (SMD 1.67, 95% CI −0.03 to 3.37; very low quality evidence). The results were significantly heterogeneous, showing variable confounding across studies ($p < 0.00001$, $I^2 = 97\%$).

Visceral protein level

Five studies reported data on the effect of ONS compared with SC on serum albumin levels. The pooled analysis showed no evidence of an effect (MD 1.48, 95% CI −0.44 to 3.41; very low-quality evidence). There was evidence of statistical heterogeneity ($p < 0.00001$, $I^2 = 95\%$).

Body composition outcomes

Body weight

Five studies reported data on the effect of ONS compared with SC on body weight (in kilograms). Pooled meta-analysis results showed no evidence of effect of ONS on body weight (MD 1.31, 95% CI −0.05 to 2.66; very low-quality evidence). The studies were significantly heterogeneous ($I^2 = 74\%$).

Body mass index and proxy measures

Five studies reported on the effect of ONS compared with SC on BMI. Pooled results demonstrated no evidence of effect of ONS in comparison with SC (MD 0.54, 95% CI −0.03 to 1.11; very low-quality evidence) with notable heterogeneity across studies ($I^2 = 62\%$). One study assessed the impact of ONS compared with SC on arm circumference, providing data at baseline and post intervention. The study reported a mean change in arm circumference among people who were malnourished or at risk of malnutrition (at a 24-week follow-up) of 0.3 cm in the intervention group and −0.8 cm in the control group. GRADE assessment was not possible for arm circumference as meta-analysis was not undertaken.

Fat-free muscle mass

Three studies reported appropriate data on fat-free muscle mass, measured using calf circumference and lean body mass. The pooled analysis demonstrated no evidence of an effect (SMD 0.23, 95% CI −0.24 to 0.69; low-quality evidence). There was substantial heterogeneity ($p = 0.09$, $I^2 = 58\%$).

Longer-term outcomes

Activities of daily living

Three studies assessed the effect of ONS compared with SC on activities of daily living (ADL). Overall, there was no evidence of an effect (SMD 0.30, $p = 0.55$, 95% CI −0.69 to 1.29; very low-quality evidence). Substantial statistical heterogeneity may have been present in the main analysis ($p = 0.0001$; $I^2 = 89\%$).

Grip strength

Seven studies reported data on the effect of ONS compared with SC on grip strength. The results of the main meta-analysis ($n = 5$ studies) indicated no evidence of an effect (SMD 0.17, $p = 0.40$; 95% CI −0.23 to 0.58; very low-quality evidence). Substantial statistical heterogeneity was detected ($I^2 > 53\%$).

Hospitalisation

Five studies assessed the effect of ONS on hospitalisation. The results of the meta-analysis ($n = 5$ studies) showed no evidence of an effect of ONS on hospitalisation [risk ratio (RR) 0.97, $p = 0.94$; 95% CI 0.46 to 2.04; very low-quality evidence]. Heterogeneity was not detected in the analysis ($I^2 = 0\%$).

Mini-nutritional assessment score

Two studies reported data on the effect of ONS versus SC on MNA score. The results of the meta-analysis ($n = 2$ studies) indicated no evidence of an effect of ONS versus SC on MNA (SMD−0.36, $p = 0.11$, 95% CI −0.81 to 0.09; very low-quality evidence). Low heterogeneity was detected between the studies ($I^2 = 6\%$).

Mobility

Three studies reported data on the effect of ONS versus SC on mobility, assessed using gait speed (m/second) and were included in the meta-analysis for this outcome. The results from the meta-analysis indicated a positive effect of ONS versus SC (MD 0.03, $p < 0.00001$, 95% CI 0.02 to 0.04; very low-quality evidence). Statistical heterogeneity was not detected ($I^2 = 0\%$).

Mortality

Four studies compared mortality of recipients of ONS with that of recipients of SC. Overall, there was no evidence of an effect of ONS on mortality (RR 0.93, $p = 0.90$, 95% CI 0.28 to 3.06; very low-quality evidence). There was no evidence of statistical heterogeneity ($I^2 = 0\%$).

Quality of life

Six studies reported data on the effect of ONS on QoL. Four of these reported overall QoL scores and two studies reported data from psychological and physical subdomains of QoL assessments. Meta-analysis was not possible (and so GRADE could not be assessed). The results showed a positive effect of ONS on overall and psychological aspects of QoL, whereas the effects on physical function were mixed.

Other outcomes

Outcomes related to reduction in falls and adverse events were synthesised narratively. These were typically poorly reported and showed mixed effects. As meta-analyses were not possible for these outcomes, GRADE could not be assessed.

Network meta-analysis

Network meta-analyses were conducted only for body weight and grip strength. There was evidence of an effect for ONS compared with SC for body weight only (mean 1.67 kg, 95% CI 0.12 to 2.93 kg).

Cost-effectiveness review

One economic evaluation study, conducted in a care home, was included in the review. This was a well-conducted study that showed that ONS could be cost-effective.

Cost-effectiveness results

With the first cost-effectiveness approach, there was no evidence of a positive effect for ONS on hospitalisation and mortality and there was no appropriate evidence on QoL, so a cost-effectiveness analysis was not conducted. With the second cost-effectiveness approach, the incremental cost-effectiveness ratio for ONS was £24,390 per QALY when using all of the RCT evidence, with a probability that ONS is cost-effective at a cost-effectiveness threshold of £30,000 per QALY of 0.36. This was for a population cohort with a baseline BMI level of 23 kg/m^2. ONS was even less likely to be cost-effective using adequately randomised controlled evidence only (£30,466 per QALY, 0.33 probability cost-effective). Using the all-randomised trial evidence, ONS was cost-effective with a baseline BMI level of 19–21 kg/m^2 with a high level of certainty when ONS cost no more than £200 per person. It was also cost-effective with a baseline BMI level of 17 kg/m^2 with a high level of certainty when ONS cost no more than £400 per person.

Conclusions

The review identified only a small number of included studies because of its focus on frail older adults specifically. There was limited evidence of the effectiveness of ONS in reducing malnutrition or its adverse outcomes in frail older adults. There was some suggestion that ONS had a modest positive significant effect on energy intake and mobility in frail older adults. The limited cost-effectiveness review indicated that ONS may be cost-effective in a care home setting. The cost-effectiveness analysis undertaken in this study suggested that ONS was not likely to be cost-effective for frail older people with a BMI index of 23 kg/m^2. ONS was only found to be cost-effective with high certainty for people with low BMI and low-cost ONS interventions.

Recommendations for further research

1. Future research should report outcomes of nutritional interventions in relation to determinants/mediators of malnutrition in frail older adults (e.g. stage of frailty, ethnicity, social isolation, socioeconomic status, comorbidities).
2. Comparing ONS with other dietary interventions and other multicomponent interventions (e.g. protein/protein-energy supplementation and exercise).
3. Qualitative or mixed-methods research is needed to explore the acceptability of interventions and the perspectives of participants.
4. Outcomes relevant to patients, such as functional status, should be considered.
5. Intervention follow-up should capture longer-term outcomes, including hospitalisation, morbidity and mortality.
6. More comprehensive reporting on SC and other comparators should be included in published outputs.
7. Cost-effectiveness studies of ONS in frail older adults with different characteristics, settings and types of ONS are needed.

Study registration

This study is registered as PROSPERO CRD42020170906.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in *Health Technology Assessment*; Vol. 26, No. 51. See the NIHR Journals Library website for further project information.

Chapter 1 Background

Malnutrition (or undernutrition) is very common in older people, affecting > 1.3 million older adults (aged ≥ 65 years) in the UK.[2] Malnutrition contributes to £23.5B per year of health and social care spending in the UK, over half of which is attributed to malnutrition in older adults.[2] Frail older people are much more likely to become malnourished than those who are not frail.[3–6] Malnutrition worsens the health of frail older people, making them more vulnerable to longer stays in hospitals, readmissions, infections and delayed recovery.[4] Finding effective ways of managing malnutrition and reducing its adverse consequences is critical for improving the health of frail older people. Current UK recommendations[7] for treating malnutrition are to provide oral nutritional support or artificial nutrition support where clinically indicated.[8] Oral nutritional support strategies include dietary advice (help with meal planning), food fortification and/or prescribed oral nutritional supplements (ONS). As guidelines and evidence reviews have not focused on frail older people, this research set out to examine the effectiveness and cost-effectiveness of ONS in this population, and to understand what effective interventions look like to inform the design of future intervention strategies.

Malnutrition and frailty in older people in the UK

The UK population is ageing rapidly. The proportion of population aged ≥ 65 years is set to increase from 12% in 2016 to 18% by 2041 and further, to 26%, by 2066, with the fastest growth expected in the ≥ 85 years age group.[9] Ageing is associated with increased risk of multimorbidity[10] and disability,[11] which represents a major challenge for future health and social care service provision and funding.[12] There is a critical need to identify effective interventions to mitigate age-related morbidity in populations who are likely to benefit most. Chronic undernutrition or malnutrition is an important contributor to morbidity and mortality in older adults and is amenable to treatment, thereby providing a potential target for intervention.

Malnutrition is the deficiency of energy, protein, vitamins and minerals that causes weight loss, muscle loss and functional limitations,[7] and it is common among older adults aged ≥ 65 years. Although malnutrition affects < 10% of independent community-dwelling older adults,[13] prevalence is much greater in settings where there are increased care needs.[14] National surveys have detected malnutrition in 28% of hospital admissions, 27% of residential care home residents and 41% of nursing home residents.[15] Malnutrition has serious adverse consequences, including physical decline, and poorer outcomes of diseases and increased complications, such as infections, delayed recovery, hospital readmissions, increased length of hospital stays, more general practitioner visits, and poor quality of life (QoL) and well-being.[2,16]

Frail older people are at a particularly high-risk of malnutrition and are three to four times more likely to be malnourished.[3–6] Frailty is conceptualised as an abnormal health state relating to loss of biological reserves causing increased vulnerability to small environmental or health changes, which can lead to disability, falls, long-term care, hospital admissions and mortality.[17,18] Different tools have been used to measure or operationalise frailty, such as the Fried frailty phenotype and the cumulative deficit model.[19,20] Around 1 in 10 people aged > 65 years and around one-quarter to half of people aged > 85 years are living with frailty.[17] Malnutrition and frailty are closely interlinked. Poor nutritional status and weight loss increase the risk of frailty,[18,21] and the presence of malnutrition further worsens

the health status of frail older people.[4] Nutrition supplementation is recommended as one of the mainstays of intervention in treating frailty (European Society for Clinical Nutrition and Metabolism); however, much of the evidence is based on short-term protein synthesis studies or micronutrient interventions (e.g. amino acids, omega 3, vitamin D) that have not shown consistent benefits on muscle mass and function.[21] Furthermore, a micronutrient treatment approach is unlikely to benefit malnutrition and broader clinical and functional outcomes that are important in frailty.

Description of current service provision

The National Institute for Health and Care Excellence (NICE) CG32 guidelines recommend that health-care professionals consider oral nutrition support to improve nutritional intake for people who can swallow safely and are malnourished or at risk of malnutrition.[7] The guidelines states that oral nutrition support includes any of the following to improve nutritional intake: food fortified with protein, carbohydrate and/or fat, plus minerals and vitamins; snacks; ONS; altered meal patterns; and dietary advice. Dietary advice is recommended (e.g. meal planning, adding nutrients to meals) for older adults at risk of malnutrition, while powdered or liquid supplements (ONS) can be prescribed to those with existing malnutrition or at high risk of developing malnutrition.[7] The cost-effectiveness of these interventions is also unknown. Evidence from reviews so far suggest that prescribed ONS is effective in reducing malnutrition and its consequences, such as delayed wound healing and infections.[22] ONS is often viewed as a mode of managing malnutrition when it is difficult for individuals to consume energy and/or nutrients from food, for example in the case of acute illness or lack of availability of food.[22] Systematic reviews have also reported the cost-effectiveness of ONS in the management of malnutrition.[23–25] Cost-effectiveness evidence suggests that the use of ONS in community settings can reduce hospital stays and admissions (estimated savings of $\geq$ £119,200 per 100,000 people).[2] However, a key research gap, highlighted in current guidelines, is evidence specifically among frail older people on oral nutritional interventions that are effective in reducing malnutrition.

Individual study findings are not, however, entirely consistent for clinical outcomes, probably because of differences in the type of ONS evaluated and study methodology.[26] Evidence is mainly derived from small trials conducted in heterogeneous populations and across health-care settings. Some reviews have included only hospital patients post surgery,[27,28] whereas others have focused on community-dwelling adults[29] and mixed populations;[25,30,31] this makes it difficult to draw conclusions about the effectiveness of ONS for high-risk populations such as frail older people.

A further gap in knowledge is whether or not prescribed ONS offer additional benefits above other oral nutrition support strategies such as fortified food or expert dietary advice. Dietary counselling is often the first means of nutritional interventions in practice.[32] This includes supporting older people with planning their diet and making meal plans and is delivered by dietitians in the community or in hospitals. Food fortification, including adding specific nutrients (e.g. vitamins, proteins) to the diet, is another form of oral nutritional support.[33] However, although ONS have also been shown to be cost-effective, the costs of other forms of nutritional support, including dietary advice, food snacks and food fortification, to manage malnutrition remain unclear and need to be elucidated.[22] In addition, reviews so far have mostly compared ONS with routine care (i.e. no nutritional support), not necessarily with dietary advice.[22,24,27]

In summary, much of the focus of previous reviews on oral nutritional interventions includes disease-related malnutrition and adult populations aged $\geq$ 18 years, and not frail older people specifically.[31,34–37] Many of these reviews and studies have mostly looked at interventions to treat malnutrition related to diseases [e.g. cancer or human immunodeficiency virus (HIV)] and after surgery, which will have different underlying mechanisms from malnutrition in frail older people. The evidence in current guidelines is also mostly from studies on disease-related malnutrition.[38,39] As noted by topic experts in the NICE CG32 guidelines,[7] there is a lack of emphasis on effective interventions to reduce malnutrition among frail older people.

Determinants of malnutrition in frail older people: understanding factors affecting adherence to and acceptability of interventions

The effective treatment and management of malnutrition should be tailored to meet the needs of frail older people. Malnutrition is multifactorial. In addition to comorbidities, several other factors may affect the nutrition of older people. These include physiological changes with ageing (loss of appetite, poor taste and smell, disability), psychosocial aspects (social support, resilience, lack of knowledge about food) and personal resources (poverty, inability to shop for food).[40–43] These factors then lead to slower eating and lack of diet variety, which in turn lead to poor dietary intake (low energy, protein, and key nutrients such as B-vitamins, vitamin A, vitamin C, iron, calcium, zinc), potential weight loss and, ultimately, a state of malnutrition.[32]

Issues of compliance and acceptability also play a crucial role in inadequate nutritional support.[22,32,44] Although ONS have been found to be effective, the uptake of and compliance with them can be poor. The taste, texture, temperature and mode of ONS (liquid, powder) all influence the extent to which ONS are consumed, particularly over prolonged periods of time. For example, change in energy density can improve compliance and uptake of ONS.[22] Similar issues of compliance are also relevant for dietary advice and counselling to ensure that diet plans are acceptable and sustainable over time. The delivery and implementation of nutritional support by clinicians and healthcare professionals can also be very variable.[44] This could be due to lack of consistency in guidelines on whether ONS with or without dietary advice is effective in older people.[44] Clinical practice has been reported by dietitians to be influenced by lack of knowledge, ease of implementation, published research and local departmental protocols.[44] Understanding ways to improve the adoption and implementations of evidence-based nutritional support interventions into routine practice is a particular gap in the existing evidence.

The initial logic model developed prior to the review drew on current evidence and feedback from the preparatory patient and public involvement/engagement (PPIE) work that was undertaken (*Figure 1*). During the project, the logic model was iteratively refined with emerging findings along with input from stakeholders to produce a final logic model.

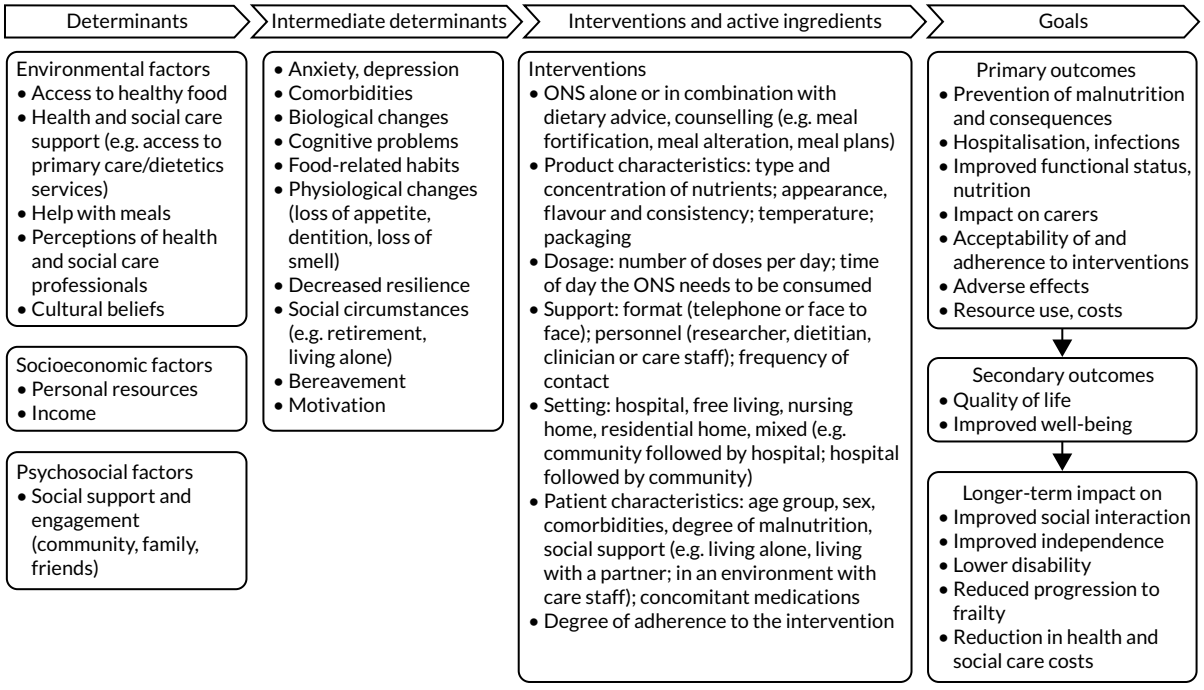


FIGURE 1 Initial logic model.

Aims and objectives

The aim of the study is to evaluate the effectiveness and cost-effectiveness of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition.

The research objectives are to:

- systematically review the effectiveness and cost-effectiveness of oral nutritional interventions which include ONS in frail older people who are malnourished or at risk of malnutrition
- identify components of interventions that are associated with increased effectiveness or adherence
- systematically review qualitative studies to assess issues related to acceptability of ONS among frail older people who are malnourished or at risk of malnutrition
- undertake economic modelling to identify the cost-effectiveness of different models of oral nutritional interventions in frail older people who are malnourished or at risk of malnutrition
- refine and develop a logic model for oral nutritional interventions (including determinants, components and outcomes) to reduce malnutrition in frail older people
- collate findings and consult with stakeholders to identify (1) recommendations for interventions with potential for testing in future research and (2) implications for practice and policy.

Chapter 2 Methods

The systematic review was registered with PROSPERO (CRD42020170906) and reported in line with PRISMA guidelines.[45] A single search was undertaken for different aspects that this review encompasses, namely effectiveness, adherence and acceptability, and cost-effectiveness.

Search strategy

The search strategy was initially developed in MEDLINE combining the concepts frail older people and nutritional support. Search terms, both text words and subject headings, were identified by an information specialist in conjunction with the project team. Articles previously identified by scoping were also used to identify relevant terms. Population terms included those relating to age, frailty, or care/nursing home settings. Nutritional support included ONS, food fortification, dietary support and malnutrition prevention. Results were restricted to human studies and those published in English. No geographic filters were applied. Publication filters were also not used as a range of publication types were relevant, which allowed the same set of papers to be screened for the cost-effectiveness review.

The searches were run on 26 and 27 February 2020, with updates conducted on 13 September 2021 (see *Appendix 1*). In total, 11,753 articles were retrieved; these were exported to EndNote (Clarivate Analytics, Philadelphia, PA, USA) reference management software and duplicate records were removed. Following this, 8428 records remained and were exported to Covidence (Melbourne, VIC, Australia) for screening. The databases searched were Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, daily and versions®, Ovid EMBASE 1974 to 2020 September 13, EBSCO*host* CINAHL, Scopus and Cochrane Library (CDSR and CENTRAL); all databases were searched from inception.

Grey literature searching encompassed a range of sources, including OpenGrey, NHS EED (NHS Economic Evaluation Database), DARE (Database of Abstracts of Reviews of Effects), HTA, IDEAS/REPeC (https://ideas.repec.org), HMIC (Healthcare Management and Information Consortium), ASPEN (American Society for Parenteral and Enteral Nutrition), BAPEN (British Association for Parenteral and Enteral Nutrition), ESPEN (European Society for Clinical Nutrition and Metabolism), European Natural Health Alliance, Canadian Malnutrition Task Force, United Kingdom Malnutrition Task Force, as well as trial registries, conference abstracts, theses and charities (659 unique resources were identified for screening). Finally, reference lists of all included studies and citations including relevant systematic reviews were screened for inclusion.

Inclusion and exclusion criteria

Types of studies

Parallel-arm, crossover and cluster-RCTs, as well as prospective, comparative non-RCTs (e.g. cohort and case–control studies), were included. Single-arm studies and systematic reviews were excluded from the effectiveness review. Mixed-methods and qualitative studies were eligible for the review of adherence and compliance.

For the cost-effectiveness review, we included full economic evaluations whether they were based on a single clinical study or model based. A full economic evaluation was defined as a study that evaluated the costs and outcomes of two or more health-care technologies.[46] Any studies published as abstracts or conference presentations were eligible for inclusion, provided that any outcome data of interest were sufficiently reported. The included lists of systematic reviews published within the last 3 years were checked for any potentially eligible studies that were missed by our searches.

Population

We included studies involving participants who were aged ≥ 65 years (mean age), able to swallow, malnourished or at risk of malnutrition, and considered to be frail. Malnutrition or risk of malnutrition was defined as undernutrition as per NICE guidelines,[7] and assessed using standardised tools [e.g. the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), MNA-Short Form].

Frailty was defined using any standardised measure, such as Fried's frailty phenotype, frailty index or the cumulative deficit model.[19,20] In a change from protocol, in discussion with clinical members of the review team we extended the definition of frailty to include the following proxy frailty criteria: participants admitted to hospital for a fall or fracture or emergency orthopaedic surgery, and participants living permanently in a care home. Studies of participants with dysphagia (inability to swallow), immune-nutrition or satiety hormone suppression, or with specific diseases (e.g. cancer, HIV), were excluded. Other conditions (e.g. dementia, stroke or diabetes) were not used as specific exclusion criteria, provided that the participants met the other population inclusion criteria listed above.

Interventions

The intervention of interest was any form of prescribable ONS, with or without dietary advice or counselling. ONS were defined as multinutrient products (e.g. ready-made liquids, puddings or powders to be mixed with fluids) that contained a mix of macronutrients (i.e. protein, carbohydrates and fat) and micronutrients (vitamins and minerals), designed to increase the energy and nutrient intake of individuals with or at risk of malnutrition. Dietary advice included intake modification, food fortification and meal alteration to improve nutritional intake.

We excluded studies evaluating disease-specific ONS (e.g. for renal, liver or critical care patients), non-commercial or home-prepared ONS formulations with only macronutrients, and artificial nutritional support (e.g. delivered through the parenteral or enteral routes).

Comparators

Studies assessing an eligible intervention against any comparator intervention were eligible for the review. Eligible comparators included standard care (SC), dietary advice or counselling. Studies with no comparator (i.e. single-arm studies) were not eligible for the review.

Outcomes

The following outcomes were eligible for the effectiveness review:

- malnutrition (undernutrition) – change in body weight, change in fat-free muscle mass, change in body mass index (BMI), change in other indicators of nutritional status, change in energy (kcal) and protein (g) levels and change in malnutrition risk (based on NICE guidelines or assessed using screening tools such as MUST or MNA)
- change in the consequences associated with malnutrition – improvement in wound healing, reduction in hospitalisation, reduction in infections and the reduction in falls.
- functional status – improvement in Timed-Up and Go (TUG) test, improvement in gait speed test, improvement in walking speed test, increase in hand grip (or other muscle) strength, improvement in activities of daily living (ADL) and improvement in self-reported mobility
- change in frailty status (e.g. change in Fried's frailty phenotype, frailty index or cumulative deficit model)
- quality of life (assessed using tools such as the EQ-5D, SF-36, Health Utilities Index, Short-Form 6 Dimensions and SF-12)
- mortality
- morbidity
- overall adverse event rates
- serious adverse events (kidney injury, hyperglycaemia, constipation, diarrhoea, nausea, vomiting, refeeding syndrome, micronutrient deficiency).

The following outcomes were eligible for the adherence and acceptability review:

- barriers to initiating the use of ONS
- facilitators of initiating the use of ONS
- proportion of treatment persistence, compliance, adherence and/or acceptance
- role of carers in delivering the intervention.

The following outcomes were eligible for the cost-effectiveness review:

- total costs
- summary health outcomes [e.g. quality-adjusted life-years (QALYs)]
- incremental cost-effectiveness ratios (ICERs)
- resource use (e.g. general practitioner, carer or specialist visits, hospital admissions, length of stay).

Deviations from the protocol

In the protocol, 'change in nutritional intake' was a measure of malnutrition. However, we changed this to just energy and protein during the extraction process. Similarly, 'serious adverse events' were not defined in the protocol but were later defined during the extraction process as kidney injury, hyperglycaemia, constipation, diarrhoea, nausea, vomiting, refeeding syndrome and micronutrient deficiency. In addition, we altered our definition of frailty to encompass more than standard measures, using the following proxy measures: hospitalised for a fall, any fracture or an emergency orthopaedic admission at the time of recruitment to the study; or permanently residing in a care or nursing home.

Selection of studies

Three reviewers (OA, EJ, CM) screened all title and abstracts identified by the search using Covidence. Full texts of potentially eligible studies were sought and then screened. Any disagreements were resolved by a third reviewer (CM, KT, SER). Where multiple reports of the same study were identified, we combined these into a single study to extract and analyse these at study level (see *Appendix 2*).

For the cost-effectiveness review, one reviewer (WM) screened the title and abstracts of the studies retrieved by the search in Covidence. For studies deemed eligible or for which it was impossible to decide eligibility from the abstract, the full text was retrieved, and two reviewers (WM, SR) independently assessed the full text for inclusion. This was conducted alongside the study selection of effectiveness studies. Two reviewers (SR and WM) made the final selection decisions about the included studies.

Data extraction

A data extraction form was created and piloted on 10% of included studies. Based on this piloting, the form was modified appropriately (e.g. introduction of the TIDieR framework[47] for reporting interventions). One reviewer extracted 50% of included studies, with a second extracting the other 50% (OA and EJ). The reviewers then checked each other's data extraction. Any disagreements between the two reviewers were resolved by arbitration to a third reviewer (LT). For the cost-effectiveness review, one reviewer (WM) extracted 100% of included studies, with a second (SR) checking the data extracted. Any changes suggested by SR were discussed and agreement was reached.

Quality assessment of included studies

The Cochrane RoB 1.0 tool was used to assess parallel-arm, crossover and cluster-RCTs.[48] The following domains were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. One review author (of OA or EJ) assessed the risk of bias for each included paper. A second reviewer (either OA or EJ) checked the assessment. Any discrepancies between the two reviewers were adjudicated by a third reviewer (LT). A tool for non-randomised studies was not needed because no studies of this type met the eligibility criteria. The quality of the included cost-effectiveness studies was assessed using the BMJ checklist.[49]

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to address the quality of the evidence.[50] Quality of evidence for each outcome was assessed based on study design, risk of bias, imprecision of estimates, inconsistency of results from different studies, indirectness of study results (i.e. lack of applicability) and publication bias.[51] The GRADE approach was used to assess the certainty of evidence for all outcomes (where possible) using the principles outlined in the Cochrane Handbook.[52] Two review authors (EJ and OA) independently assessed the certainty of evidence for each of these outcomes, resolving any disagreements by discussion and, if necessary, through arbitration with a third review author.

Meta-analysis and narrative synthesis

Meta-analysis was undertaken for RCTs with outcomes where at least two studies compared rates of an outcome (for binary variables) or mean values (for continuous variables) between persons receiving ONS (intervention recipients) and those who received SC (the control group). All studies included in the systematic review that had outcome measures that could be combined were included in meta-analyses if they met the following criteria:

- The required data were reported or calculable (mean and SD for continuous variables, number of events and sample size for binary variables).
- Trial arms included ONS versus SC as defined by triallists (e.g. the study by Parsons *et al.*[53] was excluded as it lacked an appropriate 'SC' arm).
- Outcome measures from different studies could be combined (it was deemed that data for quadriceps strength were inappropriate for inclusion in a meta-analysis in which all other studies reported handgrip strength).

Subgroup analysis was implemented on those studies deemed adequately randomised. Adequacy of randomisation was assessed using domain 1 (random sequence generation – selection bias) from the RoB 1.0 tool. The reasons for this approach included the following: the studies were expected to be at varying risk of bias across categories (there was a low expectation of finding studies at low risk of bias across all categories); random sequence allocation and allocation concealment were considered the most important items, especially as most of the outcome measures were not considered to be subjective (ADL is an exception to this); and we sought to minimise the number of sensitivity analyses. The studies included in the adequately randomised sensitivity analysis are not necessarily at low risk of bias.

Studies were deemed to be adequately randomised where a random component (e.g. using a computer random number generator) was used in the sequence generation process. Five out of 11 studies that were included in the meta-analyses were deemed inadequately randomised.[54–57] No meta-regression analyses were conducted to investigate the effect of variation in population characteristics and intervention components across studies due to the small number of studies included in the review for each outcome.

There were a mix of studies reporting final values and change from baseline (CFB) values. CFB outcomes were preferred as they remove a component of between-person variability from the analysis.[58] Sensitivity analyses were also conducted using final values. CFB, final values and standard deviations were calculated where they were not reported. The methods used to determine the standard deviation are described in *Appendix 3*.

For the binary outcomes (mortality and hospitalisation), we performed an analysis comprising all studies that reported relevant data. A Mantel–Haenszel random-effects meta-analysis was conducted. For continuous outcomes with a uniform measure across studies, an inverse variance random-effects meta-analysis was conducted for the mean difference in outcomes. For continuous outcomes with different measures across studies, standardised mean differences (SMDs) were calculated using the Hedges' *g* (adjusted) method.[59] Generic inverse variance random-effect meta-analyses were conducted. In reporting the results, statistical significance was defined at a 95% level of confidence.

As multiple measures of the same outcome were often included in a study (e.g. calf circumference as a measure of fat-free muscle mass), an evidence hierarchy was employed to decide which outcome was preferentially included in the analysis. This is displayed in *Table 1*.

TABLE 1 Outcomes in meta-analysis with details of the hierarchy used to determine preferential outcome in studies that report multiple outcomes

Outcome	Analysis method	Outcome hierarchy
Body weight	MD	Body weight (kg)
BMI	MD	BMI (kg/m^2)
Arm circumference	SMD	Arm circumference (cm)
Fat-free muscle mass	SMD	Calf circumference (cm)
		Lean body mass (kg)
Energy intake	SMD	Total energy intake (kcal/day)
		Energy intake (kcal/kg)
Protein	SMD	Total protein (g/day)
		Protein (g/kg)
Albumin	MD	Albumin (g/l)
ADL	SMD	ADL score
		IADL
Hospitalisation	RR	Readmissions
		Hospital admissions
Mortality	RR	Number of deaths
Grip strength	SMD	Handgrip strength (kg)
		Handgrip strength (kPa)
MNA	SMD	MNA
		MNA-SF
Mobility	MD	Improvement in TUG test
		Improvement in gait speed test

IADL, instrumental activities of daily living; MD, mean difference; MNA, Mini Nutritional Assessment.

Data from the longest follow-up time point available in each were included in the meta-analysis so that the longer-term impacts on outcomes could be assessed. In addition, too few studies reported multiple time points, meaning that it would not have been possible to run a meta-analysis for multiple follow-up periods. The degree of heterogeneity was estimated using the I^2 statistic, and the *p*-value of the chi-squared statistic was used to measure the strength of evidence for heterogeneity. I^2 values of 0–40% (heterogeneity might not be important), 30–60% (may represent moderate heterogeneity), 50–90% (may represent substantial heterogeneity) and 75–100% (considerable heterogeneity) were used to guide interpretation.[60] Publication bias and other small-study effects were evaluated using Egger's test and funnel plots if 10 or more studies were included in an analysis. If there were fewer than 10 studies, the power of the test would usually be too low to distinguish real asymmetry from chance.[61] All analysis was conducted in RevMan.

Narrative synthesis methods were used either to analyse outcomes with insufficient data or for those studies that did not meet the criteria for meta-analysis (e.g. cohort studies). Patterns in the data, including statistical significance and direction of effect, are summarised narratively. The results reported are included alongside the meta-analysis outcomes. A narrative synthesis was undertaken for the cost-effectiveness review to describe the similarities and differences in the study questions, methods and results.

Network meta-analysis

There were multiple comparators investigated in the studies included in the systematic review. The effectiveness of ONS compared with these was evaluated using network meta-analysis (NMA). NMA enables direct and indirect evidence of a treatment effect to be combined in the estimation of the effect. For example, if one study (AB) compares A with B, one study (AC) compares A with C and one study (BC) compares B with C, then study AC provides direct evidence for A compared with C, and studies AB and BC provide indirect evidence for A compared with C. NMA also enables an effect to be estimated for A compared with C when only indirect evidence is available.

Only RCTs were included in the NMA. All interventions included in the studies that met the inclusion criteria were included in the NMA, for example different dietary interventions and dietary interventions with exercise. The purpose was to estimate the effectiveness of ONS compared with all of the different comparators found in the review studies. The network diagrams are presented in *Appendix 4* (see *Figures 19* and *20*) and show that there are no cases of both direct and indirect evidence for any one comparison. The purpose of conducting NMAs here is to estimate treatment effects using indirect evidence. The effectiveness of every treatment compared with every other treatment can be estimated. The effect estimates for ONS compared with every other treatment are produced here. The mean and 95% credible interval of the effect estimates are calculated.

A NMA was conducted for an outcome for which there were at least three studies reporting one comparison, generally ONS compared with SC, and there was a connected network of three or more interventions. These conditions were met for two continuous outcomes. One outcome was analysed on the SMD scale and one outcome was analysed on the mean difference scale.[58,62] Analyses were conducted in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).[63] For the mean difference analysis, the WinBUGS program 5a code for a random-effects analysis with multiarm trials from the NICE Technical Support Document 2 was used.[64] For the SMD analysis, the WinBUGS program 7a code for random-effects analysis with multiarm trials from the NICE Technical Support Document 2 was used. The code requires that the data set include the variance of the baseline treatment in each trial with more than two trial arms. For the SMD analysis, the variance of baseline treatment was approximated as shown in the following equations. The equation presented here for the variance of

baseline treatment was not specifically reported in *Introduction to Meta-analysis*,[62] Chapter 4, but it makes use of formulae 4.18, 4.19, 4.20, 4.22 and 4.24 presented there:

$$var_{control} = \left(\frac{{}^{SD_C^2}/_{N_C}}{\sigma^2} + \frac{d^2}{2 \times (N_C + N_T)}\right) \times J^2 \quad (1)$$

$$d = \frac{\mu_T - \mu_C}{\sigma} \quad (2)$$

$$\sigma = \sqrt{\frac{(N_C - 1) \times SD_C^2 + (N_T - 1) \times SD_T^2}{(N_T + N_C - 2)}} \quad (3)$$

$$J = 1 - \left(\frac{3}{4 \times (N_C + N_T - 2) - 1}\right) \quad (4)$$

μ_C, SD_C, and N_C are the mean, standard deviation and sample size of the control group; μ_T, SD_T and N_T are the mean, standard deviation and sample size of the intervention group.

A common between-study variance was assumed across treatment comparisons. Multiple studies were reported for only one treatment comparison, ONS compared with SC, so the common between-study variance estimate is determined by those studies. For continuous outcomes, the between-study variance and standard deviation are on the outcome scale. The choice of prior distribution for the between-study standard deviation should be based on the specific scale. Where there are many trials with which to estimate the between-study standard deviation, the upper limit of the uniform prior distribution should be sufficiently high that the upper end of the posterior distribution of the between-study standard deviation is barely, if at all, truncated.

Where there are few studies with which to estimate the between-study standard deviation, the uniform prior distribution can have a significant effect on the posterior distribution. The mean of a uniform prior distribution is (maximum – minimum)/2, and it is not entirely 'uninformative'. One approach is to identify an informative prior from a published meta-analysis that does not include the same trials as the current study, or to elicit a prior distribution from experts. For the analyses planned, there were four different outcome scales across the analyses and few studies in each analysis. Therefore, a pragmatic decision taken here was to set the upper limit of the uniform distribution for the between-study standard deviation to be the difference between the greatest and smallest effect size for any one comparison in the network (only two analyses were eventually included in the review). For example, comparison A versus B has estimates (–0.4, –0.8, 0.3) and comparison B versus C has estimates (0.6, 0.1). The greatest difference in effect sizes is 0.3 minus –0.8 = 1.1. This is straightforward when there are no comparisons with direct and indirect evidence, as in this study. For networks with direct and indirect evidence, the difference in these estimates would need to be taken into account. The mean (0.55) of the uniform distribution (0 to 1.1) is the maximum possible between-study standard deviation described by the mean effect estimates. But these priors are not as vague as would normally be recommended. Recommended vague priors allow for a huge range of true effect estimates,[64] far greater than seen in practice. A review[65] of between-study variance estimators reported that a Bayesian approach may overestimate the between-study variance when it is close to zero and when there are few studies.

Convergence was assessed using the Brooks–Gelman–Rubin diagnostic along with a visual inspection of the trace and density plots.[66] The initial 20,000 simulations were discarded, and the results were based on a further sample of 50,000 simulations. As there were no closed loops in the network (no cases of direct and indirect evidence for any one comparison), there was no possibility of inconsistency in the network. The probability that an intervention was most effective was then estimated.

Public and patient involvement/engagement

Public and patient involvement/engagement was undertaken throughout the project, initially helping to develop the proposal and inform the initial logic model, and then scope of the review, discussing results of the review and the implications of findings. In addition, AR (PPIE lead) helped shape the research as part of the project team. The PPIE groups comprised six to eight older people (all of whom were female).

The participants in the PPIE group were members of the Newcastle branch of the Elders Council, a local organisation of older people interested in sharing their views about making the city 'a great place in which to grow old'. Recruitment to the focus groups was organised by the chairperson of the Elders Council in Newcastle and PPIE lead (AR), and the sessions were facilitated by researchers at Newcastle University. The format of the sessions was a short presentation about review progress to date, followed by open questions to discuss as a group. The online sessions were recorded, and detailed notes were taken by researchers. These notes were subsequently written up and shared with the research team. Key concepts and broad themes were identified and used to complement the data collated in the review.

Following the completion of the review, the findings were presented to a panel of practice or policy partners to allow understanding of how different stakeholders conceptualised the results and their experiences more generally concerning the use of oral nutritional interventions in this population. The main online event comprising eight stakeholders was supplemented with three one-on-one sessions with additional partners to ensure that we collated views from a range of individuals. Geriatricians, dietitians and nurse practitioners were involved in the discussions.

Chapter 3 Results of effectiveness review

The database searches identified 8428 records after duplicates had been removed. A further 659 additional records were identified and 64 records were found from citation-chaining (*Figure 2*). In total, 621 papers were screened at full-text level (the reasons for exclusion are detailed in *Report Supplementary Material 1*). Eleven studies met the inclusion criteria, two of which reported duplicate data (see *Appendix 2*).[53] In this report, we refer to the paper with the most information gathered from each but reference individual papers where appropriate (see *Appendix 5*). Included papers were published between the years 2000 and 2017.[53,67] One effectiveness study was included in the cost-effectiveness review.[23]

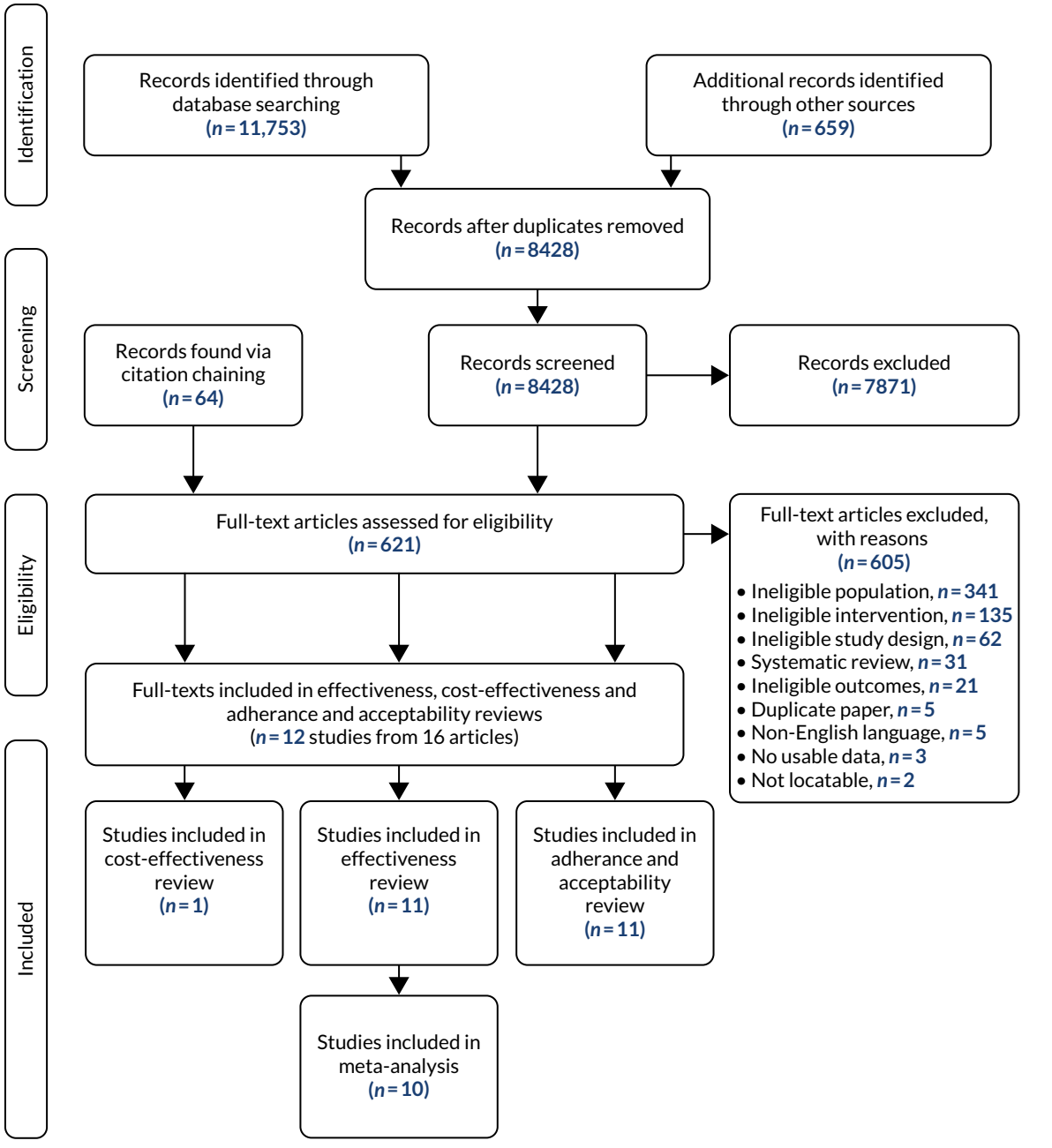


FIGURE 2 The PRISMA flow chart.

Characteristics of included studies

Eleven studies were included in the effectiveness review, all of which were RCTs. One study was a crossover RCT,[56] four studies were multiarm RCTs[57,67–69] and the remaining six studies used a parallel-group design with two groups.[53–55,70–73] In total, 882 people were recruited across the 11 studies. The smallest study recruited 39 participants[56] and the largest recruited 104.[53] *Table 2* describes the characteristics of the included studies in the review.

Two studies took place in Australia,[68,71] two in France,[57,67] one in Germany,[72] two in Sweden,[56,69] and one each in the UK,[73] Russia,[70] Canada[55] and Taiwan (Province of China).[54] Five studies were set in nursing/residential homes,[54,56,57,67,73] of which four took place in multiple nursing homes.[56,57,67,73] We acknowledge that definitions of nursing/residential homes vary internationally; however, our groupings were purely for descriptive purposes. Two further studies were set in the community[55,69] and three were set in hospital.[68,70,71] One study stated that it had been conducted with patients after they had been discharged from hospital.[72] Reporting on intervention duration and follow-up was often inadequate and lacked detail.

The type of ONS used and the comparisons varied across the studies. Six studies[54,55,57,68,71,74] compared ONS with usual care or SC in one of their arms, and two[53,72] compared ONS with dietary counselling or advice. The remaining studies contained a number of comparisons; these are detailed in *Table 2*. One study[68] either combined or compared ONS with exercise programmes. The duration of the ONS intervention ranged from 28 days[74] to 6 months,[69] with a maximum follow-up of 12 months.[69] The timing of follow-up, particularly in relation to the intervention period, was poorly reported and difficult to ascertain from the studies. Of the studies that were included in the effectiveness review, six were either fully funded or part-funded by industry. Of these, four were fully funded (including one with an unrestricted grant) and two were part-funded. A further three were not funded by industry and two studies did not include details of funding/conflict of interests.

Across the studies, participants varied in age, BMI and body weight. Most studies included both men and women, although often more women participated in the studies than men. Two studies included women only.[69,71] Participants' level of malnutrition at baseline between groups was measured using a variety of tools. Three studies used the MNA[54,57,67] and one used the MUST score.[53] One study each used mid-upper arm circumference and albumin levels,[71] and a further two studies reported excess weight loss.[55,70] One study stated that most participants were at risk of malnutrition, but it was unclear whether this was assessed using the MNA-SF.[56] Four studies did not report specific levels of malnutrition between groups at baseline.[68–70,72] Further details of the characteristics of participants in the included studies can be found in *Appendix 5*.

Some studies reported on comorbidities that may contribute to malnutrition (see *Appendix 6*). Two studies[53,67] included participants with dementia, three[53,56,68] included participants who had cognitive impairment, and one[53] included participants who had cardiovascular disease. No studies reported on participants who had diabetes, stroke or cancer. Only one study[57] reported on specific oral health issues that may affect malnutrition and related outcomes. One study[57] reported on participants who had complete or partial denture or participants who had no dentures. Two studies[54,67] reported on participants' need for assistance with feeding.

In general, studies did not report clearly on potential social determinants of malnutrition, with the exception of their living arrangements or whether the participants were receiving household or other help (see *Appendix 7*). No studies reported on the ethnicity of the participants. Of the five studies that did not take place in either nursing or residential care homes, four[55,68,71,75] reported the participants' living situation to some extent (e.g. living along, married). Luo *et al.*[74] did not describe living arrangements. Tidermark *et al.*[69] noted that their participants lived at home and were non-institutionalised but did not provide any further details. Otten *et al.*[72] reported the number of participants living alone, but not by study arm. The interventions, comparisons and modes of delivery across the studies varied and are described in *Appendix 8*.

TABLE 2 Study characteristics of included studies in the review

Study authors; country; study design	Setting	Number enrolled (withdrawals, % or people)[∞]	Duration of intervention (ONS) and follow-up	Intervention	Outcomes	Study funding source/ conflicts of interest
Cameron *et al.*;[71] Australia; RCT	Hospital: Hornsby Ku-ring-gai Hospital (a general hospital in Northern Sydney)	44 (9–56%)	Treatment duration: 40 days Follow-up duration: 40 days, 4 months	Liquid high-calorie, high-protein supplement (Novasource/Sustagen Hospital Formula Plus) and diet of choice ($n = 23$) SC – high-protein diet (with high-protein milk) ($n = 21$)	Body weight, fat-free muscle mass, BMI,[a] other indicators of nutritional status, hospitalisations, gait speed, handgrip (or other muscle) strength, ADL, mortality and number of adverse events	Northern Sydney area health service
Lauque *et al.*;[67] France; RCT	Nursing home: eight privately run 80-bed nursing homes in Toulouse	88 (0–32%)	Treatment duration: 60 days Follow-up duration: NR	ONS (Clinutren) – risk of malnutrition ($n = 19$)[b] ONS (Clinutren) – malnourished ($n = 28$)[b] No supplementation – well nourished ($n = 19$) No supplements – risk of malnutrition ($n = 22$)	Body weight, BMI, energy intake (kcal), protein intake, change in malnutrition risk, handgrip (or other muscle) strength and mortality	NR
Lee *et al.*;[54] Taiwan (Province of China); RCT	Nursing home: geriatric nursing home	92[c] (NR)	Treatment duration: 24 weeks Follow-up duration: 24 weeks, 1 year[d]	Liquid ONS ($n = 47$) and all essential micronutrients taken as an afternoon snack NR (assumed SC) ($n = 45$)	Body weight, mid-arm circumference, fat-free muscle mass, BMI and other indicators of nutritional status	Asia University
Luo *et al.*;[70] Russia; RCT	Hospital	55[b] (four or five people)	Treatment duration: 28 days Follow-up duration: NR	ONS (Ensure TwoCal) plus standard hospital food ($n = 26$) SC including normal hospital food ($n = 28$)	Body weight, serum albumin, protein intake, gait speed, chair-to-bed transfer domain from Modified Barthel Index, number of adverse events in study, nausea and pruritus caused by ONS and compliance	Abbott Nutrition (no details given of the role of industry partner in research)

continued

TABLE 2 Study characteristics of included studies in the review (*continued*)

Study authors; country; study design	Setting	Number enrolled (withdrawals, % or people)[∞]	Duration of intervention (ONS) and follow-up	Intervention	Outcomes	Study funding source/ conflicts of interest
Miller *et al*;,[68] Australia; RCT	Hospital: orthopaedic wards of Flinders Medical Centre, Adelaide	100 (3.8–8.3%)	Treatment duration: 42 days Follow-up duration: NR	Liquid ONS (Fortisip) ($n = 25$) plus standard hospital food only for 24 weeks ($n = 29$) Exercise – resistance training ($n = 25$) Liquid ONS and exercise ($n = 24$) SC (general nutrition and exercise advice, usual dietetic and physiotherapy care and onward transfer) ($n = 26$)	Body weight, BMI, hospitalisations, gait speed test, handgrip (or other muscle) strength, mortality and QoL	NHMRC Public Health Postgraduate Research Scholarship, Flinders University-Industry Collaborative Research Grant and Nutricia Australia Pty Ltd (no details given of the role of industry partner in research)
Otten *et al*.;[72] Germany; RCT	After hospital discharge	71 (NR)	Treatment duration: 3 months Follow-up duration: NR	Liquid ONS ($n = 42$) ONS with guidance ($n = 53$)	QoL	NR
Parsons *et al*.;[73] UK; RCT	Nursing home: care homes in Hampshire	104 (NR)	Treatment duration: 12 weeks Follow-up duration: NR	ONS (range of Nutricia Ltd products available to choose from) ($n = 53$) Dietary advice (specially designed diet sheet) ($n = 51$)	Body weight, change in nutritional intake, hospitalisations, mortality and QoL[e]	An unrestricted educational grant from Nutricia
Payette *et al*.;[55] Canada; RCT	Community: home	83 (9.5–9.8%)	Treatment duration: 16 weeks Follow-up duration: NR	Liquid ONS (Ensure or Ensure Plus) ($n = 41$) Usual care ($n = 41$)	Body weight, fat free muscle mass, energy intake (kcal), protein, TUG test, handgrip (or other muscle) strength, QoL	Abbott Laboratories Limited (no details given of the role of industry partner in research)

Study authors; country; study design	Setting	Number enrolled (withdrawals, % or people)∞	Duration of intervention (ONS) and follow-up	Intervention	Outcomes	Study funding source/ conflicts of interest
Tidermark *et al.*;[69] Sweden; RCT	Community	59 (two or three people)	Treatment duration: 6 months Follow-up duration: 6 months, 12 months	Protein-rich ONS (Fortimel) ($n = 20$) Protein-rich ONS (Fortimel) plus nandrolone decanoate (Deca-Durabolin) ($n = 19$) SC plus additional calcium and vitamin D for 6 months ($n = 20$)	Body weight, fat-free muscle mass, other indicators of nutritional status, reduction in infections, handgrip (or other muscle) strength, mortality and QoL	Trygg-Hansa Insurance Company, the Swedish Orthopaedic Association, the Swedish Research Council, the Novo Nordisk Foundation, Nutricia Nordica AB and Nycomed AB (no details given of the role of industry partner in research)
Tylner *et al.*;[56] Sweden; crossover RCT	Nursing home: five residential care homes in the southern Stockholm area	39 (five or six people)	Treatment duration: 12 weeks Follow-up duration: NR	Fat emulsion (Calogen Extra) and then SC (6 weeks each) ($n = 20$) SC and then fat emulsion (Calogen Extra) (6 weeks each) ($n = 19$)	Body weight, BMI, kcal, protein, other indicators of nutritional status, hospitalisations, handgrip (or other muscle) strength and serious adverse events	Nutricia Nordica AB (no details given of the role of industry partner in research)
Van Wymelbeke *et al.*;[57] France; RCT	Nursing home: eight nursing homes in Burgundy	87 (12–37%)	Treatment duration: 12 weeks Follow-up duration: NR	Liquid high-calorie, high-protein ONS (Fresenius Kabi) and diet of choice ($n = 27$)[f] Enriched brioche (with similar levels of energy and macro- and micronutrients to the ONS) ($n = 35$)[f] Usual care (normal breakfast) ($n = 25$)	BMI, kcal, protein, other indicators of nutritional status, change in malnutrition risk, hospitalisations, handgrip (or other muscle) strength and ADL	French government under the FUI (Fonds Unique Interministériel) programme through the project Farineþ

NHMRC, National Health and Medical Research Council; NR, not reported.

∞ Withdrawals from study (as a percentage range for individual trial arms).

a Cameron *et al.*[71] used self-reported weight and height at baseline. The baseline weight was based in only 12 SC participants and 11 ONS participants.

b Lauque *et al.*[67] has been included in the meta-analyses using the two arms that were adequately randomised: group B, consisting of participants who were at risk of malnutrition but did not receive ONS, and group C, consisting of participants who were at risk of malnutrition and were prescribed ONS.

c Lee *et al.*[54] originally included 92 participants but, for the purpose of meta-analysis, only the arms comprising patients who were malnourished and at risk of malnutrition were included, reducing the sample size in the meta-analysis to 62 participants. The malnourished and the at risk of malnutrition trial arms were combined in the meta-analysis.

d Lee *et al.*[54] conducted follow-up at the end of the treatment of 24 weeks and a 1-year follow-up for mortality.

e Parsons *et al.*[53] could not be included in the analyses for body weight, energy intake (kcal) and protein intake, as the study did not report sufficient mean and standard deviation data and it was not possible to calculate these data.

f Van Wymelbeke *et al.*[57] included two arms, one consisting of high-protein ONS and another of enriched brioche, which was considered an ONS. The arms were combined and a meta-analysis of the combined arm compared with SC was conducted.

Shaded rows/cells denote the trial arms in which meta-analysis was undertaken.

Quality assessment of included studies

Quality assessment was conducted using the Cochrane risk-of-bias tool ($n = 11$) for parallel-arm RCTs, multiarm RCTs, crossover RCTs or cluster-RCTs. A summary of risk-of-bias assessments across all included studies can be seen in *Appendix 9*.

Randomised controlled trials

We assessed the 11 included studies using the Cochrane risk-of-bias tool. Fewer than half of the RCTs were judged to be at low risk of bias for random sequence generation (45%),[55,57,67,69,73] allocation concealment (45%),[56,68–70,73] blinding the outcome assessor (45%)[54,55,57,68,73] and selective reporting (45%).[55,57,67,69,73] Forty-five per cent of studies were judged to be at high risk of performance bias.[57,67,69–71] Thirty-six per cent of RCTs were judged to be at high risk of attrition bias,[56,57,67,70] with 27% of RCTs also judged at unclear risk for this domain.[55,68,72] Most of the included RCTs were at unclear risk of other bias (64%).[56,57,67–69,72,73] *Figure 3* shows the assessments across studies for each domain.

Random sequence generation

One included study[67] was assessed as being at high risk of bias for random sequence generation. Five studies[54–57,72] did not provide enough detail about their method of randomisation and so were assessed as unclear risk of bias. Five studies[53,68–71] were assessed as being at low risk of bias for this domain.

Allocation concealment

One included study[71] was rated as being at high risk of bias for allocation concealment. Five studies[54,55,57,67,72] were rated as unclear. Five studies[53,56,68,69,74] were assessed as being at low risk of bias for this domain.

Blinding of participants and personnel

Five included studies[57,67,69–71] were judged to be at high risk of bias for this. Four[53,56,68,72] were assessed as being at unclear risk of bias, mainly because the methods of blinding were not clearly reported. Two studies[54,55] were assessed as being at low risk of bias for this domain.

Blinding of outcome assessment

One study[70] was deemed to be at high risk of bias for this domain. Five included studies[56,67,69,71,72] were judged to be at an unclear risk of bias. Five studies[53–55,57,68] were assessed as being at low risk of bias for this domain.

Incomplete outcome data

Four included studies[56,57,67,70] were deemed to be at high risk of attrition bias. Three studies[55,68,72] were judged to be at unclear risk of bias for this domain. Four studies[53,54,69,71] were assessed as being at low risk of bias for this domain.

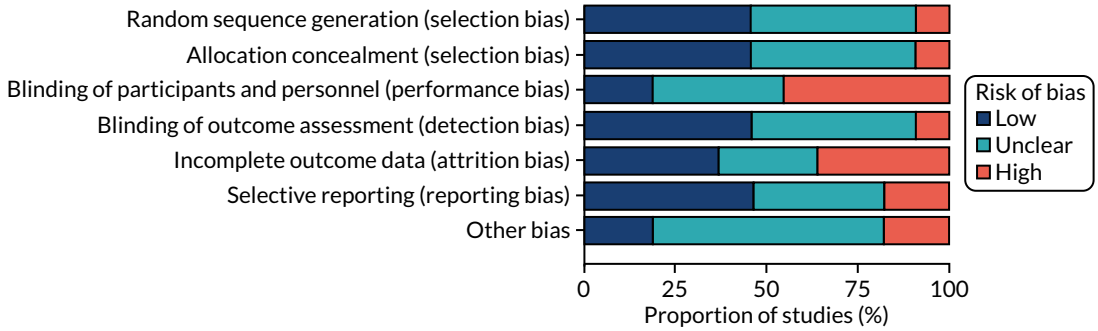


FIGURE 3 Risk-of-bias assessments across studies for each domain.

Selective reporting

Two studies[70,72] were judged to be at high risk of selective reporting bias. Four studies[54,56,68,71] were judged to be at unclear risk of bias. Five studies[53,55,57,67,69] were assessed as being at low risk of bias for this domain,

Other bias

Three included studies[67,70,71] were judged to be at high risk of other bias. Six studies[53,56,57,68,69,72] were assessed as unclear risk of bias. Two studies[54,55] were assessed as being at low risk of bias for this domain.

Summary of effectiveness results

Pairwise meta-analyses were undertaken to assess the effects of ONS compared with SC on the outcomes of interest in this review. Ten studies[53–57,67–69,71,74] were included in the pairwise meta-analyses (see *Appendix 10* for reasons why studies/outcomes were excluded from the meta-analysis). The meta-analysis results are presented alongside a narrative synthesis of the outcomes that were unable to be pooled. As fewer than 10 studies were incorporated into the meta-analyses for any outcome, it was not possible to use funnel plots and other tests for publication bias. Analysis was run using both final values and change of baseline. CFB analysis will be presented here (where possible); final value results are in *Appendices 11* and *12*.

The outcomes reported below are broadly split into three key categories, which correspond to the period over which the outcomes might be expected to induce a noticeable change. Nutritional intake outcomes and those that relate to visceral protein level (albumin) are presented first; these include total energy, protein and albumin. Following this, body composition outcomes are discussed (body weight, BMI, fat-free muscle mass, lean body mass). Then longer-term outcomes are reported (ADL, grip strength, hospitalisation, MNA, morbidity, mortality, QoL). Finally, other outcomes are narratively synthesised, including adverse events, reduction in falls and compliance. Owing to uncertainty in the duration of follow-up (and the small number of studies identified), meta-analysis was undertaken aggregating all follow-up time points together.

Nutritional intake outcomes

Six studies[53,55–57,67,70] reported data on the effect of ONS on nutritional intake outcomes. A meta-analysis was possible for energy and protein intake.

Energy (kcal) intake

Four studies reported data on the effect of ONS compared with SC on kilocalories (kcal) consumed for a CFB analysis; one[55] was undertaken in the community and three[56,57,67] were undertaken in care homes. All four studies[55–57,67] measured energy intake in kcal, which refers to the energy from food consumption. One study reported data on energy intake at final visit but no data were reported at CFB.[53] The mean and standard deviation could not be calculated as there were insufficient data. This study was not included in the CFB analysis.[53] The follow-up time point, where reported, varied between 6 weeks,[56] 90 days/3 months,[57] 16 weeks[55] and 60 days.[67] The pooled results of the meta-analysis (*Figure 4a*) show a positive effect of ONS versus SC on energy intake (SMD 1.02, $p = 0.002$, 95% CI 0.15 to 1.88). There was evidence of statistical heterogeneity ($p < 0.0001$, I^2=87%). A sensitivity analysis could not be run as there were no adequately randomised studies. GRADE scores showed very low-quality evidence for energy intake (see *Appendix 13*).

Protein intake

Four studies[55–57,70] reported data on the effect of ONS compared with SC on protein for a CFB analysis. One study[53] reported data on protein intake at final visit, but no data were reported on CFB. Insufficient data were reported in this study, and means and standard deviations at CFB could not be calculated.

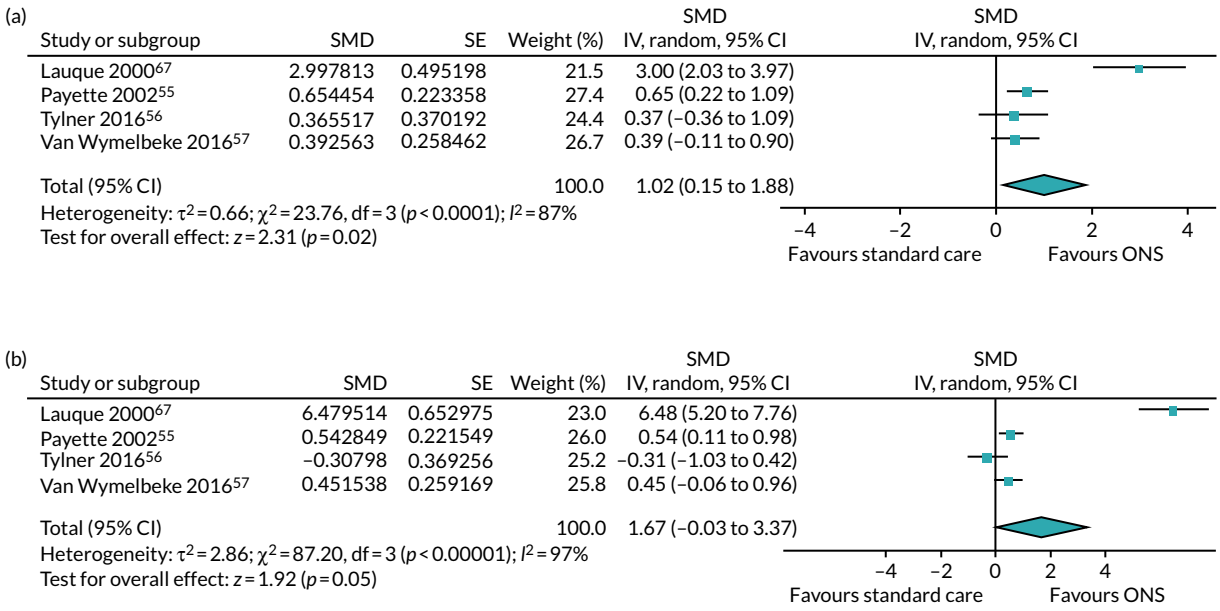


FIGURE 4 Forest plots of nutritional intake outcomes (CFB). (a) Energy intake; and (b) protein intake.

Two studies[55,56] measured protein intake in grams (g). Three studies measured total protein intake in grams per day (g/day),[55,56,67] while one study measured protein in g/kg.[57] The follow-up period varied: 6 weeks,[56] 60 days,[70] 90 days/3 months[57] or 16 weeks.[55] The pooled result (see *Figure 4b*) of the meta-analysis of CFB scores comprising all four studies shows a slightly positive effect of ONS versus SC on protein (SMD 1.67, $p = 0.05$, 95% CI −0.03 to 3.37). The data show a substantial degree of statistical heterogeneity ($p < 0.00001$, $I^2 = 97\%$). GRADE scores showed very low-quality evidence for protein intake (see *Appendix 13*).

Visceral protein level

Albumin

Five studies[54,56,57,70,71] reported data on the effect of ONS compared with SC on serum albumin, measured using the analysis of serum derived from fasting blood samples in grams per litre (g/l) for a CFB analysis. Two studies[70,71] were included in the sensitivity analysis as they had been adequately randomised. The meta-analysis results of the main analysis (*Figure 5*) show no evidence of effect of ONS versus SC on albumin (MD 1.48, $p = 0.13$, 95% CI −0.44 to 3.41). There was evidence of statistical heterogeneity ($p < 0.00001$, $I^2 = 95\%$). The pooled results of the sensitivity analysis show a slightly positive effect of ONS versus SC on serum albumin (MD 2.86, $p = 0.010$, 95% CI 0.69 to 5.03). There was moderate evidence of statistical heterogeneity ($p = 0.08$, $I^2 = 68\%$). GRADE scores showed very low-quality of evidence for albumin (see *Appendix 13*).

Body composition outcomes

Eight studies[53–57,69–71] reported data on the effect of ONS on change in body composition outcomes. A meta-analysis was possible for body weight, BMI and fat-free muscle mass.

Body weight

Five studies[54,56,69–71] reported appropriate data for inclusion in the meta-analysis of CFB scores between participants receiving ONS versus SC. Three studies[69–71] were included in the sensitivity analysis as they had been adequately randomised. The pooled results (*Figure 6a*) of the main meta-analysis comprising all five studies showed no evidence of effect of ONS versus SC on body weight CFB (MD 1.31, $p = 0.06$, 95% CI −0.05 to 2.66). Substantial statistical heterogeneity was found ($p = 0.004$, $I^2 = 74\%$) indicating a variation between sample estimates beyond what would be expected by chance

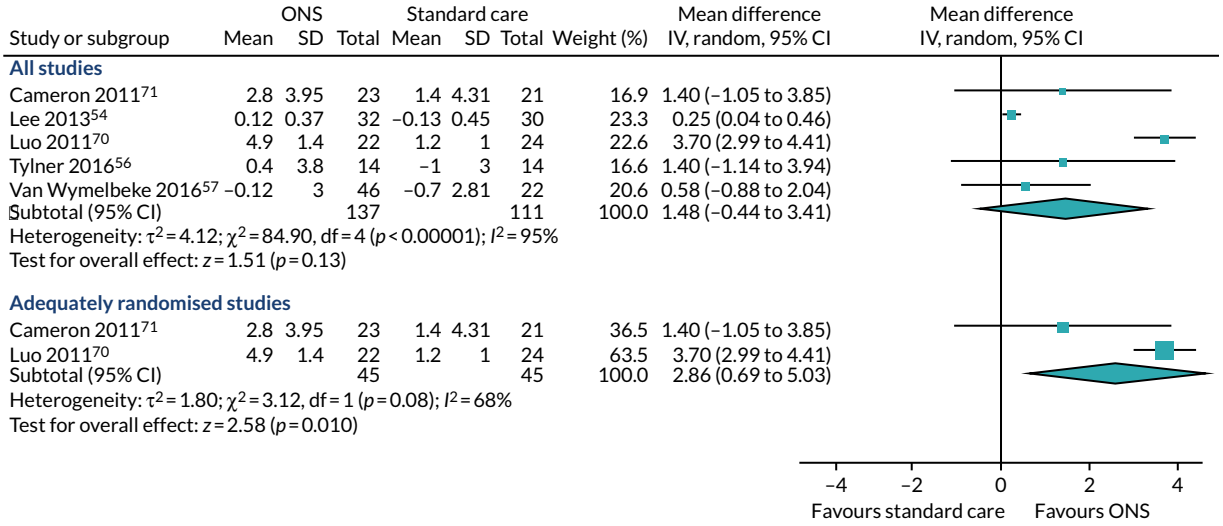
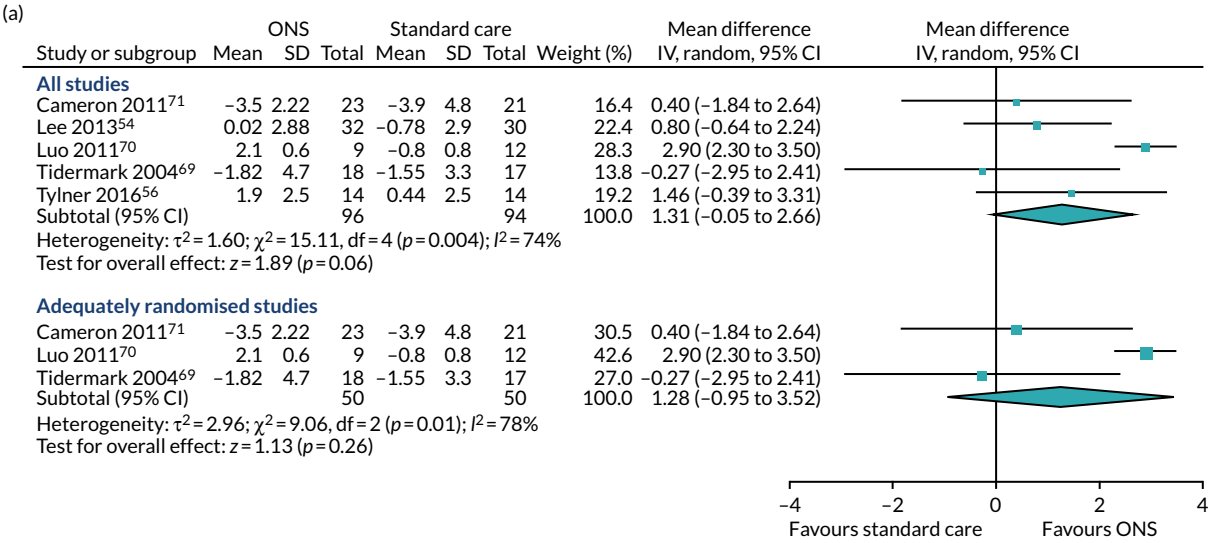


FIGURE 5 Forest plot of albumin levels (CFB).

(a)



(b)

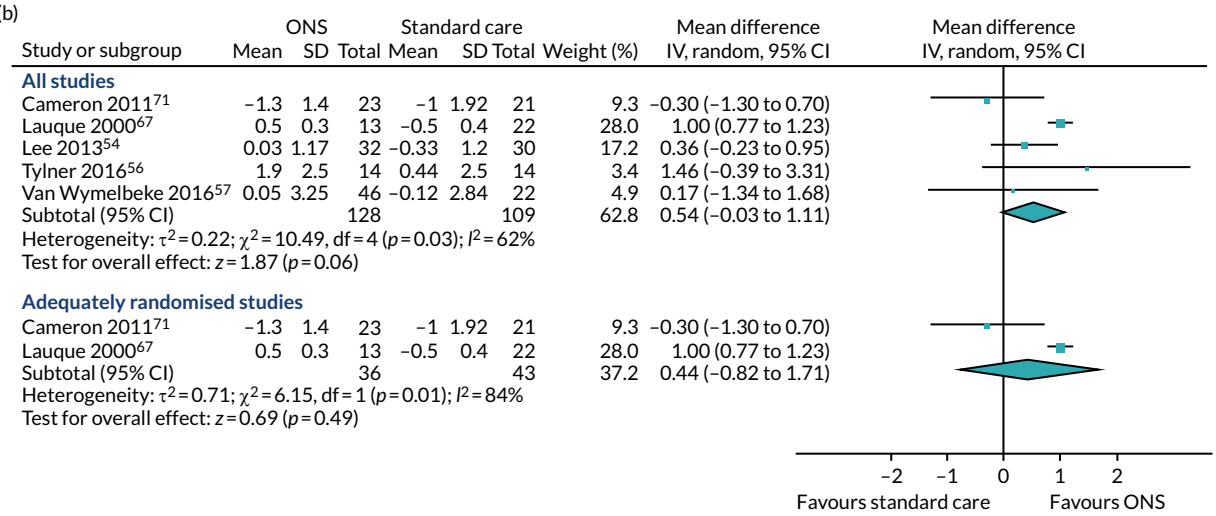


FIGURE 6 Forest plots of body weight and BMI body outcomes (CFB). (a) Body weight; and (b) BMI.

when samples are derived from the same population. Three studies[69–71] were included in the sensitivity analysis consisting of only adequately randomised studies. The pooled results (see *Figure 6a*) of the sensitivity analysis also indicate that there was no evidence of effect of ONS compared with SC on body weight (MD 1.28, $p = 0.26$, 95% CI −0.95 to 3.52). Similar to the main analysis, there was substantial heterogeneity ($p = 0.01$, $I^2 = 78\%$) indicating the presence of a variable confounding factor across the studies. GRADE scores showed very low-quality evidence for body weight (see *Appendix 13*).

Body mass index and proxy measures

Five studies[54,56,57,67,71] reported appropriate data for inclusion in the meta-analysis of CFB scores between participants receiving ONS and those receiving SC. Two studies[67,71] were included in the sensitivity analysis as they were adequately randomised. The pooled results (see *Figure 6b*) of the main meta-analysis comprising all five studies presented no evidence of effect of ONS compared with SC on BMI at CFB (MD 0.54, $p = 0.06$, 95% CI −0.03 to 1.11). There was evidence of statistical heterogeneity ($p = 0.03$, $I^2 = 62\%$). The pooled results of the sensitivity analysis indicate a mixed effect of ONS compared with SC on BMI (MD 0.44, $p = 0.54$, 95% CI −0.82 to 1.71). There was significant evidence of heterogeneity ($p = 0.01$, $I^2 = 84\%$), indicating that there may be a variable confounding factor across the studies. GRADE scores showed very low-quality evidence for BMI (see *Appendix 13*).

One study, by Lee *et al.*,[54] rated as being at unclear risk of bias for random sequence generation and allocation concealment, assessed the impact of ONS compared with SC on arm circumference, providing data at baseline and post intervention.[54] The authors reported a mean change in mid-arm circumference among people who were malnourished or at risk of malnutrition, at 24-week follow-up, of 0.3 cm in the intervention group and −0.8 cm in the control group. GRADE was unable to be assessed for arm circumference, as meta-analysis was not undertaken.

Fat free muscle mass

Three studies[54,55,69] reported data for the effect of ONS versus SC on fat-free muscle mass for a CFB analysis. Calf circumference and lean body mass were the outcomes used to measure fat-free muscle mass. A hierarchy of outcomes was applied, and calf circumference was chosen as the preferred outcome. Two studies[54,55] used calf circumference, measured in centimetres (cm), and one study[69] measured lean body mass in kilograms using dual energy X-ray absorptiometry.

As the studies used different outcome measures, a SMD was calculated using Hedges' *g* (adjusted) statistics (a measure of effect size) to standardise the different data across the three studies. Follow-up data were available for 12 weeks[54] to 16 weeks[55] and 12 months.[69] The pooled result (*Figure 7*) of the main meta-analysis of CFB scores comprising all three studies showed that the individual study estimates are inconsistent in the direction of effect (SMD 0.23, $p = 0.34$, 95% CI −0.24 to 0.69). There was evidence of heterogeneity in this analysis ($p = 0.09$, $I^2 = 58\%$). The evidence of this analysis shows that there is a variable confounding factor across studies. A sensitivity analysis could not be conducted as there were no adequately randomised studies. GRADE scores showed low-quality evidence for fat-free muscle mass (see *Appendix 13*).

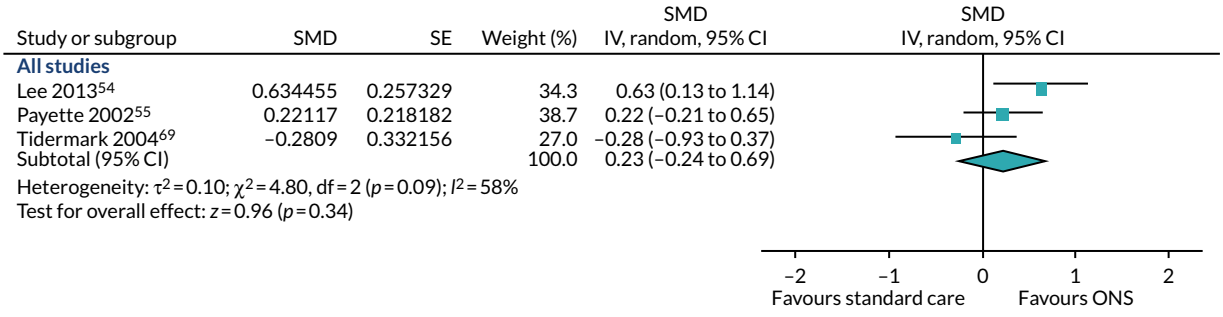


FIGURE 7 Forest plots of fat-free muscle mass (CFB).

Longer-term outcomes

Eight studies[53,56,57,67–71] reported data on the effect of ONS on longer-term outcomes related to malnutrition. A meta-analysis was possible for ADL, grip strength, MNA, mobility, hospitalisation and mortality. It was not possible to undertake a meta-analysis for outcomes on QoL; therefore, a narrative synthesis of the results for this outcome was undertaken.

Activities of daily living

Three studies[57,71,74] reported data on the effect of ONS compared with SC on ADL, which refers to the ability to perform everyday tasks (or 'activities of daily living') as a measure of disability or level of physical functioning. One study[71] measured ADL using the Barthel Index, which comprises 10 items in relation to which participants are assigned points, with a higher score indicating an increased ability to perform a task. Luo *et al.*[74] used a modified version of the Barthel Index. Van Wymelbeke *et al.*[57] used the Katz score for ADL,[57] and compared ADL in participants who received supplements, those who received an alternative dietary intervention (brioche) and those receiving SC. Data from the supplement and brioche groups were combined and compared with the SC group in the analyses presented here. Data from the longest follow-up time available from each study were used in the analyses presented here. This varied across the studies, from 90 days/3 months in Van Wymelbeke *et al.*[57] to 4 months in the study by Cameron *et al.*[71] and 24 days in the study by Luo *et al.*[74]

Post-intervention data were used for the meta-analysis, as CFB data could not be calculated for the study by Luo *et al.*[74] The pooled result of the main meta-analysis comprising all studies (*Figure 8a*) demonstrated no evidence of an effect of ONS compared with SC on ADL (SMD 0.30, $p = 0.55$; 95% CI −0.69 to 1.29).

A sensitivity analysis in which the study by Van Wymelbeke *et al.*,[57] which was not adequately randomised, was omitted also showed no evidence of an effect of ONS compared with SC on ADL (SMD 0.68, $p = 0.27$; 95% CI −0.54 to 1.90). Substantial heterogeneity was present in the main analysis ($I^2 = 89\%$) and in the sensitivity analysis ($I^2 = 88\%$). GRADE scores showed very low-quality evidence for ADL (see *Appendix 13*).

Grip strength

Seven studies[55–57,67–69,71] reported data on the effect of ONS compared with SC on grip strength. Five[56,57,67,69,71] of these reported data for a CFB meta-analysis. Each of these five studies reported data assessing handgrip strength, our primary outcome measure. Several instruments were used to

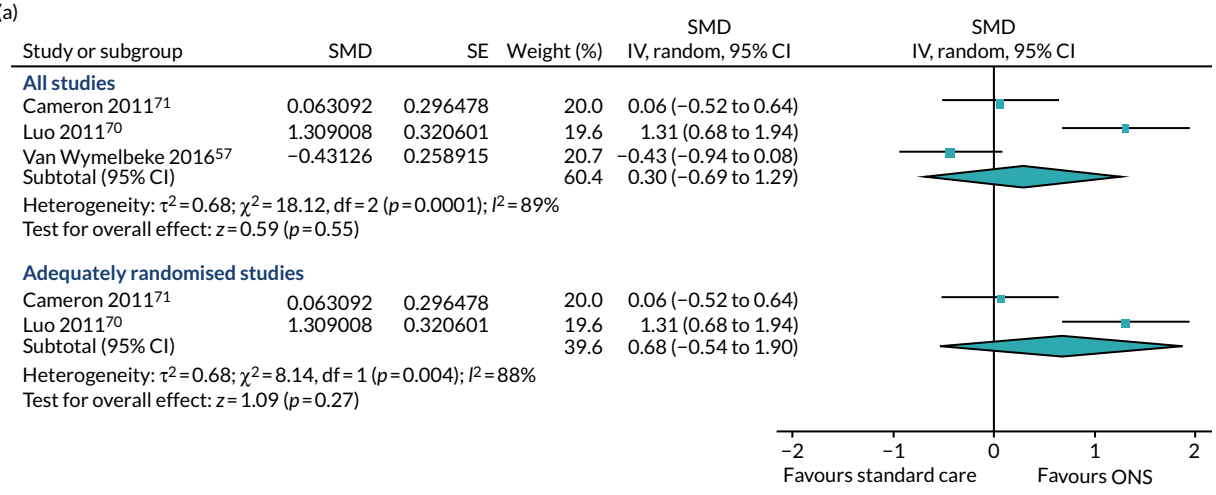


FIGURE 8 Forest plots of longer-term outcomes including (a) ADL (final values); (b) grip strength; and (c) hospitalisation (CFB). M–H, Mantel–Haenszel. (*continued*)

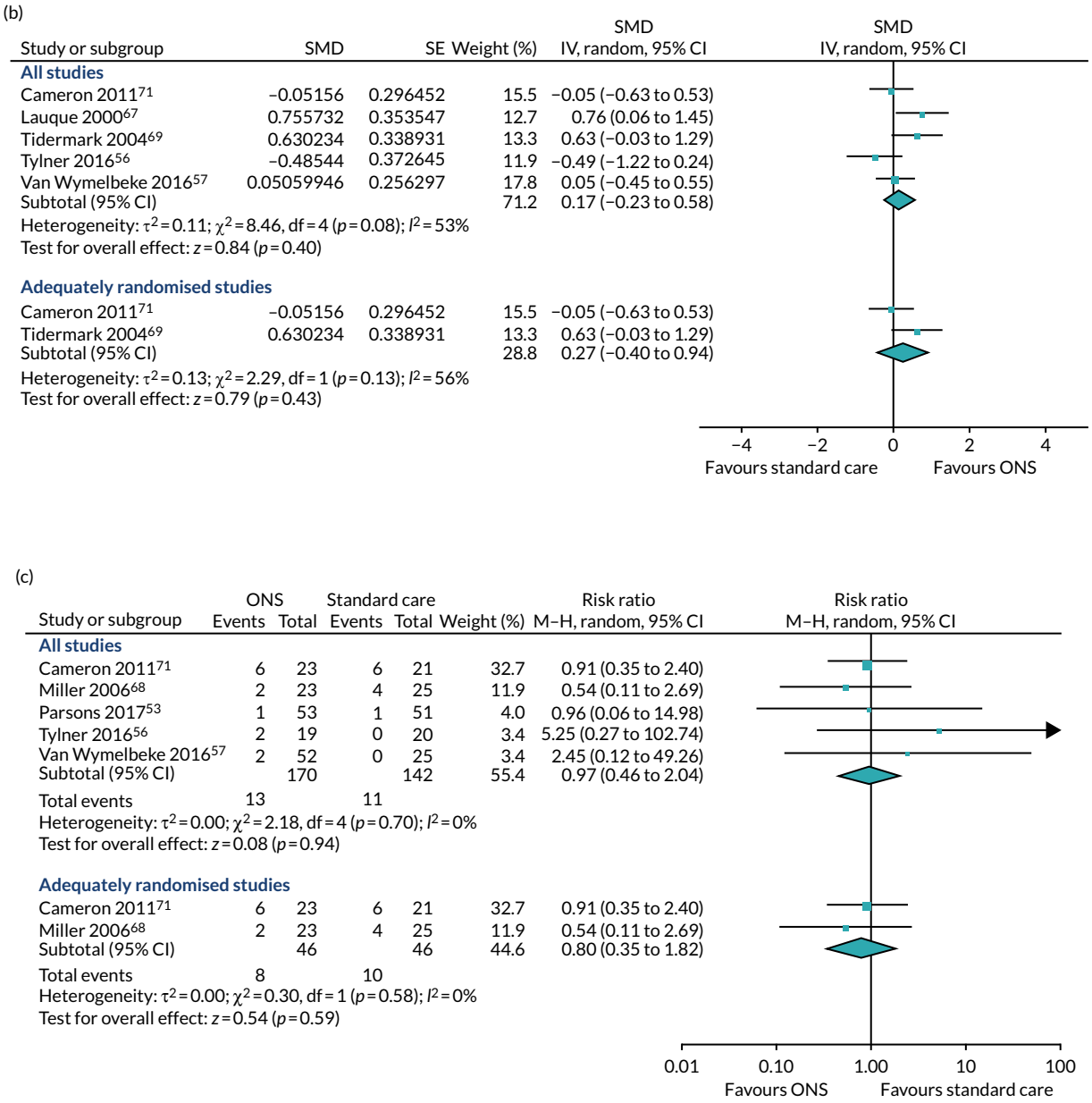


FIGURE 8 Forest plots of longer-term outcomes including (a) ADL (final values); (b) grip strength; and (c) hospitalisation (CFB). M–H, Mantel–Haenszel.

measure grip strength, including the Jamar Hydraulic Hand Dynamometer[57,71] and the Harpenden(R) dynamometer,[69] both of which use kilograms as measurement units; and the Martin vigorimeter,[56] which measures handgrip strength using kilopascal. Data from two trial arms (one in which participants were provided with ONS and the other in which participants were given brioche) were combined and compared with the SC arm for the study by Van Wymelbeke *et al.*[57] In the study by Lauque *et al.*,[67] data were compared between participants who were at risk of malnutrition and received either ONS or SC. The longest follow-up time points across the five studies ranged from 3 to 12 months. The results of the pooled meta-analysis (see *Figure 8b*) comprising studies using CFB data indicated no evidence of an effect of ONS compared with SC on grip strength (SMD 0.17, $p = 0.40$; 95% CI −0.23 to 0.58). There was also no evidence of a difference for studies with adequate randomisation (SMD 0.27, $p = 0.43$; 95% CI −0.40 to 0.94). Substantial statistical heterogeneity was found in both analyses ($I^2 > 50\%$), possibly reflecting variation in the follow-up times between studies.

Two studies were not included in the pairwise meta-analyses for this outcome (see *Appendix 10*). One of these studies from which data could be extracted[68] reported an improvement in quadriceps strength (measured in kg using the Nicholas Manual Muscle Tester) among ONS recipients compared with people receiving SC when this was assessed on a non-injured limb (mean CFB scores were 6.5 in the ONS group and 4.8 in the SC group) but not when injured limbs were assessed (mean CFB scores were 2.3 in the ONS group and 2.7 in the SC group). GRADE scores showed very low-quality evidence for grip strength (see *Appendix 13*).

Hospitalisation

Five studies[53,56,57,68,71] considered the impact of ONS on hospitalisation. All five reported data that were suitable for inclusion in the meta-analysis comparing ONS with SC on the number of hospital readmissions,[68,71] our preferred measure, or admissions.[56,57] Van Wymelbeke *et al.*[57] compared hospital admissions between participants who received supplements, brioche or SC. The brioche and SC groups were combined into one intervention arm for the analyses presented here. Follow-up time points, where reported, varied from 6 weeks[56] to 90 days/3 months.[57] Only two studies[68,71] had been adequately randomised. The pooled result of the main value meta-analysis (see *Figure 8c*) comprising all five studies showed no evidence of an effect of ONS on hospitalisation (RR 0.97, $p = 0.94$, 95% CI 0.46 to 2.04). The pooled result of the sensitivity analysis of adequately randomised studies also showed no evidence of an effect of ONS on hospitalisation (RR 0.80, $p = 0.59$; 95% CI 0.35 to 1.82). Heterogeneity was not detected in either the main or the sensitivity analysis ($I^2 = 0\%$). GRADE scores showed very low-quality evidence for hospitalisation (see *Appendix 13*).

Change in malnutrition

Two studies[57,67] reported data for the effect of ONS compared with SC on MNA score, a validated screening tool for the assessment of malnutrition risk. A higher MNA score indicates that a person has a better nutritional status. Both studies reported appropriate data for inclusion in the meta-analysis of post-intervention scores between participants receiving ONS and those receiving SC (*Figure 9a*).

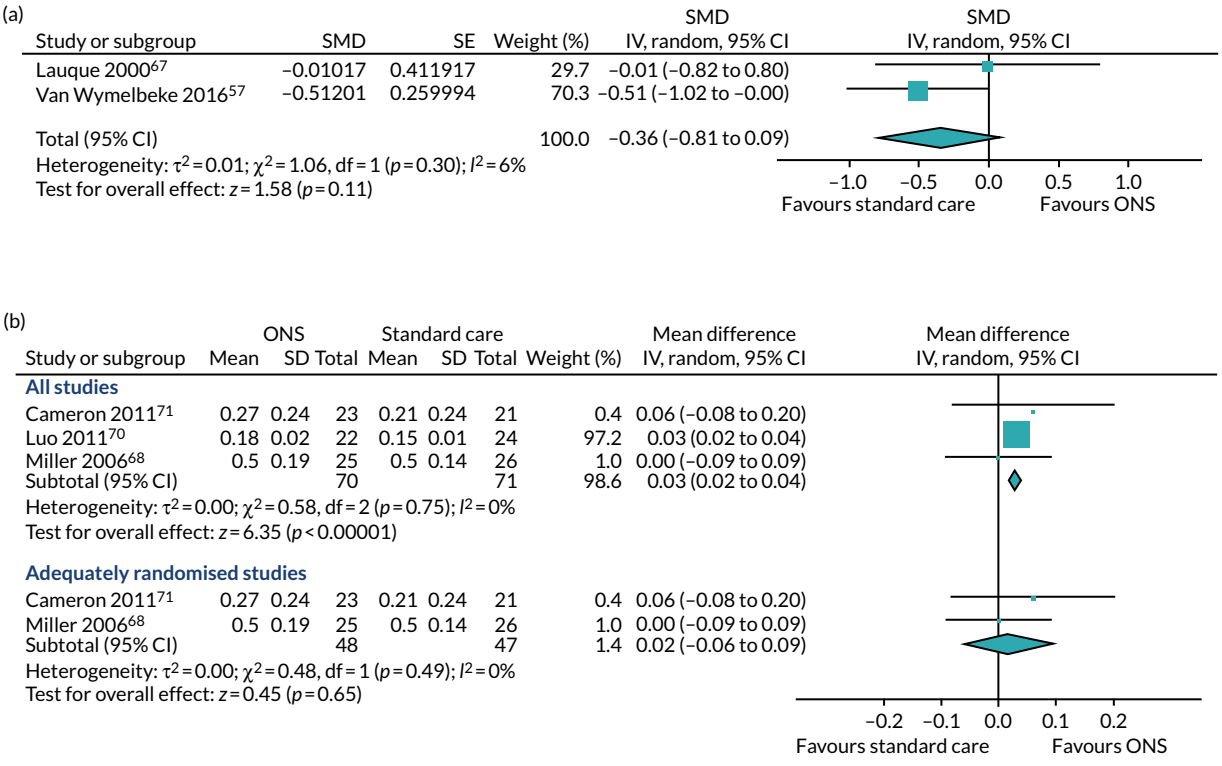


FIGURE 9 Forest plots of longer-term outcomes including (a) MNA (CFB); (b) mobility; and (c) mortality (final values). M–H, Mantel–Haenszel. (*continued*)

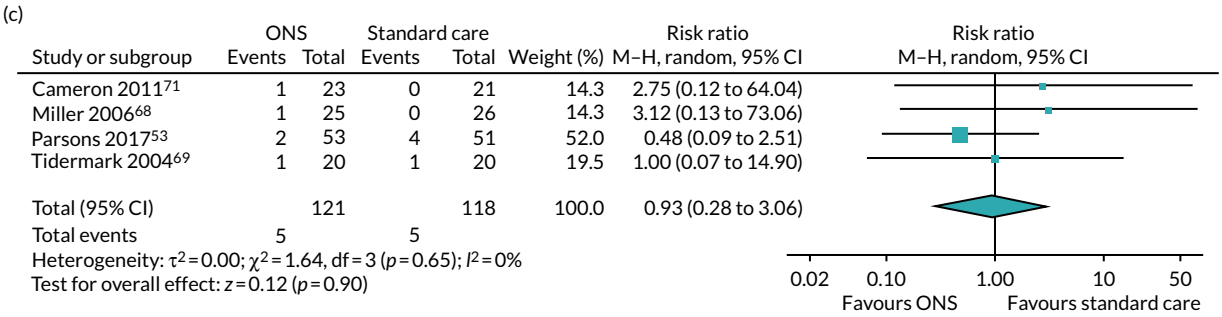


FIGURE 9 Forest plots of longer-term outcomes including (a) MNA (CFB); (b) mobility; and (c) mortality (final values). M–H, Mantel–Haenszel.

A CFB analysis could not be performed, as one of the studies[67] did not report baseline data that are required to calculate CFB scores. The 18-item MNA score was the outcome measure used in both studies.[57,67] Van Wymelbeke *et al.*[57] assessed MNA at 90 days/12 weeks, whereas Lauque *et al.*[67] assessed MNA at 60 days/8 weeks. The pooled results of the meta-analysis of post-intervention data provided no evidence of an effect of ONS compared with SC on MNA (SMD −0.36, $p = 0.11$, 95% CI −0.81 to 0.09). Low heterogeneity was detected between the studies ($I^2 = 6\%$). Neither Van Wymelbeke *et al.*[57] nor Lauque *et al.*[67] was adequately randomised; therefore, a sensitivity analysis was not undertaken. GRADE scores showed very low-quality evidence for change in malnutrition (see *Appendix 13*).

Mobility

Three studies[68,71,74] reported data for the effect of ONS compared with SC on mobility, assessed using gait speed (in m/second) in two studies,[68,71] albeit over different distances, and pace (in seconds/m in one study).[74] The data from the study that measured mobility using pace were converted to speed by dividing the number of metres walked by the average time taken. This ensured that all studies used the same outcome measure, with a larger number indicating a positive outcome, and that MD could be used for the analyses. All three studies were included in the meta-analysis, which analysed post-intervention (final value) scores as CFB data were unavailable. The longest follow-up time points were 4 months in Cameron *et al.*,[71] 12 weeks in Miller *et al.*[68] and 24 days in Luo *et al.*[74] The pooled results of the main meta-analysis indicated a positive effect of ONS compared with SC (MD 0.03), which was statistically significant ($p < 0.00001$, 95% CI 0.02 to 0.04) (see *Figure 9b*). The results of a sensitivity analysis, including two adequately randomised studies,[68,71] demonstrated no evidence of an effect of ONS versus SC on mobility (MD 0.02, $p = 0.65$, 95% CI −0.06 to 0.09). Statistical heterogeneity was not detected in the main or sensitivity analyses ($I^2 = 0\%$). GRADE scores showed very low-quality evidence for mobility (see *Appendix 13*).

Mortality

Four studies[53,68,69,71] assessed the effects of ONS on mortality and reported data that were suitable for inclusion in the pairwise meta-analysis (see *Figure 9c*) using final value analysis. Follow-up time points, where reported, varied from 12 weeks[53,68] to 4 months[71] (follow-up time was not reported in one of the studies[69]). All four studies had been adequately randomised and, therefore, a sensitivity analysis was not undertaken. The pooled result of the meta-analysis showed no evidence of an effect of ONS on mortality (RR 0.93, $p = 0.90$, 95% CI 0.28 to 3.06). There was no evidence of statistical heterogeneity ($I^2 = 0\%$). GRADE scores showed very low-quality evidence for mortality (see *Appendix 13*).

Quality of life

Four studies[55,68,72,73] reported on the effect of ONS on QoL; two[72,73] reported overall QoL scores, and two[55,68] reported data from psychological and physical subdomains of quality-of-life tools. Tidermark *et al.*[69] measured QoL using the EuroQol-5 Dimensions (EQ-5D) but reported only baseline data and so this study is not discussed here further. The results across the four studies reporting on the impact of ONS on overall quality-of-life and physical function domains were mixed,[53,55,68,72] although one[68] out of

two studies[55,68] reported a positive effect of ONS on psychological aspects of QoL compared with SC. It was not possible to undertake pairwise meta-analysis using the data from studies reporting overall QoL scores, as none of the studies reported suitable data (see *Appendix 10*). The reasons varied between studies and included lack of SC group[53,68,72,73] and lack of data on comparable QoL tools and domains between studies.[55,68]

Parsons *et al.*[53] compared EQ-5D scores between participants who received ONS and those who received dietary advice (not SC).[53] Their analysis demonstrated higher post-intervention QoL scores, assessed using the EQ-5D time trade-off (TTO) valuation technique and the EQ-5D VAS rescaled tool, among recipients of ONS than among those who received dietary advice. Intention-to-treat (ITT) analysis at week 12 for the ONS and dietary advice groups were 0.496 and 0.364, respectively, on the EQ-5D TTO measure, and 0.535 and 0.457 on the VAS rescaled tool. Mean post-intervention scores from the ITT analysis were higher (indicating increased QoL) among participants who received ONS (mean post-intervention EQ-5D score of 67.4) than among those who received dietary advice (mean post-intervention EQ-5D score of 57.3). Parsons *et al.*[53] also compared overall QoL between participants who received ONS and those who received dietary advice using the EQ-5D TTO valuation technique.[53] Based on ITT analysis, QoL was significantly higher in the ONS than in the dietary advice group at the 12-week follow-up [EQ-5D TTO scores (mean $\pm$ SE) were 0.50 ± 0.04 vs. 0.36 ± 0.05 for the ONS and dietary advice groups, respectively ($p = 0.005$)]. Otten *et al.*[72] compared QoL before and after ONS using the EuroQol visual analogue scale (EQ-VAS). CFB data indicated a mean increase in QoL of 10.8 points among ONS recipients after 3 months.

For the studies that reported data on the subdomains of QoL tools, it was not possible to carry out meta-analysis owing to a lack of at least two studies reporting comparable data (pertaining to psychological or physical aspects of QoL) that compared ONS with SC and reported mean and SD values at CFB or post intervention. With regard to psychological aspects of QoL, Payette *et al.*[55] reported data for the emotional role functioning domain of the 36-item Short Form Survey (SF-36) that showed that the ONS group had a higher post-intervention mean score (better QoL) (84.1, SD 31.4) than the control group (75.4, SD 35.8). Using the mental component score of the 12-item Short Form Survey (SF-12), Miller *et al.*[68] reported data indicating that participants who received ONS alone had higher (better) scores (post intervention mean 51.4) than those who received exercise (post-intervention mean 51.3), nutrition plus exercise (post-intervention mean 49.8) or SC (post-intervention mean 49.5).

In relation to physical aspects of QoL, Payette *et al.*[55] reported that, for the physical role functioning domain of the SF-36, mean post-intervention scores were lower among ONS recipients (63.1, SD 35) than among the SC group (69.5, SD 37.7). Miller *et al.*[68] reported a higher post-intervention mean score for the physical domain of the SF-12 among ONS recipients (post-intervention mean 31.6) than among those who received an exercise intervention (post-intervention mean 31.5), SC (post-intervention mean 30.1) and ONS plus exercise (post-intervention mean 26.9). GRADE was not assessed for QoL as no meta-analysis was undertaken.

Other outcomes

Reduction in infections

Only one study[69] reported on reduction in infections. In this study, at 12 months, deep infections engaging the hip joints were not reported in either the group receiving protein-rich supplementation alone or in the group receiving the protein-rich supplementation and nandrolone injection but were reported by 2 out of 17 participants in the control group. Finally, urinary tract infections were seen in 3 out of 18 participants in the protein-rich supplementation alone group, 5 out of 17 participants in the protein-rich supplementation plus nandrolone injection group and 3 out of 17 participants in the control group. This study had a low risk of bias across four of the seven domains reported in the risk-of-bias assessment. GRADE was not assessed for reduction in infections as no meta-analysis was undertaken.

Adverse events

Three studies[56,71,74] reported on adverse events, serious adverse events or withdrawals from treatment. Cameron *et al.*[71] stated that 5 out of 23 participants in the intervention group experienced one or more adverse event, compared with 8 out of 21 in the control group. In the study by Tylner *et al.*,[56] 1 out of 20 participants in the intervention-first group experienced gastrointestinal symptoms at 6 weeks, compared with 2 out of 19 in the control-first group. Luo *et al.*[74] reported that at 24 days there were 20 adverse effects in the intervention group compared with 24 in the control group. In the intervention arm of that study, 2 out of 22 participants experienced nausea or pruiritis as a result of taking ONS. Cameron *et al.*[71] reported that three participants (13%) in the intervention group withdrew from treatment. GRADE was not assessed for adverse events as no meta-analysis was undertaken.

Other outcomes not found in the review

Improvement in frailty, morbidity and wound healing and a reduction in falls and admission to long-term care were possible outcomes in the protocol, but no evidence for these was found in the included primary studies. GRADE was not undertaken for these outcomes. Change in frailty status was identified as an outcome of interest, but as no evidence was found it was not possible to assess this.

Summary table of meta-analyses

A complete list of all meta-analysis results for all outcomes is displayed in *Table 3*.

TABLE 3 Meta-analysis results for all studies and those adequately randomised

	All studies			Studies with adequate randomisation		
Outcome (units)	***n***	**Statistic**	**Result (95% CI)**	***n***	**Statistic**	**Result (95% CI)**
Consumption outcomes						
Energy (kcal/day)/(kcal/kg)	4	SMD	1.02 (0.15 to 1.88)[a,b]	NA	SMD	NA
Protein (g/d)/(g/kg)	4	SMD	1.67 (–0.33 to 3.37)[a]	NA	SMD	NA
Body outcomes						
Body weight (kg)	5	MD	1.31 (–0.05 to 2.66)[a]	3	MD	1.28 (–0.95 to 3.52)[a]
BMI (kg/m^2)	5	MD	0.54 (–0.03 to 1.11)[a]	2	MD	0.44 (–0.82 to 1.71)[a]
Albumin (g/l)	5	MD	1.48 (–0.44 to 3.41)[a]	2	MD	2.86 (0.69 to 5.03)[a,b]
Fat-free muscle mass (CC cm)/(kg)	3	SMD	0.23 (–0.24 to 0.69)[a]	NA	SMD	NA
MNA scores	2	SMD	–0.36 (–0.81 to 0.09)[c]	NA	MNA score	NA
Clinical events						
Wound healing	NA	NA	NA	NA	NA	NA
Infections	NA	NA	NA	NA	NA	NA
Falls	NA	NA	NA	NA	NA	NA
Hospitalisation (number/rates)	5	RR	0.97 (0.46 to 2.04)[a]	2	RR	0.8 (0.35 to 1.82)[a]
Longer-term outcomes						
ADL (scores)	3	SMD	0.30 (–0.69 to 1.29)[a]	2	SMD	0.68 (–0.54 to 1.90)[a]
Mobility (m/second)	3	MD	0.03 (0.02 to 0.04)[a,b]	2	MD	0.02 (–0.06 to 0.09)[a]
Grip strength (kg)/(kg W)/(kPa)	5	SMD	0.17 (–0.23 to 0.58)[a]	2	SMD	0.27 (–0.40 to 0.94)[a]
QoL (scores)	NA	NA	NA	NA	NA	NA
Mortality (number/rates)	4	RR	0.93 (0.28 to 3.06)[c]	NA	NA	NA

CC, calf circumference; MNA, Mini-nutritional Assessment score; NA, not applicable; RR, relative risk.
a Indicates favourable effect of ONS.
b Indicates a statistically significant effect.
c Indicates favourable effect of SC.

Network meta-analysis results

There was a connected network with at least three studies reporting effectiveness for the same comparison for two outcomes: body weight and grip strength. Six studies[54,56,67,69,71,74] were included in the body weight analysis and five studies[56,57,67,69,71] were included in the grip strength analysis. The effect estimates for ONS and other interventions compared with SC are reported in *Table 4*. The number of studies with evidence for each comparison is reported. The network diagrams are reported in *Appendix 4*. The estimates for ONS compared with SC from the meta-analyses are reported for comparison. The estimates of the between-study variance (τ^2) from the NMAs and the meta-analyses are also reported for comparison. The probability that each intervention is the most effective is also reported. Values of < 0.7 represent very high uncertainty that the intervention is the most effective. There was convergence for all estimates.

There is evidence of a difference in effect between ONS and SC for the body weight analysis (1.67, 95% CI 0.12 to 2.93). The NMA confidence intervals for the effect of each outcome were wider than those estimated in the meta-analyses because of greater estimates of the between-study variance. The estimated τ^2 from the NMAs is greater than the estimate from the meta-analyses in both analyses, but there is a greater difference in the grip analysis, for which there are fewer than six studies comparing ONS with SC. The estimated τ^2 values are particularly high in the grip strength analysis. This is because there are few studies with which to estimate τ^2. Although the estimates of τ^2 are plausible, it is suspected that they are overestimates when fewer than six studies are in the analysis.

Adherence and acceptability

In addition to the effectiveness outcomes detailed above, we looked for specific evidence regarding factors that may affect adherence to and acceptability of ONS. Specifically, we looked for research detailing barriers and facilitators, determinants and active components that may aid understanding about why some interventions may be more (or less) effective for certain groups of people. Although an inclusive search strategy was used, little relevant information was found in the included studies. The limited information that was collated was derived from the studies included in the effectiveness review. Typically, the data presented, particularly those detailing the acceptability of the ONS, were not assessed through qualitative research methods with patients/health-care professionals but were instead derived from informal observations by the research team. The results are summarised below.

Compliance with ONS was reported in seven studies.[55,57,67,68,70,71] In two studies,[67,69] data regarding compliance were reported narratively in brief with no supporting data, making it difficult to draw any firm conclusions about how well participants adhered to ONS. Lauque *et al.*[67] reported 'good' compliance

TABLE 4 Results from network meta-analysis comparing ONS with other comparators reported for BMI, body weight and fat-free body mass

	Body weight (kg)			Grip strength (SMD)		
Comparator	***n***	**Mean (95% CrI)**	***p*(best)**	***n***	**Mean (95% CrI)**	***p*(best)**
ONS	NA	NA	0.68	NA	NA	0.38
SC	6	1.67 (0.12 to 2.93)	0.01	5	0.17 (−0.41 to 0.77)	0.11
ONS + steroid	1	1.05 (−1.99 to 4.10)	0.32	1	0.22 (−0.94 to 1.40)	0.51
τ^2		1.73 (0.11 to 7.23)			0.21 (0.00 to 1.24)	
[a]SC (pairwise)		1.35 (0.34 to 2.36)			0.11 (−0.23 to 0.58)	
[a]τ^2 (pairwise)		1.57			0.11	

CrI, credible interval; *n*, the number of studies with evidence for that comparison; NA, not applicable.
a Estimates from the meta-analyses.

among those at risk of malnourishment who received ONS and those who were malnourished who received ONS but did not give further details. Tidermark *et al.*[69] measured only compliance with nandrolone injections and not with ONS.

Across the remaining studies,[55,57,67,68,70,71] the methods of measuring and reporting compliance were heterogeneous. The lowest level of compliance with ONS was reported in the study by Payette *et al.*,[55] who assessed adherence in accordance with the number of remaining 250 ml cans of supplement and a mean increase in total energy intake of $\geq$ 250 kcal per day over the study period. In this study, 23 out of 42 participants (54.8%) were noted to be compliant at 16 weeks. The highest compliance was reported by Miller *et al.*[68] In this study, 76% of 25 participants in the nutrition -only group adhered to the prescribed volume of nutritional supplement, compared with 66% of 24 participants in the ONS plus exercise group. It may be possible that the differences in compliance between these two studies are related to their setting: Payette *et al.*[55] was community based, whereas Miller *et al.*[68] was set in the orthopaedic ward of a hospital. Luo *et al.*[70] reported that 91–100% of 22 participants in the intervention group consumed their recommended intake of ONS. Van Wymelbeke *et al.*[57] was the only included study in which it was possible to directly compare compliance with ONS and compliance with another intervention. The study reported that, at 90 days, 74% of 17 participants were consuming all ONS, compared with 83% of 29 participants consuming all the brioche provided.

The precise nature of the interventions included in the effectiveness review was examined closely to understand how the delivery of the intervention may affect its effectiveness. The consistency of reporting on these active components varied across studies. *Figure 10* visually displays this information as a rose plot in which the numbers of studies reporting compliance and the energy intake, flavour and frequency of the ONS are shown in blue. Seven studies[53–57,68,70] reported frequency of ONS consumption. Five studies[53,55–57,67] reported the flavour of ONS. The flavours reported were both sweet and savoury, with strawberry the most common flavour available across all five of the studies.[53,55–57,67] The impact of ONS flavour was not linked with adherence in these five studies. Eight studies[53–57,67,70,71] reported the energy intake of the ONS they provided.

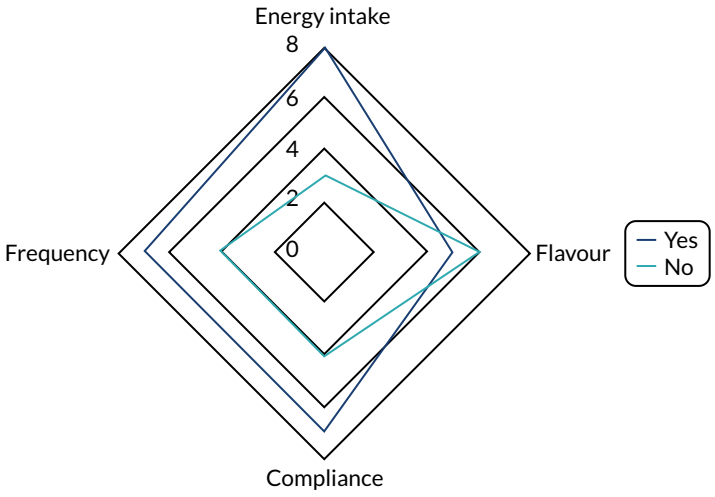


FIGURE 10 Chart showing the level of reporting of various comparators in studies.

Chapter 4 Results of cost-effectiveness review

Characteristics of included studies

One study[23] was included in the systematic review of full economic evaluations. This section reviews that study. *Tables 5* and *6* present the key study characteristics and results of the study. *Appendix 14* details the reasons for excluding studies from the cost-effectiveness review.

Comparators and setting

Elia *et al.*[23] conducted a cost-effectiveness analysis of ONS. The intervention was described as written and verbal dietary advice. The setting was care homes – roughly half were nursing homes and half were residential homes – and the study was based in the UK.[23] It was not stated if the care homes were privately or publicly owned.

Outcomes and evidence

The measure of benefit in Elia *et al.*[23] was the QALY. The clinical outcome and resource use evidence came from a single RCT. The follow-up period was 12–13 weeks. An individual patient analysis of clinical study data was conducted.[23] The time horizon of the economic analysis matched the follow-up period of the clinical study. No study perspective was reported; however, it did include costs consistent with the NHS and Personal Social Services (PSS) perspective in the UK.[23]

The resource use included in the cost analysis of outcomes and sources of unit costs is reported in *Table 6*. Hospital inpatient and outpatient, community nursing, nursing home and respiratory care costs were included.[23] Data were collected from patient history and care home records.[23] None of the total intervention costs, the unit cost of ONS or the source of ONS unit cost data were reported,[23] but the currency was reported.

Analysis

A cost–utility analysis was conducted. Confidence ellipses were reported, as was the probability of being cost-effective statistics using both bootstrapping and central limit theorem methods.[23]

Reporting of results

The total cost of ONS per participant was reported. The incremental cost-effectiveness ratio was reported but the incremental costs and benefits were not.[23] The probability of being cost-effective was reported at different thresholds.[23]

Quality appraisal of included studies

The quality of the included studies was assessed using the BMJ checklist.[49] The completed checklist is reported in *Appendix 15*. Many of the study design features that would be expected in a well-conducted study were reported in Elia *et al.*[23] Overall, 30 out of 36 items were assessed as 'yes' or 'not applicable'. Items assessed as 'no' included lack of viewpoint and justification for alternatives. Unit costs were not reported, major outcomes were not presented in a disaggregated or aggregated form, and generalisability was not discussed.

TABLE 5 Key study characteristics and results of included study in the cost-effectiveness review

Study author, setting, country and study type[a]	Intervention and comparator	Effectiveness evidence	Follow-up period	Outcomes measured	Cost-effectiveness results
Elia *et al.*[23] 2017; care homes; UK; cost–utility analysis, single study; linked to effectiveness study (Parsons *et al.*[53])	*Intervention:* ONS *Comparator:* written and verbal dietary advice	RCT	12 weeks	QALYs (combination of QoL and mortality)	Incremental QALYs: ITT 0.0174;[b] CC 0.018[b] Incremental cost: ITT £190.50;[b] CC £217.40[b] (2016 prices) ICER: ITT £10,941/QALY; CC £11,875 (2016 prices) probability cost-effective: < £20,000/QALY: ITT 0.83, CC 0.80 (2016 prices) Uncertainty: low[c]

CC, complete case analysis; ITT, intention to treat.
a The cost–utility analysis/cost-effectiveness analysis classifications are those of the reviewers, not the study authors; single study: analysis based on outcomes as reported in a single clinical without extrapolation; model-based: analysis using clinical data from two or more clinical studies or extrapolating outcomes from a single clinical study.
b Reviewers calculated result from data reported in the study.
c Reviewers categorised uncertainty as low, moderate or high.

TABLE 6 Outcome resources costed in the included studies and the sources of unit costs

Study	Setting (perspective)	Country	Inpatient	Outpatient/A&E	Community nursing/GP	Nursing home	Specialist	Medication	Social services	Unit costs
Elia *et al.*[23] 2017	55% nursing home, 45% residential home (NHS and PSS[a])	UK	Yes	Yes	Yes	Yes	Respiratory	No	No	PSSRU

A&E, accident and emergency; GP, general practitioner; PSSRU, Personal Social Services Research Unit.
a The cost data used were consistent with these perspectives. The publications did not report these perspectives.

Summary of cost-effectiveness results

Summary results from Elia *et al.* are reported in *Table 5*. The study found that ONS was associated with greater benefit than the control. ONS was associated with greater QALYs and with higher cost.[23] ONS was cost-effective at a cost-effectiveness threshold of £20,000 per QALY (one of the cost-effectiveness thresholds used by the NICE) with a 0.83 probability.[23]

Chapter 5 Development of cost-effectiveness model

The objective of the economic analysis was to evaluate the cost-effectiveness of ONS compared with SC in the studies from the effectiveness review from the perspective of the NHS and PSS. The population was frail older adults in any setting (community, care home, hospital). In addition to ONS and SC, the interventions included in this analysis were those for which evidence of effectiveness on changing BMI was available compared with ONS. The interventions evaluated were ONS and SC.

The systematic review of full economic evaluations of ONS identified one trial-based economic evaluation (see *Chapter 4*). Although it was not included in the systematic review because the intervention did not meet the inclusion criteria, one study built a decision tree based on the results of the clinical trial.[76] This type of model design could be used to model the direct effect of ONS on longer-term outcomes such as hospitalisation, mortality and QoL. Most studies of ONS reported more immediate outcomes such as the effect on BMI. To use this evidence from the systematic review, a de novo model was developed to evaluate the cost-effectiveness of ONS based on BMI outcome evidence from the systematic review of effectiveness. As described below, the model used evidence from the systematic review on the effect of ONS on change in BMI and modelled the association between BMI and mortality, hospitalisation and EQ-5D.

A cost–utility analysis was conducted that was consistent with the NICE reference case.[77] The cost and QALY outcomes associated with hospitalisation were per episode that occurred over 1 year. The QALY outcomes associated with EQ-5D outcomes were assumed to be over 1 year. The QALY outcomes associated with mortality that occurred within 1 year were life expectancy-related QALYs. The mortality-related QALY outcomes were discounted at a rate of 3.5% per annum. Costs were in Great British pounds (GBP). The price year was 2020.

Model design

The effectiveness of ONS can be measured using a variety of outcomes, and the systematic review of effectiveness investigated many of these. Outcomes researched in the systematic review are presented in *Figure 11* in the sequence in which outcomes may occur. The cost-effectiveness of ONS depends on health-related QoL and health-care resource outcomes.

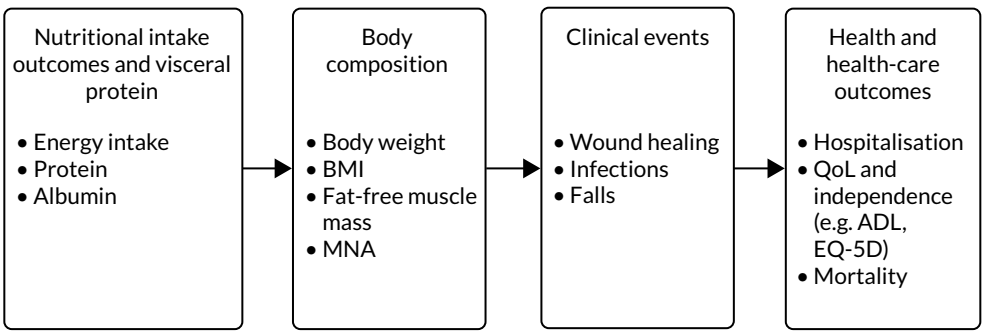


FIGURE 11 Outcomes related to ONS.

The evidence on outcomes identified in the systematic review was considered for use in two ways to evaluate the cost-effectiveness of ONS. First, the association between BMI and mortality, hospitalisation and EQ-5D was modelled, which was used to estimate the effect of ONS on these outcomes using the effectiveness estimate for ONS on BMI compared with SC and brioche from the systematic review. This approach enabled the cost–utility of ONS to be evaluated for patient cohorts with different BMI values at baseline. BMI was selected as the short-term outcome, as it is commonly used to study the relationship between health status and outcomes, and several included studies in the review reported on BMI using the same scale, meaning that the NMA could be conducted on the original scale. Second, a cost–utility analysis was planned for ONS compared with SC on mortality, hospitalisation and EQ-5D, using the effectiveness evidence from the systematic review. The analysis was to be conducted if there was evidence that ONS might be more effective than SC.

Approach 1 has its limitations. BMI is an imperfect measure of benefit from ONS consumption, as it masks gain in muscle mass versus fat mass, which is a limitation of using this outcome. More accurate measures of malnutrition, such as MNA or MUST scores, muscle mass or functional measures would have been more appropriate; however, these could not be used because of limited evidence from the effectiveness review and limited evidence for the association between MNA or MUST and outcomes such as mortality, hospitalisation and EQ-5D index utility. In addition, estimates of improved longer-term outcomes based on changes in BMI may underestimate the benefit from improved nutrition.

There is a non-linear relationship between BMI and mortality hazard, odds of hospitalisation and EQ-5D. The BMI of the model population is, therefore, very important in determining the cost-effectiveness of ONS. For the base-case analysis, a distribution of BMI values was generated from the data reported in the studies from the effectiveness review (*Figure 12*). As the cost-effectiveness of ONS can be expected to differ according to baseline BMI values, a number of analyses were conducted with a cohort population with a different baseline BMI value in each cohort.

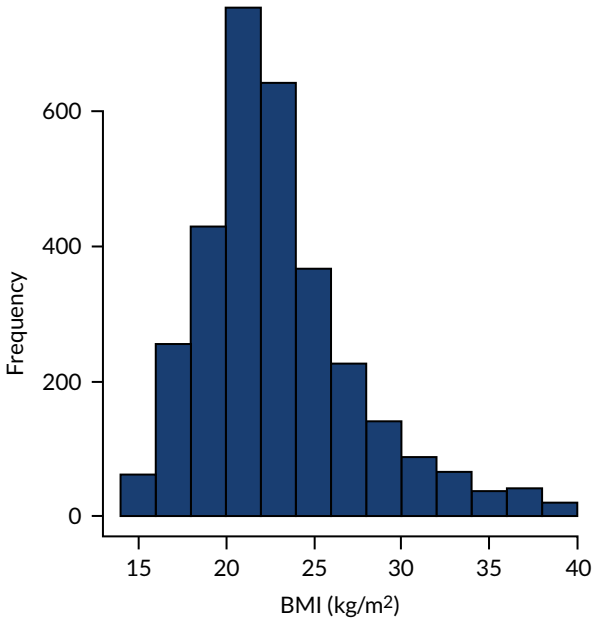


FIGURE 12 The base-case BMI distribution at baseline.

Association between body mass index and longer-term outcomes

A focused search of the literature was conducted to identify evidence of the association between BMI and mortality, hospitalisation and QoL, such as EQ-5D and ADL measures in the elderly. The focused search is described in *Appendix 16*. Only one study with appropriate evidence was found for each of the following outcomes: mortality, hospitalisation and EQ-5D. None of the economic evaluations identified in the review of economic evaluations reported statistics of the association between BMI and these outcomes. Details of these studies are presented in *Table 7*. The identification of only one study for each outcome meant that it was not possible to estimate the variation in BMI–outcome association that may be found across studies with different characteristics. The uncertainty associated with this could not be captured in the model. No studies estimating the association between BMI and ADL in the population of interest were identified.

Mortality

One study was found to provide appropriate evidence for the association between BMI and mortality.[78] The study was a prospective cohort study with a follow-up period of 1 year. The hazard ratio of mortality for each BMI category compared with the reference category is shown in *Table 8*. The hazard of mortality increases with very low BMI. There is the potential for bias here, as BMI at a certain follow-up time point in a study may not represent BMI status for the period used to estimate mortality risk, and there may be confounding factors. The hazard ratios were modelled on the log scale. In the economic model, linear interpolation was used to convert categorical estimates to hazard ratios for BMI on a continuous scale. A log-hazard ratio was sampled for each individual from the individual-specific normal distribution on the log scale, and this was transformed to the hazard ratio scale.

TABLE 7 Studies included for BMI–outcome association estimates

Study	Outcome	Statistic	Population
Nakazawa *et al.*[78]	Mortality	Hazard ratio	Nursing homes, mean age (SD) 84.3 (8.1) years, Japan
Ronneikko *et al.*[79]	Hospitalisation	Odds ratio	Home care clients (aged ≥ 63 years), Finland
Hunger *et al.*[80]	EQ-5D	Continuous (EQ-5D difference from mean by kg/m^2)	People aged ≥ 65 years, Germany

TABLE 8 Hazard ratio of mortality by BMI category

BMI (kg/m^2)	Hazard ratio of mortality (95% CI)	LN (hazard ratio)	LN (SE)
< 17.3	2.4 (1.9 to 3.1)	0.875	0.125
17.3–19.2	1.7 (1.3 to 2.3)	0.531	0.146
19.3–21.1	1.5 (1.2 to 2.0)	0.405	0.130
21.2–23.5	1.2 (0.9 to 1.6)	0.182	0.147
> 23.5	Reference category	–	–

The reference hazard of mortality was 0.0518 (0.05 probability over 1 year), taken from Nakazawa *et al.*[78] The hazard of mortality for each individual was calculated by multiplying the baseline hazard by the estimated hazard ratio for the individual. The probability of dying within the year was derived from the individual's hazard rate of dying using the formula:

$$prob_{die} = 1 - e^{-rate}. \quad (5)$$

The average life expectancy for a population aged 75–94 years was calculated using life tables from the Office for National Statistics;[81] this was 6.29 years.

It was assumed that the EQ-5D index scores for this population, if alive, would be the average in the general population for those aged > 75 years: 0.734.[82] The QALYs at this life expectancy were discounted at a rate of 3.5% per annum.

Hospitalisation

One study[79] was found to provide appropriate evidence for the association between BMI and unplanned hospitalisation. This was retrospective cohort study with a follow-up period of 1 year. The odds ratio of hospitalisation for each BMI category compared with the reference category is shown in *Table 9*. The odds of hospitalisation increase as BMI becomes lower. There is the potential for bias here, as BMI at a certain follow-up time point in a study may not represent BMI status for the period used to estimate hospitalisation risk, and there may be confounding factors. The odds ratios were modelled on the log scale. In the economic model, linear interpolation was used to convert categorical estimates to odds ratios for BMI on a continuous scale. A log-odds ratio was sampled for each individual from the individual-specific normal distribution on the log scale, and this was transformed to the odds ratio scale.

The reference probability of hospitalisation over 1 year, taken from Ronneikko *et al.*,[79] was 0.434. The relative risk of hospitalisation the year was derived from the odds ratio of hospitalisation and the reference probability ($risk_{base}$) using the formula:

$$RR = \frac{OR}{1 - risk_{base} \times (1 - OR)}. \quad (6)$$

The probability of hospitalisation for each individual was calculated by multiplying the baseline probability by the estimated relative risk for that individual.

A utility decrement of 0.706 for 2 weeks was assumed to be associated with hospitalisation. This was based on the following EQ-5D-3L dimension scores while in hospital: self-care (level 3), mobility (level 3), usual activities (level 3), pain (level 1) and anxiety (level 1). EQ-5D utility was subtracted from the mean for a ≥ 75 years population norm.[82]

A cost of £4455 was assumed to be incurred for an admission to hospital. This was the expected cost from the hip fracture non-elective codes HE11A:HE11H.[83]

TABLE 9 Odds ratio of unplanned hospitalisation by BMI category

BMI (kg/m^2)	Odds ratio of hospitalisation (95% CI)	ln (odds ratio)	ln (SE)
< 18.5	1.09 (0.94–1.27)	0.086	0.077
18.5–23.9	Reference category	–	–
24–29.9	0.85 (0.78–0.92)	–0.163	0.042
≥ 30.0	0.84 (0.76–0.93)	–0.174	0.051

EuroQol-5 Dimensions

One study[80] was found to provide appropriate evidence for the association between BMI and unplanned hospitalisation. The study was cross-sectional. The difference in the EQ-5D index from the mean was reported for many different levels of BMI. The 95% CIs were also reported. The data from the published figure were extracted using WebPlotDigitizer version 4.6 (Pacifica, CA, USA) and from the published figure were extracted using WebPlotDigitizer and are reproduced in *Figure 13*. Using linear interpolation, each individual was assigned an EQ-5D index (difference from mean) normal distribution with mean and standard error.

An increase in BMI is associated with different changes in BMI depending on the baseline BMI. These data are cross-sectional, and there may be some bias in estimating the change in EQ-5D associated with change in BMI from these data. This is particularly the case if the increase in BMI is associated with an increase in protein intake and the increase in weight is fat-free mass. The baseline BMI values assigned to the population in the analyses range from 17 to 23 kg/m^2, so change occurs in the upward part of the curve. Increased EQ-5D index utility due to increased BMI was assumed to persist for 1 year.

Effectiveness

No NMA was conducted for the BMI outcome. The effectiveness estimates used in the model were those derived from the BMI meta-analysis. In the base case, the results from all studies were included. Uncertainty in the estimates were modelled using a normal distribution.

Four out of the five studies with evidence for ONS were set in nursing homes, and the remaining study was set in a hospital. Sensitivity analysis using the effectiveness estimate from the meta-analysis included the adequately randomised trials only.

Intervention cost

The incremental cost of ONS compared with SC was calculated for each study included in the NMA of the BMI outcome. For all studies apart from Cameron *et al.*,[71] the cost of SC was assumed to be zero. For Cameron *et al.*,[71] SC was high-protein milk, which was costed as a sachet of MCTprocal® per day. Most studies stated the brand of ONS used in the study. The price of the specific product, or as close as possible, was found on online retail sites and in the *British National Formulary*.[84]

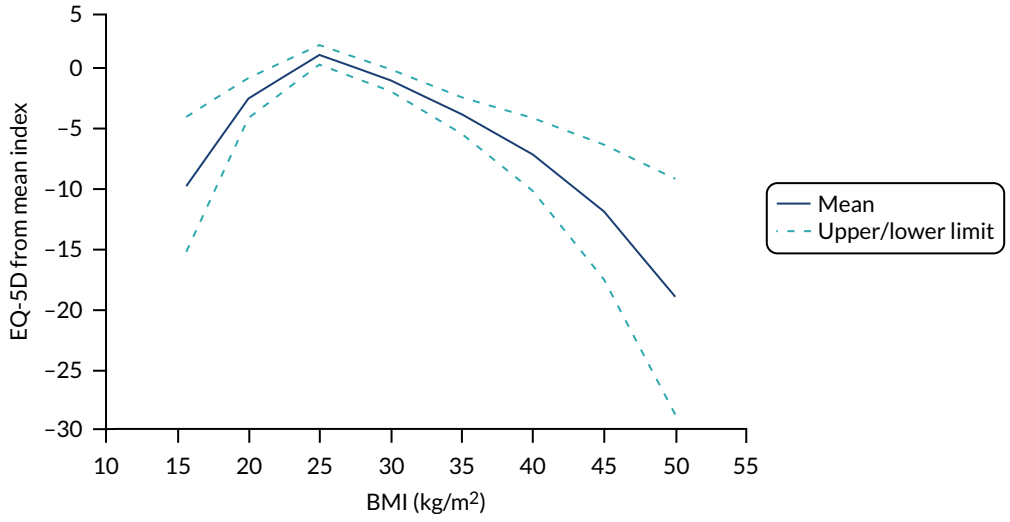


FIGURE 13 Association between BMI and EQ-5D from mean index. Derived from Hunger.[80]

The unit costs of each product identified are reported in *Table 10* along with the sources. The exchange rates used to convert to GBP, where necessary, were 1 AUD to 0.55 GBP and 1 euro to 0.86 GBP.[85,86]

The daily resource use, number of days, per-day cost and total cost of each resource and intervention are reported in *Table 11*. For most interventions, 1 minute per day of staff time was assumed for delivering the product at normal meal or snack times. In the study by Lauque *et al.*[67] an average of 2 minutes per day for each patient was costed for a dietitian who visited once per week.

The total cost per intervention in each study is reported in *Table 12*. The average cost per type of intervention was included in the analysis: £369.28 for ONS. The assumption was made in the model that ONS is given to the older person for the specific period stated in the studies and no longer. It was also assumed that all of the ONS was used (opened and either consumed or discarded).

TABLE 10 Unit costs of nutrition and staff resources

Resource	Unit cost (foreign currency)	Unit cost (£)	Source
Sustagen® Hospital Formula Active – Neutral, 840 g	AU$23.50	12.93	Pharmacyonline.au[87]
Novasource 2, 237 ml × 27 pack	–	238.00	NineLife[88]
Enriched brioche bread × 30	€40.50	33.21	Nutrisens[89]
Calogen Extra Strawberry, 200 ml	–	8.50	Nutridrinks[90]
Fortisip® Extra, 200 ml	–	2.43	BNF[91]
Fortimel Nutritional Supplement High-Protein High-Energy, 125 ml × 4	–	13.20	Sweetcare[92]
1 hour, band 6 hospital-based nurse	–	45	PSSRU 2018[93]
Nestle Resource Energy Vanilla, 200 ml × 4		11.45	Nutridrinks[94]
MCTprocal® × 30 sachets		27.42	BNF[85]

BNF, *British National Formulary*; PSSRU, Personal Social Services Research Unit.

TABLE 11 Daily resource use and cost of study interventions

Study	Intervention	Daily resource/patient	Per day unit cost (£)	Number of days	Total cost (£)
Cameron *et al.*[71]	ONS	1× 237 ml sachet Novasource® 2	8.81	40	352.59
Cameron *et al.*[71]	SC	1× MCTprocal® sachet	0.91	40	36.56
Van Wymelbeke *et al.*[57]	ONS	1× 200 ml Nestle resource energy vanilla	2.86	84	240.45
Tylner *et al.*[56]	ONS	90 ml Calogen®	3.83	42	160.65
Lee *et al.*[54]	ONS	200 ml Fortisip®	2.43	168	408.24
Lauque *et al.*[67]	ONS	300–500 g Clinutren® Nestle	6.84	60	410.55
Cameron *et al.*[71]		1 minute with nurse	0.75		
Van Wymelbeke *et al.*[57]					
Tylner *et al.*[56]					
Lee *et al.*[54]					
Lauque *et al.*[67]	ONS	2 minutes with dietitian	1.50		

TABLE 12 Incremental cost of the interventions compared with SC

Study	Intervention	Mean incremental cost (£) vs. SC
Cameron *et al.*[71]	ONS	316.03
Van Wymelbeke *et al.*[57]	ONS	303.45
Tylner *et al.*[56]	ONS	192.15
Lee *et al.*[54]	ONS	534.24
Lauque *et al.*[67]	ONS	500.55

No information was provided in the studies about unopened products. The settings were nursing homes and hospitals, so it is assumed that the older person continues to be given the ONS during the intervention delivery period.

Incremental cost-effectiveness analysis

The cost-effectiveness of ONS and other comparators was evaluated by estimating the incremental cost-effectiveness ratio (ICER) derived from an incremental cost-effectiveness analysis. The ICER was the incremental cost per QALY gained. This is calculated as the difference in the total discounted cost between the intervention (e.g. ONS) and the comparator (e.g. SC) divided by the difference in the total discounted utility between the intervention and the comparator:

$$\text{Incremental cost per QALY} = \frac{C_{ONS} - C_{SC}}{U_{ONS} - U_{SC}}. \tag{7}$$

When there are more than two technologies, the ICER for each is compared with the next most cost-effective. A technology is strictly dominated if it costs more and is less effective than a comparator. A technology is dominated by extension if there is a more effective technology with a lower ICER than the next most effective technology. If the ICER of a health technology is less than the accepted cost-effectiveness threshold, then the health technology is considered cost-effective and the decision-maker is willing to adopt the technology. The cost-effectiveness thresholds of £20,000 per QALY and £30,000 per QALY recommended by NICE[77] are used as reference cost-effectiveness thresholds in this report.

Analysis of uncertainty

The investigation into how much uncertainty in the evidence influences decision uncertainty, and the uncertainty regarding whether a health-care technology should be adopted, is a key part of an economic evaluation. When evidence is available, we specify probability distributions to represent the uncertainty in the effectiveness estimates. Uncertainty in mortality, hospitalisation and utility outcomes was described in *Chapter 5*, and uncertainty in the effectiveness estimates was described in *Chapter 3*. Probabilistic sensitivity analysis was conducted using Monte Carlo simulation, which samples from every distribution *n* times to produce a joint distribution of the costs and effects of each intervention. The number of iterations was 8000.

The net benefit of adopting a health technology is calculated for different cost-effectiveness thresholds using the following equation:

$$\text{net benefit} = \text{threshold}\left(\text{e.g.}\ \frac{£20.000}{\text{QALY}}\right) \times \text{QALYs} - \text{cost (£)}. \tag{8}$$

The proportion of simulation estimates for which the intervention has the highest net benefit represents the probability that the intervention is cost-effective. The probability that an intervention is cost-effective at different cost-effectiveness thresholds is presented in a cost-effectiveness acceptability curve.[95]

Base-case and sensitivity analyses

The base-case analysis used the average cost for ONS across the studies included in the BMI NMA. This was £369 per person. The average BMI of 23 kg/m^2 of the populations in the included studies evaluating the effect of ONS on BMI was assumed for the model population. The effect estimates from the meta-analysis were used. Sensitivity analysis was conducted based on the meta-analysis result using adequately randomised trials only.

Body mass index–outcomes association

Only one study was identified that detailed the association between BMI and each of the three outcomes in the model: mortality, hospitalisation and EQ-5D. Consequently, sensitivity analyses were conducted exploring the impact on the results of increasing and decreasing the log-hazard ratio, log-odds ratio and difference in EQ-5D index from the mean by 20%.

Cost of oral nutrition supplements and body mass index

The underlying assumption of the meta-analyses of ONS compared with SC is that the different ONS interventions used across the studies have potentially similar effectiveness. There was significant variation in the cost of the ONS intervention across the studies. Sensitivity analysis was conducted varying the cost of the ONS intervention from £200 to £800, while assuming the same effectiveness.

There is a non-linear relationship between baseline BMI and the risk of mortality, and the risk of hospitalisation and the level of EQ-5D index utility. Different analyses were run for baseline BMI values ranging from 17 to 23 kg/m^2.

Use of direct evidence of the effectiveness of oral nutrition supplements on longer-term outcomes

A cost–utility analysis was planned using the direct evidence of the effectiveness evidence of ONS on longer-term outcomes (mortality, hospitalisation and EQ-5D outcomes) if sufficient evidence were available and ONS might be more effective than SC.

Chapter 6 Cost-effectiveness results

Base-case results

The incremental cost-effectiveness results for ONS compared with SC in the base-case analysis are presented in *Table 13*. The cost of ONS intervention was £369 per person and the baseline BMI was 23 kg/m^2. The setting for the analysis was assumed to be a care home. Four out of the five studies with BMI effectiveness evidence for ONS were set in nursing homes, and the remaining study was set in a hospital. QALYs and costs were calculated in the model as incremental QALYs and costs compared with SC.

Oral nutritional supplements are associated with a greater expected benefit (0.0145 QALYs) and a higher cost (£359) than SC. The ICER for ONS was £24,390. Although this is below the cost-effectiveness threshold of £30,000 per QALY, SC is more likely to be cost-effective than ONS: the probability that ONS is cost-effective is 0.28 at the £20,000-per-QALY threshold and 0.36 at the £30,000-per-QALY threshold. The probability that ONS is cost-effective compared with SC alone is presented as a cost-effectiveness acceptability curve across the threshold range £5000–50,000 per QALY in *Figure 14*. This is because the incremental net benefit distribution is skewed. The incremental net benefit distribution is presented in *Figure 15* and shows that more than 3000 of the 8000 incremental net benefit estimates are slightly negative. The average is £81. The variation in incremental cost estimates is very low, from £320 to £384. The shape of the incremental net benefit distribution is, therefore, driven by the distribution in incremental QALY estimates. The incremental QALY distribution is presented in *Figure 16*. The incremental QALY value at which the incremental net benefit is zero, the break-even value, is 0.0118. More than 2500 of the 8000 incremental QALY estimates are positive but less than 0.0118.

Sensitivity analyses

Body mass index–outcome associations

The evidence for the association between BMI level and mortality risk, hospitalisation risk and EQ-5D index utility showed an increased risk of mortality and hospitalisation at lower levels of BMI. The EQ-5D index utility was lower (utility decrement) at low levels of BMI and at high levels of BMI. The risk of mortality and hospitalisation and the reduction in EQ-5D index utility at lower levels of BMI was reduced by 20% in one sensitivity analysis, reported in *Table 14*, and increased by 20% in another sensitivity analysis, reported in *Table 15*. Reducing the benefit from increasing BMI reduces the cost-effectiveness of ONS; the ICER increases (£30,290 per QALY). Increasing the benefit from raising BMI reduces the ICER of ONS (£19,763 per QALY). The probability that ONS is cost-effective at a threshold of £30,000 per QALY remains very low (0.3 to 0.49).

TABLE 13 The incremental cost-effectiveness results for the base case

Intervention	QALYs gained (vs. SC)	Incremental cost (£) (vs. SC)	ICER (£/QALY)	*P*(CE) £20,000/QALY	*P*(CE) £30,000/QALY
SC	–	–	–	0.72	0.64
ONS	0.0145	353	24,390	0.28	0.36

ED, dominated by extension; *P*(CE), probability cost-effective.

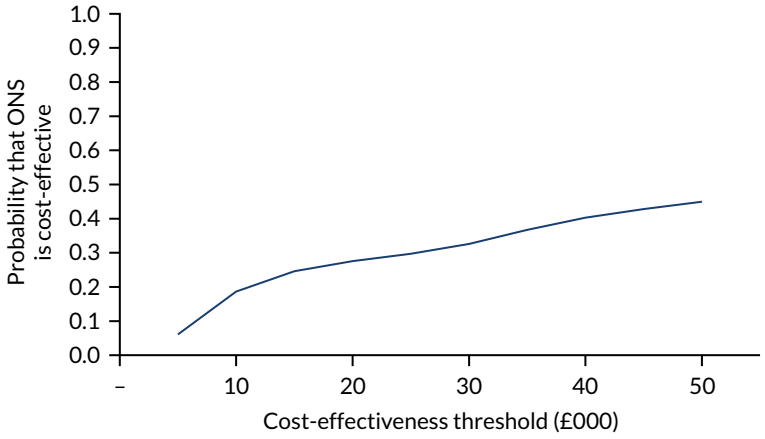


FIGURE 14 Cost-acceptability curve for ONS vs. SC.

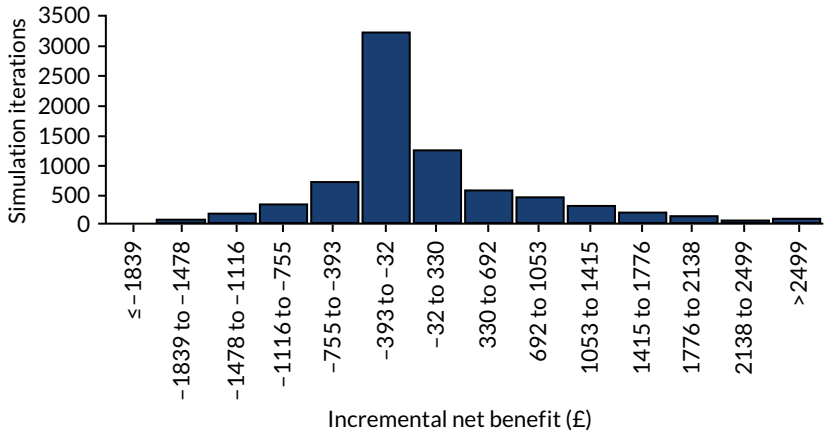


FIGURE 15 Base-case incremental net benefit distribution.

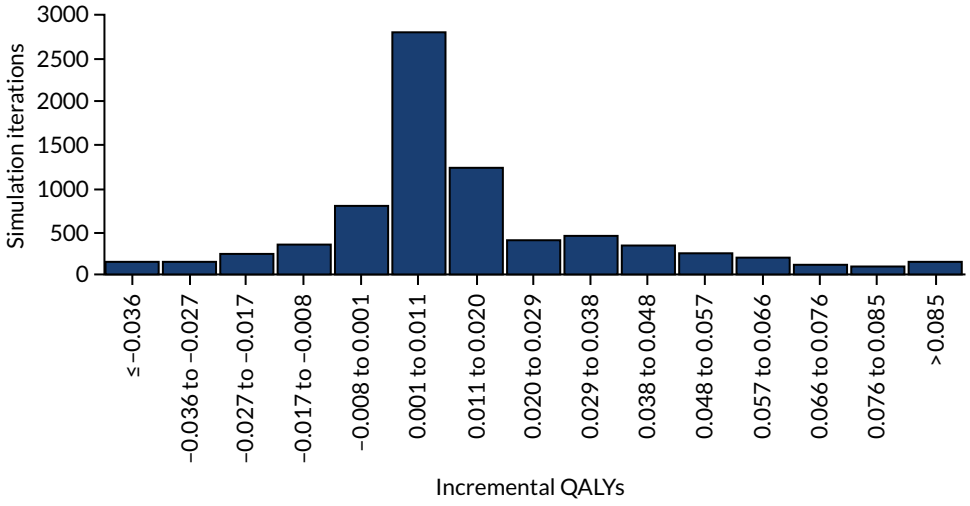


FIGURE 16 Base-case incremental QALY distribution.

TABLE 14 20% lower risk of mortality and hospitalisation, and EQ-5D index utility decrement at low BMI levels

Intervention	QALYs gained	Incremental cost (£)	ICER (£/QALY)	*P*(CE) £20,000/QALY	*P*(CE) £30,000/QALY
SC	–	–	–	0.74	0.70
ONS	0.0118	356	30,290	0.26	0.30

P(CE), probability cost-effective.

TABLE 15 20% higher risk of mortality and hospitalisation, and EQ-5D index utility decrement at low BMI levels

Intervention	QALYs gained	Incremental cost (£)	ICER (£/QALY)	*P*(CE) £20,000/QALY	*P*(CE) £30,000/QALY
SC	–	–	–	0.69	0.51
ONS	0.0177	350	19,763	0.31	0.49

P(CE), probability cost-effective.

Adequately randomised studies

A sensitivity analysis was conducted using the effectiveness evidence from only the adequately randomised trials (see *Chapter 3*, *Summary of clinical effectiveness results*, for the evidence from all trials and from only adequately randomised trials). The magnitude of the effect estimate was less and the uncertainty more in the effectiveness estimate using the only adequately randomised study evidence than when using the effectiveness evidence from all randomised controlled trials. The results are presented in *Table 16*. The incremental cost-effectiveness ratio increases to £30,466 per QALY, and the probability that ONS is cost-effective at a threshold of £30,000 per QALY is 0.33.

Oral nutritional supplement cost and body mass index levels

Analyses were run for population cohorts assuming BMI values of 17, 19, 21 and 23 kg/m^2. The cost of the ONS intervention varied for each of these from £200 per person to £800 per person. The results are presented in *Table 17* for the all randomised trials analysis and in *Table 18* for the adequately randomised trials analysis.

Given the evidence informing the model, people with lower BMI will obtain a greater benefit from an increase in BMI. The results in *Table 17* are consistent with this and show that ONS are more cost-effective for people with lower BMI. For example, the ICER for a baseline BMI value of 23 kg/m^2 and an ONS cost of £200 per person was £12,195 per QALY, whereas the ICER for a baseline BMI value of 17 kg/m^2 and an ONS cost of £200 per person was lower, at £4456 per QALY. The corresponding probability that ONS is cost-effective at a threshold of £30,000 per QALY increases from 0.65 to 0.95. The cost-effectiveness of ONS falls as the cost of ONS increases. The results for BMI of 19 kg/m^2 and 21 kg/m^2 are very similar because they fall within the same BMI category used in the studies that investigated the association between BMI and mortality, hospitalisation and EQ-5D index utility.

TABLE 16 Incremental cost-effectiveness results using the adequately randomised effectiveness evidence

Intervention	QALYs gained	Incremental cost (£)	ICER (£/QALY)	*P*(CE) £20,000/QALY	*P*(CE) £30,000/QALY
SC	–	–	–	0.72	0.67
ONS	0.0117	356	30,466	0.28	0.33

P(CE), probability cost-effective.

TABLE 17 The ICER and probability of cost-effectiveness of ONS at different baseline BMIs and ONS costs (all randomised trials)

Cost (£/person)	BMI (kg/m²)											
	17			19			21			23		
	ICER (£)	P20	P30	ICER (£)	P20	P30	ICER (£)	P20	P30	ICER (£)	P20	P30
100	1981	0.95	0.96	3944	0.91	0.93	5158	0.90	0.92	6111	0.70	0.74
200	4456	0.93	0.95	8301	0.81	0.88	8716	0.84	0.89	12,195	0.50	0.65
300	6506	0.90	0.93	12,538	0.70	0.81	14,891	0.74	0.85	18,583	0.31	0.49
400	8805	0.84	0.90	16,930	0.57	0.74	17,052	0.60	0.77	25,984	0.27	0.33
500	11,408	0.78	0.87	21,587	0.43	0.66	23,950	0.46	0.70	32,698	0.25	0.30
600	13,639	0.72	0.85	26,011	0.30	0.57	26,339	0.31	0.60	42,993	0.20	0.26
700	15,727	0.65	0.81	30,335	0.20	0.48	30,582	0.19	0.50	46,185	0.19	0.25
800	17,913	0.57	0.77	35,118	0.11	0.38	36,727	0.10	0.40	51,861	0.16	0.24

TABLE 18 The ICERs and probability of cost-effectiveness for ONS at different baseline BMIs and ONS costs (adequately randomised trials)

Cost (£/person)	BMI (kg/m²)											
	17			19			21			23		
	ICER (£)	P20	P30	ICER (£)	P20	P30	ICER (£)	P20	P30	ICER (£)	P20	P30
100	2712	0.71	0.73	3892	0.68	0.71	5677	0.68	0.70	6195	0.53	0.57
200	5280	0.70	0.72	11,172	0.59	0.64	11,045	0.63	0.66	15,955	0.38	0.47
300	8262	0.65	0.68	16,652	0.55	0.60	16,852	0.56	0.62	24,012	0.30	0.39
400	11,139	0.62	0.67	22,298	0.47	0.56	19,704	0.50	0.59	33,554	0.26	0.30
500	14,907	0.58	0.64	26,585	0.41	0.52	26,894	0.41	0.52	41,686	0.23	0.27
600	18,094	0.55	0.62	31,907	0.34	0.47	31,733	0.36	0.50	52,236	0.21	0.26
700	20,736	0.51	0.59	38,700	0.28	0.43	39,499	0.29	0.44	60,645	0.19	0.24

In the all-randomised-trials analysis, for the probability of being cost-effective to be > 0.7, the cost of ONS needs to be a maximum of £100 per person for older people with BMI of 23 kg/m² and a maximum of £400 per person for older people with BMI of 19–21 kg/m², and could be at least as high as £800 per person for older people with BMI of 17 kg/m². In the adequately randomised trials analysis, for the probability of being cost-effective to be > 0.7, the cost of ONS needs to be less than £100 per person for older people with BMI of 23 kg/m² and up to £100 per person for older people with BMI of 19–21 kg/m², and could be up to £200 for older people with BMI of 17 kg/m². The lower cost of ONS required for ONS to be cost-effective in the analysis using only the adequately randomised trials compared to the analysis using all trials reflects the greater uncertainty in the effect estimate when using only the adequately randomised trials.

The maximum cost per day of ONS was calculated using different total intervention costs, assuming 1-minute or 4-minute staff time costs per day. The results are presented in *Table 19*. For example, if the total intervention cost should be, at most, £300 per older person and the targeted duration of ONS provision is 60 days, then the cost of staff time is subtracted from the £300 and the remainder is divided by the number of days to give the maximum ONS cost per day. For 1 minute of staff time per day, this comes to £4.25.

TABLE 19 Maximum cost of ONS per day for different intervention costs, duration and staff time

	Maximum ONS cost per day (£)					
	40 days		60 days		80 days	
Total intervention cost (£)	1 minute	4 minutes	1 minute	4 minutes	1 minute	4 minutes
100	1.75	NV	0.92	NV	0.5	NV
200	4.25	2.00	2.58	0.33	1.75	NV
300	6.75	4.50	4.25	2.00	3.00	0.75
400	9.25	7.00	5.92	3.67	4.25	2.00

NV, not viable as the staff time costs more than the total intervention cost.

Three of the ONS interventions were costed at less than £4 a day (1 × 200 ml Nestle resource energy vanilla @ £2.86, 90 ml of Calogen® @ £3.83 and 200 ml of Fortisip® @ £2.43), indicating that there are ONS products that could be cost-effective for older population groups with low BMI. No staff time costs would be incurred daily in the community setting unless there were regular district nurse home visits.

Use of direct evidence of the effectiveness of oral nutritional supplements on longer-term outcomes

A cost–utility analysis was planned using the evidence of effectiveness of ONS on longer-term outcomes (mortality, hospitalisation and EQ-5D outcomes) obtained from the review. However, insufficient evidence was available to suggest effectiveness or enable the analysis.

The mortality effect estimate for ONS compared with SC was RR 0.93 (95% CI 0.28 to 3.06) for all randomised studies. There was no mortality meta-analysis estimate for adequately randomised studies. The hospitalisation effect estimate was RR 0.97 (95% CI 0.46 to 2.04) for all randomised studies and RR 0.8 (95% CI 0.35 to 1.82) for adequately randomised studies. Only one study reported EQ-5D index outcomes, and that study compared ONS with SC. ONS cost more than SC and all of the randomised trial evidence indicates that there is no evidence to support a QALY gain from ONS. The limited evidence means that there is no evidence that ONS are cost-effective from conducting a cost–utility analysis using these longer-term outcome estimates from the systematic review.

Summary of cost-effectiveness results

Two approaches to estimating the cost-effectiveness of ONS based on the systematic review were considered. There was limited evidence of the effectiveness of ONS on longer-term outcomes. Based on the available evidence, there was no evidence that ONS were cost-effective using mortality, hospitalisation and EQ-5D outcome evidence. The cost-effectiveness of ONS and SC was also estimated using the meta-analysis effectiveness evidence for the BMI outcome. The benefit of increased BMI was modelled using evidence from the literature on the association between BMI and mortality, hospitalisation and EQ-5D index utility. This evidence showed that there was a greater benefit of an increase in BMI at lower baseline BMI levels.

Oral nutritional supplements were unlikely to be cost-effective at a threshold of £30,000 per QALY for a population cohort with a baseline BMI of 23 kg/m^2. ONS were even less likely to be cost-effective when using only the adequately randomised controlled trial evidence. Using the adequately randomised trial evidence, there was no strong evidence that ONS were cost-effective at any baseline BMI level.

Using the all randomised trial evidence, ONS were cost-effective at a baseline BMI of 19–21 kg/m^2 with a high level of certainty when ONS cost no more than £2 per person. It was also cost-effective at a baseline BMI of 17 kg/m^2 with a high level of certainty when ONS cost no more than £400 per person.

Chapter 7 Public and patient involvement/engagement

Public and patient involvement/engagement took place throughout the project, from the development of the funding bid to repeated discussions with older people while the review was undertaken. In addition, a stakeholder dissemination event took place at the end of the project to both present the research findings and elicit reflections on the research.

Discussions were conducted with a PPIE group of older people drawn from the Elders Council (Newcastle upon Tyne, UK) at key time points during the review process. Our PPIE team member (AR) liaised on this input. Input was sought into the planning of the review, feedback on the scope of the review and aspects to focus on. One of the main points of feedback was that we needed to assess social factors and issues related to the uptake of ONS in the review; we included these aspects as part of our review. Further discussions were held after data extraction, when the studies included in the review were briefly described and the review team sought feedback on the outcomes that the older people would consider most important. Overwhelmingly, the older people rated QoL and functional outcomes, such as falls, morbidity and wound healing, as most important. The group also highlighted the issue of acceptability of taking ONS. While none of the older people had direct experience of using supplements on a regular basis, they questioned the acceptability of ONS over the short to medium term and hoped that more palatable alternatives would be made available.

Another key time point at which PPIE input was sought was the sharing of our preliminary research findings. The older people were unsure of the relative importance of some of the measures (e.g. albumin) and reiterated that the outcomes most significant to them related to their functional status and QoL. They wanted to see more studies focusing on these outcomes instead of, or in addition to, those relating to more clinical nutritional intake or body composition measures. While the PPIE group did not have much diversity in terms of gender and ethnicity, they highlighted the need for further research that includes different subgroups of older adults, including those in different ethnic groups. The group was also worried about the small and inconclusive evidence base, and consequently would have preferred health-care professionals to exercise caution when prescribing ONS to this population.

The review and economic modelling results were presented in an online workshop to other key stakeholders comprising geriatricians, dietitians and nurse practitioners. The workshop comprised nine stakeholders, and this was supplemented with three individual meetings. In these sessions, discussions considered the experiences of ONS, a presentation of review findings, and group discussions reflecting on the research implications. Three key points arose from the discussion. First, there was the high level of uncertainty about the evidence that this review highlighted. Many stakeholders were surprised that so few studies had been conducted. There was a discussion about the outcomes that appeared to have small positive effects (e.g. energy, mobility); however, the stakeholders questioned the limited clinical significance of these results. The health-care professionals mirrored what the older people considered, namely that functional status was a far more important and relevant outcome than small changes in nutritional intake.

Second, there was widespread concern that there were not enough high-quality studies that compared ONS with good, dietary or 'food-first' nutritional support. Although all forms of dietary interventions (e.g. food fortification, advice/counselling) were considered in the review as comparators or without ONS, most studies had limited reporting on these dietary interventions. As a result, the comparators were not given detailed consideration. The feedback was that although ONS might be suitable for a period, other dietary interventions, such as meal fortification, are likely to be more holistic, acceptable and less expensive than having to prescribe ONS to older adults. In addition, stakeholders emphasised that the wider issues underlying malnutrition, such as isolation, loss of appetite, comorbidities and

living arrangements, are extremely important in frail older adults. These underlying issues need to be addressed and ONS is only part of a wider suite of nutritional support needed for frail older adults. The stakeholders recognised the heterogeneity of older people, and how nutritional support may vary considerably depending on age, cognitive function, living conditions and other comorbidities. Messaging around what is considered a healthy diet or good nutritional support needs to be more widespread, and, furthermore, studies should consider which (if any) older people would benefit most from the use of ONS.

Chapter 8 Discussion

This systematic review has examined the impact of ONS on frail older people who are malnourished or at risk of malnutrition. Other reviews have been published looking at the impacts on adults more generally[31,37] or focusing on specific comorbidities such as cancer,[96,97] dementia[35] or dialysis therapy[98] or following discharge from hospital.[99,100] Additionally, although a cost-effectiveness analysis was undertaken in a previous review, this included children and adults, and the search is now relatively dated, having been completed in March 2014.[24] To better understand the role of ONS in the management of malnutrition in frail older people, a full effectiveness review was combined with a cost-effectiveness review and analysis using the most recent data from published studies.

Summary

Eleven primary studies were identified in the effectiveness review. A summary of characteristics of the included studies and participants, evidence quality and findings can be found in *Figure 17*. Many of the studies had industry funding. Of the 11 studies identified, six (55%) were either fully ($n = 4$) or partially funded by industry ($n = 2$). Three were funded from alternative sources and two studies did not include details of funding/conflict of interests. Given the insufficient information on role of funders and the lack of clarity about independent research, the potential limitation of conflict of interest in reporting findings cannot be ruled out in these studies.

Meta-analyses suggested positive effects of ONS versus SC for energy intake (kcal) (SMD 1.02, 95% CI 0.15 to 1.88; very low-quality evidence) or poor mobility (MD 0.03, $p < 0.00001$, 95% CI 0.02 to 0.04; very low-quality evidence), and no evidence of an effect for body weight (MD 1.31, 95% CI −0.05 to 2.66; very low-quality evidence) or BMI (MD 0.54, 95% CI −0.03 to 1.11; very low-quality evidence). Pooled results for other outcomes related to malnutrition and its adverse consequences were statistically non-significant. There was mixed narrative evidence regarding the effect of ONS on QoL. All evidence was graded as low or very low quality. NMAs were conducted only for the body weight and grip strength outcomes. The results of the NMA indicated there was evidence of an effect for ONS compared with SC for the body weight outcome only. Study quality was mixed; the method of randomisation was typically poorly reported, and, therefore, all evidence was assessed as low or very low quality using GRADE.

Although the studies included looked at the effectiveness of ONS on all their participants, there was heterogeneity in length and definition of follow-up between the studies. Follow-up spanned from 40 days to 1 year.[54,71] It was difficult to define the length of follow-up in studies, as reports often did not clearly define whether outcome assessments had been undertaken immediately post intervention or after time had elapsed. Additionally, no study reported the impact of the intervention on specific groups (e.g. ethnicity, education or marital status, or by comorbidities). Although demographic information was often reported in the methods section, it was not possible to evaluate the differential impact of ONS in these groups.

Furthermore, there was no systematic reporting in the identified studies of the types or characteristics of ONS that can influence compliance /uptake, such as flavour, and specifically sweetness. Our PPIE group reported that taste was an important factor in whether or not supplements would be consumed. Previous research has reported that age-related changes in taste lead overt sweetness to be one of the major factors contributing to the dislike of ONS.[101] Furthermore, research has demonstrated that the viscosity of the ONS also plays an important role in oral-sensory stimulation and satiety.[102] Den Boer *et al.*[102] showed that lower thickness of ONS increased intake by one-third without affecting satiation or satiety. Whereas some studies gave a choice of which ONS products could be consumed,[53,55,57,67] others either did not report this or used a single brand of ONS.

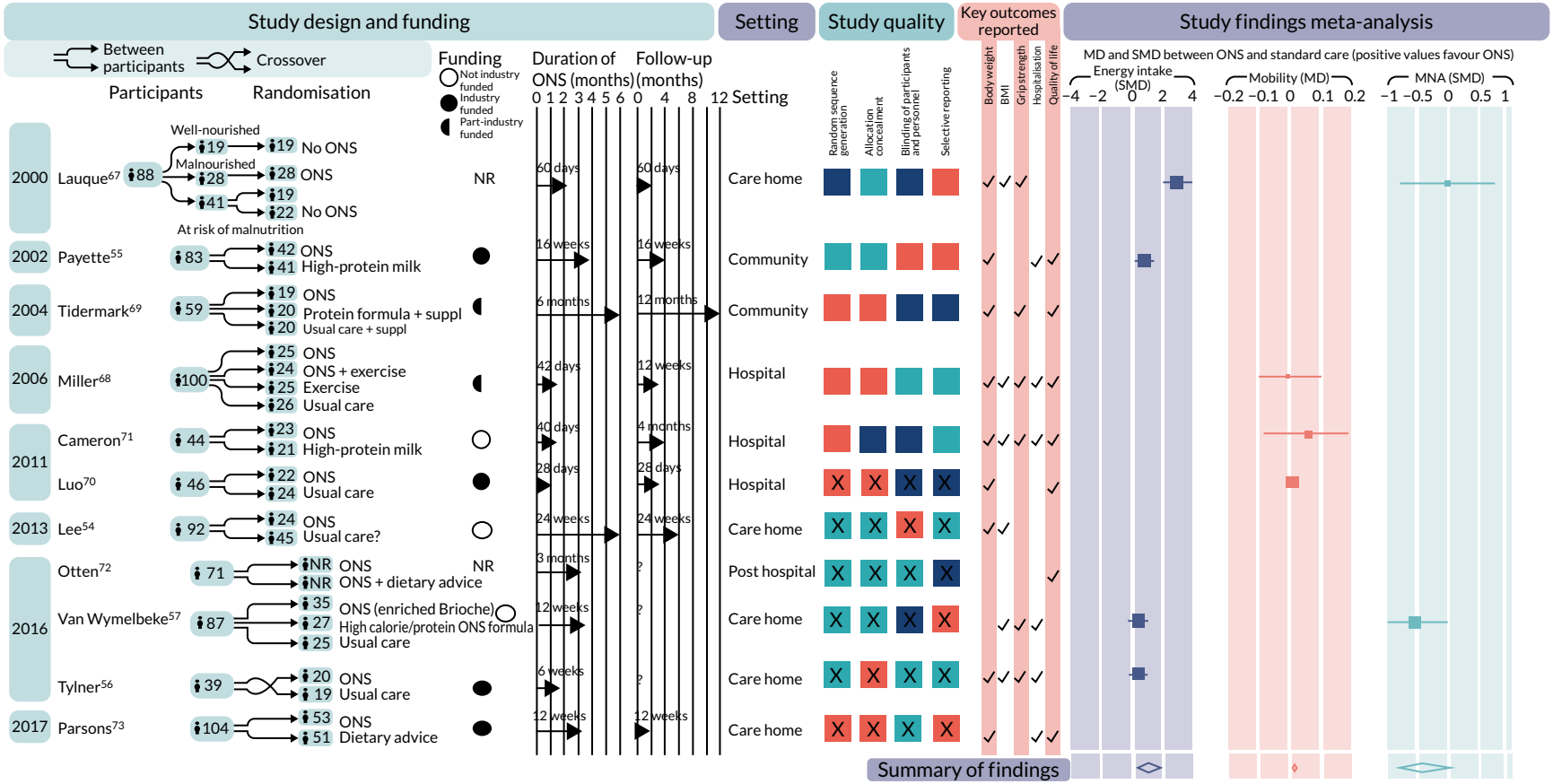


FIGURE 17 The GOfER (Graphical Overview for Evidence Reviews) diagram of included studies in the effectiveness review.

The studies in the review also lacked any detailed qualitative findings. A single study reported barriers to the use of ONS generally,[71] but none examined patient viewpoints in any detail. The discussions with our PPIE group of older people and other stakeholders (e.g. dietitians and clinicians) showed that there was a range of reasons why supplements may work for some people and not others. A lack of reporting on patient experiences in the review is especially surprising, as similar qualitative explorations of the views of both dietitians[103] and general practitioners[104] views on malnutrition management have already been undertaken.

Compliance data were reported in 7 of the 11 studies. However, there was considerable between-study heterogeneity in how compliance was determined and reported (e.g. aggregated across study arms), which made it difficult to draw firm conclusions. A previous systematic review completed by Hubbard *et al.*[105] suggested that mean compliance with ONS was 78%; interestingly, compliance was found to be lower in a hospital setting than in the community (67% vs. 81%).

One economic evaluation was identified in the systematic review. This study was conducted in a care home setting. It was well conducted and showed that ONS could be cost-effective in a care home setting when compared with dietary advice.

Two approaches to estimating the cost–utility of ONS using the evidence identified in the effectiveness systematic review were taken. The first approach was to use evidence of the effectiveness of ONS on longer-term outcomes from the systematic review, but there was little or no evidence that ONS was effective using the direct evidence of the effect of ONS on the longer-term outcomes, and so this cost–utility analysis was not conducted. The second approach was to estimate cost-effectiveness using results from the meta-analysis or NMA of effectiveness evidence for BMI in the systematic review. The longer-term consequences of changes in BMI were then modelled using evidence from the literature on the association between BMI and mortality, hospitalisation and EQ-5D index utility. The evidence base for this model design was limited; consequently, the results should be interpreted with caution. This linked evidence showed that there was a greater benefit of an increase in BMI at lower baseline BMI levels. ONS was not likely to be cost-effective at a £30,000 per QALY threshold for a population cohort with a baseline BMI of 23 kg/m^2 using all randomised trial evidence. ONS was even less cost-effective when only the adequately randomised control trial evidence was used; there was no strong evidence that ONS was cost-effective at any baseline BMI level. Using the all randomised trial evidence, ONS was cost-effective at a baseline BMI level of 19–21 kg/m^2 with a high level of certainty when ONS cost no more than £200 per person. It was also cost-effective at a baseline BMI level of 17 kg/m^2 with a high level of certainty when ONS cost no more than £400 per person.

The incremental QALYs in the economic model for ONS versus SC was 0.0145 was slightly lower than the incremental QALYs (0.0174) in the single-study-based economic evaluation by Elia *et al.*[23] The incremental cost compared with SC (£359) was higher than the incremental cost compared with dietary advice (£191). It is not known if dietary advice is cost-effective. If dietary advice were not cost-effective, then the most appropriate comparator would be SC without dietary advice.

Strengths

This review has many strengths. Our search strategy was broad and wide-ranging and included multiple databases supplemented by searching citations, reference lists of included studies and relevant systematic reviews and comprehensive grey literature sources. We included primary studies that focused on malnourished, frail older people (aged $\geq$ 65 years). However, we took the pragmatic decision to include studies in which the mean age of participants was $\geq$ 65 years to ensure that we maximised the evidence base. Two studies[53,70] included some participants aged $<$ 65 years. Furthermore, all screening, data extraction and quality assessments were carried out in duplicate to minimise human error. We also included a wide range of outcomes to ensure that the effects of ONS

could be investigated across a range of health outcomes, including those hypothesised to respond relatively quickly to ONS (e.g. kcal and protein) and those that may change over a longer period (e.g. hospitalisations, morbidity and mortality). Study authors were contacted when critical missing information was required. Meta-analyses and NMA were undertaken where possible, and the results were compared. For the meta-analyses, both CFB and final values were imputed where one or the other was missing and meta-analyses were conducted for each. A sensitivity analysis was also carried out based on study quality.

A systematic review of economic evaluations of ONS in a frail older population was conducted. Only one study was included, indicating the paucity of cost-effectiveness evidence for ONS in this population. The economic analysis conducted made use of the effectiveness evidence of ONS on BMI from the systematic review. The use of an economic model enabled cost-effectiveness to be explored for different cost assumptions and for different population cohorts defined by BMI. The key uncertainties in the model associated with the effectiveness evidence and the evidence for the association between BMI and outcomes was investigated by conducting sensitivity analyses.

Limitations of the research and deviations from protocol

There are some limitations to this review. The review identified only a small number of included studies focusing on a population of frail older adults who were either malnourished or at risk of malnutrition. This important and growing population, nonetheless, is at high risk of adverse outcomes from malnutrition, and there is limited evidence on the effectiveness of ONS to mitigate malnutrition risk in frail older adults. Therefore, we defined the scope of the review along these lines. A single search was undertaken for both the effectiveness and the cost-effectiveness reviews, which included only studies published in English, which may have excluded some potentially eligible studies. Furthermore, we also deviated from our original protocol in two ways. First, we refined the eligibility criteria with regard to frailty. In the original protocol, we specified that frailty needed to be defined according to a standardised measure such as Fried's frailty phenotype. However, on screening of the search we found that very few studies described their population as frail in these terms. We therefore decided to expand the eligibility criteria for frailty by using proxy criteria (see *Methods*). Although these were added after the screening process had begun, to avoid bias we made attempts to prevent being data-driven by asking clinical members of the wider study team for their input into and suggestions about these criteria without indicating the studies and types of data we were encountering. We also updated the searches at a later stage before finalising the results, which will have identified any missing studies related to the extended criteria of frailty. In addition, serious adverse events were defined in discussion among the research team, to only include kidney injury, hyperglycaemia, constipation, diarrhoea, nausea, vomiting, refeeding syndrome and micronutrient deficiency. These were considered the most important serious adverse events, although it is possible that others were not extracted as a result. Finally, we used GRADE to understand the strength of the evidence base, but this was not included in the protocol.

We identified a small evidence base that looked at the impact of ONS on frail, older people specifically. Most studies were based on small samples and the duration of interventions reported was typically $\leq$ 3 months. The effectiveness of ONS on malnutrition-related outcomes (e.g. grip strength, ADL, hospitalisation) is difficult to establish over a relatively short term. Furthermore, the dose of ONS typically varied across the studies, which could add to the inconsistency observed. Although 11 studies were described as RCTs, the risk-of-bias assessment suggested that there were issues with the allocation sequence generation used and a lack of reporting on how the randomisation was generated, and so forest plots of both all studies and those adequately randomised were reported.[68–71] Additionally, only a few studies reported on certain key outcomes in relation to measures of malnutrition and its consequences (e.g. wound healing, reduction of infections, and falls), and therefore a meta-analysis was not possible. There was also heterogeneity in the measures or scales used for certain outcomes (e.g. ADL, MNA and protein intake). To enable meta-analysis to be undertaken, SMDs were used to

aggregate different measures of specific outcomes. As a result, the meta-analysis results are less intuitive to interpret. Another major limitation was the lack of outcome data related to QoL and physical function outcomes, which our PPIE group highlighted as particularly important. Although QoL data were reported in four studies,[55,68,72,73] they could not be pooled because of differences in reporting, and, therefore, it was not possible to carry out a meta-analysis. The paucity of robust and consistently reported QoL data highlighted in this review is perhaps not surprising, as measures are often disparate and difficult to combine. The narrative results suggested that the effect of ONS in relation to physical function and overall QoL assessment scores were mixed; however, both studies that reported data for the psychological aspects of QoL reported a positive effect of ONS. The PPIE group questioned the impact of a slight (albeit statistically significant) improvement in energy (for example) and wanted to know whether or not ONS would improve their ability to engage with and be active in their daily lives.

One of the major findings was a lack of data on the effectiveness of interventions by key determinants. Although population characteristics (e.g. socioeconomic status, living arrangement) were reported to some extent at baseline, no studies looked at effectiveness according to these characteristics. As a result, we were unable to examine to whom ONS might be most suited. Similarly, we also set out to investigate what components of the intervention (frequency, length, type, flavour, etc.) led to greater effectiveness. However, owing to both a lack of studies and poor reporting of the nature of the intervention, it was not possible to undertake this analysis. Similarly, there were no qualitative intervention studies identified in the review that examined how patients experienced taking the supplements. Descriptive qualitative studies were identified in this population, but these were not related to a specific intervention and therefore were not eligible for inclusion.[106] Although a wide range of ONS products are available, only five studies gave a choice of flavour or type.[53,55–57,67] Older adults, who are the focus of this review, represent a diverse group, with differences in age and other factors, such as ethnicity and comorbidities. Our PPIE evidence suggested that this was likely to have a strong influence on compliance (and, therefore, potentially on effectiveness), and more research in this area is needed.

Only 10 studies met our inclusion criteria for our meta-analysis. As fewer than 10 studies were included for any outcome, funnel plots could not be used to assess publication bias. This is especially important in this review, as 6 of the 11 studies have a direct link to a company that produces the ONS (through a grant, employees as authors, or free product supply for the trial; see *Table 2*). Previous research has found evidence between pharmaceutical company sponsorship and results that strongly favour the sponsors' interest.[107] As a result, there may be trials not published that show negative results. The few studies included in the meta-analyses and the often high level of statistical heterogeneity meant that it was difficult to draw firm conclusions from the results of the meta-analyses.

Sensitivity analysis was conducted on a subset of studies that were assessed as adequately randomised. This was considered to be the most useful sensitivity analysis given the low expectation that studies would be at low risk of bias and that most of the outcome measures were considered to be objective. The exception is the ADL outcome. The classification of the subset of studies in the sensitivity analysis does not imply that the studies included are at low risk of bias and, as expected, no studies were assessed as being at low risk of bias across all categories. Overall, the quality of the reporting and the methods across the included studies was low, and this further limits the conclusions that can be drawn from the results of the meta-analyses.

We included data from the longest follow-up time points available in each study when selecting those for inclusion in the meta-analyses. Too few studies were included in the review to undertake analyses for multiple time points. The reason for choosing the longest follow-up time point was to allow for assessing longer-term impacts on outcomes. Furthermore, as in most meta-analyses, SC was very diverse and varied among the included studies. We made the pragmatic decision to include comparators that we felt were relatively 'light touch' or routine and were similar to SC in similar settings (e.g. dietary advice information sheet).

There were also several limitations associated with evaluating cost-effectiveness. There was very limited evidence identified in the systematic review on health-care resource outcomes and outcomes that affect QoL, and this limited the cost-effectiveness conclusions that could be drawn from this evidence. The cost-effectiveness of ONS was also modelled utilising the effectiveness evidence identified in the systematic review focused on linking a short-term measure of malnutrition (i.e. BMI) with longer-term outcomes (i.e. QoL, hospitalisation, mortality). The cost-effectiveness modelling method used, linking BMI effectiveness evidence with outcomes, may underestimate the cost-effectiveness of ONS. This is because change in BMI may be an imperfect proxy for improved nutrition, and the mortality, hospitalisation and EQ-5D index utility outcomes may not capture all of the health-care resource use and health outcomes that may be affected by ONS. The evidence base for the association between change in BMI and QoL and health-care resource outcomes was limited. The use of the cross-sectional study estimating the association of BMI and EQ-5D to model the association between change in BMI and EQ-5D is particularly prone to bias.[80] We also found no information on how the association between BMI and the outcomes might vary by characteristics such as age and setting. Although ONS may not be cost-effective its the average cost, it is possible that it could be cost-effective if a cheaper ONS intervention could be found.

Compared with cost-effectiveness analysis based on effectiveness evidence from a systematic review, the advantage of a trial-based economic analysis is that a comprehensive evaluation of the health-care resource and health outcomes associated with ONS can be undertaken in which all QoL outcomes can be measured using the same preference-based health-related QoL instrument. We conducted a systematic review of the trial-based economic evaluations. There was only one reasonably well-conducted economic evaluation that showed that ONS may be cost-effective in a care home setting.[23] Given the possible variations in settings and older people's characteristics, additional well-conducted studies may be needed to provide strong evidence of the cost-effectiveness of ONS in a care home. There were no economic evaluations identified conducted in other settings.

Chapter 9 Conclusions

Our review included evidence from different countries and settings and sought to assess the effectiveness and cost-effectiveness of ONS in frail older adults. The current evaluation of studies in frail older people shows that the impact of ONS on most measures related to malnutrition and its adverse consequences is very weak. There was some suggestion of a modest positive effect of ONS on energy and mobility. There was considerable variation in the reporting of ONS and other dietary interventions in studies. Over half of the studies in the effectiveness review were either not randomised or inadequately randomised, and 6 of the 11 studies were fully or partly funded by industry. None of the studies was assessed as being at low risk of bias across all risk-of-bias categories. Furthermore, many did not consistently report functional outcomes that our PPIE group identified as particularly important for older adults. Reporting on intervention duration and follow-up was often inadequate and lacked detail. No studies reported the effectiveness of ONS by determinants. We found no qualitative studies exploring patient experiences of using ONS. There were NMA results for body weight and grip strength outcomes and comparing ONS with SC or ONS with a steroid. The only evidence of an effect for ONS compared with SC was for the body weight outcome.

One study was identified in the cost-effectiveness review. This reasonably well-conducted economic evaluation concluded that ONS may be cost-effective in a care home setting. No studies evaluating the cost-effectiveness of ONS for frail older people in community and hospital settings were identified. The cost-effectiveness analysis conducted here based on the systematic review evidence did not find that ONS was cost-effective, but the evidence base was limited for this analysis. ONS may be cost-effective for older frail people with a BMI of ≤ 21 kg/m^2 with cheaper ONS products. However, as there was only one cost-effectiveness study, how the cost-effectiveness of ONS varies across population subgroups defined by, for example, age, independence and BMI is unknown.

The initial logic model developed for the project (see *Figure 1*) was used throughout as a tool for the researchers to communicate with stakeholders and understand emerging findings from the review on the impact of determinants, pathways and outcomes that relate to the use of ONS in frail older adults. The insights gained from the review and our discussions with older people (PPIE group) and other stakeholders have been used to further refine the logic model presented in *Figure 18*. The logic model depicts the results (direction of effect) from the review regarding the effectiveness of ONS versus comparators for improving health outcomes and illuminates gaps in the evidence regarding the mechanisms by which ONS exerts its effects. The 'determinants' listed in the figure are factors from background literature as well as from stakeholder and PPIE groups. These determinants are believed to influence the context in which ONS would be provided, as well as the feasibility of implementing ONS and factors related to the uptake of this and other dietary interventions. The 'interventions' illustrate a variety of approaches that can be used to influence health outcomes related to malnutrition in frail older adults. 'Active ingredients' are aspects of the intervention that are likely to influence adherence to ONS and, therefore, the effectiveness of this intervention. As found in our review, there is a need for primary studies to investigate and report the relative impacts of these determinants and active ingredients of dietary interventions on health outcomes to identify pathways with the potential to inform development of ONS and other dietary interventions with maximum effectiveness. The text in italics depicts factors that the PPIE group identified as important, on which data were not necessarily identified in the review findings.

Implications for practice/decision-makers

Insufficient evidence was available to make any firm conclusions regarding the effectiveness and cost-effectiveness of ONS in frail older adults. Overall, there was limited evidence on the effectiveness

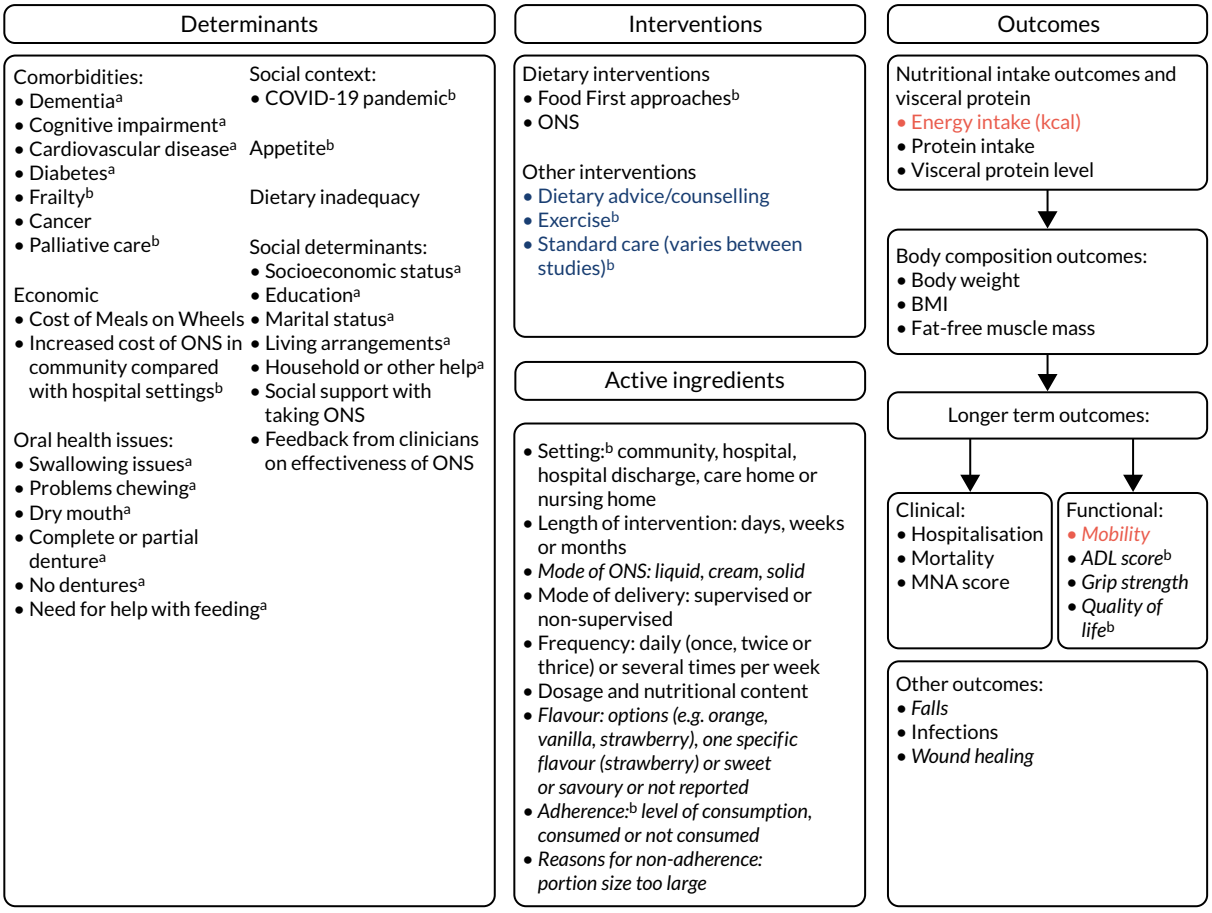


FIGURE 18 Refined logic model. a, Variable for which baseline data were reported but there was no data regarding its effect on the outcomes; b, factors identified as important by the stakeholders (dietitians). Black text without footnotes or italics indicates that no evidence was identified; blue text indicates interventions for which the effects on health outcomes were assessed in studies that were included in the review; orange text indicates that the outcome favours ONS (based on overall direction of effect); downwards arrows indicate reduction in the outcome; italics indicate factors reported as important by PPIE members.

of ONS with or without other dietary interventions in reducing the risk of malnutrition among frail older adults. There seemed to be positive effects of ONS on energy and mobility, but these were typically small, and the extent to which these are of clinical significance needs to be understood in more detail. Furthermore, it was not possible to make any recommendations about for whom ONS may be best suited or which intervention components (e.g. ONS type, with or without other dietary interventions) lead to more successful outcomes. As the effects of ONS varied greatly between studies, considerable uncertainty remains. ONS are one method of oral nutritional support and are part of a wider toolkit of dietary interventions available to health-care professionals. There remains a need to better understand the role of ONS and the extent to which this works alongside other dietary interventions. Given the limited body of evidence in the review, we were unable to make recommendations for practitioners. Our stakeholder discussions with practitioners (e.g. dietitians, care home staff, clinicians in hospitals) showed a need for further research on dietary interventions (or 'food-first' approaches), whereby dietary changes to meals and food are encouraged; and to understand the evidence for ONS in the context of these approaches, along with addressing issues underlying malnutrition in frail older adults (e.g. living conditions, comorbidities).

Implications for research

Considerable uncertainty remains about the effectiveness of ONS in reducing the risk of malnutrition in frail older adults. There is a need for high-quality, adequately powered primary studies that report on short- and long-term health outcomes as well as assess the determinants and participant characteristics that could help understand specific groups for whom ONS might be more (or less) effective.

There was also only one ONS cost-effectiveness trial-based economic evaluation in a care home setting. Further research is need in both this population and others (e.g. in hospital and at home). The cost of ONS varied greatly across studies in terms of both the ONS and staff time preparing and administering ONS. There is a lack of evidence on the relationship between the duration of ONS provision and long-term outcomes such as hospitalisation, mortality and QoL. A primary study that includes both short-term malnutrition outcomes and longer-term outcomes would provide further information about those relationships.

High-quality research with a sufficient sample size should investigate the effect of characteristics such as baseline BMI, MNA, mobility and other comorbidities on the effect of ONS. Primary studies often assume that dietary advice (including the use of ONS) can be followed and will be effective. However, in frail older people, malnutrition can be exacerbated by other factors (e.g. dementia, inability to prepare food, residential status), so there is a need for primary studies that take place in a variety of settings and accurately record (and report by) baseline characteristics. More transparent reporting of the nature of the intervention would also allow effectiveness to be measured against intervention components.

Further research on nutritional support for malnourished, frail older people should aim to close the evidence gaps identified in our review:

- Outcomes in different subgroups of frail older adults. Older people represent a diverse group. More targeted research is needed from high-quality primary studies on the differential impacts of ONS in older adults representing different groups, for example age (i.e. < 85 or > 85 years), stage of frailty, deprivation, social isolation, place of residence (e.g. at home, care homes), marital status, ethnicity and comorbidities. Future research should also routinely collect and report outcomes in relation to mediators. This would allow the further development of potential tools that could assess the effectiveness of prescribable ONS in particular groups of older adults.
- Comparison of ONS with other dietary interventions. Our review did not find studies with a wide range of dietary interventions as comparators; for example, no studies had trial arms that promoted energy-dense meals through food enrichment (e.g. choosing full-fat and full-sugar products, nourishing drinks and food enrichment). Future studies should incorporate these dietary approaches compared with, and in combination with, the use of ONS.
- More evidence on comparisons with multicomponent interventions. While some trial arms incorporated ONS alongside exercise, steroids or dietary advice, further research should examine the impact of combined interventions beyond prescribable ONS, including protein/protein-energy supplementation and exercise.
- Detailed qualitative research to explore the acceptability and perspectives of patients. There was a lack of detailed qualitative work to discuss the lived experiences of patients prescribed ONS (vs. other treatments). A mixed-methods approach incorporating detailed interviews/focus groups should be added to subsequent trials.
- Collection of outcome data most relevant to patients. Although a variety of outcomes were reported in the primary studies, our PPIE group members were more concerned with functional or QoL-related outcomes than more clinically driven outcomes. Functional status assessed with either self-report or performance-based measures should be routinely collected alongside clinical outcomes so that patients can realistically assess the likely impact of ONS and other nutritional support interventions on their daily life.

- Duration of follow-up. The length of follow-up varied greatly across the studies, and few studies looked at the impact of outcomes in the longer term. Specifically, few examined the impact on hospitalisation, morbidity and mortality.
- Detailed reporting of trial arms. Although the ONS intervention was often described in some depth, too often there was little information on SC (which varied in studies and settings) or the precise nature of dietary counselling/advice. More comprehensive reporting (e.g. using a standard checklist) of standard/usual care should be included in published trial outputs.
- Cost-effectiveness of ONS interventions across different settings. Only one study evaluated the cost-effectiveness of ONS in a nursing home, and no cost-effectiveness studies were conducted in the home or hospital setting. More primary studies with detailed cost-effectiveness reporting are needed. In addition, there was considerable variation in the cost of ONS across studies. Further research should clarify if there is any difference in effectiveness across types of ONS.

Acknowledgements

We thank the members of the Elders Council of Newcastle who were involved in the PPIE sessions that took place throughout the project.

Contributions of authors

Katie Thomson (https://orcid.org/0000-0002-9614-728X) (Research Associate) co-led the writing of the final report and co-supervised the conduct and write-up of the systematic review. She also oversaw the public engagement and led the stakeholder dissemination workshop.

Stephen Rice (https://orcid.org/0000-0002-6767-0813) (Senior Research Associate, Health Economics) co-led the writing of the protocol and the final report. He also supervised the meta-analysis, conducted the network meta-analysis and led the development of the cost-effectiveness model.

Oluwatomi Arisa (https://orcid.org/0000-0001-8581-6073) (Research Assistant, Evidence Synthesis Group) contributed to the screening of studies for the systematic review, data extraction of the systematic review, meta-analysis and the bias elicitation assessment. She also contributed to the writing of the final report.

Eugenie Johnson (https://orcid.org/0000-0003-3324-7141) (Training Fellow, Evidence Synthesis Group) contributed to the screening of studies for the systematic review, data extraction of the systematic review and the bias elicitation assessment. She also contributed to the writing of the final report.

Louise Tanner (https://orcid.org/0000-0003-2340-8677) (Research Associate, Evidence Synthesis Group) contributed to the data extraction of the systematic review and meta-analysis. She also contributed to the writing of the final report.

Christopher Marshall (https://orcid.org/0000-0002-7970-681X) (Research Associate, Evidence Synthesis Group) led the development of the protocol, was involved in screening and contributed to the writing of the final report.

Tumi Sotire (https://orcid.org/0000-0002-5330-9568) (Research Assistant, Health Economics) contributed to the cost-effectiveness model. He also contributed to the writing of the final report.

Catherine Richmond (https://orcid.org/0000-0002-2940-5197) (Research Assistant, Evidence Synthesis Group) designed and ran the searches for the systematic review, helped manage the references and referencing, and contributed to the writing of the final report.

Hannah O'Keefe (https://orcid.org/0000-0002-0107-711X) (Research Assistant, Evidence Synthesis Group) managed the references and referencing and contributed to the writing of the final report.

Wael Mohammed (https://orcid.org/0000-0003-0370-4903) (Research Assistant, Health Economics) contributed to the screening of studies and to the final report.

Margot Gosney (https://orcid.org/0000-0001-9004-7571) (Elderly Care Consultant and Professor of Elderly Care Medicine) contributed to the design and the writing of the protocol, provided advice on the review and contributed to the final report.

Anne Raffle (https://orcid.org/0000-0003-4684-2230) (Chairperson, Elders Council of Newcastle) contributed to the development of the protocol, facilitated the organisation of the PPIE sessions, provided input into the project and contributed to the final report.

Barbara Hanratty (https://orcid.org/0000-0002-3122-7190) (Professor of Primary Care and Public Health) contributed to the design and the writing of the protocol, provided advice on the effectiveness and cost-effectiveness review and contributed to the final report.

Claire T McEvoy (https://orcid.org/0000-0001-8512-3293) (Senior Lecturer in Nutrition and Ageing Research) contributed to the design and writing of the protocol, provided advice on the effectiveness and cost-effectiveness review and contributed to the final report.

Dawn Craig (https://orcid.org/0000-0002-5808-0096) (Professor of Practice in Evidence Synthesis) contributed to the design and writing of the protocol, provided advice on the effectiveness and cost-effectiveness review and contributed to the final report.

Sheena E Ramsay (https://orcid.org/0000-0002-0391-9704) (Clinical Senior Lecturer) was the principal investigator, and she oversaw the running of the project and provided clinical guidance throughout. She contributed to the design of the protocol, screening and data extraction for the systematic review, the bias elicitation assessment and the writing of the final report.

Publication

Thomson KH, Rice S, Arisa O, Johnson E, Tanner L, Marshall C, *et al.* Effectiveness and cost-effectiveness of oral nutritional supplements in frail older people who are malnourished or at risk of malnutrition: a systematic review and meta-analysis. *Lancet Healthy Longev* 2022;**3**:e654–66.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

References

1. Thomson KH, Rice S, Arisa O, Johnson E, Tanner L, Marshall C, *et al.* Effectiveness and cost-effectiveness of oral nutritional supplements in frail older people who are malnourished or at risk of malnutrition: a systematic review and meta-analysis. *Lancet Healthy Longev* 2022;**3**:e654–66.
2. British Association for Parenteral and Enteral Nutrition. *Managing Malnutrition to Improve Lives and Save Money*. Redditch: British Association for Parenteral and Enteral Nutrition; 2018.
3. Bollwein J, Volkert D, Diekmann R, Kaiser MJ, Uter W, Vidal K, *et al.* Nutritional status according to the mini nutritional assessment (MNA®) and frailty in community dwelling older persons: a close relationship. *J Nutr Health Aging* 2013;**17**:351–6. https://doi.org/10.1007/s12603-013-0009-8
4. Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and evidence gaps in the diagnosis and treatment of frailty and malnutrition. *Appl Physiol Nutr Metab* 2017;**42**:449–58. https://doi.org/10.1139/apnm-2016-0652
5. Verlaan S, Ligthart-Melis GC, Wijers SLJ, Cederholm T, Maier AB, de van der Schueren MAE. High prevalence of physical frailty among community-dwelling malnourished older adults – a systematic review and meta-analysis *J Am Med Dir Assoc* 2017;**18**:374–82. https://doi.org/10.1016/j.jamda.2016.12.074
6. Lorenzo-López L, Maseda A, de Labra C, Regueiro-Folgueira L, Rodríguez-Villamil JL, Millán-Calenti JC. Nutritional determinants of frailty in older adults: a systematic review. *BMC Geriatr* 2017;**17**:108. https://doi.org/10.1186/s12877-017-0496-2
7. National Institute for Health and Care Excellence (NICE). *Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition*. 2017. URL: www.nice.org.uk/guidance/cg32 (accessed 30 June 2021).
8. National Institute for Health and Care Excellence (NICE). *Nutrition Support in Adults*. Quality Standard [QS24]. London: NICE; 2012. URL: www.nice.org.uk/guidance/qs24/chapter/Quality-statement-2-Treatment (accessed 30 June 2021).
9. Office for National Statistics. *Living Longer: How Our Population is Changing and Why it Matters*. London: Office for National Statistics; 2019.
10. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, MODEM project. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing* 2018;**47**:374–80. https://doi.org/10.1093/ageing/afx201
11. Guzman-Castillo M, Ahmadi-Abhari S, Bandosz P, Capewell S, Steptoe A, Singh-Manoux A, *et al.* Forecasted trends in disability and life expectancy in England and Wales up to 2025: a modelling study. *Lancet Public Health* 2017;**2**:e307–13. https://doi.org/10.1016/S2468-2667(17)30091-9
12. National Institute for Health and Care Excellence (NICE). *Older People with Social Care Needs and Multiple Long-Term Conditions*. NICE Guideline [NG22]. London: NICE; 2015.
13. O'Keeffe M, Kelly M, O'Herlihy E, O'Toole PW, Kearney PM, Timmons S, *et al.* Potentially modifiable determinants of malnutrition in older adults: a systematic review. *Clin Nutr* 2018;**38**:2477–98. https://doi.org/10.1016/j.clnu.2018.12.007

14. Cereda E, Pedrolli C, Klersy C, Bonardi C, Quarleri L, Cappello S, *et al.* Nutritional status in older persons according to healthcare setting: a systematic review and meta-analysis of prevalence data using MNA®. *Clin Nutr* 2016;**35**:1282–90. https://doi.org/10.1016/j.clnu.2016.03.008

15. Russell CA, Elia M. Malnutrition in the UK: where does it begin? *Proc Nutr Soc* 2010;**69**:465–9. https://doi.org/10.1017/S0029665110001850

16. Elia M. *The Cost of Malnutrition in England and Potential Cost Savings from Nutritional Interventions (Short Version)*. Southampton: Malnutrition Action Group of BAPEN and the National Institute for Health and Care Research Southampton Biomedical Research Centre; 2015.

17. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**:752–62. https://doi.org/10.1016/S0140-6736(12)62167-9

18. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011;**27**:1–15. https://doi.org/10.1016/j.cger.2010.08.009

19. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–56. https://doi.org/10.1093/gerona/56.3.m146

20. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007;**62**:722–7. https://doi.org/10.1093/gerona/62.7.722

21. Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N, Fernández-Gutierrez N, Malafarina V. 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* 2016;**93**:89–99. https://doi.org/10.1016/j.maturitas.2016.04.009

22. Stratton RJ, Elia M. Encouraging appropriate, evidence-based use of oral nutritional supplements. *Proc Nutr Soc* 2010;**69**:477–87. https://doi.org/10.1017/S0029665110001977

23. Elia M, Parsons EL, Cawood AL, Smith TR, Stratton RJ. Cost-effectiveness of oral nutritional supplements in older malnourished care home residents. *Clin Nutr* 2018;**37**:651–8. https://doi.org/10.1016/j.clnu.2017.02.008

24. Elia M, Normand C, Norman K, Laviano A. A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in the hospital setting. *Clin Nutr* 2016;**35**:370–80. https://doi.org/10.1016/j.clnu.2015.05.010

25. Cawood AL, Green C, Stratton RJ. The budget impact of using oral nutritional supplements in older community patients at high risk of malnutrition in England. *Proc Nutr Soc* 2011;**69**:E544. https://doi.org/10.1017/S0029665110004131

26. Correa-Pérez A, Abraha I, Cherubini A, Collinson A, Dardevet D, de Groot LCPGM, *et al.* 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 Res Rev* 2019;**49**:27–48. https://doi.org/10.1016/j.arr.2018.10.011

27. Avenell A, Smith TO, Curtain JP, Mak JC, Myint PK. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database Syst Rev* 2016;**11**:CD001880. https://doi.org/10.1002/14651858.CD001880.pub6

28. Liu Y, Xue X. Systematic review of peri-operative nutritional support for patients undergoing hepatobiliary surgery. *Hepatobiliary Surg Nutr* 2015;**4**:304–12. https://doi.org/10.3978/j.issn.2304-3881.2014.12.09

29. de van der Schueren MA, Wijnhoven HA, Kruizenga HM, Visser M. A critical appraisal of nutritional intervention studies in malnourished, community dwelling older persons. *Clin Nutr* 2016;**35**:1008–14. https://doi.org/10.1016/j.clnu.2015.12.013

30. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009;**2**:CD003288. https://doi.org/10.1002/14651858.CD003288.pub3

31. Stratton RJ, Hébuterne X, Elia M. A systematic review and meta-analysis of the impact of oral nutritional supplements on hospital readmissions. *Ageing Res Rev* 2013;**12**:884–97. https://doi.org/10.1016/j.arr.2013.07.002

32. Nieuwenhuizen WF, Weenen H, Rigby P, Hetherington MM. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clin Nutr* 2010;**29**:160–9. https://doi.org/10.1016/j.clnu.2009.09.003

33. British Association of Parenteral and Enteral Nutrition (BAPEN). *Food FirstFood Enrichment*. 2016. URL: www.bapen.org.uk/nutrition-support/nutrition-by-mouth/food-first-food-enrichment (accessed 13 January 2022).

34. Arnold C, Richter MP. The effect of oral nutritional supplements on head and neck cancer. *Int J Radiat Oncol Biol Phys* 1989;**16**:1595–9. https://doi.org/10.1016/0360-3016(89)90968-1

35. Allen VJ, Methven L, Gosney MA. Use of nutritional complete supplements in older adults with dementia: systematic review and meta-analysis of clinical outcomes. *Clin Nutr* 2013;**32**:950–7. https://doi.org/10.1016/j.clnu.2013.03.015

36. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;**95**:1385–95. https://doi.org/10.3945/ajcn.111.023499

37. Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. *Ageing Res Rev* 2012;**11**:278–96. https://doi.org/10.1016/j.arr.2011.12.008

38. Holdoway A, Anderson LM, Ashworth A, Cudby S, Doyle C, Nash L, *et al. Managing Adult Malnutrition in the Community*. 3rd edn. 2021. URL: www.malnutritionpathway.co.uk/library/managing_malnutrition.pdf (accessed 17 October 2022).

39. NHS England. *Guidance – Commissioning Excellent Nutrition and Hydration 2015–2018*. Leeds: NHS England; 2015.

40. Shlisky J, Bloom DE, Beaudreault AR, Tucker KL, Keller HH, Freund-Levi Y, *et al.* Nutritional considerations for healthy aging and reduction in age-related chronic disease. *Adv Nutr* 2017;**8**:17–26. https://doi.org/10.3945/an.116.013474

41. Bloom I, Lawrence W, Barker M, Baird J, Dennison E, Sayer AA, *et al.* What influences diet quality in older people? A qualitative study among community-dwelling older adults from the Hertfordshire Cohort Study, UK. *Public Health Nutr* 2017;**20**:2685–93. https://doi.org/10.1017/S1368980017001203

42. Robinson SM. Improving nutrition to support healthy ageing: what are the opportunities for intervention? *Proc Nutr Soc* 2018;**77**:257–64. https://doi.org/10.1017/S0029665117004037

43. Streicher M, van Zwienen-Pot J, Bardon L, Nagel G, Teh R, Meisinger C, *et al.* Determinants of incident malnutrition in community-dwelling older adults: a MaNuEL multicohort meta-analysis. *J Am Geriatr Soc* 2018;**66**:2335–43. https://doi.org/10.1111/jgs.15553

44. Gibbs M, Drey N, Baldwin C. Oral nutrition support interventions for patients who are malnourished or at risk of malnutrition: a survey of clinical practice amongst UK dietitians. *J Hum Nutr Diet* 2019;**32**:108–18. https://doi.org/10.1111/jhn.12599

45. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. https://doi.org/10.1136/bmj.n71

46. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th edn. Oxford: Oxford University Press; 2015.

47. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, *et al.* Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;**348**:g1687. https://doi.org/10.1136/bmj.g1687

48. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. https://doi.org/10.1136/bmj.d5928

49. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83. https://doi.org/10.1136/bmj.313.7052.275

50. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6. https://doi.org/10.1136/bmj.39489.470347.AD

51. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;**64**:401–6. https://doi.org/10.1016/j.jclinepi.2010.07.015

52. Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, *et al.* Completing 'Summary of findings' tables and grading the certainty of the evidence. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Oxford: The Cochrane Collaboration; 2019. pp. 375–402. https://doi.org/10.1002/9781119536604.ch14

53. Parsons EL, Stratton RJ, Cawood AL, Smith TR, Elia M. Oral nutritional supplements in a randomised trial are more effective than dietary advice at improving quality of life in malnourished care home residents. *Clin Nutr* 2017;**36**:134–42. https://doi.org/10.1016/j.clnu.2016.01.002

54. Lee LC, Tsai AC, Wang JY, Hurng BS, Hsu HC, Tsai HJ. Need-based intervention is an effective strategy for improving the nutritional status of older people living in a nursing home: a randomized controlled trial. *Int J Nurs Stud* 2013;**50**:1580–8. https://doi.org/10.1016/j.ijnurstu.2013.04.004

55. Payette H, Boutier V, Coulombe C, Gray-Donald K. Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial. *J Am Diet Assoc* 2002;**102**:1088–95. https://doi.org/10.1016/S0002-8223(02)90245-2

56. Tylner S, Cederholm T, Faxén-Irving G. Effects on weight, blood lipids, serum fatty acid profile and coagulation by an energy-dense formula to older care residents: a randomized controlled crossover trial. *J Am Med Dir Assoc* 2016;**17**:275.e5–11. https://doi.org/10.1016/j.jamda.2015.12.005

57. Van Wymelbeke V, Brondel L, Bon F, Martin-Pfitzenmeyer I, Manckoundia P. 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* 2016;**15**:93–100. https://doi.org/10.1016/j.clnesp.2016.06.012

58. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.2*; 2021.

59. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002. https://doi.org/10.1136/bmj.d4002

60. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: analysing data and undertaking meta-analyses. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (Updated February 2022).* Cochrane; 2022.

61. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022).* Cochrane; 2022.

62. Borenstein M, Hedges LV, Higgins JPT, Rothstein H. *Introduction to Meta-Analysis.* Chichester: John Wiley & Sons; 2009. https://doi.org/10.1002/9780470743386

63. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;**10**:325–37. https://doi.org/10.1023/A:1008929526011

64. National Institute for Health and Care Excellence (NICE). *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.* London: NICE; 2014.

65. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, *et al.* Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;**7**:55–79. https://doi.org/10.1002/jrsm.1164

66. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;**7**:434–55. https://doi.org/10.1080/10618600.1998.10474787

67. Lauque S, Arnaud-Battandier F, Mansourian R, Guigoz Y, Paintin M, Nourhashemi F, Vellas B. Protein-energy oral supplementation in malnourished nursing-home residents. A controlled trial. *Age Ageing* 2000;**29**:51–6. https://doi.org/10.1093/ageing/29.1.51

68. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. *Clin Rehabil* 2006;**20**:311–23. https://doi.org/10.1191/0269215506cr942oa

69. Tidermark J, Ponzer S, Carlsson P, Söderqvist A, Brismar K, Tengstrand B, Cederholm T. Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. *Clin Nutr* 2004;**23**:587–96. https://doi.org/10.1016/j.clnu.2003.10.006

70. Luo M, Golubev G, Klyukvin I, Reznik L, Kuropatkin G, Oliver JS, *et al.* Oral nutrition supplement improved nutritional status in malnourished hip fracture patients: a randomized controlled study. *J Sci Res Rep* 2015;**4**:480–9. https://doi.org/10.9734/JSRR/2015/13908

71. Cameron ID, Kurrle SE, Uy C, Lockwood KA, Au L, Schaafsma FG. Effectiveness of oral nutritional supplementation for older women after a fracture: rationale, design and study of the feasibility of a randomized controlled study. *BMC Geriatr* 2011;**11**:32. https://doi.org/10.1186/1471-2318-11-32

72. Otten L, Kiselev J, Franz K, Steinhagen-Thiessen E, Müller-Werdan U, Eckardt R, *et al.* MON-P021: Effect of a three month post-hospital nutritional intervention on functional performance in frail and malnourished older dults – a randomized controlled study. *Clin Nutr* 2016;**35**:S161. https://doi.org/10.1016/S0261-5614(16)30655-0

73. Parsons EL, Stratton RJ, Cawood AL, Smith TR, Warwick H, Elia M. Randomized controlled trial in care home residents shows improved quality of life (QOL) with oral nutritional supplements. *Clin Nutr Suppl* 2011;**6**:31. https://doi.org/10.1016/S1744-1161(11)70075-8

74. Luo M, Golybev G, Klyukvin I, Reznik L, Kuropatkin G, Voss AC. Oral nutritional supplement (ONS) improved nutritional status in malnourished patients receiving hip fracture surgery. *Clin Nutr Suppl* 2011;**6**:151. https://doi.org/10.1016/S1744-1161(11)70389-1

75. de Jong N, Chin A Paw MJ, de Graaf C, van Staveren WA. Effect of dietary supplements and physical exercise on sensory perception, appetite, dietary intake and body weight in frail elderly subjects. *Br J Nutr* 2000;**83**:605–13. https://doi.org/10.1017/S0007114500000775

76. Pouysségur V, Castelli C, Antoine V, Chkair S, Bouvet S. Solid oral supplementation: economic assessment. Economic impact of the introduction of a solid oral nutritional supplement adapted to malnourished older adults with poor dental health. *Eur Geriatr Med* 2017;**8**:234–9. https://doi.org/10.1016/j.eurger.2017.04.012

77. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013*. Process and Methods [PMG9]. London: NICE; 2013.

78. Nakazawa A, Nakamura K, Kitamura K, Yoshizawa Y. Association between body mass index and mortality among institutionalized elderly adults in Japan. *Environ Health Prev Med* 2013;**18**:502–6. https://doi.org/10.1007/s12199-013-0351-9

79. Rönneikkö JK, Mäkelä M, Jämsen ER, Huhtala H, Finne-Soveri H, Noro A, Valvanne JN. Predictors for unplanned hospitalization of new home care clients. *J Am Geriatr Soc* 2017;**65**:407–14. https://doi.org/10.1111/jgs.14486

80. Hunger M, Thorand B, Schunk M, Döring A, Menn P, Peters A, Holle R. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. *Health Qual Life Outcomes* 2011;**9**:53. https://doi.org/10.1186/1477-7525-9-53

81. Office for National Statistics. *Life Tables, Principal Projections, UK*. 2018. URL: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/lifetablesprincipalprojectionunitedkingdom (accessed 5 February 2021).

82. Szende A, Janssen B, Cabases J, editors. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht: Springer; 2014. https://doi.org/10.1007/978-94-007-7596-1

83. NHS England. *2019/20 National Cost Collection Data*. 2021. URL: www.england.nhs.uk/national-cost-collection/ (accessed 26 July 2021).

84. Joint Formulary Committee. *BNF 78 (British National Formulary) September 2019*. London: BMJ Group and Pharmaceutical Press; 2019.

85. National Institute for Health and Care Excellence (NICE). *MCTprocal*. 2021. URL: https://bnf.nice.org.uk/borderline-substance/mctprocal.html (accessed 10 February 2021).

86. Pound Sterling Live. *PoundSterling LIVE*. 2021. URL: www.poundsterlinglive.com (accessed 11 May 2021).

87. Pharmacy Online. *Sustagen Hospital Formula Active Neutral 840g*. 2021. URL: www.pharmacyonline.com.au/sustagen-hospital-formula-neutral-840g (accessed 10 February 2021).

88. NineLife. *Novasource 2*. 2021. URL: www.ninelife.uk/products/novasource-renal-flavor-vanilla-nestle-nutritional-351100 (accessed 10 February 2021).

89. Nutrisens Online Store. *Brioche Bread*. 2021. URL: www.nutrisens.com/shop/en/116-brioche-bread/#/39-flavour-plain/53-packaging-box_of_30 (accessed 10 February 2021).

90. NutriDrinks. *Calogen EXTRA Strawberry (200ml)*. 2021. URL: www.nutridrinks.co.uk/calogen-extra-strawberry (accessed 10 February 2021).

91. National Institute for Health and Care Excellence (NICE). *Fortisip Extra*. 2021. URL: bnf.nice.org.uk/borderline-substance/fortisip-extra.html (accessed 10 February 2021).

92. SweetCare. *Fortimel Compact Nutritional Supplement High-Energy – Nutricia*. 2021. URL: www.sweetcare.com/nutricia-fortimel-compact-oral-nutritional-supplement-high-energy-p-002599ni (accessed 10 February 2021).

93. Curtis L, Burns A. *Unit Costs of Health and Social Care 2018*. Canterbury: Personal Social Services Research Unit, University of Kent; 2018.

94. NutriDrinks. *Nestle Resource Energy Vanilla (4x200ml)*. 2021. URL: www.nutridrinks.co.uk/nestle-resource-energy-vanilla-4 (accessed 10 February 2021).

95. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *Br J Psychiatry* 2005;**187**:106–8. https://doi.org/10.1192/bjp.187.2.106

96. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012;**104**:371–85. https://doi.org/10.1093/jnci/djr556

97. Mello AT, Borges DS, de Lima LP, Pessini J, Kammer PV, Trindade EBSM. Effect of oral nutritional supplements with or without nutritional counselling on mortality, treatment tolerance and quality of life in head-and-neck cancer patients receiving (chemo)radiotherapy: a systematic review and meta-analysis. *Br J Nutr* 2021;**125**:530–47. https://doi.org/10.1017/S0007114520002329

98. Liu PJ, Ma F, Wang QY, He SL. The effects of oral nutritional supplements in patients with maintenance dialysis therapy: a systematic review and meta-analysis of randomized clinical trials. *PLOS ONE* 2018;**13**:e0203706. https://doi.org/10.1371/journal.pone.0203706

99. Beck AM, Holst M, Rasmussen HH. Oral nutritional support of older (65 years+) medical and surgical patients after discharge from hospital: systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil* 2013;**27**:19–27. https://doi.org/10.1177/0269215512445396

100. Lidder PG, Lewis S, Duxbury M, Thomas S. Systematic review of postdischarge oral nutritional supplementation in patients undergoing GI surgery. *Nutr Clin Pract* 2009;**24**:388–94. https://doi.org/10.1177/0884533609332175

101. Kennedy O, Law C, Methven L, Mottram D, Gosney M. Investigating age-related changes in taste and affects on sensory perceptions of oral nutritional supplements. *Age Ageing* 2010;**39**:733–8. https://doi.org/10.1093/ageing/afq104

102. den Boer A, Boesveldt S, Lawlor JB. How sweetness intensity and thickness of an oral nutritional supplement affects intake and satiety. *Food Qual Prefer* 2019;**71**:406–14. https://doi.org/10.1016/j.foodqual.2018.08.009

103. Liljeberg E, Nydahl M, Lövestam E, Andersson A. A qualitative exploration of dietitians' experiences of prescribing oral nutritional supplements to patients with malnutrition: a focus on shared tailoring and behaviour change support. *J Hum Nutr Diet* 2021;**34**:858–67. https://doi.org/10.1111/jhn.12867

104. Dominguez Castro P, Reynolds CM, Kennelly S, Clyne B, Bury G, Hanlon D, *et al.* General practitioners' views on malnutrition management and oral nutritional supplementation prescription in the community: a qualitative study. *Clin Nutr ESPEN* 2020;**36**:116–27. https://doi.org/10.1016/j.clnesp.2020.01.006

105. Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. *Clin Nutr* 2012;**31**:293–312. https://doi.org/10.1016/j.clnu.2011.11.020

106. den Uijl LC, Kremer S, Jager G, van der Stelt AJ, de Graaf C, Gibson P, *et al.* That's why I take my ONS. Means–end chain as a novel approach to elucidate the personally relevant factors driving ONS consumption in nutritionally frail elderly users. *Appetite* 2015;**89**:33–40. https://doi.org/10.1016/j.appet.2015.01.016

107. Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials* 2008;**29**:109–13. https://doi.org/10.1016/j.cct.2007.08.001

108. Parsons EL, Stratton RJ, Jackson JM, Elia M. OC-039-Oral nutritional supplements are cost effective in improving quality adjusted life years in malnourished care home residents. *Gut* 2012;**61**:A17. https://doi.org/10.1136/gutjnl-2012-302514a.39

109. Parsons EL, Stratton RJ, Cawood AL, Jackson JM, Elia M. PP047-SUN oral nutritional supplements are more cost effective than dietary advice in improving quality adjusted life years (QALYS) in malnourished care home residents. *Clin Nutr Suppl* 2012;**7**:44. https://doi.org/10.1016/S1744-1161(12)70099-6

110. Schwarzer G, Carpenter JR, Rücker G. *Meta-Analysis with R*. Cham: Springer International Publishing; 2015. https://doi.org/10.1007/978-3-319-21416-0

111. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. Updated October 2013*. The GRADE Working Group; 2013. URL: https://gdt.gradepro.org/app/handbook/handbook.html (accessed 12 September 2022).

112. Edington J, Barnes R, Bryan F, Dupree E, Frost G, Hickson M, *et al.* A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. *Clin Nutr* 2004;**23**:195–204. https://doi.org/10.1016/S0261-5614(03)00107-9

113. Arnaud-Battandier F, Malvy D, Jeandel C, Schmitt C, Aussage P, Beaufrère B, Cynober L. Use of oral supplements in malnourished elderly patients living in the community: a pharmaco-economic study. *Clin Nutr* 2004;**23**:1096–103. https://doi.org/10.1016/j.clnu.2004.02.007

114. Seguy D, Hubert H, Robert J, Meunier JP, Guérin O, Raynaud-Simon A. Compliance to oral nutritional supplementation decreases the risk of hospitalisation in malnourished older adults without extra health care cost: prospective observational cohort study. *Clin Nutr* 2020;**39**:1900–7. https://doi.org/10.1016/j.clnu.2019.08.005

115. Zhong Y, Cohen JT, Goates S, Luo M, Nelson J, Neumann PJ. The cost-effectiveness of oral nutrition supplementation for malnourished older hospital patients. *Appl Health Econ Health Policy* 2017;**15**:75–83. https://doi.org/10.1007/s40258-016-0269-7

116. Freijer K, Nuijten MJC, Schols JMGA. The budget impact of oral nutritional supplements for disease related malnutrition in elderly in the community setting. *Front Pharmacol* 2012;**3**:78. https://doi.org/10.3389/fphar.2012.00078

117. Nuijten M, Mittendorf T. The health economic impact of oral nutritional supplements (ONS) in Germany. *Aktuelle Ernahrungsmedizin* 2012;**37**:126–33. https://doi.org/10.1055/s-0032-1304940

Appendix 1 Search strategies

Searches were designed in Ovid MEDLINE and translated into other databases, as follows.

Date range: inception to date searched.

Dates searched: 26 and 27 February 2020.

The searches were updated 13 September 2021.

MEDLINE (via Ovid)

1. exp Frail Elderly/
2. exp Frailty/
3. frail*.ti,ab,kw,kf.
4. ((older or aged) adj (person* or people or patient* or population*)).ti,ab,kw,kf.
5. ((geriatric or elder*) adj2 (people or person* or patient* or population*)).ti,ab,kw,kf.
6. exp Nursing Homes/ or exp Homes for the Aged/
7. ((residential or nursing or care) adj home*).ti,ab,kw,kf.
8. exp Respite Care/
9. exp Long-Term Care/
10. "home* for the aged".ti,ab,kw,kf.
11. "old age home*".ti,ab,kw,kf.
12. "skilled nursing facilit*".ti,ab,kw,kf.
13. "intermediate care facilit*".ti,ab,kw,kf.
14. "respite care".ti,ab,kw,kf.
15. "long term care facilit*".ti,ab,kw,kf.
16. or/1-15
17. Dietary Supplements/
18. Malnutrition/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
19. Nutritional Support/
20. Food, Fortified/
21. Food, Formulated/
22. "oral nutrition*".ti,ab,kw,kf.
23. "dietary counselling".ti,ab,kw,kf.
24. "dietary supplement*".ti,ab,kw,kf.
25. (food adj2 (fortif* or formulat*)).ti,ab,kw,kf.
26. "nutritional intervention*".ti,ab,kw,kf.
27. "liquid supplement*".ti,ab,kw,kf.
28. "sip feed*".ti,ab.
29. "nutrition* management".ti,ab,kw,kf.
30. (nutri* adj2 (supplement* or therapy)).ti,ab,kw,kf.
31. (maln* adj2 (prevent* or management or risk factor*)).ti,ab,kw,kf.
32. or/17-31
33. 16 and 32
34. exp animal/ not human/
35. 33 not 34
36. limit 35 to english language.

EMBASE (via Ovid)

1. exp frail elderly/
2. exp frailty/
3. frail*.ti,ab,kw.
4. ((older or aged) adj (person* or people or patient* or population*)).ti,ab,kw.
5. ((geriatric or elder*) adj2 (frail* or people or person* or patient* or population*)).ti,ab,kw.
6. exp nursing home/
7. exp home for the aged/
8. ((residential or nursing or care) adj home*).ti,ab,kw.
9. exp respite care/
10. long term care/
11. "home* for the aged".ti,ab,kw.
12. "old age home*".ti,ab,kw.
13. "skilled nursing facilit*".ti,ab,kw.
14. "intermediate care facilit*".ti,ab,kw.
15. "respite care".ti,ab,kw.
16. "long term care facilit*".ti,ab,kw.
17. or/1-16
18. dietary supplement/
19. malnutrition/dt, pc, th [Drug Therapy, Prevention, Therapy]
20. nutritional support/
21. fortified food/
22. elemental diet/
23. "oral nutrition*".ti,ab,kw.
24. "dietary counselling".ti,ab,kw.
25. "dietary supplement*".ti,ab,kw.
26. (food adj2 (fortif* or formulat*)).ti,ab,kw.
27. "nutritional intervention*".ti,ab,kw.
28. "liquid supplement*".ti,ab,kw.
29. "sip feed*".ti,ab.
30. "nutrition* management".ti,ab,kw.
31. (nutri* adj2 (supplement* or therapy)).ti,ab,kw.
32. (maln* adj2 (prevent* or management or risk factor*)).ti,ab,kw.
33. or/18-32
34. 17 and 33
35. exp animal/
36. exp human/
37. 35 not 36
38. 34 not 37
39. limit 38 to english language.

Cochrane

#1 MeSH descriptor: [Frail Elderly] explode all trees
#2 MeSH descriptor: [Frailty] explode all trees
#3 (frail*):ti,ab,kw
#4 (((older or aged) NEAR/1 (person* or people or patient* or population*))):ti,ab,kw
#5 (((geriatric or elder*) NEAR/2 (people or person* or patient* or population*))):ti,ab,kw
#6 MeSH descriptor: [Nursing Homes] explode all trees
#7 (((residential or nursing or care) NEAR/1 home*)):ti,ab,kw
#8 MeSH descriptor: [Respite Care] explode all trees

#9 MeSH descriptor: [Long-Term Care] explode all trees
#10 (home* NEXT "for the aged"):ti,ab,kw
#11 ("old age" NEXT home*):ti,ab,kw
#12 ("skilled nursing" NEXT facilit*):ti,ab,kw
#13 ("intermediate care" NEXT facilit*):ti,ab,kw
#14 ("respite care"):ti,ab,kw
#15 ("long term care" NEXT facilit*):ti,ab,kw
#16 (OR #1-#15)
#17 MeSH descriptor: [Dietary Supplements] this term only
#18 MeSH descriptor: [Malnutrition] this term only and with qualifier(s): [therapy - TH, diet therapy - DH, drug therapy - DT, prevention & control - PC]
#19 MeSH descriptor: [Nutritional Support] this term only
#20 MeSH descriptor: [Food, Fortified] this term only
#21 MeSH descriptor: [Food, Formulated] this term only
#22 (oral NEXT nutrition*):ti,ab,kw
#23 ("dietary counselling"):ti,ab,kw
#24 (dietary NEXT supplement*):ti,ab,kw
#25 ((food NEAR/2 (fortif* or formulat*))):ti,ab,kw
#26 (nutritional NEXT intervention*):ti,ab,kw
#27 (liquid NEXT supplement*):ti,ab,kw
#28 (sip NEXT feed*):ti,ab,kw
#29 (nutrition* NEXT management):ti,ab,kw
#30 ((nutri* NEAR/2 (supplement* or therapy))):ti,ab,kw
#31 ((maln* NEAR/2 (prevent* or management or risk factor*))):ti,ab,kw
#32 (OR #17-#31)
#33 #16 AND #32.

CINAHL (via EBSCO*host*)

S38 S37 AND LA English
S37 S33 NOT S36
S36 S34 NOT S35
S35 (MH "Human")
S34 (MH "Animals+")
S33 S16 AND S32
S32 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31 TI ((maln* N2 (prevent* or management or risk factor*))) OR AB ((maln* N2 (prevent* or management or risk factor*)))
S30 TI ((nutri* N2 (supplement* or therapy))) OR AB ((nutri* N2 (supplement* or therapy)))
S29 TI "nutrition* management" OR AB "nutrition* management"
S28 TI "sip feed*" OR AB "sip feed*"
S27 TI "liquid supplement*" OR AB "liquid supplement*"
S26 TI "nutritional intervention*" OR AB "nutritional intervention*"
S25 TI ((food N2 (fortif* or formulat*))) OR AB ((food N2 (fortif* or formulat*)))
S24 TI "dietary supplement*" OR AB "dietary supplement*"
S23 TI "dietary counselling" OR AB "dietary counselling"
S22 TI "oral nutrition*" OR AB "oral nutrition*"
S21 (MH "Food, Formulated")
S20 (MH "Food, Fortified")
S19 (MH "Nutritional Support")
S18 (MH "Malnutrition/DH/DT/PC/TH")

S17 (MH "Dietary Supplements")
S16 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S15 TI "long term care facilit*" OR AB "long term care facilit*"
S14 TI "respite care" OR AB "respite care"
S13 TI "intermediate care facilit*" OR AB "intermediate care facilit*"
S12 TI "skilled nursing facilit*" OR AB "skilled nursing facilit*"
S11 TI "old age home*" OR AB "old age home*"
S10 (MH "Long Term Care")
S9 (MH "Respite Care")
S8 TI (((residential or nursing or care) N1 home*)) OR AB (((residential or nursing or care) N1 home*))
S7 TI home* for the aged OR AB home* for the aged
S6 (MH "Nursing Homes+")
S5 TI (((geriatric or elder*) N2 (people or person* or patient* or population*))) OR AB (((geriatric or elder*) N2 (people or person* or patient* or population*)))
S4 TI (((older or aged) N1 (person* or people or patient* or population*))) OR AB (((older or aged) N1 (person* or people or patient* or population*)))
S3 TI frail* OR AB frail*
S2 (MH "Frailty Syndrome")
S1 (MH "Frail Elderly").

Scopus

((TITLE-ABS-KEY (frail*) OR TITLE-ABS-KEY (((older OR aged) W/1 (person* OR people OR patient* OR population*))) OR TITLE-ABS-KEY (((geriatric OR elder*) W/2 (people OR person* OR patient* OR population*))) OR TITLE-ABS-KEY (((residential OR nursing OR care) W/1 home*)) OR TITLE-ABS-KEY ("home* for the aged") OR TITLE-ABS-KEY ("old age home*") OR TITLE-ABS-KEY ("skilled nursing facilit*") OR TITLE-ABS-KEY ("intermediate care facilit*") OR TITLE-ABS-KEY ("respite care") OR TITLE-ABS-KEY ("long term care facilit*"))) AND ((TITLE-ABS-KEY ("oral nutrition*")) OR (TITLE-ABS-KEY ("dietary counselling")) OR (TITLE-ABS-KEY ("dietary supplement*")) OR (TITLE-ABS-KEY ((food W/2 (fortif* OR formulat*)))) OR (TITLE-ABS-KEY ("nutritional intervention*")) OR (TITLE-ABS-KEY ("liquid supplement*")) OR (TITLE-ABS-KEY ("sip feed*")) OR (TITLE-ABS-KEY ("nutrition* management")) OR (TITLE-ABS-KEY ((nutri* W/2 (supplement* OR therapy)))) OR (TITLE-ABS-KEY ((maln* W/2 (prevent* OR management OR "risk factor*" OR therapy))))) AND NOT INDEX (medline) AND (LIMIT-TO (LANGUAGE , "English"))

Appendix 2 Duplicate data reporting across included studies

Study ID	Paper (Covidence ID)	Study dates	Sample size	Outcomes	Decision
Parsons 2011	Parsons 2017[53]	NR	104	Health-related QoL, assessed using EQ-5D-3L and mortality	Issue: all papers report on specific economic measures. Parsons 2011[73] and 2017[53] report on QoL using the EQ-5D Decision: Parsons 2017[53] was used to report on QoL; Elia 2020[23] was used to report on economic outcomes
	Parsons 2011[73] (3954)	NR	104	QoL at baseline and 12 weeks using EQ-5D, including a TTO (range –0.073 to 1) and a VAS (score 0–100) for self-perceived health	
	Parsons 2012[108] (2744)	NR	104	QALYs calculated from QoL (measured using EQ-5D TTO, VAS rescaled and mortality); costs of health-care visits and hospital admissions (3 months prior to and during the RCT) and the interventions calculated using standard unit costs; ICER and probability that one intervention was more cost-effective than the other (cost < £20,000–30,000/QALY gained) were calculated	
	Parsons 2012[109] (4023)	NR	104	QALYs calculated from QoL measured using EQ-5D TTO, VAS and mortality *Costs of healthcare visits and hospital admissions (3 months prior to and during the RCT) and the interventions were calculated using standard unit costs. The incremental cost effectiveness ratio (ICER) and the probability that one intervention was more cost effective than the other (cost < £20,000 30,000/QALY gained) were calculated*	
	Elia 2017[23] (249)	August 2007 to March 2010	104	Costs of interventions (dietetic costs and costs of ONS where relevant as specified in the study protocol); number of QALYs gained during the intervention period, calculated using standard procedures based on a combination of QoL and mortality; cost-effectiveness analysis during the 12-week intervention period	

Study ID	Paper (Covidence ID)	Study dates	Sample size	Outcomes	Decision
Luo 2015[70]	Luo 2015[70]	2009 to 2010	46	Change in body weight in kg; change in other indicators of nutritional status measured by serum albumin and prealbumin levels; change in nutritional intake measured by the total protein in grams per litre; improvement in gait speed	Issue: the abstract did not report all outcomes that were measured. The abstract refers to the measurement of morbidity using the Modified Barthel Index, but no data were reported Decision: Luo 2015[70] was used as it a full text and reports numerous outcomes of interest
	Luo 2011[74]	NR	46	Change in body weight in kg; change in other indicators of nutritional status measured by serum albumin and prealbumin levels; morbidity measured using chair-to-bed transfer domain from the Modified Barthel Index	

Appendix 3 Final values and change from baseline calculations

Mean CFB values and standard deviations were imputed from the baseline and final values and standard deviations using the following equations:

$$Change = final - baseline. \tag{1}$$

$$SD_{change} = \sqrt{SD_{base}^2 + SD_{final}^2 - (2 \times corr \times SD_{base} \times SD_{final})}. \tag{2}$$

Mean final values and standard deviations can be imputed from CFB and baseline values and standard deviations using the following equations:

$$Final = baseline + change. \tag{3}$$

$$SD_{final} = \frac{2 \times corr \times SD_{base} + \sqrt{4 \times corr^2 \times SD_{base}^2 - 4 \times (SD_{base}^2 - SD_{change}^2)}}{2}. \tag{4}$$

There are two possible solutions for SD_{final}, but this equation always produces a real solution and a conservative one, in which a feasible value for the correlation is used.

No studies reported the standard deviation for SD_{base}, SD_{change} and SD_{final}, so the correlation could not be calculated from reported statistics. Feasible values for the correlation are described by the inequality:

$$\frac{SD_{base}^2 + SD_{final}^2}{2 \times SD_{base} \times SD_{final}} < Corr < 1. \tag{5}$$

The process for setting the correlation and standard deviation was as follows. In every case, the correlation value was varied until the standard deviation got as close to the targeted standard deviation as possible with the correlation value remaining within the feasible range. The average standard deviation across the treatment groups at baseline, CFB and final values were calculated, and the targeted standard deviation was based on the average of the standard deviations.

Change from baseline

For CFB values, the decision rule was guided by the standard deviation values for studies reporting the same outcome measure. There were two options.

Option A

Select the correlation value where the average estimated standard deviation for change values is closest to, but not higher than, the highest average standard deviation for change values for other studies that reported change values and the same outcome measure

OR

If there are no other studies that report change values, select the correlation value where the average estimated change value standard deviation is closest to but not higher than 50% the value of the average standard deviation of the standard deviations for the baseline values for that study

AND

The lowest plausible correlation value that achieves either of these.

Option B

Select the standard deviation that got as close as possible to the standard deviation of either the baseline or the final values.

Final values

For final values, the lowest correlation value was set that enabled the average standard deviation to get as close to the average standard deviation at baseline as possible. The average standard deviation was always higher due to the conservative solution used for the standard deviation for the final value.

The ratios of the calculated standard deviations to the baseline standard deviations, the ratios of the reported standard deviations to the baseline standard deviations, and the set correlations are reported in *Table 20* for each outcome. These include results for a few studies from which data were extracted but were not finally included in the review. The outcomes and context of the excluded studies are still relevant for assessing the plausibility of the imputed values.

TABLE 20 Reported and derived standard deviation ratio ranges and correlation ranges between baseline and final values

		Reported		Derived		
Outcome	**Value**	***n***	**SD ratio**	***n***	**Correlation**	**SD ratio**
Body weight	CFB	7	0.14–0.47	3	0.93–0.97	0.37–0.39
	FV	4	0.88–1.03	6	0.9–1	1.06–1.30
Calf circumference	CFB	2	0.46–0.79	3	0.89–0.94	0.34–0.48
	FV	3	0.97–1.04	2	0.91–0.99	1.42–1.52
BMI	CFB	3	0.45–0.54	5	0.88–0.94	0.34–0.50
	FV	5	0.81–1.09	3	0.93–0.98	1.27–1.36
Energy intake	CFB	4	0.13–1.65	3	0.42–0.43	1–1.32
	FV	3	0.78–1.27	3	0.44–0.82	1.21–1.65
Protein	CFB	5	0.13–2.13	3	0.5–0.7	0.98–1
	FV	3	0.9–1.32	4	0.26–1	1.13–2.14
Albumin	CFB	4	0.47–1.86	2	0.58–0.63	0.79–0.99
	FV	3	0.8–1.86	3	0.62–0.95	1.06–1.57
Grip strength	CFB	3	0.69–2.92	5	0.53–0.65	0.79–1
	FV	5	0.91–1.28	3	0.7–0.87	1.2–3.18

FV, final value.

Appendix 4 Network graphs

The network graphs for the network meta-analyses are presented in *Figures 19* and *20*. The thickness of the lines represents the relative evidence informing each comparison. The shaded areas represent the presence of at least one multiarm trial. For example, in *Figure 19* there are three studies evaluating the effectiveness of ONS compared with SC. Only one of these is a multiarm trial that compares ONS with brioche and with SC. Different shades represent the presence of different multiarm trials with different comparators. These graphs were produced using netmeta in R.[110]

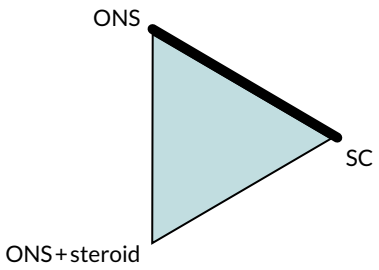


FIGURE 19 Network diagram for body weight.

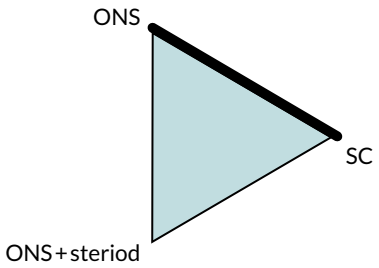


FIGURE 20 Network diagram for grip strength.

Appendix 5 Details of linked publications

Study ID	Primary reference	Other references
Cameron *et al.*[71]	Cameron ID, Kurrle SE, Uy C, Lockwood KA, Au L, Schaafsma FG. Effectiveness of oral nutritional supplementation for older women after a fracture: rationale, design and study of the feasibility of a randomised controlled study. *BMC Geriatr* 2011;**11**:1–6[71]	
Lauque *et al.*[67]	Lauque S, Arnaud-Battandier F, Mansourian R, Guigoz Y, Paintin M, *et al.* Protein-energy oral supplementation in malnourished nursing-home residents. A controlled trial. *Age Ageing* 2000;**29**:51–6[67]	
Lee *et al.*[54]	Lee L-C, Tasi AC, Wang J-Y, Hurng B-S, Hsu H-C, Tsai H-J. Need-based intervention is an effective strategy for improving the nutritional status of older people living in a nursing home: a randomized controlled trial. *Int J Nurs Stud* 2013;**50**:1580–8[54]	
Luo *et al.*[70]	Luo M, Golubev G, Klyukvin I, Rexnik L, Kupatkin G, Oliver JS, Voss Anne C. Oral nutrition supplement improved nutritional status in malnourished hip fracture patients: a randomised controlled study. *J Sci Res Rep* 2015;**4**:480–89[70]	Luo M, Golybev G, Klyukvin I, Reznik L, Kuropatkin G, Voss AC. Oral nutritional supplement (ONS) improved nutritional status in malnourished patients receiving hip fracture surgery. *Clin Nutr Suppl* 2011;**6**:151[74]
Miller *et al.*[68]	Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. *Clin Rehab* 2006;**20**:311–23[68]	
Otten *et al.*[72]	Otten L, Kiselev J, Franz K, Steinhagen-Thiessen E, Müller-Werdan U, Eckardt R, *et al.* MON-P021: effect of a three month post-hospital nutritional intervention on functional performance in frail and malnourished older adults-a randomized controlled study. *Clin Nutr* 2016;**35**:S161[72]	
Payette *et al.*[55]	Payette H, Boutier V, Coulombe C, Grey-Donald K. Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial. *J Am Dietet Assoc* 2002;**102**:1088–95[55]	
Parsons *et al.*[53]	Parsons EL, Strattion RJ, Cawood AL, Smith TR, Elia M. Oral nutritional supplements in a randomised trial are more effective than dietary advice at improving quality of life in malnourished care home residents. *Clin Nutr* 2017;**36**:134–42[53]	Parsons EL, Stratton RJ, Cawood AL, Smith TR, Warwick H, Elia M. PP021-SUN randomised controlled trial in care home residents shows improved quality of life (QOL) with oral nutritional supplements. *Clin Nutr Suppl* 2011;**6**:31[73] Parsons EL, Stratton RJ, Cawood AL, Jackson JM, Elia M. Oral nutritional supplements are more cost-effective in improving quality-adjusted life-years (QALYs) in malnourished care home residents. *Clin Nutr* 2012;**7**:PP047[109] Elia M, Parsons EL, Cawood AL, Smith TR, Stratton RJ. Cost-effectiveness of oral nutritional supplements in older malnourished care home residents. *Clin Nutr* 2018;**37**:651–8[23]

Study ID	Primary reference	Other references
		Parsons EL, Stratton RJ, Jackson JM, Elia M. OC-039 Oral nutritional supplements are cost-effective in improving quality-adjusted life-years in malnourished care home residents. *Gut* 2012;**61**:A17–A[108]
Tidermark *et al.*[69]	Tidermark J, Ponzer S, Carlsson P, Söderqvist A, Brismar K, Tengstrand B, Cederholm T. Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. *Clin Nutr* 2004;**23**:587–96[69]	
Tylner 2016[56]	Tylner S, Cederholm T, Faxén-Irving G. Effects on weight, blood lipids, serum fatty acid profile and coagulation by an energy-dense formula to older care residents: a randomized controlled crossover trial. *J Am Med Direct Assoc* 2016;**17**:275–e5[56]	
Van Wymelbeke *et al.*[57]	Van Wymelbeke V, Brondel L, Bon F, Martin-Pfitzenmeyer I, Manckoundia P. 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 2016;**15**:93–100[57]	

Appendix 6 Study population characteristics table

Study ID	Country	Setting	Number enrolled	Intervention	Number in group	Age (years)	Sex, *n* (%) male	BMI (kg/m^2)	Weight (kg)	Malnutrition score	Number of medications taken
Cameron *et al.*[71]	Australia	Hospital: Hornsby Ku-ring-gai Hospital (a general hospital in northern Sydney)	44	High-calorie, high-protein supplement and diet of choice	23	83.7 ± 5.6	0 (0)	21.5 ± 2.8	50.4 ± 6.0	MUAC mean 24.2 ± 3.1; albumin (g/l) mean 31.1 ± 5.0	NR
				High-protein milk and diet of choice	21	87.1 ± 6.2	0 (0)	21.5 ± 4.0	50.2 ± 11.8	MUAC mean 23.6 ± 2.6; albumin (g/l) mean 31.8 ± 5.4	NR
Lauque *et al.*[67]	France	Nursing home: eight privately run 80-bed nursing homes in Toulouse	88	No supplementation (well nourished)	19	87 ± 6	1 (8.3)	25.2 ± 0.8	61.0 ± 2.8	MNA: all ≥ 24	NR
				No supplements (risk of malnutrition)	22	87 ± 6	1 (6.7)	21.8 ± 0.9	52.5 ± 2.4	MNA: all 17–23.5	NR
				Oral supplements (risk of malnutrition)	19	88 ± 6	3 (20)	22.3 ± 0.7	53.9 ± 2.2	MNA: all 17–23.5	NR
				Oral supplements (malnourished)	28	87 ± 7	2 (5.7)	18.5 ± 0.5	43.9 ± 1.7	MNA: all < 17	NR
Lee *et al.*[54]	Taiwan (Province of China)	Nursing home: geriatric nursing home	92	ONS	47	65–74: 15 (31.9%) 75–84: 21 (44.7%) ≥ 85: 11 (23.4%)	19 (40.4)	20.43 ± 2.5 *n* = 43	48.62 ± 8.02 *n* = 43	MNA: 21.4 ± 3.5	2.8 ± 1.4
				NR	45	65–74: 13 (28.9%) 75–84: 20 (44.4%) ≥ 85: 12 (26.7%)	20 (44.4)	20.31 ± 2.61 *n* = 40	48.3 ± 8.47 *n* = 40	MNA: 20.7 +3.9	2.9 ± 1.5

Study ID	Country	Setting	Number enrolled	Intervention	Number in group	Age (years)	Sex, *n* (%) male	BMI (kg/m²)	Weight (kg)	Malnutrition score	Number of medications taken
Luo *et al.*[70,74]	Russia	Hospitals: hip fracture patients	55	Ensure2: nutritionally complete, calorie-dense, high-protein ONS	26	72.4 ± 1.9	4 (18)	25.1 ± 1.4	70.5 ± 3.6	NR	NR
				Standard hospital food only	29	67.3 ± 2.4	7 (29)	26.7 ± 1.7	72.9 ± 4.6	NR	NR
Miller *et al.*[68]	Australia	Hospital: orthopaedic wards of Flinders Medical Centre, Adelaide	100	Nutrition	25	83.5 ± NR	4 (16)	21.9 + NR	53 ± NR	NR	NR
				Exercise	25	84.8 ± NR	5 (20)	21.4 ± NR	52.3 ± NR	NR	NR
				Nutrition and exercise	24	82.7 ± NR	7 (29)	23.2 ± NR	57.5 ± NR	NR	NR
				Attention control	26	83.1 ± NR	5 (19)	22.1 ± NR	54.7 ± NR	NR	NR
Otten *et al.*[72]	Germany	After hospital discharge	71	Dietary counselling	NR	NR	NR	NR	NR	NR	NR
				ONS	NR	NR	NR	NR	NR	NR	NR
Parsons *et al.*[23,53,73,109]	UK	Nursing home: care homes in Hampshire	104	ONS with guidance	53	89.6 ± 6.9	8 (15.1)	NR	48.5 ± 9.9	MUST: medium risk: 22 (41.5%); high risk: 31 (58.5%)	NR
				Dietary advice	51	87.3 ± 8.7	7 (13.7)	NR	51.1 ± 8.9	MUST: medium risk: 26 (51%); high risk: 25 (49%)	NR
Payette *et al.*[55]	Canada	Community: home	83	ONS	42	81.6 ± 7.6	12 (29)	20.1 ± 2.7	53.7 ± 8.6	Excessive weight loss: 5 (12%)	5.5 ± 2.96 *n* = 39
				Control	41	78.6 ± 6.1	12 (29)	20.1 ± 3.0	52.9 ± 9.3	Excessive weight loss: 5 (12%)	4.9 ± 3.6 *n* = 36

Study ID	Country	Setting	Number enrolled	Intervention	Number in group	Age (years)	Sex, *n* (%) male	BMI (kg/m^2)	Weight (kg)	Malnutrition score	Number of medications taken
Tidermark *et al.*[69]	Sweden	Community	59	Protein-rich formula and additional calcium and vitamin D	20	83.5 ± 6.1	0 (0)	20.5 ± 2.4	53.7 ± 7.9	NR	NR
				Protein-rich formula plus nandrolone decanoate, additional calcium and vitamin D	19	81.1 ± 5.5	0 (0)	19.8 ± 2.2	50.0 ± 7.7	NR	NR
				SC plus additional calcium and vitamin D	20	84.1 ± 4.3	0 (0)	20.9 ± 2.3	56.0 ± 9.9	NR	NR
Tylner 2016[56]	Sweden	Nursing home: five residential care homes in the southern Stockholm area	39	Intervention then SC	19	87.2 ± 5.9 *n* = 14	50% *n* = 14	22.1 ± 3.4 *n* = 3.4	58.6 ± 9.9 *n* = 14	*Eleven of the individuals (79%) in each group were assessed as at risk of malnutrition* Unclear whether this is MNA-SF	NR
				Intervention then SC	20	82.2 ± 7.9 *n* = 14	29% *n* = 14	23.5 ± 4.2 *n* = 14	63.0 ± 14.2 *n* = 14.2	*Eleven of the individuals (79%) in each group were assessed as at risk of malnutrition* Unclear whether this is MNA-SF	NR
Van Wymelbeke *et al.*[57]	France	Nursing home: eight nursing homes in Burgundy	87	Enriched brioche	35	84.2 ± 7.9	6 (20.7)	29.1 ± 7.3	NR	MNA: 21.1 ± 2.8	7.6 ± 3.6
				ONS	27	90.3 ± 6.5	3 (17.7)	24.9 ± 6.4	NR	MNA: 19.9 ± 3.5	6.7 ± 2.5
				Usual care	25	87.3 ± 8.0	5 (22.7)	28.1 ± 5.8	NR	MNA: 21.8 ± 2.7	6.9 ± 3.4

MUAC, mid-upper-arm circumference.
NR denotes that the data were not individually reported for the trial arms. All studies met the inclusion criteria, but some did not report participant characteristics for the intervention and comparator arms (e.g. malnutrition assessment).

Appendix 7 Comorbidities and social determinants reported in included studies

	Comorbidities						Oral health issues						Social determinants					
Study	Dementia	Cognitive impairment	Stroke	Cardiovascular disease	Diabetes	Cancer	Swallowing issues	Problems chewing	Dry mouth	Complete or partial denture	No dentures	Need for help with feeding	Ethnicity	Socioeconomic status	Education	Marital status	Living arrangements	Household or other help
Cameron *et al.*[71]																	✗	
Lauque *et al.*[67]	✗											✗		✗			✗	
Lee *et al.*[54]												✗		✗	✗	✗	✗	✗
Luo *et al.*[70]																		
Miller *et al.*[68]		✗															✗	✗
Otten *et al.*[72]																	✗	✗
Parsons *et al.*[53]	✗	✗		✗										✗			✗	
Payette *et al.*[55]															✗	✗	✗	✗
Tidermark *et al.*[69]																	✗	
Tylner 2016[56]		✗															✗	
Van Wymelbeke *et al.*[57]										✗	✗						✗	

Appendix 8 Intervention characteristics

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
Cameron *et al.*[71]	High-calorie, high-protein supplement and diet of choice	23	One pack of supplement per day and diet of choice	Novasource per 237 ml: 475 kcal, 21.3 g protein, 51 g carbohydrate, 20.9 g fat, 375 µg vitamin A, 2.5 µg vitamin D, 250 mg calcium, 4.5 mg iron, 250 µg phosphate Sustagen Hospital Plus per 235 ml: 352.5 kcal, 17.6 g protein, 44.2 g carbohydrate, 20.9 g fat, 375 µg vitamin A, 2.5 µg vitamin D, 250 mg calcium, 4.5 mg iron, 250 µg phosphate	Supplements taken once per day; unclear when they were delivered	The supplement was given once per day from when oral intake was resumed after surgery, or from enrolment for those who did not undergo surgery. They continued usual diet otherwise. If the patient was discharged before the 40-day treatment period ended, they were given the rest of the supplements and instructions to keep drinking them as discussed
	High-protein milk and diet of choice	21	A high-protein diet with high-protein milk and diet of choice	High-protein milk per 150 ml: 194 kcal, 11 g protein, 18.75 g carbohydrate, 8.3 g fat	High-protein milk to be taken once per day; unclear when this was delivered	Given the high-protein diet with high-protein milk because this was the standard practice at the hospital, and it was deemed unethical to withdraw this. When the participants were discharged, they could follow their normal diets
Lauque *et al.*[67]	No supplementation (well nourished)	19	NA	NR	NR	NR
	No supplements (risk of malnutrition)	22	NA	NR	NR	NR
	Oral supplements (risk of malnutrition)	19	Nutritional supplements of 300–500 kcal. Four oral supplementation products (Clinutren, Nestle Clinical Nutrition, Sevres, France) were offered: Clinutren soup, Clinutren Fruit, Clinutren Dessert and Clinutren HP (Hyper-protein)	300–500 kcal Clinutren soup: 200 kcal and 10 g protein per 200 ml Clinutren Fruit: 120 kcal and 7.5 g protein per 150 ml Clinutren Dessert: 150 kcal and 12 g protein per 150 ml Clinutren HP: 200 kcal and 15 g protein per 200 ml	'Given in addition to regular meals'; no other details	The supplements were given in addition to regular meals. They were either liquid or creamy, sweet or savoury and were served hot, warm or cold. They were enriched with proteins, vitamins and minerals and contained high amounts of energy and nutrient in a small volume

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
	Oral supplements (malnourished)	28	Nutritional supplements of 300–500 kcal. Four oral supplementation products (Clinutren, Nestle Clinical Nutrition, Sevres, France) were offered: Clinutren soup, Clinutren Fruit, Clinutren Dessert and Clinutren HP (Hyper-protein)	300–500 kcal Clinutren soup: 200 kcal and 10 g protein per 200 ml Clinutren Fruit: 120 kcal and 7.5 g protein per 150 ml Clinutren Dessert: 150 kcal and 12 g protein per 150 ml Clinutren HP: 200 kcal and 15 g protein per 200 ml	'Given in addition to regular meals'; no other details	The supplements were given in addition to regular meals. They were either liquid or creamy, sweet or savoury and were served hot, warm or cold. They were enriched with proteins, vitamins and minerals and contained high amounts of energy and nutrient in a small volume
Lee *et al.*[54]	ONS	47	50 g/day soy protein-based preparation as a 'warm drink'	9.5 g protein, 250 kcal energy and all essential micronutrients	Delivered in the afternoon, daily	50 g/day soy protein-based preparation; prepared as a 'warm drink' as an afternoon snack
	NR	45	NR	NA	NA	NR
Luo *et al.*[70]	Ensure2: nutritionally complete, calorically dense, high-protein ONS	26	Standard hospital food plus Ensure TwoCal (Abbott Nutrition, Columbus, OH, USA) – a nutritionally complete, energy- and protein-dense drink including 30 vitamins and minerals	798 kcal, 34 g protein	Administered three times per day: 100 ml between meals and 200 ml as an evening snack	Two 200 ml containers given three times per day – 100 ml between breakfast and noon meal, 100 ml serving between noon and evening meal and 200 ml as a snack before going to bed
	Standard hospital food only	29	Standard hospital food and SC	NR	NR	NR
Miller *et al.*[68]	Nutrition	25	Fortisip (Nutricia Australia Pty Ltd)	Prescribed to meet 45% individual total energy requirements Fortisip: 6.3 kJ (1.5 kcal)/ml, 16% protein, 35% fat and 49% carbohydrate	Commenced 7 days after fracture; four doses of equal volume given daily. Weekly visits from weeks 7–12 provided to match participant contact in resistance training	Four equal-volume doses were administered daily. On discharge, those admitted to residential care received the supplement as described. For those discharged, home scheduling was twice per day or more. Weekly visits from weeks 7 to 12 were provided to match the participant contact in the resistance training groups

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
	Exercise	25	Latex-free resistive elastic bands (REP band, Magister Corporation, Chattanooga, TN, USA)	NR	Commenced 7 days after fracture; took place three times a week for 20–30 minutes	Three times per week, 20–30 minutes per session for 12 weeks. The programme incorporated progressive resistance training (using latex-free bands) of the hip extensors and abductors (supine), knee extensors (supine or sitting), and ankle dorsi- and plantar-flexors (supine or sitting). The frequency and duration of the resistance training programme was determined following a review of the literature that suggested positive outcomes might be achieved through triweekly training between 8 and 15 weeks
	Nutrition and exercise	24	Combination of groups 1 and 2 above	Combination of groups 1 and 2 above	Combination of groups 1 and 2 above	Combination of groups 1 and 2 above
	Attention control	26	Home visits	NA	Triweekly visits of equivalent duration in weeks 1–6 and then weekly visits at weeks 7–12 to match the home visits of the active intervention groups	The visits were limited to discussion on general information (e.g. benefits of regular exercise and nutrient-dense meals). All participants encouraged to continue treatments as prescribed during the hospital admission or by their treating health professionals

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
Otten *et al.*[72]	Dietary counselling	NR	NR	NR	For 3 months	Dietary counselling for 3 months
	ONS	NR	ONS – details not reported	NR	For 3 months	Dietary counselling for 3 months
Parsons *et al.*[53]	ONS with guidance	53	A range of ONS (drinks, soups, puddings, modules), in a range of flavours, volume (125–200 ml), energy density (1.3–4.5 kcal/ml) (Nutricia Ltd, Trowbridge, Wiltshire, UK)	1.3–4.5 kcal/ml	Daily; no other details	ONS were given so participants could take them according to choice – the majority chose ready-made liquid ONS (1.5–2.4 kcal/ml). They and care staff were given guidance on using ONS and the daily target provision was at least 600 kcal and 16 g protein. However, intake was voluntary and residents remained in the study irrespective of the quantity of ONS or food consumed
	Dietary advice	51	Given a specially designed diet sheet ('Build yourself up', Southampton Dieticians, Southampton, UK)	NR	NR	The leaflet encouraged participants to intake high-energy drinks and snacks
Payette *et al.*[55]	ONS	42	ONS: Commercial Liquid Formula (Ensure or Ensure Plus) provided by Ross Laboratories (Division of Abbott Laboratories)	235-ml can	Liquid formula was taken twice per day for a period of 16 weeks; nutritional counselling took place every 2 weeks	Subjects were provided with two 235-ml cans per day of their choice of a commercial liquid. Ensure Plus (vanilla, chocolate and strawberry) was systematically provided to the subjects and Ensure in other flavours such as orange and wild berry was used to minimise flavour fatigue *Subjects were clearly instructed not to replace their usual meals with the liquid supplement; rather, they were encouraged to use the supplements and increase overall food intake*
	Control	41	'Visited each month and given a small gift'; no other details	NR	Visited every month and given a small gift	Did not receive any treatment during this period. Were visited each month and given a small gift

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
Tidermark *et al.*[69]	Protein-rich formula and additional calcium and vitamin D	20	Protein-rich formula (Fortimel) plus additional calcium and vitamin D (400IE) (Calcichew-D3s)	Fortimel: 200 ml/day, 20 g protein/day Calcichew-D3s: 400IE	Fortimel plus additional calcium and vitamin D daily	Given daily for 6 months: 'The care programme was identical otherwise in all three groups'
	Protein-rich formula plus nandrolone decanoate, additional calcium and vitamin D	19	Protein-rich formula (Fortimel) plus nandrolone decanoate (Deca-Durabols) plus additional calcium and vitamin D (Calcichew-D3s)	Deca-Durabols: 25 mg i.m. Fortimel: 200 ml/day, 20 g protein/day Calcichew-D3s: 400IE	Fortimel plus additional calcium and vitamin D daily Deca-Durabols for 3 weeks daily	Given daily for 6 months: *The intramuscular nandrolone injections were given by a research nurse in the home of the patients* *The care programme was identical otherwise in all three groups*
	SC plus additional calcium and vitamin D	20	Standard treatment plus additional calcium and vitamin D (Calcichew-D3s)	Calcichew-D3s: 400IE 1 g calcium	Standard treatment plus additional calcium and vitamin D daily	Daily for 6 months; nature of SC not described *The care programme was identical otherwise in all three groups*
Tylner 2016[56]	Intervention then SC	19	Calogen Extra (Nutricia Advanced Medical Nutrition, Schiphol, The Netherlands), then SC (not described)	Calogen Extra: 360 kcal, 4.5 g protein, approximately 30% recommended micronutrients (including 2.7 µg vitamin D, 201 mg calcium)	Intervention was delivered 3 times daily at the same time as medication (8 a.m., 12 p.m., 8 p.m.). Regimen for SC not described	In intervention phase, each serving was registered during the 6-week intervention period and the daily dose was 90 ml. SC not described
	Intervention then SC	20	First SC (not described) and then Calogen Extra (as described in group 1)	Calogen Extra: 360 kcal, 4.5 g protein, approximately 30% recommended micronutrients (including 2.7 µg vitamin D, 201 mg calcium)	SC regimen not described. Intervention regimen as described for group A	Initial SC not described; intervention regimen for stage 2 as described for group A

Study	Intervention	Number in group	Materials used	Dosage	Regimen	Delivery details
Van Wymelbeke *et al.*[57]	Enriched brioche	35	Brioche weighed 65 g and was provided by Cerelab (Dijon, France). Designed to provide similar levels of energy and macro- and micronutrients to the ONS	Brioche: 12.8 g protein, 180 kcal, 15.5 g carbohydrate, 4 g sugar, 7.3 g lipids, 0.4 mg vitamin B1, 0.6 mg vitamin B2, 1.2 mg vitamin B6, 183 µg vitamin B9, 1.9 µg vitamin B12, 5 µg vitamin D, 23 µg selenium	One brioche roll per day, taken at breakfast, for 12 weeks	Participants were given one brioche roll per day for 12 weeks. They completed their breakfast with a hot drink, juice, butter, jam and ordinary bread if they wanted to. Three randomised flavours: orange, vanilla and honey
	ONS	27	Supplement: usual bread at breakfast replaced by an ONS. 200 ml carton of Fresenius Kabi (Nestle S.A., Labege, France)	Supplement: 14 g protein and 200 kcal; it also contained 23.6 g carbohydrate, 5.6 g sugar, 5.6 g lipids, 0.3 mg vitamin B1, 0.3 mg vitamin B2, 0.4 mg vitamin B6, 40 µg vitamin B9, 0.2 µg vitamin B12, 1 µg vitamin D, 12 µg selenium	One ONS per day, taken at breakfast, for 12 weeks	Participants received one 200-ml carton of ready-to-use energy-dense liquid per day for 12 weeks. They completed their breakfast with a hot drink, juice, butter, jam and ordinary bread if they wanted to. Three randomised flavours: strawberry, coffee and vanilla
	Usual care	25	Usual breakfast provided by the nursing homes	NA	NA – usual diet	Participants received their usual breakfast provided by the nursing homes

Appendix 9 Risk of bias/critical appraisal of included studies in effectiveness review

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cameron *et al.*[71]							
Lauque *et al.*[67]							
Lee *et al.*[54]							
Luo *et al.*[70]							
Miller *et al.*[68]							
Otten *et al.*[72]							
Parsons *et al.*[53]							
Payette *et al.*[55]							
Tidermark *et al.*[69]							
Tylner *et al.*[56]							
Van Wymelbeke *et al.*[57]							

Navy, low risk of bias; aqua, unclear risk of bias; coral, high risk of bias.

Appendix 10 Studies excluded from the pairwise meta-analyses, with reasons

Citation	Outcome(s)	Reason for exclusion from the pairwise meta-analysis
Lauque *et al.*[67]	Grip strength and MNA	Participants were not randomised to all of the trial arms
Parsons *et al.*[53]	Mortality, kcal	No comparison between ONS and SC
	Hospitalisation, QoL	No comparison between ONS and SC
	Body weight, kcal, protein	The data reported were insufficient for a meta-analysis. Mean and standard deviations were unavailable and could not be completed
Payette *et al.*[55]	Grip strength	Data were not reported in an extractable format
	QoL	This study assessed 'emotional role functioning' and 'physical role functioning' domains of the SF-36. No other studies reported comparable data; therefore, this study could not be included in the meta-analysis
Miller *et al.*[68]	Grip strength	Quadriceps strength rather than handgrip strength was assessed
	Body weight	Standard deviation was unavailable and could not be calculated
	QoL	This study assessed 'mental component' and 'physical domain' of the SF-12. No other studies reported comparable data; therefore, this study could not be included in the meta-analysis
Tidermark *et al.*[69]	QoL	Only baseline data were reported for this outcome
Otten *et al.*[72]	QoL	No SC group [a within-group comparison was made, before and after the intervention (ONS)]

Appendix 11 Forest plots for body weight and body mass index outcomes, showing both final values and change from baseline

Forest plots illustrating the difference between the use of final values and CFB are shown for body weight and BMI in *Figures 21–24*.

Body weight

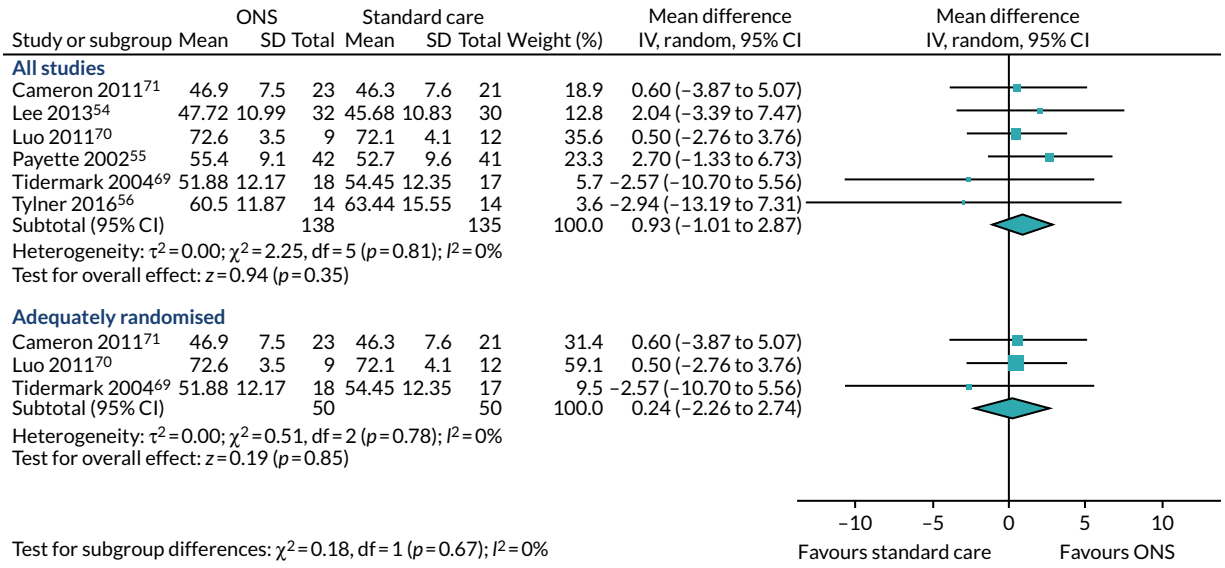


FIGURE 21 Body weight: final values.

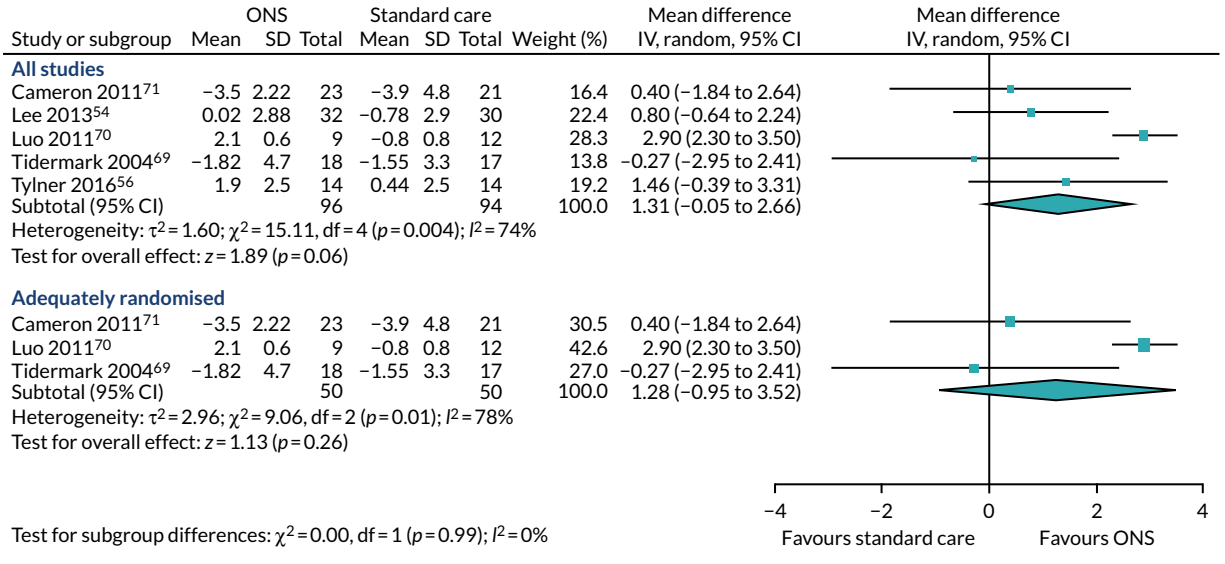


FIGURE 22 Body weight: CFB.

Body mass index

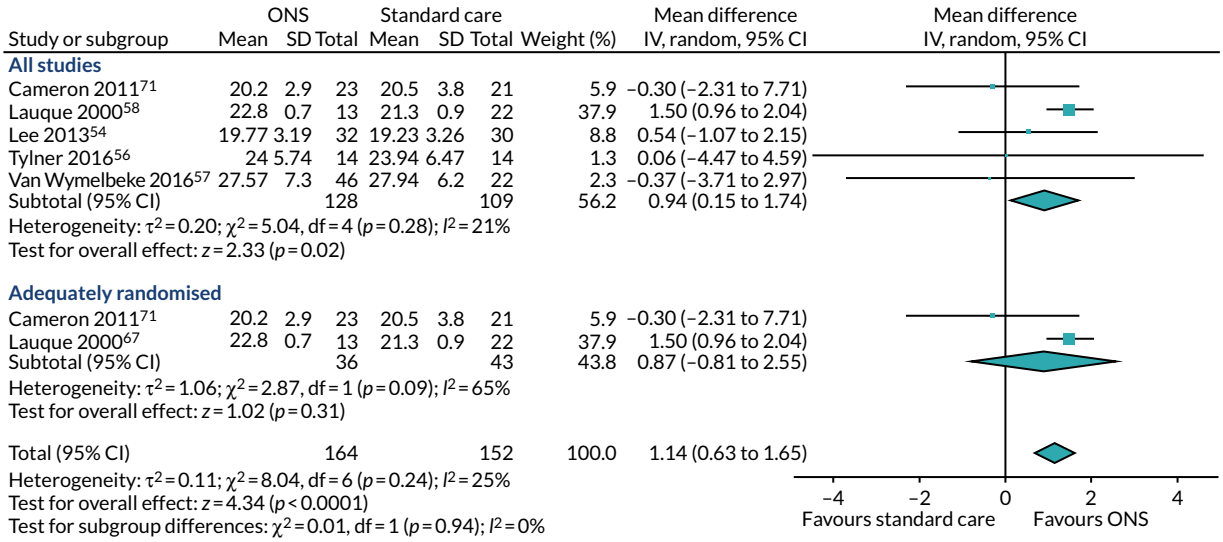


FIGURE 23 Body mass index: final values.

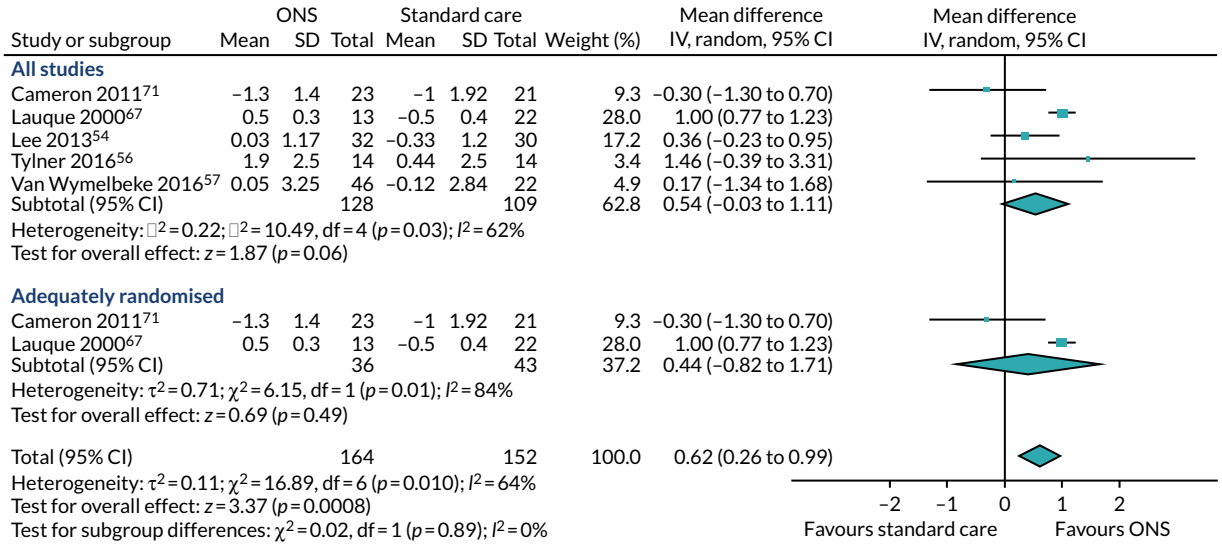


FIGURE 24 Body mass index: CFB.

Appendix 12 Meta-analysis results using final values and change from baseline results

	Adequate randomisation					All studies				
		CFB		Final values			CFB		Final values	
Outcome	Unit	*n*	Result (95% CI)	*n*	Mean (95% CI)	Unit	*n*	Mean (95% CI)	*n*	Mean (95% CI)
Consumption										
Energy (kcal/day)/(kcal/kg)	SMD	NA	NA	NA	NA	SMD	4	1.02 (0.15 to 1.88)	5	1.66 (0.40 to 2.93)
Protein (g/day)/(g/kg)	SMD	NA	NA	NA	NA	SMD	4	1.67 (–0.03 to 3.37)	5	2.11 (0.48 to 3.73)
Body										
Body weight	kg	3	1.28 (–0.95 to 3.52)	3	0.24 (–2.26 to 2.74)	kg	5	1.31 (–0.05 to 2.66)	6	0.93 (–1.01 to 2.87)
BMI (kg/m^2)	kg/m^2	2	0.44 (–0.82 to 1.71)	2	0.87 (–0.81 to 2.55)	kg/m^2	5	0.54 (–0.03 to 1.11)	5	0.94 (0.15 to 1.74)
Albumin	g/l	2	2.86 (0.69 to 5.03)	2	2.17 (0.00 to 4.33)	g/l	5	1.48 (–0.44 to 3.41)	5	1.04 (–0.63 to 2.71)
Arm circumference	NA	NA	NA	NA	NA	SMD	2	0.49 (–0.32 to 1.30)	2	0.16 (–0.28 to 0.60)
Fat-free muscle mass	SMD	NA	NA	NA	NA	SMD	3	0.23 (–0.24 to 0.69)	3	0.04 (–0.33 to 0.41)
MNA (score)	NA	NA	NA	NA	NA	SMD	NA	NA	2	–0.36 (–0.81 to 0.09)
Health outcomes										
Wound healing	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Infections	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Falls	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hospitalisation										
Hospitalisation (number/rates)	NA	NA	NA	2	0.8 (0.35 to 1.82)	NA	NA	NA	5	0.97 (0.46 to 2.04)
QoL										
ADL (score)	SMD	NA	NA	2	0.68 (–0.54 to 1.90)	SMD	2	–0.14 (–0.76 to 0.49)	3	0.30 (–0.69 to 1.29)
Mobility (m/second)	MD	NA	NA	2	0.02 (–0.06 to 0.09)	MD	NA	NA	3	0.03 (0.02 to 0.04)
Grip strength (kg/kgW/kPa)	SMD	2	0.27 (–0.40 to 0.94)	2	0.37 (–0.06 to 0.81)	SMD	5	0.17 (–0.23 to 0.58)	5	0.12 (–0.19 to 0.44)
QoL (score)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mortality										
Mortality (number/rates)	NA	NA	NA	NA	NA	NA	NA	NA	4	0.93 (0.28, 3.06)

Appendix 13 Summary of findings table

Outcome	Relative effect	Number of studies	GRADE	Comments
Energy (kcal) intake	SMD 1.02 (95% CI 0.15 to 1.88)	4	⨁⨀⨀⨀ very low[a,b,c]	
Protein intake	SMD 1.67 (95% CI −0.03 to 3.37)	4	⨁⨀⨀⨀ very low[a,b,c]	
Albumin	MD 1.48 (95% CI −0.44 to 3.41)	5	⨁⨀⨀⨀ very low[a,b,d]	
Body weight	MD 1.31 (95% CI −0.05 to 2.66)	5	⨁⨀⨀⨀ very low[d,e]	
BMI	MD 0.54 (95% CI −0.03 to 1.11)	5	⨁⨀⨀⨀ very low[e,f]	
Arm circumference	–	–	–	Narrative synthesis; GRADE not conducted
Fat-free muscle mass	SMD 0.23 (95% CI −0.24 to 0.69)	3	⨁⨁⨀⨀ low[g]	
ADL	SMD 0.30 (95% CI −0.69 to 1.29)	3	⨁⨀⨀⨀ very low[b,f,g]	
Grip strength	SMD 0.17 (95% CI −0.23 to 0.58)	5	⨁⨀⨀⨀ very low[af]	
Hospitalisations	RR 0.97 (95% CI 0.46 to 2.04)	5	⨁⨀⨀⨀ very low[d,g]	
Change in malnutrition (MNA score)	SMD −0.36 (95% CI −0.81 to 0.09)	2	⨁⨀⨀⨀ very low[f,g]	
Mobility (gait speed)	MD 0.03 (95% CI 0.02 to 0.04)	3	⨁⨀⨀⨀ very low[d,e]	
Mortality	RR 0.93 (95% CI 0.28 to 3.06)	4	⨁⨀⨀⨀ very low[d,g]	
QoL	–	–	–	Narrative synthesis; GRADE not conducted
Reduction in infection	–	–	–	Only one study, no meta-analysis; GRADE not conducted
Wound healing	–	–	–	Not reported
Reduction in falls	–	–	–	Not reported
Improvement in frailty	–	–	–	Not reported
Morbidity	–	–	–	Not reported
Admission to long-term care	–	–	–	Not reported

a Downgraded once for imprecision: wide 95% CI.
b Downgraded once for inconsistency: I^2 greater than 75%.
c Downgraded twice for risk of bias: concerns about randomisation, blinding of participants and personnel and attrition bias.
d Downgraded twice for risk of bias: concerns about allocation concealment, blinding of participants and personnel and attrition bias.
e Downgraded once for imprecision: small numbers of total participants.
f Downgraded twice for risk of bias: concerns about randomisation, allocation concealment, blinding of participants and personnel and attrition bias.
g Downgraded twice for imprecision: wide 95% CI and small number of total participants.
Adapted with permission from Evidence Prime Inc., Hamilton, ON, Canada.[111]

Appendix 14 Additional exclusions in cost-effectiveness review

The initial selection of cost-effectiveness studies was conducted alongside the selection of effectiveness studies. Subsequently, a few studies were excluded by reviewers Stephen Rice and Wael Mohammed. The reasons for exclusion are reported here.

Study	Reason for exclusion
Edington *et al.*[112]	Not a full economic evaluation. No costing of intervention
Pouyssegur *et al.*[76]	The intervention was not an ONS intervention
Arnaud-Battandier *et al.*[113]	Not a frail population
Seguy *et al.*[114]	Not a frail population
Zhong *et al.*[115]	Not a frail population
Nuitjen *et al.*[116]	Not a frail population
Nuitjen *et al.*[117]	Not a frail population

Appendix 15 Quality assessment in cost-effectiveness review

The result of the completed BMJ checklist for the included study is reported in *Table 21*.

TABLE 21 Completed BMJ checklist for included studies

Item	Elia *et al.*[23]
1. Was the research question stated?	1
2. Was the economic importance of the research question stated?	1
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	4
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	4
5. Were the alternatives being compared clearly described?	1
6. Was the form of economic evaluation stated?	1
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	1
8. Was/were the source(s) of effectiveness estimates used stated?	1
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	1
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	2
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	1
12. Were the methods used to value health states and other benefits stated?	1
13. Were the details of the subjects from whom valuations were obtained given?	3
14. Were productivity changes (if included) reported separately?	2
15. Was the relevance of productivity changes to the study question discussed?	2
16. Were quantities of resources reported separately from their unit cost?	4
17. Were the methods for the estimation of quantities and unit costs described?	1
18. Were currency and price data recorded?	1
19. Were details of price adjustments for inflation or currency conversion given?	1
20. Were details of any model used given?	2
21. Was there a justification for the choice of model used and the key parameters on which it was based?	2
22. Was the time horizon of cost and benefits stated?	1
23. Was the discount rate stated?	2
24. Was the choice of rate justified?	2
25. Was an explanation given if cost or benefits were not discounted?	1
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	1
27. Was the approach to sensitivity analysis described?	1
28. Was the choice of variables for sensitivity analysis justified?	2
29. Were the ranges over which the parameters were varied stated?	2

continued

TABLE 21 Completed BMJ checklist for included studies (*continued*)

Item	Elia *et al.*[23]
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	1
31. Was an incremental analysis reported?	1
32. Were major outcomes presented in a disaggregated as well as aggregated form?	4
33. Was the answer to the study question given?	1
34. Did conclusions follow from the data reported?	1
35. Were conclusions accompanied by the appropriate caveats?	1
36. Were generalisability issues addressed?	4

1, yes; 2, not applicable; 3, unclear; 4, no.

Appendix 16 Focused search for association between body mass index and longer-term outcomes

A focused search of the literature was conducted to identify evidence of the association between BMI and mortality, hospitalisation or QoL (e.g. EQ-5D and ADL measures). MEDLINE was searched; the search strategy is reported here.

Search strategy for body mass index outcome: MEDLINE

1. Body Mass Index/
2. BMI.ti,ab,kw,kf.
3. Body Mass Index.ti,ab,kw,kf.
4. MNA.ti,ab,kw,kf.
5. EQ-5D.tib,kw,kf.
6. Barthel Index.ti,ab,kw,kf.
7. Kartz Index.ti,ab,kw,kf.
8. Readmission.ti,ab,kw,kf.
9. Hospital admission.ti,ab,kw,kf.
10. Falls.ti,ab,kw,kf.
11. associat*.ti,ab,kw,kf.
12. or/5-10
13. Statistics as Topic/
14. relationship.ti,ab,kw,kf.
15. statistical.ti,ab,kw,kf.
16. regression.ti,ab,kw,kf.
17. exp Frail Elderly/
18. exp Frailty/
19. frail*.ti,ab,kw,kf.
20. ((older or aged) adj (person* or people or patient* or population*)).ti,ab,kw,kf.
21. ((geriatric or elder*) adj2 (people or person* or patient* or population*)).ti,ab,kw,kf.
22. exp Nursing Homes/ or exp Homes for the Aged/
23. ((residential or nursing or care) adj home*).ti,ab,kw,kf.
24. exp Respite Care/
25. exp Long-Term Care/
26. “home* for the aged”.ti,ab,kw,kf.
27. “old age home*”.ti,ab,kw,kf.
28. skilled nursing facilit*.ti,ab,kw,kf
29. .intermediate care facilit*.ti,ab,kw,kf.
30. respite care.ti,ab,kw,kf.
31. long term care facilit*.ti,ab,kw,kf.
32. or/17-31
33. 11 or 13 or 14 or 15 or 16
34. 1 or 2 or 3 or 4
35. 12 and 32 and 33 and 34
36. limit 35 to (English language and full text and humans and yr=“1980-Current”).

EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

Published by the NIHR Journals Library