

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

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Scientific summary

Oral nutritional supplements for frail older people

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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 ≥ 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 ≥ 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, EBSCOhost 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/m². 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/m² 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/m² 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/m². 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.

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